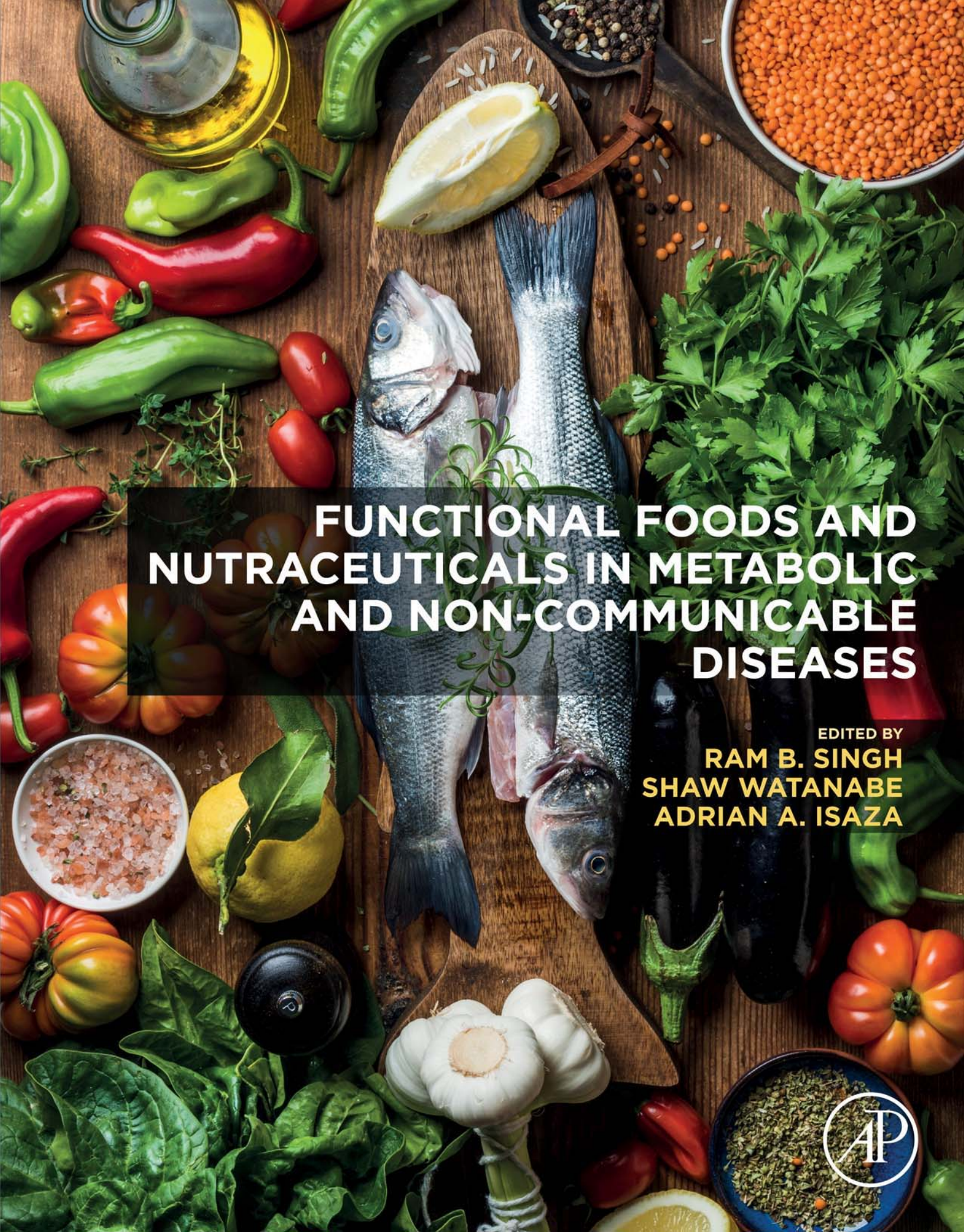


FUNCTIONAL FOODS AND NUTRACEUTICALS IN METABOLIC AND NON-COMMUNICABLE DISEASES

EDITED BY
RAM B. SINGH
SHAW WATANABE
ADRIAN A. ISAZA

Functional Foods and Nutraceuticals in Metabolic and Non-communicable Diseases

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Functional Foods and Nutraceuticals in Metabolic and Non-communicable Diseases

Edited by

Ram B. Singh
Halberg Hospital and Research Institute, Moradabad, India

Shaw Watanabe
Central Office, Life Science Promoting Association, Tokyo, Japan

Adrian A. Isaza
Alternative Medicine, Everglades University, Tampa, FL, United States





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List of contributors

Maria Abromova People's Friendship University of Russia, Moscow, Russia

Aparna Agarwal Department of Food Technology, Lady Irwin College, University of Delhi, India

Edith Ajaiyeoba Oriabure Pharmacognosy Department, Faculty of Pharmacy, University of Ibadan, Ibadan, Nigeria

Wajdy Al-Awaida Department of Biology and Biotechnology, American University of Madaba, Madaba, Jordan; Department of Biochemistry, American University of Madaba, Madaba, Jordan

O.A. Al-bawareed People's Friendship University of Russia, Moscow, Russia

Saikat Kumar Basu Performance Seed, University of Lethbridge, Lethbridge, AB, Canada

Shalini Behl School of Life Sciences, Manipal Academy of Higher Education, Dubai, United Arab Emirates; School of Natural Sciences, University of Central Lancashire, Preston, United Kingdom

M.A. Bernardo CiiEM Research Centre, Egas Moniz Higher Institute of Health Sciences, Caparica, Portugal

Kshitij Bharadwaj Department of Physiology, KG Medical University, Lucknow, India

J. Brito CiiEM Research Centre, Egas Moniz Higher Institute of Health Sciences, Caparica, Portugal

Harpal S. Buttar Department of Pathology & Laboratory Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada

William Cetzal-Ix National Technological Institute of Mexico, Technological Institute of Chiná, Campeche, Mexico

Saibal Chakravorty Metro Group of Hospitals, Noida, India

Jayeeta Chaudhury Center of Nutrition Research, Ahmedabad, India

Anil K. Chauhan Department of Dairy Science and Food Technology, Institute of Agricultural Sciences, Banaras Hindu University, Varanasi, India; Centre of Food Science and Technology, Institute of Agricultural Sciences, Banaras Hindu University, Varanasi, India

Qi Cheng Biotechnology Research Institute, Chinese Academy of Agricultural Sciences, Beijing, P.R. China; College of Life Sciences, Hebei Agricultural University, Baoding, P.R. China; Global Alliance of HeBAU-CLS&HeQis for BioAl-Manufacturing, Baoding, P.R. China; Department of Agronomy and Plant Breeding, Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, Iran; Nitrogen Fixation Laboratory, Qi Institute, Jiaxing, P.R. China

Sergey Chibisov Faculty of Medicine, People's Friendship University of Russia, Moscow, Russia

Meena Chintamaneni Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM's NMIMS, Mumbai, India

Kanokkarn Chupisanyarote Department of Internal Medicine, Faculty of Medicine, Thammasat University, Bangkok, Thailand

Germaine Cornélissen Halberg Chronobiology Center, University in Minnesota, Minneapolis, MN, United States

Yashodhara Dalal Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM's NMIMS, Mumbai, India

Teodora Handjiev Darlenska Department of Pharmacology, Sofia University, Sofia, Bulgaria

Amit Krishna De The Indian Science Congress Association, Kolkata, India

Minakshi De Department of Microbiology, Surendranath College, Calcutta University, Kolkata, India

Fabien De Meester TsimTsoum Institute, Kraków, Poland; The American University in Dubai, UAE; WSB University in Torun, Poland

Mira Dewi Department of Community Nutrition, Faculty of Human Ecology, IPB University, IPB Campus Dramaga, Bogor, Indonesia

ParnikaDilip Dicholkar Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM's NMIMS, Mumbai, India

Galal Nagib Elkilany Gulf Medical College, Ajnam, United Arab Emirates; The Tsim Tsoum Institute, Krakow, Poland

Justo R. Enríquez-Nolasco National Technological Institute of Mexico, Technological Institute of Chiná, Campeche, Mexico

Ghizal Fatima Department of Biotechnology, Era's Medical College and Hospitals, Lucknow, India

Jan Fedacko Faculty of Medicine, PJ Safaric University, Kosice, Slovakia; Department of Internal Medicine, PJ Safaric University, Kosice, Slovakia

Al Mukhlas Fikri Department of Community Nutrition, Faculty of Human Ecology, IPB University, Bogor, Indonesia; Department of Nutrition, Faculty of Health Sciences, University of Singaperbangsa Karawang, Karawang, Indonesia

Ramesh K. Goyal Delhi Pharmaceutical University and Technical Sciences, New Delhi, India

Om Kumari Gupta Metro Group of Hospitals, Noida, India

Anna Gvozdjáková Centre of Nutrition and Heart, Medical Hospital and Research Centre, Moradabad, India; Pharmacobiochemical Laboratory of 3rd Medical Department, Medical Faculty, Comenius University in Bratislava, Bratislava, Slovakia

Najah Hadi Faculty of Medical Sciences, University of Kufa, Kufa, Iraq; Department of Pharmacology and Therapeutics, Faculty of Medicine, University of Kufa, Kufa, Iraq

Ghazi Halabi Halberg Chronomedicine and Cardiology Center, Aley, Lebanon

Svetslav Handjiev Department of Pharmacology, Sofia University, Sofia, Bulgaria

Carlin Hanoman School of Medicine, Faculty of Health Sciences, University of Guyana, Guyana; School of Natural Sciences, College of Science and Technology, University of Central Lancashire, Preston, United Kingdom

Hardinsyah Hardinsyah Southeast Asia Probiotics Scientific and Regulatory Experts Network (SEA PROBIOTICS SREN), Bogor, Indonesia; Department of Community Nutrition, Faculty of Human Ecology, Bogor Agricultural University, Bogor, Indonesia

Hiroyuki Hashimoto Tsuno Shokuhin Kogyo, Co. Ltd. Wakayama, Japan

Siti Helmyati Department of Nutrition and Health, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia; Center for Health and Human Nutrition, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

Kyle D. Hilsabeck McCord Research, Coralville, IA, United States

Rie Horiuchi Department of Food Sciences and Nutrition, School of Food Science and Nutrition, Mukogawa Women's University, Nishinomiya, Japan

Krasimira Hristova University National Heart Hospital, Sofia, Bulgaria

Arif Hussain School of Life Sciences, Manipal Academy of Higher Education, Dubai, United Arab Emirates

Laila A. Hussein Department of Nutrition, National Research Center, Giza, Egypt

Josiah Ifie Biochemistry Department, College of Medicine, Kampala International University, Western Campus, Ishaka, Uganda

Asha Inbanathan School of Life Sciences, Manipal Academy of Higher Education, Dubai, United Arab Emirates

Adrian Isaza Alternative Medicine, Everglades University, Tampa, FL, United States

Arunporn Itharat Department of Applied Thai Traditional Medicine, Thammasat University, Kluangnueng, Thailand

Poonam Jaglan Department of Food Science and Technology, School of Agriculture, Lovely Professional University, Phagwara, India

Ekta Jain Department of Dairy Technology and Food Technology, Institute of Agricultural Sciences, Banaras Hindu University, India

Monica Jain The American University in Dubai, UAE; WSB University in Torun, Poland

Ibrahim Jantan Faculty of Health and Medical Sciences, Taylor's University, Subang Jaya, Malaysia

Lekh Juneja Lifescience Association, Tokyo, Japan

Lekh Raj Juneja Halberg Hospital and Research Institute, Moradabad, India; The Rohto Pharmaceutical Co. Ltd, Osaka, Japan

Yasuo Kagawa Kagawa Nutrition University Toshimaku, Tokyo, Japan

Tom C. Karagiannis Epigenomic Medicine Program, Department of Diabetes, Central Clinical School, Monash University, Prahan, VIC, Australia

Kumar Kartikey Halberg Hospital and Research Institute, Moradabad, India

Ginpreet Kaur Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM's NMIMS, Mumbai, India

Shairy Khan Halburg Hospital and Research Institute, Moradabad, India

Elena Kharlitskaya People's Friendship University of Russia, Moscow, Russia

Mojgan Khatibi Endocrinology and Metabolism Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran

Mozhgan Khatibi Endocrinology and Metabolism Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran

Mehdi Khoshkharam Department of Agronomy and Plant Breeding, Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, Iran; Department of Agronomy and Plant Breeding, Faculty of Agriculture, Islamic Azad University, Isfahan (Khorasgan) Branch, Isfahan, Iran

Kota Kikuchi Ministry of Agriculture, Forestry, and Fisheries, Tokyo, Japan

T. Kiyoi Division of Analytical Bio-medicine, Advanced Research Support Center, Ehime University, Toon, Japan

Jarmila Kucharská Pharmacobiochemical Laboratory of 3rd Medical Department, Medical Faculty, Comenius University in Bratislava, Bratislava, Slovakia

Ashwani Kumar Department of Food Technology and Nutrition, Lovely Professional University, Phagwara, India

Maushmi S. Kumar Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM's NMIMS, Mumbai, India

Mukul Kumar Department of Food Technology and Nutrition, Lovely Professional University, Phagwara, India

Pooja Kumari Department of Pharmaceutical Sciences, Lovely Professional University, Phagwara, India

Tyler W. LeBaron Molecular Hydrogen Institute, Enoch, UT, USA; Centre of Experimental Medicine, Institute for Heart Research, Slovak Academy of Sciences, Bratislava, Slovak Republic; Department of Kinesiology and Outdoor Recreation, Southern Utah University, Cedar City, UT, United States

Duo Li Institute of Nutrition & Health, Qingdao University, Qingdao, P.R. China

S. Liu Department of Pharmacology, Ehime University Graduate School of Medicine, Toon, Japan

Anathi Magadlela School of Life Sciences, University of KwaZulu-Natal, Pietermaritzburg, South Africa

Miguel A. Magaña-Magaña Division of Graduate Studies and Research, National Technological Institute of Mexico, Technological Institute of Conkal, Yucatán, Mexico

Aminat Magomedova Department of Population, Faculty of Economics, Moscow State University by Lomonosov, Moscow, Russia

Anuj Maheshwari Department of Medicine, BBD CODS, BBD University, Lucknow, India

Abella Mann Epigenomic Medicine Program, Department of Diabetes, Central Clinical School, Monash University, Prahan, VIC, Australia

Jesús F. Martínez-Puc Division of Graduate Studies and Research, National Technological Institute of Mexico, Technological Institute of Conkal, Yucatán, Mexico; National Technological Institute of Mexico, Technological Institute of Chiná, Campeche, Mexico

Mana Matsuo Ministry of Agriculture, Forestry, and Fisheries, Tokyo, Japan

Kamlesh Kumar Mauraya Department of Dairy Technology and Food Technology, Institute of Agricultural Sciences, Banaras Hindu University, India

D. Elizabeth McCord McCord Research, Coralville, IA, United States

Ammar Mehdi Career Dental and Medical College, Lucknow, India

Farzana Mehdi Department of Biotechnology, Era's Medical College and Hospitals, Lucknow, India

M.F. Mesquita CiiEM Research Centre, Egas Moniz Higher Institute of Health Sciences, Caparica, Portugal

Richa Mishra Department of Home Science, Arya Mahila Degree College, Banaras Hindu University, India; Department of Home Science, Arya Mahila PG College, Banaras Hindu University, Varanasi, India

Sanjay Mishra School of Biotechnology, IFTM University, Moradabad, India

M. Mogi Division of Analytical Bio-medicine, Advanced Research Support Center, Ehime University, Toon, Japan; Department of Pharmacology, Ehime University Graduate School of Medicine, Toon, Japan

Viliam Mojto 3rd Department of Internal Medicine, Faculty of Medicine, Comenius University, Bratislava, Russia

Maria Mojtova Centre of Nutrition and Heart, Medical Hospital and Research Centre, Moradabad, India; University in Nitra, Slovakia - Univerzita Konštantína Filozofa v Nitre

M. Moncada CiiEM Research Centre, Egas Moniz Higher Institute of Health Sciences, Caparica, Portugal

Ade Heri Mulyati Department of Community Nutrition, Faculty of Human Ecology, IPB University, Bogor, Indonesia; Department of Chemistry, Faculty of Mathematics and Natural Sciences, IPB University, Bogor, Indonesia

Teiji Nakamura Kanagawa University of Human Services, Yokohama, Japan

Paul Nash Centre for Ageing & Dementia Research, Swansea University, Swansea, United Kingdom

Bichitra N. Nayak Department of Human Nutritional Sciences, University of Manitoba, Winnipeg, MB, Canada

Sarah Nwozo Onyenibe Biochemistry Department, Faculty of Basic Medical Science, College of Medicine, University of Ibadan, Ibadan, Nigeria

Shabnam Omidvar Social Determinants of Health Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran

Ekasit On-Saard Department of Agro-Industry, Faculty of Agriculture, Ubon Ratchathani University, Ubon Ratchathani, Thailand

Wiriya On-Saard Department of Agro-Industry, Faculty of Agriculture, Ubon Ratchathani University, Ubon Ratchathani, Thailand

Kenichi Otsubo Niigata Pharmaceutical University, Niigata, Japan

Hyun-Ryul Park Emeritus of Chung-Ang University, Seoul, South Korea; International Society for Heal-Being Studies, Seoul, South Korea

Daniel Pella Faculty of Medicine, PJ Safaric University, Kosice, Slovakia; Faculty of Medicine, PJ Safaric University, Kosice, Slovakia Pellad

Dominic Pella Department of Cardiology, Eastern Slovak Institute of Cardiovascular Diseases

Dominik Pella Faculty of Medicine, PJ Safaric University, Kosice, Slovakia; East Slovak Institute of Medical Sciences, Kosice, Slovakia; School of Public Health and Community Medicine, Hebrew University Hadassah Medical School, Jerusalem, 91120 Israel and Safaric University, Kosice, Slovakia

Eleni Pitsillou Epigenomic Medicine Program, Department of Diabetes, Central Clinical School, Monash University, Prahan, VIC, Australia

Priya All India Institute of Medical Sciences (AIIMS), New Delhi, India

Sudha R Velluri National University SanDiego, California, United States

Dinesh Chandra Rai Department of Dairy Technology and Food Technology, Institute of Agricultural Sciences, Banaras Hindu University, India

Richa H. Rai Delhi Pharmaceutical University and Technical Sciences, New Delhi, India; School of Physiotherapy, Delhi Pharmaceutical Sciences and Research University, New Delhi, India

Zuzana Rausová Pharmacobiochemical Laboratory of 3rd Medical Department, Medical Faculty, Comenius University in Bratislava, Bratislava, Slovakia

Somansh Rawal School of Biotechnology, IFTM University, Moradabad, India; Halberg Hospital and Research Institute, Moradabad, India

Nancy B. Ray McCord Research, Coralville, IA, United States

Hardinsyah Ridwan Southeast Asia Probiotics Scientific and Regulatory Experts Network (SEA PROBIOTICS SREN), Indonesia

Khemraj Rupee School of Medicine, Faculty of Health Sciences, University of Guyana, Guyana

Sunil Rupee School of Medicine, Faculty of Health Sciences, University of Guyana, Guyana

Madhvi Saxena University College of Engineering, Vinoba Bhave University, Hazaribhag, India

Prashant Saxena Department of Biotechnology, KS Vira College of Engineering & Management, Bijnor, India

Mohamad Hesam Shahrajabian Biotechnology Research Institute, Chinese Academy of Agricultural Sciences, Beijing, P.R. China; College of Life Sciences, Hebei Agricultural University, Baoding, P. R. China; Global Alliance of HeBAU-CLS&HeQis for BioAl-Manufacturing, Baoding, P.R. China; Department of Agronomy and Plant Breeding, Faculty of Agriculture, Islamic Azad University, Isfahan (Khorasgan) Branch, Isfahan, Iran; Nitrogen Fixation Laboratory, Qi Institute, Jiaxing, P.R. China

Asha Sharma Nutra-V Natural Care Private Limited, Lucknow, India

Divyank Sharma Halberg Hospital and Research Institute, Moradabad, India

Avinash Shenoy Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM's NMIMS, Mumbai, India

M.L. Silva CiiEM Research Centre, Egas Moniz Higher Institute of Health Sciences, Caparica, Portugal

Jaipaul Singh National Heart Hospital, Al Ain, United Arab Emirates; School of Natural Sciences, College of Science and Technology, University of Central Lancashire, Preston, United Kingdom; School of Forensic and Applied Sciences, University of Central Lancashire, Preston, United Kingdom

Mukta Singh Department of Home Science, Mahila Maha Vidyalaya, Banaras Hindu University, Varanasi, India

Raj K. Singh Biochemistry Department, Era's Lucknow Medical College and Hospital, Lucknow, India

Rajesh K. Singh Biochemistry Department, Era's Lucknow Medical College and Hospital, Lucknow, India

Ram B. Singh Internal Medicine (Cardiology), Hallberg Hospital and Research Institute, Moradabad, India; The Tsim Tsoum Institute, Krakow, Poland; Faculty of Medicine, PJ Safaric University, Kosice, Slovakia; Halberg Hospital and Research Center, Civil Lines, Moradabad, India; Centre of Nutrition and Heart, Medical Hospital and Research Centre, Moradabad, India

Reema Singh Centre of Nutrition and Heart, Medical Hospital and Research Centre, Moradabad, India

Manal M.A. Smail University of Central Lancashire, Preston, United Kingdom; UAE University, United Arab Emirates; Fatima College for Health Sciences, Abu Dhabi, United Arab Emirates

Sonia Suchday Department of Psychology, Pace University, New York, NY, United States

Ahmad Sulaeman Department of Community Nutrition, Faculty of Human Ecology, IPB University, Bogor, Indonesia; Department of Community Nutrition, Faculty of Human Ecology, Bogor Agricultural University, Bogor, Indonesia

Zuzana Sumbalová Pharmacobiochemical Laboratory of 3rd Medical Department, Medical Faculty, Comenius University in Bratislava, Bratislava, Slovakia

Wenli Sun Biotechnology Research Institute, Chinese Academy of Agricultural Sciences, Beijing, P.R. China; College of Life Sciences, Hebei Agricultural University, Baoding, P.R. China; Global Alliance of HeBAU-CLS&HeQis for BioAl-Manufacturing, Baoding, P.R. China; Nitrogen Fixation Laboratory, Qi Institute, Jiaxing, P.R. China

Madhumitha Kedhari Sundaram School of Life Sciences, Manipal Academy of Higher Education, Dubai, United Arab Emirates

Masahito Takahashi Medical Rice Association

Toru Takahashi Department of Food and Nutrition, Faculty of Human Sciences, Kanazawagakuin University, Kanazawa, Japan; Graduate School of Human Environment Science, Fukuoka Women's University, Fukuoka, Japan; Department of Health and Nutrition, Faculty of Human Health, Kanazawa Gakuin University, Kanazawa, Japan; Department of Population, Faculty of Economics, Moscow State University by Lomonosov, Moscow, Russia

Alex Tarnava Drink HRW, New Westminster, BC, Canada; Natural Wellness Now Health Products Inc., New Westminster, BC, Canada

Istvan G. Télessy Department of Pharmaceutics, Faculty of Pharmacy, University of Pécs, Pécs, Hungary

Poonam Tiwari Division of Nutrition, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India; Department of Dietetics, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India

Miki Tokunaga Department of Health and Nutrition, Faculty of Human Health, Kanazawa Gakuin University, Kanazawa, Japan

Rukam S. Tomar Department of Genetics, Junagarh Agricultural University, Junagarh, India

V.I. Torshin Department of Physiology, RUDN University, Moscow, Russia

Abhishek Dutt Tripathi Centre of Food Science and Technology, Institute of Agricultural Sciences, Banaras Hindu University, Varanasi, India; Department of Dairy Technology and Food Technology, Institute of Agricultural Sciences, Banaras Hindu University, India

Garima Tyagi Alternative medicine, Everglades University, Tampa, FL, United States

Viola Vargova Faculty of Medicine, PJ Safaric University, Kosice, Slovakia

Narsingh Verma King George Medical University, Lucknow, India

Aastha Visen Nutra-V Inc., Toronto, ON, Canada

Pradeep K.S. Visen Nutra-V Inc., Toronto, ON, Canada; Formerly, University of Toronto, Toronto, ON, Canada

Srishti Visen Nutra-V Inc., Toronto, ON, Canada

Shaw Watanabe Clinical & Functional Nutriology, Life Science, Japan

Sanit Wichansawakun Department of Internal Medicine, Faculty of Medicine, Thammasat University, Bangkok, Thailand

Maria Wigati Center for Health and Human Nutrition, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

Agnieszka Wilczynska The American University in Dubai, UAE; WSB University in Torun, Poland; Institute of Psychology, Silesian University, Katowice, Poland; The Tsim Tsoum Institute, Krakow, Poland

Douglas W. Wilson Formerly, School of Medicine, Pharmacy, Health and Wellbeing, Durham University, Durham, United Kingdom; Centre for Ageing & Dementia Research, Swansea University, Swansea, United Kingdom

Wannisa Wongpipathpong Department of Internal Medicine, Faculty of Medicine, Thammasat University, Bangkok, Thailand

Poonam Yadav Department of Dairy Science and Food Technology, Institute of Agricultural Sciences, Banaras Hindu University, Varanasi, India; Centre of Food Science and Technology, Institute of Agricultural Sciences, Banaras Hindu University, Varanasi, India

Kazuyoshi Yazawa Lifescience Association, Tokyo, Japan

Sara Sarrafi Zadeb Medical Sciences and Technology Department, Science and Research Branch, Islamic Azad University, Tehran, Iran

Foreword

Here we have another book on food and diet regimens reviewing the multifaceted structural and functional relationships in the health of the human body and mind. It is amazing to consider the number of efforts that must be deployed by the scientific community to eventually reach the market when the prevalence of chronic non-communicable diseases is skyrocketing the world over.

The lead editor of this book, Dr. Ram B. Singh, also edited a previous contribution to the literature on functional diet regimens in which a new definition of food security, adapted to modern times, was given [1]. As defined by the Food and Agriculture Organization of the United Nations in 2003, "Food security exists when all people, at all times, have physical, social and economic access to sufficient, safe and nutritious food which meets their dietary needs and food preferences for an active and healthy life" [2]. Dr. Singh expanded this definition to include the physical, social, mental, and spiritual aspects of such a life, "with the aim of supporting human development. Functional/design food specifically addresses variations in genotypes and phenotypes which must be taken care of at metabolic and biochemical levels for sustaining food security at large, globally."

Security involves taking care of the recipient's holistic health and development based on scientific evidence. Consensus is not a prerequisite to progress in the field. Public relations can be an efficient tool to elaborate and transmit social responsibility. This book targets a similar audience, backed up by the United Nations, other authorities, and expert panels. It is and will remain a reference for those who are devoting their lifetimes to securing and promoting health for the human race—a noble mission.

Fabien De Meester[1] and Ronald Ross Watson[2]
[1]DMF Ltd Co, [2]University of Arizona, Tucson, AZ, United States

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Preface

This volume, *Functional Food and Nutraceuticals in the Management of Non-communicable Diseases*, is the second in a series after the publication of the previous volume, *Functional Food Security in Global Health*, published in 2018. Both volumes are inspired by the ancient knowledge of nutrition in health and diseases mentioned in Vedic literature (7000−5000 BCE). An earlier book entitled *Wild-Type Foods in Health Promotion and Disease Prevention*, edited by Fabien De Meester and Ronald Watson and published in 2008, has also been a source of inspiration in the writing of this volume. We appreciate that the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) have now awakened to understand the value of high-quality diets in health promotion and disease prevention. The WHO is aware that 47% of deaths are related to nutrition, and the FAO has estimated that adequate food is produced in a year optimal to prevent these deaths. However, it remains unclear how much functional food was available in the world in previous years and how much functional food will be required in the future to achieve the Sustainable Development Goals in the 2030 Agenda for Sustainable Development adopted by all members of the United Nations.

This volume provides knowledge from various authors from all over the world indicating that behavioral risk factors, in particular, dietary intakes, as well as protective dietary factors are important in health promotion and the management of diseases. Many experts have a strong belief in the inverse care law proposed by Julian Tudor Hart in a paper published in 1971 and beginning with the following statement [1,2]: "The availability of good medical care tends to vary with the need for it in the population served. This inverse care law operates more completely where medical care is most exposed to market forces, and less so where such exposure is reduced." This opening statement from Julian Tudor Hart's paper on the inverse care law is still relevant today, and the paper is considered one of the landmark publications in *The Lancet*'s nearly 200-year history [2]. Some experts propose that the resonance of Tudor Hart's definition of the inverse care law has global and timeless importance [1,2]. The editors of this volume share similar views that disadvantaged populations need more health care than advantaged populations but receive less. However, the editors wish to emphasize that besides health care, people need the healthiness and happiness promoted by healthy diets and lifestyle, which are impossible to provide by any government or nongovernmental agency unless people are health educated and motivated to adhere to a protective healthy diet, to ignore the "taste" to some extent, and to avoid unhealthy diets promoted by the food industry. Such populations are in minority in any part of the world, which is challenging for all of us working on health promotion.

In the editorial included in this volume, the editors emphasize the ten qualities of a high-quality diet. Chapter 1, Western Diets and Risk of Non-communicable Diseases, discusses Western diets and risks for diseases related to undernutrition and overnutrition. Chapter 2, Estimates of Functional Food and Nutraceutical Availability in the World, With Reference to Food Peroxidation and Food Safety, provides estimates of functional food and nutraceuticals available in the world. In Chapter 3, Epigenetic Modulation of Nutritional Factors With Reference to Microgravity Conditions for Plants and Animals: A New Biotechnological Approach for Developing Functional Foods, a new hypothesis is proposed on epigenetic modulation of nutritional factors with reference to microgravity conditions for plants and animals as a new approach for developing functional foods. Chapters 4−10 discuss evolutionary diets and functional foods, with specific emphasis on functional foods available in India, China, Africa, and Iran as traditional foods and the discovery of medical rice in Thailand and Japan, emphasizing the role of these foods in the prevention of diseases. Chapters 11−16 highlight the role of polyunsaturated fatty acids, olive oil and olive fruit, and modern versus wild eggs as well as fish and fish peptides as functional foods with reference to the periconception and perinatal periods and immunity. Chapters 17−26 describe the agricultural parts of food and nutrition as well as the role of new functional and traditional foods such as sumac, quark cheese, cocoa, beans, soybeans, selected fruits, millets, and nuts. Chapters 27−29 discuss spices with particular emphasis on fenugreek seeds and cinnamon. The role of prebiotics and probiotics is discussed in Chapters 30−32, and Chapters 33 and 34 are devoted to bee products and the flavonoid contents of honey with an

emphasis on propolis. Chapters 35–37 highlight the role of genetically modified foods and foods to improve brain function and cancer.

The effects of the modified Indo-Mediterranean neuroprotective diet (MIND) on emotion, cognition, and depression are discussed in Chapter 39, The Role of Modified Indo-Mediterranean Neuroprotective Diet on Emotion, Cognition, and Depression, and Chapter 40, Role of Nutraceuticals, Functional Foods, and Spices in the Management of Metabolic Syndrome and Related Disorders. Chapters 41–47 extend the description from functional foods to nutraceuticals, vitamins, minerals, polyphenolics, and flavonoids. Finally, coenzyme Q10, molecular hydrogen, and amino acids, in particular tryptophan, are the topics of Chapters 48–52.

The book is a collection of papers written by experts in the fields of nutrition, food, epidemiology, internal medicine, pharmacy, and marketing. This volume makes a valuable contribution to discussions about functional foods and nutraceuticals, the food industry, and pharmacology. The globalization of Indo-Mediterranean-style diets and health and how to achieve functional foods and nutraceuticals for worldwide health promotion may be important for the prevention of non-communicable diseases as well as for sustainable development goals of the United Nations [3,4]. The views expressed in the various articles are those of the authors. We, the editors, are grateful to the authors for their efforts as well as to Ms. Ruby for editing all the manuscripts quite efficiently.

Ram B. Singh, Shaw Watanabe and Adrian Isaza

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Editorial: the 10 qualities of a high-quality diet

High-quality foods are unrefined, unprocessed, or minimally processed foods. They include whole grains, vegetables, nuts, fruits, healthy vegetable oils (e.g., mustard oil, rapeseed oil, olive oil), and healthy sources of proteins, such as pulses, beans, cottage cheese, chicken, fish, and other seafoods [1−3]. These foods are also recommended in the Healthy Eating Plate (Fig. 1) [3]. Dietary guidelines have altered over recent years as research has become more accurate in determining what we should eat to attain optimal health and body weight, in particular, body mass index and waist circumference [1−5]. The evidence available to date indicates that calories have a tremendous role. However, focusing on the quality of foods is equally important for the prevention of weight gain and promoting weight loss [3,4]. Here, we want to highlight the role of the 10 qualities of foods that may be determinants of the beneficial effects of a high-quality diet.

Shifting national dietary guidelines

The Harvard T.H. Chan School of Public Health suggested using its Healthy Eating Plate as a guide for creating healthy, balanced meals, whether served on a plate or packed in a lunch box [3]. The International College of Nutrition and the International College of Cardiology have proposed modifying the guidelines of the National Cholesterol Education Program of the American Heart Association and the American College of Cardiology [1,2]. Most health agencies, including the World Health Organization (WHO), advise that in a healthy diet, approximately 30% of total daily calories should come from healthy fats such as rapeseed oil, mustard oil, or olive oil [1−3]. This means eating

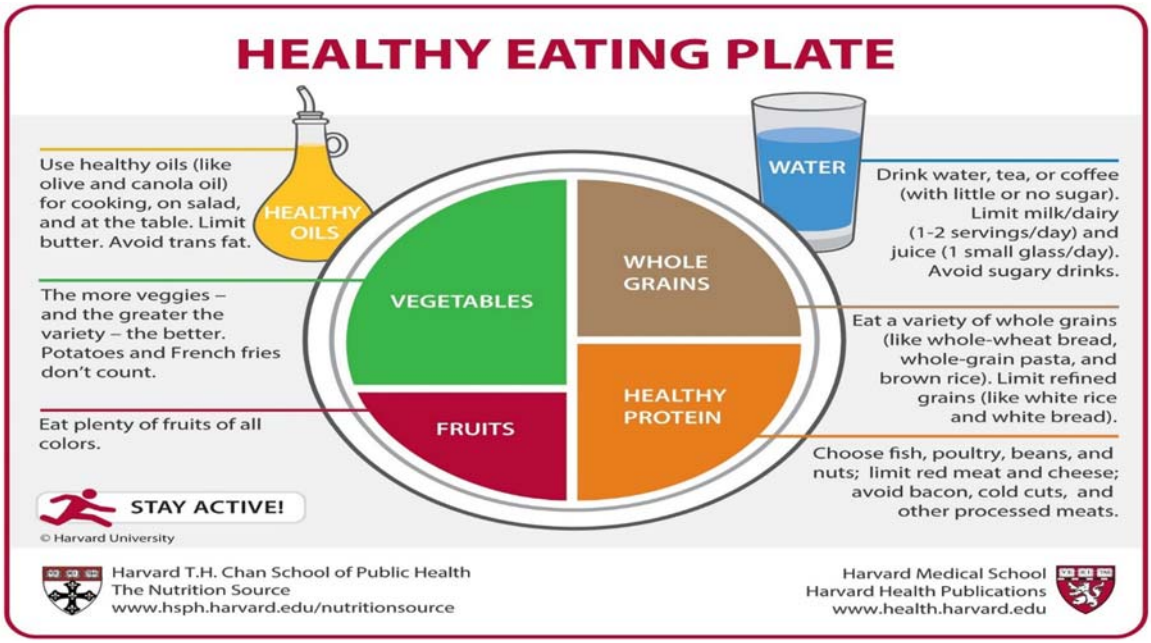


FIGURE 1 In the best diet, quality counts. *Adapted from The best diet, quality counts. Harvard TH Chan School of Public Health. https://www.hsph.harvard.edu/nutritionsource/healthy-weight/best-diet-quality-counts/ [accessed January 2021].*

about 50−80 g of fat each day, which provides the body with energy as well as fatty acids for the metabolic demands of body tissues. However, the body changes only about 10% of fat into glucose; the rest is used as fatty acids in the tissues for physiological and metabolic functions. Some guidelines have advised lower intake of fat among Asians because it varies between 15% and 25% in traditional diets and the Japanese have the longest life expectancy [1,2]. The consumption of fat is also lower among Chinese, Koreans, and South Asians without any evidence of undernutrition [1]. The guidelines for body mass index and waist girth for obesity and central obesity are also lower for Asians. Therefore it is logical that guidelines for fatty acid intake for Asians are lower for Asians [1,2]. In view of these observations, most health agencies have proposed food-based guidelines [3−6].

The US Dietary Guidelines recommend limiting the consumption of saturated fatty acids (SFAs) to fewer than 10% of calories to decrease the incidences of cardiovascular diseases (CVDs) [6]. The quality of SFAs has different biologic effects, which are further modified by the food matrix and the carbohydrate content of the diet. There is evidence that certain foods that are relatively rich in SFAs, such as whole-fat dairy foods, dark chocolate, and unprocessed meat may not be associated with increased risk of CVDs or diabetes, possibly as a result of food diversity. It seems that there is no landmark evidence that the current population-wide arbitrary upper limits on saturated fat intake in the diets will prevent CVDs or reduce mortality. However, a large body of evidence from cohort studies and clinical trials has demonstrated that the quality of diets has a role in the prevention of morbidity and mortality due to CVDs and diabetes as well as to other chronic diseases [6−10]. All the clinical trial results published in the last three decades using Mediterranean-style diets have reported a significant decline in cardiovascular events and all causes of mortality [11−14].

An Indo-Mediterranean diet that is rich in high-quality foods is also high in nutrient density with high food diversity and low glycemic index (GI), with lower saturated fat, salt, and sugar but high in omega-3 fatty acids, flavonoids, and other nitric oxide−activating foods, which may be protective against CVDs as well as other non-communicable diseases (NCDs) [6−14]. A metaanalysis of studies relating to three randomized, controlled, single-blind trials on the role of Indo-Mediterranean-style foods and nutrients in the prevention of CVDs, including heart failure, has also been published [11]. In these studies, the intervention and control groups ($N = 1446$ and $N = 1320$, respectively) were compared for behavioral risk factors, food intake, fatty acid intake, and the ratio of polyunsaturated fatty acid to flavonoid intake. The results revealed marked beneficial effects of Indo-Mediterranean-style foods and nutrients on heart failure and arrhythmias, almost similar to the effects of Mediterranean diets.

A large body of evidence has shown that a diet that is rich in healthy plant-based foods and has fewer foods from animal sources foods (up to five servings per week, which may include fish, other seafood, and poultry) can confer both improved health and environmental benefits.

The Paris Agreement and the UN Sustainable Development Goals (SDGs) depend on the quality of food consumption and food production and on the safety of farming with reference to how much food is lost or wasted [4]. It is important that food systems should transition from being a net source of greenhouse gas emissions to a net sink while conserving food quality. It seems that a shift toward a healthy plant-based diet in conjunction with seafood may be central to this goal. Any gas that has the property of absorbing infrared radiation (net heat energy) emitted from the earth's surface and reradiating it back to the earth's surface thus contributes to the greenhouse effect. Thus greenhouse gases are those gases that absorb and emit radiant energy within the thermal infrared range. The primary greenhouse gases in the earth's atmosphere that are related to food production and consumption are water vapor, carbon dioxide, methane, nitrous oxide, and ozone, which have may have adverse effects on the environment and health. The most important of these are carbon dioxide, methane, and water vapor. Unfortunately, food consumption is rarely considered a solution for sustainability in meeting climate targets outlined by nationally determined contributions.

Recently, the EAT-Lancet Commission on Food, Planet, Health brought all of this evidence together and proposed scientific targets for healthy diets and sustainable food systems [4]. The commission concluded that achieving healthy diets from sustainable food systems for 10 billion people by 2050 is possible but only with a significant reduction in animal source foods in some countries (mainly G20 countries) and a universal increase in healthy plant-based foods in our diets. Thus a shift toward the Planetary Health Diet, composed predominantly of healthy plant-based foods, can optimize human health while decreasing the impacts of the environmental factors [4].

Food consumption patterns in most of the G20 countries are not aligned with those of a healthy high-quality diet. Hence most national dietary guidelines are not ambitious enough to bring food systems within planetary boundaries, including limiting global warming to 1.5°C [1,2,5−7]. This is important because guidelines are a necessary component of food policy and an essential first step in promoting healthy eating habits for increased intake of high-quality foods via health education programs or public awareness campaigns [5−7]. Since there is a trend toward increased intake of unhealthy foods, characterized by overconsumption of red meat, butter, sugar, salt, and highly processed refined foods

and underconsumption of high-quality foods, there has been a marked increase in the risk for NCDs. It is possible that at the global level, unhealthy diet quality now poses a greater risk to morbidity and mortality than sedentary behavior, alcoholism, unsafe sex, drug addiction, and tobacco use combined [4,7]. The world's population still faces burdens of undernutrition, with more than 820 million people having insufficient food and many more consuming low-quality foods. Therefore all of the health agencies need to make an extraordinary effort to shift dietary patterns toward high-quality foods with a sustainable food system and a global commitment to reversing trends of poor-quality diets in the rest of the world [15]. It is important to educate people and governments about high-quality foods and traditional diets and their effects on health and risk of NCDs [15]. Thus it is prudent to choose foods that have the 10 qualities of high-quality foods, as listed in Table 1.

Food diversity

The associations of food quality, dietary diversity, and nutrient adequacy with health and risk for diseases are continuous and graded [1−4,16]. The growth of infants and children with an emphasis on periconception and perinatal factors and socioeconomic status of the family and community are known to be influenced by food consumption as well as food production. Food diversity can be measured by using a simple count of foods or food groups over a given reference period with due consideration to traditional diets. There is a consistent positive association between food diversity and growth of infants and children, and evidence from a multicountry analysis suggests that food diversity at the household level is strongly associated with social class and availability of total energy from food quantity, indicating that food diversity may be a useful indicator of food security [16]. Although the contribution of animal foods to nutrient adequacy is indisputable, there is definite scope for Indo-Mediterranean high-quality plant foods, which may provide all the 10 qualities of high-quality foods and may be adequate for infant and child growth as well as for prevention of NCDs in later life [11−14]. There is clearly an unmet need for a promising measurement tool for the assessment of food diversity to improve and harmonize measurement approaches and indicators. Cohort studies indicate that high-quality foods with food diversity can decrease morbidity and mortality and increase healthy and possibly happy life expectancy [6−14]. The Healthy Eating Plate (see Fig. 1) is a prudent approach for providing high-quality diets with food diversity to individuals and communities, which may include traditional foods of the community and country [3].

In many non-Western countries, cereal-based carbohydrates provide approximately 60% of total energy intake1 compared with 42% for Caucasians 2. The consumption of such high-carbohydrate diets yields high glucose and insulin responses, thus contributing to insulin resistance. Nonetheless, the quality of carbohydrates consumed is as important as the quantity. Poor-quality carbohydrates are quickly digested and absorbed, thereby giving rise to high blood glucose and insulin spikes. Observational studies have shown that the consumption of low-GI foods is associated with a lower risk of type 2 diabetes mellitus, significantly less insulin resistance, and a lower prevalence of the metabolic syndrome4. However, the vast majority of these published GI values are of European, Australian, and North American origin.

TABLE 1 The 10 qualities of high-quality foods.

Qualities of foods	Examples of foods
1. Slowly absorbed foods	Nuts, vegetables, whole grains
2. Food diversity	Whole grains, beans, vegetables
3. High nutrient density	Nuts, vegetables, whole grains
4. No trans fat	Grilled foods, boiled foods
5. No/low refined sugar	Guavas, apples, papayas, oranges
6. Low salt	Fruits, vegetables, nuts
7. Moderate fat	Nuts, pulses, beans
8. High fiber	Vegetables, whole grains, fruits
9. Beneficial effects on gut microbiota.	Vegetables, whole grains, fruits
10. Nonperoxidation foods	Fresh foods, without frying
11. Foods requiring mastication	Whole grains, nuts, fruits

Glycemic index

The concept of the GI may provide a useful marker in selecting the most appropriate carbohydrate-containing foods or for the maintenance of health and the treatment of some diseases. Eating high-carbohydrate, rapidly absorbed foods may be associated with a rapid increase in triglyceride and free fatty acid levels as well as a higher amount and activity of nuclear factor kappa B, a transcriptional factor that regulates the activity of at least 125 genes, most of which are proinflammatory. High-GI foods also increase proinflammatory transcription factors, activating protein 1 and early growth response protein 1, which are markers of endothelial dysfunction.

The GI may be defined as a numerical figure that represents the ability of a high-carbohydrate food to increase blood glucose levels. GI can be expressed as a percentage of the incremental area under the glycemic response curve (AUC) produced by a food portion with 50 g carbohydrate in comparison with the AUC elicited by a standard reference food of 50 g glucose or white bread in the same participant [17]. It seems that the slower is the rate of carbohydrate absorption into the blood, the lower is the rise in blood glucose level and the lower is the GI value. A value of GI of 70 or more is considered high, a GI value less than 55 is low, and a GI value of 56−69 inclusive is medium, where glucose = 100 [17]. The GI food-based intervention could be an important tool in the management and prevention of diabetes and CVDs. GI data for non-Western foods are scarce in the Middle East and South Asia, in contrast to the current international GI tables [17]. Low-GI foods are known to decrease insulin demand and lipid concentrations, improve blood glucose control, and reduce body weight; thus they may prevent glycemia-induced cardiovascular complications. It is known that non-Western traditional foods have lower GI, whereas foods with higher GI include fast foods, such as tater tots and French fries; some spreads, such as margarine spreads or peanut butter; some snack foods, such as chips, crackers, and cookies; most fried foods, including fried chicken, onion rings, and nuggets; nondairy creamer; and pre-prepared cake frostings.

Dietary fatty acids

In Western countries the limit for fat intake is 30% of total calorie intake, including 10% energy from saturated fat, and rest from monounsaturated and polyunsaturated fatty acids, including omega-3 fatty acids [4−7]. The intake of trans fat in foods is limited, up to 3% in most guidelines in most countries [1−4]. Astrup et al. explore how policy options for eliminating or reducing trans fats in the food supply chain could contribute to decreasing the disease burden caused by the intake of industrially produced trans fats in the WHO European Region [4].

The recommendation to limit dietary saturated fat intake has persisted despite mounting evidence to the contrary [5,7]. Most recent metaanalyses of randomized trials and observational studies found no beneficial effects on CVD and total mortality from reducing SFA intake; instead, they have found protective effects against stroke [5]. Although ingestion of saturated fats increases low-density lipoprotein (LDL) cholesterol, this is not on account of increasing levels of small, dense LDL particles, but rather larger LDL particles, which have only mild adverse effects on the occurrence of CVD risk. It seems that the health effects of foods cannot be predicted by their content in any nutrient group without considering the overall macronutrient distribution. Whole-fat dairy products, unprocessed meat, and dark chocolate are SFA-rich foods with a complex matrix that are not associated with increased risk of CVDs. The totality of available evidence does not support further limiting the intake of such foods [5,7] (Fig. 2).

Flexitarian diet and microbiota

There is evidence that eating a diet that is rich in vegetables, whole grains, nuts, and fruits as well as fish intake has a beneficial effect on the gut microbiota, whereas meat consumption has adverse effects [18]. Some experts advise that eating a flexitarian diet—more plant foods with meat in moderation—may be a healthy approach for health promotion and prevention of CVDs with improved SDGs [4,5,18−20]. Diet and lifestyle factors plays an important role in shaping the gut microbiota [18−21]. In a recent study, dietary intake and gut microbiota were analyzed in a community-dwelling cohort of 441 Colombians. Microbial diversity was higher in individuals with increased intake of nutrients obtained from plant food sources, whereas the intake of food groups and nutrients was correlated with microbiota structure. Interestingly, short-chain fatty acid producers were more prevalent in the microbiota of individuals consuming diets that were rich in fiber and plant food sources, such as fruits, vegetables, and beans [18]. However, an inflammatory microbiota composed of bile-tolerant and putrefactive microorganisms along with opportunistic pathogens thrived in individuals who consumed diets that were rich in animal food sources and of low quality, that is, rich in ultraprocessed foods and low in dietary fiber [18]. It is clear that diet is strongly associated with the gut microbial community, and there are generalizable connections between healthy and adverse effects.

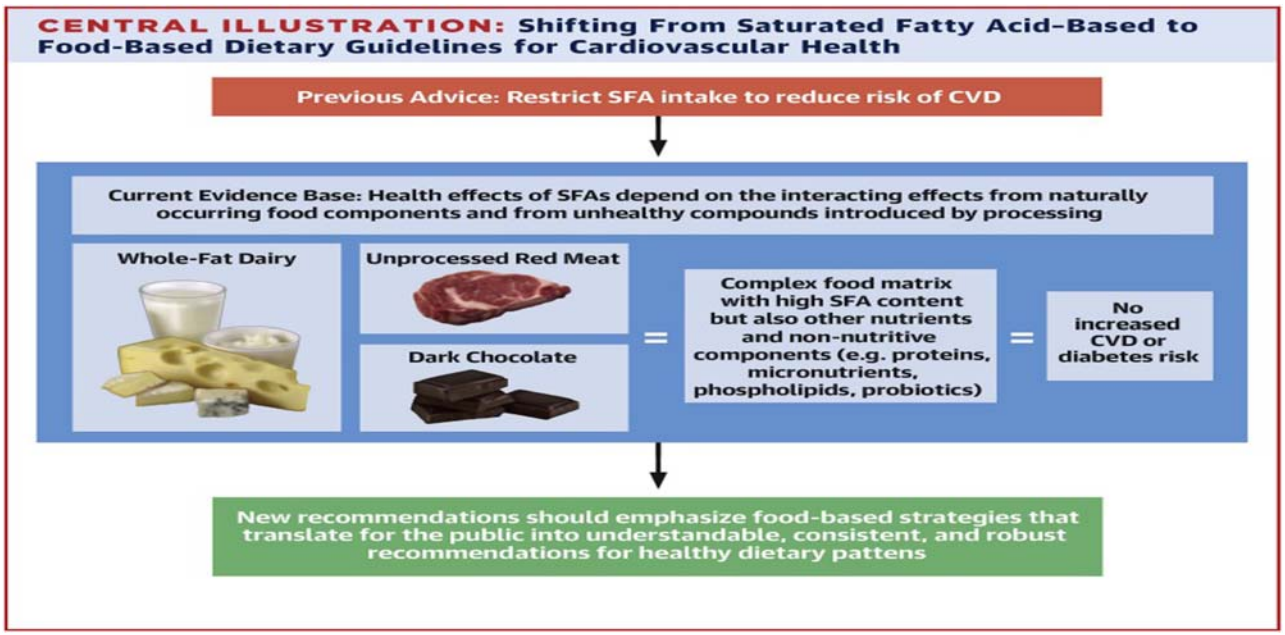


FIGURE 2 Effects of fatty acid intake on cardiovascular diseases. *Adapted from Astrup A, Magkos F, Bier DM, Brenna JT, Otto MCD, Hill JO, et al. Saturated fats and health: a reassessment and proposal for food-based recommendations: JACC State-of-the-Art Review, J Am Coll of Cardiol 2020;76:844–57, ISSN 0735-1097, https://doi.org/10.1016/j.jacc.2020.05.077.*

Diets for good health, a healthy life expectancy, and sustainability

It has been proposed that diets for a better future and healthy life expectancy may depend on the health effects and sustainability of diets and foods available for consumption [4–7,18–20]. It seems that dietary transitions to healthy foods would decrease total global food-related greenhouse gas emissions and enable more equitable distribution of these emissions around the globe. This may enable us to address all forms of malnutrition worldwide while leaving our children a thriving and healthy planet. It is possible that that the world cannot achieve this goal without leadership from the G20 countries, as this is a critically important goal. In the G20 countries, most food consumption patterns are not aligned with those of a healthy flexitarian diet, and most national dietary guidelines are not ambitious enough to bring food systems within planetary boundaries, including limiting global warming to 1.5°C [4–7]. Countries such as China, India, and Indonesia have current consumption patterns that are aligned with the model necessary to protect health and the planet, which appears to be a result of less modernization and the continuation of traditional food consumption patterns [1,2]. However, a shift in all other G20 countries is critical, owing to attack by advertising food industry, for protecting the planet and its people.

A lower amount of physical activity is a major risk factor for CVDs and diabetes. Hence increased physical activity may be necessary to prevent diseases. In a cohort study of 403,681 participants, a higher proportion of vigorous physical activity to total moderate to vigorous physical activity was associated with statistically significantly lower all-cause mortality [21]. It seems that most of the health benefits associated with meeting recommended weekly physical exercise goals may be achieved through moderate physical activity. However, the results of this cohort study suggest that an increased proportion of vigorous physical activity is associated with additional health benefits [21].

In brief, the 10 characteristics of a high-quality diet appear to be fundamental for a better future, good health, and healthy life expectancy. It is possible to demonstrate the leading role G20 countries can and must take to realize the exponential changes required for a healthy and sustainable world. The report by the EAT-Lancet investigators also indicates that current food consumption patterns and the efficacy of national dietary guidelines in G20 countries are far from those of the Planetary Health Diet recommended by the EAT-Lancet Commission. However, the G20 countries have clear opportunities to lead in the reduction of greenhouse gas emissions and realize the health and economic benefits of shifting toward healthier and more sustainable diets, which are likely to serve the SDGs of the United Nations.

Ram B. Singh[1], Shaw Watanabe[2] and Adrian Isaza[3]
[1]Halberg Hospital and Research Institute, Moradabad, India, [2]Life Science Institute, Tokyo, Japan, [3]Everglades University, Tampa, FL, United States

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Section 1

Functional food and nutraceutical availability

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Chapter 1

Western diets and risk of non-communicable diseases

Jan Fedacko[1], Toru Takahashi[2], Ram B. Singh[3], Dominik Pella[4], Sergey Chibisov[5], Krasimira Hristova[6], Daniel Pella[1], Galal Nagib Elkilany[7,8], Lekh Raj Juneja[9], Shalini Behl[10], Jaipaul Singh[11] and Manal M.A. Smail[12]

[1]Faculty of Medicine, PJ Safaric University, Kosice, Slovakia, [2]Graduate School of Human Environment Science, Fukuoka Women's University, Fukuoka, Japan, [3]Halberg Hospital and Research Center, Civil Lines, Moradabad, India, [4]East Slovak Institute of Medical Sciences, Kosice, Slovakia, [5]Faculty of Medicine, People's Friendship University of Russia, Moscow, Russia, [6]University National Heart Hospital, Sofia, Bulgaria, [7]Gulf Medical College, Ajnam, United Arab Emirates, [8]The Tsim Tsoum Institute, Krakow, Poland, [9]The Rohto Pharmaceutical Co. Ltd, Osaka, Japan, [10]School of Natural Sciences, University of Central Lancashire, Preston, United Kingdom, [11]School of Natural Sciences, College of Science and Technology, University of Central Lancashire, Preston, United Kingdom, [12]UAE University, United Arab Emirates

Introduction

The United Nations Decade of Action on Nutrition is an initiative covering the years 2016−25 to eradicate hunger, end malnutrition in all its forms—undernutrition, micronutrient deficiencies, overweight, and obesity—and reduce the burden of diet-related non-communicable diseases (NCDs) in all age groups [1]. The relationship between dietary habits and chronic NCDs has been extensively examined [2−5]. Long-term randomized trials with NCD endpoints have not been feasible for most dietary factors, but synthesis of other lines of epidemiological evidence, including long-term prospective observational studies and short-term trials of intermediate outcomes, have provided supporting evidence for potential causal relationships between specific dietary factors (e.g., fruits, vegetables, processed meat, and trans fat intake) and NCDs (coronary artery disease, diabetes, and colorectal cancer). The Global Burden of Disease study, involving 195 countries and territories from 1980 through 2015, aimed to create a healthier, more sustainable food system, indicating that functional food security for global health could be a useful approach for health promotion and diseases prevention [4,5].

Humans started farming some 10,000 years ago in Babylonia (present-day Iraq, near the Tigris River), an adaptation that led to unprecedented technical development, agriculture, industry, and commerce. Since the earth is able to produce foods, it was worshiped by the. In Babylonia the major crops included barley, dates, wheat, lentils, peas, beans, olives, pomegranates, grapes, and vegetables. Pistachios were grown in the royal gardens. Because the climate of Mesopotamia was dry with little rainfall, farmers depended on flooding by the Tigris and Euphrates Rivers for water for their crops. The silt left behind from the floodwater made the soil fertile. The most important crops in Mesopotamia, including Babylonia, were wheat and barley. Farmers also grew dates, grapes, figs, melons, and apples. Favorite vegetables included eggplants, onions, radishes, beans, lettuce, and sesame seeds (https://mesopotamia.mrdonn.org) agriculture, [accessed 02.20].

The invention of farming in Mesopotamia was associated with building houses with stones, around 6000 BCE. Irrigation began at about the same time in Egypt and Mesopotamia (present-day Iraq and Iran) using the water of the flooding Nile River (Egypt) or the Tigris and Euphrates Rivers (Mesopotamia). The floodwaters, which occurred from July through December, were diverted to fields for 40−60 days. The Sumerians in Babylonia believed that God lived in the sky, so to worship God, ziggurats were built in each town; these included a high platform for a temple. Thus the lifestyle of primitive hunter−gatherers was altered by living in houses and going to ziggurats for worship, possibly with adequate daily physical activity during farming and climbing for worshiping. The preagricultural human diet consisted of naturally available wild foods—fruits, vegetables, green leaves, seeds, honey, eggs, fish, and meat from running animals—which shaped modern humans' genetic nutritional requirements [2] (see Fig. 1.1).

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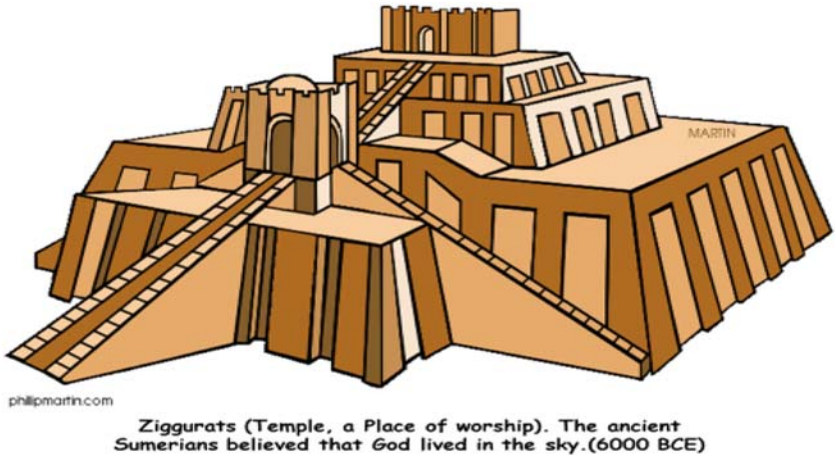


FIGURE 1.1 A ziggurat, a high platform for a temple in ancient Mesopotamia. *Modified from website.*

There are very few primitive hunter−gatherers in the world today. The population of India, which includes approximately 1.38 billion people, mainly consists of farmers, but the rapidly growing towns have increasing numbers of poor urban slum dwellers and an increasingly affluent society [2,5]. After 1910, in the 20th century, industrialization and urbanization added stress and increased the refining, processing, storing, and distribution of foods in the continuous search for a better economic model [2,8,9]. Population studies indicate that physical inactivity, Western dietary patterns, alcoholism, tobacco use, and mental stress are important risk factors for the emergence of NCDs [2−8]. Underlying these primary risk factors, the epidemic of NCDs has been attributed to obesity resulting from urbanization and environmental transitions, including work pattern changes from heavy labor to sedentary occupations, increased computerization and mechanization, and improved transportation due to automobiles [4,5,9]. Obesity is also a risk factor of NCDs, including cardiovascular diseases (CVDs), type 2 diabetes mellitus, bone and joint diseases, cancer, and neuropsychiatric diseases [4,5]. Table 1.1 shows the global dietary transition at various stages of human development [10,11].

Economic development has led to drastic changes in food production, food processing, and distribution systems that have increased the accessibility of unhealthful foods [9]. Fast-food restaurants have shown exponential global expansion in the last few decades, resulting in increased availability of ready-prepared and fast foods at affordable prices in economically developed countries, resulting in increased morbidity and mortality due to NCDs [4−6]. It is clear from the World Health Organization (WHO) Series on the Double Burden of Malnutrition that nutrition and malnutrition need to be approached from multiple perspectives in light of their multiple manifestations [6−8]. The double burden of malnutrition is the coexistence of undernutrition (stunting and wasting) alongside overnutrition (overweight and obesity) at individual, community, population, city, and country levels [6−8,12]. Singh and coworkers also described the triple burden of diseases, including undernutrition, overnutrition, and physical inactivity [13]. An enormous amount of literature has been published to explore how this coexistence is affecting low-income, middle-income, and high-income countries proposed by the WHO and World Bank [6−8,14−16,24,25]. It seems that undernutrition and overnutrition are interconnected; therefore multiple approaches that simultaneously address multiple dimensions should be implemented for the policy solutions required for diseases prevention [8]. The WHO has been gradually repositioning itself to adapt to this new nutrition reality of multiple targets across varied manifestations, moving away from a single approach [15,16]. Clinical and experimental studies indicate that a life-course approach, starting from father and mother to offspring and childhood, arise necessary for health promotion and disease prevention [17].

Interestingly, a recent study has demonstrated that increased consumption of functional foods improves health, while consumption of Western-type foods worsens the risk of NCDs across the world, with heterogeneity across regions and countries [24,25]. These global data on functional food and Western-type food consumption provide the best estimates of global nutrition dynamics around the world. In turn, these inform policies and priorities for reducing the health and economic burdens of Western-type diets and NCDs [18]. The Japanese and the Mediterranean traditional diets are considered prudent diets and appear to share a common standard (an omega-6/omega-3 ratio of $\sim$1/1) in conjunction with

TABLE 1.1 Dietary transition from Mesopotamia to modern diets and emergence of non-communicable diseases (NCDs).

Mesopotamian diets	Pattern 1: hunter–gatherers	Pattern 2: food scarcity, poverty	Pattern 3: receding food scarcity and poverty	Pattern 4: more food, less exercise (homo economicus)	Pattern 5: healthy behavior (homo modestis)
Nutrition profileWheat, barley, beans, vegetables, apples, onions, radish, grapes, pistachios, pomegranates, Nutritional status	Plants, low-fat wild animals, diet diversity by collecting foods Robust, lean population; few nutritional deficiencies	Cereals predominant, diet less varied Children and women suffer most from low-fat intake, nutritional deficiency diseases emerge, stature declines	Fewer starchy staples; more fruit, vegetables, animal protein; low variety continues Continued MCH nutrition problems, many deficiencies disappear, weaning diseases emerge, stature grows	More fat (animal products, trans fat, omega-6 fatty acids), sugar, processed foods; less fiber, less omega-3 fatty acids and flavonoids Obesity, problems for elderly (osteoporosis, fractures, etc.), type 2 diabetes mellitus, hypertension, stroke, heart attack, brain degeneration, psychological disorders, and cancer	Higher-quality fats, reduced refined carbohydrates, more whole grains, fruit, vegetables rich in omega-3 fatty acids and flavonoids Reduction in body fat and obesity, and NCDs, improvement in health (epigenetic modulation and transgenerational inheritance, natural selection)
Economy Household Income and assets	Hunter–gatherers Primitive, onset of fire subsistence, primitive stone tools	Agriculture, animal husbandry, homemaking begin; shift to monocultures Labor-intensive, primitive technology begins (clay cooking vessels) Subsistence, few tools	Second agricultural revolution (crop rotation, fertilizer), Industrial Revolution, women join paid labor force Primitive water systems, clay stoves, cooking technology advances Increases in income disparity and agricultural tools industrialization	Fewer jobs with heavy physical activity, service sector and mechanization, household technology revolution Household technology mechanizes and proliferates Rapid growth in income and income disparities, technology proliferation	Service sector mechanization and industrial robotization dominate, increase in leisure exercise offsets sedentary jobs Significant reduction in food preparation costs as a result of technologic change Decrease in income growth, increase in home and leisure technologies
Professional skill/ education	Hunting	Stock breeding, cultivation	Industry, intensive agriculture	Processed unhealthy foods increased	Functional foods availability increases

(*Continued*)

TABLE 1.1 (Continued)

Mesopotamian diets	Pattern 1: hunter–gatherers	Pattern 2: food scarcity, poverty	Pattern 3: receding food scarcity and poverty	Pattern 4: more food, less exercise (homo economicus)	Pattern 5: healthy behavior (homo modestis)
Demographic profile Mortality Age structure Housing Food processing	Low fertility, high mortality, low life expectancy Young population Rural, low density Nonexistent	Age of Malthus; high natural fertility, short life expectancy, high infant and maternal mortality Young, very few elderly Rural, a few small, crowded cities Food storage begins Nonexistent	Mortality declines slowly, then rapidly; fertility static, then declines; small, cumulative population growth, which later explodes Chiefly young, shift to older population begins Chiefly rural, move to cities increases, international migration begins, megacities develop Storage processes (drying, salting) begin, canning and processing technologies emerge, with food refining and milling	Life expectancy hits unique levels (ages 60–70), huge decline and fluctuations in fertility (e.g., postwar baby boom) Rapid decline in fertility, rapid increase in proportion of elderly person Dispersal of urban population decrease in rural green space Numerous food-transforming technologies	Life expectancy extends to ages 70 and 90 years, disability-free period increases Increases in the proportion of elderly >75 years of age Lower-density cities rejuvenate, increase in urbanization of rural areas encircling cities Technologies create functional foods and food constituent substitutes (i.e., macronutrient substitutes), genetically modified foods

MCH, Maternal and child health.
Sources: Modified from Juneja LR, Wilczynska A, Singh RB, Takahashi T, Pella D, Chibisov S, et al. Evolutionary diet, Western diet and non-communicable diseases. In: Singh RB, Watson RR, Takahashi T, editors. Role of functional food security in global health. San Diego: Elsevier; 2018 p. 71 [2]; De Meester F, Takahashi T, Singh RB, Toda E, Hristova K, Fedacko J, et al. Nutrition in transition from Homo erectus to Homo modesties. World Heart J 2013;5:33–46 [10]; Popkin (2006).

high intake of a diet rich in functional foods, although diet and lifestyle in Japan made the transition from poverty in the 1950s to affluence by the year 1980s without increases in CVDs and other chronic diseases [19]. This review examines the available evidence on globalization of diets with risk of NCDs.

Role of the global health community in the prevention of NCDs

Despite sufficient evidence that Western-type foods, sedentary behavior, tobacco, alcoholism, and psychosocial stress are primary risk factors for NCDs, the world health's communities are failing to respond effectively to the rising burden of these diseases [20–23]. The great majority of governments and health communities have failed to initiate strategies to counteract the market and health systems. Most of the food systems have contributed to unhealthful diets with their high calorie content, large portion sizes, and large amounts of processed meat, highly refined carbohydrates, sugary beverages, excess salt intake, and unhealthy fats [1,15,16,24,25]. This modern pattern of food availability, along with changes in lifestyle and in political systems led by profits. translate into unprecedented new challenges, opportunities, and threats for humankind in the form of increased morbidity and mortality due to NCDs [1,15,16,24,25]. The impact of these changes on our total health are clear from a review showing that Americans die sooner, since they are least likely to reach the age of 50 years and have higher rates of diseases or injuries than people in 16 other economically wealthy countries [1,26]. There appears to be a globalization of wealth without much improvement in health behavior because the health budget of the Western countries do not have a target for health education and there is hardly any government policy to provide functional foods at an affordable cost, despite much higher health budgets than are

available in low-income countries [1,26]. Takahashi and coworkers contend that the West has built the worst model of health, despite enormous research conducted in these countries [26].

It has been proposed that the physical activity, sleep, sun exposure, and dietary needs of humans are genetically determined; hence changing these habits may be difficult, although rapid urbanization has been associated with alterations in many of these behaviors [1,2]. Prevention and treatment of NCDs are concerns of ministries and departments of health, of food and nutrition, of agriculture, of commerce, and of urban development in most countries. These departments and ministries as well as concerned industries and agencies employ millions of people in every country of the world [1]. One of the most relevant examples is a ministry of health that regulates the pharmaceutical industry, medical colleges, nursing colleges, pharmacy colleges, and related industries that generate employment for several million doctors, nurses, pharmacists and paramedical staff members. The pharmaceutical industry gives employment to people working in manufacturing as well as marketing and clinical trials of drugs at a cost that exceeds billions of dollars [1]. These financial gains and employment concerns given to people do not allow political elites to concentrate on developing policies of prevention. These concerns are important for economic prosperity of developed as well as developing countries, causing anxiety over a recalibration of priorities among global health leaders. An advocacy strategy based on four diseases and four risk factors seems increasingly out of touch with the realities in poor countries. Many political leaders believe that NCDs are just too big and too complex a challenge and need a different universal approach [15–17,25].

In Geneva the WHO emphasized four urgent issues: health emergencies; universal health coverage; women's, children's, and adolescents' health; and climate change [8,16]. There is universal agreement that NCDs cause significant decline in economic as well as human development; hence sustainable development goals cannot be achieved unless these diseases are controlled. Therefore investment in the prevention and treatment of NCDs can enable economic growth in the concerned communities and countries [26]. However, individual health security as well as global health security, which means universal health coverage, may be difficult to achieve via existing methods of prevention of NCDs [8,15–17,25–30]. The WHO estimates that in 2015, 15.0 million people between the ages of 30 and 69 died from NCDs, as shown in Table 1.2 [31].

Global nutritional dynamics, health education, and health promotion

Previous studies by several investigators and other published papers have clearly reported that there are food and nutrition dynamics as well social class dynamics in which an increase in socioeconomic status is associated with increased intake of a Western-type diet and sedentary behavior, resulting in a decrease in undernutrition and an increase in NCDs [2,11–14,32–37]. However, other studies have reported that a further increase in socioeconomic status in association with health education is associated with an increased intake of functional foods and an increase in leisure time physical activity, resulting in a decline in NCDs [8–10,12,32–37]. Thus NCDs come in a wave. First, they occur to affluent populations with high income and those who are becoming rich during economic growth in developing countries, such as India, China, Korea, and Indonesia. There is a decline in NCDs in affluent and educated populations after learning the method of prevention. Population health education that occurs with further economic growth is associated with globalization of prudent diets and physical activity and decreases in tobacco and alcohol use, resulting in a decline in NCDs [8–10,34–36] (see Fig. 1.1).

TABLE 1.2 Current situation of global non-communicable diseases in 2015.

Low-income countries: men 0.4 million, women 0.4 million, total 0.9 million, 6%
Lower middle-income countries: men 3.6 million, women 2.6 million, total 6.1 million, 41%
Upper middle-income countries: men 3.5 million, women 2.4 million, total 5.8 million, 39%
High-income countries: men 1.4 million, women 0.8 million, total 2.2 million, 15%
Total: 8.9 million; men 6.2 million, women 15.0 million, 100%

Source: Modified from WHO. Tackling NCDs: "best buys" and other recommended interventions for the prevention and control of non-communicable diseases. Geneva: World Health Organization, 2017 [16].

Is life expectancy either healthy or happy?

Life expectancy is increasing rapidly in most countries of the world, but this is mainly because of improved economic capability to afford modern medical care as well as some marginal effects due to changes in diets and lifestyle. This is not a healthy life expectancy; nor it is a happy life expectancy. Hence it is pertinent to emphasize the role of diet and lifestyle to popularize a healthy life expectancy as well as a happy life expectancy to achieve total health [26,28−30]. Some experts suggest that happiness may be used for prevention and treatment of diseases [29]. Cohort studies indicate that chronic anxiety, aggression, and depression may be associated with neuroendocrine dysfunctions and lack of happiness, which may predispose the individual to poor social and physical health, leading to cardiometabolic diseases (CMDs) [28]. Dopamine, serotonin, oxytocin, and endorphins are the neurotransmitters responsible for the happiness of the mind, which may be blunted by stress hormones released as a result of psychological diseases.

In a more recent analysis, 980 urban (495 men and 485 women) and 900 rural (510 men and 390 women) subjects over 25 years of age were randomly selected and recruited from urban and rural populations [28]. Assessment of happiness was made from their answers to a new questionnaire involving happiness of mind, which included questions related to social, psychological, and spiritual behaviors [28]. The prevalence of happiness was 62.4% ($N = 612$) among urban and 63.2% ($N = 569$) among rural subjects, with overall prevalence of 62.8% ($N = 1181$). The prevalence of happiness was significantly greater among subjects older than 45 years of age among both urban and rural populations compared to subjects between 25 and 45 years of age, and the trend was significant. The overall prevalence of happiness was also significantly greater among subjects over the age of 45 years compared to subject younger than 45 years of age. The prevalence of happiness overall showed a graded increase with age from 25 to 84 years in both sexes among urban and rural populations, and the trends were significant ($P < .02$). The overall prevalence of tobacco intake was 16.2% ($N = 304$), and the overall prevalence of alcoholism was 1.96%. The frequency of tobacco intake and alcoholism were significantly lower among subjects with happiness compared to those with no happiness. However, among subjects with happiness the frequency of moderate alcohol intake was significantly greater compared to urban subjects who displayed little or no happiness. The prevalence of coronary artery disease (CAD) was significantly lower among subjects with happiness compared to those with no happiness, in both urban (5.06 vs 12.2%, $P < .01$) and rural populations (2.09% vs 3.92%, $P < .05$), indicating that happiness may be protective against CAD. Moderate intake of alcohol may be in favor of happiness. Happiness may be protective against CMDs. However further analysis and research are necessary to verify the role of happiness, compared to healthiness, in health promotion and disease prevention [28,29].

In a previous assessment of nutritional dynamics, diet quality based on healthy items showed global improvement [by 2.2 points, 95% uncertainty interval (UI): 0.9−3.5] [30]. There was a worsening of unhealthy items in the diets (−2.5, UI: −3.3 to −1.7) [30]. In 2010 the global mean scores for healthy food patterns were 44.0 (standard deviation: 10.5) and for unhealthy diets, 52.1 (standard deviation: 18.6), showing nonsignificant intercorrelation ($r = -0 \cdot 08$) between countries. There was a significant improvement in diets in older populations compared with younger adults and in women compared with men ($P < .0001$ each). Interestingly, low-income countries had relatively unhealthy dietary patterns compared with diets in high-income nations based on healthy food items (+2.5 points, 95% UI: 0.3−4.1) but substantially poorer diets based on unhealthy food items (−33.0, UI: −37.8 to −28.3). Diets and their trends were very heterogeneous regions. For example, both types of dietary patterns improved in high-income countries but worsened in some low-income countries in Africa and Asia. While middle-income countries showed the highest improvement in dietary patterns in comparison to high- and lower-income countries on the basis of healthy items, the largest deterioration was in dietary patterns based on unhealthy items. It is clear that economic development was associated with improved intake of healthy items of foods, while consumption of unhealthy items worsened across the world, with heterogeneity across regions and countries [30]. These global data provide the best estimates to date of nutrition transitions across the world and can be used to inform policies and priorities for reducing the health and economic burdens of poor diet quality.

The main attributes of social classes are general education; health education; occupation; household income; housing; and availability of automobiles, televisions, and other luxury items [11−13,32−37]. In high-income countries, consumer durables and housing are important determinant of lifestyle, including physical activity, occupational stress, and social health [9−13]. These attributes are also important determinants of food consumption patterns as well as social behavior, which may be the important attributes of societal determinants of health and diseases, and misuse of any substance independently could cause morbidity and mortality [10−13,30,32−37]. Therefore the pathways for development of NCDs are sedentary behavior, excessive intake of Western-type foods, tobacco use, emotional stress, and alcoholism among individuals and wealthy populations with an underlying lack of general and health education, which may be important determinants of mortality in many countries [38,39]. Nutritional aspects of health education appear to be

a basic mechanism for intracommunity alterations in nutritional dynamics. It could be a most important attribute because knowledge and attitudes about healthy foods and physical activity can substantially reduce NCDs and improve physical, social, mental, and spiritual health, leading to health promotion [29,30,32].

Globalization of western-type diets and health

In developing countries, such as India, China, Indonesia, Brazil, Pakistan, Philippines, Thailand, and Bangladesh, higher social classes, particularly with an increase in income and greater availability of ready-prepared foods, have been observed to have higher risks of NCDs, such as CVDs including CAD, stroke, hypertension, and type 2 diabetes mellitus [2–4].

Figs. 1.2 and 1.3 show the fat intake transition in the populations of seven provinces in China. The data indicated that there was an increase in fat intake among subjects with higher incomes in 1989–93, evidence of a dietary transition with economic growth [20]. However, some experts have proposed that both poverty and wealth may be primary causes of disability and deaths due to NCDs, which do not appear to be absolutely correct. Major dietary changes have occurred during the last 100 years after industrialization and urbanization, causing increased intake of total and saturated fatty acids, trans fatty acids and linoleic acid, and meat from grain-fed cattle raised in feedlots, rather than meat

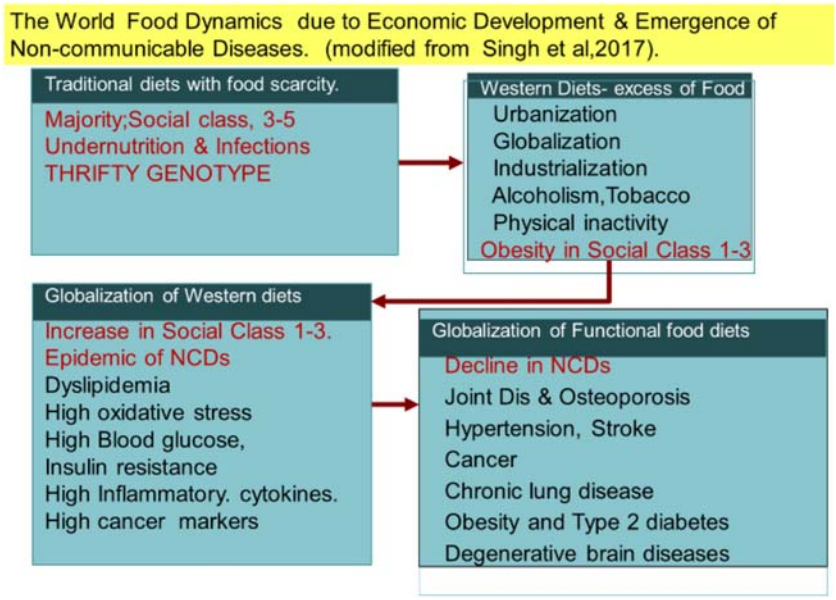


FIGURE 1.2 Pathway for globalization of Western and Indo-Mediterranean-style diets and risk of non-communicable diseases. *Modified from Juneja LR, Wilczynska A, Singh RB, Takahashi T, Pella D, Chibisov S, et al. Evolutionary diet, Western diet and non-communicable diseases. In: Singh RB, Watson RR, Takahashi T. (editors) Role of functional food security in global health. San Diego: Elsevier; 2018, p. 71 [2].*

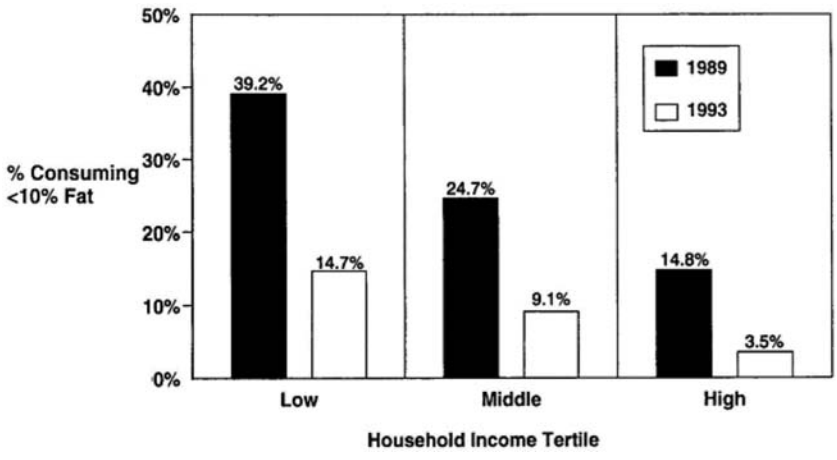


FIGURE 1.3 The proportion of subjects consuming less than 10% fat was significantly higher among lower social classes in 1989 but reduced significantly in 1993 in China.

from free-range animals [1−3,11−13,18,20−23,26]. In general, there has been an increase in the intake of refined carbohydrates and a decrease in the intake of complex carbohydrates, essential amino acids, minerals, omega-3 fatty acids, vitamins, and antioxidants. These dietary changes, in conjunction with sedentary behavior, mental strain, pollution, tobacco consumption, and alcoholism, particularly after 1910, may have caused damage to our genes, leading to a rapid emergence of phenotypes of CVDs and other chronic diseases [1−3,11−13,18,20−23,26,31]. In wealthy countries there has been a marked reduction in deaths due to communicable diseases and emergence of morbidity and mortality due to CVDs, which are now declining [10−13]. With increases in income there are changes in food quality toward an energy-rich Western-type diet and a lifestyle characterized by the use of automobiles, lack of physical activity, and increases in occupational stress, alcoholism, and tobacco consumption [10−13,18,20−23,26,31].

Modified from Popkin BM, Adair LS, Ng SW. Now and then: the global nutrition transition: the pandemic of obesity in developing countries. Nutr Rev 2012;70:3−21 [11]. The food system transition has been associated with a marked increase in large chain supermarkets, which have displaced fresh local food and farmstands, resulting in decreased availability of affordable fruits and vegetables directly sold by the farmers and increased availability of highly processed foods, high-energy snacks, and sugary beverages [10−13,18,20−23,26,31]. Apart from changes in human dietary patterns, most parts of the world undergoing epidemiological transition have experienced a livestock revolution, characterized by increased production of beef, pork, dairy products, eggs, and poultry, drastically so in Asian countries [9−13,18,20−23,26,31]. The food and nutrition transitions are also characterized by increased refinement of grain products. The whole grains are milled and processed to produce refined grains such as polished white rice and refined wheat flour, which reduce the nutritional content of grains, including their fiber, micronutrients, and phytochemicals. Increased intake of these foods has been associated with increased risk of CMDs and other chronic diseases [7−13]. Industrialization and urbanization have also been associated with greater consumption of proatherogenic foods during the transition from lower social classes (poverty) to higher social classes [1−3,10,18,20−23,26,31]. The different diets and lifestyle habits can cause differences in the food and nutrient intake among rural and urban populations as well as among Western and Asian populations during the transition from poverty to affluence [10−13,18,20−23,26]. Western-type diets consumed by lower social classes in the developed countries and higher social classes in developing countries may be associated with marked reductions in the consumption of omega-3 fatty acids, vitamins, antioxidants, and amino acids and significant increases in the intakes of carbohydrates, (mainly refined) fat (saturated, trans fat, and linoleic acid), and salt compared to the Paleolithic period.

The Nurses' Health Study included 88,520 women aged 34−59 years without previously diagnosed CAD, stroke, or diabetes in 1980, who were followed from 1980 to 2004 [38]. The results showed that after 24 years of follow-up, 3105 incident cases of CAD (nonfatal myocardial infarction and fatal congenital heart disease) were ascertained. After standard and dietary risk factors were adjusted for, the risk ratios (RRs) and 95% confidence intervals (CIs) of congenital heart disease, according to categories of cumulative average of servings of sugar-sweetened beverage (SSB) consumed ($<$1/month, 1−4/month, 2−6/week, 1/day, and $\pm$2/day) were 1.0, 0.96 (0.87, 1.06), 1.04 (0.95, 1.14), 1.23 (1.06, 1.43), and 1.35 (1.07, 1.69) (P for trend $<$.001). Regular consumption of SSBs is associated with a higher risk of CAD in women. Artificially sweetened beverages were not associated with CAD [38]. Recently, a Diet and Health Study included the general population from six states and two metropolitan areas in the United States, and 16-year follow-up data involved 536,969 subjects aged 50−71 years at baseline [21]. All-cause mortality (hazard ratio for the highest vs the lowest fifth: 1.26, 95% CI: 1.23−1.29) and deaths due to nine different causes were associated with red meat intake, and these findings indicated increased risk. All-cause and cause-specific mortality rates were also associated with increased intake of processed and unprocessed meats [21]. Heme iron and nitrates/nitrites from processed meat were independently associated with increased risks of all-cause and cause-specific mortality. The highest fifth of white meat (poultry and fish) intake was associated with a 25% reduction in risk of all-cause mortality compared with the lowest intake level. Almost all causes of deaths showed an inverse association with white meat intake. It is possible that increased risks of all causes of mortality and deaths were due to nine different causes associated with both processed and unprocessed red meat, which can be accounted for, in part, by heme iron and nitrates and nitrites from processed meat. They also show reduced risks associated with substituting white meat, particularly unprocessed white meat [21].

Globalization of prudent diets and protection from NCDs

Functional foods, such as green leafy vegetables, are rich sources of antioxidants, magnesium, omega-3 fatty acids, and carotenoids and appear to be important in the Mediterranean region [1−3,30,32−36]. The protective effects of prudent diets—Mediterranean-type diets, Indo-Mediterranean diet, Japanese diet, and the DASH diet—have been documented in the several previous studies [1−3,33−36]. The WHO and its experts have clearly mentioned that eating 400 g/day of

fruits, vegetables, and legumes can protect against NCDs [2,4,5]. Other experts from Asia and Europe have observed that increased supplementation with functional foods can decrease the risk of NCDs [12,33−36]. The South Korean government initiated innovative interventions for promoting increased intake of functional foods to prevent NCDs [19]. The trend of pursuing healthy foods had already began in the mid-1980s when NCDs became a major health concern in South Korea. This trend reflects efforts by health professionals and governments to solve health problems by improving dietary patterns. The traditional Korean diet is low in fat and high in vegetables, and the government has put a lot of effort into advertising and teaching the public that the traditional Korean diet is healthy and that adoption of Western eating habits may lead to obesity and metabolic syndrome [19]. Most of the experts in Korea and Japan are working on reviving the traditional diet using approaches that are acceptable to the contemporary citizens, such as publishing traditional recipes with slight modifications [33]. This approach has also been used in other Asian countries but with only little success, owing to aggressive advertising by multinational companies [1−3]. The North Karelia Project, which was carried out in eastern Finland, was able to produce favorable changes in diet under the supervision of health professionals [18,20,31,34−36]. The proportions of saturated fats, salt, and sugar were decreased while the proportion of unsaturated fats and vegetable consumption increased, indicating a choice for functional foods. It may be that the mass media and community involvement together with changes in legislation, which were the main tools in this intervention, influenced the dietary habits of the whole Finnish population. Pietinen et al. estimated that between 1972 and 1992 a major decrease in total serum cholesterol (1 mmol/L on average) took place because of changes in the diet from Western foods to functional foods: fruits and vegetables, poultry, and seafood [36].

In 2012, 702,308 cardiometabolic deaths occurred in U.S. adults, including 506,100 from heart disease (371,266 CAD, 35,019 hypertensive heart disease, and 99,815 other CVDs), 128,294 from stroke (16,125 ischemic, 32,591 hemorrhagic, and 79,578 other), and 67,914 from type 2 diabetes mellitus [39]. High sodium (66,508 deaths in 2012; 9.5% of all cardiometabolic deaths) was associated with the largest number of cardiometabolic deaths, followed by low nuts/seeds (59,374; 8.5%), high processed meats (57,766; 8.2%), low seafood omega-3 fatty acids (54,626; 7.8%), low vegetables (53,410; 7.6%), low fruits (52,547; 7.5%), and high SSBs (51,694; 7.4%). Between 2002 and 2012, population-adjusted U.S. deaths from CMD per year decreased by 26.5%. The greatest decline was associated with insufficient polyunsaturated fats (−20.8% relative change; 95% UI: −18.5% to −22.8%), nuts/seeds (−18.0%; 95% UI, −14.6% to −21.0%), and excess SSBs (−14.5%; 95% UI: −12.0% to −16.9%). The greatest increase was associated with unprocessed red meats (+14.4%; 95% UI, 9.1%−19.5%). It is possible that dietary factors were estimated to be associated with a substantial proportion of deaths from heart disease, stroke, and type 2 diabetes mellitus [39]. An increased intake of nuts, fruits, vegetables, and seafood omega-3 fatty acids and a lower intake of salt without processed meat may be protective against these deaths. In an Indian study, death records were studied, including those of 2222 decedents (1385 men and 837 women) aged 25−64 years [29,40]. The findings showed that sedentary behavior, excess salt intake, and other typical Western dietary habits were significantly more common among decedents belonging to higher social classes 1−3, compared to those within lower social classes 4 and 5 (see Table 1.4). Lack of knowledge regarding health education was significantly more common among decedents in the lower social classes, who died more often as a result of communicable diseases. The study also revealed that deaths associated with diabetes mellitus and due to circulatory diseases were significantly more common among higher social classes 1−3, compared to lower social classes 4 and 5. However, deaths due to malignant diseases and chronic lung diseases were not associated with social class, with the exception of the social class of women with breast cancer, but total proportion of deaths due to NCDs including these causes were significantly greater among higher social classes 1−3 compared to lower social classes 4 and 5. The findings indicate that sedentary behavior, a typical Western diet, and excessive salt intake in conjunction with an underlying lack of health education may be the predisposing factors for deaths among decedents of higher social classes 1−3. Functional food intake was inversely associated with risk of deaths due to NCDs [40].

Clinical evidence on the role of Mediterranean-style diets as functional food is very strong because such diets are known to reduce all-cause mortality. The EPIC-NL study involved a cohort of 40,011 subjects with a follow-up of 10−15 years [41]. The Mediterranean diet included daily intakes of vegetables, fruits, legumes and nuts, grains, fish, fatty acids, meat, dairy, and alcohol (wine and beer). Among 34,708 participants who were free of CVD at baseline, 4881 CVD events occurred, and 487 people died from CVD. Increased intake of Mediterranean diet by 2 units (range 0−9) was inversely associated with fatal CVD (hazard ratio (HR): 0.78 95% CI: 0.69−0.88), total CVD (HR: 0.95, CI: 0.91−0.98), myocardial infarction, stroke, and pulmonary embolism [30,41]. It is clear that a better adherence to a Mediterranean-style diet was more strongly associated with fatal CVDs than with total CVDs. The associations were strongest for incident myocardial infarction, stroke, and pulmonary embolism. The effects of fruit and vegetable intake on the incidence of CAD were examined in a meta-analysis involving 278,459 subjects with 9143 CAD events during a median follow-up of 11 years [42]. Among subjects consuming more than five servings per day of fruit and vegetables, the pooled RR of CAD was significantly greater compared with subjects consuming fewer than three servings per day

($P = .0001$ vs .06). This meta-analysis reported that increased consumption of fruit and vegetables, from fewer than three to more than five servings per day is related to a 17% reduction in CAD, whereas increased intake to three to five servings per day is associated with a smaller and borderline significant reduction in CAD risk [42]. These results provide strong evidence supporting the idea that five or more servings per day of fruit and vegetables can provide substantial protection from CVDs. A large cohort study involving 72,113 female nurses who were free of CAD, stroke, diabetes, and cancer examined the association of dietary pattern with risk of NCDs [43]. During a follow-up of 18 years, 6011 deaths occurred: 3319 (52%) as a result of cancer, 1154 (19%) resulting from CVDs, and 1718 (29%) resulting from other causes. There was a 17% lower risk of total mortality among subjects who were most adherent to the prudent diet (highest vs lowest quintile of adherence), a 28% lower risk of CVD mortality, and a 30% lower risk of mortality from non-CVD, noncancer causes. Cancer was not associated with the inverse prudent dietary pattern. A comparison of the highest and lowest quintiles of adherence showed that consumption of a Western diet was associated with increased total mortality (21%), CVD mortality (22%), cancer mortality (16%), and mortality from non-CVD, noncancer causes (31%). Hence except for cancer, risk relationships for the prudent and Western dietary patterns appear to be the inverse of each other: Mortality increased as adherence to the prudent diet decreased and adherence to the Western diet increased [43].

The INTERHEART study examined the relationship between dietary patterns and risk of acute coronary syndrome (ACS) in a standardized case-control study involving participants from 52 countries [44]. Using the principle component analysis technique, the authors identified three major dietary patterns: Oriental (high intake of tofu, soy sauce, and other sauces), Western (high in fried foods, salty snacks, eggs, and meat), and prudent (high in fruit and vegetables). Consistent with previous studies in single within-population cohort studies, the authors found an inverse association between the prudent pattern score and the risk of ACS and a significant positive association between the Western pattern score and increased risk of ACS. The Oriental pattern was not significantly associated with risk. The investigators constructed a dietary risk score based on seven food items on the food frequency questionnaire (meat, salty snacks, fried foods, fruits, green leafy vegetables, cooked vegetables, and other raw vegetables) and found that a higher score (indicating a poor diet) was strongly associated with ACS risk: Those in the highest quartile of the score had a nearly twofold increased risk even after adjustment for established coronary risk factors. In sensitivity analyses the investigators found a consistent association for the composite diet score between men and women and across different regions of the world (North America, Western Europe, Australia, Central Europe, the Middle East, Africa, South Asia, Southeast Asia, China, and South America). On the basis of an arbitrary cut point of the score (the top three quartiles vs the bottom quartile), the investigators estimated that 30% of myocardial infarctions could be explained by unhealthy diets worldwide [44]. Although Western-style food pattern changes are widely believed to adversely influence the risk of chronic diseases, few epidemiological studies have directly linked dietary patterns and mortality from coronary heart disease. The INTERHEART study is the first large study to quantify eating patterns in all geographic regions of the world. It provides evidence that despite different food habits in various populations, reproducible patterns can be found in diverse regions of the world. These findings are important because there has been a concern that dietary patterns derived through a data-driven approach such as principle component analysis may be highly unstable and nonreproducible because of very different eating habits in different populations.

The PREDIMED study prospectively examined 1868 participants who were free of metabolic syndrome at baseline, in which 930 incident cases of metabolic syndrome were documented during a median follow-up of 3.24 years [45]. Increased consumption of more than five servings per week of SSBs was compared with consumption of fewer than one serving per week, while all subjects were consuming Mediterranean-style diets. The consumption of more than five servings per week of all the types of beverages analyzed was associated with an increased risk of metabolic syndrome and some of its components [45]. However, for SSBs and bottled fruit juices these associations must be interpreted with caution because of the low frequency of consumption in this population. The occasional intake of SSBs and artificially sweetened beverages (one to five servings per week) was not associated with a high risk of metabolic syndrome in middle-aged and elderly individuals at high risk of CVD. It is clear that despite Mediterranean diets, excess consumption of sugar-sweetened products may have adverse effects. Total and cause-specific mortality among 47,994 women in the Nurses' Health Study and 25,745 men in the Health Professionals Follow-up Study from 1998 through 2010 were examined in relation to changes in diet quality over the preceding 12 years (1986−98) [23]. Dietary intakes were assessed with the use of the Alternate Healthy Eating Index-2010 score, the Alternate Mediterranean Diet score, and the Dietary Approaches to Stop Hypertension (DASH) diet score. The greatest improvement in diet quality (13%−33% improvement) as compared with those who had a relatively stable diet quality (0%−3% improvement) in the 12-year period were as follows: 0.91 (95% CI: 0.85−0.97) according to changes in the Alternate Healthy Eating Index score, 0.84 (95 CI%: 0.78−0.91) according to changes in the Alternate Mediterranean Diet score and 0.89 (95% CI:

0.84−0.95) according to changes in the DASH score [23]. An improved quality of diet was significantly associated with a reduction in total mortality of 8%−17% with the use of the three diet indexes and a 7%−15% reduction in the risk of death from CVDs with the use of the Alternate Healthy Eating Index and Alternate Mediterranean Diet. The risk of death from any cause was significantly lower—by 14% (95% CI: 8−19) when assessed with the Alternate Healthy Eating Index score, by 11% (95% CI: 5−18) when assessed with the Alternate Mediterranean Diet score, and by 9% (95% CI: 2−15) when assessed with the DASH score—than the risk among participants with consistently low diet scores over time [23]. It is clear that improvement in diet quality during a follow-up of 12 years was consistently associated with a decreased risk of death. The Global Burden of Diseases study examined global, regional, and national age- and sex-specific all-cause and cause-specific mortality for 240 causes of death from 1990 to 2013 [22]. Vegetables, fruit, fish, omega-3 fatty acids, fiber, nuts and seeds, and whole-grain intakes were inversely associated with mortality. Increased intake of salt, processed meat, and trans fat and high alcohol intake were positively associated with mortality in ten high-population countries [22].

A previous study demonstrated that nutritional management of blood glucose levels is a strategic target in the prevention and management of type 2 diabetes mellitus [23]. In such circumstances the population and the people should be given health education to implement such an approach, because it is essential to understand the effect of food on glycemic regulation for prevention of hyperglycemia. The results from human dietary interventions exploring the impact of dietary components and food consumption patterns on blood glucose levels are important for prevention of adverse effects of glycemia [23]. Major macronutrients such as carbohydrates, protein, fat, micronutrient vitamins and minerals, nonnutrient phytochemicals, and additional foods, including low-calorie sweeteners, vinegar, and alcohol, can influence blood glucose levels [23]. These dietary components from functional foods have significant and clinically relevant effects on blood glucose modulation. Reduction in excess body weight, increased physical activity, and a functional food dietary regime to regulate blood glucose levels will not only be advantageous in the management of diabetes, but will also benefit the health of the population and limit the increasing worldwide incidence of diabetes and its cardiovascular complications [23]. Recently, dietary-patterning analysis has been increasingly used as an alternative method to traditional single-nutrient analysis because dietary-patterning analysis can assess the cumulative effects of the totality of nutrients in the diet [12,33−39]. Habitual food consumption patterns are typically quantified by statistical methods, such as factor or cluster analysis, or by using diet-quality indexes based on prevailing dietary recommendations or healthful traditional diets, such as the Mediterranean-style diet, and the Indo-Mediterranean-style diet. Principle component analysis is commonly used to define dietary patterns using food consumption information to identify common underlying dimensions (factors or patterns) of food intake. The method aggregates specific food items based on the grading, by which these food items are correlated with each other. A summary score for each pattern is then derived and can be used to examine relationships between various eating patterns and outcomes of interest, such as CAD and other chronic diseases. Previous validation studies found that two major patterns (the prudent and Western patterns) that were identified through principle component analysis of food consumption data assessed by food frequency questionnaires were reproducible over time and correlated reasonably well with the patterns identified from diet records (Fig. 1.4).

In high-income countries, lower social classes 3 and 4 have poor health behavior and greater risk factors for CVD and cancer mortality, as well as all-cause mortality than higher social classes [12,21−23,33−39]. The higher social

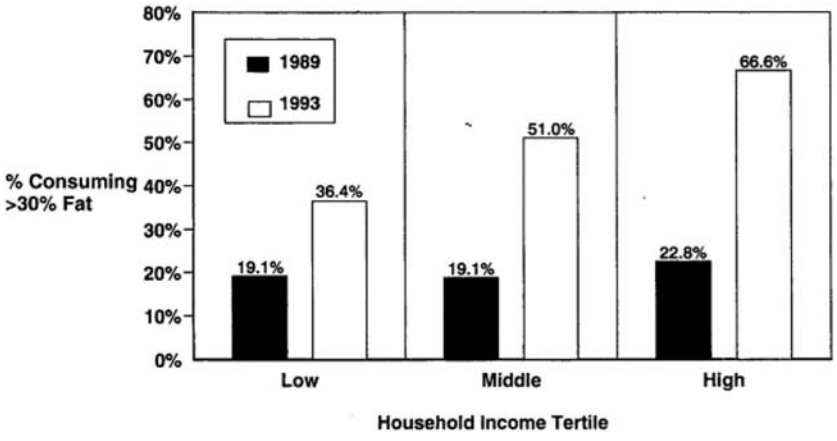


FIGURE 1.4 The proportion of subjects consuming more than 30% fat became significantly higher among all social classes between 1989 and 1993 in China. *Modified from Popkin BM, Adair LS, Ng SW. Now and then: the global nutrition transition: the pandemic of obesity in developing countries. Nutr Rev 2012;70:3−21 [11].*

classes (1 and 2) appear to have greater access to health education, spare time to increase physical activity, and additional resources to maintain prudent diets than do the lower social classes in the developed countries. This situation is in contrast to lower social classes 3–5 in developing countries, who are living with a scarcity of foods and irregular employment [30,32,33]. Physically demanding occupations are common in developing countries but uncommon in developed countries [12,21–23,33–46]. It seems that in developing societies, urban populations have a double burden of diseases related to overeating as well as malnutrition because occupational physical activity decreases along with changes in social class [12,33–46]. Other experts agreed with the above global nutrition dynamics in which the world is shifting rapidly toward a diet linked with NCDs [3] (see Table 1.1 and Fig. 1.1). In view of the technological advancements, humans now live in a nutritional environment that completely differs from that for which our genetic constitution was selected.

Randomized, controlled trials with Mediterranean-style diets

Cross-sectional surveys and cohort studies provide an association of dietary factors with risk of certain diseases without any definite proof for cause and effects. Hence prospective cohort studies with randomized, controlled trial are necessary to provide proof that Mediterranean-style diets are effective in the prevention of NCDs [12,33–37,47–63]. In a previous randomized, controlled trial involving 406 patients with acute myocardial infarction the experimental group received significantly greater amounts of fruits, vegetables, whole grains, nuts, and mustard oil and lower amount of refined bread, biscuits, sugar, butter, and clarified butter compared to the control diet group at 1 year and 2 years of follow-up [47,48] (see Tables 1.3–1.6). Total adherence score to a Paleolithic-style diet and a prudent diet were significant in both the groups. The omega-6/omega-3 fatty acid ratio of the diet, which was much higher before entry into the study (32.5 ± 3.3), was brought down to significantly lower levels in the Paleolithic-style diet group A ($N = 204$) compared to the control diet group B ($N = 202$) at entry into the study (3.5 ± 0.76 vs 24.0 ± 2.4 kJ/day, $P < .001$). The fatty

TABLE 1.3 Effect of an omega-3 fatty acid-rich Paleolithic-style diet in patients with acute myocardial infarction.

	Paleolithic-style diet group ($N = 204$)		Standard diet group ($N = 202$)	
Foods and nutrients	**4–7 days**	**After 1 year**	**4–7 days**	**After 1 year**
Fruits and vegetables (g/day)	508.4 (28.66)*	575 (91.4)**	254.4 (17.2)	220.5 (19.6)
Potato, radish	60.5 (6.8)	115 (12.7)**	72.0 (12.5)	155.6 (32.5)
Legumes and pulses (g/day)	80.5 (6.6)**	95.0 (8.9)**	52.5 (4.6)	45.6 (5.6)
Almonds and walnuts (g/day)	82.4 (5.7)**	75.5 (5.2)**	—	—
Fish (g/day)	52.5 (6.5)**	22.4 (4.1)**	20.2 (3.1)	10.5 (3.5)
Chicken (g/day)	–	10.2 (3.2)*	76.2 (6.5)	66.5 (10.5)
Mustard or soybean oil	18.4 (3.9)*	31.5 (5.5)**	10.5 (2.3)	6.8 (2.8)
Butter or clarified butter (g/day)	2.5 (0.6)**	3.3 (0.71)*	10.5 (2.6)	12.6 (3.5)
Skim milk (mL/day)	161.2 (12.0)	152 (14.5)*	150.2 (8.0)	165.5 (16.1)
Wheat chapatti	5.5 (1.6)**	30.6 (5.5)	50.6 (6.6)	55.6 (7.8)
Bread, biscuits (g/day)	10.6 (2.2)*	25.5 (6.2)**	230.6 (20.1)	212.2 (18.1)
Rice and wheat cereals (g/day)	25.6 (2.4)	30.6 (5.5)	30.2 (3.1)	35.6 (4.8)
Honey or raisins (g/day)	2.6 (0.8)	5.5 (1.2)	—	—
Sugar (g/day)	16.4 (3.7)*	12.6 (3.4)*	25.5 (5.4)	30.5 (7.6)
Total adherence score (%)	65.2 (17.2)	63.9 (14.8)	123.0 (30.0)	71.0 (30.0)
Total foods	1027 (232)	1184.6 (254)	983.4 (213)	862 (204)

P values for mean (standard deviation) were obtained by comparison of intervention and control groups after 1 week and after 1 year. *$P < .05$, **$P < .01$.
Sources: He FJ, Nowson CA, Lucas M, MacGregor GA. Increased consumption of fruit and vegetables is related to a reduced risk of coronary heart disease: meta-analysis of cohort studies. J Hum Hyperten 2007;21:717–28 [42]; Singh RB, Sharma JP, Rastogi V, Raghuvanshi RS, Moshiri M, Verma SP, et al. Prevalence of coronary artery disease and coronary risk factors in rural and urban populations of north India. Eur Heart J 1997;18(11):1728–35 [37].

TABLE 1.4 Effect of an omega-3 fatty acid-rich Paleolithic-style diet in patients with acute myocardial infarction.

	Paleolithic-style diet group ($N = 204$)		Standard diet group ($N = 202$)	
Foods and nutrients (g/day)	**4–7 Days**	**After 1 year**	**4–7 Days**	**After 1 year**
Fruits and vegetables	508.4 ± 28.66**	575 ± 91.4**	254.4 ± 17.2	220.5 ± 19.6
Potato, radish,	60.5 ± 6.8	115 ± 12.7**	72.0 ± 12.5	155.6 ± 32.5
Whole grains	80.5 ± 6.6**	95.0 ± 8.9**	52.5 ± 4.6	45.6 ± 5.6
Almonds and walnuts	82.4 ± 5.7**	75.5 ± 5.2**	—	6.7 ± 1.0
Fish	52.5 ± 6.5**	22.4 ± 4.1**	20.2 ± 3.1	10.5 ± 3.5
Chicken	—	10.2 ± 3.2*	76.2 ± 6.5	66.5 ± 10.5
Mustard or soybean oil	18.4 ± 3.9*	31.5 ± 5.5**	10.5 ± 2.3	6.8 ± 2.8
Butter or clarified butter	2.5 ± 0.6**	3.3 ± 0.71*	10.5 ± 2.6	12.6 ± 3.5
Skim milk (mL/day)	161.2 ± 12.0	152 ± 14.5*	150.2 ± 8.0	165.5 ± 16.1
Wheat chapatti	5.5 ± 1.6**	30.6 ± 5.5	50.6 ± 6.6	55.6 ± 7.8
Bread, biscuits, sugar	27.1 ± 4.2*	20.5 ± 6.4**	255.6 ± 22.1	232.2 ± 18.1
Rice and wheat cereals	25.6 ± 2.4	30.6 ± 5.5	30.2 ± 3.1	35.6 ± 4.8
Honey or raisins	2.6 ± 0.8	5.5 ± 1.2	—	—
Spices; turmeric, cumin, coriander, fenugreek	6.4 ± 3.7*	18.6 ± 3.4**	5.5 ± 1.0	7.5 ± 2.6
Curd, yogurt	17.3 ± 3.4	22.6 ± 4.7*	6.6 ± 2.0	9.1 ± 2.2
Total adherence score (%)	65.2 ± 17.2	63.9 ± 14.8*	123.0 ± 30.0	71.0 ± 30.0
Total foods	1027 ± 232	1184.6 ± 254	983.4 ± 213	862 ± 204

P values mean ± standard deviation were obtained by comparison of intervention and control groups during 1 week and after 1 year; *$P < .05$,**$P < .01$.9.
Sources: Singh RB, Rastogi SS, Verma R, Laxmi B, Singh R, Ghosh S, et al. Randomized, controlled trial of cardioprotective diet in patients with acute myocardial infarction: results of one year follow up. BMJ 1992;304: 1015–9 [47]; Singh RB, Fedacko J, Vargova V, Niaz MA, Rastogi SS, Ghosh S. Effect of low ω-6/ω-3 ratio fatty acid Paleolithic style diet in patients with acute coronary syndromes. A randomized, single blind, controlled trial. World Heart J 2012;3:71–84 [48]; Singh RB, Singh AK, Sharma JP, Singh RK, Kumar A, Singh G, et al. Nutrition in chronocardiology: we are indebted Professor Franz Halberg. Open Nutr J 2012; 5(Suppl):45–65 [50].

acid ratio remained significantly much lower in the experimental group compared to the control group after 1 year of follow-up (4.4 ± 0.56 vs 22.3 ± 2.1 kJ/day, $P < .001$). Total mortality was 14.7% in the Paleolithic-style diet group and 25.2% in the control group after a follow-up of 2 years (see Table 1.6). The association between the omega-6/omega-3 ratio of fatty acids and mortality showed a gradient in both the groups independently as well as among total number of deaths. A lower omega-6/omega-3 fatty acid ratio from 1 to 10 was associated with a significantly lower mortality rate, whereas an increase in the omega-6/omega-3 fatty acid ratio to more than 10 was associated with greater mortality (see Fig. 1.5 and Tables 1.3–1.6). A low omega-6/omega-3 fatty acid ratio in the Paleolithic-style diet, achieved by increasing the amount of omega-3 fatty acid and decreasing the amount of omega-6 fatty acid can cause a significant decline in cardiovascular and all-cause of mortality (see Fig. 1.6).

It is possible that apart from the ratio of fatty acids, increased availability of flavonoids may also influence protective effects of omega-6 and omega-3 fatty acids by inhibiting oxidative stress-induced inflammation [61–63]. Since acute coronary syndromes and sudden cardiac death are more common in the morning in association with large meals, it would be pertinent to select functional foods for breakfast comprising about 500 kilocalories to have the beneficial effects of functional nutrients. This approach is based on the finding of increased energy metabolism and higher oxidative stress in the morning; reported by Halberg and coworkers [49,50]. Eating breakfast caused no increase in body weight compared to same amount of energy in the evening, which increases body weight [49,50]. Diet can also influence the brain, liver, and heart connections, leading to NCDs [49,50].

An Indo-Mediterranean-style diet that is rich in omega-3 fatty acids and flavonoids and other nitric oxide–activating foods may be protective against CVDs as well as other NCDs [51–62]. All the clinical trials that have been published

TABLE 1.5 Fatty acid consumption in the Paleolithic-style diet group and the standard diet group.

Parameters	Before entry	At entry		After 1 year	
	All patients ($N = 406$)	Paleolithic ($N = 204$)	Standard ($N = 202$)	Paleolithic ($N = 204$)	Standard ($N = 202$)
Saturated fatty acid (kJ/day)	10.0 (0.39)	7.0 (0.22)	10.0 (0.38)	7.2 (0.24)	10.8 (0.36)
Monounsaturated fatty acid (kJ/day)	9.3 (0.38)	9.5 (0.37)	7.6 (0.26)	8.0 (0.35)	10.2 (0.32)
Polyunsaturated fatty acid (kJ/day)	6.7 (0.30)	8.1 (0.44)	6.5 (0.39)	8.6 (0.39)	7.0 (0.26)
Omega-6 fatty acid (kJ/day)	6.5 (0.29)	6.3 (0.28)	6.3 (0.29)	7.0 (0.36)	6.2 (0.24)
Omega-3 fatty acid (kJ/day)	0.2 (0.07)	1.8 (0.13)**	0.2 (0.082)	1.6 (0.12)**	0.3 (0.083)
Omega-6/omega-3 ratio (kJ/day)	32.5 (3.3)**	3.5 (0.76)**	31.5 (2.4)	4.4 (0.56)**	20.6 (2.1)
Main dietary oil	Peanut	Mustard	Sunflower	Mustard	Sunflower
Flavonoids (mg/day)	56.7 (5.6)	98.6 (7.3)**	58.2 (4.3)	96.7 (4.8)**	59.8 (5.3)

Values are mean ± standard deviation; $^{**}P < .01$.
Source: Singh RB, Fedacko J, Vargova V, Niaz MA, Rastogi SS, Ghosh S. Effect of low ω-6/ω-3 ratio fatty acid Paleolithic style diet in patients with acute coronary syndromes. A randomized, single blind, controlled trial. World Heart J 2012;3:71–84 [48].

TABLE 1.6 Numbers and rate ratios for endpoints in the Paleolithic-style diet group and the standard diet group after 2 years of follow-up.

Events	Paleolithic-style diet ($N = 204$)	Control diet ($N = 202$)	Adjusted rate ratio (95% confidence interval)
Total cardiac mortality	27 (13.2)**	45 (22.3)	0.59 (0.52–0.67)
Fatal myocardial infarction	18 (8.8)**	27 (13.3)	0.66 (0.61–0.73)
Sudden cardiac death	9 (4.4)*	18 (8.9)	0.50 (0.38–0.73)
Total cardiovascular mortality	30 (14.7)**	50 (24.7)	0.50 (0.42–0.59)
Total mortality	30 (14.7)**	51 (25.2)	0.59 (0.51–0.67)

Values are number (%); $^{**}P < .001$, $^{*}P < .01$; Total deaths; adjustment made for baseline age, gender, body mass index, cholesterol, and blood pressure.
Source: Singh RB, Fedacko J, Vargova V, Niaz MA, Rastogi SS, Ghosh S. Effect of low ω-6/ω-3 ratio fatty acid Paleolithic style diet in patients with acute coronary syndromes. A randomized, single blind, controlled trial. World Heart J 2012;3:71–84 [48].

in the last three decades using Mediterranean-style diets have reported a significant decline in cardiovascular events and all causes of mortality [51–62]. The role of diets in the pathogenesis and prevention of endothelial dysfunction is well known; however, the effects of diets on cardiomyocyte dysfunction is controversial [59,60]. In a meta-analysis of three randomized, controlled single-blind trials studying the role of Indo-Mediterranean-style foods and nutrients in the prevention of CVDs, including heart failure (HF), the intervention and control groups were compared for behavioral risk factors, food intake, fatty acid intake, and ratio of polyunsaturated fatty acid to flavonoid intake ($N = 1446$ vs $N = 1320$) [61].

The criteria for the diagnosis of preheart failure (PHF) and HF were electrocardiographic and radiological increases in size of the heart. The effects of Indo-Mediterranean-style foods on the parameters of PHF and HF and arrhythmias were significantly lower in the intervention group compared to the control group. At baseline, all the parameters of HF

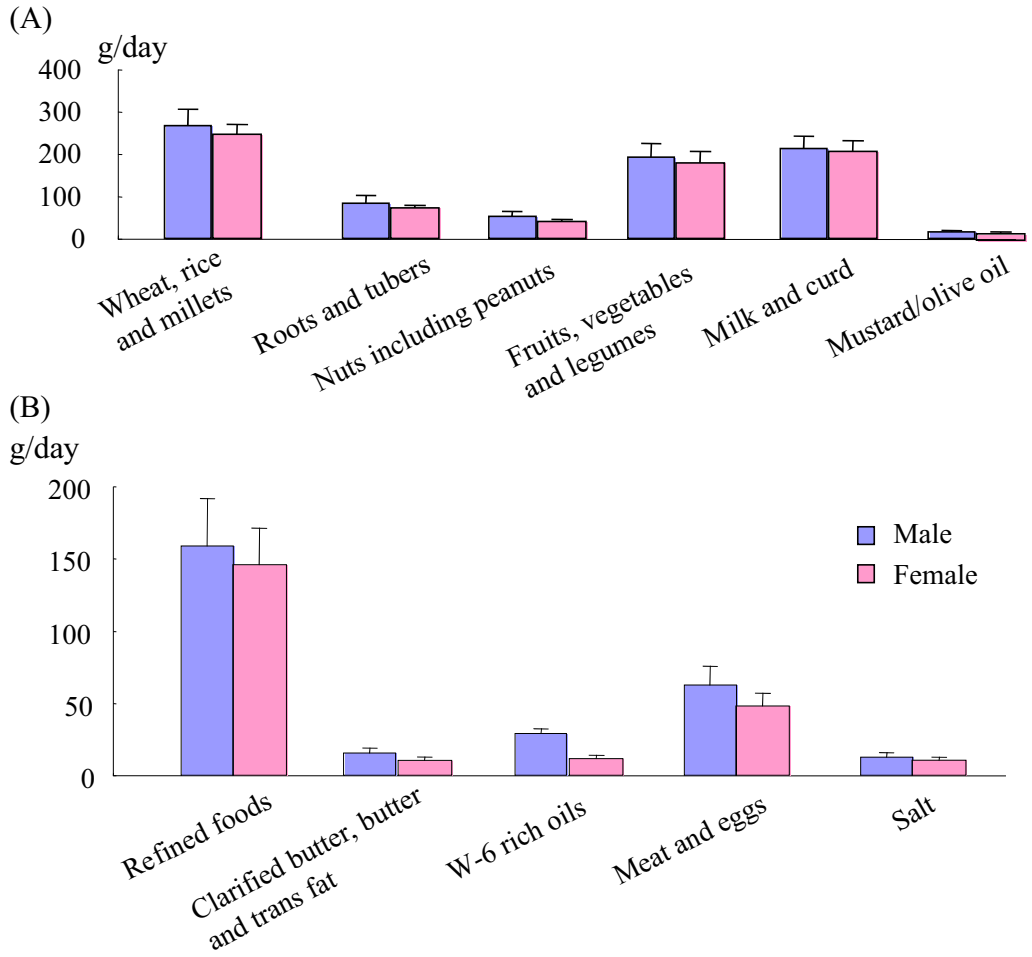


FIGURE 1.5 Food consumption pattern among subjects who died from various causes. (A) Paleolithic-style diet. (B) Standard diet. *Modified from Singh RB, Visen P, Sharma D, Sharma S, Mondol R, Sharma JP, et al. Study of functional foods consumption patterns among decedents dying due to various causes of death. Open Nutra J 2015;8:16–28 [40].*

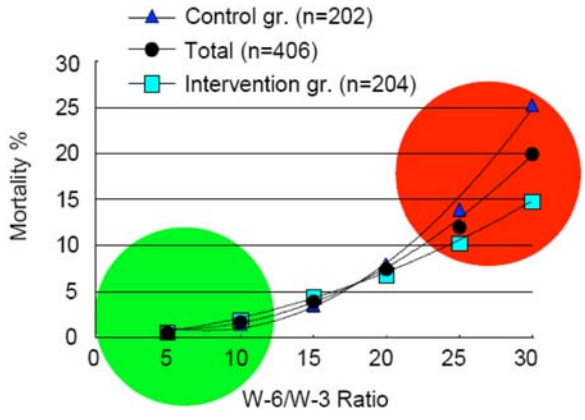


FIGURE 1.6 Effect of a low omega-6/omega-3 fatty acid ratio diet on mortality. *Modified from Singh RB, Fedacko J, Vargova V, Niaz MA, Rastogi SS, Ghosh S. Effect of low ω-6/ω-3 ratio fatty acid Paleolithic style diet in patients with acute coronary syndromes. A randomized, single blind, controlled trial. World Heart J 2012;3:71–84 [48].*

showed no significant differences between the intervention and control groups. However, after a follow-up of 2 years, left ventricular strain (odds ratio (OR): 0.57, CI: 0.50–0.65, $P < .01$), left ventricular hypertrophy (OR: 0.69, CI: 0.64–0.75, $P < .01$), as well as, NYHA (New York Heart Association) class II–IV HF (OR: 0.59, CI: 0.50–0.68,

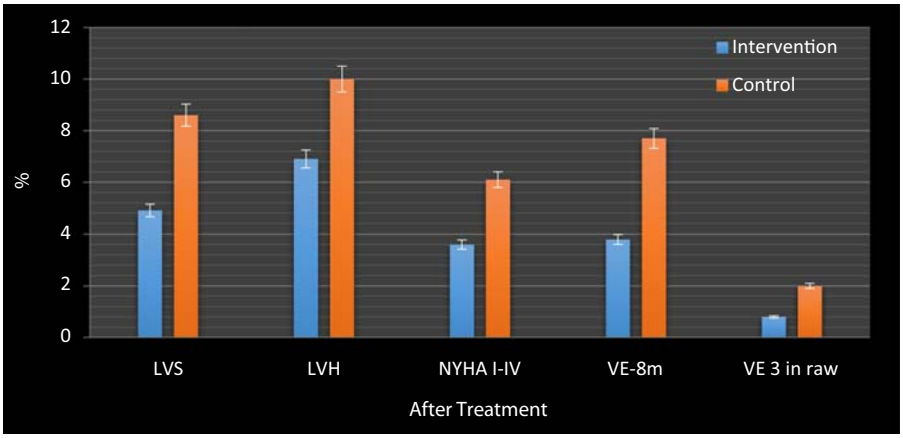


FIGURE 1.7 Effects of an Indo-Mediterranean-style diet on heart failure in patients at high risk of heart disease at entry and after treatment. *Modified from Singh RB, Takahashi T, Fatima G, Horuichi R, Fedacko J, Huzova Z. Effects of antioxidant rich Indo-Mediterranean foods on pre-heart failure: results from the randomized controlled trials. Open Inflamm J 2020;8:1–10 [61].*

$P < .05$) were significantly lower in the intervention group compared to the control group. The incidence of cardiac arrhythmias was also significantly lower in the intervention group compared to the control group (OR: 0.49, CI: 0.42–0.56, $P < .01$) (see Fig. 1.7). Total mortality due to CVDs was significantly lower in the intervention group compared to control group.

This meta-analysis and further studies by speckle-tracking echocardiography indicate that treatment with prudent diets can influence cardiomycyte function and dysfunction. These beneficial effects of diets may cause significant declines in PHF, HF, and arrhythmias, possibly owing to the antiinflammatory effects of such diets, which may be important mechanisms for reduction in cardiovascular mortality in patients with recent myocardial infarction and a high risk of CVDs [61–63]. Further studies have demonstrated that diet can address the majority of the mechanisms—oxidative stress, inflammation, dyslipidemia, hyperlipidemia, and cell signaling—that are important in the pathogenesis and prevention of NCDs [59–64]. Recently, there has been a greater emphasis on functional food production due to increased requirements via functional farming and development of functional foods by genetic engineering [64,65]. These studies have indicated that the approach to functional food security or reduction in food insecurity by the WHO and the Food and Agriculture Organization may be useful in the prevention of NCDs [66]. The Sustainable Development Goals (SDGs) were launched by the U.N. General Assembly in September 2015, leading to assessment of health based on these goals by different countries [67]. The original global SDG framework included 17 goals, 169 targets, and 232 unique indicators. Of these, 12 goals, 33 targets, and 57 indicators have been identified as health-related SDGs. The goals pertaining to health promotion and metabolic risk are concerned with environmental, occupational, and behavioral factors without emphasis on preconception factors in the father and mother that can influence the health of the next generation [17,67]. The Millennium Development Goals were the first step in the broader scope of health in the SDGs ranging from maternal and child health and infectious diseases to NCDs, injuries, risk factors, and health system functions. Therefore regular monitoring of the health-related SDGs is important in the light of diet and lifestyle changes and other health behaviors, such as role of meditation, prayer, optimism, and happiness in the prevention of NCDs. Identification of important gaps in resources and rates of progress should be taken into account in light of the emerging challenges that can influence the trajectory of progress in health and health systems. The broader complexity of the health-related agenda of SDGs requires regular monitoring and accountability to sustain a policy focus and funding for execution by governments [67].

Conclusion

In brief, there are rapid changes in food consumption patterns and health behavior in various populations of all the countries during the transition from poverty to economic development. The nutritional transition has been relatively more rapid during the last 100–160 years, resulting in the increased consumption of saturated fatty acids, trans fat, refined carbohydrates, and linoleic acid and decreased consumption of omega-3 fatty acids and flavonoids from meat from grain-fed cattle raised in feedlots rather than meat from free-range animals, resulting in marked increases in morbidity and mortality due to CMDs. Population characteristics, such as dietary intakes, in conjunction with sedentary behavior appear to be the main causes of poor social, mental, and spiritual health as well as of hyperlipidemia, hyperglycemia, oxidative stress, and inflammation, which are important mechanisms in the pathogenesis and prevention of

diet-related NCDs. It seems that through education, psychological intervention, adherence, and indoctrination, a cultural change in which families take heed of advice on dietary intervention and prevention of NCDs that will give each generation healthier outcomes can help to reduce the health burden on individuals and countries, and we may eventually see even a world unification on this.

Acknowledgment

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Further reading

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Chapter 2

Estimates of functional food and nutraceutical availability in the world, with reference to food peroxidation and food safety

Richa Mishra[1], Abhishek Dutt Tripathi[2], Ram B. Singh[3], Rukam S. Tomar[4], Douglas W. Wilson[5] and Manal M.A. Smail[6]

[1]Department of Home Science, Arya Mahila PG College, Banaras Hindu University, Varanasi, India, [2]Centre of Food Science and Technology, Institute of Agricultural Sciences, Banaras Hindu University, Varanasi, India, [3]Halberg Hospital and Research Center, Civil Lines, Moradabad, India, [4]Department of Genetics, Junagadh Agricultural University, Junagadh, India, [5]Formerly, School of Medicine, Pharmacy, Health and Wellbeing, Durham University, Durham, United Kingdom, [6]University of Central Lancashire, Preston, United Kingdom

Introduction

Reviews of food consumption patterns from the evolution of *Homo sapiens* to *Homo erectus* and the progression from hunter-gatherers to modern people indicate that there have been marked changes in the diets over human history. Rapid increases in industrialization and urbanization have been associated with increased availability of ready-prepared refined foods that are high in sugar, salt, and trans fat and low in phytochemicals, essential fatty acids, and essential amino acids [1−3]. It seems that suboptimal diets, characterized by deficiencies in micronutrients, antioxidants, and flavonoids and excessive amounts of lower-quality foods that are rich in salt, sugar, refined carbohydrates, trans fat, and red and processed meat are responsible for approximately one-half of deaths due to non-communicable diseases (NCDs) [1,2]. The great majority of foods manufactured by the food industry are of poor quality and unhealthy, but there have also been marked changes in an attempt by industry to develop healthy foods, so the food for this century may be of improved quality with more diversity. There is an unmet need to achieve global nutrition and diet-related NCD targets by 2025 and contribute to the realization of sustainable development goals by 2030 [1−3]. The guidelines published by the Food and Agriculture Organization (FAO) of the United Nations emphasize that full use of available food biodiversity to enhance the nutritional status of populations. To do this, a better understanding of food biodiversity in dietary intake is required [2,3]. However, only a few national and regional food consumption surveys exist that report food biodiversity, particularly at the cultivar or breed level. This review aims to highlight the estimates of functional foods available in the world for human consumption.

The Food and Agriculture Organization estimates of functional foods

The FAO report disclosed in 2019 that approximately 1.3 billion metric tons of food was produced in 1 year [3]. The FAO and the World Health Organization (WHO) recommend that each adult consume at least 400 g of fruit and vegetables on a daily basis to prevent chronic NCDs, including heart diseases, cancer, diabetes, and obesity, and to counter micronutrient deficiencies. Therefore the U.N. General Assembly established a new international year and specific days devoted to food and agriculture. The FAO welcomes global recognition of production of fruits, vegetables, and tea as well as food loss and waste [4]. The U.N. General Assembly adopted resolutions designating 2021 as the

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International Year of Fruits and Vegetables, May 21 as International Tea Day, and September 29 as International Day of Awareness of Food Loss and Waste, following requests made by the FAO Conference.

Although 1.3 billion metric tons of food is produced every year, poor-quality diets are still a threat to the public around the world, compared to morbidity and mortality caused by malaria, tuberculosis, measles, pneumonia, and diarrhea. Interestingly, diet-related factors may be responsible for six of the top nine contributors to the global burden of diseases. While obesity is the universal risk factor for NCDs, undernutrition may be largely responsible for the rest of the diseases. Although the world is producing much more food than is consumed, an estimated three billion people have suboptimal diets, which is apparent from the report of the U.N. Food and Agriculture Organization [4]. It is emphasized that consuming increased amounts of nutrient-rich foods that have already been produced would result in savings in terms of farming land use and water and energy consumption, which are important factors in food production. Water and energy are also required by the food industry for food fortification and food manufacturing for dietary needs. Apart from this, if food wastage can be avoided during various stages of food production and consumption, the scale and pace of food production would not need to be increased to meet the demand of an estimated additional one billion people by 2030.

Quality of foods and diets

The traditional demand for food security was achieved by increasing the production of staple crops. There was little or no emphasis on food quality or high nutrient density; hence governments and scientists worked hard to develop bigger sizes of grains and other foods with lower micronutrient content. These extraordinary efforts have been successful in decreasing undernutrition due to increased consumption of energy-rich foods with deficiency of micronutrients resulting in a double burden of diseases. However, health care experts and policymakers have recognized this problem and are increasingly acknowledging the challenge of meeting the demand for a healthy diet rather than just calories in the foods. We need to congratulate the FAO, because the total supply of calories to the world has been always greater than it needs. Despite adequate food available in the world, undernutrition as well as problems related to overnutrition are still common, owing to the poor quality of foods and diets. An increased awareness of consumers about the health benefits of foods and their nutritional benefits for potential disease prevention and health enhancement is the driving force of the global functional food and nutraceutical market. Functional foods are nutrient-rich foods that can influence some physiological mechanisms of the body, providing health benefits beyond energy content. The qualities of healthy foods and diets are given in Table 2.1.

If, and only if, the above characteristics and qualities of foods and diets are given sufficient consideration, we will be able to provide enough high-quality foods to meet the health agenda of the WHO and the International College of Nutrition. The FAO is recommending increased intake of fruits, vegetables, whole grains, and nuts with greater dietary

TABLE 2.1 Nutritional characteristics and quality of foods and diets.

Characteristics	Functional food and diets	Unhealthy food and diets
Nutrient density	High in micronutrients	Lower in micronutrients, high energy
Food diversity	Variety of foods	Lower number of foods and nutrients
Salt	Lower in salt	High in salt
Sugar	Lower in sugar	High in sugar
Refining, preserving, and processing	Least processing.	Higher refining, preserving, and processing
Fat and saturated fat	Lower fat	High fat
Trans fat	No trans fat	Excess of trans fat
Peroxidation	Lower	Higher
Probiotics	High in probiotics	No or least probiotics
Fiber content	High in dietary fiber	Low in fiber
Glycemic index	Low glycemic index	High glycemic index
Pesticides use in preservation	No pesticides	Pesticides present

diversity to tackle the need for food diversity [1−3]. The future of the functional food market looks bright; the worldwide revenue for functional foods is projected to increase from about 300 billion U.S. dollars (US$) in 2017 to over 440 billion US$ in 2022. At present, there is no universally accepted definition of functional foods. But according to the International Food Information Council (IFIC), functional foods are "foods or food components that may provide benefits beyond basic nutrition." The popular product types worldwide include vitamins, minerals, dietary supplements, functional beverages such as sport and energy drinks, and products fortified with probiotics. There is a need to stop the use of pesticides to prevent the growth of fungus and to preserve the foods by determining their functional roles and use of flavonoids present in the plants.

Some studies, including several European Commission-funded projects, have led to the understanding of the potential mechanisms of biologically active components in food, which could improve health and probably reduce the risk of diseases while enhancing our overall well-being. Functional foods and nutraceutical products are helping to improve health, reducing the health care costs, and supporting the economic development in rural areas. Growing demand for functional foods is also helping the producers to diversify their agriculture and marine-based crops and promoting research and innovation [1−5]. There is growing demand for functional foods, especially in developed economies, owing to increasing awareness toward health benefits of functional foods and an increase in disposable income.

Nutraceuticals

Nutraceuticals are organically active phytochemicals that have medical advantages. These might be conveyed in dietary supplements or potentially in functional foods or drugs [6]. These items are probably going to assume a fundamental part in human health and lifespan [6,7]. The utilization of these items by the majority of the public is without a medical prescription or supervision. Nutraceuticals are food supplements that are helpful in treating and preventing disease [6]. Nutraceuticals may also be fortified food products that are used to provide medical benefits. Nutraceutical foods are specially designed and formulated for nutrition and dietary management of disease. They have distinctive nutritional value in comparison to normal foods.

According to a 2020 report, the global nutraceutical market size is projected to reach 722.49 billion US$ by 2027, expanding at a compound annual growth rate (CAGR) of 8.3% over the forecast period 2030 [6]. The increased demand for nutraceuticals will have a substantial impact on the industry's growth. Increasing awareness of the importance of calorie reduction for management of weight in most countries, including the United States, China, and India, is expected to promote the application of nutraceuticals for health care. The demand for nutraceuticals is increasing at the global level as the result of increased awareness of their use for improving the cognitive behavior as well as digestive and immune systems of consumers. The demand for dietary nutraceuticals shows a growing trend among consumers to alter dietary habits, which is also likely to boost the demand for nutraceuticals. The consumer belief that improper diet results in illness with increased costs of pharmaceuticals is also considered to boost the demand for nutraceuticals. It is also possible that it would help governments, as it would result in lower expenditure on health care and low social security costs. However, it should be noted that long-term use of calcium as an inorganic salt to treat bone and joint problems and also possibly as a supplement to tackle calcium deficiency has been found to lead to more calcium deposits in the vascular system of the heart and the brain [7]. Low exposure to sunlight exposure, for example, among housebound older people, individuals who wear veiled, those with dark skin living at higher latitudes, and those who live and work in closed air-conditioned rooms, often leads to vitamin D deficiency. It is reversible with 400−800 IU of calciferol per day. Supplementation of calcium produces a 1% increase in bone density in the first year of use without further increases subsequently. There has not been any benefit in terms of bone density in clinical trials with vitamin D except in analyses of subgroups with baseline levels of 25-hydroxyvitamin D at less than 30 nmol/L. Most experts agree that increased supplementation with calcium, vitamin D, or their combination does not prevent fractures. However, a large study in vitamin D-deficient nursing home residents reported the prevention of fractures by supplementation [7]. Correction of severe vitamin D deficiency (<25 nmol/L) is an important step before the use of potent antiresorptive drugs to avoid hypocalcemia. Calcium supplements cause gastrointestinal side effects, particularly constipation, and increase the risk of kidney stones and probably heart attacks by about 20%. Low-dose vitamin D is safe, but doses greater than 4000 IU/day have been associated with more falls and fractures. Unfortunately, many experts do not agree, currently, to support the use of either calcium or vitamin D supplements in healthy community-dwelling adults [7]. Iron, iodine, folic acid, B vitamins, calcium, vitamin D, zinc, magnesium, selenium, coenzyme Q10, and some of the flavonoids (resveratrol, cocoa flavanol) are the most commonly used nutraceuticals in most countries of the world. Many essential amino acids, such as taurine, cysteine, and arginine, as well as L-carnitine and fatty acids, omega-3 fatty acids [fish oil, alpha-linolenic acid (ALA)], arachidonic acid, gamma-linolenic acid, and dihomo-gamma-linolenic acids

as well as probiotics are also used as nutraceuticals in many parts of the world [6,7]. Many experts suggest that spices, condiments and herbs with medicinal value, such as fenugreek, cinnamon, garlic, brown rice, and red rice, that are rich in flavonoids and other therapeutic contents should also be considered nutraceuticals [6,7].

Increases in income and consumer awareness of health issues and rapid urbanization are likely to boost growth of the nutraceutical market in the coming years. A positive outlook toward health and nutrition on account of the rapid emergence of obesity, along with cardiovascular diseases (CVDs) and neurodegenerative diseases, is anticipated to enhance the demand for nutraceuticals. The increase in awareness and evolution of diets that are rich in wellness-focused functional food, such as the ketogenic diet and the Paleolithic, Mediterranean, and Indo-Mediterranean-style diets, are driving food producers to manufacture products to appeal to these consumers. Many products that contain functional foods, such as cocoa products, probiotics, and omega-3 fatty acids, are commonly used in yogurt to reduce the risk of NCDs and develop the quality of intestinal microflora. Use of whole grains and nuts and use of cocoa are among extraordinary efforts by manufacturers to promote population health. These efforts may be projected to fuel the market growth of nutraceutical products further over the coming years [6,7]. However, many food and nutraceutical manufacturers are not giving much consideration to excess use of sugar, salt, saturated fat, trans fat, and pesticides to make foods more stable but unhealthy.

Peroxidation of foods during processing, storage and heating

Lipid oxidation has long been recognized as a major problem during the storage of fatty acids in foods. Oxidation of foods is a major cause of deterioration in the quality of food and food products [8,9]. Oxidation can occur in triglycerides, phospholipids, and unsaturated fatty acids of food, because lipids are divided into two main classes: polar lipids (phospholipids) and neutral lipids (triglycerides) [9]. In ancient and traditional cultures, it is forbidden to advise that such foods be given to pregnant women for fear of ill effects on the fetus. Oxidation of foods occurs during food processing, food storage, and cooking of foods. It occurs by several molecular mechanisms, such as generation of reactive oxygen precursors and free radicals [9]. Several experiments in which oxidized vegetable oils were administered to animals showed that these oils can damage neurons, beta cells of the pancreas, and cardiovascular cells. The mechanisms of these complications are oxidative stress and inflammation, which may increase the risk of degenerative diseases of brain, diabetes mellitus, and CVDs [10–12]. If these results hold true in humans, regularly eating oxidized oils and other foods could be a threat to our health [10–12]. Oxidation causes many interactions among food constituents, leading to both desirable and undesirable products. Food lipids are the foods components that are most susceptible to oxidation; therefore oxidation reactions are one of the major sources of deterioration that occurs during the manufacturing, storage, distribution, and final preparation of foods [8,9]. It has been observed that lipid oxidation products are omnipresent in foods, although much variation exists in the kinds and levels present. Despite low levels of these compounds, the problem of lipid oxidation severely compromises the quality of some food products and limits the shelf life of others. Oxidative changes can cause rancidity, which may be experienced as off flavors, loss of color, and altered nutrient value, and may produce toxic compounds, which can be detrimental to the health of consumers [8,9,13,14].

The food industry is using excessive amounts of saturated fat and trans fat to increase the stability of foods, which may have adverse effects on health. However, antioxidants and chelating agents are the most helpful inhibitors of lipid oxidation that are considered safe. In nature, most oils are rich in tocopherols, and some oils—olive oil, palm oil, and rice bran oil—are rich in flavonoids and polyphenolics and remain stable for longer periods [8,9,13]. In India, clarified butter has been used as a stable fat for cooking because of its stability, which may be on account of high content of stearic acid, which has potential antioxidant activity [13]. In a recent large cohort study, frequent consumption of fried foods, especially fried chicken and fried fish and/or shellfish, was associated with a higher risk of all-cause and cardiovascular mortality [14]. The effects can vary from one country to another; in Mediterranean countries, fried foods are consumed at home as frequently as away from home, with pan frying and deep frying commonly used. However, the types of oil used for frying in Spain are olive oil and sunflower oil, which may partially explain the differences observed between subjects in the United States and those in Spain [14]. In studies conducted in Mediterranean countries, olive oil consumption was associated with a decreased risk of overall and cardiovascular mortality [14]. It is clear that there is a need to examine the associations between fried foods and mortality in different settings because the results of studies from one setting are not necessarily applicable to another. No previous study has examined the association of fried food intake with risk of death due to cancer. Despite the scarcity in evidence, there is a need to find agents that can be used to prevent lipid oxidation that occurs during the cooking, processing, and storage of foods [15].

Most of the processed foods that are available in the market are popular, but their consumption may have adverse effects, although the market is expected to grow globally [16]. Food manufacturing involves food processing, which

may be associated with lipid oxidation in foods due to the presence of polyunsaturated fatty acids and cholesterol [8,9]. All of the food manufacturing/processing techniques can promote lipid oxidation in meats and meat products, grains, dairy products, and fats as well as oils. As was described earlier, there is a link between dietary oxidized lipid consumption and risk of CVDs, which prompts us to emphasize the underlying mechanisms of nutrient peroxidation [14].

Mechanisms of oxidation and peroxidation of foods

Enzymic browning is commonly observed in fruits and vegetables. This is an oxidation reaction, due to oxygen in the air, that takes place in some foods and nonfood items and is known to cause brown color in sliced fruits [8,9]. High temperatures tend to cause a high degree of lipid oxidation and nutrient loss; hence foods are stored in coolers and refrigerators to prevent oxidation [10]. In one study, food storage was found to have a significant influence on the contents of lipids, proteins, total sugars, and moisture in peanuts but did not influence the ash content [11]. The fatty acid and amino acid compositions appear to change significantly during storage, owing to variations in temperatures.

In view of these findings, several steps may be taken to prevent oxidation in specific foods and to elucidate possible methods and mechanisms of inhibition of adverse effects [8−14]. There should be standardization and development of a set of analytical procedures for evaluating the level of lipid oxidation in foods, to reduce the level of oxidation, and to isolate oxidized lipids in individual foods under conditions that protect them from breakdown of the unstable products and formation of new products. There is an urgent need to study methods to identify the oxidation products from lipids, the lipid extraction, and analysis of the synergistic effects of peroxidizing lipids and adjoining food constituents. Identification and investigation of the content of antioxidants present in foods may also help the food industry to prevent oxidation of foods. The majority of muscle foods, such as precooked, restructured meat products and even fresh meat, are highly prone to lipid oxidation, which is characterized by discoloration, drip losses, off flavor, and loss of vitamins and essential fatty acids with increased generation of toxic products [15−20].

Frying can make foods more palatable as a result of better texture, aroma, and flavor, which may lead to excess energy intake [10]. However, frying deteriorates oils through the process of oxidation and hydrogenation, leading to a loss of unsaturated fatty acids such as linoleic acid and ALA and an increase in the corresponding trans fatty acids such as trans linoleic acid [15−19]. A systemic review, including cohort studies, indicated that increased consumption of trans unsaturated and saturated fatty acids can increase the risk of all-cause mortality, CVDs, and type 2 diabetes [19]. Another possibility is the higher levels of dietary advanced glycation end products as a result of frying [21,22], which could have an important role in the development of CVDs, mainly through induction of oxidative stress and inflammation [23−25].

Previous studies have shown that higher levels of dietary advanced glycation end products were associated with a higher risk of all-cause and CVD mortality [26,27]. Moreover, frying at a high temperature can lead to acrylamide formation in some foods, such as French fries and potato chips. Dietary acrylamide has been associated with a higher risk of all-cause, CVD, and cancer mortality [14,25,28]. One possible explanation for the lack of association between fried foods and cancer mortality in some of the studies could be that the dietary intake of acrylamide from fried foods might not be high enough to have an effect on cancer mortality; it could also be because of the different types of cancers. More research is needed to examine the associations between fried foods and cancers at different sites in the body. Apart from this, repeated use of cooking fat may inhibit the activity of paraoxonase, an enzyme that inhibits the activity of low density lipoprotein cholesterol [30] which is involved in the pathogenesis of atherosclerosis [30]. Some fried foods, such as fried chicken or fried fish, could be ultraprocessed foods that are usually high in added sodium, which also partially contributes to the higher risk of mortality related to these foods [31]. It is possible that total potato consumption may not be related to risk for many chronic diseases but could pose a small increase in risk for diabetes if the potatoes are eaten after being boiled [32]. There was a clear connection between consumption of French fries and risk of hypertension and diabetes mellitus. The impact of different preparation procedures could not be assessed in this study [32]. In a metaanalysis of 410,701 participants included in this analysis, 76,921 persons died during the 15.6 years of follow-up [33]. Intake of baked, boiled, or mashed potatoes, French fries, or potato salad seven or more times per week was associated with a higher risk of overall mortality in models adjusted only for age and sex ($HR_{C4vsC1} = 1.17$). However, the results were attenuated in fully adjusted models ($HR_{C4vsC1} = 1.02$). Potato consumption was not associated with risk of mortality caused by cancer ($HR_{C4vsC1} = 1.04$), heart disease ($HR_{C4vsC1} = 1.00$), respiratory disease ($HR_{C4vsC1} = 1.16$), or diabetes ($HR_{C4vsC1} = 0.91$). The only statistically significant association was that between French fry consumption and cancer-related mortality ($HR_{C4vsC1} = 1.27$), a finding for which uncontrolled confounding could not be ruled out. It seems that there is only a little evidence (possibly due to acrylamide in French fries), indicating that potato consumption is associated with all-cause or cause-specific mortality [14,33,34]. A food analysis study has demonstrated high levels of 4-hydroxynonenal, a toxic aldehyde, in French fries from fast-food restaurants [34].

Prevention of peroxidation of foods

As was mentioned earlier in the chapter, oxidation of foods occurs by several molecular mechanisms characterized by the generation of reactive oxygen species and free radicals. Lipid peroxidation is the oxidative degradation of lipids, in which free radicals "steal" electrons from the lipids, resulting in damage. Oxidation of lipids is the major cause of deterioration in the quality of foods and products made from foods [8,10–12]. Oxidation has been long been recognized as a major problem in the storage of fatty acids in foods. Oxidation of food products may be minimized by removing prooxidants such as metals, free fatty acids, and oxidized compounds and by protecting foods from light. Evacuation of air by reduction of pressure or adding oxygen scavengers can also decrease oxidation.

Natural or synthetic antioxidants, metal chelating agents, physical conditions, vacuum packaging, and encapsulation techniques can be used to minimize the adverse effects of oxidation. However, the role of synthetic antioxidants is quite debatable, owing to certain risks to human health. Milk proteins and their bioactive peptides are natural molecules that offer a promising potential for the meat industry. A variety of milk proteins and peptides, such as caseinates, skim milk, milk coprecipitates, and whey proteins, are used to prevent lipid oxidation in meat products either in the form of added ingredients or as edible coatings [15]. There are several ingredients, such as tocopherol, tocotrienols, oryzanol, stearic acid, butylated hydroxytoluene, and oxidized products from antioxidants such as tocopherol quinone or free radical inhibitors, for which guidelines should be developed. Apart from the prevention of lipid oxidation, these molecules also provide nutritional benefits and improve the technological processing and shelf life of meat and meat products. These novel food technologies that limit food lipid oxidation should be introduced to the marketplace, but there is a need to conduct clinical trials to establish their role in human health.

Further research is warranted to develop preventive methods by fully understanding the mechanisms for the associations of fried foods with all-cause and CVD mortality. These studies could compare the same foods fried with different types of frying oils, fried with the same oil at different temperatures, or cooked by using different methods, such as grilling, slow heating at low temperature for a long time, and steam cooking. These comparisons may help in determining the role of type of oils, with or without polyphenolics, the extent of oil degradation, and the changes in the food itself in the associations of fried foods with all-cause and CVD mortality. It may be important to explore the associations of fried foods with different cancer types to better understand the associations between fried foods and cancer by in vitro experiments with cancer-producing endothelial cell linings.

Since probiotics are considered important nutraceuticals or functional food products, these are projected to expand at a CAGR of 10.1% over the forecast period. This estimate is due to the increasing use of probiotics as a primary ingredient by most food-manufacturing companies to provide better nourishment and prevent diseases caused by harmful bacteria. Antioxidants, vitamins, and minerals together accounted for over 40.71% market share in 2019, owing to the high interest of consumers in the relationship between diet and health, which, in turn, has increased demand for these products. Vitamins have also emerged as dietary supplements, accounting for the largest segment in 2019, and they are expected to expand at a CAGR of 5.8% in the coming years. However, in terms of product, functional food accounted for the largest share in 2019 and generated revenue of 187.51 billion US$. Increases in the cost of health care, coupled with the growing geriatric population around the world, are expected to drive the functional food segment over the forecast period. The Asia-Pacific region is expected to witness the fastest growth, owing to its greater population and increased awareness of functional foods over the forecast period. In addition, aggressive marketing and expansion of the retail chain in countries such as India, Japan, and China have increased the consumption of dietary supplements and functional foods in this region.

Recent advancements in food technology, plant breeding, and genetic engineering have provided various regions of the world with adequate foods, resulting in a decrease in undernutrition and increases in obesity and NCDs. Since functional foods and nutraceuticals can reduce these problems, there is a need to produce more functional foods and to ensure that they are used more efficiently and equitably in a multifaceted and linked global strategy for sustainable and equitable functional food security for the world population. Since data on functional food availability and functional food consumption are not available for all the countries, it is difficult to assess what quantities of functional foods will be needed for health promotion and diseases prevention by the year 2050. It may be possible to make some estimates from U.S. functional food statistics [35].

Estimates of food production for the global population

The FAO reported that the world population is projected to grow by 34% from 6.8 billion today to 9.1 billion in 2050. It is difficult to estimate the availability and cost of functional food and nutraceuticals because of these variable

population estimates. However, it is clear that the future of functional food production by the farmers and the food industry looks bright. The IFIC defines functional foods as "foods or food components that may provide benefits beyond basic nutrition." These foods include foods that are rich in vitamins, dietary supplements, foods used in sport and energy drinks, and food products fortified with probiotics [35]. By this definition, the worldwide revenue for functional food in 2017 was 300 billion US$. It is projected to increase to over 440 billion US$ in 2022 [35]. The global functional foods market size is projected to reach 275.77 billion US$ by 2025, according to a new report by Grand View Research, Inc. It is anticipated to expand at a CAGR of 7.9% during the forecast period.

In the future, rapid economic development is likely to cause a rapid dietary transition toward higher consumption of refined manufactured foods, meat, fruits, and vegetables relative to that of cereals, requiring commensurate shifts in output and adding pressure on natural resources [36]. However, owing to their benefits and the increasing importance of a healthy lifestyle, functional food products may become a part of consumers' everyday lives in all the countries of the world [35–37], resulting in an increasing market share. The functional food ingredients market is estimated to be valued at 68.60 billion US$ in 2018 and is projected to reach 94.21 billion US$ by 2023, at a CAGR of 6.6% [38]. The revenue of the functional foods market in 2019 was 174.75 billion US$. In the United States the nutraceutical functional foods market is 250 billion US$, while the drug market is 150 billion US$. Each year, about 1000 new products are coming onto the market, and about 29,000 dietary supplements are available in the United States. The Asia-Pacific region accounted for over 45% of the global market in 2017 and is expected to maintain its lead position over the forecast period. Increasing urbanization and the rising geriatric population in countries such as India and China are expected to aid the regional growth. The worldwide market for functional foods is expected to grow at a CAGR of roughly 20% over the next five years, will reach 153,600 million US$ in 2023, from 153,600 million US$ in 2017, according to a new study [39]. This report focuses on the functional foods in the global market, especially in North America, Europe, and Asia-Pacific, South America, the Middle East, and Africa. This report categorizes the market based on manufacturers, regions, type, and application [39].

Estimates of total functional foods available for consumption

There is no agreement on the exact definition of functional foods; hence the exact quantities of functional foods available in the world are not known. Fruits, vegetables, legumes, nuts, spices, olive oil, mustard oil or canola oil, and flax seed oil are common functional foods [35–39,41]. In clinical studies, these foods have been demonstrated to be useful in the management of obesity, metabolic syndrome, type 2 diabetes, and CVDs [39,41–44]. These foods are rich in essential and nonessential amino acids, omega-3 fatty acids, monounsaturated fatty acids, antioxidants, vitamins, and minerals, which are known to be protective against CVDs and other chronic diseases [39,41]. Table 2.2 lists the major nutrient contents of different foods available for consumption.

The micronutrient content of the foods can be altered by organic farming, altering soil in the general farming, plant breeding, and genetic engineering. The food industry has a particular role in developing functional foods by incorporating protective micronutrients in the food matrix [40]. There is a considerable focus on the development of value-added functional food products to combat various diseases, such as CVDs, diabetes, cancer, anemia, and other chronic diseases [40,43–45]. Overwhelming evidence from epidemiological, in vivo, in vitro, and trial data indicate that a plant-based diet can reduce the risk of chronic diseases, particularly CVDs, diabetes, and cancer. Epidemiological studies and intervention trials showed that cancer risk in people who consume diets that are high in fruits and vegetables was only one-half of that in people who consumed lower amounts of these foods [40,43–46]. In view of these studies, food consumption per person per day in grams in 10 high-population countries and the European Union reveals that the intake of such foods is increasing [39] (Table 2.3).

Estimates of functional food consumption

The increasing demand for nutritional and fortifying food additives is one of the major drivers of growth. Functional ingredients such as probiotics and omega-3 fatty acids are extensively consumed through yogurt and fish oils to reduce the instances and risks associated with CVDs while improving the quality of intestinal microflora [39–42,46,47]. The increasing trend of consuming these products is expected to be sustained throughout the forecast period, thereby favoring market growth. Another important factor augmenting demand is rising consumer awareness regarding gut health. This is in reaction to reported cases of death due to intestinal inflammation and other bowel disorders. Consumption of probiotics helps to fight bad bacteria in such cases while aiding immunity in humans, thereby enhancing gut health. Among the various available products, probiotic yogurts are the most widely consumed products with proven digestive

TABLE 2.2 Bioactive components from fruits products and their potential benefits.

S. No.	Source of functional food	Component	Potential benefit	Reference
Fruits, vegetables, and cereals				
1	Pink pumpkin	Lycopene	Anticarcinogenic activity against prostate cancer	http://foodinsight.org
2	Fruit skin	Insoluble fiber	Maintain the gastrointestinal tract, reduce colon cancer	http://foodinsight.org
3	Apples, citrus fruit	Soluble fiber	Reduce risk of cardiovascular disease	http://foodinsight.org
4	Berries, cherries, red grapes	Anthocyanins: cyanidin, delphinidin, malvidin	Cellular antioxidant, healthy brain function	http://foodinsight.org
12	Tea, cocoa, chocolate	Catechins, epicatechins	Good for heart	http://foodinsight.org
13	Red wine, peanuts, cinnamon	Procyanidins, proanthocyanidins	Maintenance of urinary tract	http://foodinsight.org
5	Citrus fruit	Flavanones: hesperetin, naringenin	Cellular antioxidant defense	http://foodinsight.org
6	Apples, pears, citrus	Caffeic acid, ferulic acid	Cellular antioxidant and maintenance eye and heart	http://foodinsight.org
	Soybeans, soy-based foods	Isoflavones: daidzein, genistein	Bone and immune health, healthy brain function; in women, support menopausal health	http://foodinsight.org
8	Guava, sweet red and green pepper, kiwi, citrus fruit, strawberries	Vitamin C	Neutralize free radicals, which may damage cells and support immune system	http://foodinsight.org
9	Citrus fruit peels (lemon and other citrus fruit)	Limonoids	Protection of lung tissue	

health claims. However, the functional food industry also has its share of challenges, which have hindered the growth of the functional foods market. These include issues associated with product availability and claims regarding insufficient nutrients derived from various functional food types.

According to a functional foods market forecast for 2020−30, functional dairy products will remain the leading submarket, which will account for 30.8% of the global market by 2030 [46]. This segment will be followed by the functional baby food submarket with a share of 21.3% and the functional bakery and cereal submarket with a share of 18.6%. The submarkets of other functional foods will grow significantly until 2030 as a result of an increasing demand for functional soups and other products that currently account for a small share of the global functional foods market. Epidemiological studies and randomized controlled intervention trials indicate that increased consumption of refined and sweetened foods and decreased intake of fruits, vegetables, fiber, and polyunsaturated fatty acids, in particular omega-3 fatty acids, are significantly associated with mortality [38−41,45,46]. In view of these studies, the WHO and World Heart Federation have reviewed the association of nutritional factors and other risk factors with mortality due to CVDs in 10 high-population countries [39] (Fig. 2.1).

TABLE 2.3 Food consumption per person per day in 10 high populous countries and the European Union (in grams).

Country	Fruits	Vegetables	Dairy products		Fish, seafood	Poultry	Vegetable oil	Spices, herbs	Tea	Coffee	Wheat	Rice	Cashew nut
			Milk	Cheese									
China	537.00	900.00	78.33	0.55	40.00	35.00	22.50	10.38	2.55	167.30	178.40	216.90	0.64
India	199.00	194.00	136.90	–	40.00	5.00	24.44	8.22	1.77	222.00	167.30	196.00	0.54
United States	613.00	358.00	316.66	42.77	20.00	142.00	85.00	2.53	1.42	52.32	222.00	20.52	4.93
Indonesia	184.00	100.00	15.55	0.28	51.00	19.50	28.05	2.97	1.02	144.10	52.32	364.38	-
Brazil	515.00	130.00	377.00	1.11	12.00	112.00	48.61	0.33	5.52	341.64	144.10	93.69	-
Pakistan	86.66	87.00	286.11	–	1.00	12.22	33.33	4.38	1.83	54.79	341.64	33.42	-
Nigeria	163.00	191.00	15.00	0.28	38.00	5.00	32.22	3.66	0.33	56.71	54.79	82.46	-
Bangladesh	64.65	58.00	51.66	–	8.00	3.88	17.22	8.50	1.11	268.76	56.71	473.97	-
Russia	620.00	288.00	344.44	0.02	43.00	64.16	36.38	0.66	3.58	113.50	268.76	13.42	1.64
Japan	140.00	291.00	129.44	7.50	134.00	53.05	43.33	3.44	1.50	300.27	113.50	118.63	-
European Union	274.00	325.00	211.11	46.11	5.00	60.27	55.83	2.08	1.61	13.33	300.27	14.24	3.15
Total	3396.31	2922.00	1962.20	98.61	392.00	512.08	426.91	47.15	22.24	52.38	1899.79	1613.39	10.90
Total/year	1,239,653.15	1,066,530	716,203	35,992.65	143,080	186,880	155,822	17,209	8117	18,980	693,135	588,745	3978

Source: Singh and Tomar et al. (2016). https://www.elsevier.com/books/the-role-of-functional-food-security-in-global-health/watson/978-0-12-813148-0.

Functional food intake and other risk factors in relation to mortality in ten high populous countries (modified from GBD Study 2015).

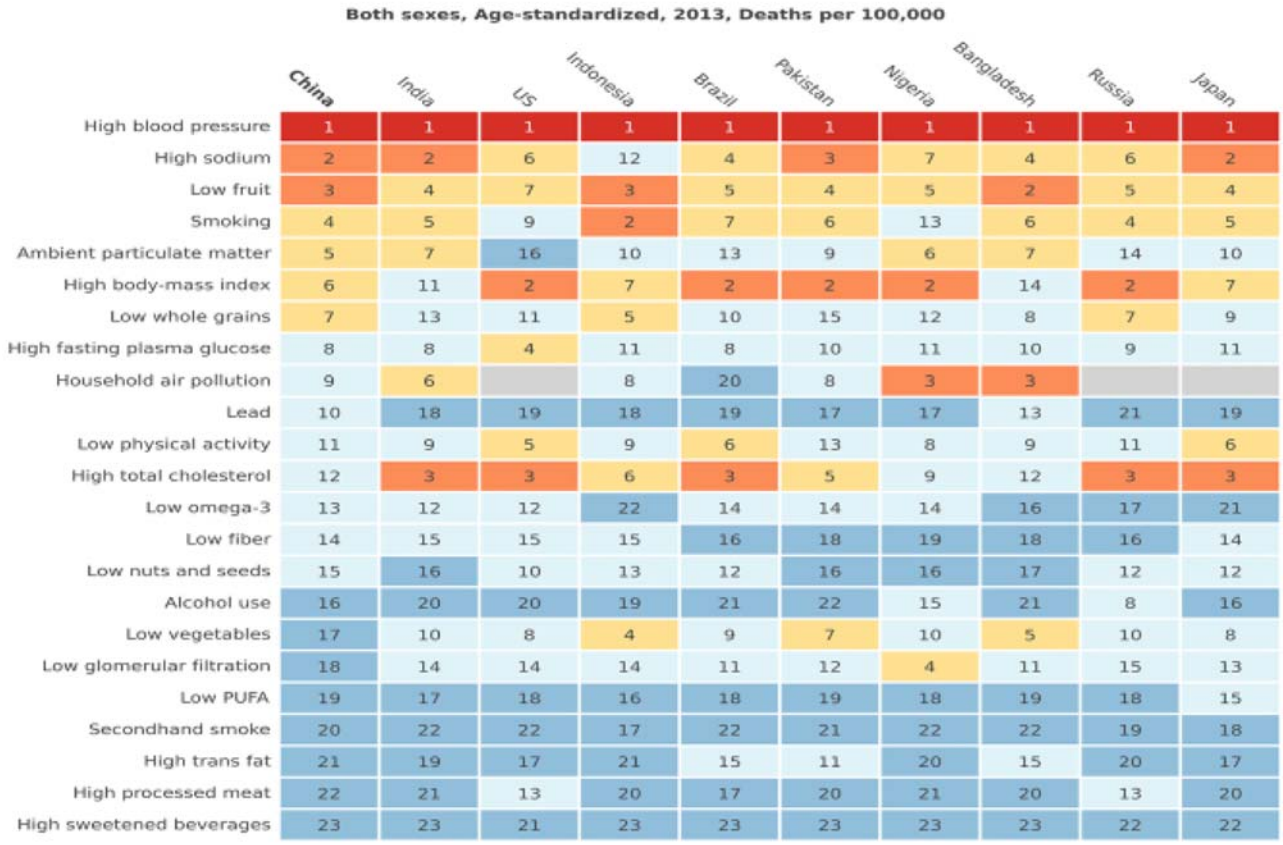


FIGURE 2.1 Functional food intake and risk of mortality in 10 high-population countries. *Modified from GBD study, reference Sacco RL, Roth GA, Reddy KS, Arnett DK, Bonita R, Gaziano TA, et al. The heart of 25 by 25: achieving the goal of reducing global and regional premature deaths from cardiovascular diseases and stroke: a modeling study from the American Heart Association and World Heart Federation. Circulation 2016;133 [published online before print May 9, 2016] doi:10.1161/CIR.0000000000000395, Lancet 2015.*

Since some foods have been found to have numerous beneficial effects on health promotion and disease prevention, some experts have proposed a functional food portfolio for health and nutrition of the South Asians [42,43]. In this portfolio, apart from different Mediterranean types of foods, millet, spices, pulses, and porridge are given special consideration, owing to the high content of flavonoids and polyphenolics in these foods. Singh's functional food portfolio for health promotion and disease prevention advocates that in the consumption of Indo-Mediterranean food, consumers have the choice of selecting vegetarian food substitutes (soybeans, pulses, cottage cheese, and yogurt) in place of animal foods (Table 2.4).

The Asia-Pacific region emerged as the largest market for functional foods in 2018, owing to a considerable rise in consumers; disposable income. The industry is also strengthened by the support offered by government bodies in various countries in this region. In this regard, to combat concerns associated with malnutrition, various government bodies have been increasingly focusing on food fortification. This development has also been influencing consumer behavior, thereby driving the regional demand for functional food products [41]. The Asia-Pacific region accounted for over 45% of the global market in 2017 and is expected to maintain its lead position over the forecast period. Increasing urbanization and a rising geriatric population in countries such as India and China is forecast to aid the regional growth. The global functional foods market was valued at 153,600 million US$ in 2018 and is expected to reach 260,400 million US $ by the end of 2025, growing at a CAGR of 6.8% during 2019−2025 [46].

The market for functional food is increasing, as consumers prefer balanced diets and food that not only takes care of their appetite but also helps to enhance their immunity. This, along with product innovations in terms of flavors and

TABLE 2.4 Singh's functional food portfolio for health promotion and disease prevention (for a vegetarian diet, replace meats and seafood with soybeans, pulses, cottage cheese, and yogurt).

Category of foods	Amount (g/day)	Functional foods	Nutrient/mechanism
Fruits	200–300	Apple, grapes, guavas, berries	Flavonoids, vitamin C
Vegetables	200–300	Green leaves, gourds	Flavonoids, carotenoids
Nuts	30–50	Walnuts, almond, peanuts	Amino acids, omega-3 fatty acids in walnut, low glycemic index, monounsaturated fatty acids
Whole grains	400–500	Gram, beans, peas, millet, soybeans, pulses, porridge	Flavonoids, amino acids, complex carbohydrates
Fish, seafood	50–100	Salmon, any oily fish (e.g., mackerel)	Omega-3 fatty acids, amino acids, selenium, CoQ10
Poultry	50–100	Hen eggs, quail, chicken, duck	Amino acids,
Curd/yogurt	100–200	Prebiotics, probiotics	Immunity, gut microbiome
Spices	10–20	Turmeric, fenugreek, cumin, coriander	Flavonoids, minerals
Miscellaneous	5–10	Cocoa, tea, coffee	Flavanols, polyphenols
Fats and oils	30–100	Olive, mustard, canola oils	Polyphenols, flavonoids, omega-3 fatty acids, monounsaturated fatty acids

variant offerings, presents significant opportunities for the growth of applications in the functional food ingredients market. Factors that are further fueling consumer interest in functional foods are the rapid advances in science and technology, increases in health care costs, aging, and growth in the interest in attaining wellness through diet.

Estimates of Food and Agriculture Organization for functional foods production

The exact quantity of functional food production and consumption have not been assessed by the FAO and the WHO, although Western dietary patterns have been demonstrated to be causative of NCDs and functional foods to be protective against them [39,42,43,45]. The FAO has estimated that in the first half of this century, global demand for food, feed, and fiber is expected to grow by 70% [44]. There will be growing pressure on already scarce agricultural resources due to demand for new and traditional agricultural produce. With rapid urbanization, agriculture will be forced to compete for land and water, and it may also be required to serve on other major fronts: adapting to and contributing to the mitigation of climate change, helping to preserve natural habitats, and maintaining biodiversity. Farmers will need new technologies to produce more from less land with fewer hands. This perspective for 2050 provides an opportunity for current public and private investments to be sufficient to ensure adequate potential for agricultural production. This approach possibly may encourage research for technological breakthroughs in sustainable use of natural resources, infrastructure for markets, information, and communication [47].

The FAO agenda for functional food production, such as for pulses and legumes, appears to promote their cultivation because these foods are considered functional foods that can substitute for wheat and corn and provide functional food security [44,47–49]. The 68th U.N. General Assembly of the FAO/UNO declared 2016 the International Year of Pulses (IYP) (A/RES/68/231) to support food security, which is in fact functional food security [47]. The sustainable development of health adopted by the global community in the 2030 agenda is not possible without adequate production of pulses and legumes as well as vegetables, nuts, and fruits [44,47]. Since the IYP in 2016 brought to the forefront the challenges faced by the sector, there is a need to emphasize the production of vegetables and nuts that have more potential to be functional foods. Such efforts may galvanize stakeholders to ensure the successful role of pulses and other functional foods in food and nutrition security, poverty alleviation, and sustainability. The main pulses are lentils, red beans, green beans, kidney beans, grams, and peas. Pulses are rich in magnesium, potassium, calcium, and other

minerals as well as in antioxidant flavonoids and essential and nonessential amino acids, apart from high carbohydrates [47,48].

Table 2.5 shows the increasing trend of fruit and vegetable production in Europe. The European Union (EU) supports the production of fruits and vegetables through the Common Market Organization for fruit and vegetables [50]. The main agenda of EU is to do the following:

1. Prepare a more competitive and market-oriented sector.
2. Enable less crisis-related instability in producers' income.
3. Promote more consumption of fruit and vegetables in the EU.
4. Increase the use of ecocompatible cultivation and production techniques.

The EU agricultural price statistics are based on voluntary agreements between EUROSTAT and the member states. Collection of absolute prices and calculating corresponding average prices for each country, as well as calculating price indices and periodically updating the weights, is the responsibility of the EU. Price indices are reported quarterly and annually and absolute prices are reported annually. The agricultural prices expressed in national currency are converted into euros by EUROSTAT using the fixed exchange rates or financial market exchange rates, in order to allow comparisons among the EU countries. EUROSTAT is responsible for calculating indices for the EU.

Increased intake of nuts and pulses has been demonstrated to protect against CVDs, diabetes mellitus, and cancer; hence it is important to know about nut production [42,43]. It is possible that the production of peanuts, walnuts, almonds, and pulses in kilotons in 10 high-population countries as well as in the EU may be optimal. The total production of peanuts (40,475 kilotons), almonds (2741.386 kilotons), walnuts (3425.834 kilotons) and pulses (72,936 kilotons) appear to be adequate in the present year, but with increases in consumption due to health professional advice, greater production would be required in these countries as well as other countries (Table 2.6).

Since mortality and morbidity data in relation to food intakes are available in the EU and the 10 high-population countries, it may be interesting to assess the food production patterns in these high-population countries as well as in the European Union. The consumption of fruits, vegetables, and nuts appears to be optimal in China, India, the United States, Brazil, Russia, Japan, and the EU countries at this stage of health education and human development [50]. However, in Indonesia, Pakistan, Bangladesh, and Nigeria the production of fruits, vegetables, and nuts appears to be lower, and more efforts are needed to increase production. Total production of fruits (650,684 tons), vegetables (1,113,768 tons), milk (759,754 tons), cheese (20,256 tons), seafood (721,930 tons), spices and herbs (2169.383 tons), tea (5034.9 tons), coffee (9209.0 tons), and cashew nuts (4354.112 tons) appears to be adequate for the year 2017 but greater production will be needed, as a result of increased consumption with health education, by the years 2025 and 2050 [44,47–49,51–54]. In general, poultry (106,014 tons), wheat (713,183 tons), and rice (745,710 tons) as such are not considered to be functional foods, but some of the products and varieties, such as porridge from wheat and brown rice, are functional foods. Similarly, eggs and chicken can be made functional by feeding flax seed and tea leaves to hens, resulting in an increase in fatty acids and flavonoids in these animal products. The data on production of total vegetable oils are not yet specifically calculated for all the high populous countries (Table 2.7). However, production of oils is known for many countries of the world, as shown in Figs. 2.2 and 2.3.

The World Largest Market Research Store in 2017 provided estimates of the costs of food and nutraceuticals [6]. The global nutraceutical market should reach $285.0 billion by 2021 from $198.7 billion in 2016 at a CAGR of 7.5% from 2016 to 2021. The functional beverages market should reach $105.5 billion by 2021 from $71.5 billion in 2016 at a CAGR of 8.1% from 2016 to 2021. The functional food market should reach $92.3 billion by 2021 from $64.6 billion in 2016 at a CAGR of 7.4% from 2016 to 2021 (Fig. 2.4) (Source: Visiongain, 2020; Report given by Research and Market).

Estimates of functional foods with reference to nutrients

The global functional foods market size was estimated at 161.49 billion US$ in 2018. It is anticipated to register a CAGR of 7.9% during the forecast period. Increasing demand for nutritional and fortifying food additives is anticipated to drive the growth. Food and beverage manufacturers are deploying fortification of nutritional additives, such as omega-3 fatty acids, fibers, vitamins, and minerals, in their product offerings [3–6]. The major motive for incorporating these additives in the food and beverage industries is to increase the nutritional content in food items [41].

Functional ingredients such as omega-3 and cocoa flavonoids and probiotics are frequently used in yogurt to reduce the risk of CVDs and to improve the quality of intestinal microflora. Such a trend is expected to fuel the market over the forecast years [6] (see Fig. 2.5).

TABLE 2.5 Fruit and vegetable production in Europe, 2015.

	Tomatoes	Carrots	Onions	Apples	Peaches	Oranges
EU-28	17,562.2	5087.3	6109.4	12,698.1	2540.0	5961.2
Belgium	253.1	245.4	108.3	284.2	0.0	0.0
Bulgaria	121.7	7.9	8.9	58.4	34.4	0.0
Czech Republic	5.6	23.5	27.2	155.4	1.6	0.0
Denmark	10.6	89.2	53.4	35.7	0.0	0.0
Germany	80.9	526.9	553.3	973.5	0.0	0.0
Estonia	0.9	18.1	0.2	1.6	0.0	0.0
Ireland	4.4	40.2	4.6	18.8	0.0	0.0
Greece	995.1	32.5	211.0	278.5	626.6	909.7
Spain	4832.7	410.9	1247.6	598.2	720.9	3098.3
France	787.9	560.0	368.7	1967.1	114.7	3.7
Croatia	36.3	10.9	29.4	96.2	3.7	0.2
Italy	6410.3	533.0	378.3	2441.6	921.2	1 668.7
Cyprus	16.1	2.3	7.0	4.9	2.3	32.8
Latvia	6.1	8.8	5.7	7.8	0.0	–
Lithuania	7.7	38.0	22.2	65.0	0.0	0.0
Luxembourg	0.1	1.0	0.1	2.4	0.0	0.0
Hungary	200.4	78.2	60.3	511.5	37.4	0.0
Malta	12.0	1.3	8.1	0.0	0.7	1.2
Netherlands	890.0	563.4	1504.1	335.9	0.0	0.0
Austria	55.7	66.8	168.1	287.6	2.9	0.0
Poland	789.6	677.7	548.4	3 168.8	9.9	0.0
Portugal	1407.0	97.5	59.4	325.0	35.6	246.6
Romania	464.8	122.1	218.2	459.1	20.5	0.0
Slovenia	5.7	3.4	7.2	83.9	5.6	0.0
Slovakia	19.5	10.1	16.9	46.3	2.1	–
Finland	36.5	72.0	20.2	6.0	0.0	0.0
Sweden	14.8	115.6	64.6	25.4	0.0	0.0
United Kingdom	97.2	731.0	408.1	459.6	0.0	0.0
Iceland	0.1	0.6	0.0	0.0	0.0	0.0
Switzerland	45.7	71.6	41.2	141.7	0.0	0.0
Montenegro	2.7	0.0	1.0	2.8	0.0	0.0
FYR of Macedonia	173.4	4.3	59.5	136.9	12.0	–
Albania	256.5	6.9	90.5	91.8	–	8.4
Turkey	12.615.0	535.0	2021.0	2570.0	561.0	1817.0
Bosnia and Herzegovina	41.2	17.1	37.7	91.5	9.2	0.0

Source: Modified from <http://ec.europa.eu/eurostat/statistics-explained/index.php/agricultural-crops#vegetables>.

TABLE 2.6 Production of nuts and pulses (in kilotons).

Country	Peanuts	Almonds	Walnuts	Pulses
Bangladesh	51.9	–	–	240
Brazil	334	–	5.817	2804
China	16,800	44.178	1700	4528
India	4695	1.400	40.000	16,704
Indonesia	1251	–	–	286
Japan	17.3	–	–	87.2
Nigeria	3071	–	–	2560
Pakistan	71.4	21.649	11.500	603
Russia	–	–	2.250	2220
European Union	8.40	–	177.663	3246
United States	3,058	1545.500	425.820	2358
Total	40,475	2741.386	3425.834	72,936

Source: From <https://ec.europa.eu/eurostat/statistics-explained/index.php?title = Agricultural-cropes#vegetables>.

A 2019 Grand View Research report suggests various findings for functional food [41]:

- In terms of ingredients, vitamins emerged as the largest segment in 2018, registering a revenue of 36.16 billion US $. The segment is expected to expand at a CAGR of 7.7% over the forecast period.
- In terms of product, soy is expected to register the fastest CAGR over the forecast period. The growing popularity of products such as milk drinks, spreads, and yogurts across the globe has contributed significantly to the growth of this segment.
- In terms of application, cardiovascular health emerged as the largest segment in 2018 and is expected to maintain its pole position over the forecast period. High prevalence of CVDs and reported cases of deaths pertaining to the same have increased the application of functional food products in this segment.
- The Asia-Pacific region is expected to witness the fastest growth over the forecast period. Led by countries such as China, India, and Japan, the functional foods market is driven by various government initiatives to promote healthy lifestyles.
- The market represents a highly competitive landscape with a sizable number of players sharing the market space. The key players have been focusing on global expansion while strengthening their positions in domestic markets.

According to different stakeholders, the total demand for food and feed will grow more slowly, so satisfying the expected demand for food and feed will require a substantial growth in food production of 70% by 2050, involving an additional quantity of nearly 1 billion tons of cereals and 200 million tons of meat [48,50–55]. It is important at this stage of planning to include more legumes and millets in the estimates for cereals and white meat in place of red meat. The most commonly available functional foods are vegetables, fruits, nuts, whole grains (legumes and millet), white meats (chicken, eggs, fish, and other seafood), yogurt, vegetable oils (canola oil, rapeseed oil, and olive oil), spices, cocoa, tea, and coffee. Red and white meat and eggs from hens that have been fed flax seeds (omega-3 fatty acids) and tea leaves (flavonoids) are also made functional by the food industry. The production of functional foods such as dietary fiber, vitamins and minerals, carotenoids, fatty acids, probiotics, and other miscellaneous foods is expected to increase twofold in 2025 compared to 2014. However, this may be insufficient to meet the demand.

Estimates of functional food production in India

According to the Assocham Knowledge Report of 2018, the Indian nutraceuticals market is expected to grow from $4 billion in 2017 to $18 billion in 2025, representing a growth of 21% CAGR [48]. India has not yet developed expertise in food processing and food preservation by maintaining the functional food status of the foods. In India a report from

TABLE 2.7 Food production in 10 high-population countries and the European Union (in kilotons).

Country	Fruits	Vegetables	Dairy products	Total seafood	Poultry	Vegetable oil	Spices, herbs	Tea	Coffee	Wheat	Rice	Cashew Nuts	
			Milk	Cheese									
China	148,945	570,523	42,749	278	65,201	18,039		99.402	1804.6	92.0	1,21,727	205,015	0.750
India	75,491	114,344	1,32,431	1.50	10,078	2309		1504	1135	314	93,510	159,200	725
United States	26,499	36,144	90,865	5009	5465	19,944		–	–	3.270	57967	8613	–
Indonesia	17,881	10,465	1365	44.6	10,828	1768		5.726	143.4	691.163	–	71280	116.915
Brazil	38,441	11,055	32,454	–	1275	12,101		–	1.496	3037.0	5718	11,759	80.630
Pakistan	6026	5071	37,861	–	600	839		74.737	–	–	24,231	9800	–
Nigeria	11,055	12,809	566	8.76	1027	155		6.366	–	3.00	80	4700	900
Bangladesh	3607	4123	3519	1.00	3684	216		155	60.0	–	–	51,500	–
Russia	2920	15,680	1750	609	4608	3285		–	0.09	–	52,091	935	–
Japan	3035	11,413	7630	124	4164	1443		–	85.9	–	812	10,758	–
European Union	54,936	64,421	1,55,533	9058	615,000	13,092		–	0.136	–	143,333	2787	–
Total	650,684	1,113,768	759,754	20,256	721,930	106,014	495,170	2169.383	5034.9	9209.0	713,183	745,710	4354.112

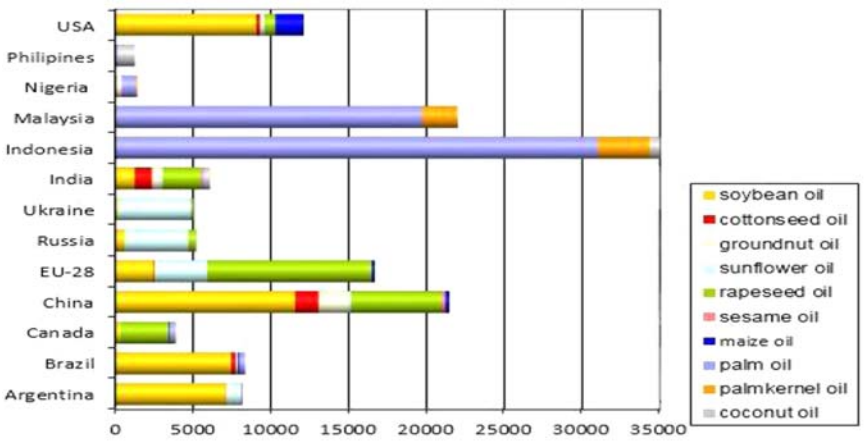


FIGURE 2.2 Vegetable oil production in developing and developed countries. *Modified from <http://fediol.post-site.com/web/world%20production%20data/1011306087/list1187970075/f1.html>.*

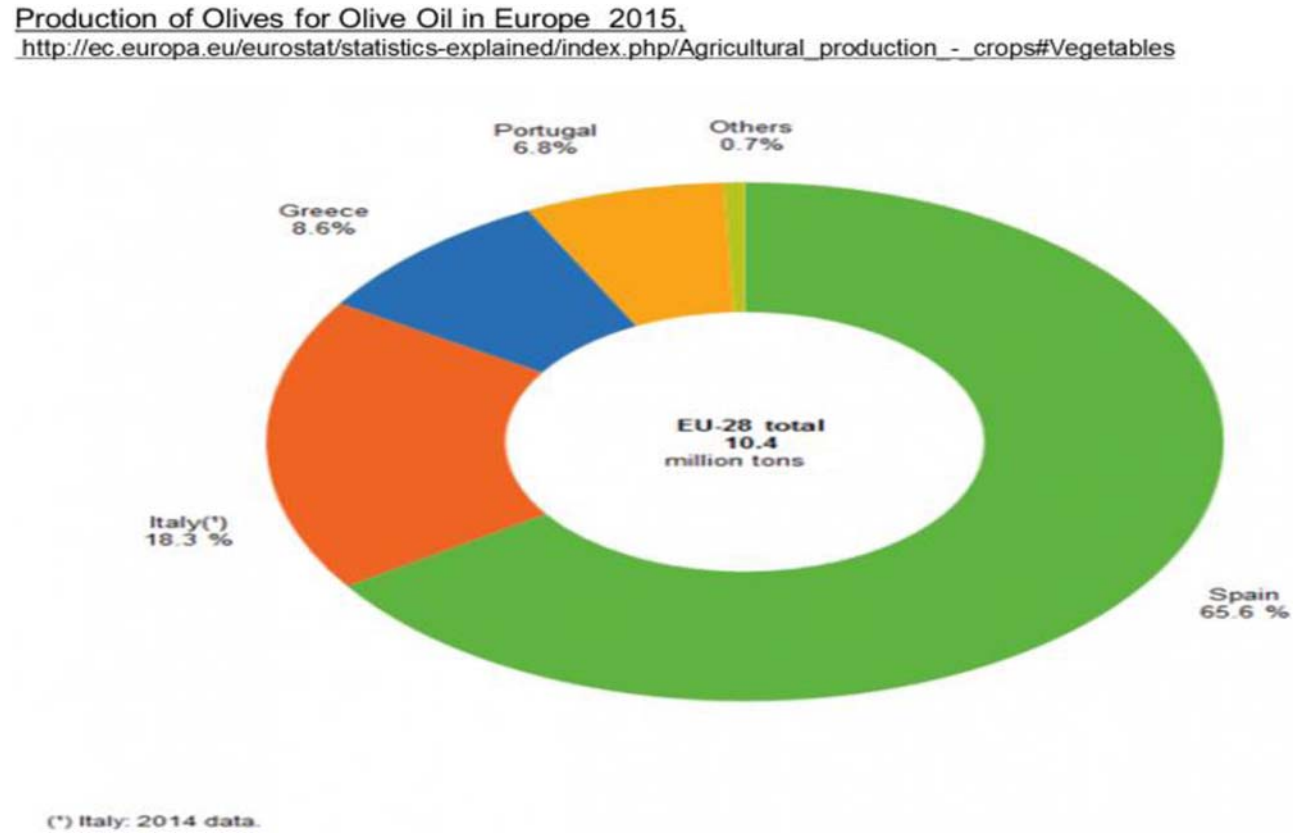


FIGURE 2.3 Olive fruit production in Europe in 2015. *Modified from <http://www.ec.europe.eu 2015>.*

the Second Advance Estimates of Production of Food grains, Oilseeds and other Commercial Crops for 2019−20 projected that production of most of the crops for agriculture year 2019−20 would be estimated higher than their normal production [53,54]. Total horticulture production in 2019−20 is expected to be 313.35 million tons (mt), about 0.84% higher than 2018−19, according to first advance estimates. As per the final estimates, the total horticulture production of the country in 2018−19 was estimated to be 310.74 mt, only marginally higher than the previous year. Vegetable production was estimated to be around 183.17 mt, while fruit production was estimated to be around 97.97 mt.

The production of vegetables, aromatics and medicinal plants, and plantation crops is expected to increase, while production of fruits, flowers, and spices is expected to decrease. Fruit production is expected to decrease by 2.27% in

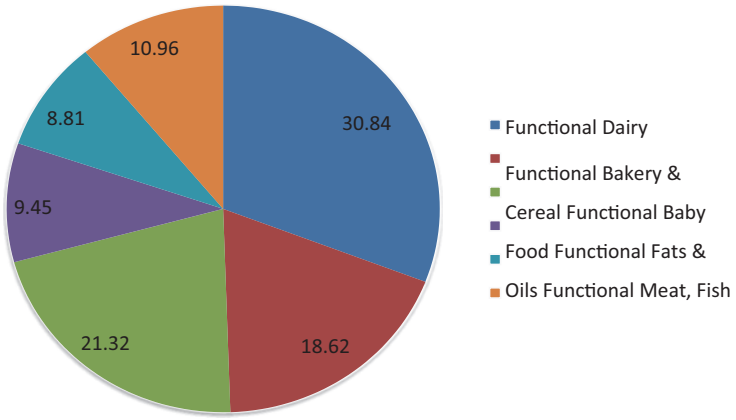


FIGURE 2.4 Leading functional food submarkets share forecast, 2030. *From Visiongain (2020).*

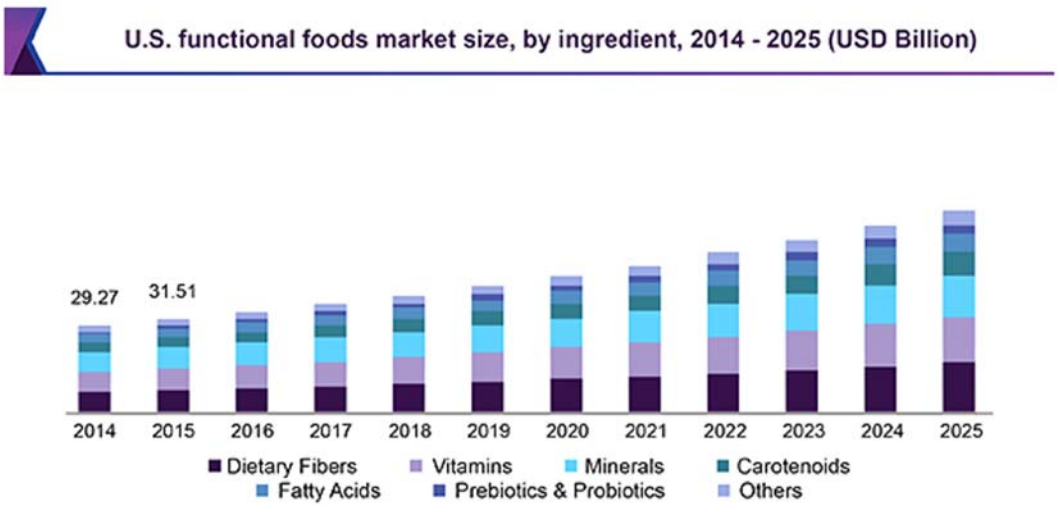


FIGURE 2.5 U.S. functional foods market. *From <http://www.grandviewresearch.com>.*

2019−20 in comparison to 2018−19. This decrease is mainly due to loss in production of grapes, bananas, mangos, citrus fruits, papayas, and pomegranates. Vegetable production is likely to increase by 2.64% in 2019−20 over 2018−19, owing to increased production of onions, potatoes, and tomatoes. Tomato production is expected to be 19.33 million tons as compared to 19.01 million tons in 2018−19. Onion production is expected to be 24.45 million tons as compared to 22.82 million tons in 2018−19, potato production is expected to be 51.94 million tons as compared to 50.19 million tons in 2018−19 [53]. Vegetables production, on the other hand, is projected to be higher by 2.64%. Onion production is expected to be 24.45 mt (increase of 7.17%) compared to 22.82 mt in 2018−19. Potato production is expected to be 51.94 mt, an increase of 3.49%. It was 50.19 mt in 2018−19. Tomato production is expected to be 19.33 mt (increase of 1.68%) compared to 19.01 mt in 2018−19.

Production of vegetables is estimated to be around 169 mt, which is about 1.5% higher than the previous year. Production of spices is estimated to be around 7 mt, which is 14% higher than the previous year. Production of onions is estimated to be around 209 lakh tons (1 lakh ton = 100,000 tons), which is 11% higher than the previous year. Production of potatoes is estimated to be around 434 lakh tons, which is 10% lower than the previous year. Production of tomatoes is estimated to be around 187 lakh tons, which is about 15% higher than the previous year. Production of fruits is estimated to be 90 mt, which is 1% higher than the previous year.

In the year 2015−16 total horticulture production of India was estimated to be around 286 mt, which is 2% higher than the previous year [42]. The horticulture production of India during 2016−17 is estimated to be around 287 mt, which is marginally higher than that in 2015−16. Total horticulture production in 2019−20 (1st Advance Estimates) is expected to be 0.84% higher than that in 2018−19. An increase in vegetables, aromatics, medicinal plants, and plantation crops is envisaged, but a decrease in fruits, flowers, and spices is expected. In 2019−20, fruit production is

expected to be lower by 2.27% in 2019−20 over 2018−19. This is mainly due to loss in production of grapes, bananas, mangos, citrus fruit, papayas, and pomegranates.

Recent data from the Global Burden of Disease study indicate that the world population will decline to 8.79 billion, by 2100 (see Fig. 2.6) [56]. The results indicate that continued trends in the attainment of female education and access to contraceptives may cause rapid declines in fertility and slow population growth [56]. A sustained total fertility rate lower than the replacement level in many countries, such as Japan, Northern Europe including Central and Eastern Europe, China, and India, will have economic, social, environmental, and geopolitical consequences. There is an unmet need to alter the options for policy to adapt to continued low fertility. More emphasis should be given to providing support to female motivation and fertility, which will be crucial in the next few decades. A decline in population may be associated with a reduction in demand for functional foods and a decrease in environmental degradation, which are necessary for sustainable development goals of the United Nations.

In brief, total food production in the year 2016 was 1.3 billion tons, which is gradually increasing with increase in demand. It is difficult to estimate the total amounts of functional foods available in the world for human consumption. Commonly available functional foods are vegetables, fruits, nuts, whole grains (legumes and millet), white meats (chicken, eggs, fish, and other seafoods), yogurt, vegetable oils (canola oil/rapeseed oil, and olive oil), spices, cocoa, tea, and coffee. Some foods, such as red and white meat and eggs from animals, can be made functional after feeding flax seeds (omega-3 fatty acids) and tea leaves (flavonoids) to the mothers by the food industry. The production of nutraceuticals—antioxidants and polyphenolics, vitamins, minerals, essential amino acids and fatty acids, probiotics, and cocoa products—is rapidly increasing. Among nutraceuticals, vitamins emerged as the largest segment in 2018, registering a revenue of 36.16 billion US$. This segment is expected to expand at a CAGR of 7.7% over the forecast period up to 2030. In terms of product, soy is expected to register the fastest CAGR over the forecast period. The growing popularity of products such as milk drinks, spreads, and yogurts across the globe has contributed significantly to the growth of this segment.

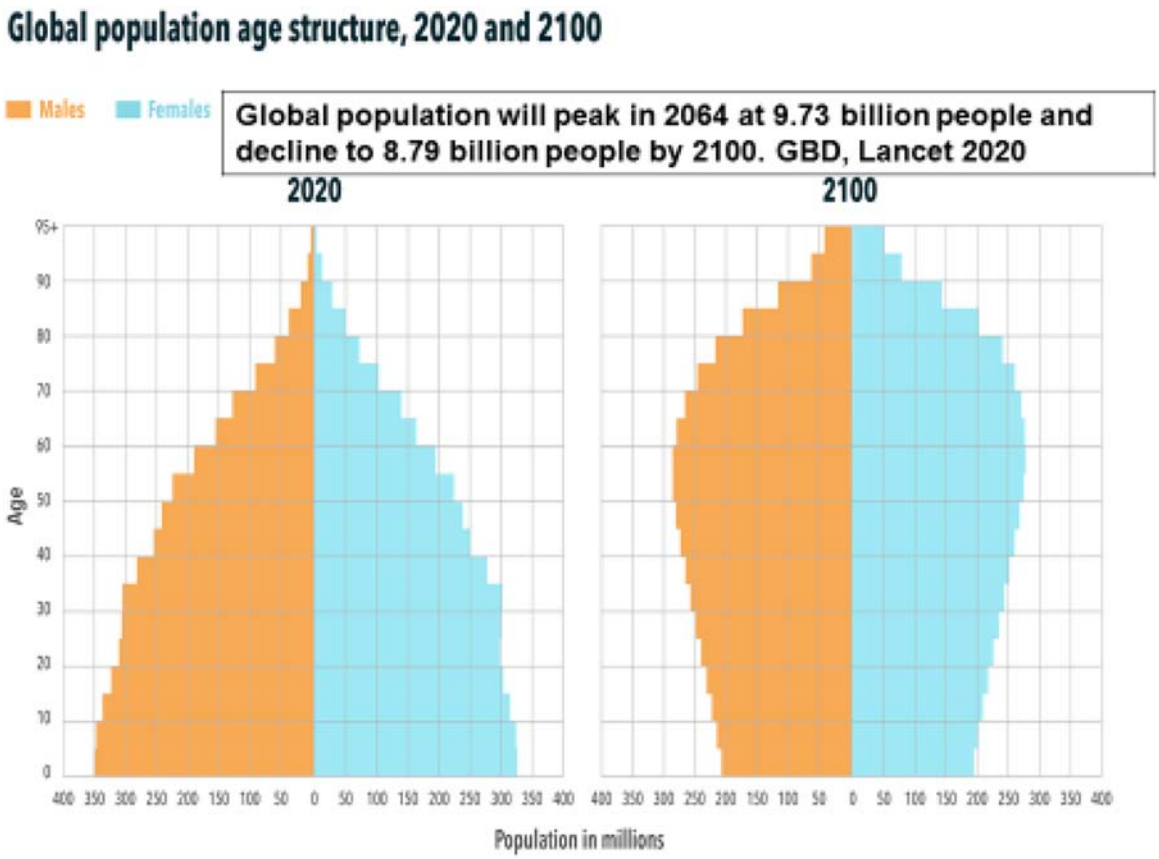


FIGURE 2.6 Estimates of global increase in population with a peak in 2064 and a decline by 2100.

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Chapter 3

Epigenetic modulation of nutritional factors with reference to microgravity conditions for plants and animals: a new biotechnological approach for developing functional foods

Rie Horiuchi[1], Ram B. Singh[2], Toru Takahashi[3], Saikat Kumar Basu[4], Rukam S. Tomar[5], Wajdy Al-Awaida[6], Harpal S. Buttar[7] and Miki Tokunaga[3]

[1]*Department of Food Sciences and Nutrition, School of Food Science and Nutrition, Mukogawa Women's University, Nishinomiya, Japan,* [2]*The Tsim Tsoum Institute, Krakow, Poland,* [3]*Department of Health and Nutrition, Faculty of Human Health, Kanazawa Gakuin University, Kanazawa, Japan,* [4]*Performance Seed, University of Lethbridge, Lethbridge, AB, Canada,* [5]*Department of Genetics, Junagarh Agricultural University, Junagarh, India,* [6]*Department of Biochemistry, American University of Madaba, Madaba, Jordan,* [7]*Department of Pathology & Laboratory Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada*

Introduction

Life is adapted to gravitational forces from the earth, sun, and moon. The physiological and life processes of organisms, including plants, have evolved under these cosmological conditions. The quality of the foods produced by farming, animal, and plant origin is determined by soil, water, and other environmental factors such as microgravity, radiation, temperature, humidity, time duration in growing, pesticides, fertilizers, and hormones that are important in influencing epigenetic and genetic inheritance [1−4]. The epigenome represents surface of the gene, having a multitude of biochemical components that can cross-talk to the genome to alter its biological functions and biochemistry as well as its physiology and metabolism to achieve capability for the survival of the fittest [1]. Epigenetic variations such as histone modifications, DNA methylation, and RNA alterations can provide an evolutionarily and ecologically important source of phenotypic variation among individuals and can act as a mechanism for adaptation [1]. *On the Origin of Species* by Charles Darwin was published in 1859 and predicted that "Natural selection can act only by taking advantage of slight successive variations; it can never take a leap, but must advance by the shortest and slowest steps" [5] In 1942, Julian Huxley brought Darwin's concept into the 20th century and incorporated the knowledge of genes based on Gregor Mendel's experiments on inheritance. However, in neither concepts is a reference to epigenome and epigenetic damage or epigenetic modulation, which can change the phenotypes in such a way as to appear that there is a genetic change due to natural selection. Such phenotypes of plants and animals are likely to have unique characteristics in nutrient content that may be exploited as functional foods.

Recently, microgravity conditions have been demonstrated to have a strong influence on the nutrient quality of foods [2−5]. Use of biotechnological methods along with microgravity conditions during germination of seeds or during fertilization of eggs in animals can change the nutrient quality and/or contents, leading to improvement in the quality of food production [5]. Several environmental factors that control the growth of animal and plant cells may be identified under microgravity conditions. It is possible that plant cells are resilient to adaptation by developing certain bioactive molecules via sustainable mechanisms that allow them to survive under microgravity conditions [5,7]. These bioactive molecules may have additional pharmacological properties, such as enhanced antioxidant activity due to increased content and quality of polyphenolics and flavonoids, which may be exploited for the management of diseases. Since the

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antioxidant actions of flavonoid and polyphenolic compounds have a major role in inhibiting oxidative stress leading to atherosclerosis, carcinogenesis, osteoporosis. and brain degeneration, these pharmacologically active molecules may be useful for the prevention of non-communicable diseases (NCDs). Epigenetic inheritance or epigenetic modulation of genes can also alter the function of foods originating from both animals and plants, due to alterations in the nutrient content of the cells which are under the influence of soil and water that are important factors for the growth of plants [1]. Therefore genetic variations in the plant cells appear to be the basic determinants of the nutrient contents of fruits, edible leaves, and seeds of the plant foods which may be important for health promotion and well-being. Similarly, nutrient contents of the animal foods can also change due to epigenetic variations, which need to be defined for inclusion of the altered food in the functional food category [1]. (Table 3.1) This review aims to highlight the role of epigenetics in the interaction of genes and environment which could be exploited via biotechnology in the development of novel plants, animal-derived foods and functional foods.

Sprouted foods

We describe several details of Singh's approach to the development of functional foods [1]. The use of sprouts and young plantlets in human nutrition is increasing because they often contain phytochemicals with multiple high-value nutrients, which can modulate epigenetic functions. Recently, sprouts have been proposed as a major source for the extraction and purification of several phytochemicals to be used in food supplements or nutraceuticals [2–4]. In a recent study, biochemical analysis of nutrients revealed that the total phenolic content and antioxidant activity in seeds, sprouts, and grasses between 10 and 13 days increased with the number of days [2]. The 10- to 13-day-old grasses showed the highest total phenolic content as well as antioxidant activity. However, the antioxidant activity in the sprouts and grasses were one-fifth and two-thirds of the ascorbic acid standard, respectively. During growth and development of new plants, grains act as a storage organ for proteins, carbohydrates, vitamins, minerals, and oils that are

TABLE 3.1 Chemical compounds in various crops, fruits, and vegetables.

Chemical compounds	Crops, fruits, and vegetables
Genistein	Soybeans
Resveratrol	Grapes
Epigallocatechin-3-gallate	Green tea
Ascorbic acid	Fruits
Resveratrol	Peanuts, berries, grape species
Genistein	Soybean
Kaempferol and phloretin	Apples
Apigenin and luteolin	Celery
Hesperidin and quercetin	Citrus
Caffeic acid and chlorogenic acid	Coffee
Allylmercaptan and diallyl disulfide	Garlic
Anthocyanin, piceatannol and procyanidin	Grapes
Theophylline	Green tea
Biochanin A, daidzein, and equol	Soybeans
Curcumin	Turmeric
Folate or folic acid (known as pteroylglutamic acid)	Green vegetables and animal liver
Sulforaphane (an isothiocyanate)	Cruciferous vegetables (e.g., broccoli, kale, cabbage, radish, mustard)
Selenium (different forms, including selenocysteine, sodium selenite, and sodium selenide)	Cereals, nuts, and vegetables

required for metabolic functions [3]. It seems that during the process of germination and sprouting of seeds, certain nutrient contents are increased that may be important for health promotion. The high nutritive values of these foods, whole grains, sprouts, and grasses is characterized by increased levels of amino acids, fiber, trace elements, vitamins, flavonoids, and phenolic acids [2]. Our traditional foods include cereal grasses at 1−2 weeks of age, which are called microgreens and are increasingly being used as natural health supplements. A previous study reported that grains of einkorn and emmer contained twice the amount of phenolic acids as compared to soft and durum wheat and spelt, with p-coumaric acid accounting for about 50% of total amount phenolic acids [3]. Total phenols and free phenolic acids increased during the passage from grains to sprouts and wheatgrass. Neutral and acid detergent fiber content increased with sprouting only in einkorn and emmer, indicating that the grains of einkorn and emmer and the sprouts and wheatgrass of all *Triticum* species may have potential value for the development of functional foods [3].

In contrast to outdoor conditions, industrialization of sprout production, carried out under artificial lights, may affect the yield, composition, and biomass and could influence energy- and labor-related economic costs [4]. There is scientific evidence that light-emitting diodes can influence the synthesis of free and bound phenolics and antioxidant activity of sprouts and wheatgrass of various species [4]. After 3 days of grain incubation in the dark, three light treatments of varying radiation wavelengths were applied for the same total photon flux density. The impact of light was generally not significant for sprouts but was much greater and species-specific for wheatgrass. Artificial light exposure generally increased free and total content of polyphenol, flavonoid, tannins, and phenolic acids [4]. The antioxidant activity was increased by blue light in einkorn and decreased by red light in both species. Compared to sunlight, blue and red lights resulted in energy saving.

Microgravity conditions

The earth's environment is characterized by gravity, which has remained constant throughout the entire process of biological evolution. Life is adapted to a constant gravitational force, and despite some limiting factors, biological processes in organisms have evolved under this natural constancy. Many plants have adequate sustainable mechanisms, allowing them to survive under microgravity conditions. Recently, responses of plant cells to the microgravity stimulus have been examined, using various approaches of microgravity conditions to identify genes and epigenetic alterations with levels of altered expression [5−12]. It is possible that microgravity signals can be transduced into molecular signaling cascades, which lead to plant adaptation. However, the mechanisms by which gravity influences growth and development of plants are unclear. It is possible to uncouple cellular growth and proliferation under simulated reduced gravity, as found in meristematic cells from seedlings grown in real or simulated microgravity conditions The levels and gene transcription of the tested cell cycle regulators and the distribution of cell cycle phases can be changed via alterations in microgravity conditions [5−8].

In an in vitro experiment, cell cultures of *Arabidopsis thaliana* were exposed to different altered gravity conditions to examine the effects of simulated reduced gravity (simulated microgravity, simulated Mars gravity), and hypergravity (2 × G) [5]. Alterations in epigenetics leading to cell proliferation, cell growth were evaluated, after 3, 14, and 24 hours of exposure. Compared to hypergravity, the most relevant alterations were found in the 24-hour treatment, being more significant for simulated reduced gravity. The findings revealed that ribosome biogenesis was reduced according to the levels of transcription of nucleolar proteins and the number of inactive nucleoli in the genes. There were also alterations in the epigenetic modifications of chromatin. The results from other studies indicated that gravity alterations can cause serious disturbance in growth and cell proliferation, suggesting that normal gravity conditions are important for the cellular growth and physiological development of plants [5−9].

Microgravity conditions appear to be an important environmental determinant of plant stress that has been demonstrated during space flights [10,11]. It is possible that epigenetic alterations are involved in plant adaptation to environmental stress. A number of studies have demonstrated that DNA methylation leads to control of gene mRNA levels and plays important roles in abiotic and biotic stresses [8−11]. Environmental changes may cause drought-related stress, predisposing rice to global DNA methylation alteration [12], and stress due to salt-induced OsMYB91 gene expression, leading to the reduced cytosine methylation level in its promoter region [13]. There may be widespread alterations in DNA methylation of the poplar genome in response to treatment via drought, indicating that the local environment may induce adaptation [14]. In view of these observations it appears that epigenetic variations in transposable element regions can be affected by environmental stresses.

Low-temperature treatment leads to demethylation of the Ac/Ds transposon region in maize roots via silencing of the ZmMET1 gene, indicating an association between environmental stresses and DNA methylation alterations [14]. Cokus et al. have demonstrated that DNA cytosine methylation functions as an important controller of gene mRNA levels [15]. Experiments with *A. thaliana* have discovered that many endogenous genes are methylated either within their promoters or within their transcribed regions and that gene methylation is highly correlated with transcription

levels [15]. Since plants show a variety of methylations under the influence of different genetic pathways, there is a lack of detailed information on the methylation status of each cytosine in any given genome. DNA cytosine methylation is mostly detected at CpG sites and can also occur at CHG and CHH residues (H indicates A, T, or C) in the *Arabidopsis* genome. The findings of another study showed that methylation in the gene body is detected at CpG sites, while CpG, CHH, and CHG site methylation occurs elsewhere and in repetitive regions [15]. The CG methylation is enriched in transposable element and gene bodies, but non-CG methylation is mostly present in these elements. It is possible that methylation of gene promoter regions inhibits gene expression, while methylation within introns and exons can promote gene transcription. The major CG methyltransferase is MET1 and CMT3, which is the main CHG methyltransferase, whereas DRM2 is the main CHH methyltransferase that is guided by small RNAs.

The Food and Agricultural Organization and the World Health Organization have emphasized the need for food security globally, thus underlying the urgency for developing healthy functional foods in the world to meet the demand for prevention of NCDs [16,17]. Recently, development of functional foods using epigenetic biotechnology has been suggested to provide protection to pregnant mothers and fetuses against environmental pollution [18]. Feeding of functional foods such as flax seed and linseed diets and tea leaves to chickens and other animals has provided evidence of the enrichment of eggs and meat with the nutrients of these functional foods [19–21]. When 10%, 20%, and 30% flax seed were fed to laying hens for 28 days and the eggs were collected for chemical analysis in the last 3 days of the feeding period, the eggs showed large increases in omega-3 fatty acids at all levels of flax seed administration [19]. Cheronian and Sim fed laying hens with 8% and 16% flax seed diets supplemented with pyridoxine and demonstrated increased omega-3 fatty acids in the eggs as well as omega-3 fatty acids in the brain tissue of embryos and chicks from the hens that had been fed ground flax seed [20]. The longer-chain omega-3 fatty acids were deposited exclusively in the phospholipids, and the fatty acid content of chicks was significantly altered by egg yolk lipids. In another investigation, Cherian and Sim found that elongation of omega-3 fatty acids occurs during incubation [20]. Chu and Kummerow were the first to feed linseed oil to chickens, and they reported higher levels of linolenic acid in the chickens [21]. For his scientific discovery, Dr. Sim received Dr. R.B. Singh's Felicitation Award during the 2002 World Congress of Clinical Nutrition in Banff, Alberta, Canada.

Epigenetic mechanisms of evolution and functional foods

The genotype manifests as a result of interactions between the environment and the genome as well as the epigenome, which result in phenotypes [22–24]. The environmental factors in general and nutrition factors in particular have been implicated in the pathobiology of genetic variations and epigenetic damage–provoked inheritance, leading to the emergence of chronic diseases of affluence, such as cardiovascular diseases, type 2 diabetes, and various cancer type; bone and musculoskeletal diseases; and degenerative disorders of the brain, as shown in Fig. 3.1 [4–11]. There is a need to

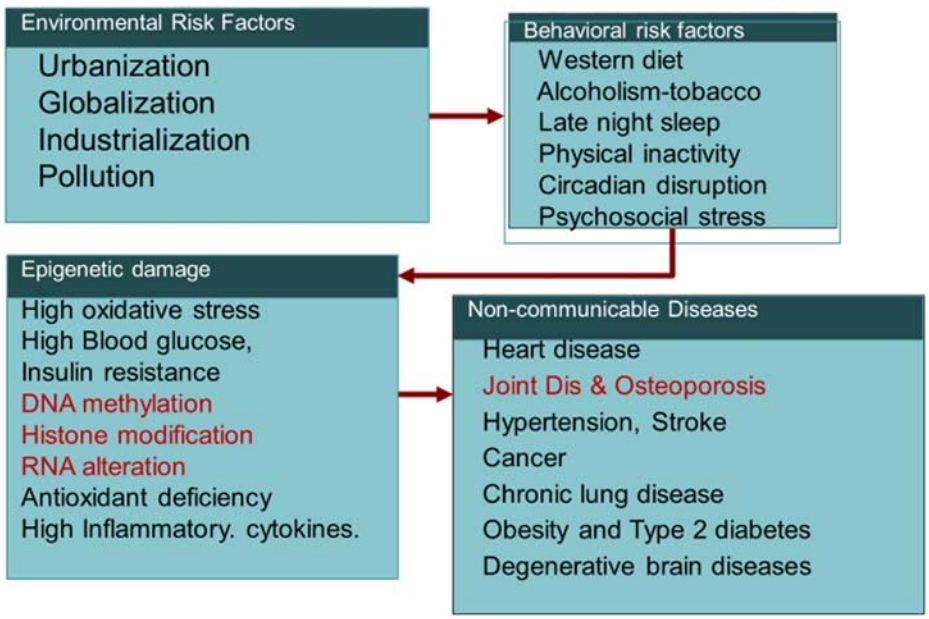


FIGURE 3.1 Effects of environmental factors on behavioral and epigenetic biomarkers and development of non-communicable diseases. *Modified from Singh et al. (1999).*

assess whether increases in chronic diseases are due to epigenetic inheritance leading to the development of phenotypes such as proinflammatory cytokines or due to the interaction of a thrifty gene (developed during scarcity) with environmental factors, such as diets rich in saturated fat and refined carbohydrates [32−36].

As was mentioned earlier, epigenetic inheritance or epigenetic modulation can alter the composition and function of foods of both animal and plant origin, owing to alterations in the nutrient content of the cells, which are under the influence of the soil and water that are important for the growth of the plants [32,37]. Therefore genetic variations in plant cells appear to be basic determinants of the nutrient content of fruits, leaves, and seeds of the plant foods ,which may be important for maximizing health benefits. Several studies have been done in chickens fed on flax seeds and tea leaves to determine the transfer of nutrient components from feeds into eggs [32,37]. It was found that significant amounts of omega-3 fatty acids from feed were deposited in egg yolk lipids. The nutrient content of animal foods can also alter, owing to epigenetic variations, which need to be defined for inclusion of such foods into the functional food category [32,37].

It was alluded to earlier that environmental factors in general and nutrition in particular have been implicated in the pathobiology of genetic variations and epigenetic damage induced through inheritance, leading to the emergence of chronic diseases of affluence, that is, cardiovascular diseases, type 2 diabetes, some cancers, bone and joint diseases, and neurodegenerative abnormalities depicted in Fig. 3.1 [24−31]. Hence there is a need to assess the risk factors for the increased occurrence of chronic diseases and the impact of epigenetic inheritance leading to the development of phenotypes, proinflammatory cytokines, interaction of a thrifty gene (developed during scarcity) with environmental factors, and excessive intake of saturated fats, sugary drinks, and refined carbohydrates [32−36].

Functional foods can evolve directly from plants that are provided nutrient-rich soil and sufficient water. It has been proposed that dramatic adaptations can occur in the form of major morphological changes in the plants and animals, which appear to be similar to changes in structure from prehistoric humans to modern-day humans and various human populations [22−24]. These adaptations may be common among animals as well as among plants that may be used as functional foods. It is possible that maladaptations of the genome may be responsible for the development of genetic diseases or new species of plants and animals [22−24]. In many species of plants and animals, new phenotypes have been observed to occur rapidly in the last 100 years as a result of rapid environmental changes [22−32].

It is proposed that plants and animals with some level of genetic variations have evolved through changes in gene frequency and gene sequence, induced mostly by natural selection or by epigenetic inheritance [22−31]. The progress in evolutionary biology, biochemistry, genomics, developmental biology, and systems biology and the impact of the environment on genes concerning the mechanism of evolution have grown significantly [24−32]. It is possible that some lineages have greater “evolvability” than others, independent of how much baseline genetic variation is present. Heritable phenotype variations may depend on the biology and biochemistry of the genes as well as on their status of DNA methylation and hypomethylation of the epigenome [28].

An epigenome showing histone, DNA, and a chromosome is illustrated in Fig. 3.2. Epigenetic mechanisms, such as DNA methylation and histone modification, can cause stable alterations in gene activity without any changes in the underlying DNA sequence. DNA methylation is associated with silencing of transposon and, imprinting and silencing of both transgenes and endogenous genes. DNA methylation can cause heritable phenotypic modifications in the absence of changes in DNA sequence. Nutritional factors, such as choline, pyrodoxin, vitamin B12, omega-3 fatty acids, and folic acid, if given during pregnancy can trigger DNA methylation, which may have evolutionary consequences, even in the absence of sequence variation. However, the extent to which environmentally induced methylation changes are transmitted to offspring remains largely unknown, as does whether the observed methylation variation is truly independent. In mammals, resetting of DNA methylation takes place during early embryonic development [28−37]. Nutrients with epigenetic functions are listed in Table 3.2.

In plants, a considerable proportion of DNA methylation marks can be stably transmitted from parents to offspring for development of segregating phenotypes, depending on the micronutrient content in the parent or offspring tissues. In one experimental study [26], genetically identical apomictic dandelion (*Taraxacum officinale*) plants were exposed to different ecological stresses, and apomictic offspring were raised in a common unstressed environment. Only methylation-sensitive amplified fragment length polymorphism markers were used to screen genome-wide methylation alterations triggered by stress treatments to assess the heritability of induced changes. These changes may be translated into quality and quantity of the nutrient content of the fruits, leaf, or seed of the plant that are determinants of the functions of the foods available for human consumption. In a previous study, a yeast prion provided a mechanism for genetic variation and diversity of phenotype, indicating that nearly half of the conditions having the prion led to significant phenotypic effects in some of the strains, which uncovered previously hidden phenotypic variation in the yeast cells [27]. The low ratio of omega-6 fatty acids to omega-3 fatty acids with high amino acids, flavonoids, and coenzyme Q10 present in the cell membrane to which species adapted during evolution may have beneficial effects on DNA

National human genome Research Institutehttps://www.genome.gov/27532724/modified

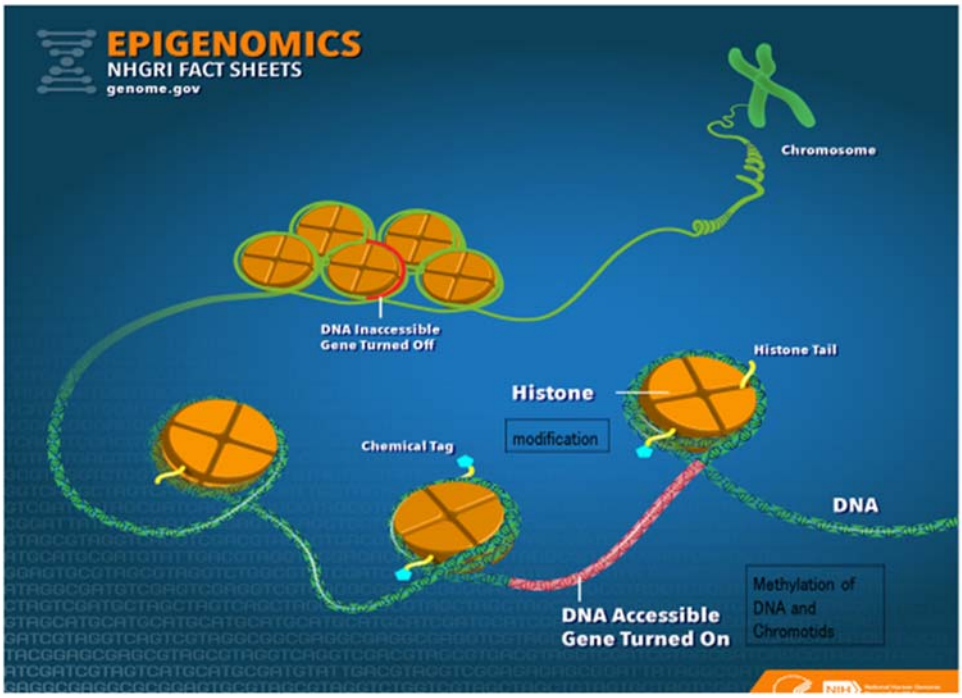


FIGURE 3.2 Epigenome showing histone, DNA, and chromosome, which are methylated as a result of oxidative stress and inflammation.

methylation and therefore on this phenotypic diversity, resulting in diversity of functional foods [28–37]. The prion can pass from mother to daughter yeast cells when they divide either mitotically or meiotically, despite a lineage in which they revert back to nonprion state selection, resulting into the beneficial adaptations [27] (Table 3.3).

The process known as natural selection may not actually be "natural," but we are largely ignorant about the environmental factors that cause phenotypic variations by altering the composition of epigenome. This may be clearer from the evidence on the facilitation of genetic variation in a perspective of functional foods that are known to cause health promotion and decline in phenotypes related to diseases.

The enrichment of nutrients may be accomplished by feeding domesticated birds and other animals a diet close to that of their wild ancestors [32,37–41]. The diets of these animals may include a wider range of seeds and green vegetation than is normally the case in modern farming practice. After long-term feeding of diets containing omega-3 fatty acids, the eggs or milk or meat of these animals becomes rich in omega-3 fatty acids and polyphenolics that are obtained from the feed. In his experiments with hens, Sim used flax seed and other experts used tea leaves to enhance omega-3 fatty acids and flavonols in the chicken eggs [22,37]. These investigators did not study the epigenome effect in the experimental animals, but it is quite likely that epigenetic modulation is an important mechanism involved in long-term feeding studies.

Environmental factors and genetic variations among humans

Approximately 15 million years ago, our ancestors ate mostly fruits, vegetables, seeds, and honey, a diet that contained little or no fat. They adapted by evolving mutation for conversion of fructose from the fruit to fat for metabolic functions, which allowed them to survive seasonal periods of famine when fruit and vegetable plants were scarce. This epigenetic inheritance of fat-accumulating phenotype has become an adverse genetic variation for modern humans, although it was protective for the survival of our ancestors. It is proposed that high-fructose corn syrups, sugar, and refined starches are rapidly converted to fat in the modern human body because of this mutation, resulting in an obese phenotype causing weight increase and obesity, insulin resistance, type 2 diabetes, and cardiovascular diseases (CVDs). Since the diet of ancient humans was rich in micronutrients, adverse effects of fructose-rich foods were inhibited by these functional foods.

TABLE 3.2 Nutrients with epigenetic functions.

Chemical compounds	Function
Epigallaocatechin-3-gallate	Maintains DNA methylation (274, 275, 276). Acts as a histone modifier and miRNA modulator. Potent HAT inhibitor properties targeting various HAT enzymes, including p300, CBP, Tip60, and PCAF (270). Reactivates ERa expression and resensitizes antihormone treatment (tamoxifen) in ER-negative breast cancer (276). Affects Polycomb group (PcG) proteins, which can compact chromatin and silence cancer-related genes via regulating histone methylation and acetylation (277). Modulates miRNA expression in human nasopharyngeal carcinoma CNE2 cells (278), osteoarthritis chondrocytes (279), osteosarcoma cells (280), and spontaneously hypertensive rat (281).
Resveratrol	Exhibits antioxidant, antiinflammatory, antiangiogenic, and anticancer properties through epigenetic regulations via its abilities of DNMT (268, 283, 284, 285, 286) and HDAC inhibition (283, 285, 287, 288, 289). Is also associated with SIRT1 activation in various metabolic pathways (292, 293, 294, 295, 296, 297, 298). Acts as a miRNA regulator in thrombus resolution (299), type 2 diabetes (T2D) treatment (300), clinical pancreatic ductal adenocarcinoma (PDAC) prevention (301), osteoarthritis therapy (302), and antiinflammation (303).
Genistein	Inhibits obesity, insulin resistance, and metabolic diseases, preventing inflammation and multiple cancers (305). Also exhibits striking effects on DNA methylation (285, 306, 307, 308, 309), and histone modification (285, 306, 309, 310). Was also found to repress human telomerase reverse trancriptase (hTERT), which is the catalytic subunit of human telomerase, by locus-specific hypomethylation as well as chromatin structure remodeling of the hTERT promoter in breast cancer models (317). May act as a miRNA modulator in breast, prostate, colorectal, and renal cancer prevention (271, 318, 319, 320, 321).
Isothiocyanates.	Have potent activity in HDAC inhibition (269, 409,410, 411, 412). Sulforaphane (SFN) has properties in DNMT inhibition (276, 414, 415), and miRNA modulation (414, 416, 417, 418).
Withaferin A	Has antiinflammatory (423, 424), antimetastatic (425), antiangiogenesis (426), and antitumor activity (427, 428, 429), anticancer (430). Has been associated with a decreased chromatin accessibility at the IL-6 gene promoter region (432). Acts as DNMT and HDAC inhibitors in breast cancer cells, and these activities are strengthened once combined with SFN (269, 411).

A similar epigenetic inheritance has been observed among populations when they migrate from rural areas to urban environments and from the developing countries of South Asia to the Western world [22–24]. South Asians are known to be highly susceptible to central obesity, type 2 diabetes, insulin resistance, and CVDs [22]. A complex set of physical and chemical factors come into play during development that can influence structures and functions going beyond simple genome to phenotype translation [27–32]. Complex gene and environment interactions and sudden morphological reorganizations occur during development, and as observed in experiments and natural setups, there may be discordance between genotype and phenotype [22–24,27–32].

Effects of nutrients and the agouti gene

Nutritional modulation of epigenetic inheritance has been demonstrated in the yellow agouti mouse, an epigenetic biosensor for nutritional and environmental changes. These fat and yellow mice owe their appearance to epigenetic modification that removes methyl groups from the normally methylated agouti gene [31]. In a developing mouse fetus, if the above modification occurs shortly after fertilization, the baby mouse may exhibit the yellow fur and an obese phenotype with greater risk of developing cancer and diabetes [31]. However, the genetic code remains unchanged from that of

TABLE 3.3 Vitamins, minerals, and amino acids with epigenetic functions.

Nutrient	Function
Vitamin C	Increases collagen cross-linking (358)
	Ascorbate, the form of vitamin C existing under physiological pH conditions, is found to be involved in active DNA demethylation (360, 361, 362, 363, 364, 365, 366) and histone demethylation (360, 367, 368, 369) as well as epigenome reprogramming (358) in a cofactor manner.
	Has a role in H3K9me2 demethylation in mouse embryonic stem cells (368).
Vitamin D	Has roles in regulating transcriptional responses and underlying epigenetic mechanisms (372).
	Vitamin D treatment is negatively correlated with promoter methylation status of the adenomatous polyposis (*APC*) gene, a tumor suppressor gene in colorectal cancer (375), as well as dickkopf-related protein 1 (*DKK1*) (376), E-cadherin (377), PDZ-LIM domain containing protein 2 (PDLIM2) (378), and *p21* (379).
	Also has anticancer properties through miRNA modulation (382).
Folate	Takes part in the methionine cycle and ultimately offers methyl for DNA and protein methylation, thereby changing chromatin structure and modulating gene expression (384).
	Folate depletion can cause both hypomethylation and hypermethylation of DNA (386).
	Its supplementation has been shown to reduce the risk of cancer (387, 388) through regulation of DNA methylation patterns (389, 390).
Choline	Has a role in methylation of cytosine in DNA, lysine in histones, and adenine in RNA as well as other molecules (391, 392).
	Dietary supplementation with choline changed methylation levels of *CpG* sites in the genes *IGF2*, *Srebf2*, *Agpat3*, *Esr 1*, *Fasn*, and *Cdkn3* (396, 397, 398).
	Low choline intake increases overall risk for lung cancer, nasopharyngeal cancer, and breast cancer and also reduces cancer (400).
	Choline can inhibit cancer development via modifying epigenetic markers (400).
Selenium	Promotes successful and healthy pregnancies through protecting against oxidative stress (435).
	In both mouse and rat studies, diet supplemented with selenium resulted in increased DNA methylation in colon tissue (439, 440) and decreased global DNA methylation in liver (441, 442) and heart (443) as well as increased methylation in the exon-specific locus on *Tp53* (442) and promoter regions of two inflammatory-related genes (*TLR2* and *ICAM1*) (444).
Magnesium	In the latest version of the human proteome, the total number of human proteins for putative magnesium binding sites is 3751. Among these proteins, 2688 inherit annotation directly from human templates, and 1063 inherit annotation from templates of other organisms. Protein structures are highly conserved inside a given cluster.

Source: Piovesan D, Profiti G, Martelli PL, Casadio R. 3,751 magnesium binding sites have been detected on human proteins. BMC Bioinformatics 2012;13 (Suppl. 14):S10. Epub 2012 Sep 7.

normal mice. In this study, the nutrient intake was altered to provide methyl group donors in mouse mothers to cause methylation or demethylation of the agouti gene.

Increased supplementation of choline, betaine, folic acid, and vitamin B12 in the diet of pregnant yellow agouti mice was able to decrease the incidence of deleterious phenotypes in offspring by donating methyl group and allowing for the remethylation of the agouti gene. If these mice are born with the agouti phenotype, they can pass that deleterious epigenetic trait to their offspring regardless of their diet during pregnancy. The results of this study indicate that nutrients can cause phenotypic changes that can be passed on through cell division and mating to the offspring, owing to their possible influence on (natural) selection [31]. It is therefore likely that "we are what we eat," as the saying goes, and what our parents ate and potentially what our grandparents ate. It may also be important to point out that we are not only "what we eat" but also we are "when we eat" and when our parents and grandparents were eating [32,37]. There is a need to study the effects of a low PUFA/flavonoid ratio diet with high arginine, taurine, cysteine, and coenzyme Q10 on the remethylation of the agouti gene and their effects on phenotypic variations. This approach can be

exploited for food production from animal sources by feeding the animals green leaves, seeds, and grass from wild sources [37–41].

It should be emphasized that the described mode of genetic inheritance needs to last more than a few generations before it can earn a place in the evolutionary concept. Epigenetic inheritance appears to be widespread, but this does not mean that it lasts and causes evolutionarily important effects. It is not clear that if epigenetic changes are not stable for 20–30 generations, they would be relevant to evolution. Several experiments related to epigenetics are under way to establish the role of environmental factors in inheritance.

The evolutionary diet, the environment, and health

Recently, fossil studies from Germany on material from Jebel Irhoud, Morocco, revealed a mosaic of features with early or recent anatomically modern humans and more primitive neurocranial and endocranial morphology [33]. This study documents that early stages of *Homo sapien*s in which key features of modern morphology were established involved possibly the whole African continent, rather than Ethiopia alone, approximately 315,000 years ago.

A fundamental view of evolution has been that the genetic makeup of contemporary humans shows only minor difference from that of the modern human who appeared in Africa during the ancient period [33,34,37]. However, during the past 50,000 years, human evolution has been comparatively rapid, as has been revealed by the molecular geneticists [33]. Since 10,000 years ago, there have been marked changes in the food supply with the development of agriculture. However, it is of interest to note that there has been only a little change in our genes during the past ten centuries, which may be due to the presence of omega-3 fatty acids, amino acids, vitamins, and minerals in our diet and the absence of any dramatic changes in the environment [33–36]. Nevertheless, there must have been some structural modifications in individual DNA sequences, which may be due to the presence of fatty acids, flavonoids, amino acids, vitamins, and minerals in our diet and the lack of any dramatic changes in the environment [33–36]. In addition, there must have been some structural modifications in individual DNA sequences and altered gene regulation and in the epigenome. A major effect in epigenetics would include DNA methylation, translational histone, and noncoding RNA modifications showing that epigenetic modifications have major functional changes [26,37]. Although similar to genetic features of DNA heritability, epigenetic mechanisms may differ with potential reversibility by environmental and nutritional factors, which makes them potentially crucial for their role in complex and multifactorial diseases.

Increased evolutionary rapidity in humans compared with rates for other primates has resulted from unprecedented demographic expansion, which has provided a far larger pool of mutations upon which natural selection can operate. The human diaspora that has exposed humans to environmental changes appears to be quite different from those of their ancestral land in Africa, and this rapid change may predispose humans to deleterious epigenetic inheritance [23–27]. Our genes appear to be similar to the genes of our ancestors during the Paleolithic period (40,000 years ago), the time when our genetic profile was established. It is only during the last 100–160 years that dietary intakes and environment have changed significantly, causing increased intake of saturated fatty acids, trans fat, and linoleic acid and decreased intake of omega-3 fatty acids, as a result of consumption of meat from grain-fed animals that are raised in feedlots rather than meat from free-ranging animals [35]. The food and nutrient intake among hunter-gatherers and among people during the Paleolithic period showed no remarkable differences. However, since industrialization there has been a marked reduction in the consumption of omega-3 fatty acids, vitamins, antioxidants, and proteins and a significant increase in the intake of carbohydrates (mainly refined), fat (saturated fat, trans fat, and linoleic acid) and salt compared to the Paleolithic period [1–4,13–20]. There have also been marked changes in environmental factors, salt intake, and quality of food and nutrients, which, in turn, may have deleterious effects on epigenetic inheritance, resulting in NCDs and chronic diseases [37–43].

Eggs as functional foods after hens are fed functional foods

Nature dictates the ingestion of fatty acids in a balanced ratio (omega-6:omega-3 = 1:1) as part of a dietary lipid pattern in which monounsaturated fatty acids comprise the major fat component (polyunsaturated:monounsaturated:saturated = 1:6:1) [25]. These ratios represent the overall distribution of fats in a natural untamed environment. Circulating plasma fatty acids, such as the ratio of omega-6 fatty acids to omega-3 fatty acids, in conjunction with a high PUFA/flavonoid ratio in the diets gives an indication of the proinflammatory status of blood vessels and other cells, such as cardiomyocytes, beta cells of the pancreas, and neurons [25]. Of major importance appear to be the essential dietary nutrients (essential amino acids, fatty acids, antioxidant vitamins, flavonoids, and minerals) and the functional component of the dietary regimen (sports, spiritualism, etc.) because these factors may play an important role in epigenetic

modulation and regulation. It is not yet clear how these nutrients are incorporated in egg yolk or whether feeding-induced epigenetic modulation plays some role. The conventional eggs that are sold in a standard supermarket are produced from hens that are usually raised in overfilled hen houses or a cage and never see the light of day. They are usually fed grain-based feed supplemented with vitamins and minerals and may also be treated with antibiotics and hormones. Chickens that lay organic eggs or Columbus eggs are not treated with hormones and receive organic feed and may have some access to the outdoors [22,27,41,44]. Pastured eggs are produced by chickens that are allowed to roam free, eating plants and insects (their natural food) along with some commercial feed. Omega-3-enriched eggs are basically like those of conventional chickens, except that their feed is supplemented with an omega-3 source such as flax seed and may have had some access to the outside.

When 10%, 20%, and 30% flax seed were fed to laying hens for a 28-day period and the eggs were collected for analysis in the last 3 days of the period, the eggs showed large increases in omega-3 fatty acids at all levels of flax seed administration [19]. Cheronian and Sim (1991) fed flax seed to laying hens at 8% and 16% in diets that were supplemented with pyridoxine and demonstrated increased omega-3 fatty acids in the eggs and in the brain tissue of embryos and chicks from the hens that were fed the ground flax seed (19). The longer-chain omega-3 fatty acids were deposited exclusively in the phospholipids, and the fatty acid content of chicks was significantly altered by egg yolk lipids. Cherian and Sim also found that elongation of omega-3 fatty acids occurs during incubation (20). Chu and Kummerow were the first to feed linseed oil to chickens and reported higher levels of linolenic acid in the chickens (20). Sim was awarded Singh's felicitation award during the World Congress of Clinical Nutrition in Banff, Alberta, Canada, in 2002. Omega-3-enriched eggs had 39% less arachidonic acid, an inflammatory omega-6 fatty acid of which most people eat too much. The omega-3-enriched eggs had five times as much omega-3 fatty acid as the conventional eggs. There was very little difference between organic and conventional eggs. It is clear that hens that are fed an omega-3-enriched diet lay eggs that are much higher in omega-3 than conventional eggs (40,43). Eggs from pastured hens are more nutritious than the conventional eggs at the supermarket. They are higher in vitamin A and E and omega-3 fatty acids and lower in cholesterol and saturated fat [41,44,45]. The advantages of simultaneous enrichment of eggs, milk, or meat with other nutrients, such as vitamin E, carotenoids, selenium, and DHA, include better stability of polyunsaturated fatty acids during egg storage and cooking, high availability of such nutrients as vitamin E and carotenoids, absence of off-taste, and improved antioxidant and omega-3 status of people who consume these eggs. A review of the relevant scientific literature shows that designer eggs that are rich in omega-3 and antioxidants can be considered to be a new type of functional food [44,45], It is possible that by feeding animals with nutritious feeds, there is enrichment of eggs, milk, or meat [44,45]. This method can make the animal foods—eggs, milk, and meat—low in saturated fat and cholesterol and high in omega-3 fatty acid, vitamins E and A, and selenium. Pigment-enriched eggs and many more types of modified or enriched animal foods can easily be obtained for specific purposes by this method.

A recent study revealed that the mineral nutrient composition of vegetables, fruits, and grains is not declining as a result of changes in soil [46]. Allegations of decline due to agricultural soil mineral depletion are unfounded, although some high-yield varieties show a dilution effect of lower mineral concentrations. It seems that the changes are within natural variation ranges and are not nutritionally significant; hence eating the recommended daily servings should provide adequate nutrition. However, this study examined only minerals without mention of the concentrations of other nutrients, which can alter as a result of epigenetic modulation of the epigenome of seeds grown in mineral-deficient soil. It is important to develop wild-type feed for animals, which should be rich in omega-3 fatty acids, antioxidants, minerals, amino acids, and other nutrients [47]. The content of flax seed in feed for laying hens should not exceed 10%, because an increase to 15% adversely affects feed conversion and the weight of the product, such as eggs from hens, which may be due to antiestrogenic effects [48]. Such diets can be used in other animals, such as lambs, goats, pigs, cows, and buffalos, for producing healthy meats and milk. There is a need to study epigenomes among animal species that receive such feeds to demonstrate the effects on epigenetic marks or epigenetic regulation. Previous studies also indicate that food and nutrient intake, energy expenditure, and body adiposity are regulated by physiology and metabolism of foods and nutrients [39–42]. Central and peripheral signals from central and peripheral areas communicate information about the current state of energy balance and food quality to key brain regions, including the hypothalamus and the brain stem [40]. Hunger and satiety represent coordinated responses to these signals, which include neural and hormonal messages from the gut. Our understanding of how neural and hormonal brain-gut signaling regulates energy homeostasis has advanced considerably, and it is possible that the gut-brain-body connection is regulated by genes and epigenes. Gut hormones have various physiological functions that include specifically targeting the brain to regulate appetite. New research suggests that gut hormones can be used to specifically regulate energy homeostasis in humans and offer a target for genetic modulation. Epigenetic alterations have also been observed in patients with hypertension, and gut hormones under the influence of probiotics can prevent the development of CVDs, including hypertension [40].

Epigenetic modulation in plants for food production

Epigenetic modulation is characterized by alteration in chromatin structure, remodeled histone proteins, or methylated DNA, often mediated by environmental factors, and can pass from parent to offspring without changing the actual sequence of the inherited genome. If epigenetic inheritance plays any role in evolutionary change, it should be possible to demonstrate that the changes are stable, causing heritable effects through several generations, and can be associated with alteration in the biochemical content of plant or animal foods [29,32,37]. In an experiment, two groups of genetically identical *Arabodopsis* plants (*Brassicaceae* family) were exposed to either hot or cold weather conditions for P and F1 generations [30]. The next generation (F2) from both groups was grown at a normal temperature, but the offspring (F3) from both groups were grown in either hot or cold conditions. The F3 plants, grown in hot conditions and descended from P and F1 plants, also grown in hot conditions produced five times more seeds compared to F3 plants grown in hot conditions but descended from cold-treated ancestors [30]. These mutations may have occurred as a result of epigenetic factors affecting flower productions and early-stage seed survival due to molecular adaptations in these plants. There is a need to study the biochemistry of seeds and leaves to find out whether the increase in quantity of seeds was also associated with an increase in certain useful dietary nutrients in the seeds that can improve the quality of seeds to be considered for making functional foods.

For healthy growth, plants require nitrogen (N_2) and at least 13 mineral macronutrients: phosphorus (P), potassium (K), calcium (Ca), magnesium (Mg), sulfur (S), chlorine (Cl), boron (B), iron (Fe), manganese (Mn), copper (Cu), zinc (Zn), nickel (Ni), and molybdenum (Mo) [49]. Selenium (Se) and chromium (Cr) also appear to be important micronutrients for plant growth because they are found in abundance in certain foods. Crop production is often limited by low phytoavailability of essential mineral elements and/or the presence of excessive concentrations of potentially toxic minerals, such as sodium (Na), Cl, B, Fe, Mn, and aluminum (Al), mercury (Hg), arsenic (As), lead (Pb), and cadmium (Cd) in the soil solution. The activities of key transport proteins determine species-specific tissue and cellular ionomes. Some toxic minerals in the soils should be avoided, since minerals play an important role in plant physiology [49]. Iron is needed for chlorophyll formation and oxygen transfer. Without adequate iron, leaves turn yellow, but leaf veins remain green. Adding too much lime to the soil can lead to an iron deficiency. Manganese works as a channel for a variety of enzymes and is essential for chlorophyll formation. Deficiency of manganese causes a variety of indicators, depending on the type of plant. The most common signs include yellowing of leaves with green veins or grayish-white specks that appear on the leaves. Excess manganese may deplete iron in the soil and cause symptoms similar to those exhibited with a lack of manganese. Boron works as a vehicle for the interchange of sugars, for reproduction, and for cellular intake of water. Deficiency of boron causes plant distortion with hollow stems and malformed fruits as well as scorched, curled, and sometimes mottled leaves.

Zinc is important for the production of proteins or amino acids, which affects how big plants grow and whether or not they mature. Zinc deficiency causes plants to produce less fruit and brings about yellowing of leaves between veins, often accompanied by purple or dead spots with small, deformed leaves growing close together, which could be a manifestation of epigenetic damage [49]. Copper is also important for the production of proteins and plays an important role in reproduction. Copper deficiency causes bluish-green leaves that might wither or never unfold. It may cause rosettes on growing tips. Molybdenum is vital to nitrate enzymes and the formation of root nodules in beans and peas. Lack of molybdenum causes the leaves to produce yellow mottling and dead spots and often growing tips are distorted or killed. Lack of the right amount of chlorine in soil might affect carbohydrate metabolism and photosynthesis as well as cause stubby roots and wilting. It is proposed that deficiencies of certain of these nutrients, such as zinc and copper, can have adverse effects on amino acid metabolism, leading to epigenetic damage, and supplementation can be beneficial. Epigenetic gene regulation affects genome integrity by maintaining, over generations, silencing in repetitive sequences and transposons [50].

In plants, epigenetic regulation plays a key role in phenomena such as genomic imprinting and paramutation, mainly by enforcing a silenced chromatin state through DNA methylation and/or chromatin modifications, leading to gene silencing. The silenced states are then maintained transgenerationally by epigenetic machinery [56]. Although several components involved in the maintenance of transcriptional gene silencing have been identified in plants, the detailed mechanisms, which may be distinct among different plant species, are not fully understood. Technological advances in plant epigenetics are providing unprecedented opportunities to monitor chromatin modifications, gene expression, and genome structure [50–52]. Many classical epigenetic phenomena, such as transposable element inactivation, imprinting, paramutation, transgene silencing, and cosuppression, have been first documented in plants [52–58]. Recent studies have demonstrated that plants are heavily dependent upon changes in gene expression to respond to environmental stimuli, and chromatin-based regulation of gene expression is likely crucial for these responses [30–35]. The level of

chromatin "resetting" during sexual reproduction appears to be lower in plants in comparison with animal species [50,51]. It potentially allows inheritance of epimutations acquired during plant life, and many plant species can propagate asexually and produce vegetative clones, providing opportunities for mitotic inheritance of epigenetic states, leading to important traits [50–54]. Study of nutrient contents in these new traits and how to alter nutrient contents may be the future of functional food production using biotechnology methods [50].

Epigenetic markers in the form of DNA methylation can influence cytosines in different sequence contexts such as CG, CHG, and CHH (where H is any base other than G) and at different types of loci in plant genomes. The silencing of transposons, which are called genomic parasites and invade the genome of their hosts, may be an important mechanism of epigenetic regulation [50,51]. The repetitive nature of transposons and the fact that they generate large insertion/deletion polymorphisms among genotypes has led to difficulties in monitoring the link between transposon polymorphism and variation in DNA methylation. Epigenetic silencing influences the vast majority of transposons that are highly methylated [51,52]. Eukaryotic genomes consist of two types of DNA, genic and intergenic, in which the genic regions are associated with an open euchromatic state and the inactive, intergenic regions are associated with a closed heterochromatic state. Segregation of the genome into active and repressed regions requires complex sets of enzymes to direct appropriate, context-specific activity of RNA polymerases. It is possible that a conflict would emerge at the boundaries of intergenic and genic regions, where regions of genetic repression must cooperate or at least not interfere with the expression of genes and epigenes. Mammalian and plant DNA methylation is restricted to symmetrical CG sequences, but plants also have significant levels of cytosine methylation in the symmetric context CHG (where H is A, Cm or T) and even in asymmetric sequences. Cytosine DNA methylation is a heritable epigenetic marker that is present in many eukaryotic organisms and is performed by DNA-methyltransferases that catalyze transfer of a methyl group from S-adenosyl-l-methionine to cytosine bases in DNA (see Fig. 3.3).

The CHH methylation is maintained owing to RNA-dependent methylation of DNA (RdDM) and requires the plant-specific RNA polymerases IV and V. Polymerase IV generates precursor transcripts of 24-nt small RNAs that target scaffold transcripts from polymerase V by sequence complementarity and recruit the domains rearranged methyltransferase 2 [52]. Zhang and coworkers demonstrated a new link between RdDM and the chromatin-remodeling factor PICKLE (PKL), indicating that PKL is required for the accumulation of transcripts generated by polymerase V and for the positioning of polymerase V–stabilized nucleosomes at a subset of RdDM target loci [53]. The results link

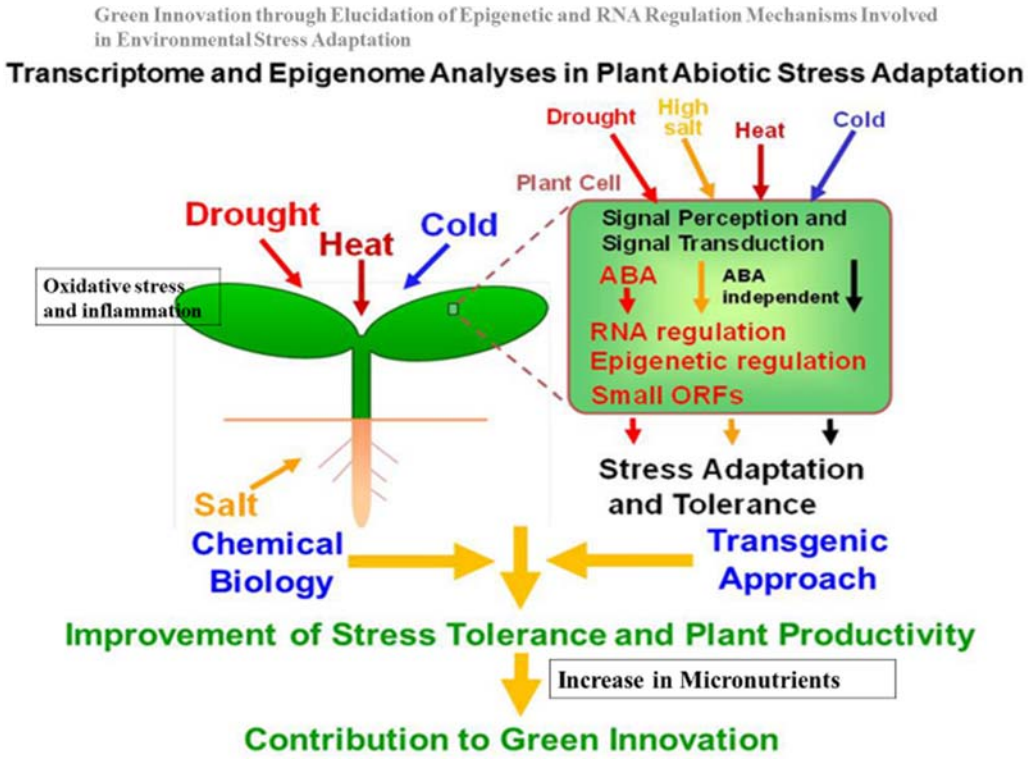


FIGURE 3.3 Effects of oxidative stress and inflammation on epigenetic alterations. *ABA, Arabidopsis abscisic acid; ORFs, open reading frames.*

nucleosome positioning with the initiation of RdDM, consistent with the previously proposed role of SWI/SNF chromatin-remodeling complexes in establishing positioned nucleosomes on specific loci primed for RdDM [54]. The plant development is regulated by PICKEL and, in particular, regulates the access of Polycomb group proteins to its targets as well as SWI/SNF complexes also have a role in the development of plants (five of the phytochrome interacting factor 4 to nucleosome-free regions) [56]. It is possible that the dual functional role of chromatin-remodeling factors in regulating plant development and RdDM may have both processes more closely connected than is widely appreciated. The gene body methylation indicating moderate levels of CG methylation found within the exons of transcribed genes correlates with intermediate levels of expression [57]. More studies should be conducted to demonstrate the role of nutrition in the epigenetic regulation for the development of new functional foods and new perspective for health promotion and prevention of obesity and other diseases [42,43,50–64].

In summary, the evolution of animal and plant foods has occurred with human evolution. The diets of our prehistoric ancestors were rich in vegetables, leaves, roots, fruits, seeds, milk, and honey. Fish and meats were also available to early humans. These foods are rich in flavonoids, fiber, omega-3 fatty acids, antioxidants, vitamins, and minerals as well as amino acids. However, supplementation of flavonoids with PUFA and optimal levels of omega-6 and omega-3 fatty acids to achieve a ratio of 1:1 in the tissues with optimal choline, betaine, folic acid, and vitamin B_{12} as well as other essential amino acids, antioxidants, and vitamins can modulate methylation of DNA, causing reduction in phenotypes for health or disease by epigenetic regulation. Feeding diets that are high in flavonoids and omega-3 fatty acids and other nutrients to animals can increase these nutrients in the eggs, milk, and skeletal muscle of these animals and may modulate the epigenome with beneficial effects. However, further research is necessary to determine the relationship of environmental factors such as microgravity, solar radiation, drought, soil quality, and nutrition in epigenetic regulation for the development of new functional foods and new perspectives for health promotion and disease prevention.

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Section 2

Evolutionary diet and functional foods available in the world

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Chapter 4

Beneficial effects of gourds in health and diseases

Najah Hadi[1], Poonam Tiwari[2], Ram B. Singh[3], Khemraj Rupee[4], Sunil Rupee[4], Carlin Hanoman[4,5] and Jaipaul Singh[5,*]

[1]*Department of Pharmacology and Therapeutics, Faculty of Medicine, University of Kufa, Kufa, Iraq,* [2]*Department of Dietetics, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India,* [3]*Halberg Hospital and Research Center, Civil Lines, Moradabad, India,* [4]*School of Medicine, Faculty of Health Sciences, University of Guyana, Guyana,* [5]*School of Natural Sciences, College of Science and Technology, University of Central Lancashire, Preston, United Kingdom*

**Corresponding author. e-mail address: Jsingh3@uclan.ac.uk*

Introduction

The oldest evidence of the use of medicinal plants for the preparation of drugs was found on a Sumerian clay slab from Nagpur in India (3000 BCE). On the slab, 12 different drug recipes for medicinal preparations were written involving over 250 different plants, including poppy, henbane, and mandrake. Most of these preparations possessed alkaloid and antioxidant properties. Gourds belong to family of Cucurbitaceae, which are known as cucurbits. The cucurbits include a variety of gourds which are used as vegetables. Commonly used vegetable gourds are ash gourd (*kumehenra* in Hindi), bitter gourd (*karela* in Hindi), bottle gourd (*loki* in Hindi), pointed gourd (*kundru* in Hindi), and snake gourd (*perval* in Hindi) (see Table 4.1) [1,2]. India is believed to be the primary and secondary centers of origin for such species as ash gourd, bottle gourd, snake gourd, bitter gourd, ivy gourd, and pointed gourd [2]. Ash gourd, bitter gourd, and bottle gourd have been extensively studied, and several health benefits and functional components have been reported about these gourds [2]. However, there has been little research on snake gourd, ridge gourd, ivy gourd, and pointed gourd exploring their therapeutic benefits. More research needs to be conducted to further understand the nutritional and medicinal potentials of gourd vegetables and to determine how to raise the interest of the agricultural sector and increase the confidence of consumers, leading to increased production and use of these vegetables.

TABLE 4.1 Common names, alternative names, and scientific names of selected gourds.

Common name (Indian name)	Alternative name(s)	Scientific name
Ash or white gourd (*kumerha*)	Ash or white pumpkin	*Benincasa hispida*
Bitter gourd (*karela*)	Bitter cucumber, melon	*Memodica charantia*
Bottle gourd (*lauki*)	Malina	*Lagenaria siceraria*
Ridge gourd (*torai*)	Dodka, roxb	*Luffa acutangula*
Snake gourd (*chichinda*)	Chichingo	*Trichoscnthes cucumerina*
Ivy gourd (*kundru*)	Little gourd, baby melon	*Coccinia glandis*

Source: Modified from references Devaki C, Wadikar D, Patki P. Vegetable gourds—guards of human health: a critical appraisal. Nutr Food Sci 2015;45:125–44. https://doi.org/10.1108/NFS-12-2013-0146; Subramani B, Krishnamurthy B. Effects of Momordica Charantia (bitter gourd) on oxidative stress and pro-inflammatory marker in metabolic syndrome using a high-fructose diet induced rat model. Biomed Pharmacol J 2019;12(1). https://bit.ly/2VAzNcs [1,7].

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The gourds are used in a variety of ways. Common preparation methods include fried in snacks and curries (bitter gourd, bottle gourd, pointed gourd), boiled in vegetable curries (ash gourd, snake gourd, pointed gourd), pickled (ash gourd, pointed gourd), or candied (ash gourd, pointed gourd) [4,5]. The fruits of all the gourds are used for their therapeutic properties, including antiinflammatory, analgesic and antipyretic, nootropic, antidepressant, anorectic, anxiolytic, diuretic, antioxidant, antihistamine, antidiarrheal, angiotensin-converting enzyme (ACE) inhibition, renal, and gastroprotective activities [1–3]. This review aims to describe nutritional and therapeutic benefits and functions of gourds with particular attention to ash, bottle, and bitter gourds for comparison.

Gourds as functional foods

The role of gourd vegetables as functional food has inspired many experts to conduct further research and to do several comprehensive reviews of these vegetables, owing to their potential medicinal properties and phytochemical contents [5–7]. Nutrient contents are important characteristics in defining the therapeutic quality of a particular food. The nutritional composition of the edible portion (pulp) of gourd vegetables indicates a high moisture content, accounting for more than 92% of the edible weight portion [6,7]. The amount of protein and ash are in the range of 0.2%–1.6% and 0.4%–0.8%, respectively. Fat content is low, contributing to less than 0.3% by weight of the edible portion. Apart from macronutrients, vitamins and minerals are the essential nutrients found in all the gourds (see Tables 4.2 and 4.3).

Flavonoids and polyphenolics are protective phytochemicals that plants generate to fight environmental factors, including insects and infecting agents: bacteria, viruses, and fungi. Recently, these agents have been found to be protective and are required by the body to normalize physiological functions, and these phytochemicals can be obtained by daily food intake. Among the different gourd vegetables, thiamine content ranged from 0.03 to 0.07 mg, riboflavin from 0.01 to 0.09 mg, niacin from 0.2 to 0.5 mg, and vitamin C from 1 to 88 mg per 100 g of the vegetables. The highest amount of vitamin C is found in bitter gourd (see Table 4.3) [6,7]. Among the minerals, calcium was the major mineral present in gourd vegetables, with concentrations ranging between 20 and 30 mg/100 g (see Table 4.3) [6]. Bioactive components of gourd vegetables contain an array of novel and biologically active phytochemicals, including minerals and vitamins, polyphenolics, triterpenes, proteins, and steroids (see Table 4.4).

Ash gourd (*Kumehrah*)

The name ash gourd was derived from the color of the gourd's skin, which is similar to the color of ash. It is also called wax gourd in some regions in India because the skin has a waxy shine. The ash gourd is also called winter gourd because it can be cultivated even during rainy seasons in winter.

The ash gourd, or *kumehrah* (*Benincasa hispida*), originated in South Asia, mainly in India, and the fruit found its place in Ayurvedic preparations, in which it was referred to in Sanskrit as *kushmanda* [8,9]. It is widely grown throughout South and Southeast Asia, including Myanmar, Malaysia, China, Japan, and almost all countries of Southeast Asia, as a prominent crop. Since it cannot survive extreme cold, it is not grown in Western countries. The ash gourd has been reported to have anticancer effects. It is also beneficial in treating diabetes, inflammatory diseases, and kidney dysfunctions as well as in the treatment of nausea, vomiting, gastritis, and esophagitis. Its extracts are used in treatment of headache and anxiety disorders as well as depression and epilepsy. Ash gourd juice may be protective against cold, fever, bronchitis, allergies, and asthma [10].

Ash gourd is also used widely in food preparations in India, China, Taiwan, and the Philippines because of its delicacy, aromatic flavor, and soft texture and is used during festival times as a ritual food. Sweets made out of ash gourd are famous in North India. The firm flesh of the older fruits is also candied with sugar and can be dried for later use as *petha* in India. In South India, ash gourd is used in every household in daily preparations of several dishes, including sambhar, koottu, salads, and juice. It is grown throughout the old world tropics and is less common in the new world tropics [11–15]. Ash gourd is grown for both its immature and mature fruits. In India it is used extensively in curries and is offered to the gods in religious ceremonies. The ripe fruits have juicy greenish-white flesh with a flat taste. Ash gourd juice is also processed and preserved by aseptic processing and is stable for up to eight months under ambient conditions [15].A blend of beverages from ash gourd and mint that was aseptically processed and sterilized at 95°C and packed in tetra pack (six-layered) showed stability for eight months [16]. In China ash gourds are often stuffed with meat, shrimp, and vegetables and then steamed in a pot [17]. It has been reported that it is now possible to stabilize ash

TABLE 4.2 Mineral contents of gourd vegetables per 100 g of each gourd.

Name of gourd (per 100 g)	Sodium (mg)	Potassium (mg)	Calcium (mg)	Copper (mg)	Iron (mg)	Magnesium (mg)	Manganese (mg)	Phosphorus (mg)	Selenium	Zinc, (mg)
Bottle gourd	2.0	150	26	0.034	0.20	11	0.089	13	0.2 mg	0.70
Bitter gourd	5.0	296	19	0.034	0.43	17	0.089	—	—	0.80
Snake gourd	33.0	359.1	5.1%	—	5.7%	6.7%	12.5%	5%	—	
Ash gourd	6.0	111	19	—	0.4	10	0.058	19	0.2 μg	0.61
Ridge gourd	3.0	139	20	—	0.36	14	—	32	—	0.07

TABLE 4.3 Vitamin contents of gourd vegetables per 100 g of each gourd.

Name of Gourd (per 100 g)	Folate	Niacin	B5	B6	B2	B1	A	C	E
Bottle gourd	6 μg	0.320 mg	152 mg	0.040 mg	0.02 mg	0.029 mg	19 IU	10.1 mg	
Bitter gourd	72 μg	0.0400 mg	0.212 mg	0.043 mg	0.040 mg	0.040 mg	471 IU	84 mg	
Snake gourd				11.3%			9.8%	30.5%	1.1
Ash gourd	5 μg	0.400 mg	0.133 mg	0.035 mg	0.11 mg	0.04 mg	0	13 mg	
Ridge gourd	7 μg	0.0400 mg	—	0.043 mg	0.060 mg	0.050 mg	410 IU	12 mg	

gourd juice and a blend of ash gourd and mint juice by subjecting the juices to irradiation treatment. It was also reported that the developed juices were stable for up to eight months with a good acceptability score and that the juices were microbiologically safe to consume.

Composition of ash gourd

The composition of gourds is given Tables 4.2–4.4. According to the U.S. Department of Agriculture's nutrient database, each 100 g of ash gourd contains 13 kcal of energy, 0 mg of fat, 3 g of carbohydrates, 2.9 g of fiber, 4 g of protein, 13 mg of vitamin C, 0.1 mg of riboflavin, 0.4 mg of niacin, 5 μg of folate, 0.1 mg of pantothenic acid, 19 mg of calcium, 4 mg of iron, 10 mg of magnesium, 19 mg of phosphorus, 6 mg of potassium, 111 mg sodium, 0.6 mg of zinc. and 0.1 mg of manganese. The famous Ayurvedic preparation *Kooshmanda rasayana* is made of ash gourd fruit because of its high phytochemical content. These include carotenoids (carotenes); peptides (beneincasins, hispin); phenolics sterols (lupeol, lupeol acetate, beta-sitasterol); triterpenes (alnusenol, multiflorenol, isomultiflorenol); and uronic acid. It is valued for bioactives and therapeutic agents such as triterpenes, phenolics, sterols, glycosides, and soluble dietary fiber (see Tables 4.1–4.4) (Fig. 4.1).

Previous studies have indicated that ash gourd has been used as an antibiotic and purgative vermifuge for cough, fever, cardiovascular and liver disorders, and kidney disorders [10–14]. It may also protect patients from seizures, cough, fever, heart conditions, and liver disorders [13,14]. Ash gourd has been found to have hypoglycemic and hypolipidemic effects in diabetes by causing a 42% decline in blood glucose levels after 21 days of administration [15–17]. In another study, supplementation of ash gourd juice to dyslipidemic subjects for 45 days revealed a small increase in high-density lipoprotein (HDL) cholesterol, a decrease in very low-density lipoprotein (VLDL) cholesterol, an increase in the serum cholesterol/HDL cholesterol ratio, and a decrease in the triglyceride/HDL cholesterol ratio [1,17].

In another study, supplementation of ash gourd fermented beverage to a geriatric population for a period of two months showed a significant decline in fasting blood glucose from 90.8 to 82.2 mg/dL and a decrease in postprandial blood glucose from 137.4 to 122.4 mg/dL, along with a 9 mg/dL decrease in serum cholesterol, a 22 mg/dL decrease in triglycerides and a 6.9 mg/dL decrease in low-density lipoprotein (LDL) cholesterol [17,18]. In elderly subjects, supplementation of ash gourd fermented beverage for two months was associated with a significant improvement in body mass index, blood glucose levels, lipid profile, and hemoglobin levels in the experimental group compared with those in the control group [18]. It is clear that supplementation of ash gourd may be associated with significant improvement in blood glucose, blood lipid profile, hemoglobin levels, and body weight. The seeds of the ash gourd have a higher amount of phenolic content compared to pulp, and the seeds are known to provide greater antioxidant activity, owing to the higher total phenolic content and superoxide dismutase activity. These functions of ash gourd may be responsible for the antioxidation and inhibition of ACE activity. which may provide protective effects against cardiometabolic diseases and cancers.

In a pilot study, 90 newly diagnosed type 2 diabetic mellitus (T2DM) patients were divided into three experimental groups. All the patients had fasting blood glucose ranging between 120 and 300 mg/dL. One group received bitter gourd juice; the second and third groups received knol khol (kohlrabi) and ash gourd juices, respectively [19]. The mean fasting blood glucose concentration in the bitter gourd group 90 minutes after intake of juice declined significant compared with the fasting level prior to intake. The decline in blood glucose was much faster in comparison to patients who drank either ash gourd juice or knol khol juice. In another study, oral administration of alcoholic extract of ash gourd at doses of 50, 100 and 200 mg/kg body weight was associated with a significant decline in blood glucose in a dose-dependent manner [20]. Bitter gourd juice appears to reduce blood glucose more rapidly, while knol khol juice reduces blood

TABLE 4.4 Total phenols, flavonoids, tannins, and carotenoid contents of different gourd vegetables.

	Total phenols (mg GE/100 g)			Total flavonoids (mg QE/100 g)			Tannin content (mg CE/100 g)			Carotenoids content (mg beta-carotene/100 g)		
	ME	EE	BE	ME	EE	BE	ME	EE	BE	ME	EE	BE
Cucurbita pepo	519.81 ± 2.35^{g}	336.25 ± 1.52^{e}	272.01 ± 1.57^{d}	64.34 ± 1.37^{g}	56.83 ± 0.59^{f}	45.03 ± 0.90^{c}	18.11 ± 4.80^{c}	7.72 ± 1.47^{b}	6.81 ± 3.36^{a}	3.78 ± 0.08^{c}	1.19 ± 0.10^{b}	2.44 ± 0.08^{b}
Cucurbita maxima	62.53 ± 0.92^{a}	56.11 ± 0.69^{a}	53.15 ± 0.80^{a}	3.72 ± 0.20^{a}	3.73 ± 0.22^{a}	10.41 ± 0.39^{a}	2.94 ± 0.20^{a}	1.81 ± 0.76^{a}	7.63 ± 1.34^{a}	0.50 ± 0.03^{a}	0.24 ± 0.05^{a}	0.25 ± 0.03^{a}
Trichosanthes dioica	163.22 ± 1.53^{b}	118.82 ± 1.11^{b}	100.54 ± 1.00^{b}	30.26 ± 0.44^{c}	25.24 ± 0.20^{b}	34.95 ± 0.25^{b}	11.24 ± 1.29^{b}	8.44 ± 0.81^{b}	17.3 ± 1.07^{c}	3.82 ± 0.06^{c}	1.34 ± 0.04^{b}	5.11 ± 0.09^{d}
Luffa acutangula (ridge gourd)	228.62 ± 1.77^{d}	156.23 ± 2.02^{c}	251.12 ± 1.19^{c}	32.51 ± 0.41^{d}	27.91 ± 0.52^{c}	65.36 ± 0.26^{d}	3.11 ± 1.71^{a}	8.41 ± 2.07^{b}	15.5 ± 1.07^{bc}	2.43 ± 0.05^{b}	2.31 ± 0.10^{c}	3.42 ± 0.05^{c}
Lagenaria siceraria (bottle gourd)	355.17 ± 0.91^{e}	463.64 ± 1.37^{g}	658.96 ± 2.41^{f}	54.32 ± 0.39^{f}	84.85 ± 0.35^{g}	278.95 ± 0.55^{g}	6.64 ± 0.96^{ab}	8.13 ± 1.40^{b}	10.6 ± 2.03^{abc}	7.34 ± 0.03^{e}	14.8 ± 0.10^{e}	19.41 ± 0.18^{f}
Momordica charantia (bitter gourd)	501.73 ± 2.52^{f}	440.79 ± 2.12^{f}	451.84 ± 3.49^{e}	47.87 ± 0.43^{e}	46.93 ± 0.56^{e}	104.17 ± 0.57^{e}	$6.42 \pm 1.84^{a,b}$	24.42 ± 1.92^{c}	$9.69 \pm 4.74^{a,b}$	15.7 ± 0.11^{f}	20.4 ± 0.13^{f}	22.05 ± 0.21^{g}
Luffa cylindrica (ash gourd)	216.30 ± 2.09^{c}	300.06 ± 2.51^{d}	275.16 ± 2.62^{d}	24.51 ± 0.48^{b}	45.44 ± 0.72^{d}	146.38 ± 0.75^{f}	2.91 ± 1.64^{a}	9.25 ± 2.27^{b}	5.64 ± 2.37^{a}	4.63 ± 0.10^{d}	9.94 ± 0.16^{d}	12.94 ± 0.17^{e}
Mean	292.48	267.41	294.68	36.79	41.56	97.89	7.33	9.74	10.45	5.45	7.17	9.37
F-Statistics at d.f. = 6,14 ($P = .000$)	$F = 26{,}852.9$	$F = 25{,}904.2$	$F = 29{,}559.6$	$F = 3072.1$	$F = 8496.7$	$F = 77{,}986.6$	$F = 16.9$	$F = 54.9$	$F = 8.6$	$F = 14.374$	$F = 17{,}520.2$	$F = 15{,}457.5$

Values are presented as mean ± SD ($n = 3$) and refer to the dry weight. Means in columns followed by different letters differed significantly at the 5% level of significance ($P < .05$). *BE*, Butanolic extract; *CE*, catechin equivalent; *EE*, ethanolic extract; *GE*, gallic acid equivalent; *ME*, methanolic extract; *QE*, quercetin equivalent.



FIGURE 4.1 An ash gourd.

glucose level gradually over a longer period of 120 minutes, indicating the beneficial effects of these foods in patients with T2DM [19,20]. One of these studies also found that supplementation of ash gourd juice to adults in desert areas reduced the percentage of anemia from 60% to 33% [20]. This trial, by the Defense Food Research Laboratory and Desert Medicine Research Laboratory on adults in desert areas of Rajasthan, revealed that supplementation of ash gourd juice decreased gastritis significantly from 50% to 29.7%, urinary tract infection from 34.7% to 16%, breathlessness from 25% to 5%, and thirst from 97% to 81% ($P < .05$) [20]. Some workers also reported that the controlled fermentation and particle size can improve nutritional quality of ash gourd fermented beverages [21,22]. In vitro and in vivo studies conducted on ash gourd fruit revealed that its juice and extract have antioxidant activity, especially on human tissues such as the liver and brain [23,24].

Ash gourd contains certain active components, such as terpenes, flavonoid C-glycosides, and sterols, that have antioxidant effects, which in turn can inhibit gastric mucosal injury by scavenging the free radicals with increased production of superoxide dismutase and vitamin C in rats [25]. Ash gourd can also protect the body from peptic ulcer and hemorrhage, and it possesses antibiotic and purgative vermifuge properties [11]. Effects of an extract of ash gourd on allergic inflammation were examined in mice, and the extract was found to be effective against allergic inflammation [26]. Hypoglycemic, hypolipidemic, and antioxidant effects of ash gourd have been observed in other experimental studies [27,28]. Similarly, it was reported that ash gourd can improve memory deficit and compulsive behavior [11,29,30]. In the rat model of Alzheimer's disease, ash gourd supplementation (400 mg/kg body weight) was associated with a protective effect on memory function [29]. It is possible that tryptophan present in the ash gourd is responsible for enhancing the biosynthesis of serotonin to facilitate anticompulsive effect [30]. It seems that majority of the beneficial effects of ash gourd appear to be due to the flavonoids, polyphenolics, and carotenoid contents of this vegetable. Therefore it is of paramount importance to ascertain how much ash gourd should be consumed daily by people and animals to provide adequate amount of these bioactive agents in the foods. It is equally important to find out whether the antioxidant contents and other phytochemicals of ash gourd are heat labile and whether ash gourd should be eaten raw or cooked to provide the maximum protective benefits.

In summary, many vegetables are excellent sources of essential phytochemicals that are beneficial to health and in the delay and prevention of diseases that have inflicted humankind. Ash gourd is commonly consumed as a vegetable and used for making sweets and the dish known as sambhar in South India. Ash gourd is rich in carotenoids, peptides, phenolics, triterpenes, and uronic acid. Ash gourd is also rich in vitamins and minerals. It is also beneficial as an antibiotic and purgative vermifuge for cough and fever and in treating heart, liver, and kidney diseases and disorders. The higher antioxidant capacity of the seed may result from the higher total phenolis contents and superoxide dismutase activity. The antioxidation properties and ACE activity inhibition of ash gourd can provide protective effects against such major non-communicable diseases (NCDs) as obesity, diabetes, cardiovascular disease, and cancers.

Bottle gourd (*Lauki*)

In India the bottle gourd (*Lagenaria siceraria*) is popularly known as *lauki, ghia*, or *dudhi*. The bottle gourd belongs to the family Cucurbitaceae, which comprises about 118 genera and 825 species [31,32]. The bottle gourd is a popular



FIGURE 4.2 A bottle gourd.

vegetable crop in India. The production of bottle gourd is influenced by a number of factors, including nutritional, environmental, cultural operation, and use of plant growth regulators. Since bottle gourd is considered a medicinal plant, it plays a major role in the treatment of several diseases related to cardiometabolic risk factors and mental diseases. In Ayurveda, bottle gourd supplementation is advised for the treatment of weight loss, diabetes mellitus, hypertension, flatulence, and liver diseases and for its cooling properties [31–33]. The juice of bottle gourd is widely used as complementary and alternative therapy in India. Since ancient times, the bottle gourd has been known for its curative properties in the treatment of gastric ulcer, piles, jaundice, diabetes, colitis, insanity, hypertension, diabetes, heart failure, and skin diseases. Its fruit pulp is used as an emetic and a purgative and for its cooling, diuretic, antibilious, and pectoral properties. After being boiled in oil, the pulp is used to treat rheumatism and insomnia. In many tropical and subtropical regions, bottle gourd is grown as an annual herbaceous climbing plant and has a long history of traditional use as medicine and food (see Fig. 4.2).

Composition of bottle gourd

A wide range of chemical compounds, including sterols, terpenoids, flavonoids, and saponins, have been isolated from the bottle gourd [31]. Its extracts have been found to possess various pharmacological properties. Outlined below is a comprehensive review of its ethnomedical uses, chemical constituents, and pharmacological profile as a medicinal plant. The chemical composition of bottle gourd, including vitamins, minerals, and phytochemicals, is given in Tables 4.2–4.4. Particular attention is given to its analgesic, antiinflammatory, antihyperlipidemic, diuretic, hepatoprotective, anthelmintic, and antibacterial effects so that its potential uses in the pharmaceutical industry can be better appreciated and evaluated [31–33]. Several organic chemical compounds, including vitamin B complex, pectin, dietary soluble fiber, ascorbic acid, beta-carotene, amino acids and minerals, have been isolated from this species [32]. Therefore the bottle gourd is considered to have great therapeutic health benefits. However, bottle gourd juice may have adverse effects on liver function, acute gastritis, and loose stools [34,35]. Bottle gourd also contains cardolenides such as periplogenin glycosides, carotenoids, and beta-carotene and phenolics such as (E)-4-hydroxymethyl-phenyl-6-Ocaffeayl-b-*O*-glucopyranoside, 1-(2-hydroxy-4-hydroxymethyl)-phenyl-6-*O*-caffeayl-b-D-glucopyranoside protocatechuic acid, gallic acid, caffeic acid, and 3,4-dimethoxy cinnamic acid flavone-C glycosides, ellagitannins, polysaccharides such as galacturanates, triterpene, and cucurbitane as well as friedoleananetype and sterols such as fructosterol and camposterol (see Table 4.4 and Fig. 4.3).

Bottle gourd is of great value for vegetarians, since it contains several important constituents that are required for good health and well-being. In India, interest in bottle gourd has been growing among consumers because consumption of bottle gourd has become associated with a number of benefits, and it may be regarded as a natural guard against diseases [35–39]. A blended juice from bottle gourd with basil leaves was developed by in-pack pasteurization [36]. The juice was stable for up to six months at room temperature without any remarkable changes in terms of quality markers such as total soluble solids and acidity. However, losses in vitamin C and beta-carotene were reported to the level of 74% and 57%, respectively, over the storage period. Cell wall polysaccharides from *chalkumra* (*Benincasa hispida*) fruit were also prepared with isolation and characterization of pectins [37]. In Ayurveda, bottle gourd is advocated for treatment of diabetes

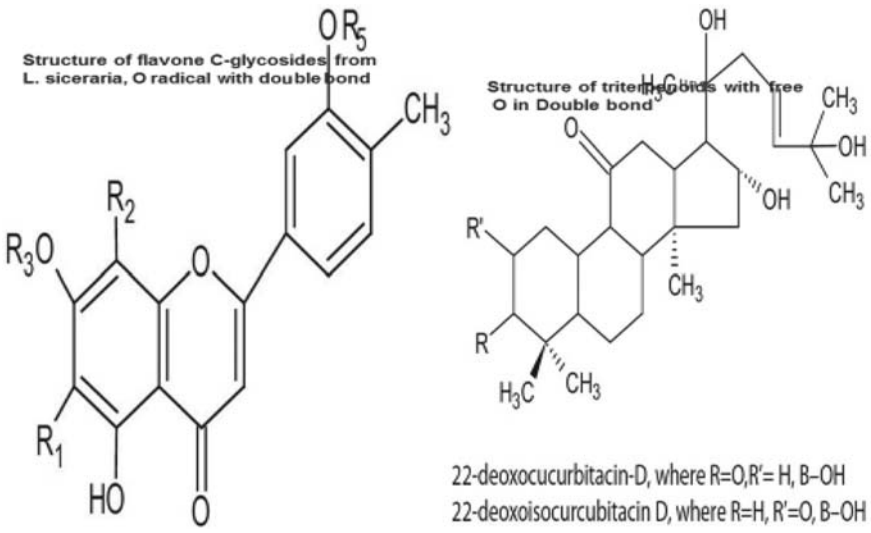


FIGURE 4.3 Chemical structure of two typical bioactive agents present in ash gourd. *Modified from reference Roopan SM, Devi Rajeswari V, Kalpana VN, Elango G. Biotechnology and pharmacological evaluation of Indian vegetable crop* Lagenaria siceraria*: an overview. Appl Microbiol Biotechnol 2016;100(3):1153–62. doi:10.1007/s00253-015-7190-0 [32].*

mellitus, hypertension, flatulence, liver diseases, weight loss, and other associated benefits, such as its cooling properties. The nutritive value of bottle gourd makes it a popular ingredient in sweet curries, soups, jams, juices, beverages, cakes, ice creams, and tea. The literature available on functional properties, health benefits, and applications of bottle gourd in various food products has been reviewed [38,39]. Bottle gourd has been used for the treatment of cough and diabetes, blood lipids, insomnia, rheumatism, heart disease, and cancer and as a diuretic and general tonic [35–44].

Gangwal et al. [41] examined the immunomodulatory activity of extracts of bottle gourd that were administered to rats. The results showed significant inhibition of hemagglutination antibody titer and carbon clearance with a significant increase in white blood cell counts in mice, indicating a decline in immunomodulatory activity. Methanolic extracts of bottle gourds in doses of 200 and 400 mg/kg body weight administered for nine days revealed that the extract inhibited growth of cancer, indicating anticancer activity [42]. Cardioprotective activity of bottle gourd was evaluated in a rat model for two days, and there was significant decline in the cardiac mitochondrial enzymes and significantly lower activities of lysosomal enzymes in heart tissues [43]. Hemeda et al. [44] examined the hypolipidemic effects of bottle gourd by feeding of raw bottle gourd seed (10%) to rats given as a high-cholesterol diet. After 30 days of feeding with bottle gourd seeds, there was a significant increase in serum HDL cholesterol and decreased LDL cholesterol concentrations [44].

Bitter gourd (*Karela*)

Bitter gourd, also called bitter melon, belongs to family *Cucurbitaceae* and is native to subtropical and tropical areas in Asia, in particular India, and some other parts of the globe, including Africa and the Caribbean and part of South America. In Indian cuisines it is usually referred to as *karela* [1,45–47]. Bitter gourd is used as a vegetable in many countries, but since time immemorial, it has also been used for therapy for numerous ailments, such as diabetes mellitus, obesity, hypertension, cancer, gastric ulcer, and many inflammatory diseases. Bitter gourd has numerous medicinal uses in treating fevers, gastrointestinal complaints, painful menstruation, and skin conditions and in wound healing [1,45–55]. Bitter gourd is often used in folk medicine to treat diabetes mellitus, which has also been observed in trials in experimental animals models and humans [45–55], A significant number of studies have established the hypoglycemic, hypolipidemic, and antitumor activities of bitter gourd [1,45–61]. The morphology of the plant indicates that it is a herbaceous plant that grows around 5 m and bears simple, alternate leaves of 4–12 cm with three to seven deeply separate lobes. Bitter gourd is similar to a small cucumber, usually oblong in shape and eaten green and fresh to have the maximum beneficial effects (see Fig. 4.4).

Composition of bitter gourd

Aside from its skin, bitter gourd consists of pulp and large flat seeds surrounding a comparatively thin layer of flesh, guarding the nutritional composition [62–68]. Bitter gourd contains 91.8% water, 0.20% fat, 4.2% carbohydrates, and 1.4% fiber per 100 g. The proteins that are present in bitter melon seeds are of good quality and meet the amino acids



FIGURE 4.4 Bitter gourds.

requirements laid down by the Food and Agriculture Organization, World Health Organization, and United Nations University for preschool children. The proteins in the bitter gourd are fractionated into albumin, globulin, and glutelin, which are present in the amounts of 49.3%, 29.3%, and 3.1%, respectively. The molecular weight of these proteins usually varies from 45 to 55 kDa [62,63]. The seeds of bitter gourd contain nearly 35%−40% oil. The fatty acid profile indicates that the seeds contain 3.33% and 36.71% of MUFA (monounsaturated fatty acid) and SFA (saturated fatty acids), respectively. The largest amount (59.96%) of PUFA (polyunsaturated fatty acids) in bitter gourd includes alpha-eleostearic acid (54.26%), a conjugated linolenic acid that is of significant importance in nutrition [64,65]. Bitter gourd has a healthy mineral profile, including potassium, magnesium, calcium, manganese, sodium, iron, and phosphorus in the highest amounts, particularly in the fruit and leaves (see Tables 4.2−4.4 [68]). However, the seeds are one of the naturally best sources of chromium and zinc, Typical amounts of chromium and zinc are 5.65 mg/100 g and 45.45 mg/100 g, respectively.

Bitter gourd also comprises of over 68 different compounds, including minerals and vitamins [67]. Some of the phytochemicals include glucosides, charantin, steroidal saponin, alkaloids, momordium, carbohydrates, ascorbic acid, gallic acid, ceulic acid, and other phytochemicals [67]. By using Folin-Ciocalteu reagent, quantitative measurement of the phenolic compounds has identified an occurrence of 42.36 mg GAE/g in bitter gourd. The occurrence of gallic acid in bitter melon as the main phenolic acid has been showed by HPLC examination of the gourd's phenolic contents. Many other phenolic components are found to be present in bitter melon extract, such as epicatechin, chlorogenic acid, catechin, and gentisic and ceulic acids (see Table 4.4). Bitter melon also contains many other phytochemicals, including alkaloids such as momordicine; carotenoids such as cryptaxanthin and beta-carotene; zeananthin peptides such as gumarin (insulin-like); phenolics such as catechnin and epicatechin, gallic, caffeic, coumaric, genitisic, and chlorogenic acids; saponins including goyasaponins; and triterpenoids such as cucurbitane-type glycosides (momordin, cucurbitacin, and charantin) and oleanone-type glycosides

Therapeutic clinical uses of bitter gourd

Bitter gourd supplementation in patients with diabetes mellitus revealed that the majority of the patients experienced hypoglycemic and hypolipidemic benefits after drinking an aqueous homogenized suspension of the vegetable pulp [69]. In another study, supplementation of bitter gourd fermented beverage (45 mL) among patients with diabetes mellitus showed a significant decline in polyphagia by 38%, fatigue by 37%, polyurea by 33%, general weakness by 31%, and burning feet by 19% [70]. There was a 24%−31% reduction in fasting blood glucose and a 18%−25% decrease in postprandial blood glucose. Another study reported that supplementation of bitter gourd fermented beverage (45 mL) among patients with diabetes mellitus, for a period of five months was associated with significant reduction in fasting blood glucose from 210 to 120 mg/dL (43%) and a decrease in postprandial blood glucose from 283 to 167 mg/dL (41%). On average, glucose reduced from 161.05 ± 3 8.17 to 118.24 ± 25.39 mg/dL [71]. HbA1c levels indicated that the diabetic subjects had fairly good control of glucose levels. In a clinical study of 42 patients of with metabolic

syndrome (21 men and 21 women) with a mean age of 45.7 ± 11.4 years (23−63 years), 4.8 g of lyophilized wild bitter gold powder in capsules daily was administered for three months [72]. There was a significant ($P < .021$) decline of 19.5% in the incidence of metabolic syndrome after a follow-up of 3 months. The patients' waist circumference decreased significantly after the supplementation of wild bitter gourd. Further studies are necessary to provide proof for this function of bitter gourd in the treatment of metabolic syndrome.

Experimental studies

Several experimental studies confirmed the role of bitter gourd in the treatment of diabetes, oxidative stress, and hyperlipidemia [47,56,61,69,73−75]. In an experiment, mice with grade II and grade III metabolic syndrome were treated with bitter gourd (600 mg/kg/day), and the results showed a reversal of the parameters of metabolic syndrome to almost normal levels. These data revealed the therapeutic efficacy of bitter melon compared to the standard therapy. The biological basis of the effects of bitter gourd involved the inhibition of the inflammatory pathway in metabolic syndrome at the levels of both reactive oxygen species generation and transcription of proinflammatory marker NF-κB [7]. In their study, Chaturvedi and George [47] reported that supplementation of bitter gourd to 5 normal rats and 20 diabetic rats maintained normal glucose levels in all experimental groups, reduced triglycerides and LDL cholesterol levels, and increased levels of HDL cholesterol [47]. It also improved antioxidant status, with a decrease in the levels of thiobarbituric acid reactive substances and improvement in glutathione [47]. Treatment of alloxan-induced diabetic rats for 15 days with aqueous extract at a dose of 500 mg/kg produced a 59.88% decline in fasting blood glucose along with body weight [56]. Popovich et al. [61] reported that supplementation of bitter gourd resulted in a decrease in lipid accumulation and significantly ($P < .05$) decreased in intracellular triglycerides. Another experiment found that bitter gourd juice supplementation for 24 hours reduced secretion of new triglycerides ($P < .05$) and decreased microsomal triglyceride transfer protein with VLDL-lowering effects [69]. The extract from a butanol-soluble fraction of hot air-dried bitter gourd powder was investigated on blood glucose and neutral fat levels in Wistar rats. The results revealed marked inhibition of disaccharidase activity and reduced the levels of blood glucose and blood neutral fat [70]. In another study, Ragasa et al. [73] reported that the extract from bitter gourd supplementation resulted in significant blood glucose−lowering activity after 0.5−1 hour. Similarly, a study by Klomann et al. [74] showed that daily supplementation with bitter gourd to 45 four-week-old male db/db mice (150 mg/kg body weight) for five weeks [74] resulted in a significant decline in weight gain and glycated hemoglobin levels and a reduction in lipid peroxidation (from 9.3% to 8.0%) [74]. In another experiment, alkali-extracted bitter gourd polysaccharides lowered blood sugar levels, improved glucose tolerance, and increased the content of hepatic glycogen significantly at doses of 200−400 mg/kg body weight [75]. Supplementation with bitter gourd to mice for 28 days significantly reduced fasting blood glucose levels, hepatic malondialdehyde levels, glycogen content, blood cholesterol, triglycerides, and LDL cholesterol levels and markedly increased HDL cholesterol and serum insulin levels [76]. Male mice fed with bitter gourd over 12 weeks showed significantly lower body weight and plasma glucose, insulin, and leptin levels as well as muscle lipid content [77]. Yadav et al. [78,79] found that supplementation of ethanol extract of bitter gourd induced the highest hypoglycemic and antihyperglycemic activity in rats. Bitter gourd also exerted anticancer activity in a number of different cancer lines [58−60]. In an interesting experimental study, subchronic bitter gourd extract administration in alloxan-induced diabetic rats demonstrated antihyperglycemic effect by significantly reducing blood glucose, HbA1c, serum cholesterol, and triglyceride levels [80].

In Fisher 344 male rats, bitter gourd diet containing 2% or 4% extract administered on azoxymethane (AOM)-induced aberrant crypt foci (ACF) was associated with significant reduction in the incidence of AOM-induced ACF by reducing the risk of colon cancer [81]. The immunomodulatory activity of bitter gourd on intestinal immunity was examined by monitoring the TGF-beta and IL-7 release from Caco-2 cells and the IL-10 and IL-12 from THP-1 cells [53]. These cells are usually employed as in vitro models of the intestinal epithelium and monocyte/macrophages, respectively. After 3 weeks of feeding with bitter gourd, there was a significant decline in the intestinal release of IL-7 and an increase in the TGF-beta and IL-10. These effects of bitter gourd indicate a degree of systemic immunity involving a decrease in the number of lymphocytes, increases in the populations of Th cells and NK cells, and increase in the Ig production of lymphocytes [53]. It is possible that bitter gourd may induce both intestinal and also systemic antiinflammatory responses.

Mechanisms of action of bitter gourds

The antioxidant activities of the extracts of bitter gourd were evaluated by using assays to assess DPPH (1,1-diphenyl-2-picryl-hydrazyl) and hydroxyl radical scavenging activities, metal-chelating activity, and the reducing power of the extracts [82]. The phenolic, flavonol, and flavonoid content of the extracts were also determined. All extracts inhibited

the formation of cross-linked advanced glycation end products (AGEs) and CML in a dose-dependent manner, metal chelating factor being the most potent. The antioxidant activity of the fruit of bitter gourd was higher than that of the metal chelating power (MCP) of bitter gourd pulp, but MCP showed the highest metal-chelating activity. Bitter gourd flesh or fruit had the highest phenolic and flavonoid contents, whereas MCP had the highest flavonol content. Bitter gourd has hypoglycemic effects, but this study shows that its extracts are also capable of preventing AGE formation in vitro. This activity may be due to the antioxidant properties, particularly the total phenolic content of the extracts. The use of bitter gourd deserves more attention, as it not only may reduce hyperglycemia but also may protect the body against the buildup of tissue AGEs and reduce oxidative stress in patients with diabetes [82].

In another study, the healing of acetic acid−induced gastric ulcers was increased by different doses of the extract of bitter gourd [83]. In pylorus-ligated rats the extract showed a significant decrease in ulcer index, total acidity, free acidity, and pepsin content and an increase in gastric mucosal content. The extract also reduced the ulcer index in stress-induced, ethanol-induced, and indomethacin-induced gastric ulcers and cysteamine-induced duodenal ulcers. It is clear that the methanolic extract of bitter gourd fruit increases healing of gastric ulcers and also prevents development of gastric ulcers and duodenal ulcers in rats [83]. Previous reports revealed that the extract of bitter gourd inhibits activation of nuclear transcription factor-κB (NF-κB) but activates peroxisome proliferator−activated receptor (PPAR) [84]. In addition, cucurbitane-type triterpene glycosides are the main bioactive components of the bitter gourd fruit. The results showed that compounds 6 and 8 of the glycosides were found to inhibit NF-κB activation stimulated by tumor necrosis factor alpha (TNF-α) in a dose-dependent manner [83]. With 50% inhibition concentration (IC (50)) values of 0.4 μM, compounds 6 and 8 were more potent inhibitors than the positive control, sulfasalazine (IC(50) = 0.9 μM). Compounds 4, 6, and 8 also inhibited TNF-α-induced expressions of inducible nitric oxide synthase and cyclooxygenase-2 mRNA. However, only compound 13 significantly increased PPAR-γ transactivation. In previous studies, the aqueous ethanolic extract (AEE) of unripe fruit of bitter melon was demonstrated to inhibit cytokine-induced apoptosis via modulating Bcl-2 family and caspase cascades in MIN6N8 pancreatic beta-cells. This study determines whether the antiapoptotic effect of AEE-BM is mediated by suppressing the activation of mitogen-activated protein kinases (MAPKs) and nuclear factor-κB (NF-κB), major upstream effectors of Bcl-2 family and caspase cascades, in cytokine-treated MIN6N8 cells [85]. The results showed that the AEE-BM suppressed the activation of MAPKs, including stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK), p38, and p44/42 and the activity of NF-κB. The findings suggest that bitter gourd protects pancreatic beta-cells through downregulation of MAPKs and NF-κB [85].

Several medicinal properties of the bitter gourd have been studied by various researchers, such as antidiabetic, antiulcerogenic, antimutagenic, antioxidant, antitumor, antilipolytic, analgesic, abortifacient, antiviral, hypoglycemic, and immunomodulatory effects [84−86]. In vitro studies have revealed that the bitter gourd proteins (alpha- and beta-monorcharin) have inhibitory effects against the HIV virus. The leaf extracts have broad-spectrum antimicrobial activity as well as antiviral effects [86]. On oral ingestion, many in vivo studies have reported the relatively low toxicity of all parts of the bitter gourd plant. Recently, bitter gourd products such as concentrated fruit and seed extracts can be found in capsules and tablets as well as in whole herb/vine powder forms, and these supplements are becoming more widely available in many countries globally. Out of 535 identified species used to manage diabetes and its sequelae, More than 104 species are used to manage diabetes. In vitro and in vivo studies also found that preclinical experimental evidence of hypoglycemic effect for 16 of the 20 species have been reported by at least two sources [87]. However, only seven of these species have been reported in more than three studies: *Momordica charantia* L., *Neurolaena lobata* (L.) R. Br. ex Cass., *Tecoma stans* (L.) Juss. ex Kunth, *Persea americana* Mill., *Psidium guajava* L., *Anacardium occidentale* L., and *Hamelia patens* Jacq. Several of the species that are used to manage diabetes in Central America are also used to treat conditions that may arise from diabetes, including diabetic-induced kidney disease, urinary problems, and skin conditions. In Asia as well as in Central America, a large number of medicinal plants are used to treat this condition and its sequelae, although relatively few species are widely used across the region. There may be variation in the availability and quality of pharmacological, chemical, and clinical studies to explain traditional use to manage diabetes.

Bitter gourd palatability

The bitterness of bitter gourd juice and bitter gourd vegetable usually restricts consumption. The bitterness is due mainly to two of its compound: momordicine and charantin. However, some experts used fermentation process to reduce the bitterness without affecting the glucose-lowering component of this vegetable [57,71]. The juice and extract of bitter gourd and the leaves have been highly regarded for blood sugar−lowering activity. The fresh aqueous extract of the whole fruit is more effective than dried powder or dietary consumption. The results of tests on patients with

diabetes mellitus suggested that the fresh juice from bitter gourd seeds brought about a significant reduction in plasma glucose concentration and an improvement in the response to oral glucose-load proteins, alpha-momorcharin, and beta-momorcharin. These data revealed a hepatotoxic effect on isolated rat hepatocytes. A sensory evaluation of bitter gourd in a convenience sample of 50 self-reported nondiabetic adults showed that tomato-based recipes that included bitter gourd were acceptable to most of the participants and readily acceptable as compared with recipes containing spices such as curry powder [88]. Health information did not have a significant effect on willingness to consume bitter melon but positively affected the classification. The findings confirmed that incorporation of bitter foods in commonly consumed food dishes could mask the bitter taste of bitter melon. Furthermore, providing positive health information can elicit a change in the intent to consume bitter melon−containing dishes despite mixed palatability results.

Other gourd vegetables (snake gourd, pointed gourd, ridge gourd, ivy gourd)

Experiments employing rat model in vivo demonstrated that gourd fruits such as perval and snake gourds could lower total serum cholesterol and blood sugar [89−91]. Another study reported a similar trend with oral administration of aqueous fruit extract (50 mL/kg body weight) to normal and diabetic rats. Additional clinical trials are essential to corroborate and confirm these properties of perval and snake gourds [92]. Likewise, in a study in which T2DM patients consumed pointed gourd, the results revealed significant reductions in levels of serum glucose and fatty acids compared to the values prior to the consumption of pointed gourd [93]. Several studies have reported that snake gourd (*Trichosanthes cucumerina* L. and *Trichosanthes anguina* L. of the Cucurbitaceae family) contains such phytochemicals as carotenoids, carotene, lycopene, lutein, phenolics, flavonoids, tannins, saponins, sterols, beta-sitasterol, triterpenes, and cucurbitacins. The snake gourd plant has been used for treatment of diabetes, epilepsy, and peptic ulcer and it can also induce a diuretic effect [94,95].

Sponge gourd, ridge gourd, and pointed gourd are distantly related to ash gourd, bottle gourd, and bitter gourd. However, the mature plants and seeds of pointed gourd contain abundant amount of common triterpenes, such as alpha- and beta-amyrins and cycloartenol. Of late, Cucurbitaceae are also valued as sources of lectins, which are usually in legumes. Lectins from legume seeds have been the most widely studied. However, in recent years, other plant families, especially Cucurbitaceae, have become a good source of plant lectins [96]. Lectins are proteins that have diverse bioactive properties in both animals and plants. Pectic polysaccharides were obtained from ash gourd fruits by sequential extraction with ammonium oxalate, dilute acids, and cold dilute alkali. The highest yield of polysaccharides was obtained with oxalate and HCl. Three phenolic compounds, namely, astilbin (120 mg), catechin (103 mg), and naringenin (79 mg), were obtained from the separation of 2 g of crude phenolic component extract of these fruits. It seems that 2-hexenal, n-hexanal, and n-hexyl formate and 2,5-dimethylpyrazine, 2, 6-dimethylpyrazine, 2,3,5-trimethylpyrazine, 2-methyl pyrazine, and 2-ethyl-5-methylpyrazine were the major compounds in the ash gourd beverage. Ash gourd was found to contain such phytochemicals as acetoin, octanol, and nonanol. Acetoin was identified as the key constituent existing as glycosidic conjugate of medicinal values.

The roots of pointed gourds have a strong purgative action. In contrast, the unripe fruits and tender shoots, typically consumed in curries, have laxative, hepatoprotective, and antioxidant effects. These are due to the saponin, tannins, carotenene, and vitamin C contents of the plant [93]. The immature fruits (rarely young shoots) and leaves of snake gourd are used as cooked vegetables. A galactose-specific lectin with agglutination activity is present in the seeds. The seeds also contain a ribosome-inactivating protein. The chloroform extract of snake gourd roots showed significant antibacterial activity against *Pseudomonas aeruginosa*, and the seed extracts showed hematicidal activity. The ridge gourd is consumed mainly in the form of vegetable curry in India. Isolation of two trypsin inhibitors and a ribosome-inactivating peptide (luffangulin) has been done from ridged gourd seeds. The glycoprotein luffacutin, isolated from the seeds, exhibits abortifacient, antitumor, ribosome-inactivating, and immunomodulatory activities. The fruits, stems, and leaves of ivy gourd have medicinal uses, including reduction in high blood pressure and the treatment of abscesses. The roots are believed to heal illness associated with endocrine system disorders such as diabetes mellitus, intestinal troubles, bronchial inflammation, and skin disorders. Polyprenol (C60-polyprenol), a yellow bioactive component of ivy gourd, has been shown to have antidyslipidemic and antioxidant activity [78,79]. In rats with induced liver damage, ivy gourd (tindori) extracts seemed to exert a protective effect. Ivy gourd and its extracts also have other beneficial effects on the body, including the regulation of endogenous malanine transaminase, aspirate transiminase, serum alkaline phosphate, serum acid, phosphate, serum bilirubin, serum cholesterol, and serum triglycerides. Spiny gourd is traditionally used for a variety of internal and external purposes, including the treatment of inflammatory swelling, diarrhea, and skin infections such as sores, carbuncles, furuncles, and boils in both humans and animals.

Flavonoids, phenolics, and carotenoids with regard to NCDs

Data from the literature reveal that all the plant gourds contain a number of similar phytochemicals, especially polyphenolics and flavonoids, which are responsible for their healing effects on the body, especially in diseases and disorders as obesity, diabetes, cancer, metabolic syndrome, cardiovascular diseases and hypertension, peptic ulcers, renal failure, respiratory dysfunction, and others. Most of these diseases and disorders are classified as NCDs, and they are responsible for millions of deaths annually, costing governments globally over 5 trillion U.S. dollars to diagnose, treat, and care for the patients so that they can enjoy a better quality of life. Most plant-based food products are rich sources of flavonoids and represent the second largest group of polyphenols present in the human diet [97–100]. Flavonoids can be divided into several subclasses, based on variations in the structure, with the basic structure allowing for a large number of different substitutions in the A, B, and C rings (see Fig. 4.5).

These subclasses of flavonoids are flavonols, flavanones, anthocyanins, flavones, isoflavones, and the most common subclass flavanols [97–99]. Flavanols exist in both the monomer form as catechins and the polymer form as proanthocyanidins, and they are found predominantly in cocoa, apples, and tea [101–104].

Of the total daily intake of flavonoids (50–200 mg/day), only a small proportion of flavonoids ingested are absorbed intact, and the rate and extent to which they are absorbed vary greatly according to a number of factors. These include the structure of the molecule, the matrix in which it is bound, and interactions with other components, as well as interindividual differences such as age, sex, and composition of the colonic microbiota [98,100]. Once ingested, flavonoids pass through the stomach and into the small intestine, where phase I metabolism occurs [99]. The flavonoids undergo phase II metabolism in the epithelial cells of the small intestine to form conjugated metabolites, which enter the circulation via the portal vein [99]. However, only an estimated 5%–10% of total polyphenol intake is absorbed in the small intestine [100]. The remaining larger amount of flavonoids is retained in the large intestine, where the colonic microflora can degrade them into low-molecular-weight metabolites, which can be subsequently absorbed by the body [100]. These metabolites have unique protective effects on the cardiovascular system, central nervous system, beta cells of the pancreas, and adipocytes [99–106]. The majority of the metabolites from the bloodstream are transported around the body, whereby they can act on the relevant tissues, including the neurons to prevent dementia, cardiomyocytes to prevent cardiac hypertrophy, beta cells of pancreas to prevent insulin resistance, adipocytes to prevent obesity, and endothelial cells to prevent endothelial dysfunction and atherosclerosis [99–108]. In addition, some metabolites are transported to the liver for further metabolism before ultimately being excreted [99–108]. It is possible that variations in bioavailability of flavonoids can make them more difficult to study their effects within the body. In turn, this can lead to discrepancies in the findings in various studies.

Conclusion

This comparative study has described extensively the different gourd vegetables from the family Cucurbitaceae. These different gourd plants contain several novel and biologically active agents and phytochemicals, including proteins, minerals, vitamins, triterpenes and steroids polyphenolics, flavonoids, and others. These phytochemicals are known for their potential medicinal, pharmaceutical, and beneficial cost-effective uses to protect health against various diseases and disorders. Among the gourds, ash gourd, bitter gourd, and bottle gourd have been extensively reported in the

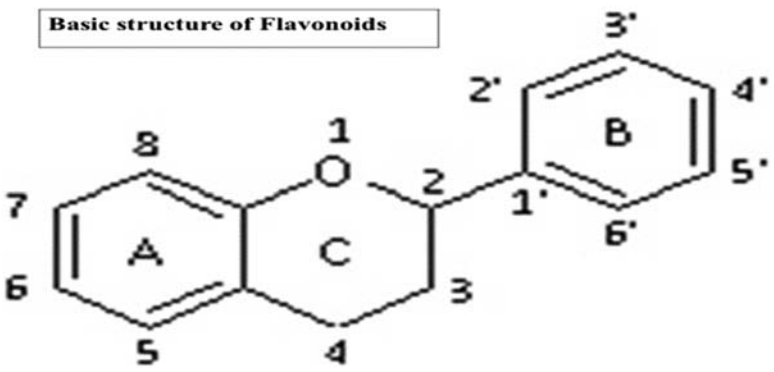


FIGURE 4.5 Basic chemical structure of flavonoids showing A, B, and C rings and free oxygen radical in single bond.

literature for their health benefits for comparison. It can be concluded that gourd vegetables hold great potential as valuable ingredients not only for functional food but also for the nutraceutical industry. Future research needs to be concentrated on ridge gourd, snake gourd, ivy gourd, and spiny gourd, since they have not been explored much for their medicinal potential and possible benefits.

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Chapter 5

Effects of guava fruit intake on cardiometabolic diseases

Ram B. Singh[1], Douglas W. Wilson[2,3], Sergey Chibisov[4], Elena Kharlitskaya[5], Maria Abromova[5] and Manal M.A. Smail[6]

[1]Halberg Hospital and Research Institute, Moradabad, India, [2]Formerly, School of Medicine, Pharmacy Health and Wellbeing, Durham, United Kingdom, [3]Centre for Ageing and Dementia Research, Swansea University, Swansea, United Kingdom, [4]Faculty of Medicine, People's Friendship University of Russia, Moscow, Russia, [5]People's Friendship University of Russia, Moscow, Russia, [6]UAE University, United Arab Emirates

Introduction

Guava is a tropical tree that is said to have originated in Mexico, Central America, and South America. In the United States, guava trees are found in Hawaii, the Virgin Islands, Florida, and a few sheltered areas in California and Texas [1−3]. Guava is a very important crops in Mexico, cultivated over 36,447 acres, and production is about 192,850 tons. In Mexico and America, *Pichi*, *posh*, and *enandi* are the names commonly used for guava [4]. The first commercial guava planting was reputed to have occurred around 1912 in Florida at Palma Sola [4], although Seminole Indians had cultivated guava a century before that. The plant is known by the common name *guava* in English, *guayabo* in Spanish, *goyave* and *goyavier* in French, *guaveboom* in Dutch, *goiaba* and *goaibeira* in Portuguese, and *jambubatu* in Malaya.

The exact origin of the guava tree is not known. Guava is native to tropical America, where it grows wild, but it has become almost a staple fruit in many Asian countries [1−3]. Guava is the fourth most important commercial fruits in India [2], after mango, banana, and citrus fruits. Guava was introduced into India in the 17th century and has been successfully grown all over India. The total area of cultivation and production of guava in India are 1.90 lakh hectare and 1.68 million tons. Major guava-producing states are Bihar, Uttar Pradesh, Maharashtra, Karnataka, Orissa, West Bengal, Andhra Pradesh, and Tamil Nadu. Guava trees may bloom all year in mild climates, but its main season for blooming is early spring [1,2]. The fruit matures between 90 and 150 days after the flowers bloom. The fruit changes color and becomes noticeably softer when it is ripe, and fruit that is allowed to ripen on the tree may have better taste and flavor. The fruits are oval in shape with light green or yellow skin and contain edible seeds. The leaves of guava are used in herbal team and the leaf extract is used as a supplement and herbal medicine [1,3]. Guava plants grow widely in tropical areas because they can be grown in a wide range of soils [4,5]. Guava belongs to phylum Magnoliophyta, class Magnoliopsida, and Myrtaceae family [1]. It has about 133 genera and more than 3800 species. *Psidium guajava* and all its parts have a long history of medicinal value [3]. Guava (*P. guajava*) fruit is appreciated both as a fresh fruit and as an industrially processed product in the form of juices, jellies, and sweets. This review aims to determine the role of guava fruit in health and diseases.

Composition of guava fruit

Guava (*P. guajava* Linn.) is a small tropical tree that is widely grown for its fruit, which is commonly known for its nutritional, medicinal, and pharmacological values [1]. Guava fruit is included among the superfruits that is low in calories, high in dietary fiber, and rich in antioxidant vitamins (vitamin C, lutein, and beta-carotene) as well as minerals [2]. Guava is consumed with its skin and is considered a "poor man's apple" in tropical and subtropical countries. Guava fruit is rich in phytochemicals (flavonoids, minerals and vitamins) and hence is considered a superfruit nutritionally. The nutrient composition of the fruit and leaves to a large extent reflects the soil mineral composition and geographic regions and varies with climate, maturity, cultivar, and agricultural practices [1,3]. The composition of fruits may therefore vary from region to region, owing

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to different climatic conditions and nutrients in the soil [4]. Limited data exist on the mineral content of tropical fruits, but the fruits are considered useful for their contribution to nutritional security [2,6,7].

Guava fruits are amazingly rich in antioxidants, vitamin C, flavonoids, potassium, and fiber, which give them many health benefits. Each 100 g of unpeeled guava fruit provides 68 kcal of energy, 5.2 g of fiber, 11.2 g of carbohydrates, 0.9 g of protein, 0.3 g of fat, 10 mg of calcium, 28 mg of phosphorus, 0.27 mg of iron, 212 mg of vitamin C, 0.040 mg of riboflavin, 1.040 mg of niacin, 0.110 mg of vitamin B6, 59 μg of folate, 5.5 mg of sodium, 24 mg of magnesium, 91 mg of potassium, 0.14 mg of copper, and 0.16 mg of zinc. Guava contains flavonoids (myricetin in sungkai fruit) in the amount of 80.38 mg/100 g dry weight of guava, the highest amount (93.75 mg) being in the skin [8,9], Red peal guava also contain beta carotene. In another study from Pakistan, high amounts of antioxidants were reported in maroon flesh cultivars [10]. Total antioxidants (11.33 ± 3.46 μmol), total phenolics (168.21 ± 49.47 mg), total flavonoids (82.69 ± 44.44 mg), and catechin (41.51 ± 14.98 mg) per 100 g of guava were quite high.

Effects of guava fruits on health and diseases

Guava (*P. guajava*) is a well-known tropical tree that is grown mainly for fruit, which has a long history of use for medicinal purposes. It has been used for the treatment of diarrhea, dysentery, gastroenteritis, dental caries, obesity, hypertension, diabetes, and hyperlipidemia as well as for pain relief and improvement in locomotor coordination. For a long time the different parts of the guava tree have been examined for its medicinal role. The leaf has been reported to have a hypoglycemic effect [1,3] However, the role of guava fruit in regulating blood glucose and lipoproteins in human is still not clear. In experiments, guava fruit water extract showed impressive efficacy in improving dyslipidemia [11–14]. The guava fruit is known to contain free sugar; however, despite the sugar, the fruit juice showed a hypoglycemic effect in streptozotocin-induced diabetic rats [12]. Interestingly, peel of the raw fruit also revealed blood glucose–lowering effects along with hypolipidemic and hepatoprotective activity [13]. The ripe fruit peel may have hyperglycemic activity in rats with diabetes [14]. However, no such effect has been observed if the fruits are consumed along with normal diets in humans [6,7].

In a clinical study by Kumari et al., 45 students were chosen subject to exclusion criteria and randomly allocated to 15 students in each of three groups. For six weeks, group A was supplemented with 400 g of ripe guava with peel, and group B was supplements with 400 g of ripe guava without peel [2]. The other 15 subjects were treated as control group C. Supplementation of ripe guava fruit with peel was associated with significant ($P < .05$) reduction in body mass index as well as reduction in systolic and diastolic blood pressures ($P < .05$) in group A, whereas fasting blood glucose, total cholesterol, and triglycerides were significantly increased ($P < .05$). Group B subjects showed a significant decline ($P < .05$) in body mass index as well as blood pressure without a significant decrease in fasting blood glucose. However, serum cholesterol, triglycerides, and low–density-lipoprotein cholesterol levels decreased significantly ($P < .05$), indicating that guava pulp without peel may have a favorable effects [2]. It is possible that guava fruit without peel is more effective in lowering blood sugar and blood lipids with increase in high-density-lipoprotein (HDL) cholesterol. Previous studies have reported that inclusion of high-fiber foods such as oats, fruits, and vegetables in the diet can decrease fat intake and modulate blood lipids [6,7]. Singh et al. examined this hypothesis, administering guava fruit among 61 group A and 59 group B patients with essential hypertension, preferably before meals in a foods-to-eat approach rather than foods-to-restrict [6]. In a 12-week randomized and single-blind trial, mean age, male sex, mean body mass index, percentages of risk factors and mean levels of blood lipids were comparable between groups A and B at entry into the study [6]. The results revealed a significant net decline of 9.9% in serum total cholesterol as well as in triglycerides (7.7%) and systolic and diastolic blood pressures (9.0/8.0 mmHg). There was a significant 8.0% net increase HDL after 12 weeks of guava fruit therapy in group A. (Table 5.1).

Table 5.2 shows that an increased intake of guava fruit also caused a significant increase in serum potassium and magnesium levels with a significant decline in serum sodium [6]. It is possible that a part of the decline in blood pressure is attributable to these electrolyte alterations. It seems that the addition of moderate amounts of guava fruit in the diet may cause modification in dietary fatty acids and carbohydrates, providing significant amounts of soluble dietary fiber and antioxidant flavonoids, vitamins and minerals without any adverse effects.

In another randomized, single-blind, controlled trial, the effects of guava intake on blood pressure and blood lipids were examined in patients with essential hypertension [7]. This randomized, controlled, single-blind trial included 72 patients with hypertension in the intervention group receiving 0.5–1.0 kg of guava daily (group A) compared with 73 patients on usual diet (group B) [7]. A four-week follow-up revealed that group A patients had a 7.5/8.5 mmHg net decrease in mean systolic and diastolic blood pressure compared with group B. There was a significant reduction in serum total cholesterol (7.9%) and in triglycerides (7.0%) and a nonsignificant increase in HDL cholesterol (4.6%) in group A compared with group B (Table 5.3).

TABLE 5.1 Effects of guava fruit intake on blood glucose, blood pressure, and blood lipids and estimated 10-year risk of coronary artery disease among patients with hypertension. Risk score is based on Framingham [6].

Data	Intervention group A ($n = 61$)		Control group B ($n = 59$)	
	Baseline	After 12 weeks	Baseline	After 12 weeks
Fasting blood glucose (mg/dL)	108 ± 10	−10.7*	110 ± 11	−5.2
Total cholesterol (mg/dL)	226 ± 20	−27.6*	223 ± 18	−5.6
Triglycerides (mg/dL)	166 ± 18	−18.6*	162 ± 15	−5.8
High-density-lipoprotein cholesterol (mg/dL)	44 ± 8	+2.4*	46 ± 11	−1.2
Blood pressure (mmHg)				
Systolic	163 ± 6	−13.6*	161 ± 7	−4.6
Diastolic	106 ± 4	−11*	104 ± 5	−3.0
Body weight (kg)	67 ± 9	−2.2	69 ± 11	−1.8
Estimated 10 years risk of coronary artery disease (%)				
Male	52 ± 19	−13.4*	50 ± 22	−2.6
Female	30 ± 12	−10.3*	36 ± 15	−2.1

*$P < .01$, significant by two-sample *t*-test using analysis of variance.
Source: Modified from reference Singh RB, Rastogi SS, Singh R. Effects of guava intake on serum total and high-density lipoprotein cholesterol levels and on systemic blood pressure. Am J Cardiol 1992;70:1287−1291.

TABLE 5.2 Effects of guava fruit intake on macrominerals related to blood pressures [6].

Data	Intervention group ($n = 61$)		Control group ($n = 59$)	
	Baseline	After 12 weeks	Baseline	After 12 weeks
Sodium (mEq/L)	144 ± 12	−6.8*	149 ± 14	−4.5
Potassium (mEq/L)	4.2 ± 0.4	+0.6*	4.5 ± 4	−0.2
Calcium (mg/dL)	9 ± 0.5	+0.06	9 ± 0.5	−0.1
Serum magnesium (mg/dL)	1.6 5 ± 0.3	+0.06*	1.6 ± 0.3	+0.5
Serum albumin (mg/dL)	4.4 ± 0.5	−0.1	4.4 ± 0.5	+0.2

*$P < .05$, significant by two-sample *t*-test and analysis of variance by comparing changes in the two groups.
Source: Modified from reference Singh RB, Rastogi SS, Singh R. Effects of guava intake on serum total and high-density lipoprotein cholesterol levels and on systemic blood pressure. Am J Cardiol 1992;70:1287−1291.

Table 5.4 shows that mean serum concentrations of sodium was significantly decreased, whereas concentrations of serum potassium and magnesium significantly increased in the intervention group compared to the control group. It is possible that an increased consumption of guava fruit can cause a substantial reduction in blood pressure and blood lipids as a result of the higher potassium and flavonoid content as well as fiber in guava fruit.

Can hypopotassemia and hypomagnesemia aggravate hypertension?

A subgroup of 32 patients in the intervention group A and 34 patients in the control group B showed hypopotassemia (serum potassium <3.7 mEq/L) along with hypomagnesemia (serum magnesium < 1.5 mg/dL) (Table 5.5). These patients were receiving a long-term hydrochlorothiazide (25−100 mg/day) diuretic for reduction in blood pressure with or without nifedipine (10−60 mg/day). Hydrochlorothiazide is known to cause hyponatremia, hypopotassemia, and hypomagnesemia with an increase in uric acid [15].

TABLE 5.3 Effects of guava intake on blood lipids, blood glucose, and blood pressures [7].

Data	Intervention group A ($n = 70$)		Control group B ($n = 72$)	
	At entry	After 4 weeks	At entry	After 4 weeks
Fasting blood glucose (mg/dL)	110 ± 7.5	−10.0*	110.2 ± 9.5	−3.2
Serum cholesterol (mg/dL)	221.0 ± 22.5	−17.3*	223.0 ± 25.0	−50
Serum triglycerides (mg/dL)	163.5 ± 10.5	−17.2*	158.5 ± 16.8	−6.0
HDL cholesterol (mg/dL)	44.8 ± 10.0	− + 2.3	46.3 ± 12.1	−1.1
Blood pressure (mmHg)				
Systolic	162.5 ± 8.5	−12.0*	46.2 ± 10.5	−4.2 − 1.7
Diastolic	104.5 ± 6.5	−10.2*	102.0 ±	

*$P < .02$, significant by two-sample *t*-test and analysis of variance.
Source: Modified from reference Singh RB, Rastogi SS, Singh NK, Ghosh S, Gupta S, Niaz MA. Can guava fruit intake decrease blood pressure and blood lipids? J Hum Hypertens 1993;7(1):33−38.

TABLE 5.4 Effects of guava intake on minerals in the intervention and control groups [7].

Data	Intervention group A ($n = 70$)		Control group B ($n = 72$)	
	At entry	After 4 weeks	At entry	After 4 weeks
Serum sodium (MEq/L)	144.0 ± 12.5	−5.8*	140.0 ± 14.0	−4.5
Serum potassium (mEq/L)	4.1 ± 0.35	+0.7*	4.5 ± 0.4	−0.3
Serum calcium (mg/dL)	9.4 ± 0.51	+0.6	9.7 ± 0.55	−0.1
Serum magnesium (mg/dL)	1.65 ± 0.26	+0.05*	1.6 ± 0.28	+0.06
Serum albumin (mg/dL)	4.4 ± 0.51	+0.1	4.4 ± 0.30	+0.2

*$P < .02$; value was obtained by analysis of variance.
Source: Modified from reference Singh RB, Rastogi SS, Singh NK, Ghosh S, Gupta S, Niaz MA. Can guava fruit intake decrease blood pressure and blood lipids? J Hum Hypertens 1993Feb;7(1):33−38.

TABLE 5.5 Effects of guava intake on blood pressures in relation to potassium and magnesium levels [7].

	Intervention group A ($n = 32$)		Control group B ($n = 34$)	
	At entry	After 4 weeks	At entry	After 4 weeks
Blood pressure (mmHg)				
Systolic	166.3 ± 13.4	154.5 ± 11.2*	162.7 ± 11.8	163.2 ± 11.0
Diastolic	106.5 ± 7.2	100.1 ± 6.5*	104.1 ± 5.3	105.1 ± 5.7
Serum potassium (mEq/L)	3.50 ± 0.31	4.0 ± 0.36*	3.51 ± 0.32	3.50 ± 0.33
Serum magnesium (mg/L)	1.45 ± 0.14	1.67 ± 0.17*	1.47 ± 0.13	1.52 ± 0.14

Hypomagnesemia, <1.5 mg/dL, hypopotassemia <3.7 MEq/L. *$P < .01$, obtained by Student's *t*-test.
Source: Modified from reference Singh RB, Rastogi SS, Singh NK, Ghosh S, Gupta S, Niaz MA. Can guava fruit intake decrease blood pressure and blood lipids? J Hum Hypertens 1993;7(1):33−38.

Among this subgroup of patients, despite higher doses of hydrochlorothiazide (50−100 mg/day) and nifedipine (50−60 mg/day), the systolic and diastolic blood pressures were uncontrolled (> 140/90 mm Hg), indicating that hypertension may be resistant. Interestingly, guava supplementation for 4 weeks was associated with a significant decline in both systolic and diastolic blood pressures along with a significant increase in serum magnesium and potassium in the intervention group without such changes in the control group (Table 5.5). The results indicated that diuretic-induced potassium and magnesium deficits can aggravate hypertension and repair of the deficiency by guava supplementation may modulate blood pressures [6,7,15]. Since flavonoids are also known to decrease blood pressure and blood lipids, it is possible that part of the benefit may be due to the antiinflammatory and vasodilator effects of flavonoids [16]. Cardioprotective—in particular, antihypertensive—effects of fruits and vegetables have also been reported in other studies, including the DASH trial [17−24]. Apart from the beneficial effects of guava fruit, guava leaves have been found to provide antidiabetic, antioxidant, and other pharmacological effects [25−28].

Guava contains a large number of organic inorganic compound; antioxidants polyphenols and phytochemicals including essential oils, polysaccharides, minerals, vitamins, enzymes, and triterpenoid acid alkaloids, steroids, glycosides, tannins, flavonoids, and saponins which can provide various health benefits [11,29−38]. A higher content of vitamin C and vitamin An and a good source of the pectin which is an important dietary fiber have multiple health effects. The high content of flavonoids [38], fructose sugar [32], and carotenoids [33] are useful in health promotion and disease prevention. Guava has antiviral compounds, antiinflammatory compounds and the phenolic compounds that help to cure cancerous cells and prevent skin aging [35]. Guava possesses antiviral, antiinflammatory, antiplaque, and antimutagenic activities [34−39]. The extract from guava fruit shows antinociceptive activity and is also effective in liver damage inflammation and serum production. Ethanolic extract of guava can increase sperm quality as well as quantity and can be used for the treatment of infertile males [37,38]. The presence of terpenes, caryophyllene oxide and *p*-selinene produces relaxation effects [36]. A high content of important antioxidants can provide radioprotective effects.

Mechanisms

In an experimental study, treatment with guava fruit water extract reduced lipid peroxidation and serum lipid profiles among rats with streptozotocin-nicotinamide-induced diabetes [11]. It has been demonstrated that various extracts prepared from guava (*P. guajava*) inhibit sodium-dependent glucose cotransporter 1 (SGLT1)- and glucose transporter 2 (GLUT2)-mediated glucose transport in vitro (Caco-2 cells) and in vivo (C57BL/6N mice) [29]. In a randomized, controlled clinical study, 31 volunteers performed an oral glucose tolerance test in which the control group received a glucose solution and the intervention group received a glucose solution containing a guava fruit extract prepared by supercritical CO_2 extraction. The findings revealed that, in comparison to the control group, supplementation of guava

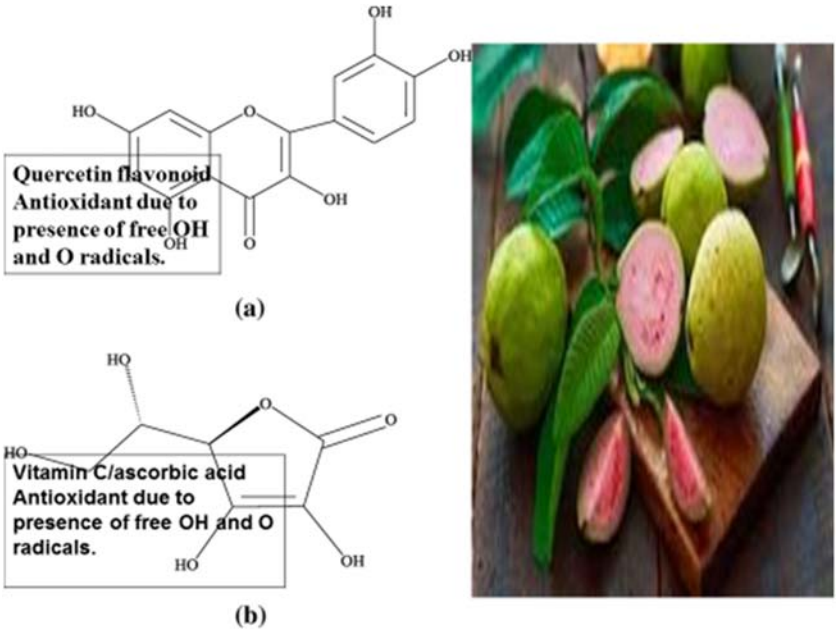


FIGURE 5.1 Chemical structure of quercetin and ascorbic acid showing free oxygen and OH radicals, indicating free radical scavenging effects [30]. *Modified from reference Naseer S, Hussain S, Naeem N. et al. The phytochemistry and medicinal value of Psidium guajava (guava). Clin Phytosci 2018;4:32. https://doi.org/10.1186/s40816−018−0093−8.*

fruit extract resulted in a reduced increase in postprandial glucose response in the intervention group over the basal fasting plasma glucose levels after 30 minutes (Δ control 2.60 ± 1.09 mmol/L versus Δ intervention 1.96 ± 0.96 mmol/L; $P = .039$) and 90 minutes (Δ control 0.44 ± 0.74 mmol/L vs Δ intervention -0.18 ± 0.88 mmol/L; $P = .023$). The findings confirm that guava fruit extract can inhibit intestinal glucose resorption, possibly in combination with reduced insulin secretion, indicating its beneficial effects in patients with diabetes. The guava fruit is rich in ascorbic acid, saponin, oleanolic acid, lyxopyranoside, arabopyranoside, guaijavarin, quercetin, and flavonoids [34,38,39]. The flavonoids, ascorbic acid, and citric acid are the major ingredients of guava that provide antimutagenic activity [35]. The chemical structures of quercetin and ascorbic acid showing free oxygen and hydroxyl radical are shown in Fig. 5.1.

Extract in ethyl acetate of guava has the ability to inhibit the effects of antigen along with inhibition of the release of the beta-hexosaminidase with histamine into RBL-2H3 cells. These inhibitor effects also can prevent the release of TNF-α and IL-4 mRNA, leading to histamine inhibition and increased nitric acid production [40,41]. There is continuous interaction between the body tissues and environmental factors; pollutants, drug therapy, and infections act as oxidants that are inhibited by antioxidants in cells. Antioxidants are molecules that retard the oxidation process and maintain the integrity of cells. The oxidation reactions in the body tissues may produce free radicals, which damage the cells by starting various chain reactions. Free radicals, which damage the cells, predispose the individual to chronic diseases, such as atherosclerosis, diabetes, and cancer. Antioxidants, polyphenolics and flavonoids, beta-carotene, lycopene, vitamins C, E, and A, and other substances present in guava terminate the free radicals and stop the chain reactions [40,41].

Conclusion

In brief, guava is a well-known tree grown in tropical areas for fruit, which may be used for health promotion and prevention of diseases. Guava may be effective against hypertension, diabetes, obesity, hyperlipidemia, and resistant hypertension, owing to its high content of potassium, magnesium, flavonoids, and fiber. The phenolic compounds in guava possesses potential antioxidant activity, which may provide antiviral, antiinflammatory, antiplaque, and antinociceptive, and antimutagenic activities. These biological activities make guava quite helpful for the preventions and treatment of cardiometabolic diseases and other chronic diseases. The leaves contain many fungistatic and bacteriostatic agents and important antioxidants, such as quercetin, which can stop the germ infection and thymus production.

Conflict of interest has not been declared by the authors.

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Chapter 6

Exploring the quality of foods from ancient China based on traditional Chinese medicine

Mohamad Hesam Shahrajabian[1,2], Wenli Sun[1], Qi Cheng[1,3,4] and Mehdi Khoshkharam[2]

[1]Biotechnology Research Institute, Chinese Academy of Agricultural Sciences, Beijing, P.R. China, [2]Department of Agronomy and Plant Breeding, Faculty of Agriculture, Islamic Azad University, Isfahan (Khorasgan) Branch, Isfahan, Iran, [3]College of Life Sciences, Hebei Agricultural University, Hebei, P.R. China, [4]Global Alliance of HeBAU-CLS&HeQis for BioAl-Manufacturing, Baoding, P.R. China

Introduction

There are many parameters that influence the functional food market and its potential in China. Functional foods and beverages are products with ingredients that are added for specific health benefits beyond basic nutrition. Food with functional claims and nutritional supplements are both included in the system of classification. Nutritional supplements are products that are intended to supply vitamins or minerals to replenish dietary insufficiency, defend against nutritional deficiency, and reduce the risk of chronic degenerative diseases. In recent decades, the functional food industries have been developing rapidly, and functional foods have been accepted by the public in many countries as a result of the demand for healthier foods and products. Traditional Chinese medicine (TCM) has played a positive role in the management of many diseases [1−5]. TCM is an empirical healthcare system based on human experience dating back several thousand years ago. It stands out as the only one with such a long history among the world's traditional medical systems [6−10]. The most important parameter is providing healthy diets for the decades to come in a world with rapid population growth [11−19]. In China, using such familiar ingredients could increase consumption, as there is a long history of using herbal medicine. With the increasing needs and demand for a healthier life in Chinese society, functional foods are becoming more and more popular. However, from the market perspective, functional foods are difficult to quantity because of the different definitions of the term that are used in the world.

Jujube

The Chinese jujube (*Ziziphus jujube* Mill.), which originated in China and has a history of over 4000 years, is recognized as the most important fruit species belongings to the Rhamnaceae family [20]. Chinese jujube and Indian jujube (*Ziziphus mauritiana* Lamk.) are largely used in traditional Asian medicine as superfruits. Indian jujube is known as ber, desert apple, or Indian plum, and it also belongs to family Rhamnaceae; it is a tropical or subtropical fruit native to the northern hemisphere [21]. Li et al. [22] discovered that Chinese jujube originates from sour jujube (*Ziziphus acidojujuba* Mill.) and is an economically important genus in the Rhamnaceae family. They also concluded that most jujube cultivars have a certain correlation with their origin, and there are obvious gene exchanges between sour jujube and jujube cultivars. Jujube pulp is eaten mostly fresh but may be dried or processed to be used in bread, cakes, compotes, and candy [23]. Descriptions of the flower, fruit and trunk, branches, culture, and other characteristics of jujube is shown in Table 6.1. World distribution of Chinese jujube is shown in Table 6.2.

Jujube nutritional composition and chemical constituents

Chinese jujubes are lower in water content and titratable acidity and higher in total sugars (mostly reducing sugars) and phenolics. Chinese jujubes are very rich in ascorbic acid (vitamin C), which increased with maturation to 559 mg/100 g

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TABLE 6.1 Descriptions of the flower, fruit and trunk, branches, culture, and other characteristics of jujube.

Height	457–1070 cm
Spread	305–915 cm
Crown uniformity	Irregular outline or silhouette
Crown shape	Oval, round
Crown density	Open
Growth rate	Medium
Texture	Fine
Foliage	
Leaf arrangement	Alternate
Leaf type	Simple
Leaf margin	Crenate, serrulate
Leaf shape	Lanceolate, ovate
Leaf venation	Bowed
Leaf type and persistence	Deciduous
Leaf blade length	5–10.5 cm, less than 5.5 cm
Leaf color	Green
Fall color	Yellow
Fall characteristic	Showy
Flower	
Flower color	Yellow
Flower characteristics	Inconspicuous and not showy; spring flower
Fruit	
Fruit shape	Oval, round
Fruit length	2.5–12.5 cm
Fruit covering	Fleshy
Fruit color	Black, red
Fruit characteristics	Attracts squirrels and other mammals; fruit, twigs, or foliar cause significant litter; showy
Trunk and branches	
Trunk/bark/branches	Grows mostly upright and will not droop; not particularly showy; should be grown with a single leader; thorns present on the trunk or branches
Breakage	Resistant
Current year twig color	Brown
Current year twig thickness	Medium
Culture	
Light requirement	Grows in part shade/part sun; also grows in full sun
Soil tolerances	Clay, loam, sand, slightly alkaline, acidic, well-drained
Drought tolerance	High
Other characteristics	
Roots	Surface roots usually not a problem

TABLE 6.2 World distribution of Chinese jujube.

Region	Country
Asia	Afghanistan, Armenia, Azerbaijan, Bengal, Burma, China, Cyprus, India, Iraq, Iran, Israel, Japan, Kyrgyzstan, Lebanon, Malaysia, Mongolia, Pakistan, Palestine, South Korea, Syria, Thailand, Turkey, Turkmenistan, Uzbekistan
Europe	Bulgaria, England, France, Germany, Greece, Italy, Czech, Macedonia, Portugal, Romania, Russia, Slovenia, Spain, Ukraine, Yugoslavia
Africa	Egypt, Tanzania, Tunisia
North America	Canada, United States
Oceania	Australia, New Zealand

TABLE 6.3 General composition of *Ziziphus mauritiana* seeds.

Content	Dry weight (g/100 g)
Moisture	4.21 ± 0.30
Ash	2.79 ± 0.27
Protein	36.10 ± 0.57
Crude fiber	11.04 ± 0.88
Lipids	27.40 ± 0.11
Carbohydrate	21.26 ± 0.63

Carbohydrates were estimated by difference. The values are means and standard deviation for those determinations.

fresh weight. Fruits held at 0°C for 26 days exhibited sheet pitting due to chilling injury. Yan et al. [24] found that five essential elements and two toxic elements (except cadmium) varied widely in their contents in the four jujube fruits. They intended knowledge of the contents of these elements to provide consumers with information on the quality of jujube fruits. Chen et al. [25] reported that the Junzao cultivar contained relatively low levels of total dietary fiber, protein, total sugar, and total titratable acids. The Huizao cultivar possessed an intermediate level of sugar-to-acid ratio and ascorbic acid. The Dazao cultivar showed a high level of total dietary fiber, protein, sugar, and total acids. In their experiment, principal components analysis indicated that the parameters that differentiated these jujube cultivars appeared to be total dietary fiber, protein, total sugar, fructose, glucose, sucrose, and total titratable acids. Rahman et al. [26] noted that Chinese jujubes consist of 51.99%−71.75% edible part, 82.35%−89.63% carbohydrates, 4.43%−6.01% protein, 0.48%−0.63% lipids, 2.80%−4.80% polysaccharides, 45.64−88.97 mg/100 g ascorbic acid, 132.16−196.58 mg/100 g phenolics, and 101.17−132.04 mg/100 g flavonoids in dry matter. Ertop and Atasoy [27] found that the jujube fruit is rich in minerals and fiber and is a good source of food for direct consumption, and it may be a good additive for different foods when dried. In their study, they found that jujube fruit, especially in dried and powdered form, can be valorized in future studies as a fortifying and hydrocolloid ingredient in different types of products because of its high carbohydrate content. Huang et al. [28] also found that the fruits are nutritious, being high in flavonoids and vitamins C, B1, and B2, and therefore can be considered a so-called functional food, having nutritional as well as medicinal uses. Jujube as a nutritious fruit is especially important for low-income people because of its lower cost in comparison to other available fruits. Furthermore, it can be grown successfully in unfertile land and drought-prone areas. It is also a less perishable fruit, and large-scale cultivation of this fruit can provide economic benefit for farmers and help to maintain the national economic level. The general composition of *Z. mauritiana* seeds is shown in Table 6.3. The mineral composition of seeds of *Z. mauritiana* is shown in Table 6.4.

Traditional medicinal uses and potential health benefits of jujube in modern medicine

The jujube leaf, which is the main byproduct of jujube, has been used in TCM for thousands of years to improve sleep, to nourish the heart and soothe the nerves, and to reduce hemorrhaging and diarrhea. In Iranian traditional medicine,

TABLE 6.4 Mineral composition of the seeds of *Ziziphus mauritiana*.

Content	Dry weight (mg/100 g)
Sodium (Na)	154.79 ± 10.50
Magnesium (Mg)	6.23 ± 0.12
Potassium (K)	589.08 ± 10.69
Zinc (Zn)	3.52 ± 0.05
Manganese (Mn)	1.15 ± 0.14
Iron (Fe)	1.21 ± 0.15
Phosphorus (P)	585.43 ± 41.29

The values are means and standard deviations for three determinations.

local traditional healers used powders of stem bark and leaves of jujube to cure wounds and oral wounds as aphthous. Hamedi et al. [29] discovered that jujube fruits are widely used in Iranian folk medicine as an antitussive and laxative agent and blood pressure reducer. Jujube has also been used in TCM for many years with its various and numerous health benefits, such as antiinflammatory, anticancer, gastrointestinal protective, antioxidant, antiinsomnia, and neuroprotective. Mill Goetz [30] reported that jujube fruits and seeds are used in Chinese and Korean traditional medicine, in which they are believed to alleviate stress. In Persian traditional medicine, jujube is used in combination with other herbal medicines to treat colds, flu, and coughing. Jujube fruit contains flavonoids, vitamins, amino acids, organic acids, polysaccharides, and microelements, which are useful in treating spleen diseases and nourishment of the blood in TCM. Tahergorabi et al. [31] stated that different parts of jujube can be used for curing different kinds of illness, such as diabetes, diarrhea, skin infections, liver complaints, urinary disorders, obesity, fever, pharyngitis, bronchitis, anemia, cancer, and insomnia and of course for blood purification and tonification of the gastrointestinal tract. Hemmati et al. [32] reported that jujube causes a decrease in the blood levels of glucose and lipids, and it has been reported to cause a significant decline in triglyceride, low-density lipoprotein (LDL) cholesterol levels. Mahajan and Chopda [33] found that the roots and bark are used to treat dysentery, and the bark cures boils and is good for the treatment of diarrhea. They also mentioned that an aqueous paste of the leaves is applied externally to relieve a burning sensation. Furthermore, they reported that the seeds cure eye diseases and are useful in leucorrhea, and the kernels increase flesh and strength and have a sedative effect. Recent phytochemical research on jujube fruits have revealed their effects, such as the anticancer, antiinflammatory, antiobesity, immune stimulant, antioxidant, hepatoprotective, and gastrointestinal protective activities and inhibition of foam cell formation in macrophages. Researchers have also mentioned that jujube fruits are rich in bioactive compounds and can be complementary in healthy eating. Shi et al. [34] indicated that the skin color changes of jujube fruit during maturation are due to changes in the levels of flavonoids, carotenoids, and anthocyanins. They concluded that the color changes are also associated with changes in antioxidant activity. Hoshyar et al. [35] indicated that *Z. jujube* ameliorates the adverse effects of N-methyl-N-nitrosourea carcinogenesis and could be useful for treating mammary tumors in humans. Betulinic acid and jujuboside B could be the active components showing beneficial effects on the cardiovascular system. Motevali et al. [36] stated that jujube is a valuable medicinal plant, consumed either as fresh fruit or in dried form in Iran. Drying jujube guarantees a longer shelf life while preserving its quality to be used in the medical and pharmaceutical industries. Taechakulwanijya et al. [37] have found that all jujube seed extracts were not toxic to Vero cells, and all jujubes cultivars tested are promising candidates for more elaborate study of their anticancer mechanisms. Vafaei and Abdollahzadeh [38] indicated that jujube fruit extract could accelerate burn wound healing among Balb/c mice. It has been reported that triterpenic acids were considered to be active ingredients for the antiinflammatory and anticancer activities. The aqueous ethanol extract of the jujube leaf was used as energetic constituent for hepatitis and wound healing in animal trials. Shahrahmani et al. [39] showed that *Z. jujube* fruit lotion can treat sore nipples faster than breast milk over a period of 10 days. Also, nipple pain in the jujube lotion group was less than that in the breast milk group. Gheibi et al. [40] found that the accessibility and affordability of jujube fruit and the side effects of routine drugs, taking a combination of jujube fruit with low doses of routine pharmaceutical drugs can improve and cure ulcerative colitis disease. Neuronal beneficial properties of jujube are shown in Table 6.5. Safizadeh et al. [41] concluded that levels of BUN, creatinine, urate, and liver enzymes in all extracts increased. They have suggested that administration of high doses of jujube (up 5000 mg/kg) is reasonably safe and did not cause

TABLE 6.5 The most important pharmacological properties of jujube.

1. Antidiabetic effects
2. Hypnotic-sedative and anxiolytic effect
3. Neuroprotective activity
4. Sweetness inhibitor
5. Anticancer activity
6. Antimicrobial activity
7. Antiulcer activity
8. Antiinflammatory and antispastic effect
9. Antiallergic activity
10. Permeability enhancement activity
11. Cognitive activities
12. Antifertility/contraceptive property
13. Hypotensive and antinephritic effect
14. Cardiovascular activity
15. Immunostimulant effects
16. Antioxidant effects
17. Wound-healing activity

hepatotoxicity and nephrotoxicity in rats. A combination of *Z. jujube* and green tea extracts exerts excellent cytotoxic activity in HepG2 cells via reducing the expression of APRIL; also, jujube extract and green tea extract mixture might provide a lead to a new drug design to treat hepatocellular carcinoma in the future APRIL. Anbarasi and Brindha [42] found that methanolic extract of dried bark of *Z, jujube* was found to cause a significant decrease in the levels of total cholesterol, triglycerides, LDL cholesterol, and glucose in streptozotocin-induced diabetes in rats. *Z. jujube* powder possesses hypolipidemic and antiobesity properties and did not show any negative impact on liver function as measured by ALT and AST. The jujube polysaccharides, which are composed of glucose (23%), xylose (31.3%), mannose (12.9%), and fructose (21.6%), possess antioxidant effects, and this may have contributed to the observed effects. It has been proven that the insecticide effects of jujube leaves are caused by inhibiting the digestive and mitochondrial enzymes that lead to growth retarding of the larvae. The most important pharmacological properties of jujube are shown in Table 6.5.

Lotus

Lian (*Nelumbo nucifera*), commonly known as lotus, is an amazing aquatic perennial that is native to a large area spanning from Vietnam to Afghanistan. Lotus is a herbaceous perennial, belonging to Nelumbonaceae family of aquatic plants [43]. Lotus seeds and roots are a major crop in Hubei, Hunan, Fujian, and Jiangxi provinces. In Chinese culture, its uses range from religious symbolism to tasty foods [44]. Lotus is popular in Asian countries as an economically important aquatic vegetable. China is the largest producer and consumer, with of 45,000 tons of dry seeds per year produced from cultivation of an area of approximately 0.5−0.7 million hectares of land. The health benefits of the many different parts of this plant have long been known in China. On the basis of Chinese medical herbology and pharmacology, the lotus and its various parts are among the most versatile herbs in traditional Chinese herbal medicine. Each part of the plant has separate and distinct properties. The most commonly used names of the lotus in Chinese medicine are *lian zi* (lotus seed), *lian fang* (lotus root receptacles), and *lian ye* (lotus leaf). This unique plant has special properties in addition to being a powerful herb in Chinese medicine. Its seeds have ability to germinate after being dormant for more than a millennium. The surface structure of the leaf allows drops of water to roll off, taking dirt and insects with them while leaving the leaf clean and dry. The most important point about this crop is that each part of the lotus plant has special uses, such as the flower, the leaves, the stem, the rhizome, the seeds, the heart of the lotus seed, and of course the root. In TCM, lotus roots are plants that belong to the category of herbs that stop bleeding. As the name indicates, these herbs tend to have hemostatic properties, meaning that they help stop various types of hemorrhages. Furthermore, lotus roots are plants that are neutral in nature. This means that lotus roots typically do not affect the balance in the body. Balance between *yin* and *yang* is a key health concept in TCM. Eating too many "hot" (*yang*) ingredients can lead to an imbalance whereby one has a *yang* excess. The inverse is true as well: Too many "cold" (*yin*) ingredients can lead to a *yin* excess. Lotus roots also taste sour and sweet. The so-called five elements theory in TCM states that the taste of ingredients is a key determinant of their action in the body. Sour ingredients such as lotus roots help with

TABLE 6.6 Taxonomic classification of lotus.

Kingdom	Plantae: plants
Subkingdom	Tracheobionta: vascular plants
Super division	Spermatophyta: seed plants
Division	Magnoliophyta: flowering plants
Class	Magnoliopsida
Subclass	Magnoliidae
Superorder	Protaenae
Order	Proteales
Family	Nymphaeaceae: lotus family
Genus	*Nelumbo* Adams: lotus
Species	*Nelumbo nucifera* Gaen.: sacred lotus

TABLE 6.7 Synonyms of lotus in different languages.

English	Sacred lotus
Hindi	Kanwal, kamal
Sanskrit	Ambuja
Tamil	Ambal, thamarai, padma, pankaja, kamala
Bengal	Padma
Gujarat	Suriyakamal
Malayalam	Tamara
French	Nelumbo
German	Indische lotosblume
Persian	Nilufer

digestion and restrain abnormal discharges of fluids from the body, such as diarrhea or heavy sweating. On the other hand, sweet ingredients tend to slow down acute reactions and detoxify the body. They also have a tonic effect because they replenish *qi* and blood. The tastes of ingredients in TCM also determine what organs and meridians they target. Lotus roots are thought to target the stomach, the liver, and the lung. In TCM the stomach is responsible for receiving and ripening ingested food and fluids. It is also tasked with descending the digested elements downwards to the small intestine. The liver is often referred as the body's "general" because it is in charge of regulating the movements of *qi* and body fluids. It also takes a leading role in balancing the emotions. In addition to performing respiration, the lungs are thought to be a key part of the production chain for *qi* and the body fluids that nourish the body. Lotus grows in warm temperate to tropical climates, in a range of shallow (up to about 2.5 m deep) wetland habitats, including flood plains, ponds, lakes, pools, lagoons, marshes, swamps, and the backwaters of reservoirs. Taxonomic classification of lotus is shown in Table 6.6. Synonyms of lotus in different languages are listed in Table 6.7.

Lotus composition and chemical constituents

Luo et al. [45] reported that starch, protein, and lipids, the major components in lotus seeds, affected the taste and cooking properties of the food. The chemical compositions, gelatinization properties, crystal structure of the starch, compositions of fatty acids, and soluble protein of lotus seeds stored for 24 months, stored for 12 months, and fresh were studied. The overall starch, protein, and lipid contents in lotus seeds remained unchanged during storage, but structural changes occurred. The contents of

amylose and free fatty acid increased significantly during prolonged storage, and the solubility of protein decreased dramatically. The energy in lotus seeds comes chiefly from carbohydrates and protein, in contrast to other tree nuts, whose high calorific value is mainly because of fats. After evaluation of the protein nutrition value for lotus seed, Chen et al. [46] found that the crude protein content and fat content were 19.99% and 6.82%, respectively. The total content of 17 amino acids was 178.05 mg/g dry matter, in which the content of seven essential amino acids was 64.71 mg/g and the content of delicious amino acid was 58.15 mg/g. The essential amino acids accounted for 36.34% of the total amino acids, which was lower than egg protein pattern but higher than World Health Organization/Food and Agriculture Organization pattern. Varieties in the nutritional value and the organoleptic, therapeutic, and functional properties of the lotus are due to the varieties in the types, contents, and metabolic properties of the phenolic compounds [47]. Lotus seeds The nutrition profile of dried lotus seeds and value per 100 g are shown in Table 6.8. The nutritive value of lotus seeds is presented in Table 6.9. The percent concentration of various elements of *Nelumbo nucifera* (seeds) is presented in Table 6.10. Phytochemical analysis of *N. nucifera* seeds is presented in Table 6.11. Bioactive compounds in methanol extract of *N. nucifera* are shown in Table 6.12. Major chemical constituents present in lotus seeds are shown in Fig. 6.1.

Lotus health benefits

All parts of the lotus plant are used. The rhizome is used as food, the seed as medicine, the thalamus as fruit, the leaves as plate (*thali*), the stalks as pickle, the petals for color extraction, and the tender leaves as food after being blended

TABLE 6.8 Lotus seeds nutrition profile of dried lotus seeds and value per 100 g.

Component	Nutrient value	Percentage of RDA
Energy	332 kcal	17%
Carbohydrate	64.47 g	49%
Protein	15.41 g	27%
Total fat	1.97 g	10%
Cholesterol	0 mg	0%
Vitamins		
Folates	104 μg	26%
Niacin	1.60 mg	10%
Pantothenic acid	0.851 mg	17%
Pyridoxine	0.629 mg	48%
Riboflavin	0.150 mg	11.5%
Thiamin	0.640 mg	53%
Vitamin A	50 IU	1.66%
Electrolytes		
Sodium	5 mg	$<1\%$
Potassium	1368 mg	29%
Minerals		
Calcium	163 mg	16%
Copper	0.350 mg	39%
Iron	3.53 mg	44%
Magnesium	210 mg	52%
Manganese	2.318 mg	100%
Phosphorus	626 mg	89%
Zinc	1.05 mg	95%

TABLE 6.9 Nutritive value of lotus seeds [48].

Ash (%)	4.50
Moisture content (%)	10.50
Crude fat (%)	1.93
Protein (%)	10.60
Carbohydrate (%)	72.17
Crude fiber (%)	2.70
Energy (cal/100 gm)	348.45

TABLE 6.10 Percent concentration of various elements of *Nelumbo nucifera* (seeds) [48].

Chromium	0.0042
Sodium	1.00
Potassium	28.5
Calcium	22.10
Magnesium	9.20
Copper	0.0463
Zinc	0.0840
Manganese	0.356
Iron	0.1990

TABLE 6.11 Phytochemical analysis of *Nelumbo nucifera* seeds [49].

Chemical test	*N. nucidera* (methanol)
Alkaloids	—
Carbohydrates	+++
Saponins	—
Proteins	+++
Phenolic compounds	++
Flavonoids	+
Tannins	—

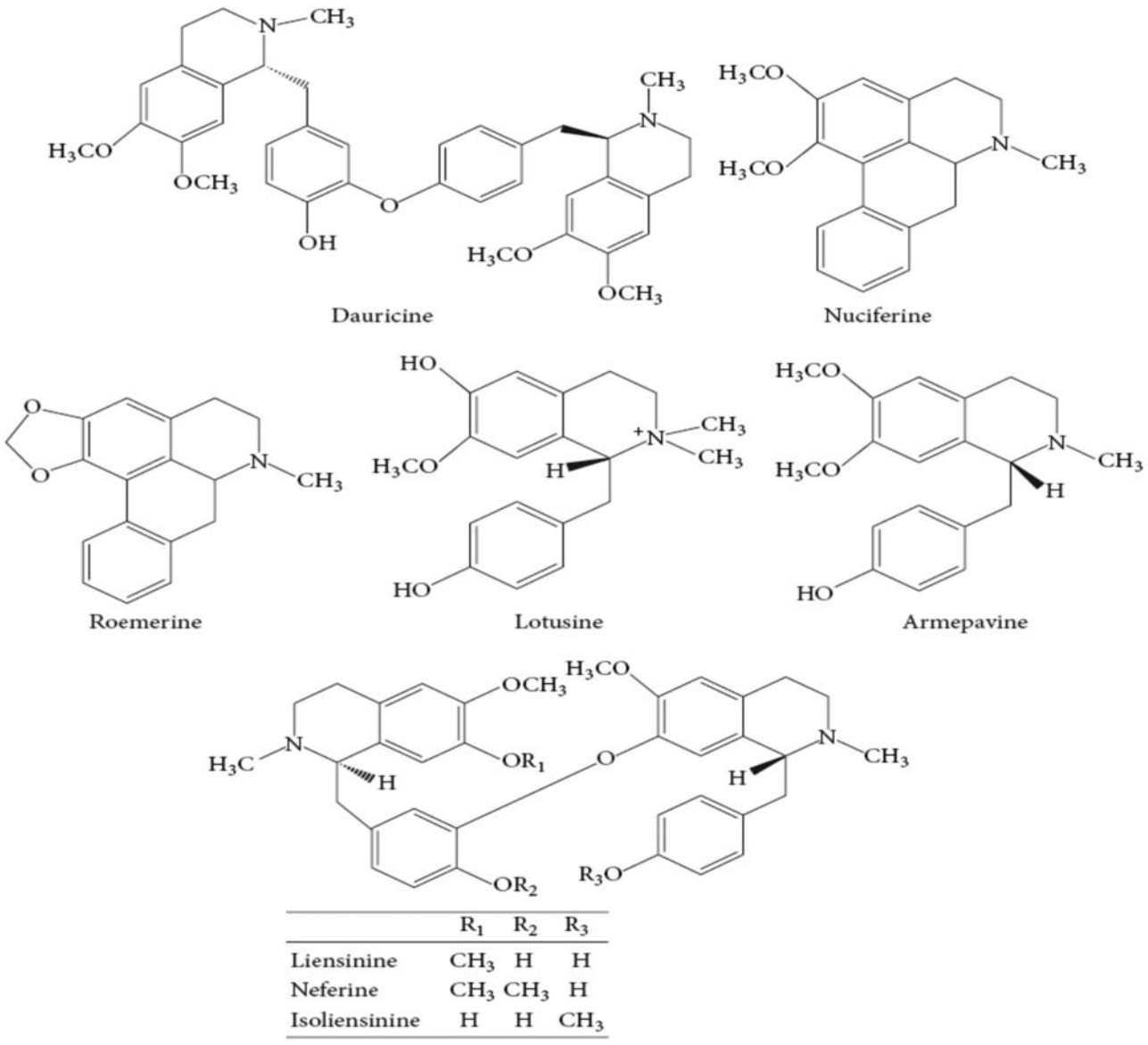
(—) denotes absent, (+) denotes mild, (++) denotes average, (+++) denotes large.

with vegetables [52]. The seeds are roasted or candied for eating directly; made into a paste for producing sauces and cake fillings; and cooked in soups, usually with chicken or beans. In TCM, lotus seeds and plumule have special therapeutic importance. Various researchers have suggested that alkaloids in lotus plumule, such as liensiline, neferine, and isoliensiline, possess sedative, antispasmodic, and antihypertensive properties, which is beneficial to heart. TCM recognizes lotus seed as a *yin* energy food. It dispels excess heat from the heart and reduces spontaneous bleeding episodes due to heat. On the basis of TCM, lotus seed falls into the category of a sweet-flavored food. The alkaloid compounds

TABLE 6.12 Bioactive compounds in methanol extract of *Nelumbo nucifera* rhizome [50].

Compound	Retention time	Mass	Formula
Betulinic acid	21.28	456.3529	$C_{30}H_{48}O_3$
Rutin	16.98	610.1399	$C_{27}H_{30}O_{16}$
Isoquercetin	16.12	464.0916	$C_{21}H_{20}O_{12}$
2R-aminohexadecanoic acid	15.17	271.2451	$C_{16}H_{33}NO_2$
Phytosphingosine	14.91	317.2858	$C_{18}H_{39}NO_3$
Sphinganine	14.80	273.2650	$C_{16}H_{35}NO_2$
Phorbol	14.48	364.1825	$C_{20}H_{28}O_6$
Ginkgolide B	14.33	424.1431	$C_{20}H_{24}O_{10}$
Tetrahydroxy-2,6-dimethyl anthroquinone	13.90	300.0619	$C_{16}H_{12}O_6$
Pseudouridine	13.08	244.0665	$C_9H_{12}N_2O_6$
p-Hydroxyphenobarbital	10.09	248.0782	$C_{12}H_{12}N_2O_4$
Fluoroacetate	1.20	78.0112	$C_{12}H_{12}N_2O_6$
Isoamyl nitrite	1.14	117.0762	$C_5H_{11}NO_2$
Metronidazole	1.03	171.0647	$C_6H_9N_3O_3$
Napthaldehyde	0.89	156.0596	$C_{11}H_8O$
Acetoin	0.38	88.0523	$C_4H_8O_2$

actually slow down acute reactions and neutralize the toxic effects of other foods, and they lubricate and nourish the body. In TCM, lotus plumule has been advocated for sleep promotion and to ease conditions associated with seminal and vaginal discharge. Lotus is one of the most important perennial plants with both floating and aerial orbicular leaves. Leaves that are floating have a flat shape, whereas the aerial leaves are cup shaped. The lotus is an aquatic rhizomatous herb consists of elongated, slender, nodal roots with a creeping stem. Lotus seeds are classified as astringents, being sweet and neutral, and benefit the spleen, kidney, and heart. The sweet taste and nourishing qualities of the seed are responsible for the benefit to the spleen; this helps stop diarrhea associated with *qi* deficiency. The astringent quality helps to prevent loss of kidney function, and the seeds are used to treat weak sexual function in men and leukorrhea in women. The seed also has calming properties that alleviate restlessness, palpitations, and insomnia (more so in the whole seed with embryo). The medicinal dosage is 6−15 g when the lotus is combined with other herbs that have similar applications and double that when lotus is used as the main ingredient. Cao et al. [53] found that lotus seed epicarp and lotus seedpod ameliorated obesity, insulin resistance, and oxidative damage in obese mice, suggesting that these parts of the lotus are good candidates for value-added functional food and nutraceutical ingredients. The lotus leaves (*heye*) are also bitter but neutral and are said to benefit the stomach, spleen, and liver. They are used for treatment of summer heat syndrome and dampness accumulation; they also contain the lotus alkaloids with hypotensive effect. Lotus leaf has become popular for lowering blood lipids and treating fatty liver; for that purpose, it is commonly combined with crataegus, which promotes blood circulation and lowers blood fats. Lotus stems (*hegeng*) are used medicinally in the same way as the leaves for treatment of summer heat and are used also to treat tightness in the chest due to obstruction of *qi* circulation. Zeng et al. [54] determined that lotus seed protein is a nutritionally well-balanced protein and might be of significance in the formulation of diets for humans. Kim et al. [55] stated that lotus seed increased the viscosity of soy porridge as well as its antioxidant and antibacterial effects. Kim and Shin [56] concluded that the high antioxidant capacity of lotus seedpod water fraction could be available as a natural additive in food. Modern pharmacological actions of lotus seeds are as follows: (1) The oxoushinsunine has an inhibitory effect on nasopharyngeal cancer. (2) The noncrystalline alkaloid N-9 can lower blood pressure. (3) The alkaloids have significant cardiac effects. (4) The liensinine has strong anticalcium and antiarrhythmic effects. (5) The raffinose is a tonic for both young and old, especially for bedridden patients, postpartum woman, and the frail elderly. (6) The liensinine can control sexual desire. Jeon et al. [57] found that palmitic acid methyl ester clearly induced melanogenesis as the result of increased tyrosinase



	R_1	R_2	R_3
Liensinine	CH_3	H	H
Neferine	CH_3	CH_3	H
Isoliensinine	H	H	CH_3

FIGURE 6.1 Major chemical constituents present in *Nelumbo nucifera* seeds [51].

expression, thereby indicating that it may play a role in the regulation of melanin content. They reported that lotus flower oil may prove useful in the development of gray hair prevention agents or tanning reagents. Wang et al. [58] noted that lysicamine extracted from lotus leaves may be a potential antibacterial and antiinflammation agent for oral infection. Activities of different parts of the plant are listed in Table 6.13.

Coix lacryma-jobi

Coix origin, Coix nutritional composition, and chemical constituents

Coix lacryma-jobi L. is a distant relative of maize in the Maydae tribe of the grass family, Poaceae or Graminaeae [60,61]. It is commonly named Job's tears, adlay, mayuen, Chinese pearl barley, and hatomugi. Job's tears seeds are mainly produced in East and South-East Asia, including China, Japan, the Philippines, Burma, and Thailand [62]. The current planting area in China is estimated to be around 73,000 hectares with a grain yield of 0.22 million tons [63]. It has higher protein content than other cereals, which makes it a good source of nutrition for humans and animals [64]. It has been documented that *C. lacryma-jobi* seed was found at the Hemudu site, indicating that *C. lacryma-jobi* has been cultivated in China for more than 6000 years [65]. Job's tears is a short-lived or long-lived clumping grass that grows

along waterways, in other damp sites, and in roadside ditches. This native of tropical Asia has long been cultivated for its beadlike seeds, resulting in its becoming widely naturalized throughout the tropical and subtropical regions of the world. Job's tears is a robust grass that usually grows 1−2 m tall. Its upright stems are relatively thick and produce prop roots from their lower joints. The alternately arranged leaves are large (10−50 cm long and 2−5 cm wide) and have a stem-clasping base. These leaves are mostly hairless, but their margins may be fringed with fine hairs. The chemical composition of whole-grain and degermed Job's tears flours is shown in Table 6.14. The composition of coix seed is compared with that of other grains in Table 6.15.

TABLE 6.13 Activities of different parts of the plant [59].

Activity	Part of plant used
Aldose reductase inhibitory	Flower
Antiarrhythmic	Seed
Antibacterial	Flower
Anticancer	Leaves
Antidiarrheal	Rhizome
Antifertility	Seed
Antifibrosis	Seed
Antiischemic	Seed
Antiinflammatory	Seed, rhizome
Antiobesity	Leaves
Antioxidant	Leaves, flower, rhizome
Antiplatelet	Flower
Antiproliferative	Seed
Antipyretic activity	Flower, rhizome
Antiviral	Seed, Leaves
Aphrodisiac	Flower
Cardiovascular activity	Leaves
Diuretic activity	Rhizome
Hepatoprotective	Seed, leaves
Hypocholesterolemic	Leaves
Hypoglycemic	Flowers, rhizome
Immunomodulatory	Seed, rhizome
Lipolytic	Leaves
Psychopharmacological	Rhizome

TABLE 6.14 Chemical composition of whole-grain and degermed Job's tears flours.

	Whole-grain flour		Degermed flour	
Composition	White	Black	White	Black
Protein (%)	13.54 ± 0.12^{b}	16.85 ± 0.28^{a}	13.18 ± 0.20^{b}	16.46 ± 0.33^{a}
Lipid (%)	4.86 ± 0.14^{b}	5.35 ± 0.16^{a}	0.91 ± 0.02^{c}	1.09 ± 0.01^{c}
Ash (%)	1.74 ± 0.02^{a}	1.17 ± 0.01^{b}	0.59 ± 0.02^{c}	0.23 ± 0.01^{d}

^{a,b,c,d}Different letters within the same row indicate a significant difference ($P < .05$).

Coix health benefits

Hsu et al. [66] reported that adlay seeds have been used to treat warts, chapped skin, rheumatism, and neuralgia, and it is an antiinflammatory and anthelmintic agent. Furthermore, a number of benzoxaziones in adlay seeds exhibit antiinflammatory activity [67]. Liu et al. [67] found that coix seed can inhibit the proliferation of tumor, inhibit the invasion and metastasis of tumor cells, inhibit the formation of tumor blood vessels, induce apoptosis of tumor cells, have synergistic and attenuating effects on chemotherapy, enhance the sensitivity of tumor cells to tumors, adjust the body's immune function, and relieve the pain of advanced tumors. *C. lachrymal-jobi* L. has been used for a long time in China for treating inflammatory diseases, warts, neuralgia, and neoplastic diseases. Numata et al. [68] reported that adlay grains may have antitumor activity. Han et al. [69] discovered that the compositions of proteins and polysaccharides of coix seed had the most effect in regulating the water transport of spleen deficiency and wet dampness in a rat model. Das et al. [70] reported that the chloroform extracts (leaves and seeds) showed efficacy for both bacterial infections and parasitic disease, which ensure the traditional uses of *C. lacryma-jobi* L. Xi et al. [71] revealed that the proportion of palmitic acid and linoleic acid to oleic acid displayed a highly significant positive correlation with the inhibition rates of Job's tears seed oil for T24 cells and thus can be an important indicator for quality control for Job's tears. Root extract of *C. lacryma-jobi* is commonly used for treatment of snake bites by traditional healers of south India, in particular coastal Karnatake [72]. Son et al. [73] stated that *Coix lacryma-jobi* inhibited migration, invasion, and adhesion of colon cancer cells and tube formation by HUVECs via repression of the ERK1/2 and AKT pathways under hypoxic conditions. Geetha et al. [74] showed that *C. lacryma-jobi* seed extract have antiinflammatory activity in the models studies. The effects of *C. lacryma-jobi* seed extracts on various biochemical parameters are shown in Table 6.16.

TABLE 6.15 Composition of coix seed compared with other grains (per 100 g).

	Coix	Rice	Wheat	Maize	Millet
Energy (cal)	358	349	354	362	353
Protein (%)	14.2	7.8	9.9	8.4	9.7
Fat	3.6	1.3	1.8	4.3	3.5
Starch (%)	67.2	76.6	74.6	70.2	72.8
P (mg)	299	203	268		240
Mg (mg)	126				
Ca (mg)	49.0	9	38		
Fe (mg)	2.90		4.2	34	29
Zn (mg)	1.89				4.7
Mn (mg)	1.89				

TABLE 6.16 Effect of *Coix lacryma-jobi* seed extracts on various biochemical parameters [74].

Group	Serum alkaline phosphatase	Serum cholesterol	Serum triglyceride	Total protein
Normal control	46.71 ± 1.09	42.11 ± 1.50	112.68 ± 1.65	10.21 ± 1.14
Negative control	85.01 ± 0.45	111.39 ± 1.69	82.03 ± 1.88	6.29 ± 0.45
Test 200 mg/kg	32.64 ± 1.33	62.40 ± 1.06	91.06 ± 1.94	10.21 ± 0.96
Test 400 mg/kg	41.25 ± 1.45	33.10 ± 1.21	108.40 ± 1.45	11.50 ± 0.78
Standard silymarin 100 mg/kg	40.44 ± 1.03	32.86 ± 1.59	95.56 ± 1.82	9.15 ± 0.97

Values are mean ± standard error of the mean.

Dry lily bulb

Origin and health benefits and constitution of lily bulb

Lilies are attractive flowering plants that is grown in pots or used as cut flowers [75,76]. The lily flower has long been used by many cultures as a symbol of tranquility, peace, and prosperity. The Roman Catholic Church uses lily flowers to symbolize the Virgin Mary and to represent its own state of independence and prosperity. The Chinese culture uses lily bulb to make desserts for festivities and weddings to symbolize good luck and longevity of marriages. *Lilium* is recognized as a valuable cut flower, and many plant-breeding companies are working on the development of new cultivars of the species belonging to different sections of the genus [77]. Lilies grow best in well-drained soil. Organic matter should be added to heavy clay or sandy soils before planting. Dry lily buds (*huang hua*) are also known as golden needles and tiger lilies. Dried lily buds are among the most notable of edible flowers in Chinese cuisine. The lily has been used in China as both a food and a medicinal plant for more than 2000 years. Dried lily buds are typically yellow gold in color and are generally 2−3 inches long. Lilies are known to have a delicate flower, often described as musky, earthy, and sometimes even sweet or slightly tart. Dried lily buds are used for their unique aroma, which is fruity and flowery. Dried lily flowers are used in Chinese cooking as a flavor enhancer, primarily in vegetarian dishes but also in various stews and soups.

Dried lilies are also a very important ingredient in Buddha's Delight (Jai cuisine), moo shu vegetables, and Beijing-style noodle sauce. The best-quality lily buds are produced in the Qu country in the Southwestern Sichuan province. They contain seven stigmas and filaments and have six to eight petals. In TCM, lily buds aid brain function, help in blood clotting, help to cool the blood, and aid urination. Lily bulb has three primary sets of active components: alkaloids (steroidal alkaloids, such as etioline as well as small pyrrolines like jatrophine, also called lilidine), steroidal saponins, and phenols (mainly flavonoids). The combination of steroidal alkaloids and steroidal saponins is likely responsible for the treatment of various nervous system disorders.

Lilies are a good source of starch and protein. Lily bulbs are said to contain calcium, iron, phosphorus, folate, potassium and vitamins B1, B2, and C. According to the principles of TCM, lily bulbs have sweet and slightly cold properties and are associated with the lung and heart meridians. Lily bulbs are used to relieve coughs, dry throats, and other respiratory conditions; to clear away heat; and to treat insomnia and heart palpitations. Its tonic properties make lily bulb a good herb for promoting restful sleep and treating restlessness and irritability. Lily bulb is often combined with other herbs, such as scrophularia, rehmannia root, and anemarrhena. Lily bulbs provide protein and starch. In addition, they contain small amounts of calcium, iron, phosphorus, and vitamins B1, B2 and C. In TCM the lily bulb is considered sweet and cooling in properties. The herb is also associated to the lung and heart meridians and helps to relieve coughs, dry throats, clear heat, and moisten the lung. Dried lily bulb is also used as a herb to calm the spirit, promote restful sleep, and lessen irritability. Fresh and dried lily bulb can be used in both sweet dessert soups and savory soups in Chinese cooking. Like all herbs, lily bulb should be used in moderation, and the consumer should consult with a physician first. According to traditional Chinese herbology, individuals with wind cold or diarrhea should avoid using lily bulb.

For lung and kidney *yin* deficiency associated with chronic bronchitis, asthma, or chronic pharyngitis, combine lily bulbs with prepared rehmannia (Shu Di huang), unprepared rehmannia (Di Huang), dwarf lilyturf roots (Mai Dong), white peony roots (Bai Shao), dong quai (Dang Gui), ningpo figwort roots (Xuan Shen), platycodon roots (Jie Geng), fritillary bulbs (Chuan Bei Mu), and liquorice (Gan Cao). For irritability, restlessness, nervous anxiety, and insomnia, combine lily bulbs with lotus seeds (Lian Zi), glehnia roots (Bei Sha Shen), jujube seeds (Suan Zao Ren), biota seeds (Bo Zi Ren), and poria-cocos mushrooms (Fu Ling). For lung abscesses, combine lily bulbs with snow ear mushrooms (Bai Mu Er) and glehnia roots (Bei Sha Shen). For *yin* deficiency with dry cough and bloody sputum, combine lily bulbs with coltsfoot flowers (Kuan Dong Hua). For mild cases of insomnia and anxiety, combine lily bulbs with longans (Long Yan Rou). The most important health benefits of lily bulb are shown in Table 6.17.

TABLE 6.17 The most important health benefits of lily bulb.

1. Improving sleep quality
2. Treating low-grade fever
3. Alleviating symptoms of irritable bowel syndrome
4. Stopping heart palpitations
5. Preventing and stopping diarrhea
6. Improving concentration and focus

Tremella

Origin, chemical constituents, and health benefits of Tremella

Tremella is a genus of fungi in the family Tremellaceae. Over 100 species of Tremella are currently recognized worldwide [78]. Two species, *Tremella fuciformis* and *T. aurantialba*, are commercially cultivated for food. Tremella is rich in polysaccharides, triterpenoids, protein, dietary fiber, vitamins, and chitin [79]. Tremella was one of the original genera created by Linnaeus in his *Species Plantarum* of 1753. The name comes from the Latin *tremere*, meaning "to tremble" [80]. Linnaeus placed Tremella in the algae, including within it a variety of gelatinous growth, including seaweeds, cyanobacteria, and myxomycetes as well as fungi [81]. *Tremella fuciformis* is one of the great superfood mushrooms and longevity tonic herbs in TCM. Use of Tremella dates back as far as 200 AD, when it was including in one of the earliest TCM classics: the material by Shen Nong ben Cao Jing, the father of Chinese medicine.

In ancient times, like many of the other revered medicinal mushrooms such as reishi and *Cordyceps sinensis*, Tremella was reserved for royalty, members of the ruling family, or rich people who could afford this highly valued superfood [82]. The Tremella mushroom belongs to the jelly fungus family and has many different names. In Chinese it is called silver ear mushroom or white wood-ear mushroom. In Japanese, it is called *shiro kikurage*, which translates to "white tree jellyfish." It is also commonly known as snow fungus and the beauty mushroom. Tremella has been a popular staple of Chinese cuisine for centuries. It is rich in dietary fibers, protein, minerals, and antioxidants and high in vitamin D. It is used in China in a variety of dishes from antiaging soups to desserts. Tremella has been used for thousands of years by Chinese and Japanese herbalists as a potent *jing* and *chi* (*qi*) tonic. It is believed to nourish the lungs, kidneys, heart, brain, and stomach and acts as a powerful tonic for the immune system. Tremella has been used clinically to help clear heat and dryness; to replenish fluids in the body (*yin* deficiency); to treat chest congestion, asthma, and constipation; to balance blood sugar levels and cholesterol (reduces LDL levels); and to lower inflammation. Its rehydration and fluid replenishment qualities may be the best reasons to support its claims as one of the best beauty foods for the skin. In ancient China, Yang Guidei was one of the Four Great Beauties, an imperial concubine who is considered one of the most beautiful women in Chinese history. She used Tremella regularly to maintain her glowing complexion and youthful skin. Tremella's polysaccharides also stimulates the production of superoxide dismutase (SOD) in the brain and liver. SOD is one of the most important superantioxidant enzymes in the body. SOD helps to protect and regenerate skin and effectively prevents wrinkling and sagging of the skin. Tremella contains a large quantity of vitamin D, a considerable amount of protein, other vitamins, minerals, immune-boosting polysaccharides, trace minerals, carbohydrates, and a little fat [83]. Wang et al. [84] reported that Tremella polysaccharides are the major component and activity unit of Tremella. Park et al. [85] concluded that *T. fuciformis* might potentially be used as a precautionary agent in neurodegenerative disease, such as Alzheimer's disease. Shen et al. [86] indicated that *T. fuciformis* polysaccharide (TFPS) alleviated hydrogen peroxide–induced oxidative stress and apoptosis in skin fibroblasts via upregulation of SIRT1 expression, indicating that TFPS may act as a potential therapeutic agent for oxidative stress–associated skin diseases and aging. Results of the GC-Ms analysis of the constituent oil from *T. fuciformis* is shown in Table 6.18. The composition of Tremella polysaccharides is presented in Table 6.19. The most famous beauty and skin-enhancing properties of Tremella mushroom are presented in Table 6.20. Proven health benefits of Tremella are shown in Table 6.21.

TABLE 6.18 Results of the GC-Ms analysis of the constituent oils from *T. fuciformis* [87].

S/N	Compound	Retention time (min)	Percentage of the total	Molecular formula	Molecular weight (g/mol)
1	9,19-Cyclolanost-24-en-3-ol, (3.beta)-	20.766 24.672	32.681	$C_{32}H_{52}O_2$	468.754
2	Lanosterol	21.079 23.034	17.845	$C_{30}H_{50}O$	426.710
3	Acetic acid, 7-Isopropenyl-1,4a-dimethyl-3-oxo-2,3,4,4a,5,6,7,8-octahydronaphthalen-2-yl ester	22.42	21.334	$C_{17}H_{26}O_4$	294.390
4	2(1H)Naphthalenone, 3,5,6,7,8,8a-hexahydro4,8a-dimethyl-6-(1-methylethenyl)-	22.560	9.609	$C_{15}H_{22}O$	218.335
5	Lupeol	22.825 23.230	18.531	$C_{30}H_{50}O$	426.729

TABLE 6.19 Composition of *Tremella* polysaccharides [88].

Organism	Moisture content (%)	Ash content (%)	Protein content (%)	Protein content (%)	Acetyl group content (%)	Carbohydrate content (%)
T. fuciformis (TFU)	11.4 ± 0.1	3.4 ± 0.2	5.7 ± 0.2	0.8 ± 0.1	2.9 ± 0.1	76.6 ± 0.0

TABLE 6.20 The most famous beauty and skin-enhancing properties of Tremella mushroom.

1. Nourishes skin
2. Naturally moisturizes
3. Improves elasticity
4. Slows skin aging
5. Brightens complexion
6. Deeply hydrates inside and out

TABLE 6.21 Proven health benefits of Tremella mushrooms.

1. Creates youthful skin
2. Improved memory and learning capabilities
3. Lowers cholesterol
4. Neurological damage repair
5. Lowers blood sugar
6. Antiinflammatory for the skin and whole body
7. Great for chronic coughs
8. Cancer
9. Protects the liver
10. Prevents osteoporosis
11. Stomach health
12. Intestinal health
13. Weight loss
14. Protects the circulatory system
15. Antiaging agent

Conclusion

China is the home of TCM. There is an ancient saying that food and medicine come from the same source, which is also the foundation of functional foods today. In recent years, China has been one of the world's most important and developed markets for functional foods, which are based on traditional dietary culture and the rapid economic development among individuals and communities. Functional food is defined as a food that has special health functions. It is suitable for consumption by special groups of people and has the function of regulating human body functions but is not used for therapeutic purposes.

Jujube (Chinese date) (*Z. jujube* Mill.) belongs to the Rhamnacease family and is a traditionally popular fruit crop that is native to China. Jujube is a commonly used species, as its fruit possess food value. The most important pharmacological properties of jujube are its antidiabetic, hypnotic-sedative, and anxiolytic effects; neuroprotective activity; sweetness inhibitor; anticancer activity; antiulcer activity; antiinflammatory effect; antispastic effect; antiallergic activity; permeability enhancement activity; cognitive activities; antifertility effect; hypertensive and antinephritic effect; cardiovascular activity; immunostimulant effects; antioxidant effects; and wound-healing activity.

In TCM, lotus roots are plants that belong to the "Herbs that stop bleeding" category. As the name indicates, these herbs tend to have hemostatic properties, meaning that they help to stop various types of hemorrhages. Furthermore, lotus roots are plants that are neutral in nature; this means that lotus roots typically do not affect the balance in the body. Lotus has various notable pharmacological activities, such as antiischemic, antioxidant, anticancer, antiviral,

antiobesity, lipolytic, hypocholesterolemic, antipyretic, hepatoprotective, hypogylcemic, antidiarrheal, antifungal, antibacterial, antiinflammatory, and diuretic activities.

It is documented that *Coix lacryma-jobi* seed was found at the Hemudu site, indicating that *C. lacryma-jobi* has been cultivated in China for more than 6000 years. Coix is a source of ornamental beads, a stable source of sustenance, and a productive fodder grass that is increasingly viewed as a potential energy source. Root extract of *C. lacryma-jobi* is commonly used for treatment of snake bites by traditional healers of south India.

Lily flowers have long been used by many cultures as a symbol of tranquility, peace, and prosperity. In Chinese traditional medicine, lily buds aid brain function, help blood clots, help to cool the blood, and aid urination. Lily bulb has three primary sets of active components: alkaloids (steroidal alkaloids, such as etioline as well as small pyrrolines such as jatrophine, also called lilidine), steroidal saponins, and phenols (mainly flavonoids). The combination of steroidal alkaloids and steroidal saponins is likely responsible for the effects in the treatment of various nervous system disorders. Lilies are good source of starch and protein. Lily bulbs are said to contain calcium, iron, phosphorus, folate, potassium, and vitamins B1, B2, and C. According to the principles of TCM, lily bulbs have sweet and slightly cold properties and are associated with the lung and heart meridians. Lily bulbs are used to relieve coughs, dry throats, and other respiratory conditions; to clear away heat; and to treat insomnia and heart palpitations. Its tonic properties make it a good herb for promoting restful sleep and treating restlessness and irritability. Lily bulb is often combined with other herbs, such as scrophularia, rehmannia root, and anemarrhena. The health benefits of the lily bulb are as follows: Lily bulbs provide protein and starch. Additionally, they contain small amounts of calcium, iron, phosphorus, and vitamins B1, B2, and C, In TCM the lily bulb is considered sweet and cooling in properties. The herb is also associated with the lung and heart meridians and helps to relieve coughs and dry throats, clear heat, and moisten the lung.

Tremella use dates back as far as 200 AD, when it was including in one of the earliest TCM classics: the material by Shen Nong ben Cao Jing, the father of Chinese medicine. Tremella has been a popular staple of Chinese cuisine for centuries, rich in dietary fibers, protein, minerals, antioxidants, and high in vitamin D. It is used in China in a variety of dishes from antiaging soups to desserts. Tremella has traditionally been used for thousands of years by Chinese and Japanese herbalists as a potent *jing* and *chi* (*qi*) tonic. It is believed to nourish the lungs, kidneys, heart, brain, and stomach and acts as a powerful tonic for the immune system. Tremella has been clinically used to help clear heat and dryness; to replenish fluids in the body (*yin* deficiency); to treat chest congestion, asthma, and constipation; to balance blood sugar levels and cholesterol (reduces LDL levels); and to lower inflammation. Fruits and herbs used in TCM are increasingly and extensively used by a substantial part of the population. Jujube has numerous important pharmacological activities and can be considered a valuable source of nutraceuticals.

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Chapter 7

Use of plant foods from West Africa in the management of metabolic syndrome

Sarah Nwozo Onyenibe[1], Josiah Ifie[2] and Edith Ajaiyeoba Oriabure[3]

[1]Biochemistry Department, Faculty of Basic Medical Science, College of Medicine, University of Ibadan, Ibadan, Nigeria, [2]Biochemistry Department, College of Medicine, Kampala International University, Western Campus, Ishaka, Uganda, [3]Pharmacognosy Department, Faculty of Pharmacy, University of Ibadan, Ibadan, Nigeria

Introduction

Plants contain phytochemicals that confer protection on their consumers from attack by microbes and predators. These secondary metabolites have shown both actual healing and disease-preventing ability. Most of these compounds can make foods more palatable as spices and can be used as medicines that are capable of cleansing the alimentary and circulatory system thus removing potent carcinogens [1]. Phytochemicals derived from plants can be classified chemically as phenolics (tannins, lignins, anthocyanins, isoflavones, flavones, flavonoids, and coumarins), sugar-based derivatives (simple sugars, nonstarch polysaccharides, and ascorbic acid), and those composed of isoprene units (terpenoids, simple terpenes, carotenes, vitamin E derivatives, and saponins). Some other plant-based nutrients are amino acids, simple short-chain peptides, minerals, and fatty acid derivatives. Most fruits and vegetables are rich in fiber and mineral elements, especially the essential ones, and also have a high content of antioxidants with free radical scavenging ability. Consumption of vegetables could reduce the risk of cancer, especially colon cancer, as a result of the presence of dietary fiber, polyphenols, and antiinflammatory effects [2].

Imbalance in the production and mopping out of free radicals could lead to oxidative stress, which has been implicated in the etiology of many diseases, as it causes oxidation of vital cellular components, such as DNA and cell lipid membranes, causing damage to muscles and other tissues in the body. Antioxidants can terminate these chain reactions by inhibiting radical intermediates and decreasing oxidative reactions by being oxidized themselves [3]. The body has its own antioxidant system, but a continual intake of meals prepared from foods that are rich in naturally occurring antioxidants such as tocopherol, ascorbic acid, urates, and mineral elements with free radical scavenging ability, is a great way to curb oxidative stress and ensure good health. Flavonoids have been reported to have antioxidant, antiinflammatory, antiviral, antiplatelet, antiallergic, and antitumor effects. The intake of foods that are rich in flavonoids could cause a boost in antioxidant capacity of the cellular matrix, which might not be due to the flavonoids itself but most likely can be attributed to increased production of uric acid as a result of flavonoids excretion. Cardiac-glycoside affects the heart, nervous system, stomach, and intestines by elevating myocardial contraction, which invariably increases the force and rate of blood flow. Saponins could interfere with membrane bilayers, leading to red cell lysis [4].

The risk factors of metabolic syndrome are closely related to those of cardiovascular ailments, including hypertension; general obesity, especially of the upper part of the body; hyperlipidemia; and elevated blood sugar levels [5]. Some factors that contribute to the development of metabolic syndrome are hereditary, such as a family history of adult onset type 2 diabetes. Insulin resistance, hypertension, race, environmental factors, and a lifestyle devoid of physical activity could be some predisposing risk factors that would greatly increase the chance of developing metabolic syndrome [6,7]. The environmental risk factors for metabolic syndrome development are controllable and include a sedentary lifestyle, physical inactivity, and eating habits. Metabolic syndrome is a major public health concern, as it has been estimated that around 20%−25% of the adult population in the world have metabolic syndrome. Those with this condition are three times more likely to suffer ischemic heart attack and are twice as likely to die compared to those who do not have the syndrome [8]. This multifactorial condition has a worrisome growth in prevalence, sometimes with

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accompanying life-threatening effects, and there is an urgent need for successful interventions and research efforts in search of new strategies and methodologies to reduce the burden on the healthcare system of managing the disease [6].

Plants are an important source of drugs, and many people depend on herbal medicines as an alternative and complimentary therapy for numerous diseases. Ethnopharmacological surveys traditional medicine systems have found that over 1200 plants are used in herbal medicine preparations [9]. Considerable research has been carried out using medicinal plants to mitigate various disease conditions, and the results have demonstrated that the use of medicinal plants provides efficient and cost-effective therapeutic solutions. Diet can be used to manage levels of lipids and lipoproteins in the blood.

Some West African plant foods

Xylopia aethiopica (Dunal) A. Rich belongs to the family Annonaceae. Some common names are Ethiopian pepper, African grain, and uda. Other *Xylopia* species are *Xylopia parviflora* and *Xylopia quintassi*. Traditional medicinal uses are treatment for cough or fibroids, as a postpartum tonic to hinder blood loss, for enhancement of fertility, for easy child delivery, as an antihypertensive treatment, and as an antioxidant-rich plant stimulating breast milk production [10,11]. The fruit and seeds are often used as condiments in soup preparation. The fruit has been analyzed for proximate content of crude lipid (9.58/100 g), crude ash (5.89/100 g), crude fiber (8.66/100 g), moisture (8.43/100 g), crude protein (12.4/100 g), and carbohydrate (63.65/100 g). Potassium and calcium are the predominant minerals, and the seeds contain linoleic acid (45.1/100 g), oleic acid (26.5/100 g), and palmitic acid (18.0/100 g) [12]. Xylopic acid (15β-acetoxy-(-)-kaur-16-en-19-oic acid) has been isolated as the major chemical constituent, and the following essential oils are found: beta-pinene, 1,8-cineol, α-terpineol, terpinene-4-ol, paradol, bisobolene, linalool(-)-β-ocimene, alpha-farnesene, alpha-pinene, myrtrenol, and beta-phellandrene [13]. *X. aethiopica* in animal studies has been shown to confer protection against the development of atherosclerosis and cardiovascular diseases as well as eliciting antidiabetic activity [14,15]

Piper guineense Schum. and Thonn. (African black pepper), locally known as *iyere* in Yoruba and *uziza* in Igbo, is a climbing perennial plant that belongs to the family Piperaceae. The major constituents of the fruit essential oils are beta-pinene (23.2%), beta-caryophyllene (6.9%), and bicyclogermacrene (6%). and it was found to inhibit the growth of common disease-causing microbial organisms [16]. A proximate analysis of the seeds found crude lipids (4.04 ± 0.12) and carbohydrates (65.46 ± 0.85); the leaves had a high protein content (15.17 ± 0.39), crude fiber (20.99 ± 0.16), and ash (1.98 ± 0.03); mineral analysis of the leaves revealed that the seeds are rich in chromium (Cr), zinc (Zn), potassium (K), sodium (Na), and phosphorus (P); the leaves contain magnesium (Mg), calcium (Ca), manganese (Mn), and copper (Cu) [17]. There are three main varieties, namely, *Piper umbellatum*, *Piper nigrum* and *Piper guineense*, and they were found to contain N-pyrrolidyl-2,4-octadecadienamide and N-piperidyl-2,4-octadeadienamide [18]. Furthermore, the *Piper* species elicited antiatherogenic and antioxidant effects in hamsters that were fed a high-cholesterol diet; it caused a lowering of plasma total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and malondialdehyde (MDA) levels [19]. It also caused a 20%−30% decrease in body weight as well as favorable serum lipid levels in rats on high-fat diet compared to untreated hypercholesterolemic group, and it attenuated diabetes in female rats, with favorable electrolyte levels and blood lipid parameters [20,21]. The fruit and leaves are eaten as vegetables for soup and the fruit as spice. It is often used as a condiment for pepper soup for mothers after childbirth, and it might prevent high cholesterol and altered serum ions, which is important in disease prevention [21] (Fig. 7.1).

Monodora myristica (Gaertn.) Dunal belongs to the family Annonaceae and is a tropical tree found in Nigeria and other countries in tropics. Some plant secondary metabolites that are present in abundance in the seeds are steroids, phlobatannins, anthraquinones, and alkaloids, while flavonoids and saponins are found in low concentrations. The proximate composition per 100 g crude powdered dry sample is as follows: 28.4 g carbohydrates; 22.7 g lipids; 19.1 g of fiber; moisture 11.2 g; protein 9.6 g; ash 2.6 g, with a high content of Mg, K, and Ca, while iron (Fe), Na, and Zn were present in minute quantities [22]. Thus *M. myristica* seed is a rich source of valuable nutrients. All plant parts are useful both medicinally as well as in the diet; the stem, bark, and flowers contain phenols, beta-carotene, vitamins, and proteins [23]. Some of the phytochemicals have been shown to have desirable health effects, such as diuretic, antihypertensive, antiinflammatory, hypocholesterolemic, hypoglycemic, hepatoprotective, and antimicrobial effects as well as enhancement of cardiac function and circulatory activities [24]. In animal studies, the aqueous extract has been shown to confer hepatoprotection in cadmium-induced hepatotoxicity as well as causing a significant decreases in triglycerides, cholesterol, and LDL cholesterol while increasing high-density-lipoprotein (HDL) cholesterol [23,25].

Myristica fragrans Houtt. belongs to the family Myristicaceae and is commonly known as nutmeg. It is rich in phenols, flavonins, alkaloids, and tannins but has low quantities of chalcones, steroids, saponins, terpenes, and glycosides



FIGURE 7.1 *Piper guineense* leaves and seeds.

[26]. The spice is used in cooking and baking. Nutmeg is an oily seed with about 20%–30% fixed seed fat and 5%–10% volatile oils, which have been shown to contain eugenol, camphrene, lignin, myristicin, and myristic acid. The essential oil are safrol, myrsiticin, limonene, sabinene, alpha-pinene, and beta-pinene [27,28]. *M. fragrans* has shown antioxidant activity, which has been attributed to the presence of eugenol, myristicin, and sabinene and has shown anti-obesity activity in obese mice exposed to a high-fat diet by reducing body weight, blood glucose level, and LDL cholesterol level and increasing the lean body mass [28]. It has been effective at a dose of 500 mg/kg in diabetic rabbits in a 60-day experiment where there was reduced total cholesterol in both the heart, liver tissues, LDL cholesterol, and very low density (VLDL) cholesterol. Moreover it enhanced the excretion of phospholipids and cholesterol in the fecal waste and a concomitant lowering of cholesterol and triglyceride levels in the liver, heart, and aorta [28].

Garcinia kola (Heckel) belongs to the family Guttiferae, and the common names are bitter kola, *orogbo* in Yoruba, *aki-inu* in Ukwani, and *ugolu* in Igbo. It is commonly chewed. It is also used in traditional ceremonies as the art of kola nut presentation. The tree is not really common, and it seldom seen, as it grows deep in the forest. It is commonly believed that the plant outlives those who planted it and might not fruit during their lifetime. Much work has been done on this seed, with many health benefits attached to it; hence it is given in meetings and gatherings, and it is quite commonly eaten. The chemical constituents of bitter kola are complex bioflavonoids named kolaviron (KV), Garcinia biflavonoid 1 (GB 1), Garcinia biflavonoid 2 (GB 2), and kolaflavonone (KF); antioxidant and antiinflammatory properties of *G. kola* have been attributed to KV [29]. *G. kola* markedly reduced blood glucose and glycated hemoglobin levels and ameliorated the lipid profile by lowering serum cholesterol levels, triglycerides concentrations, and blood pressure [30]. In another study, KV caused lower relative weight of rat heart, decreased total cholesterol, LDL cholesterol, and triglyceride levels, while the HDL- cholesterol levels increased significantly in rats fed high-cholesterol diet; hence KV has antiatherogenic properties [31]. These health benefits can be obtained from the consumption of fresh bitter kola; it does not need any preparation. However the daily consumption should be just two or three seeds, as it might be addictive (Fig. 7.2).

Citrullus colocynthis (L.) Schrad belongs to the family Cucurbitaceae, and its common names are bitter cucumber and bitter apple. The chemical constituents are alkaloids, gums, resins, and cucurbitacins B, E1 glycoside, and E2 glycoside [32]. The fruit has antioxidant properties resulting from the presence of flavonoids, which are phenolic compounds, and is used traditionally as an antivenoms and antidiabetic plant drug [33]. In human experiments, *C. colocynthis* fruit extract at 125 mg/day caused a marked decrease in glycated hemoglobin, an index of effective blood sugar management, in fasting blood glucose in a two-month study without adverse drug reactions [34]. In another study using patients with high lipid levels at a dose of 300 mg/day, the dried fruit powder caused decreases in both triglyceride and total cholesterol levels, which were similar to those of normolipidemic control [35].

Strychnos spinosa, a spice used in cooking soup, belongs to the family Loganiaceae. The unripe fruit is poisonous, owing to the presence of strychnine, a cardiac glycoside, but the matured dry fruits are edible and have been shown to have antioxidant activity. Some phytochemicals that are present in the fruit are tannins, saponin, anthraquinone, phenols, phlobatannins, cardenoides, glycosides, and alkaloids [26]. Some food nutrients that are present in the fruit are



FIGURE 7.2 *Garcinia kola.*

fiber, Zn, Fe, and water-soluble vitamins such as riboflavin, thiamine, and ascorbic acid [36]. *S. spinosa* has been reported to have an antidiabetic effect, as it showed alpha-glucosidase and alpha-amylase activity that was comparable to standard diabetic regimen acarbose. *S. spinosa* is used traditionally to enhance breast milk production in nursing mothers and for management of stomach ulcer, snake bite, and diarrhea [37].

Solanum species available in West Africa are *Solanum macrocarpon* (Schaff.), *Solanum aetheopicum* (L.), *Solanum kumbala*, *Solanum gilo* (L.) and *Solanum melongena* (L.). They can be eaten either raw or cooked and can be used in preparing yam sauce, as a condiment for the popular African salad, and as a healthy snack; it is often served along with peppered peanut butter as kola for entertaining guests. Both the leaves and fruits are edible; the leaves are used as a vegetable for soup, commonly called *igbagba* in Yoruba and *anhara* in Igbo. It is used traditionally in the management of diabetes in Nigeria [38]. Some food micronutrients that are present are Fe, Ca, and water-soluble vitamins. The fruits have a high moisture content, usually about 90%, are low in fat, and contain about 1.4% each of fiber and protein [39]. The low lipid content makes the fruits a good snack for overweight and obese individuals and possibly those with cardiovascular ailments. The purple oblong fruited eggplant is rich in simple sugars, anthocyanins, solasodine phenols, and proteins [40]. *S. melongena* caused weight loss; animals on a 10% plant diet gained more weight than those on a 20% compounded feed [39]. The same plant has showed ameliorative potentials in diabetic rabbits that were given diets high in saturated fat by reducing the sugar level, decreasing the gain in body weight, and enhancing HDL cholesterol levels, while total serum cholesterol, triglyceride, and LDL cholesterol levels decreased significantly compared to those in the untreated negative control group [41]

Capscicum annuum L. is the common red pepper. It has a high content of vitamin C, carotenoids, and antioxidants; is low in calories; and can be used either fresh or as condiment in cooking. This is the common red pepper, of which there are about five varieties in Nigeria based on their shape. All pepper types are referred to as *ose* in Igbo and *ata* in Yoruba. *Ata wewe*, a thin, short type, incidentally has two phenotypes, which differ not only in shape but also in that one is very peppery and the other is not too hot. *Shongbon*, a bigger, longer type, is about the size of an adult finger and not too peppery. *Ata rodo* is a short, fat variety that is often used in cooking stew. *Tatashe* is a big, thick, fleshy type, with bitter seeds that are often discarded in cooking. Red pepper owes its color to the presence of carotenoids and also contains phenyl propanoid alkaloid (capsaicin), which gives it a pungent smell, and dehydrocapsaicin [42]. It has been shown to modulate serum lipid in animals fed a high-fat diet where there was marked reduction in total cholesterol, triglyceride, and LDL cholesterol levels and an increase in HDL cholesterol level [43]. Decreased serum cholesterol could be due to increased intestinal absorption or the production in the liver or induction of biliary secretion of cholesterol and increased cholesterol excretion in the feces. Dietary cholesterol reduces fatty acid oxidation, which in turn increases the levels of triglycerides in the liver and cellular flow. The nutritive importance of red pepper comes from the colored pigment, which serves a protective role against oxidative stress and also has antiinflammatory properties, a phenomenon that has been implicated in the etiology of many diseases. It is a "must have" in most of our meals.

Dennettia tripetala (Bak.f.) belongs to the family Annonaceae and is commonly known as pepper fruit in English, *ata igbere* in Yoruba, and *mmimi* in Igbo. Some of its traditional uses are for the treatment of diabetes, diarrhea, toothache, fever, cough, and nausea [44]. The fruits, either ripe or unripe, and the tender leaves of the plant are eaten fresh. The following have been isolated from the n-hexane fraction of the seeds: phenyl ethyl alcohol, 3-carene, caryophyllene, ethyl ester, and linoleic acid. Phytochemical screening showed the presence of tannins, steroids, terpenoids, flavonoids, and cardiac glycosides. The fruit contains proteins, fiber, sugars, moisture, lipids, and ash. Ripening increases the moisture content as well as the proportion of vitamins, such as retinol, tocopherol, and ascorbic acid. This highly nutritious plant has also shown insecticidal activity and antiinflammatory, analgesic, and antimicrobial properties [44]. *D. tripetala* has been shown to have a lipid modulatory activity and a blood glucose-lowering effect exceeding that of the standard drug Tolbutamide, possibly via increasing the concentration of proteins capable of utilizing glucose within the cytoplasm to the cell membrane [45]. An increase in fat and amino acid utilization from an enhanced rate of gluconeogenesis could elevate glycogenolysis, thereby causing a significant reduction in uptake of carbohydrates for energy production in the cell.

Cymbopogon citratus Stapf is commonly known as lemongrass. The fresh leaves are used as condiment for cooking soup, and it is one of the traditionally used ingredients alongside pawpaw leaves, neem leaves (dogonyaro), and guava leaves for malaria treatment by steam inhalation followed by drinking a cup of the hot infusion. The essential oil of the minty leaves of *C. citratus* have been identified as citronellal, terpinolene, geraniol, alpha-citral, beta-citral, geranyl acetate, terpinol methylheptenone, and myrecene. The phenolic and flavonoids that are present in the leaves have been identified as quercetin, kaemferol, apiginin, isoorientin-2′-O-rhamnoside, and luteolin. The leaves have antioxidant, antimycobacterial, antimutagenic, antimalarial, antifungal, and hypoglycemic activity [46]. Furthermore, the lipid-lowering and antidiabetic effects of the water and ethanol extract of *C. citratus* have been demonstrated in studies of animals on a high- cholesterol diet and with streptozotocin-induced diabetes [47,48]. The total serum cholesterol, triglyceride, and LDL cholesterol levels were reduced compared to those in the untreated hypercholesterolemic group, and the blood sugar level was significantly lower relative to that in negative control rats.

Talinum triangulare is commonly known as waterleaf, most often grows in the wild as the rains start, but in some places it is now cultivated. Flavonoids, polyphenols, alkaloids, saponins, cardiac glycosides, and tannins are some plant secondary metabolites present in the leaves [49]. In the dry leave sample, the values were as follows: flavonoids (69.80 mg/100 g), alkaloids (55.56 mg/100 g), saponins (1.48 mg/100 g), and tannin (1.44 mg/100 g); in the fresh wet sample, the values were as follows: flavonoid (58.33 mg/100 g), alkaloid (13.89 mg/100 g), saponin (1.37 mg/100 g), and tannins (1.09 mg/100 g). *T. triangulare* leaves in proximate composition had a high moisture content of 90%, carbohydrate 4.4%, protein 2.4%, fat 0.4%, and the remainder ash content [49]. Some biological effects of the plant are antiinflammatory, prooxidant. and hypoglycemic effects. The leaves had a nonsignificant effect on the lipid profile in normal rats that had been given different doses of the plant extract [50]. Healthy normal rats as well as streptozotocin-induced diabetic animals that were given 250 mg/kg body weight had significantly decreased fasting blood sugar levels compared to those of untreated diabetic rats. In an oral glucose tolerant test in normal control rats, coadministration of 1.2 g/kg glucose and waterleaf extract significantly lowered blood sugar levels, as it did in streptozotocin-induced diabetic rats given the extract [51]. In rats on high-cholesterol feed, *T. triangulare* significantly decreased the elevated serum lipid profile parameters, such as triglyceride, total serum cholesterol, LDL and VLDL cholesterol [52]. MDA was as restored as well as altered hematological indices to near normal as in control rats in a dose-dependent manner.

Cucurbita pepo L. belongs to the family Cucurbitaceae and is an annual climbing plant that thrives in warm places. The leaves are often eaten as vegetable for soup, and the immature fruits are used for herbal preparations, while the matured fruits are used in making drinks, and as soup thickeners. In Eastern Nigeria it used for cooking either yam pottage or yam sauce. The common variety of *C. pepo* is dark yellow. but white and orange varieties are available. Some of the chemical components are proteins, seed oils, sterols, carbohydrates, and p-aminaobenzoic acid [53]. Proximate content are sugars (66%), fat (2.3%), protein (3%), and moisture. *C. pepo* is a rich source of carotenoids (171.9 μg/g). The nutrient content in 100 g of fruit was found to be crude fiber (11.46%), calories (80 kcal), and ash content (16%) and was analyzed to contain Mg (190 mg/kg), Ca (179 mg/kg), K (160 mg/kg), Na (159 mg/kg), lead (0.29 mg/kg), Mn (0.50 mg/kg), Fe (1.37 mg/kg), P (11.38 mg/kg), Ni (0.5 mg/kg), and Cu (25 mg/kg) [54]. The seed oils of *C. pepo* contain polyunsaturated fatty acids, polysterols, proteins, antioxidants, vitamins, carotenoids, and mineral elements. By using gas chromatography-mass spectrometry, the seed oils were analyzed to be stearic acid (8.67%), palmitoleic acid (0.5%), palmitic acid (10.68%) but the unsaturated fatty acids are linoleic (39.84%), oleic (38.42%), linolenic acid (0.68%), and gadoleic acid (1.14%) [55]. The carotenoids have been identified to be chrysanthemaxathin, alpha-cryptoxanthin, beta-cryptoxanthin, epimer flavoxanthin, violaxanthin, beta-carotene, alpha-carotene, 13(13′)-cis-lutein, lutein, lutein epoxide, and 15-cislutein [53]. An antidiabetic effect in nonionic copolymer−induced diabetes with

impaired beta cell function has been reported, and *C. pepo* caused a lowering in glycemic index, lipid profile, and insulinemic levels [56].

Pterocarpus soyauxii Taub. is a vegetable that is quite popular in eastern Nigeria. It is commonly known as *oha*, *uha*, or *ora*, depending on the dialect. The proximate content of the leaves, in descending order, was crude protein (29.5%), crude carbohydrate (25.95%), crude fiber (17.2%), moisture (17.2%), ash (5.7%), and fat (4.15%) [57]. Minerals present were also analyzed as Mg (41.0), Na (32.0), Ca (4.04), Zn (1.39), Fe (0.60), K (0.31), Cu (0.21), and Mn (0.17) in milligrams per 100 g of dried leaf sample, while chromium and lead were absent. Vitamin C (0.4470 mg/g) and vitamin A (0.2044 mg/g) were detected to be present. The plant secondary metabolites tannins, saponins, alkaloids, and glycosides were present, but steroids, flavonoids, and phenols were absent [58]. Feeding rats the leaves of *P. soyauxii* to animals on high-fat diets with streptozotocin-induced diabetes has been shown to not only exact hypoglycemic and hypolipidemic effects but also to protect the rat brain from scarring [59].

Pterocarpus santalinoides L. Heritex PC belongs to the family Fabaceae (Papilnoideae). It is common in Ghana, Nigeria, Senegal, and Cameroon. The local names in the languages of the three major tribes in Nigeria are *gbenghe* (Yoruba), *gundurugyadar kurmi* (Hausa), and *uturukpa* (Igbo). The leaves are used in cooking soup especially for the elderly. Traditionally, they are used to treat heart disease, stroke, and inflammation. Phytochemicals found in the leaves were tannins, saponin-glycosides, terpenoids, alkaloids, and flavonoids, and the extract showed antimicrobial activity against common strains [60,61]. In alloxan-induced diabetes in rats the leaf ethanol extract exerted a blood glucose−lowering effect [62]. This might result from reducing glucagon secretion and insulin release by decreasing insulin resistance. Thus the digestion and absorption of sugar could slow down, and hepatic glucose release could decrease. LDL and VLDL lipoprotein cholesterol, which are associated with the development of atherosclerosis as they are involved in transportation of cholesterol to peripheral tissues, were found to decrease in guinea pigs that were given a *P. santalinoides* leaf infusion. On the other hand, HDL cholesterol, which carries cholesterol to the liver for degradation to bile, thus preventing the development atheromas, increased [63]. In a feeding experiment at a very high dose of 5000 mg/kg body weight, no abnormality, toxicity, or mortality was observed, and a 50% increase in HDL was seen by day 14, as well as significant decreases in LDL, VLDL, and triglyceride levels [64] (Fig. 7.3).

Gnetum africanum Welw. is commonly known as *ukazi* in Igbo and *afang* in Ibibio. The leaves can be eaten either raw in salads or cooked, and they are often used in preparing soups and stews. Some plant secondary metabolites that are present in the leaves are anthocyanidins, phenolics, flavonoids, tannins, saponins, glycosides, cyanogenic glycosides, and cardiac glycosides. It is worth noting that the concentrations of antinutrients such as oxalates, glucosinolates, and tannins are below toxic levels [65]. In a long-term (six months) feeding experiment in rats, ingestion of *G. africanum* leaves caused increases in body weight, hemoglobin concentration, and enzymatic antioxidants but decreases in serum cholesterol and lipid peroxidation [66] Furthermore, the leaf extract caused a decrease in blood glucose level at six hours post administration of 1600 mg/kg body weight; reduced cholesterol, LDL, VLDL, and plasma sugar levels; and



FIGURE 7.3 *Pterocarpus santalinoides.*

a reversal of pancreatic cell destruction in diabetic rats [67,68], thus providing protection against hyperlipidemia and hyperglycemia.

Terminalia catappa L. is commonly known as tropical almond and belongs to the Combretaceae plant family. The fresh fleshy fruit, which is often wine colored, encloses the edible nut, which is covered by a hard husklike fiber that is not easy to crack open. Inside the husk is the edible nut. The fruit is high in tannic acid and contains 1.95 g of protein, 12.03 g of carbohydrate, and 1.21 g of ash [26]. Other food components in the fruit are 2.09 μg of beta-carotene and 138 mg of ascorbic acid. The seeds contain 4.27% ash, 4.94% fiber, 23.78% protein, 51.8% fat, 16.02% sugar, and 4.13% moisture. The seed oils have been extracted, and the oils that were present were identified as stearic, palmitic, palmitoleic, oleic, linoleic, arachidic, and myristic acids [69]. 1-degalloyl-eugeniin, 2,3-(4,4′,5,5′,6,6′- hexahydroxy-diphenoyl)-glucose, quercetin, terflavin A&B, gentisic acid, terctain, tergallagin, corilagin, punicalin, punicalagin, kaemferol, chebulagic acid, and granatin B have been isolated from the leaves [69]. The fruits are rich in micronutrients such as vitamins B1, B2, and B6 and in potassium and phosphorus. The fruit and leaves have shown antidiabetic effect as well as lipid-lowering activity in animal model induced diabetes using alloxan, with evidence of regeneration of rat pancreatic tissue [70,71]; these effects can be attributed to the secondary metabolites that are present, such as phenols, beta-carotene, and flavonoids.

Myrianthus arboreus P. Beauv. belongs to the family Urticaceae. It is a tropical tree that is common in Nigeria and other place in West and Central Africa. Its common names are monkey mango. The leaves are edible and are used in soup making. The leaves have been analyzed for proximate composition as follows: 18.74%crude protein and 11.6% crude fiber. The antinutrients in the leaves have been quantified per 100 g sample as 25 mg phytic acid, 0.006 mg mycotoxin, 341.2 μg trypsin protease inhibitor, 1860 mg saponins, 4750 mg tannin, 640 mg alkaloids, and 15 mg oxalate[72]. Amino acid analysis showed that the leaves contain leucin, isoleucine, threonine, methionine, and cysteine [72] *M. arboreus* is also a rich source of phenolic compounds. The stem and root bark have shown blood glucose−lowering ability and a modulatory effect on serum lipids in streptozotocin-induced diabetes in rats [73,74] (Fig. 7.4).

Pentaclethra macrophylla Benth. belongs to the Fabaceae family. Its common name is oil bean seed. In Nigeria it is known as *ugba* in Igbo, *apara* in Yoruba, and *ukpagba* in Efik. The *P. macrophylla* tree is indigenous to Nigeria. Ugba is eaten with relish, particularly in the eastern part of Nigeria, in meals such as *iji ashisha* (yam, spinach, jute mallow, palm oil meal), African salad, or a ceremonial food or as a protein source. It leaves the dining table quickly, possibly owing to considerable time involved in getting it into edible form. Phytochemical screening revealed the presence of alkaloids, tannins, flavonoids, phenols, and cyanogenic glycosides [75]. Some minerals that are present in the raw seed are Ca (47.70 mg/kg), Mn (11.30 mg/kg), Zn (162.65 mg/kg), Fe (141.50 mg/kg), Mg (3348 mg/kg), K (7623 mg/kg), and Na (351.95 mg/kg) [76]. Cooking for different time durations decreased the quantities of these minerals. *P. macrophylla* has lipid-lowering and blood sugar−lowering abilities in experimental rats in which diabetes was induced by using alloxan [77]. Rabbits that were given a diet high in saturated fats, that were made diabetic using 30% sucrose feeding, and that were on supplementation with fermented *P. macrophylla* seed showed a significant ($P < .05$) reduction



FIGURE 7.4 *Myrianthus arboreus.*

in fasting blood sugar levels, glycated hemoglobin (HBA1C), and alpha-amylase and a significant increase ($P < .05$) in glucose-6-phosphate dehydrogenase (G6PDH) when compared with the negative control animals [78]. This finding is in agreement with a report of numerous medicinal properties that has been attributed to the seeds of *P. macrophylla* [79]. A high-fat diet and 30% sucrose feeding resulted in an altered lipid profile, as there was a significant ($P < .05$) increase in the levels of triglycerides, total cholesterol, and LDL cholesterol and a significant decrease in HDL cholesterol in negative controls relative to the normal controls. However, feeding with fermented *P. macrophylla* seeds effected changes in lipid profile; there was a significant ($P < 0.05$) decrease in triglyceride and serum total cholesterol levels and a concomitant significant ($P < 0.05$) increase in HDL compared to negative controls, and this effect was similar to that of the reference drug [78] (Fig. 7.5).

Uvaria afzelii Sc. Elliot belongs to the family Annonaceae. Its common names are *gbogbonishe* in Yoruba, *umimi ofia* in Igbo, and *osu-umimi* in Ukwani. *U. afzelii* is commonly grown in southern part of Nigeria, especially in the eastern states. It is used locally to treat cough and other infections. Some chemical constituents of the plant are phenolics, triterpenoids, flavonoids, syncarpic acid, uvafzelic acid, syncarpurea, afzeliindanone, dimethoxym emorydone, atteucinol, and 2−hydroxydemethoxym atteucinol [80,81]. In an animal study, it caused weight gain and ameliorated elevate blood sugar and lipid profiles [100]. The blood sugar−lowering ability was tested in nondiabetic subjects using an extract. It was also administered to alloxan-diabetic rats, and fractions of the crude extract had blood sugar−reducing activity. The LD_{50} was 693 mg/kg. All tested extracts had lower blood glucose activity than glibenclamide in normal rats, but in hyperglycemic rats, there was a concentration-dependent activity, and it was comparable to the standard drug [82]. At 400 mg/kg the extract was 58% more active than the reference, but the ethyl acetate fraction exhibited greater activity than glibenclamide at all concentrations, and two new compounds, 4-bromophenol and 2-hydroxy-3-(4-hydroxyphenyl)acrylic acid, were obtained from chromatographic separation [83].

Detarium senegalense JF Gmelin belongs to the family Caesalpinaceae, and it is common in tropical regions of Africa. Its common English name is tallow tree, and in eastern Nigeria it is called *ofo*. The leaves are eaten as vegetable for soups, used in an enema for dysentery, and used as an eye wash for conjunctivitis. The seeds are used in eastern Nigeria as a thickener in soups and stews. The fruit pulp is rich in vitamins [84] and contains soluble dietary fiber in the form of mucus and lignans, and a water-soluble nonstarch polysaccharide has been reported in seed flour of the plant [85]. The seed flour has been analyzed for proximate content [86,87] and is rich in carbohydrates and, other nutrients, but the amount of crude protein is relatively low (about 12 g/100 g) in seed powder [85]. Anthocyanidin alkaloid (2-methoxyamine 3,4,5,7-tetrahydroxy anthocynadine) with antibacterial activity has been isolated from the stem bark [88,89,90]. In a human study, incorporation of the seed flour into stew and bread lowered the blood glucose level in normal subjects, and gum from the seed has been reported to have promising antidiabetic properties in rats [91].

Cajanus cajan, also known as the pigeon pea, is a local legume that has a complete nutritional composition. In comparison to soybeans, it has higher levels of dietary fiber, total mineral content, and vitamin C as well as a lower fat content [92]. This local leguminous plant has also been used traditionally as functional food [93], and there is evidence supporting its functional role. Ariviani et al. reported its ability to improve plasma antioxidant status, indicated by a decrease of plasma MDA level reaching 37.16% [92], and it has the capability of increasing the HDL cholesterol level and lowering the plasma levels of triglycerides, LDL cholesterol, and total cholesterol [94]. *C. cajan* intake was also reported to be capable of providing hypoglycemic effects in humans and diabetic rats [95].



FIGURE 7.5 *Pentaclethra macrophylla.*

Treculia africana Decne. belongs to the family Moraceae. It is commonly known as African breadfruit, and in eastern Nigeria it is called *ukwa*. This tree plant is native to tropical regions in West Africa and East Africa. The fruit is edible. The matured fruit is allowed to ferment, and then the seeds are removed, and the fruit is cleaned out and dehulled. It is hardly ever eaten raw but might be roasted, baked, or boiled. It is traditionally eaten either roasted as a snack with coconut and palm kernel nut or as porridge with a long cooking time. *T. africana* has been shown to be a rich source of plant protein, with higher levels than are found in animals and marine fishes, with a seed oil content of 18.54% [96]. Previously, this delicacy was not expensive, but increased awareness of its nutritional potential has increased the economic value tremendously in eastern Nigeria. Ethnomedicinally, it is used as a worm expeller, for febrile sickness, and as a purgative. In the middle belt of Nigeria and southern Nigeria it is used in the treatment of diabetes. *T. africana* leaves, twigs, and stem bark have been used for dental disorders [97]. and the root bark has shown antidiabetic activity in alloxan-induced rats [98]. Various studies have been done involving reducing the cooking time, improving the protein digestibility, and using alternate methods of preparation of the seed flower [99–101]. In another study, the plant extract had a hypoglycemic effect in alloxan-diabetic rats at a very low dose of 10 mg/kg. The diethyl ether soluble fraction had a 27.1% blood glucose–lowering effect at 4 hours post administration and a maximum therapeutic potency of 69.4% at 240 hours; similarly, the reference drug metformin at a dose of 0.5 mg/kg had a potency of 26.4% and 65.8% at 4 hours and 240 hours, respectively [98] (Fig. 7.6).

Parkia biglobosa (Jacq) Benth, commonly known as the African locust bean, belongs to the family Fabaceae. It can be eaten raw or cooked. Its common names are *dawadawa* in Hausa and *iru* in Yoruba. *P. biglobosa* is used as a protein- and fat-rich flavoring for soup and stew. The proximate composition of *P. biglobosa* has been shown to be 1.8% crude fat, 11.8% crude fiber, 4.8% ash, 67.30% carbohydrate, 6.5% protein, and 8.4% moisture [102]. Phytochemical analysis showed carotenoids (49.175 μg/100 g), ascorbic acid (191.20 mg/100 g), total phenols (204.60 mg/100 g), phytic acid (60.00 mg/100 g), saponins (17.80 mg/100 g), tannins (81.00 mg/100 g), and hydrocyanic acid (17.30 mg/100 g) [103]. Feeding alloxan-induced diabetic rats 6 g/kg body weight with fermented aqueous and methanol extract caused 69.2% and 64.4% reductions, respectively, in the fasting plasma glucose level compared to 70.4% for glibeniclamide, the reference drug [103]. Animals that were given the aqueous extract had weight gain, and those that were given the methanol extract lost weight, as did the untreated alloxan-diabetic rats. Furthermore, animals that were given the plant extract all had elevated HDL cholesterol and reduced LDL cholesterol levels [103]. In another study, chloroform, hexane, and mother liquor fractions was evaluated in glucose-loaded and alloxan-induced diabetic rats, methanol caused 64% and 44.1% decrease in glucose-loaded and alloxan-diabetic rats [104]. A chloroform fraction of *P. biglobosa* caused a 65.7% reduction in their blood sugar level. This was significant compared to the reference drug, and consumption of this plant food should be encouraged [104].

Digitaria exilis Stapf has two main types. *D. exilis* Stapf, known as *acha* in northern Nigeria, and *D. Iburua* Stapf, known as iburu. *D. exilis* Stapf is a traditional cereal grain; acha is the white variety, while iburu is black [105]. Some common names are hungry rice, Asian millet, fundi, findi, and fonio. Acha is cultivated throughout West Africa, and it



FIGURE 7.6 *Treculia africana.*

is commonly eaten as whole grain in the form of couscous, gwete, tuwo, and acha jollof. It has become very popular recently as a nutraceutical against common non-communicable diseases such as diabetes, hypertension, hypercholesterol. and obesity. Some phytochemicals that are present in *D. exilis* Stapf are flavonoids, phenolics, phlobatannins, tannins, saponins, anthraquinones, cardenolides, alkaloids, and cardiac glycoside [106]. The protein and fat content of this cereal grain was 6.53% and 1.91%, respectively, per dry weight [107]. Acha has all the essential amino acids except lysine, and the seed oils contain the unsaturated healthy oils olieic acid (30.5%) and linoleic acid (47.4%) [107]. In streptozotocin-induced diabetic rats that were administered acha extract, the levels of glucose-6-phosphatase, fructose-1,6-bisphosphatase, and markers of kidney toxicity such as albumin, urea, creatinine, and blood glucose significantly increased, while body weight, pancreas weight, and pancreatic insulin decreased [107]. Acha extract significantly reduced body and pancreas weights, decreased plasma glucose and the kidney indices, and elevated the concentrations of carbohydrate-metabolizing enzymes, comparable to effects of the reference drug metformin and control nondiabetic animals. In another study, which used dehulled and undehulled, ground and unground, and cooked and uncooked *D. exilis* Stapf, rats that were given the dehulled form had 61.3%, 52,7%, and 53.18% glycemic index, while rats that were given the undehulled form had 51.98%, 46.4%, and 50.5% glycemic index, respectively. Thus not only does acha have an antidiabetic effect, but the undehulled grain is more effective in controlling blood sugar [108].

Discussion

Epidemiological studies have found that food constituents such as carotenoids, mainly beta-carotene and lycopene, lower the prevalence of metabolic syndrome [109,110]. Furthermore, the incidence of obesity decreased, as did serum concentrations of triglycerides in middle-aged and older men. Similarly, prolonged intake of food that is rich in antioxidants has been shown to confer protection against many diseases, such as cancer, diabetes, and neurodegenerative and cardiovascular diseases. To ameliorate the pathological and negative impacts of the high generation of reactive oxygen species, both exogenous and endogenous antioxidant defense pathways act in a synergistic cascade to help restore homeostasis [111]. The antioxidant systems included antioxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase and nonenzymatic antioxidants such as vitamin C, vitamin E, glutathione, and albumin [112]. These antioxidants are present in the diet of humans, especially in vegetables and fruits [113,114]. Vegetables have been shown to be a rich source of antioxidants due to the presence of epigallocatechin gallate, resveratrol, phytosterol, myricetin, and gingerol, to mention a few. Phytochemicals, which are substances produced by plants or secondary metabolites such as carotenoids, flavonoids, saponins, alkaloids, and phenols, have been shown to directly or indirectly influence the numerous pathways of molecular signal transduction involving cell proliferation and migration, inflammation cascade, metabolic disorders, and oxidative stress [115,116].

There has been a significant increase in the development of diabetes mellitus worldwide, and it is a public health concern. This has gone along with the increased incidence of obesity arising from the transition from simple, locally prepared meals to fast foods and Western-style diets. There are potent antidiabetic and lipid-lowering drugs, but these medications have side effects and have high cost, and they are not accessible to the vast majority of people worldwide. We evaluated the nutrient composition of common locally available foods, using proximate composition and phytochemical screening. This compilation of food items has shown that these foods are not only rich in nutrients but also have medicinal qualities that lower blood sugar and lipid levels. Consumption of these fruits, vegetables, spices, and grains offers a cheaper, healthier way to manage and prevent metabolic syndrome. This is important, as the foods are safe and do not have side effects such as dizziness, nausea, vomiting, weight gain, fluid retention, edema, and headache, which are associated with the use of antidiabetic drugs. Moreover, improperly managed diabetes is a major cause of death, kidney damage, lower limb amputations, erectile dysfunction, and diabetic ketoacidosis and might aggravate other aging-related maladies. The probable mechanistic pathway for the antidiabetic activity of the food could be by inhibition of enzymes involved in the metabolism of starch, such as alpha-amylase and alpha-glucosidase activity, enzymes that are involved in glycolysis, pentose phosphate, gluconeogenesis, and glycogenolysis pathways. It could be via enzymatic activation such as catalase, superoxide dismutase, the peroxidases, and other antioxidant enzymes that would hinder oxidative damage, plant metabolites with insulin-like activity, increased secretion of insulin, and enhanced glucose transporters.

Hypercholesterolemia is a lipid metabolism disorder that is characterized by high blood cholesterol, triglyceride, LDL cholesterol, and VLDL cholesterol levels, and this is a well-documented risk factor in the development of atherosclerosis, stroke, and other cardiovascular ailments. Dyslipidemia is a major problem in many societies, especially in the aging population, and there is a strong positive correlation between cardiovascular diseases and abnormal lipid levels. Diet could confer protection against various diseases, and diets that are high in red meat, processed meats such

as sausages, fried foods, and junk foods have been associated with higher risk of development of diseases and elevated serum cholesterol. Diets that are rich in spices, fruits, vegetables, whole grains, and nuts have been known to contribute to colon-healthy meals, increase levels of antioxidants, reduce blood sugar levels, modulate weight gain, and alter serum lipid levels. Seeds, fruits, vegetable, spices, whole grains, and root tubers with high contents of nonhydrolyzable polysaccharides not only have calorific nutritive value but also contribute to well-balanced nutrition. Food consumption plays a crucial role in management of disease, especially diseases related to dietary indiscretion. An abnormal lipid level plays a role in the onset of atherosclerosis, but aging, hormone replacement therapy, a family history of coronary heart disease, smoking of any type, hypertension, diabetes mellitus, and alcohol consumption can increase the blood cholesterol level. The plant foods that we evaluated had serum lipid-lowering abilities and could produce a favorable lipid profile. Regulation of the cholesterol level occurs via the synthesis, absorption, and excretion. Approximately 700−900 mg of cholesterol is synthesized per day, and 300−500 mg is absorbed daily from dietary sources. Excretion from the alimentary canal is about 600 mg/day, conversion to bile acids is 400 mg/day, sloughing skin is 85 rag/day, biosynthesis of steroid hormones is 50 mg/day, and cholesterol is required by cell membrane both in the maitainence of menbrane integrity and fluidity. Many plant-based foods—vegetables, fruits, and spices—have hypotensive, hypolipidemic, and antidiabetic properties, and their use in meals is a cheap, efficacious means of managing the killer trio that is globally involved in metabolic syndrome.

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Chapter 8

Best quality foods of Iran for the prevention of non-communicable diseases

Poonam Tiwari[1], Ghizal Fatima[2], Ram B. Singh[3], Farzana Mehdi[2], Wajdy Al-Awaida[4], Najah Hadi[5], Ammar Mehdi[6], Mohamad Hesam Shahrajabian[7], Mojgan Khatibi[8], Shabnam Omidvar[9] and Sara Sarrafi Zadeb[10]

[1]Department of Dietetics, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India, [2]Department of Biotechnology, Era's Medical College and Hospitals, Lucknow, India, [3]Halberg Hospital and Research Center, Civil Lines, Moradabad, India, [4]Department of Biology and Biotechnology, American University of Madaba, Madaba, Jordan, [5]Faculty of Medical Sciences, University of Kufa, Kufa, Iraq, [6]Career Dental and Medical College, Lucknow, India, [7]Biotechnology Research Institute, Chinese Academy of Agricultural Sciences, Beijing, P.R. China, [8]Endocrinology and Metabolism Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran, [9]Social Determinants of Health Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran, [10]Medical Sciences and Technology Department, Science and Research Branch, Islamic Azad University, Tehran, Iran

Introduction

A number of fresh and dry fruits are available in Iran, including Persian peaches, pomegranates, pistachios, figs, apricots, apples, and grapes [1,2]. In general, fruit is an important component of the Iranian diet, and the country benefits from a variety of favorable meteorological conditions suitable for fruit production [1,2]. The northern seaside lands of the Caspian Sea have the finest conditions for fruit production. Iran ranks first in the world in the production of pomegranates and pistachios, Iran ranks second in dates, third in figs and cherries, and seventh in grapes [2]. Iran has. 2.7 million hectares of orchards that are being harvested with an annual production of 16.5 million tons. Per capita production of fruits around the globe is 80 kg, while in Iran it is 200 kg, according to official Food and Agriculture Organization statistics [3]. In recent years, Iran produced 4.5 million tons of citrus fruits and 3 million tons of apples yearly and has been ranked between eighth and tenth in yearly global fruit production [2,3]. Fruits are an important component of a healthy diet. Reduced fruit consumption is linked to poor health and increased risk of non-communicable diseases (NCDs) [4,5]. An estimated 3.9 million deaths worldwide were attributable to inadequate fruit consumption in 2017. Including fruits and vegetables as part of the daily diet may reduce the risk of some NCDs, including cardiovascular diseases (CVDs) and certain types of cancer [4]. Limited evidence suggests that when consumed as part of a healthy diet that is low in fat, sugars, and sodium, fruits may also help in the prevention of obesity, an independent risk factor for NCDs [5,6]. Moreover, fruits and vegetables are rich sources of vitamins, antioxidants, and minerals as well as dietary fiber and a host of beneficial nonnutrient substances including plant sterols, flavonoids, and other antioxidants [2]. This review aims to high light the recent status of research on the role of fruits and nuts that are known to decrease the risk of NCDs [3].

Functional foods and prevention of non-communicable diseases

Diet represents the most important modifiable factor to prevent CVDs. There is evidence that plant-based dietary patterns are associated with lower risk of CVDs [5,6]. Several epidemiological studies demonstrated that fruit intake was inversely associated with the risk of cardiovascular events [7−10]. It is estimated that a diet low in fruits is the third most important risk factor of CVDs, following high blood pressure (BP) and cigarette smoking, accounting for more than 5 million deaths worldwide in 2010 [11]. Furthermore, fruits, such as grapes, blueberries, pomegranates, apples, hawthorn berries, and avocados, have been widely studied and have shown strong cardiovascular protective effects. In addition, the effectiveness of fruit intake in the primary prevention of CVDs has been revealed by growing clinical data

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in patients with metabolic risk factors: hypertension, dyslipidemia, diabetes, and overweight/obesity. In all guidelines, nonpharmacological methods have been advised as the first line of therapy for the treatment of CVDs and diabetes. Some fruit extracts possess potent antihypertensive, lipid-lowering, and hypoglycemic activities, which has inspired many researchers to explore new therapies for CVDs [12–15]. The cardioprotective mechanisms of fruits are not entirely clear, but their outstanding antioxidant and free radical scavenging properties indicate that polyphenolics and flavonoids may be potential bioactive agents that provide the benefits [11].

Pistachios

Increased consumption of nuts has been found to be protective against CVDs and other chronic diseases [11,12]. All the ancient cultures, including the Assyrians and the Greeks, knew that pistachios could be used as medicine in the form of aphrodisiacs and antidotes [13,14]. Emperor Tiberius, the Roman consul of the province in the ancient period, introduced pistachios into Italy. The Queen of Sheba (Assyria, c.10th century BCE) monopolized a limited crop of nuts for her exclusive use [14]. Evidence of pistachio consumption has been found in archeological excavations, indicating that the pistachio has long been associated with human activities [13]. In southeastern Iran and Afghanistan, remains of pistachio nuts dating from 6000 BCE have been found. These area were probably the first cultivated regions, close to where pistachio trees grew wild. They were widely cultivated in the ancient Persian Empire, from where their cultivation gradually expanded to the west.

The word *pistachio* comes from the Greek word *pistákion* [πιστάκιον], "the green nut." The tree widely cultivated in the Mediterranean region, although it originated in central and southwest Asia [13,14]. It seems that after its popularity in Italy and Iran, the pistachio had spread into Mediterranean regions in southern Europe and North Africa [12–14]. The cultivation of pistachio trees was started around the 10th century in China and more recently in Australia, New Mexico, and California [12–15]. The benefits of pistachio nuts include promotion of health in general and prevention of NCDs. Clinical studies have shown that pistachios also have a positive effect on men's sexual health [14]. Increased supplementation of pistachio may cause a decrease in body weight and serum cholesterol and an improvement in cardiac health [12–15].

In an experimental study, supplementation of pistachios produced the greatest gamma wave response, which is critical for enhancing cognitive processing, information retention, learning, perception, and rapid eye movement during sleep [6]. By contrast, peanuts, which are actually legumes, produced the highest delta response, which is associated with an increase in immunity and deep sleep, with improved brain function. Electroencephalographic (EEG) wave band activity recorded from nine regions of the scalp was associated with cerebral cortical function to confirm these findings.

Composition of the pistachio nut

Dry roasted pistachios, which have a lower fat content (43.4 g/100 g) compared to other nuts, are composed mainly of saturated fatty acid (SFA) (5.6 g), polyunsaturated fatty acid (13.3 g), and monounsaturated fatty acid (24.5 g) [16]. Of the fatty acids, oleic and linoleic acids represent more than half of the total fat content in pistachios. The essential amino acid ratio in the pistachio is higher than that in most other commonly available nuts (walnuts, almonds, pecans, and hazelnuts), with a high percentage of branched-chain amino acids [17]. Thus, pistachios are also a rich source of vegetable protein (21% of total weight). The amount of total carbohydrates is low to moderate (29% by weight), but they are richer in fiber than other nuts with a 10% by weight of insoluble forms and 0.3% of soluble forms [13]. The values are approximates of weight [13,16–19].

Polyphenolics and flavonoids have been identified in all nuts except macadamias and Brazil nuts. The main flavonoids in nuts are flavan-3-ols, flavonols, and anthocyanins with lesser amounts of flavanones and isoflavones [20–23]. The resveratrol content in pistachios ranges from 9 to 167 μg/100 g, with the most produced in the Ohadi and Siirt cultivars. Among all the nuts, pistachios have the highest content of lignans, with 0.2 mg/100 g. Interestingly, almonds and pistachios are the only nuts that contain flavonols, mainly as isorhamnetin and quercetin. Pistachios have the highest isoflavone content: 3.63 mg/100 g; in contrast, peanuts contain 0.26 mg isoflavones/100 g, epigallocatechin [20–23]. However, toasting pistachios decreases their proanthocyanidin content to 12% of that found in the raw nut. Fig. 8.1 shows the total content of phenols and proanthocyanidins in pistachios.

Pistachios are also rich source of the minerals potassium, magnesium, phosphorus, and calcium. The main vitamins in pistachio are vitamin A, vitamin E (especially gamma-tocopherol), vitamin C, vitamin B, vitamin K, and folate [14,18,22] (Table 8.1). Pistachios are also a rich source of lutein and zeaxanthin (xanthophyll carotenoids) and phenolic compounds, including anthocyanins, flavonoids, and proanthocyanidins [20–23]. The antioxidant contents of pistachios

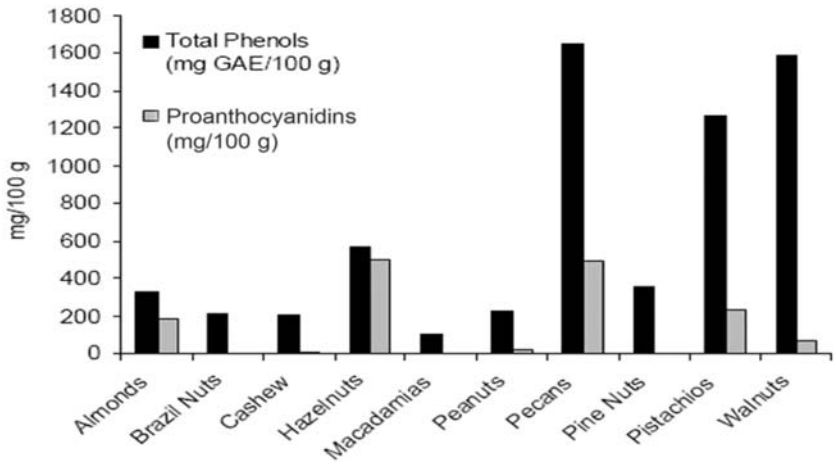


FIGURE 8.1 Content of phenols and proanthocyanidins in various nuts [23]. *Modified from Bolling BW, McKay DL, Blumberg JB. The phytochemical composition and antioxidant actions of tree nuts. Asia Pac J Clin Nutr 2010;19 (1):117–123.*

TABLE 8.1 Nutritive value of nuts and oilseeds.

	Almonds	Peanuts	Pistachio	Walnuts	Hazelnuts	Pecans	Macadamia nuts
Energy (kJ)	254	2176	22257	2809			
Total fat (g)	58.49	39.63	42.49	64.27			
Proteins (g)	18.4	23.65	23.35	14.92			
Carbohydrates (g)	3.4	17.27	15.82	10.14			
Water (g)	4.37	6.97	4.68	3.56			
Ashes (g)	2.62	2.11	3.02	1.72			

Source: IFCT tables 2017. NIN(ICMR) (Note: Other nuts mentioned in the original table were not found in IFCT authentic data of Indian foods.)

is significant and their capacity is considerable. Pistachios are the nuts that have the highest content of phytosterols, including stigmasterol, campesterol, and beta-sitosterol [19]. The composition of pistachios indicate that they are a rich source of a diverse set of bioactive nutrients, and pistachios may be considered a health-promoting functional food. (see Tables 8.1 and 8.2).

Effects of pistachio intake on cardiovascular diseases and diabetes

Increased consumption of nuts has been associated with a reduced risk of CVDs [11]. The effects of tree nuts and peanuts on cardiovascular risk factors have been established in clinical and epidemiological studies [13,14,16,17]. Randomized, controlled trials using walnuts and almonds have revealed that increased intake of these nuts can cause significant declines in total cholesterol and low-density lipoprotein (LDL) cholesterol as well as triglycerides without a decline in high-density lipoprotein (HDL) cholesterol. However, there is little evidence of a role for pistachios in terms of CVD risk factors, dose-response relations, and mechanisms of decline in blood lipids. Pistachios, a nutrient-dense nut, have a unique nutrient and fatty acid profile. Their high content of unsaturated fatty acids and numerous antioxidants, including polyphenols and flavonoids, gamma-tocopherol, beta-carotene, lutein, selenium, and phytoestrogens, may be responsible for the cardiovascular benefits seen in subjects who consumed pistachios [18,19,24].

In a randomized crossover controlled-feeding study, 28 subjects with LDL cholesterol ≥ 2.86 mmol/L were administered three isoenergetic diets for four weeks each [15]. After the subjects consumed a Western-type diet for two weeks, baseline data were assessed among all the participants. The intervention diets included a lower-fat control diet having 25% total fat, 8% SFAs, 9% monounsaturated fatty acids (MUFAs), and 5% polyunsaturated fatty acids (PUFAs); 1 serving/day of pistachio diet 1 having 10% of energy from pistachios, 30% total fat, 8% SFAs, 12% MUFAs, and 6% PUFAs; and 2 servings/day of pistachio diet 2, having 20% of energy from pistachios, 34% total fat,

TABLE 8.2 Vitamin and other nutrient content of pistachios per 100 g.

Vitamin A (μg)	16
Vitamin B_6 (mg)	0.96
Vitamin B_{12} (mg)	N/A
Vitamin C (mg)	N/A
Vitamin D (IU)	1.80
Alpha-tocopherol (mg)	31.41
Beta-tocopherol (mg)	4.10
Gamma-tocopherol (mg)	8.48
Delta-tocopherol (mg)	1.55
Vitamin K (μg)	18.65
Folate (μg)	64
Choline (mg)	87.8
Betaine (mg)	1
Thiamine (mg)	0.98
Riboflavin (mg)	0.04
Niacin (mg)	0.86
Pantothenic acid (mg)	0.58
Lutein (μg)	171
Alpha-carotene (μg)	N/A
Beta-carotene (μg)	N/A
Isoflavon (mg)	3.63
Lignan (mg)	0.2
Resveratrol (ug)	9–167
Total phenols (mg)	1300
Proanthocyanidins (mg)	200

8% SFAs, 15% MUFAs, and 8% PUFAs. Treatment with pistachio diet 2 was associated with a decline ($P < .05$ compared with the control diet) in total cholesterol (−8%), LDL cholesterol (−11.6%), non-HDL cholesterol (−11%), apolipoprotein (apo) B (−4%), apo B/apo A-I (−4%), and activity of stearoyl-CoA desaturase (SCD) (−1%). The pistachio 1 and pistachio 2 diets revealed a dose-dependent reduction ($P < .05$) of total cholesterol/HDL cholesterol (−1% and −8%, respectively), LDL cholesterol/HDL cholesterol (−3% and −11%%, respectively), and non-HDL cholesterol/HDL cholesterol (−2% and −10%)%, respectively [5]. It is possible that an increased intake of pistachios in a healthy diet can have a beneficial effect on risk factors of CVDs, owing to the effects of pistachios on activity of stearoyl-CoA desaturase enzyme in a dose-dependent manner. It is possible that the rich content of phytosterols (279 mg total phytosterols/100 g; 210 mg beta-sitosterol/100 g as the predominant phytosterol) may have been responsible for decline in blood lipoproteins among patients who consumed pistachios [25]. The content of phytosterols in pistachios appear to be much higher than that in other nuts. Previous studies have not reported plasma fatty acid profiles or evaluated other potential mechanisms of action. However, some studies have shown beneficial effects of pistachios (15%−20% of energy) on lipids and lipoproteins, although significant decreases in LDL cholesterol, very low-density lipoprotein cholesterol, apo A-I, and apo B have not been reported [26]. The beneficial effects of pistachios may be due to their fatty acid composition, and phytosterols has been proposed as the primary mechanism for lipid-lowering [11,26]. Clinical studies have assessed the effects of nutrients and foods on concentrations of apo A-I and apo B, which have been shown

to have antiatherogenic and proatherogenic effects, respectively, but individual lipid particles include various types of apolipoproteins [26–28]. The lipoprotein profiles defined by apolipoproteins A and B possibly can determine their relative proatherogenic nature and rate of clearance, and unsaturated fatty acids affect apolipoprotein-defined lipoprotein profiles [27,28].

Obesity is a risk factor for CVDs and diabetes and may be associated with neurodegeneration and cognitive dysfunctions [24]. Since increased intake of pistachios has been found to reduce blood lipoproteins and dyslipidemia, hepatic steatosis, and systemic and adipose tissue inflammation in mice that are fed a high-fat diet (HFD), pistachios may have beneficial effects on body weight. A recent study examined the neuroprotective effects of pistachio intake in mice that were fed a HFD. All three groups of mice were administered a standard diet (STD), a HFD, or a supplemented HFD with pistachio (HFD-P) for 16 weeks. The results revealed that the pistachio diet significantly reduced the serum levels of triglycerides and cholesterol in the HFD model. A higher number of fragmented nuclei were found in HFD cerebral cortex compared to mice that were fed STD and HFD-P. There was a significant decline in reactive oxygen species, singlet oxygen, and phosphorylated extracellular signal-regulated kinase and an increase of superoxide dismutase 2 and heme oxygenase expression that were found in the brain tissues of the HFD-P samples compared to HFD. The impairment in mitochondrial function observed in HFD mice was partially recovered in HFD-P mice. It is possible that the regular intake of pistachios may be protective in preventing obesity-related neurodegeneration [24]. It may also reduce both metabolic and cellular dysfunctions, although no difference was observed in the index of insulin resistance between HFD and HFD-P. Increased consumption of pistachios has also been reported to have beneficial effects on inflammation, endothelial function, and blood glucose among patients with diabetes mellitus [28–30].

Pomegranates

Approximately, an estimated 915,000 tons of pomegranates were produced in Iran in the Iranian year that ended on March 20, 2019, which was a 22% increase compared with the previous year. In India the pomegranate is grown in central and south India and in the states of Himachal Pradesh and Rajasthan. The botanical name of pomegranate is *Punica granatum* L. The potentiality of use of the high-value nutraceutical compounds in pomegranate peel have not been exploited so far on a commercial scale. Similarly, the use of high-value pomegranate seed oil as an active ingredient of food, pharmaceuticals, or cosmetic products has not yet been explored in India. Clinical and experimental studies have demonstrated that pomegranate fruit may be used for the management of obesity, diabetes mellitus, hypertension, atherosclerosis, and even cancer [31–34]. The polyphenols, in the pomegranates have been reported to have health benefits relating to their antioxidant and antiinflammatory properties [31]. There is evidence of the therapeutic effects of pomegranate juice on chronic inflammatory diseases, such as metabolic syndrome, diabetes mellitus, CVDs, inflammatory bowel disease (IBD), rheumatoid arthritis, and other inflammation-associated conditions [31–34]. Most studies of the therapeutic effects of pomegranate juice have focused on its ability to treat prostate cancer, diabetes, and atherosclerosis [31–35]. However, pomegranate juice has shown therapeutic potential for many other illnesses. A few clinical trials have highlighted the positive effects of pomegranate juice and extract consumption on CVDs [36]. The beneficial effects of pomegranate components have also been observed in animal models for respiratory diseases, rheumatoid arthritis, neurodegenerative diseases, and hyperlipidemia. Furthermore, there exists strong evidence from rodent models suggesting that pomegranate juice can be used to effectively to treat IBD, and as an antiinflammatory agent to treat coronary artery disease. The effects of pomegranate intake should be further investigated by conducting larger and more well-defined human trials. Therefore there is an enormous scope for entrepreneurship development using pomegranate for the production of high-value ingredients for the food, pharmaceutical, and cosmetic industries. This review aims to present available evidence on the role of pomegranates in the prevention of NCDs.

Composition of pomegranate fruit

The pomegranate fruit contains approximately 40% arils, 10% seeds, and 50% peel [35]. The fruit is rich in flavonoids, anthocyanins, punicic acid, ellagitannins, alkaloids, fructose, sucrose, glucose, simple organic acids, and other components [35]. Pomegranate arils contain 85% water, 10% total sugars (mainly fructose and glucose), 1.5% pectin, organic acid such as ascorbic acid, citric acid, and malic acid, and bioactive compounds such as phenolics and flavonoids, principally anthocyanins. Pomegranate arils provide 12% of the daily value for vitamin C and 16% for vitamin K per 100-g serving. The red color of the juice can be attributed to anthocyanins, such as delphinidin, cyanidin, and pelargonidin glycosides. Pomegranate juice is rich in fructose, sucrose, and glucose. It also contain a few simple organic acids: ascorbic acid, citric acid, fumaric acid, and malic acid. In addition, it contains small amounts of all amino acids, specifically

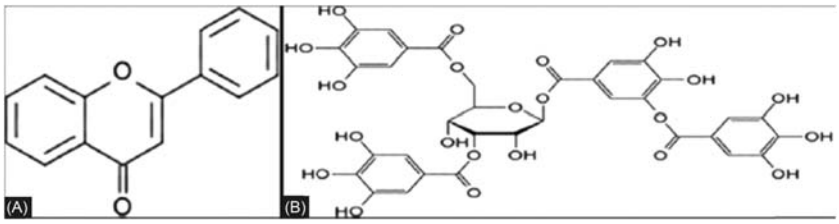


FIGURE 8.2 Chemical structure. (A) Flavone backbone. (B) Tannic acid [35]. *Modified from Newman RA, Lansky EP, Block ML. Pomegranate: The most medicinal fruit. Laguna beach, California: Basic Health Publications; 2007. A wealth of phytochemicals; p. 120.*

proline, methionine, and valine. Both the juice and the peel are rich in polyphenols. The largest classes of polyphenols are tannins and flavonoids, which indicate the pharmacological potential of pomegranates resulting from their antioxidant and preservative activities [35] (see Fig. 8.2).

Ellagitannin is a type of tannin that is a potential antioxidant and may be broken down into hydroxybenzoic acids such as ellagic acid. It is commonly used in plastic surgeries, owing to its potential antioxidant and preservative actions, which prevent the death of the skin flap after skin transplantation. Two other ellagitannins that are found in both pomegranate juice and peel are punicalagin and punicalin. Other classes of pomegranate flavonoids are anthocyanins, flavan 3-ols, and flavonols [35]. The juice and peel of pomegranate are also rich in catechins with a high antiinflammatory and antioxidant activity. All the polyphenols and flavonoids that are present in the pomegranate possess antioxidant activity with indirect inhibition of inflammatory markers such as tumor necrosis factor alpha (TNF-α) and other cytokines [35].

The seeds of the pomegranate contain about 18% oil in the dried and cleaned white seeds. The oil is rich in punicic acid (65%), which is a triple conjugated 18-carbon fatty acid. There are some phytoestrogen compounds in pomegranate seeds that have sex steroid hormones similar to those in humans. The 17-alpha-estradiol is a mirror-image version of estrogen [35]. Pomegranate peel is also an important source of bioactive compounds such as phenolics, flavonoids, ellagitannins, proanthocyanidin compounds, minerals,(mainly potassium, nitrogen, calcium, phosphorus, magnesium, and sodium), and complex polysaccharides. Pomegranate seeds are approximately 10% of the fruit weight. Pomegranate seeds are excellent sources of dietary fiber. The soft-seeded varieties of pomegranate contain seed oil in the amount of 25%–26% (volume/weight). The pomegranate seed oil contains more than 70% of conjugated linolenic acid. Pomegranate seed oil contains punicic acid (65.3%), palmitic acid (4.8%), stearic acid (2.3%), oleic acid (6.3%), and linoleic acid (6.6%).

Mechanisms of beneficial effects

Since pomegranate fruits are rich source of polyphenolics and flavonoids, all the components—juice and seeds—can inhibit oxidative stress as a result of presence of free oxygen and hydroxyl group radicals in its chemical structure [35]. A decline in free radical generation may be associated with a reduction in inflammation leading to protection of smooth muscle cell function, endothelial function, beta cells of the pancreas, adipocytes, and cardiomyocytes that are susceptible to damage due to free radicals produced on account of dietary factors and other environmental risk factors [35] (Fig. 8.3).

Effects of pomegranate fruit on cardiovascular diseases and other chronic diseases

CVDs, including hypertension, are one of the most important preventable cause of morbidity and premature death and develop as a result of unhealthy diet and lifestyle factors. Since the pomegranate is a polyphenol-rich functional fruit with diverse medicinal properties, it may have a role in decreasing BP. Experimental and clinical evidence has demonstrated that pomegranate intake can decrease BP as a result of its different mechanisms, such as vasodilatation [34,36–39].

Effects of pomegranate fruit in hypertension

Clinical trials and metaanalyses of studies that have been conducted to examine the impact of pomegranate on BP have shown varying results [37–39]. In all the metaanalyses the aim was to critically appraise and evaluate the effect of pomegranate on BP in adults, using evidence from randomized clinical trials. The analysis included eight randomized, controlled trials, comprising 619 participants. The studies, which varied in their reporting quality, compared pomegranate juice or capsules with a control group. This metaanalysis reported that in two studies, there were significant

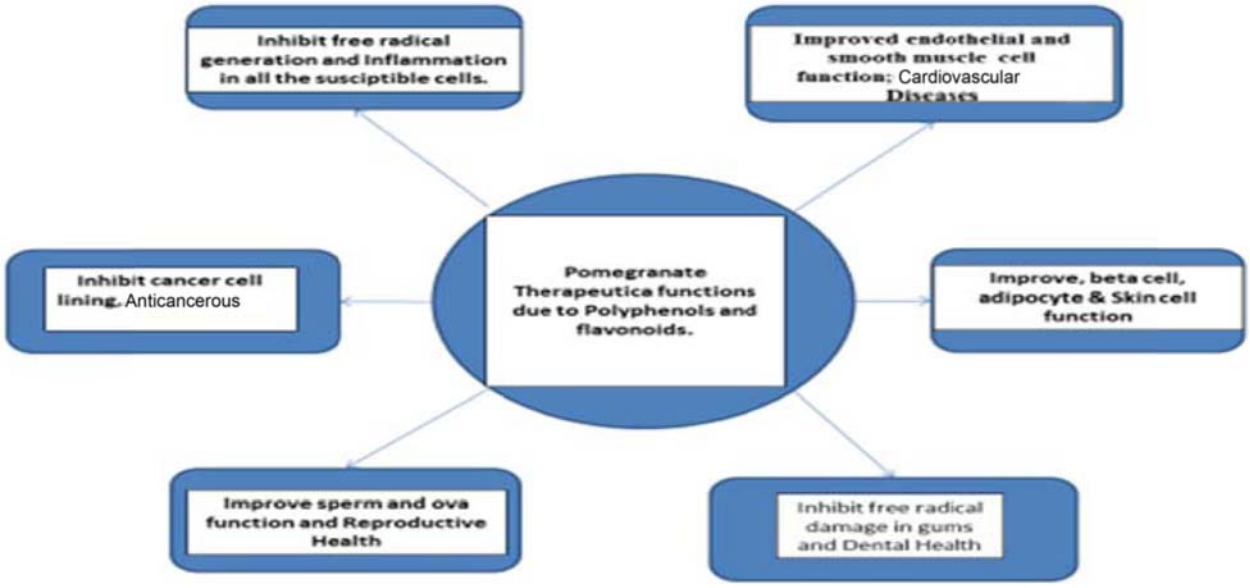


FIGURE 8.3 Mechanisms of beneficial effects of pomegranate fruit in non-communicable diseases.

reductions in systolic BP favoring pomegranate ($P = .002$ and $P < .001$) [37]. In three studies, no significant differences between groups were observed. Three studies failed to report between-group differences. Only two studies found a significant decrease in diastolic BP favoring pomegranate ($P = .038$, $P < .001$). Four studies reported no significant between-group differences, and two studies did not report between-group differences [37]. This metaanalysis concluded that the evidence from clinical trials fails to convincingly indicate a beneficial effect of pomegranate on BP.

Another metaanalysis of clinical trials was performed using a random-effects model, using sensitivity analysis and publication bias for quality control [38]. The synthesis of data from eight randomized, controlled trials revealed significant declines in both systolic (weighed mean difference (WMD): −4.96 mmHg, 95% CI: −7.67 to −2.25, $P < .001$) and diastolic BP (WMD: −2.01 mmHg, 95% CI: −3.71 to −0.31, $P = .021$) after pomegranate juice consumption. Effects on systolic BP remained stable to sensitivity analyses [8]. Pomegranate juice reduced systolic BP regardless of the duration (>12 weeks: WMD = −4.36 mmHg, 95% CI: −7.89 to −0.82, $P = .016$; <12 weeks: WMD = −5.83 mmHg, 95% CI: −10.05 to −1.61, $P = .007$) and dose consumed (>240 cc pomegranate juice per day: WMD = −3.62 mmHg, 95% CI: −6.62 to −0.63, $P = .018$; <240 cc pomegranate juice per day: WMD = −11.01 mmHg, 95% CI: −17.38 to −4.65, $P = .001$), whereas doses greater than 240 cc provided a borderline significant effect in reducing diastolic BP. It is clear from this metaanalysis that pomegranate juice supplementation showed consistent benefits for BP [38].

In a narrative review, the antihypertensive properties of different parts of pomegranate were assessed [39], and the mechanisms and phytochemicals responsible for these effects were identified. The review included clinical and experimental studies on the efficacy of consuming different parts of pomegranate (juice, peels, fruit extract, and seed oil) in lowering BP [39]. The results of animal and clinical studies indicate that pomegranate juice supplementation for both short term and long term can reduce BP. These effects are accompanied by antioxidant and antiatherosclerotic actions that collectively improve endothelial and smooth muscle function, leading to improved cardiovascular health. The antihypertensive effects were observed were both on systolic and diastolic BP, for both pomegranate juice and seed oil. It is possible to conclude that pomegranate juice possesses antioxidant, antihypertensive and antiatherosclerotic properties without any adverse effects.

Clinical and experimental studies indicate that pomegranate juice can exert antiatherogenic, antioxidant, antihypertensive, and antiinflammatory effects [31−39]. However, there is an unmet need to determine the potential antihypertensive and cardioprotective benefits of pomegranate juice. Angiotensin-converting enzyme (ACE) is a protein that plays an important role in controlling BP by causing vasoconstriction of smooth muscle cells of the arteries [40]. Increased levels of ACE may cause an increase in BP. Dietary supplementation of pomegranate juice, which is rich in tannins, provides antiatherosclerotic properties that could be related to its potent antioxidative characteristics. The effect of pomegranate juice supplementation (50 mL, 1.5 mmol of total polyphenols per day), on BP and ACE was examined among hypertensive patients [40]. After two weeks the findings revealed a 36% decrease in serum ACE activity and a 5% reduction in systolic BP. A similar dose-dependent inhibitory effect (31%) of pomegranate juice on serum ACE activity was observed in vitro. Since reduction in serum ACE activity has been found to attenuate atherosclerosis,

pomegranate juice can offer a wide protection against CVDs, which could be related to its inhibitory effect on oxidative stress and on serum ACE activity. Angiotensin I is converted in to angiotensin II (an oxidant proinflammatory agent) due to presence of ACE; hence an increase or decrease in ACE can alter BP and endothelial function.

Effects of pomegranate in diabetes

Pomegranate and its juice may have therapeutic hypoglycemic effects, including increased insulin sensitivity, inhibition of alpha-glucosidase, and impact on the function of glucose transporter type 4, with improvement in blood lipid profiles [41,42]. Diabetes mellitus is a disease resulting from defects in insulin secretion or action that may be due to dysfunction of the beta cells of the pancreas. The present study examined the effects of pomegranate juice on blood glucose and insulin levels in adult male rats [41]. The study included 90 adult male Wistar rats, randomly divided into five groups: a control group, a sham group, and experimental (diabetic and nondiabetic) groups 1, 2, and 3. The control group ($N = 9$) and the sham group ($N = 9$) received only distilled water, but the diabetic and nondiabetic groups 1, 2 and 3 received 1, 2, and 4 cc of pomegranate juice for 21 days through gavage. After 21 days, treatment with a minimum dose of pomegranate juice caused a significant reduction in the glycemic index at the levels of $P = .05$, $P = .005$, and $P = .0005$, respectively, with an increase in insulin levels of $P = .023$, $P = .015$, and $P = .002$, respectively, in the diabetic group compared to the control group. No significant effect was observed in the nondiabetic rats.

A case study examined the influence of concentrated pomegranate juice on fasting blood sugar, lipid profile, total antioxidant capacity, and BP in patients with type 2 diabetes mellitus [42]. The results revealed that HDL cholesterol and total antioxidant capacity significantly increased ($P < .001$). No changes were noted in levels of fasting blood sugar, triglycerides, LDL cholesterol, and BP after the intervention. It is possible that pomegranate juice has significant positive effects on HDL cholesterol and total antioxidant capacity in patients with type 2 diabetes without any significant effects on blood glucose, LDL cholesterol, and triglycerides [42]. Another study examined the effect of pomegranate juice on levels of melatonin, insulin, and fasting blood glucose in subjects with impaired fasting glucose or prediabetes [43]. All the patients ($N = 28$) were administered pomegranate juice and compared with healthy subjects. Patients with prediabetes, but not healthy individuals showed significant hypoglycemic response ($P < .0001$) to pomegranate juice 3 hours after ingestion of the juice. In addition, homeostatic model assessment of insulin resistance was significantly decreased ($P < .0001$) among people with prediabetes, 3 hours after ingestion of the juice. Moreover, 1 hour after juice, administration, there was a significant decrease in melatonin and increase in insulin observed among healthy ($P = .0284$, $P = .0017$) and prediabetic ($P = .0056$, $P = .0007$) subjects, respectively [42]. It is possible that fresh juice can lower melatonin, increase the level of insulin, and ameliorate insulin resistance in patients with prediabetes [43]. Thus there is a controversy about the role of pomegranate juice in diabetes because one study found no effect on blood glucose and BP [42,43].

A systematic review and metaanalysis of randomized controlled trials was conducted to evaluate the precise effects of pomegranate supplementation on measures of glucose control, insulin levels, and insulin sensitivity in humans [44]. This metaanalysis included 16 trials with 538 participants in which pooled estimates indicated that pomegranate juice failed to cause a significant decline in fasting blood glucose, fasting blood insulin, and HOMA-IR. These results were robust in sensitivity analysis without any publication bias in the current analysis. Further large-scale clinical trials with longer duration are required to confirm these results. The seeds of pomegranate fruit are also an important source of fatty acids, which can alter lipoprotein metabolism; hence seeds should be chewed along with juice to achieve the complete effects of pomegranate fruit (Table 8.3).

TABLE 8.3 Content of pomegranate seed oil.

Fatty acid profile	Bhagwa seeds	Ganesh seeds
Linolenic acid (%)	68.7	69.8
Linoleic acid (%)	13.9	11.4
Oleic acid (%)	12.0	9.1
Palmitic acid (%)	2.1	2.4
Stearic acid (%)	1.9	2.1

The results are surprising because therapeutic dietary approaches and guidelines from health agencies strongly recommend that diets high in vegetables, fruits, and whole grains are useful for prevention of CVDs, diabetes mellitus, and other chronic diseases. The essential micronutrients and fiber of plant-based diets contain a wide variety of polyphenols, specifically flavonoid compounds [45]. There is consistent evidence that flavonoids may confer specific benefits for risk reduction in diabetes mellitus and CVDs through pathways influencing glucose absorption and insulin sensitivity and/or secretion and decline in BP [15]. Many experts reiterate that pomegranate juice is rich in unique bioactive compound polyphenols that are useful in the management of various diseases and disorders, such as hypertension, heart disease, Alzheimer's disease, diabetes, and cancer [31−34,45,46]. It is possible that polyphenols decrease oxidative stress and inflammation in prediabetes, which inhibits the inflammation in the beta cells of the pancreas that are exposed to free radical induced damage by diet and lifestyle factors. The present research indicates that certain flavonoids, explicitly anthocyanins and flavan-3-ols, and foods that are rich in these compounds may have an important role in dietary algorithms for prevention of risk factors for CVDs: oxidative stress, inflammation, obesity, diabetes mellitus, hypertension, C-reactive protein, anemia, and the development of diabetes, CVDs, and atherosclerosis [45−50]. However, a large long-term randomized trial would be necessary to confirm the role of pomegranate fruit in CVDs and diabetes.

Peaches

The specific name *Prunas persica* (peaches) refers to the origin of its widespread cultivation in Persia (modern-day Iran), from which it migrated to Europe. The flowers are produced in early spring before the leaves; they are solitary or paired, 2.5−3 cm in diameter, pink, with five petals. The fruit has yellow or whitish flesh with a delicate aroma. The skin of peaches may be either velvety (peaches) or smooth (nectarines) in different cultivars. The flesh is very delicate and easily bruised in some cultivars but is fairly firm in some commercial varieties, especially when green. Iranian peaches can be red, pink, yellow, or a combination of those colors [51−53]. On one side of the fruit is a distinctive vertical indentation. Peaches have many antidisease properties, such as anticancer, antiallergic, antitumor, antibacterial, antimicrobial, and antiinflammatory [52−56]. The peach tree is a fast-growing evergreen tree that is found in Iran, India, Spain, and China. Phenolic compounds, which are known to have antiinflammatory and antiobesity properties, are also present in peaches. There are a few more reasons to eat peaches for losing weight, because it has a high nutritive value, which is important for prevention of CVDs and diabetes and for health promotion [53−56] (Fig. 8.4).

Composition of peaches

The composition of peaches has examined by several experts [56−62]. Each peach fruit contains 59 cal, 1 g of protein, 14 g of carbohydrate, 0 g of fat, 2 g of fiber, and 13 g of sugar. Peaches do not contain a significant amount of any nutrient, but the most important contents providing therapeutic benefits are polyphenols and flavonoids [56−62]. However, a cup of diced peach provides 11.1 mg of vitamin C and contributes to the recommended daily allowance (RDA) of potassium, fiber, and iron. This amount of vitamin C equates to 12.33% of the RDA for an adult male and 14.80% of the RDA for an adult female, according to guidelines from the U.S. Department of Agriculture [63]. One medium peach provides nearly 10% of the daily minimum fiber target. The carotenoids present in the *P. persica* moisture content of fruits (skin plus flesh), expressed as grams of water per 100 g of fresh weight were found to be 77.66% ± 1.63%, 85.85% ± 2.79%, and 87.00% ± 5.08% for persimmon (*Diospyros kaki)*, peach (*P. persica*), and apricot (*P. armeniaca*), respectively [53]. One peach weighing 168 g provides 65.5 cal, 1.53 g of protein, 0.42 g of fat, 16 g



FIGURE 8.4 Peaches. *https://www.medicalnewstoday.com/articles/274620, 2020.*

of carbohydrate, 14.10 g of sugar, and 2.52 g of fiber. Peaches also provide trace amounts of vitamins A, E, and K as well as magnesium and phosphorus.

The phenolic compounds and antioxidant content of peaches have been examined by many experts [57−62]. In an analysis of peaches in China, neochlorogenic acid, chlorogenic acid, procyanidin B1, catechin, cyandin-3-*O*-glucoside, quercetin-3-*O*-galactoside (Q3GAL), quercetin-3-*O*-glucoside (Q3GLU), quercetin-3-*O*-rutinoside, and kaempferol-3-*O*-rutinoside were identified and quantified [62]. The flavonols were primarily detected in the peel, and only trace amounts of Q3GAL and Q3GLU were detected in the pulp of some peach cultivars, consistent with previous studies [62]. The peel of four nectarine cultivars showed relatively high Q3GLU contents, ranging from 388.36 (HY003) to 581.21 mg/kg dry weight (DW) (HY002), while the melting peach cultivars showed a relatively low Q3GLU content, with values below 70 mg/kg DW. Similarly, the peels of four nectarine cultivars showed relatively high Q3GAL contents, ranging from 267.38 (HY003) to 396.49 mg/kg DW (HY002), while the melting peach cultivars showed a relatively low Q3GAL content, with values below 70 mg/kg DW. Q3R and K3R were detected only in the peels of peach fruits, ranging in concentration from 59.15 to 193.25 mg/kg DW for Q3R and from 16.91 to 110.86 mg/kg DW for K3R in the cultivars tested [62].

Beneficial effects of peaches in cardiovascular diseases and diabetes

Epidemiological studies have shown that the consumption of fruit and vegetables has health benefits against chronic diseases, such as cardiovascular disease, cancer, and diabetes [63−65]. It has been estimated that less than 10% of most Western populations consume adequate levels of whole fruits and dietary fiber, typical intake being about half of the recommended levels [64]. Evidence of the beneficial health effects of consuming adequate levels of whole fruits has been steadily growing, especially regarding their bioactive fiber prebiotic effects and role in improved weight control, wellness, and healthy aging. The potential health benefits of fruit intake include protecting colonic gastrointestinal health (e.g., constipation, irritable bowel syndrome, inflammatory bowel diseases, and diverticular disease); promoting long-term weight management; reducing the risk of CVDs, type 2 diabetes, and metabolic syndrome; defending against colorectal and lung cancers; improving the odds of successful aging; reducing the severity of asthma and chronic obstructive pulmonary disease; enhancing psychological well-being and lowering the risk of depression; contributing to higher bone mineral density in children and adults; reducing the risk of seborrheic dermatitis; and helping to attenuate the severity of autism spectrum disorder [64]. Low whole fruit intake represents a potentially more serious global population health threat than was previously recognized, especially in light of the emerging research on the benefits of whole fruit and fruit fiber [64]

The health-promoting properties of fruits and vegetables are mainly due to the presence of different antioxidant components, including phenolics and flavonoids [62−65]. Phenolic compounds are a large group of plant secondary metabolites. It has been estimated that more than 8000 dietary phenolics have been identified, and their distribution and accumulation profiles can be affected by both genetic and environmental factors. In an experimental study, the beneficial effects of feeding syrup of peaches and pears (peel and pulp) and green tea on the reversal of the changes produced by feeding a high-sucrose diet on plasma lipid profile, plasma antioxidant activity, and antioxidant enzymes in red blood cells' hemolysate were examined [65]. A high-sucrose diet induced hyperlipidemia, as manifested by significant ($P \leq .05$) increases in the levels of cholesterol, triglycerides, and LDL cholesterol in plasma from 103.33 ± 1.8, 61.17 ± 0.48, and 26.6 ± 5.01 mg/dL to 136.67 ± 2.2, 81.3 ± 1.5, and 64.6 ± 6.5 mg/dL, respectively. The HDL cholesterol level was not significantly affected. Triglyceride levels in heart muscles increased significantly ($P \leq .05$) from the level of 194.14 ± 4.35 μg/g in the negative control to 269.72 ± 5.39 μg/g. Administration of fruit syrups and green tea resulted in a significant variable reduction in the elevated levels of total cholesterol, triglycerides, and LDL cholesterol in the heart. Administration of sucrose resulted also in elevation of malondialdehyde in plasma from 5.06 ± 0.18 in the negative control group to 14.81 ± 0.48 μmol/L in the positive control group. This was accompanied by a reduction in the activities of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT) and a decrease in the concentration of reduced glutathione (GSH) in plasma, indicating lipid peroxidation. The activities of SOD, GSH-Px, and CAT in the negative control group were 8.96 ± 0.19, 315.67 ± 5.86, 209 ± 2.18 U/gHb, respectively, and were reduced significantly in the positive control group to 4.7 ± 0.2, 273.83 ± 7.85, and 207 ± 2.53 U/g Hb, respectively. There was a significant decrease in the level of total antioxidant status (TAS) in plasma from 1.45 ± 0.09 nmol/L to 0.88 ± 0.09 nmol/L. Intake of syrup of peaches and pears (peel and pulp) and green tea increased the level of TAS and GSH and decreased the level of LDL cholesterol. The treatment also decreased significantly ($P \leq .05$) the levels of plasma cholesterol, triglycerides, and heart triglycerides [65]. The activities of SOD and GSH-Px were increased following the treatment. It is possible that syrup of peaches and pears (peel and pulp) and green tea modulate lipid

metabolism and enhance antioxidant status, and in this respect, green tea produced the best effect, followed by peels of pears and peaches. The beneficial effect produced by fruit syrups and green tea may be due to their contents of phytochemicals [65].

Diabetes mellitus is a chronic metabolic disease characterized by a high blood glucose concentration [66]. Nowadays, type 2 diabetes or insulin-resistant diabetes is the most common type of diabetes, mainly owing to unhealthy lifestyle. Healthy habits such as appropriate nutritional approaches or the consumption of certain natural products or food supplements have been suggested as nonpharmacological strategies for the treatment and prevention of type 2 diabetes. Some of the main bioactive compounds from plant foods are polyphenols, which are important mainly for their antioxidant capacity in oxidative stress conditions and aging. Anthocyanins are polyphenols of the flavonoid group that act as pigments in plants, especially in fruits such as berries. A search of in vitro, in vivo, and human studies on the antidiabetic properties of anthocyanins has been performed in different electronic databases. Results of this review demonstrate that these compounds have the ability to inhibit different enzymes and to influence the gene expression and metabolic pathways of glucose, such as AMPK, being able to modulate diabetes and other associated disorders, such as hyperlipidemia, overweight, obesity, and cardiovascular diseases. Additionally, human interventional studies have shown that high doses of anthocyanins have potential in the prevention or treatment of type 2 diabetes; nevertheless, anthocyanins used in these studies should be standardized and quantified in order to make general conclusions about their use and to verify benefits for the human population.

Many studies have indicated that consumption of vegetables and fruits is positively related to a lower incidence of several chronic NCDs [55–57]. In addition to preventing constipation and supporting good digestive health, peach fiber helps to manage blood glucose levels as a result of its flavonoid contents [66]. Peaches also contain prebiotics, which feed beneficial bacteria in the gut that are tied to antiinflammation, immunity, and mood. Peaches support immunity in three ways. One medium peach supplies over 15% of the RDA for vitamin C. Several types of immune cells need this nutrient for their production, function, and protection. The vitamin A in peaches (one medium fruit provides 10% of the RDA) helps to form the mucous membranes in the respiratory tract. Stronger membranes form better protective barriers to keep germs out of the bloodstream. *P. persica* (L.) gum exudates are produced by the trunks and fruits in peach gummosis. Clinically, these exudates have been used to treat diabetes in China, although the underlying molecular mechanism remains unclear [55]. In the current study, a novel peach gum–derived polysaccharide was isolated, designated as PGPSD, and its antidiabetic effect was assessed in mice. This polysaccharide was composed of arabinose, xylose, and galactose in the molar ratio of 5.98:1:3.55, with the average molecular weight at 1.00×10^6 Da. The animal study demonstrated that the PGPSD polysaccharide significantly lowered postprandial blood glucose in streptozotocin-induced diabetic mice [55]. Histology and immunohistochemistry results further confirmed that the application of PGPSD polysaccharide partially restored the pancreatic islets in diabetic mice and enhanced the expression of pancreatic duodenal homeobox-1, insulin, and hexokinase 1. Collectively, the data suggested that the peach gum–derived polysaccharide had a meaningful potential as a noninsulin therapeutic compound in the treatment of diabetes [55].

Although the composition of fruit and vegetable juices is different from that of the edible portion of fruits and vegetables, the juices contain polyphenols and vitamins from fruits and vegetables. Drinking vegetable and fruit juices is very popular in many countries and an efficient way to increase consumption of fruits and vegetables [55]. The studies showed that fruit and vegetable juices affect cardiovascular risk factors, such as lowering BP and improving blood lipid profiles. The main mechanisms of action included antioxidant effects, improvement of aspects of the cardiovascular system, inhibition of platelet aggregation, antiinflammatory effects, and prevention of hyperhomocysteinemia [55].

Polyphenols from fruits have been implied in the prevention of risk factors for cardiometabolic disorders. The purpose of this study was to investigate whether the consumption of peach and plum juice has a protective effect against obesity and metabolic disorders that promote the development of CVDs [56]. Obese Zucker and lean rats were fed with peach and plum juice ad libitum or placebo. Body weight gain, biochemical markers, and molecular markers for inflammation and cardiovascular disease in heart tissue were quantified. The results showed that peach and plum juice consumption protected against a combination of obesity-induced metabolic disorders, including hyperglycemia, insulin and leptin resistance, dyslipidemia, and low-density lipoprotein oxidation. This was accompanied by a decreased expression of proatherogenic and proinflammatory biomarkers in plasma and heart tissues, including intercellular cell adhesion molecule 1, monocyte chemotactic protein 1, NF-κB, and foam cell adherence to aortic arches. In addition, peach and plum juice consumption decreased the levels of angiotensin II in plasma and its receptor Agtr1 in heart tissues, suggesting a role of peach and plum polyphenols as peroxisome proliferator-activated receptor-γ agonists. Furthermore, only plum juice significantly prevented body weight gain and increased the ratio of HDL lipoprotein cholesterol to total cholesterol in plasma. This effect is most likely attributed to the plum's higher content of polyphenols (three times that of

the peach) [56]. Altogether, these results imply that cardioprotective effects can be achieved by replacing drinks that are high in sugar content with fruit juices that are rich in polyphenols in a diet.

Effects of peaches on cancers

Peaches also enhance immunity by way of their natural antimicrobial properties. The polyphenol antioxidants in peaches have been shown to inhibit the growth and spread of cancer cells, particularly breast cancer. One study that followed women for 24 years found that two fruits in particular stood out as being protective. A higher intake of berries and peaches was associated with a lower risk of estrogen receptor−negative breast cancer among postmenopausal women [63]. Peaches, nectarines, and plums are the most important stone fruit in the world, but little is known about their effect on human health [52,65]. Over 100 genotypes of peaches and plums with a range of flesh colors (white, yellow, and red) were analyzed for their total phenolics carotenoid, and anthocyanin contents and their antioxidant activity. In general, the level of total phenolics was well correlated with the antioxidant activity [52]. The levels changed dramatically among the stone fruit varieties that were examined, indicating that varieties with improved levels of these phytochemicals could be developed. Selected plums and red-fleshed peaches had equal or greater amounts of phenolics and antioxidant activity than blueberries. Antiproliferative assays with three breast cell lines indicated that peach and plum phytochemicals inhibited the cell proliferation for estrogen receptor−negative MDA-MB-435 breast cancer cells but not the estrogen-positive breast cancer MCF-7 line or the normal breast cell MCF-10A line. Proliferation studies with MBA-MD-435 cells and assays to measure the LDL cholesterol oxidation inhibition activity with the extracts from 26 peach, nectarine, and plum cultivars indicated a range of effectiveness. Although there is a strong correlation between total phenolic and antioxidant activity, there is no obvious linear relationship between either total phenolic content or total antioxidant activity and either bioactivity measured, suggesting that there are distinct mechanisms other than a reactive oxygen species scavenging mechanism that are responsible for these bioactivities.

Comments

Pistachios, pomegranates, and peaches are rich source of flavonoids and polyphenols that are protective against NCDs [62−66]. Epidemiological studies have demonstrated that all are beneficial in the prevention of CVDs, diabetes mellitus, and other chronic diseases [63,64]. All three fruits have beneficial effects on neurodegenerative diseases as well as on the microbiome [67−70]. The evidence for protective effects of pistachios is much stronger than is the evidence for pomegranates and peaches. Recent results have shown that both pistachios and almonds have a potential prebiotic effect in healthy populations and that the effect of the former is greater [70]. In this study, pistachios' microbiota modulation increased the number of butyrate-producing bacteria, identified as potentially beneficial, whereas bifidobacteria were not affected [70]. Regulation of the phyla composition or the production of regulatory and protective butyrate molecules by the gut microbiota could be mediators of the protective function of pistachios and other nuts. Alpha-tocopherol, resveratrol in skin, and other antioxidants are helpful in different types of cancer [51]. The skin of nuts contains considerable amounts of resveratrol, which has been widely studied for its role in cancer, but new research is changing this focus to other diseases such as Alzheimer's disease or Parkinson's disease [52,53]. The amounts of various flavonoids in pistachio are greater than those in almonds: flavon-3-ols (6.85 vs 4.47 mg), flavanones (n.d. vs 0.38 mg), flavonols (1.46 vs 7.93 mg), anthocyanins (6.06 vs 2.46 mg), isoflavons (3.63 vs 0.01 mg), and total flavonoids (18.0 vs 15.25 mg). The beneficial effects of flavonoids on the brain may be due to increased production of acetylcholinesterase inhibitor [67]. It inhibits acetylcholinesterase from breaking down acetylcholine into choline and acetate, thereby increasing both the level and duration of action of the neurotransmitter acetylcholine in the central nervous system, autonomic ganglia, and neuromuscular junction. An epidemiological study of 8950 children aged 2−5 years has revealed that drinking 100% fruit juice regularly at age 2 is associated with higher odds of becoming overweight between ages 2 and 4 years [71]. Therefore people are discouraged from consuming excessive amounts of fruit juice as part of a larger effort to avoid unhealthy weight gain in young children

In brief, experimental and epidemiological studies have demonstrated that pistachios, pomegranates, and peaches are beneficial in the prevention of CVDs, diabetes mellitus, and other chronic diseases. All three fruits have beneficial effects on neurodegenerative diseases as well as on the microbiome. These nuts and fruits—pistachio, pomegranates, and peaches—are rich sources of flavonoids and polyphenols, which appear to be protective against NCDs. The evidence for protective effects of pistachios is much stronger than that for pomegranates and peaches. Recent results indicate that both pistachios and almonds may also have a prebiotic effect in healthy populations and that the effect of the former is greater. The contents of various flavonoids in pistachios are greater than those in almonds, and it is possible

that pistachio may have greater beneficial effects than those of pomegranate and peaches. Large and long-term cohort studies should be conducted to provide further proof regarding the role of pistachios, pomegranates, and peaches in the prevention of NCDs.

Conflict of interest

Conflict of interest has not been reported by any of the authors.

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Chapter 9

Medical rice: discovery of a new food

Shaw Watanabe[1], Masahito Takahashi[2], Hiroyuki Hashimoto[3], Kota Kikuchi[4], Mana Matsuo[4] and Kenichi Otsubo[5]

[1]*Clinical & Functional Nutriology, Life Science, Tokyo, Japan,* [2]*Medical Rice Association,* [3]*Tsuno Shokuhin Kogyo, Co. Ltd. Wakayama, Japan,* [4]*Ministry of Agriculture, Forestry, and Fisheries, Tokyo, Japan,* [5]*Niigata Pharmaceutical University, Niigata, Japan*

Expanding medical costs in countries with aging populations

An innovative solution is required from a rapidly growing aging society

The number of people in Japan over the age of 100 exceeded 80,450 in 2020, of whom 9475 were men and 70,975 were women [1]. In 1963, when the Elderly Welfare Law was implemented, the number of centenarians was only 153. In 1998 it exceeded 10,000, rapidly expanding to over 50,000 in 2012, and it is estimated to exceed 100,000 during the next five years. The Japanese speed of aging, defined as the number of years required for the percentage of the population aged 65 and over to rise from 7% to 14%, is 26 years. In Asian countries this speed is expected to be even shorter than that in Japan. South Korea and Vietnam are expected to take only 18 years, Singapore 19 years, Thailand 22 years, and China 23 years.

Japan will become an ultraelderly society in 2025, when the percentage of the population that is over 65 will reach 35%. However, a severe problem is the increasing necessity of medical and nursing care services; in 2025, medical costs will increase by 24%, and nursing care benefit costs will increase by 36%. Elderly people often have multiple diseases and problems of polypharmacy. The extension of healthy life expectancy is required to be the carriers in our elderly society [2].

Along with extension of the life span, healthy life expectancy is also increasing. It was 74.21 years for women and 71.19 years for men in 2013. However, the gap between survival and healthy old age has not shrunk, nine years in men and 12 years in women, and it pushed up medical care necessity. During the 1990s and 2000s the number geriatric hospitals and nursing rose continuously, from 2260 in 1990 to 6254 in 2011, an increase of 277% (3994 nursing homes) in just over 20 years. However, a decrease in the gap between survival and healthy age did not occur.

The necessity of prevention to reduce medical and care cost

The main reasons for older adults' need of nursing care are lifestyle-related diseases, such as cerebrovascular disease, cardiac disease, respiratory disease, and cancer, which account for one-third of this need. About half is due to dementia, frailty, joint trouble, and bone fracture. Physiological deterioration is commonly observed in older people, particularly in cardiac, renal, and respiratory functions and muscle strength. The frailty, sarcopenia, osteoporosis, and dementia are the targets of treatment to keep older adults from being bedridden.

We have proposed the importance of keeping healthy from a preclinical state [3]. In the preclinical stage, the person's laboratory test results may be abnormal but the patient feels healthy, as in metabolic syndrome. Alternatively, the person may feel very ill, perhaps with depression and insomnia, but there is no laboratory test abnormality. Western medicine tends to prescribe drugs for these preclinical people easily. However, patients in these preclinical stages could return to normal by proper intervention without drug therapy.

The frequency of polypharmacy and potential drug interactions makes it challenging to balance therapy's benefits and harms in older patients.

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Western and Eastern nutritional science

In Japan, two independent streams of nutrition have been present. Western nutritional science was built by Tadasu Saiki (1886−1959). He studied physiology at Yale University with Professor Chittenden, and after returning to Japan, he developed a concept of nutritional science and built the Imperial Institute of Nutrition in 1912 [4]. He also made a school educate dietitians in 1924, which was the world's first trial. His work improved the Japanese health status significantly through the balance of dietary intake. He took part in the Bandung Conference held by the League of Nations in 1937, and the participant countries expressed the necessity of setting up an institute of nutrition in each nation.

is the other stream of nutrition was instigated by Sagen Ishizuka (1851−1909), a successor of Eastern medicine in the Tokugawa era who studied Western medicine after the Meiji revolution [4]. He considered the balance of sodium and potassium to be essential. Brown rice had the best balance. so he recommended a diet of brown rice and green and yellow vegetables. Saiki stressed the importance of significant nutrients, and Ishizuka's theory included the balance of yin and yang. He promoted five principles: Life depends on food, humans are fit to eat crops, domestic foods support life, and the whole diet provides necessary nutrients. Both streams developed independently, but I have tried to integrate them for nutrition education (*Shoku-Iku*) [5]. Japan's Basic Law on Food Education (*Shokuiku kihonhō*) was passed in 2005, and eating instruction now starts in childhood [6]. The health of older people depends on their lifestyle from the young adult age.

Accumulating evidence from recent randomized controlled trial and cohort studies with more extended observation periods calls for revolutionary dietary therapy changes. With the increases in lifestyle-related diseases, nutritional habits and physical exercise have become more important than drug therapy. To meet the increasingly older population's health challenges, proper eating education and practices become more important to build a healthy aging society [7]. Insufficient nutrition in older people often progresses to senile diseases. A comprehensive preventive method for Alzheimer's disease could be implemented soon [8].

Functional ingredients in rice bran

Recent studies have clarified that brown rice contains substances that have various effects on physiological functions in addition to being a source of ordinary nutrients.

Functional components of brown rice, such as gamma-oryzanol, could control diabetes, and gamma-aminobutyric acid (GABA) may help to maintain good mental health [9−13]. Rice bran was initially known to have rich amounts of vitamins and minerals. Various substances such as long-chain fatty acids, ferulic acid, and inositol are also included. In that sense, brown rice's influence on health is extremely beneficial. and brown rice could be called "medical rice." [14,15] We have proposed the term *medical rice* when the rice has additional pharmacological effects other than ordinary nutrients. They include the functional ingredients of brown rice (Fig. 9.1).

Many functional ingredients are present in rice bran and rice oil.

For rice to be considered *medical rice*, there needs to be medical evidence and a quantitative standard. For example, we can speak of medical rice for diabetes (glycemic index <55), medical rice for chronic kidney disease (protein <1/10, no potassium, low phosphate), medical rice for mental health (high GABA, gamma-oryzanol, and/or ferulic acid), and medical rice for cancer prevention (high antioxidant capacity). Organic cultivation is necessary to avoid toxic substances

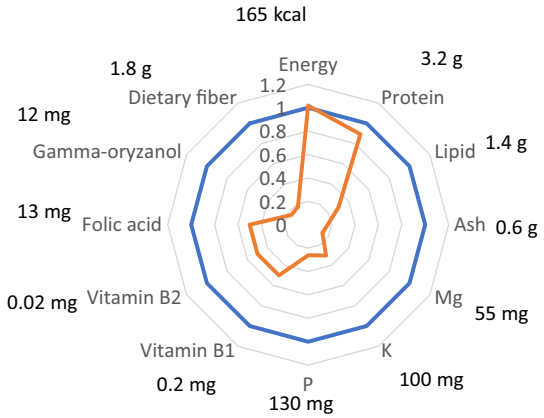


FIGURE 9.1 Functional ingredients in brown rice (*blue*) and polished white rice (*brown*) in 100 g of boiled rice. Polishing reduces most factors reduce by 20%−30%. The antioxidant capacity of the rice is lost.

from fertilizers and insecticides. Since rice is an excellent nutritious substrate for growth of harmful fungi, organic production must control every step. Arsenic and cadmium bioaccumulation needs to be reduced by careful irrigation in the paddy field [7].

The taste of brown rice is often unfavorable. We tried to find the reason for this unpopularity in the Genmai Taste Contest G1 Grand Prix tournament in December 2019. It was the first gathering of this kind, and 54 types of organic brown rice (22 species) entered the contest from all over Japan. Five experts judged the rice entries at prescreening and selected 18 for the final tournament.

Ingredients of these 18 *genmai* are listed below; the nutrients of brown rice and white rice meal in the *Standard Tables of Food Composition in Japan*, 7th Revised Version[1], are shown below for reference. Dietary fiber is high in this organic *genmai* (Tables 9.1, 9.2, and 9.3) (Fig. 9.2).

Levels of folic acid, alpha-tocopherol, and gammaγ-oryzanol are also higher in organic brown rice than those listed in the *Standard Tables of Food Composition in Japan* (Table 9.4) (Fig. 9.3).

In the case of fatty acids, C16:0 palmitin, C18:1 oleic acid, and C18:2 linolic acid constitute significant components (Table 9.5) (Figs. 9.4 and 9.5).

Gamma-oryzanol is known to decrease stress and solve various kinds of dependency by suppressing vesicular stress in the hypothalamus [13]. It is absorbed from the intestine and delivered to the brain across the blood-brain barrier. High concentrations in the brain need further study on its metabolism and action.

Effects of brown rice on well-being

We tried to certify Sagen's group (macrobiotics) by modern epidemiological methods in the Genmai Evidence for Nutritional Kenko Innovation (GENKI) study. Our study clarified the characteristics of obese people and brown rice eaters among 6000 participants. Polished white rice eaters had three times more risk of becoming obese, compared to only 0.3 among brown rice eaters. The odds ratio of white rice eaters was 1.68 ($P = .000$), and that of brown rice eaters was 0.45 ($P = .000$).

There were 1223 participants from groups promoting a brown rice diet. Brown rice eaters had a lower body mass index (BMI) in men and women of all ages. The average BMI in males was 22.0 ± 3.2 kg/m^2 and 20.7 ± 2.8 kg/m^2 in females. Dietary habits consisting of brown rice, plenty of vegetables, and meat avoidance seemed to support a healthy life and quality of life. Obese people were more likely to eat white rice and had a high risk of lifestyle-related diseases, such as diabetes and hypertension. By contrast, brown rice eaters were less obese and had a good lifestyle with a low risk of illness. In addition, brown rice eaters had healthy bowel movements, which suggested a good intestinal environment (Fig. 9.6).

Obese people had various lifestyle-related diseases with an odds ratio (OR) of 2−3, while the OR of brown rice eaters was less than 0.3 [16]. The good bowel movement and stool figures of brown rice eaters suggested an excellent intestinal environment, which helped to avoid obesity and maintain better health [15].

Dietary fibers in rice bran help to maintain a good balance of bacterial flora, which support the immune system. The intestinal microbiota is composed of producers of butyric acid and other short-chain fatty acids. Brown rice eaters showed a high abundance of *Firmicutes* and a low relative abundance of *Fusobacterium* in the intestinal microbiota at the phylum level. The abundance of microbiota at species level showed significant amounts of *Faecalibacterium prausnitzii* (5.28%), *Blautia wexlerae* (3.67%), *Fusicatenibacter saccharivorans* (3.41%), *Megamonas funiformis* (3.35%), *Collinsella aerofaciens* (3.21%), and *Bacteroides vulgatus* (3.12%) [15]. They belong to the Firmicutes phyla and butyrate-producing bacteria. Butyrate is the preferred energy source for the colon epithelial cells, contributes to maintaining the intestinal mucosa's epithelial barrier functions, and has immunomodulatory and antiinflammatory properties. *Blautia* is considered to control intestinal immunity. Dietary fiber in brown rice seems to be the most important factor, but other ingredients could influence bacterial coexistence. *Bifidobacterium adolescentis* (2.35%), *B. longum* (1.92%), *Bacteroides uniformis* (2.22%), *B. plebelius* (1.96%), *B. dorei* (1.71%), and *Akkermansia muciniphila* (2.16%) were also important. Brown rice eaters, compared with white rice eaters, had less *Actinobacteria* (12.1 vs 8.5% $P = .078$) and *Fusobacterium* (1.6 vs 0.018%, $P = .011$), which are pathogenic in intestinal conditions.

The association between microbiota (phylum) and short-chain fatty acids in the feces showed a positive association between n-butyrate and *Bacteroidetes*, propionate, n-valeric acid, *Euryarchaeota*, isovaleric acid, and *Verrucomicrobia*.

1. Standard Tables of Food Composition in Japan - 2015 - (Seventh Revised Version) https://www.mext.go.jp/en/policy/science_technology/policy/title01/detail01/1374030.htm.

TABLE 9.1 Major nutrients in the 18 types of organic brown rice selected for the G1 Grand Prix contest.

Nutrients per 100 g of boiled rice									
Species	***N***	**Energy (kcal)**	**Water (g)**	**Protein (g)**	**Lipid (g)**	**Carbohydrate (g)**	**Glucose (mg)**	**Ash (g)**	**Dietary fiber (g)**
Koshihikari	9	159.78 ± 7.51	61.04 ± 1.84	2.744 ± 0.18	1.23 ± 0.10	34.39 ± 1.82	48.11 ± 11.14	0.589 ± 0.06	1.83 ± 0.15
Akitakomach	3	163.33 ± 8.02	60.27 ± 1.90	3.07 ± 0.15	1.37 ± 0.15	34.67 ± 1.66	47.67 ± 29.30	0.63 ± 0.06	1.90 ± 0.26
Oborozuki	1	164	60.1	3.2	1.3	34.8	23	0.6	1.6
Kinumusume	1	156	62.2	2.8	1.4	33	74	0.6	1.3
Tsjgaruroma	1	168	59.3	2.4	1.5	36.2	43	0.6	2
Tuyahime	1	174	57.6	3	1.3	37.5	67	0.6	1.6
Natuhonoka	1	161	61	2.9	1.4	34.1	58	0.6	1.8
Hinohikari	1	155	62.3	3.2	1.2	32.8	122	0.5	1.5
Brown rice	FCT[a]	165	60	2.8	1	35.6		0.6	1.4
White rice	FCT[a]	168	60	2.5	0.3	37.1		0.1	0.3
合計[b]	20	161.95 ± 7.05	60.64 ± 1.68	2.84 ± 0.25	1.23 ± 0.26	34.73 ± 1.72	53.78 ± 23.20	0.57 ± 0.12	1.69 ± 0.40
Group median		163.33	60.35	2.84	1.27	34.87	48.50	0.59	1.74

[a]*From Standard Tables of Food Composition in Japan, 7th Revised Version, 2015.*
[b]*Average from: Standard Tables of Food Composition in Japan - 2015 - (Seventh Revised Version)* https://www.mext.go.jp/en/policy/science_technology/policy/title01/detail01/1374030.htm.

TABLE 9.2 Minerals in the 18 types of organic brown rice selected for the G1 Grand Prix contest.

Species	*N*	Na (mg)	K (mg)	Ca (mg)	Mg (mg)	P (mg)	Fe (mg)	Zn (mg)	Cu (mg)	Mn (mg)	NaCl (g)	As (mg)	Cd (mg)
Koshihikari	9	2.6 ± 0.56	93.29 ± 8.09	6.56 ± 0.53	52.85 ± 3.03	126.67 ± 7.07	0.48 ± 0.08	0.95 ± 0.06	0.04 ± 0.05	0.86 ± 0.23	0.01 ± 0.00	0.03 ± 0.05	0.01 ± 0.02
Akitakomachi	3	2.70 ± 0.62	102.97 ± 8.23	6.67 ± 1.15	55.63 ± 4.62	130.00 ± 10.00	0.43 ± 0.06	0.98 ± 0.10	0.10 ± 0.10	1.30 ± 0.26	0.01 ± 0.00	0.07 ± 0.06	0.00 ± 0.00
Oborozuki	1	2	107	7	52.8	130	0.8	0.96	0	1.1	0.01	0	0
Kinumusume	1	2	107	7	47.7	130	0.4	0.82	0.1	0.95	0.01	0	0
Tsugaruroman	1	2.4	93.9	7	49.5	120	0.3	0.86	0.1	0.87	0.01	0.1	0
Tuyahime	1	2.9	98.2	8	56.7	140	0.5	1	0	1.1	0.01	0	0
Natuhonoka	1	2.5	92.4	7	52.6	130	0.5	1.1	0	0.76	0.01	0	0
Hinohikari	1	2.6	89.2	6	43.7	110	0.6	0.88	0	0.72	0.01	0.1	0
Brown rice	ave	1	95	7	49	130	0.6	0.8	0.12	1.04	1.4		
White rice	ave	1	29	3	7	34	0.1	0.6	0.1	0.36	0.3		
Total	20	2.40 ± 067	93.01	6.55 ± 1.05	50.08 ± 10.86	122.7 ± 22.30	0.47 ± 0.14	0.924 ± 0.11	0.06 ± 0.06	0.93 ± 0.28	0.09 ± 0.31	0.04 ± 0.05	0.00 ± 0.02
Median		2.50	94.45	6.65	52.70	126.67	0.47	0.93	0.06	0.89	0.04	0.04	0.00

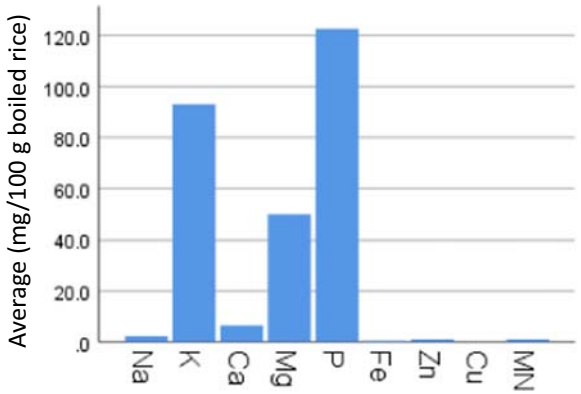


FIGURE 9.2 Average mineral contents (mg/100 g boiled rice) in the 18 types of organic brown rice selected for the G1 Grand Prix contest. A balance of minerals is maintained in these types of brown rice, although they are of different species and grown in different areas.

TABLE 9.3 Vitamin and gamma-oryzanol in the 18 types of organic brown rice selected for the G1 Grand Prix contest (mg/100 g boiled rice).

Species	*N*	Vitamin Bl	Vitamin B2	Folic acid	Vitamin E (alpha-tocopherol)	Beta-tocopherol	Gamma-tocopherol	Delta-tocopherol	Gamma-oryzanol
Koshihikari	9	0.16 ± 0.03	0 ± 0	13.00 ± 1.87	0.58 ± 1.16	0	0.022 ± 0.04	0	11.91 ± 2.08
Akitakomach	3	0.20 ± 0.04	0	12.33 ± 1.52	0.67 ± 0.06	0	0	0	12.47 ± 1.39
Oborozuki	1	0.20	0	14	0.7	0	0.1	0	10.92
Kir imi si me	1	0.18	0	12	0.6	0	0	0	10.14
Tsugaruroman	1	0.14	0	12	0.6	0	0	0	9.02
Tuyahime	1	0.19	0	10	0.4	0	0	0	11.44
Natuhonoka	1	0.15	0	15	0.7	0	0.1	0	11.31
Hinohikari	1	0.17	0	12	0.5	0	0	0	8.97
Brown rice	FCT[a]	0.16	0.02	10	0.5		0.1		
White rice	FCT[a]	0.08	0.01	6	0	0	0	0	
Total	20	0.17 ± 0.04	002 ± 0.0	12.25 ± 2.27	0.61 ± 0.20	0	0.03 ± 0.04	0	11.47 ± 1.83
Median		0.168	0.001	12.167	0.609	0	0.025	0	11.31

[a]From *Standard Tables of Food Composition in Japan*, 7th Revised Version, 2015.

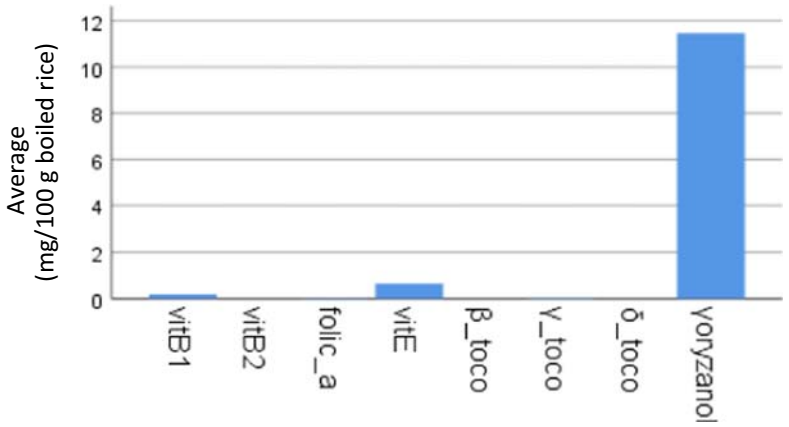


FIGURE 9.3 Vitamin and gamma-oryzanol in the 18 types of organic brown rice selected for the G1 Grand Prix contest (mg/100 g boiled rice).

TABLE 9.4 Fatty acids in the 18 types of organic brown rice for the G1 selected Grand Prix contest.

Species	*N*	C14:0 miristin	C16:0 palmitin	C16:1 palmitrain	C17:0 heptadecan	C18:0 stealin	C18:1 olein	C18:2 linol	C18:3 linolen	C20:0 rachidin	C20:1 icosen	C22:0 behen	C24:0 lignoserin
Koshi hi kari	9	0.83 ± 0.11	23.07 ± 1.08	0.07 ± 0.05	0.00	2.61 ± 0.28	36.32 ± 2.02	33.63 ± 1.29	1.19 ± 0.09	0.89 ± 0.13	0.44 ± 0.05	0.28 ± 0.08	0.67 ± 0.07
Akitakomachi	3	0.77 ± 0.06	21.93 ± 0.58	0.07 ± 0.06	0.00	2.53 ± 0.32	39.00 ± 0.96	32.37 ± 0.64	1.07 ± 0.06	0.87 ± 0.15	0.47 ± 0.05	0.33 ± 0.06	0.60 ± 0.00
Oborozuki	1	0.70	23.30	0.20	0.30	2.60	35.30	34.40	1.20	0.90	0.40	0.20	0.50
Kinumusume	1	0.60	24.40	0.00	0.00	2.00	33.70	36.20	1.20	0.70	0.40	0.20	0.60
Tsugaruroman	1	0.70	23.60	0.10	0.00	2.60	37.30	32.20	1.10	0.70	0.50	0.20	0.50
Tuyahime	1	0.60	22.90	0.10	0.00	2.40	37.30	32.80	1.10	1.00	0.40	0.30	0.60
Natuhonoka	1	0.80	22.50	0.10	0.00	2.70	38.50	32.00	1.10	0.30	0.50	0.30	0.70
Hinohikari	1	0.70	26.10	0.10	0.00	3.10	31.60	34.90	1.30	0.30	0.40	0.30	0.70
Total	18	0.77 ± 0.11	23.12 ± 1.22	0.08 ± 0.05	0.02 ± 0.07	2.58 ± 0.30	36.59 ± 2.35	33.46 ± 1.38	1.16 ± 0.09	0.86 ± 0.12	0.444 ± 0.05	0.28 ± 0.07	0.63 ± 0.08
Median		0.77	22.98	0.08	0.02	2.57	36.85	33.23	1.16	0.86	0.44	0.27	0.63

C10:0 decan, C12:0 laurin, C14:1 pentodecan, C15:1 pentodecen, C17:1 heptadecen, C20:2 eicosadien, C20:3 eicosatrine, C20:4 arachidon, C22:2 docosadiene, and C22:6 docosahexaen are not present.

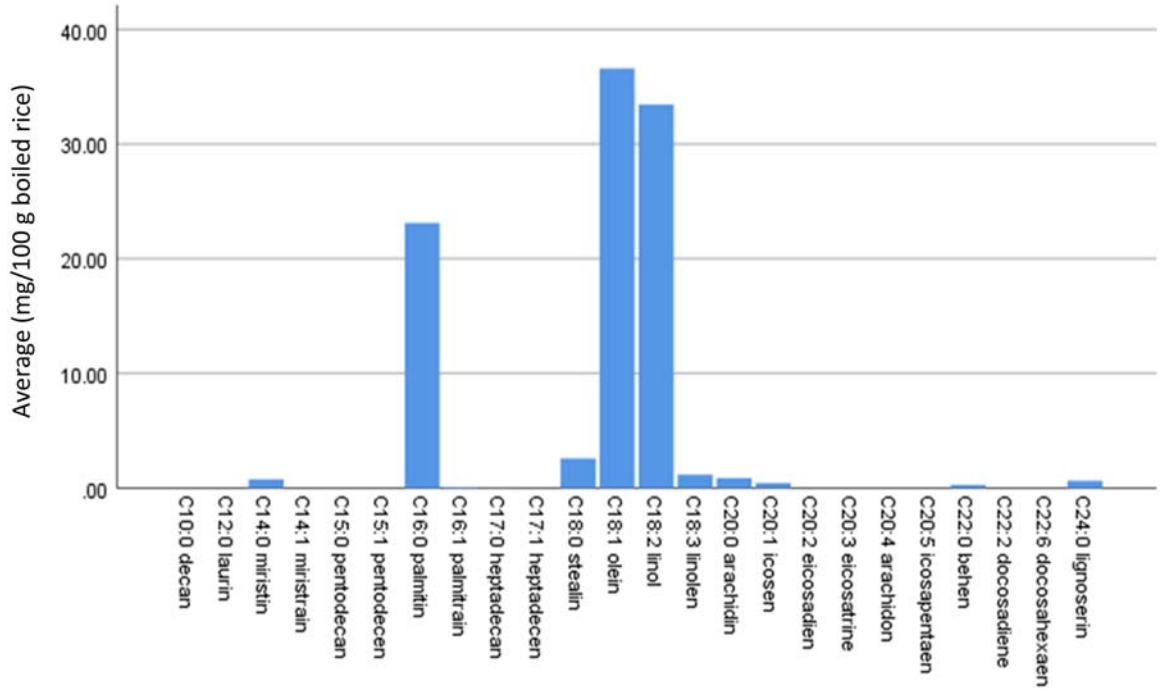


FIGURE 9.4 Fatty acids (%) in the 18 types of organic brown rice selected for the G1 Grand Prix contest.

TABLE 9.5 Amino acids in the 18 types of organic brown selected rice for the G1 Grand Prix contest.

species	n	arg (mg)	ala (mg)	gly (mg)	pro (mg)	glutamin (mg)	ser (mg)	asp_a (mg)	GABA (mg)
Koshihikari	9	1.56 ± 0.53	2.78 ± 0.83	0.11 ± 0.33	0.33 ± 0.50	2.44 ± 1.51	0.44 ± 0.73	4.67 ± 1.58	5.11 ± 0.60
Akitakomachi	3	1.33 ± 0.58	2.67 ± 0.58	0.00 ± 0.00	0.33 ± 0.58	1.67 ± 0.58	1.00 ± 0.00	4.67 ± 0.58	6.00 ± 2.00
Oborozuki	1	1.00	2.00	0.00	0.00	3.00	0.00	5.00	5.00
Kinumusume	1	3.00	3.00	0.00	0.00	2.00	1.00	5.00	6.00
Tsugaruroman	1	0.00	2.00	0.00	0.00	3.00	1.00	6.00	5.00
Tuyahime	1	2.00	3.00	0.00	1.00	2.00	1.00	4.00	5.00
Natuhonoka	1	1.00	4.00	0.00	1.00	3.00	1.00	5.00	4.00
Hinohikari	1	0.00	1.00	0.00	0.00	2.00	2.00	4.00	5.00
Brown rice	18	1.39 ± 0.78	2.67 ± 0.84	0.06 ± 0.24	0.33 ± 0.49	2.33 ± 1.14	0.72 ± 0.67	4.72 ± 1.18	5.22 ± 0.94
White rice		1.40	2.64	0.06	0.33	2.21	0.69	4.62	5.14
lys, his, phe, tyr, leu, i_leu, meth, val, thr, tryp, cys are not present.									

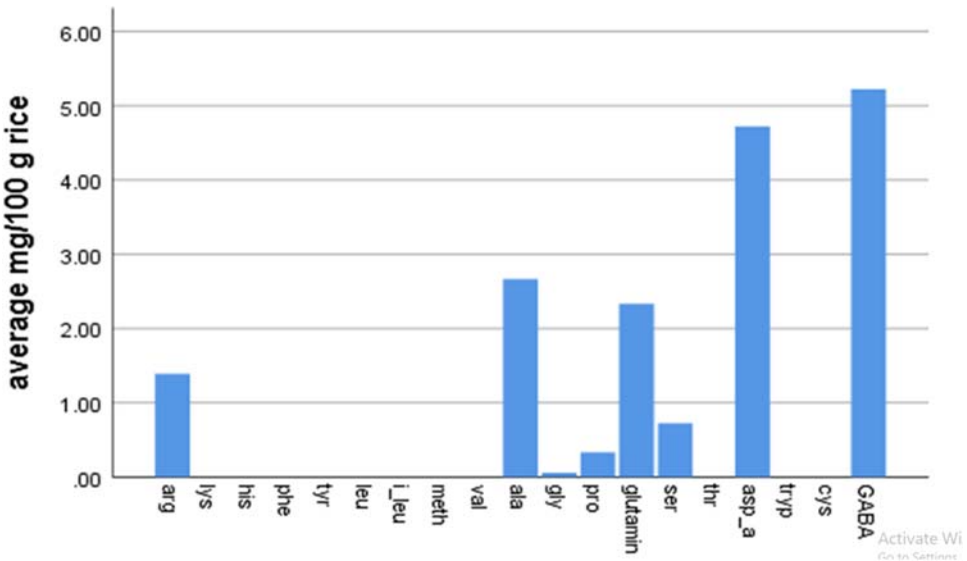


FIGURE 9.5 Amino acids and GABA in the 18 types of organic brown rice selected for the G1 Grand Prix contest.

Short-chain fatty acids seemed to be copresent, but there is no association between the normal form and the isoform. (Table 9.6) [16].

A population approach to reduce obesity is efficient, and brown rice as a staple food could provide a useful tool [7]. So brown rice could be considered to be typical medical rice by contributing to a healthy life [2,17]. Organic brown rice contains many functional ingredients, such as GABA, gamma-oryzanol, ferulic acids with high antioxidant function, and dietary fiber. Wax-free brown rice has been developed to improve palatability by scraping the surface wax layer from the rice grain [18]. Wax-free brown rice contains almost all the nutrients of brown rice. Dietary fibers remained the same as in brown rice, although water-soluble fiber seemed to be more easily dissolved than insoluble dietary fiber during boiling.

From wax-free brown rice, a low-protein brown rice has been produced [19,20]. The protein in rice is stored in two different types of compartments. The major proteins are prolamin and glutelin. Prolamin is the alcohol-soluble protein that remained after salt extraction of globulin. Glutelin is the dilute-acid or dilute-alkaline soluble protein after prolamin extraction. Most of the prolamin is present at the periphery in whole rice grains, so enzymatic digestion could easily remove prolamin on polished white rice. Still, it has been challenging to remove prolamin from brown rice directly. Removal of the wax layer made it possible to immerse the enzyme solution beneath the bran layer. Removal of rice protein yielded a low-protein brown rice, which is beneficial for patients with chronic kidney disease [21,22]

TABLE 9.6 Correlation between fecal microbiota and short-chain fatty acids.

	Fermicutes	Actinobacteria	Bacteroidetes	Euryarchaeota	Fusobacteria	Proteobacteria	Synergistetes	Verrucomicrobi	acetate	propionate	n_butyrate	i_butyrate	n_valeric	i_valeric	n_caproat
Fermicutes	1	-.738**	-0.268	-0.122	-0.023	0.022	-0.168	-0.059	-0.045	-0.105	-0.104	0.208	-0.258	0.232	0.22
Actinobacteria	-.738**	1	-0.286	0.017	-0.007	0.01	-0.142	-0.197	-0.066	-0.066	-0.225	-0.183	0.085	-0.228	-0.168
Bacteroidetes	-0.268	-0.286	1	-0.108	0.027	-0.209	0.215	0.024	0.305	0.207	.482**	0.066	0.111	0.025	-0.32
Euryarchaeota	-0.122	0.017	-0.108	1	-0.081	-0.174	0.099	0.096	0.047	.488**	0.103	-0.282	.726**	-0.211	-0.333
Fusobacteria	-0.023	-0.007	0.027	-0.081	1	-0.18	-0.105	.387*	0.176	0.233	0.152	0.373	0.089	0.315	.c
Proteobacteria	0.022	0.01	-0.209	-0.174	-0.18	1	-0.111	-0.208	0.012	-0.139	0.204	0.062	-0.017	-0.025	0.502
Synergistetes	-0.168	-0.142	0.215	0.099	-0.105	-0.111	1	.481**	-0.124	-0.068	0.111	0.069	0.032	0.083	-0.049
Verrucomicrobia	-0.059	-0.197	0.024	0.096	.387*	-0.208	.481**	1	-0.192	0.011	0.115	0.311	0.045	.396*	-0.333
acetate	-0.045	-0.066	0.305	0.047	0.176	0.012	-0.124	-0.192	1	.531**	.486**	0.235	0.344	0.072	-0.723
propionate	-0.105	-0.066	0.207	.488**	0.233	-0.139	-0.068	0.011	.531**	1	0.308	0.065	.624**	0.032	-0.796
n_butyrate	-0.104	-0.225	.482**	0.103	0.152	0.204	0.111	0.115	.486**	0.308	1	0.078	.435*	0.016	0.19
i_butyrate	0.208	-0.183	0.066	-0.282	0.373	0.062	0.069	0.311	0.235	0.065	0.078	1	0.13	.914**	.c
n_valeric	-0.258	0.085	0.111	.726**	0.089	-0.017	0.032	0.045	0.344	.624**	.435*	0.13	1	0.104	-0.808
i_valeric	0.232	-0.228	0.025	-0.211	0.315	-0.025	0.083	.396*	0.072	0.032	0.016	.914**	0.104	1	-0.587
n_caproate	0.22	-0.168	-0.32	-0.333	.c	0.502	-0.049	-0.333	-0.723	-0.796	0.19	.c	-0.808	-0.587	1

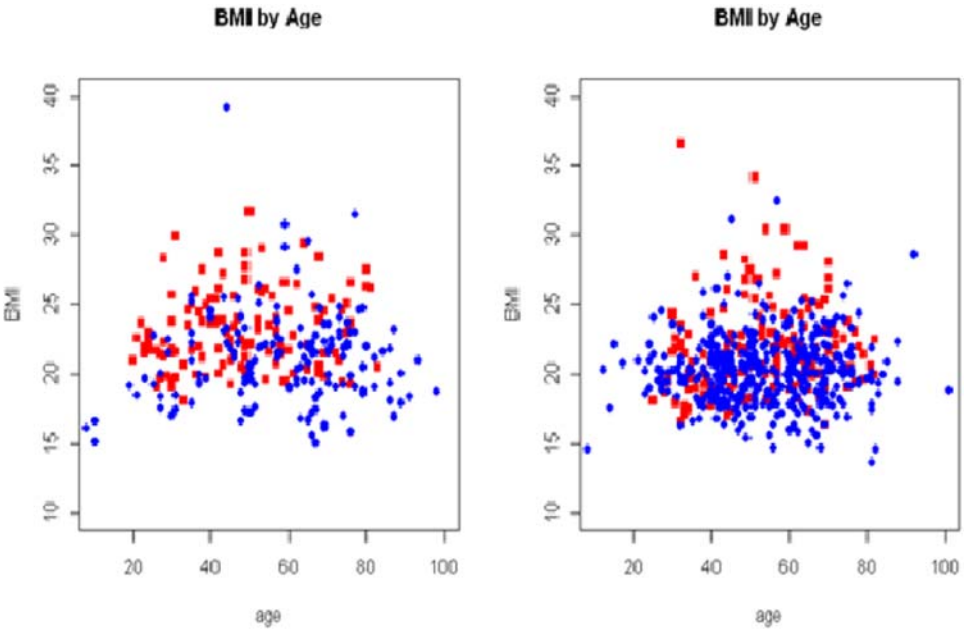


FIGURE 9.6 Body mass index (BMI) by age. In both males (*left*) and females (*right*), white rice eaters (*red dots*) tended to have a higher BMI than brown rice eaters (*blue dots*). This trend is more apparent as the subjects aged.

Gamma-oryzanol, dietary fiber, and folic acid have a cross-association with various ingredients. Minerals are associated with each other. In Table 9.7, red denotes a positive association, and blue denotes a negative association.

Gamma-oryzanol is a mixture of ferulic acid esters of phytosterols and triterpenoids, particularly cycloartenyl ferulate, 24-methylenecycloartanyl ferulate and campesteryl ferulate, which together account for 80% of gamma-oryzanol [23,24]. An experimental comparison between gamma-oryzanol and ferulic acid about the effects on fatty liver showed that gamma-oryzanol had more potent effects [23]. Orally administered gamma-oryzanol was absorbed quickly and was retained most in the brain [12].

Each axis contains known functional ingredients, such as dietary fiber, GABA, gamma-oryzanol, and vitamin E. So brown rice could be considered to be typical medical rice by contributing to a healthy life [7]. Organic brown rice contains many functional ingredients, such as gamma-oryzanol and GABA, ferulic acids with high antioxidant function, and dietary fiber (Figs 9.7 and 9.8).

TABLE 9.7 Correlation analysis of the ingredients of organic brown rice.

	γ oryzano	GABA	arg	ala	gly	pro	glutamin	ser	asp_a	dietaryfibe	K	Ca	Mg	P	MN	vitE	vitB1	vitB2	folic_a	C16:0 palr	C18:0 stez	C18:1 olei	C18:2 lino	C18:3 lino	C20:0 ara	C20:1 icos	C24:0 lign
γ oryzanol	1	-0.045	0.133	0.3	0.115	0.031	-.685**	-.592**	-.594**	0.131	0.197	0.009	.542*	0.399	0.001	.536*	0.356	.c	-0.193	-0.374	0.035	0.296	-0.256	-0.052	0.206	0.259	0.266
	0.858		0.598	0.227	0.65	0.904	0.002	0.01	0.009	0.605	0.433	0.973	0.02	0.101	0.997	0.022	0.147	0	0.442	0.126	0.889	0.233	0.306	0.838	0.412	0.298	0.287
GABA	-0.045	1	0.357	0.025	0.206	-.557*	-0.073	0.197	0.112	0.111	.639**	.477*	0.396	0.461	0.291	0.18	0.418	.c	0.077	-0.137	0.141	0.009	0.075	-0.03	-0.223	0.027	-0.027
	0.858		0.146	0.922	0.412	0.016	0.773	0.434	0.659	0.661	0.004	0.046	0.104	0.054	0.242	0.475	0.084	0	0.761	0.588	0.578	0.971	0.768	0.905	0.374	0.915	0.915
arg	0.133	0.357	1	0.39	-0.125	0.104	-0.089	-0.232	-0.132	-0.362	0.224	0.333	0.175	0.453	0.06	-0.057	0.308	.c	-0.18	-0.115	-0.431	-0.084	0.365	0.142	-0.078	-0.164	-0.033
	0.598	0.146		0.109	0.622	0.681	0.726	0.353	0.602	0.14	0.372	0.177	0.486	0.059	0.813	0.821	0.213	0	0.476	0.65	0.074	0.739	0.137	0.574	0.759	0.514	0.897
ala	0.3	0.025	0.39	1	0.396	0.289	0.123	0.035	0.139	0.118	0.158	0.244	0.36	.537*	-0.273	.510*	0.028	.c	0.219	-.559*	0.213	0.412	-0.295	-0.331	0.319	0.228	0.091
	0.227	0.922	0.109		0.104	0.245	0.627	0.891	0.583	0.642	0.53	0.329	0.142	0.022	0.272	0.031	0.911	0	0.384	0.016	0.396	0.09	0.234	0.18	0.197	0.362	0.719
gly	0.115	0.206	-0.125	0.396	1	-0.171	0.146	0.104	0.271	0.254	0.436	0.104	0.334	0.386	-0.138	0.436	0.134	.c	0.187	-0.249	.521*	0.107	-0.173	-0.166	.480*	-0.217	.542*
	0.65	0.412	0.622	0.104		0.496	0.563	0.682	0.277	0.309	0.07	0.682	0.176	0.114	0.586	0.071	0.595	0	0.458	0.319	0.027	0.672	0.491	0.509	0.044	0.387	0.02
pro	0.031	-.557*	0.104	0.289	-0.171	1	0	-0.06	-0.034	-0.204	-0.328	-0.06	-0.065	0.098	0.144	-0.387	0.098	.c	-0.095	-0.221	-0.164	0.339	-0.33	-0.221	0.228	0.079	0
	0.904	0.016	0.681	0.245	0.496		1	0.812	0.893	0.418	0.184	0.812	0.796	0.699	0.568	0.113	0.699	0	0.709	0.378	0.515	0.169	0.181	0.379	0.364	0.755	1
glutamin	-.685**	-0.073	-0.089	0.123	0.146	0	1	.515*	.863**	0.245	-0.222	0.052	-0.287	-0.271	-0.211	-0.165	-.522*	.c	-.595**	0.007	0.087	-0.08	0.132	-0.094	0.055	-0.27	-0.135
	0.002	0.773	0.726	0.627	0.563	1		0.029	0	0.328	0.376	0.839	0.248	0.276	0.4	0.513	0.026	0	0.009	0.978	0.73	0.753	0.601	0.711	0.827	0.279	0.594
ser	-.592**	0.197	-0.232	0.035	0.104	-0.06	.515*		1	.568*	0.076	-0.019	0.08	-0.347	-0.254	-0.071	-0.227	-0.263	.c	0.289	0.073	0.302	-0.017	-0.038	-0.282	-0.067	-0.134	-0.038
	0.01	0.434	0.353	0.891	0.682	0.812	0.029		0.014	0.764	0.94	0.751	0.158	0.309	0.779	0.365	0.291	0	0.245	0.775	0.223	0.947	0.682	0.256	0.792	0.597	0.88
asp_a	-.594**	0.112	-0.132	0.139	0.271	-0.034	.863**	.568*	1	0.317	0.082	0.046	-0.225	-0.084	0.085	-0.027	-0.346	.c	.573*	-0.053	0.02	0.022	0.062	-0.269	-0.078	-0.174	-0.152
	0.009	0.659	0.602	0.583	0.277	0.893	0	0.014		0.199	0.746	0.857	0.37	0.741	0.736	0.917	0.159	0	0.013	0.836	0.938	0.93	0.808	0.28	0.758	0.491	0.548
dietaryfiber	0.131	0.111	-0.362	0.118	0.254	-0.204	0.245	0.076	0.317	1	.714**	.630**	.873**	.778**	0.416	.769**	0.303	-.532*	.680**	-.594**	0.258	.590**	-.597**	-.516*	0.313	.515*	0.047
K	0.197	.639**	0.224	0.158	0.436	-0.328	-0.222	-0.019	0.082	.714**	1	.824**	.897**	.942**	.614**	.726**	.730**	-0.38	.578**	-0.227	0.036	0.124	-0.003	-0.268	-0.072	-0.169	0
Ca	0.009	.477*	0.333	0.244	0.104	-0.06	0.052	0.08	0.046	.630**	.824**	1	.833**	.873**	0.359	.509*	.633**	-0.271	.514*	-0.251	0.094	0.222	-0.184	-0.091	-0.067	0.038	-0.153
Mg	.542*	0.396	0.175	0.36	0.334	-0.065	-0.287	-0.347	-0.225	.873**	.897**	.833**	1	.965**	.533*	.766**	.820**	-.448*	.600**	-.696**	0.094	.601**	-.536*	-0.35	.477*	0.323	0.098
P	0.399	0.461	0.453	.537*	0.386	0.098	-0.271	-0.254	-0.084	.778**	.942**	.873**	.965**	1	.558*	.743**	.675**	-0.357	.575**	-.511*	0.028	0.404	-0.288	-0.306	0.232	0.17	0.062
MN	0.001	0.291	0.06	-0.273	-0.138	0.144	-0.211	-0.071	0.085	0.416	.614**	0.359	.533*	.558*	1	0.211	.535*	-0.132	0.166	-0.201	-0.44	0.278	-0.138	-0.395	-0.047	-0.003	-0.203
vitE	.536*	0.18	-0.057	.510*	0.436	-0.387	-0.165	-0.227	-0.027	.769**	.726**	.509*	.766**	.743**	0.211	1	0.4	-0.436	.608**	-0.37	0.399	0.193	-0.18	-0.127	0.197	0.428	0.122
vitB1	0.356	0.418	0.308	0.028	0.134	0.098	-.522*	-0.263	-0.346	0.303	.730**	.633**	.820**	.675**	.535*	0.4	1	-0.29	0.158	-0.074	0.064	0.004	0.01	0.147	-0.021	-0.132	0.015
vitB2	.c	.c	.c	.c	.c	.c	.c	.c	.c	-.532*	-0.38	-0.271	-.448*	-0.357	-0.132	-0.436	-0.29	1	-.510*	.c	.c	.c	.c	.c	.c	.c	.c
folic_a	-0.193	0.077	-0.18	0.219	0.187	-0.095	.595**	0.289	.573*	.680**	.578**	.514*	.600**	.575**	0.166	.608**	0.158	-.510*	1	-0.135	0.293	0.059	-0.055	-0.111	-0.165	0.015	0.12
C16:0 palmitin	-0.374	-0.137	-0.115	-.559*	-0.249	-0.221	0.007	0.073	-0.053	-.584**	-0.227	-0.251	-.696**	-.511*	-0.201	-0.37	-0.074	.c	-0.135	1	-0.16	-.928**	.789**	.774**	-.524*	-.505*	0.117
C18:0 stealin	0.035	0.141	-0.431	0.213	.521*	-0.164	0.087	0.302	0.02	0.258	0.036	0.094	0.094	0.028	-0.44	0.399	0.064	.c	0.293	-0.16	1	0.094	-0.35	-0.025	0.269	0.169	0.285
C18:1 olein	0.296	0.009	-0.084	0.412	0.107	0.339	-0.08	-0.017	0.022	.590**	0.124	0.222	.601**	0.404	0.278	0.193	0.004	.c	0.059	-.928**	0.094	1	-.922**	-.859**	0.399	.606**	-0.184
C18:2 linol	-0.256	0.075	0.365	-0.295	-0.173	-0.33	0.132	-0.038	0.062	-.597**	-0.003	-0.184	-.536*	-0.288	-0.138	-0.18	0.01	.c	-0.055	.789**	-0.35	-.922**	1	.739**	-0.413	-.656**	0.063
C18:3 linolen	-0.052	-0.03	0.142	-0.331	-0.166	-0.221	-0.094	-0.282	-0.269	-.516*	-0.268	-0.091	-0.35	-0.306	-0.395	-0.127	0.147	.c	-0.111	.774**	-0.025	-.859**	.739**	1	-0.295	-0.363	0.195
C20:0 arachidin	0.206	-0.223	-0.078	0.319	.480*	0.228	0.055	-0.067	-0.078	0.313	-0.072	-0.067	.477*	0.232	-0.047	0.197	-0.021	.c	-0.165	-.524*	0.269	0.399	-0.413	-0.295	1	0.01	0.144
C20:1 icosen	0.259	0.027	-0.164	0.228	-0.217	0.079	-0.27	-0.134	-0.174	.515*	-0.169	0.038	0.323	0.17	-0.003	0.428	-0.132	.c	0.015	-.505*	0.169	.606**	-.656**	-0.363	0.01	1	-0.25
C24:0 lignoseri	0.266	-0.027	-0.033	0.091	.542*	0	-0.135	-0.038	-0.152	0.047	0	-0.153	0.098	0.062	-0.203	0.122	0.015	.c	0.12	0.117	0.285	-0.184	0.063	0.195	0.144	-0.25	1

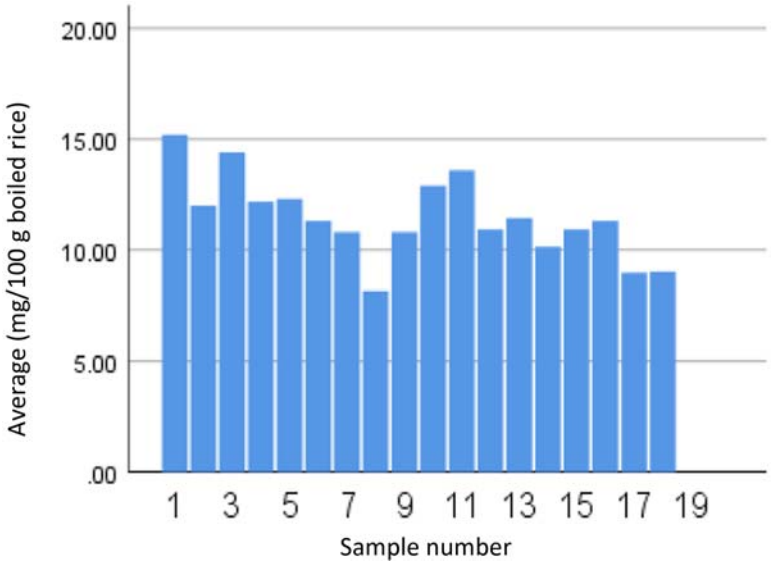


FIGURE 9.7 Gamma-oryzanol content in 100-g samples of boiled organic brown rice. Even though the samples were from the same species, activity varied by 11.91 ± 2.06 mg/100 g rice. Daily consumption may be more than 50 mg if one eats a 500-g rice meal.

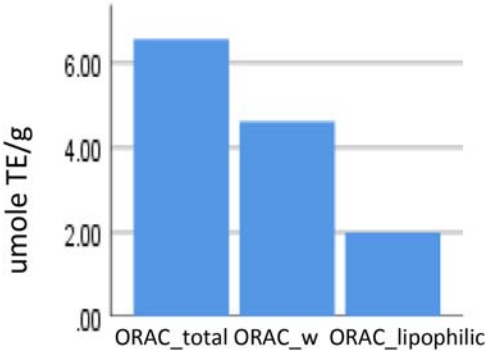


FIGURE 9.8 Antioxidant activity of brown rice. ORAC activity of 100 g boiled rice is 4.6 ± 1.3 μmol TE g (water-soluble), 2.0 ± 0.3 μmol TE g (lipid-soluble), and 6.5 ± 1.3 μmol TE g (total ORAC).

TABLE 9.8 Chief component analysis of the ingredients in organic brown rice.

Component	1	2	3	4	5	6	7
C18:1 olein	0.952	0.042	0.068	0.052	0.166	-0.091	0.121
C18:2 linol	-0.922	0.102	-0.097	0.002	-0.164	-0.084	-0.046
C16:0 palmitin	-0.86	-0.138	-0.02	-0.249	-0.206	0.032	-0.242
C18:3 linolen	-0.821	-0.218	0.16	0.021	0.047	0.173	-0.232
dietaryfiber	0.759	0.017	-0.259	0.189	-0.249	0.253	-0.114
C20:1 icosen	0.67	-0.179	0.193	0.349	0.016	-0.187	-0.442
Mg	0.584	0.364	0.309	0.19	0.334	0.263	0.134
K	-0.002	0.902	0.095	0.155	0.219	0.043	0.122
GABA	-0.004	0.764	-0.096	0.1	0.244	0.065	-0.287
MN	0.302	0.681	0.21	-0.427	-0.24	-0.152	0.001
P	0.278	0.57	0.261	0.265	0.535	0.075	0.217
glutamin	-0.016	-0.118	-0.934	-0.072	0.033	-0.064	0.176
folic_a	0.099	-0.002	-0.737	0.261	0.076	0.245	-0.235
γ oryzanol	0.223	0.015	0.698	0.459	0.058	0.274	0
vitB1	-0.149	0.549	0.559	-0.083	0.414	0.052	0.073
vitE	0.206	0.184	0.076	0.912	-0.142	0.169	-0.016
ala	0.25	-0.047	-0.101	0.656	0.437	-0.026	0.377
Ca	0.103	0.27	-0.063	-0.066	0.887	-0.044	-0.082
Zn	0.369	0.285	0.024	0.164	0.565	0.559	0.026
C24:0 lignoserin	-0.146	-0.073	0.073	0.048	-0.036	0.915	0.112
gly	0.062	0.301	-0.201	0.32	0.056	0.578	0.531
C20:0 arachidin	0.395	-0.147	0.107	0.084	-0.026	0.183	0.766

Correlation coefficients between gamma-oryzanol, antioxidant activity, and other factors are shown in Table 9.8. Total ORAC is associated with water-soluble ORAC and protein content.

Protein is also related to vitamin B1, but gamma-oryzanol does not seem to have antioxidant activity in the in vivo state of brown rice. A complex metabolic network should be reevaluated [23,24].

Definition of medical rice

Medical rice

We have proposed the term *medical rice* when the rice has additional pharmacological effects other than those of ordinary nutrients (Table 9.10) [7,17,18]. Medical rice needs to achieve a quantitative standard. For example, medical rice for diabetes (glycemic index <55), medical rice for chronic kidney disease (protein $<1/10$), medical rice for mental health (high GABA), gamma-oryzanol and/or ferulic acid, and medical rice for cancer prevention by high antioxidant capacity [1−16]. Organic cultivation is necessary to avoid toxic substances from fertilizers and insecticides (Table 9.10).

In many countries, rice supplies, dietary energy, protein, and fat to contribute to health. Many different rice types have been developed in Japan and other rice-producing countries. More than 200 species have been cultivated from Hokkaido (north Japan) to Okinawa (south Japan). Several varieties are expected to prevent various diseases and be used for dietary therapy. The health effects of brown rice are empirically well known, and the physiological and pharmacological activity of rice bran strongly supports the use of brown rice. These can be classified as a new concept: medical rice. With society's aging, the increase in medical expenses has become enormous, and the cost burden is being forced on too many countries. Increasing the elderly who are independent to maintain a healthy society is essential. We know that diet and exercise are very useful for this.

Primary prevention and treatment at the preclinical stage should be socially acceptable methods and technology should be universally accessible to individuals and families in the community through their full participation [25,26].

TABLE 9.9 Correlation coefficients between gamma-oryzanol, antioxidant activity, and other factors.

	γ oryzanol	GABA	folic_a	protein	Mg	vitE	vitB1	ORAC_tot	ORAC_w	ORAC_l
γ oryzanol	1	-0.045	-0.193	0.167	.542*	.536*	0.356	0.326	0.194	0.191
GABA	-0.045	1	0.077	0.198	0.396	0.18	0.418	-0.059	-0.022	-0.182
folic_a	-0.193	0.077	1	0.201	.600**	.608**	0.158	-0.059	-0.159	-0.1
protein	0.167	0.198	0.201	1	0.34	0.295	.573**	.490*	0.388	0.07
Mg	.542*	0.396	.600**	0.34	1	.766**	.620**	0.02	-0.084	0.252
vitE	.536*	0.18	.608**	0.295	.766**	1	0.4	0.235	0.19	-0.117
vitB1	0.356	0.418	0.158	.573**	.620**	0.4	1	0.052	0.174	-0.052
ORAC_tot	0.326	-0.059	-0.059	.490*	0.02	0.235	0.052	1	.878**	0.265
ORAC_w	0.194	-0.022	-0.159	0.388	-0.084	0.19	0.174	.878**	1	0
ORAC_l	0.191	-0.182	-0.1	0.07	0.252	-0.117	-0.052	0.265	0	1

TABLE 9.10 Candidate of medical rice.

Medical rice for well-being: Organic brown rice
Medical rice for diabetes: Rice with a low glycemic index
Medical rice for kidney disease: Low-protein, low-potassium, low-phosphate rice
Medical rice for mental health: Brown rice high in GABA, gamma-oryzanol, and ferulic acids
Rice for cancer prevention: Unpolished rice with high antioxidant ability
Wax-free brown rice
Low-protein brown rice
No-gluterin rice powder for celiac disease

The cost should be something that the community and country can afford to maintain at every stage of their development in the spirit of self-reliance and self-determination.

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COI: None of the authors have any benefit to the company or country.

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Chapter 10

The role of rice as a whole grain in the management of metabolic syndrome

Siti Helmyati[1,2] **and Maria Wigati**[2]

[1]Department of Nutrition and Health, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia, [2]Center for Health and Human Nutrition, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

Among public health promoters, frequent discussions have been conducted about the positive and negative impacts of rice consumption. This staple food is considered to be an excellent source of carbohydrates and protein, yet it is linked to metabolic syndrome and cardiometabolic disorders. There are ongoing debates about how to maximize the nutrient values of rice, specifically for Asian populations, who eat a higher proportion of rice than that of Western countries in daily consumption. For starving areas of the world, rice distribution is seen as a panacea, providing sustenance for the frail not only at early, critical ages when malnutrition can be particularly devastating but also for the ailing elderly, who may suffer from comorbidities of non-communicable illnesses, including diabetes, liver and kidney dysfunction, cardiovascular diseases, and metabolic syndrome. The controversies concerning disease prevention and rice consumption are often focused on a core question: Does the consumption of rice bring benefits that are greater than the increased risks of various illnesses?

Metabolic syndrome is now a global epidemic in both developing and developed countries [1]. A comparison between Indonesian and Dutch populations showed that the prevalence of metabolic syndrome is significantly higher in Indonesian women than in men, but the reverse is seen in the Dutch population. Approximately 46% of Indonesian women and 36% of Dutch men have metabolic syndrome [2]. Similar to this pattern, it was estimated that the prevalence of metabolic syndrome among Asian countries is higher than that in Western countries. In most Asian countries, 20% or more of adults suffer from metabolic syndrome [3].

The World Health Organization in 1999 outlined the diagnostic requirements for metabolic syndrome as the presence of insulin resistance >110 mg/dL, 2 hours glucose >140 mg/dL along with any two or more of the following:

1. High-density lipoprotein (HDL) cholesterol < 35 mg/dL (men) or < 40 mg/dL (women)
2. Triglycerides > 150 mg/dL
3. Waist-hip ratio > 0.9 (men) or > 0.85 (women) or body mass index (BMI) > 30 kg/m^2
4. Blood pressure > 140/90 mmHg.

The prominent factors of metabolic syndrome differ by country because there are many variations within the human genome as well as differences in ethnicity and sociocultural environment that affect health. As an example, the accompanying factors in the Indonesian population are hypertension and hyperglycemia, while in the Dutch population they are hypertension and abdominal obesity [2]. Those components can also vary in a country with various ethnicities [4], suggesting that in a diverse population there can be role different gene responses to metabolic syndrome−inducing factors. Nutrigenetic and nutrigenomic research has emphasized the role of the human gene as one of the risk factors of type 2 diabetes mellitus (T2DM), and metabolic syndrome [5].

Rice consumption has been blamed for various chronic diseases. A study of Iranian adults showed there is increased risk of developing metabolic syndrome if white rice consumption constitutes more than 25.5% of total energy [6]. The research conducted by Hu et al. [7] supported the finding that there was an increased risk of T2DM up to 11% for each serving of white rice per day. Additionally, a metaanalysis by Greenwood et al. [8] stated that the risk of T2DM increased by 8% per 5 glycemic index units.

T2DM is a condition of comorbidities caused by an excessive amount of blood glucose, which leads to insulin resistance. When the condition happens over a long period, it causes the beta cells of the pancreas to become unable to

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TABLE 10.1 Rice production worldwide (millions of tons).

Region	5-year average[a]	2018	Estimated 2019
North Africa	6.6	4.1	6.7
West Africa	18.2	20.6	21.3
Central Africa	0.6	0.7	0.7
Southern Africa	4.2	4.1	4.5
Eastern, Southern, and Southeast Asia	678.4	694.0	690.5
Central and Western Asia	4.4	4.5	5.1
Central America and Caribbean	2.9	3.0	3.1
South America	24.7	25.0	23.0
North America	9.4	10.2	8.4
Europe	4.0	3.9	4.0
Oceania	0.7	0.6	0.1

[a]*From 2014–18.*
Source: Food and Agriculture Organization. Crop prospects and food situation-quarterly global report. Crop Prospect Food Situat 2020. doi: 10.4060/c.8032en.

regulate blood glucose concentration [9]. T2DM also causes alteration of several blood parameters. Impaired blood glucose metabolism is known to disturb the levels of inflammatory biomarkers, such as C-reactive protein, adipokines, insulin-like growth factor axis, and body iron stores, causing endothelial dysfunction and other unhealthy conditions [10,11].

White rice consumption significantly increases the risk of chronic diseases by as much as 40% in women but not in men [12]. This pattern is similar to the findings of Sigit et al. [2], who mentioned that the prevalence of metabolic syndrome among the Indonesian population is higher in women than in men. Globally, women, who can play an important role in giving excellent nutrition education for their family, at the same time must overcome food insecurities to provide a diverse diet. Several studies agreed about how women in developing countries tend to have a homogenous eating habit which is considered to be one of the causes of metabolic syndrome [13–15].

White rice is the most prominent type of rice consumed by most Asians. In South Korea, rice makes up 64% of the total consumption of staple foods and provides more than 40% of the population's energy sources [16].

Rice production in most regions has increased from year to year [17]. However, there are widely different trends in its consumption rate. The US Department of Agriculture reported that there has been a decline of rice consumption, projected at 490 million tons, in Brazil, Burma, Japan, South Korea, Nigeria, and Thailand. Meanwhile, rice productions appears to be increasing in Bangladesh, China, Egypt, India, the Philippines, and Vietnam [18]. In most countries of Southeast Asia, such as Bangladesh, Thailand, Cambodia, Indonesia, Myanmar, Vietnam, and Lao PDR, rice intake constitutes 50%–80% of total energy [19]. This situation depicts how some countries in the world have started to lower their consumption of rice to prevent metabolic syndrome, as reported by some researchers in Japan and Korea [20,21] (Table 10.1).

White rice is the major staple food for most Asian countries, such as India, China, Japan, Korea, Thailand, and Indonesia. The association of white rice consumption and diseases is stronger in Asian countries than in Western countries. The average consumption of rice in Asia is three to four servings per day, while in Western countries it is one to two servings per week [7]. The incidence of chronic diseases related to rice consumption is mostly due to the sugar content, which is measured by the glycemic index of rice. Of 10 types of Indonesian white rice, only one is considered to have a low glycemic index, while the glycemic index of the others ranges from 70 to 94 [22]. By comparison, the glycemic index of Thailand cooked white rice ranged from 52 to 62, which is categorized as low to medium [23].

Varieties of rice

There are several varieties of rice that are commonly cultivated in some areas in the world, mostly in Asia, Africa, and a few places in America and Europe [17]. China and India are the two countries with the largest rice production, and they are the major exporters of rice in the world.

White rice

White rice is the most cultivated rice in the world and is grown mainly in Asia. Paddy rice (typically *Oryza sativa*) goes through a milling and polishing process to remove its bran and hull, which leaves only the white parts. This kind of rice has a sweet taste due to the presence of amylose and amylopectin. It also has many cultivars that have different and specific characteristics. *Japonica* rice has a round shape and a sticky texture and is consumed mainly in East Asia, including China, South Korea, and Japan. *Indica* rice is consumed mainly in South and Southeast Asian countries, including Thailand and India [16,24].

Colored rice

Colored rice includes red, black, and purple rice, which are other cultivars of rice grown in several countries in the world [24]. Colored rice is not as widely consumed as white rice but still provides the basic needs for some populations. Another type of colored rice is brown rice, which has the same characteristics as white rice but is not polished but maintains its brown-colored bran. The bran is high in crude fiber and thus good for the gastrointestinal health. By contrast, red and black rice have a different pigment in the outer layer of the rice grain (Fig. 10.1). The nutritional values of these types of rice are superior to "just" white rice. However, the taste is considered bland, and the texture is hard, so few people like to eat this rice on a daily basis except for the nutritional benefits [25]. Colored rice is believed to have more beneficial active compounds, which include antioxidants and flavonoids. Phenolic acids, anthocyanins, tocopherol, and tocotrienols are commonly identified antioxidants that promote pigmentation in colored rice. Generally, black rice bran has the highest anthocyanin, which means that it has higher antioxidant activities in addition to cyanidin 3-*O*-glucoside, peonidin 3-*O*-glucoside, malvidin 3-*O*-glucoside, and others [26]. Almost all parts of colored rice can be utilized as functional food (Fig. 10.1).

Genetically modified rice

Genetically modified (GM) rice has been grown since the 1990s. This type of rice is developed through advances in biotechnology, which can introduce a gene or genes into the rice's genome. Different genes of rice express different traits. *Osnas2*, *Gm* ferritin, and *Af* phytase, for example, are the genes that are responsible for the presence of iron. The others are Daffodil phytoene synthase and Erwinia phytoene desaturase, which are responsible for the beta-carotene content of rice. The presence of beta-carotene-related genes could increase the amount of beta-carotene in GM rice to a level 2.3 times higher than that in wild or traditionally cultivated rice [27]. Many researchers from Europe and Asia work hard with the hope of creating a new variety of rice with a higher yield that is resistant to pests, diseases, and herbicides; is more tolerant of growing conditions; and has higher nutritional values and health benefits [28]. Although



FIGURE 10.1 Mixture of white, brown, and black rice.

hopes are high, there is little literature available comparing the benefits and disadvantages of GM rice [29,30]. Despite the controversy, GM rice is helping developing countries in tackling and reducing their micronutrient deficiency problems. One example is the success of "golden rice," a GM rice with newly introduced genes from maize and soil microorganisms that produces significant amounts of beta-carotene [31].

Nutrient contents of rice

Rice provides the main source of energy for most Asian countries. Its nutritional value, however, varies depending on the species and environment. A review by Priya et al. [24] briefly summarizes the nutrient content of several types of rice, showing that milled rice has a higher carbohydrate content and a lower percentage of crude fiber compared to rough or brown rice (Table 10.2).

In general, white rice provides more energy from carbohydrates. Polished rice tends to have lower resistant starch, which makes it easier to digest and increases insulin demand. Many studies have revealed that an excessive amount of white rice consumption is associated with poor insulin response [7,35]. Higher rice consumption was related to high triglyceride levels in the Chinese population [36], which was similar to the findings in Iranian adults, who developed a higher serum triglyceride concentration. Higher white rice consumption was also associated with higher blood pressure [6].

The goodness of white rice cultivars is mostly in its hull and bran [37]. Rice oil is located in the bran with up to 80% of its content in the form of unsaturated fatty acids. Juliano (1985) and Pedersen and Eggum (1983) in Chaudhari et al. [31]. reported the differences in micronutrient amounts between rough rice and milling fraction. Although it was clarified that rice bran has more micronutrient contents, the numbers are in need of being updated after two decades.

TABLE 10.2 Nutritional values of rice [24,32–34].

Rice	Carbohydrate (g)	Protein (g)	Fat (g)	Crude fiber (g)
White rice				
Rough rice	64.0–73.0	5.8–7.7	1.5–2.3	7.2–10.4
Brown rice	71.31–84.75	5.9–11.0	1.6–2.8	0.22–0.95
Raw hand-pounded rice	76.7	7.5	1.0	0.6
Milled rice	74.80 ± 0.85	9.16 ± 0.75	1.24 ± 0.08	1.04 ± 0.18
Parboiled rice	77.16 ± 0.76	7.81 ± 0.63	0.55 ± 0.08	0.65 ± 0.08
White rice	76.8–86.56	5.8–7.7	0.5–2.3	0.01–0.78
Rice bran	34.0–62.0	11.3–14.9	15.0–19.7	7.0–11.4
Rice hull	22.0–34.0	2.0–2.8	0.3–0.8	34.5–45.9
Colored rice				
Red rice	70.75–81.29	7.16–10.85	1.15–3.19	0.28–0.61
Sri Lanka red rice	75.45 ± 0.09	9.63 ± 0.04	1.15 ± 0.03	2.82 ± 0.55
China red rice	74.66 ± 0.27	9.72 ± 0.04	2.35 ± 0.03	2.52 ± 0.24
Indian black rice	78.0 ± 0.03	8.8 ± 0.05	1.0 ± 0.07	0.3 ± 0.06
Indian red rice	75.86 2.31	8.16 ± 0.45	0.92 ± 0.13	2.5 ± 0.28
Indonesian red rice	70.03%	9.25%	2.5%	3.97%
Indonesian black rice	85%	1.04%	1.9%	0.8%
Genetically modified rice				
Golden rice	60.5% – 69.2%	3.16%–11.3%	1.31%–4.8%	26.9%–35.8%

Sources: Rathna Priya TS, Eliazer Nelson ARL, Ravichandran K, Antony U. Nutritional and functional properties of coloured rice varieties of South India: a review. J Ethn Foods 2019;6:1–11. doi: 10.1186/s42779–019-0017–3; Kristamini PH. Potential development of red rice as germplasm of Yogyakarta. J Litbang Pertan 2009;28:88–95; Mangiri J, Mayulu N, Kawengian SES. Overview of the nutrient content of black rice (*Oryza sativa* L.) cultivars Pare Ambo Sulawesi Selatan. EBiomedik 2016;4; Mallikarjuna Swamy BP, Samia M, Boncodin R, Marundan S, Rebong DB, Ordonio RL, et al. Compositional analysis of genetically engineered GR2E "Golden Rice" comparison conventional rice 2019. J Agric Food Chem 67:7986–7994. https://doi.org/10.1021/acs.jafc.9b01524.

In this report, rice bran contained much higher levels of niacin (26.7−40.0 mg), alpha-tocopherol (2.6−13.3 mg), calcium (30−120 mg), iron (8.6−43 mg), and zinc (4.3−25.8 mg) than white rice.

Colored rice and rice bran provide more health benefits than polished rice. Substituting brown rice for white rice has proved to make a significant change in insulin response among overweight Asian Indians [35]. Although the proof of the benefits exists, more initiatives to lower the consumption of white rice still need to be instituted.

Rice modification: the impacts on health

Modification of rice consumption proposes a prevention strategy against chronic diseases. In some countries these initiatives have been made into public policy and have become a common dietary habit for the people. However, in some other areas of the world, mostly in developing countries, dependence on white rice is still high. Colored rice and local-based staple foods that have higher nutrients value are less popular [18]. This situation has happened since the Green Revolution in the 1940s−70s. The term *Green Revolution* refers to improving all nations' food security by developing high-yielding cereal grains, especially through rice and wheat cultivation [38]. In Indonesia the situation has replaced many of the traditional dietary habits of the people. The consumption of maize, cassava, sago, and sorghum continues to be lower from year to year. Now those foods are considered to be low social foods, which is, of course, not entirely true. A similar condition pihappened in India, where indigenous crops have tended to have lower production since that time [39].

There are many staple foods in the world that can replace or complement white rice consumption. For example, there are nonrice foods such as wheat, corn, potatoes, cassava, yams, sago, and colored rice groups, which include brown, red, and black rice. Nonrice staple foods often have a lower production rate, except for wheat grain, making it difficult for them to meet the demand. Some have a high glycemic index, which is a disadvantage for metabolic syndrome prevention. The local staple foods in Cote d'Ivoire, such as pounded yam with eggplant sauce, have a glycemic index of 94. Another tasty food combination is cassava paste with granules of palm nut sauce, which has a glycemic index of 86. All are classified as having a high glycemic index and being unhealthy [40]. Research in 1987 also provided an example of processed wheat foods that have a high glycemic index such as bread, biscuits, and puffed wheat [41]. On the other hand, a study of the effects of white bread consumption among seven Japanese adults showed different results. White bread consumption has been a major staple food in Japan, alongside white rice over the last 50 years. This study proposed that white bread has more indigestible fiber, which is marked by a higher number of fecal *Bifidobacterium* genus and plasma short-chain fatty acids, than white rice [42].

White rice consumption is linked to some negative health outcomes, such as T2DM and other cardiometabolic disorders. However, rice also has several beneficial nutrients, including active compounds, that have a good effect on health.

Brown rice and metabolic syndrome

Brown rice has been emphasized for its health advantages. The guidelines for diabetic patients always include the consumption of brown rice as the main dietary advice. Consuming brown rice with a strictly followed vegan diet (no meat) for patients with T2DM proved to provide better glycemic control than occurred with patients who followed a conventional diet for T2DM [43]. Another study showed improvement for HbA1c, low-density lipoprotein (LDL) cholesterol and total cholesterol among people with metabolic syndrome after they consumed brown rice for 12 weeks [44]. Following a strict vegetarian diet in which brown rice replaces white rice also helped to reduce the need for medication. It helped in maintaining blood glucose and blood pressure until the patients could stop taking drug treatments [45]. Brown rice appears to have a better impact if it is combined with other low-glycemic foods such as are commonly consumed in vegetarian or vegan diets. A study involving brown rice, which was mixed with barley and amaranth showed that it helped to improve the viscosity and flavor [46]. Diets that are rich in plant-based food with a low glycemic index have more health benefits, such as lower serum lipid and blood pressure [47] and improved endothelial functions [46]. The consumption of brown rice to substitute for white rice may have a positive effect on inflammation markers [44,46]. The consumption of brown rice as part of a vegetarian diet can also improve the gut microbiota balance. It increases the number of *Fermicutes* phylum bacteria, which are important to regulate intestinal immunity. The numbers of *Actinobacteria* and *Fusobacterium*, which are pathogenic bacteria in the gut, were decreased [48]. Brown rice and other whole-grain cereals are a part of the Mediterranean diet. This type of dietary habit combines more vegetables, fruits, whole-grain cereal, and fish, which increase the diet's antioxidant content [49]. Despite the higher value of its nutrient contents, the rate of brown rice consumption is still less than that of white rice. A study in China showed that the main barriers to acceptability of brown rice are its higher price and the taste. However, there is a chance to increase its popularity by increasing the awareness of the health benefits of brown rice [50].

Cooking methods and type 2 diabetes mellitus

Cooking methods may affect the glycemic index of rice. Parboiled white rice tends to have effects similar to those of brown rice in terms of glucose response and satiety [51]. Satiety is associated with the content of resistant starch of rice. Cooked white rice can increase the amount of its resistant starch after it is cooled down to a temperature of 4°C for 24 hours. Cold storage for 24 hours and parboiled rice seem to have a higher amount of resistant starch up to 30% [52]. The preparation induces crystallization of amylose and amylopectin of rice thus making it less digestible and lowering the glycemic index of the rice [53]. However, reheating cold rice to more than 65°C could reverse the retrogradation of polysaccharides, resulting in a lower effect on the reduction of glucose response [52]. Reheating parboiled rice (up to 65°C) has been shown to significantly lower the blood glucose level (1.7 times) in comparison to freshly cooked medium-grain white rice. Reheated rice has a lower glycemic response compared to fresh cooked white rice. This type of cooking method also resulted in a better appearance, a better taste, and a more palatable texture than freshly cooked rice [54,55].

Several interesting findings in Chapagai et al. [56] showed that different cooking methods can either increase or reduce the nutrient value of rice. The protein content of brown rice can increase by 10%−12% after cooking, while the amount of fat did not change significantly after several cooking methods. The iron content of brown rice was observed to decrease by 10%−38% after pressure cooking and 29%−53% when using a rice cooker. However, the amount of zinc, phytate, and thiamine remained similar whether the rice was uncooked or cooked. Cooking methods also affect the physical properties of rice. Cooking gelatinizes and swells the starch granules, lowering the starch content of rice. The reducing amount is proportional with increasing protein content [57].

Rice as functional foods

Rice can be processed and extracted as nutraceutical compounds that provide health benefits. Combinations of fermented red rice, sterol esters and stanols, curcumin, and olive polyphenols are effective to protect endothelial cells from damage and can be a prevention strategy for metabolic syndrome [58]. Rice bran contains several bioactive compounds, such as ferulic acid, inositol hexaphosphate, compesterol, beta-sitosterol, linoleic acid, tocotrienol, and coumaric acids. These compounds have health benefits, including antioxidant and antiinflammatory activities, and can lower lipid peroxidation [31]. The bioactive compounds inside rice bran oil can help to decrease total and LDL cholesterol, decrease ApoB, increase HDL cholesterol, and inhibit platelet aggregation. Its water-soluble compounds, including phytic acid, inositol, and others, have shown antidiabetic effects and help to prevent metabolic syndrome [20]. Rice endosperm protein can be extracted as a safe source of protein for hemodialysis patients [59]. Moreover, a combination of sesame oil and rice bran oil as a cooking oil showed significant antihypertensive and lipid-lowering action [60]. Its functional properties are due to the presence of the peptides leucine, arginine, and alanine inside the rice bran, which activate endothelial nitric oxide synthase and induce vasorelaxation [61]. These compounds made from rice have the potential to be used as functional foods, nutraceuticals, and disease-preventing drug treatments as well as serving as a main staple food.

The positive effects of rice bran make unpolished rice preferable to white rice. A study of the Puzhuthikar, Elipaipoo Samba, Valan Samba, and Garudan Samba varieties of brown rice cultivars in India showed that these rice varieties have a significantly higher mineral content and antioxidant activity than white rice. The assessment of mineral content showed potassium (116.2−178.4 mg), magnesium (61.66−97.57 mg), calcium (12.2−46.04 mg), iron (2.48−7.4 mg), and zinc (1.44−2.71 mg) [62]. The antioxidant activities were observed to be higher in brown rice. The antioxidant and phenolic compounds seem to have inhibitory effects on diabetic enzymes, pancreatic alpha-amylase, and intestinal alpha-glucosidase [63]. These findings confirm the opinion that bioactive compounds in brown rice and other colored rice have the potential to be metabolic syndrome prevention agents [26,64]. As supported by Ruffo et al. [65], black rice extract has alpha-glucosidase inhibition activity of 45%, 58% of alpha-amylase inhibition activity, angiotensin-converting enzyme inhibition activity of 57%, and 2.34 mg GAE per milligram of total phenolic content. These findings verify the potency of black rice as a functional food to prevent chronic diseases, since those enzymes are known to be regulators of metabolic syndrome's prominent factors, such as blood pressure.

Functional foods experts in Japan have labeled brown rice the "medical rice." The label considers the nutrient content of brown rice, which has been shown to help to relieve the burden of patients with diabetes, chronic kidney disorders, and other non-communicable diseases. Japanese people believe that the term *healthy eating* refers to maintaining a macrobiotic balance. This is done practically with combinations from plant-based foods, such as beans, with brown rice as the source of energy, which are planted and grown organically. Medical rice for health refers to organic brown rice with essential nutrients and functional ingredients, while medical rice for diabetes is superhard rice or rice powder with a low glycemic index of no more than 50 [20,48].

Genetic response to rice consumption

Variation in the human genome affects a person's tendency to have higher or lower blood parameters, including how easy it is to manage their health problems. The patients older than age 40 years tend to have four times the rate of metabolic syndrome in comparison to younger patients. The presence of the risk factors is also 50% higher in older men than in women. There is wide heterogeneity of the metabolic syndrome risk factors related to age and sex [66]. This suggests that personalized nutrition can be an effective way to address metabolic syndrome or cardiometabolic disorders [5]. The apolipoprotein A5 gene (*APOA5*)-1331 T > C is an example of a polymorphism that is correlated with higher triglycerides concentration among patients with T2DM and is also known to increase the risk of cardiovascular disease [67]. There is a significant association between the polymorphisms and the types of staple food intake. Among CC allele individuals who have a greater risk of high triglycerides level, the substitution of brown rice and legumes for white rice has a good effect to decrease triglycerides concentration. On the other hand, the intake of brown rice and legumes seems to have lowering effects on fasting blood glucose and triglycerides levels, no matter the genotype [68]. Patients with prediabetes or T2DM tend to have an alteration of some biomarkers. Lipoprotein-associated phospholipase A2 (Lp-PLA2) is always reported to be higher in patients with T2DM. In a study in which consumption of legumes or brown rice was substituted for white rice consumption, similar effects were seen on improving the adipokines parameter compared to only white rice [69]. Diabetic patients are more prone to Alzheimer's disease and dementia. The substitution of unpolished brown or black rice for white rice seems to have beneficial effects of lowering body fat and reducing blood glucose while also increasing the ratio of amyloid beta 42/40 peptide. A higher ratio of amyloid beta 42/40 peptide means there is inhibition activity toward amyloid beta production, which tends to be prevalent among patients with Alzheimer's disease [70].

Research into the effects of black rice is more limited than research into the effects of brown rice. A study in animals showed the prospective effect of black rice to prevent metabolic syndrome at the gene level. The expressions of a fatty acid synthase–related gene such as peroxisome proliferator-activated receptor gamma (PPAR-γ), fatty acid synthase, and sterol regulatory element–binding protein 1c (SREBP-1c) were significantly lower. The addition of black rice is also known to increase cholesterol metabolism through upregulating the hepatic expression of liver X receptor (LXRα) and cytochrome P450 family 7 subfamilies A member 1 (CYP7A1) significantly [71]. This benefit is supported by a study in diabetic rats, which showed that germinated Thai black rice extracts could lower plasma glucose, cholesterol, and triglyceride levels and insulin resistance and increase insulin secretion. The researchers claimed that these effects were similar to that of the drug metformin [72].

Dietary pattern and metabolic syndrome

Dietary patterns are connected with the risk of metabolic syndrome. The Western diet, characterized by a higher intake of red meat, trans fat, and sugar while also being lower in fiber and micronutrients, is related to abnormal blood pressure, triglyceride levels, and fasting blood glucose levels [73,74]. This type of diet has become popular in many countries, where the traditional foods are being forsaken. However, some studies in Asian countries have revealed that the Western diet was not associated with the risk of metabolic syndrome [75,76]. A study among 547 Japanese workers showed that a Westernized diet (high consumption of bread, confectioneries, and dairy products and lower consumption of rice) was not associated with an increased risk of metabolic syndrome. On the other hand, high consumption of animal products does appear to increase the risk of hypertension. The study also reported that a relatively healthy diet (vegetables, fruits, soy products, mushrooms, and green tea) was not associated with a lower prevalence of metabolic syndrome [76]. Another study reported that a group that was used to eating white rice tended to consume lower amounts of grains, fruits, and seeds, which leads to lower calcium, vitamin, and fiber intake [21]. This can be due to the variability of dietary components. In a country where rice provides more than 50% of total energy, it seems that the nutrient value of different varieties of rice affects the risk of metabolic syndrome and its component factors. The Mediterranean diet is famous for its healthy nutrition, involving daily consumption of whole-grain rice. This diet combines more vegetables and fruits with whole-grain cereal, giving it a higher antioxidant content, which is important for health [49]. A genetic study showed that people who are prone to alteration of blood biomarkers should consume a healthier diet. One study showed a significant association between rs3093068, a gene polymorphism affecting C-reactive protein levels, and the Mediterranean diet [77].

Substitution of colored rice for white rice

The Green Revolution that happened in the 1940s–70s in most countries due to food shortage was revealed to have a negative impact in that local-based staple foods were replaced by white rice [38,39]. However, there is an interesting

lesson from South Korea. In the time of difficulty, the government instituted a policy of mixing multiple grains with rice to save more white rice [16]. This behavior has seemed to carry over to the present, as is seen in how many Korean cuisines are using multiple grains or beans to mix with their rice. As an excellent example, there is a delicious dish made of glutinous rice, red bean, beans, sorghum, and millet [78].

Substituting either brown, red, or black rice for white rice seems the simplest change to prevent a future epidemic of metabolic syndrome. However, some of the literature has suggested otherwise, indicating that substitution of brown rice for white rice for 16 weeks did not have a significant impact on lowering the risk of metabolic syndrome. However, in individuals with T2DM, several accompanying factors, such as blood pressure and high cholesterol level, can be improved with brown rice substitution [79]. Analysis in different countries found that consumption of colored rice was always lower than that of white rice, owing to lower availability, lower access, and lower acceptability of colored rice [25,44,50]. Many South Koreans have various rice-eating patterns, with only white rice, white rice and beans, white rice and multiple grains, and white rice in a mixture. One large study including more than 20,000 participants confirmed that the risk factors for metabolic syndrome were lower in the groups that ate rice with beans and rice with multiple grains. There were also benefits for postmenopausal women who showed better lowering effects of the risk factors [80].

In our experience of white rice substitution we found that the acceptance and a positive attitude toward brown and black rice were challenging [25]. Young adults tend to stick with white rice as the main staple food in Indonesia. Although their curiosity about trying a new type of food is also high, they still do not often choose to eat brown or black rice as part of their common diet. Many barriers appeared in our study. First, brown and black rice cost more than white rice, and not all people could afford them. Second, people are not used to the texture and appearance of brown and black rice. The organoleptic properties of brown and black rice are perceived as strange for some people, which lowers their appetite. Organoleptic characteristics, especially for the texture, could be improved by modifying the

TABLE 10.3 Evaluating the preference of seven rice mixtures.

Code	White rice (%)	Brown rice (%)	Black rice (%)	Rice:Water ratio[a]
F1	75	25	0	2:3
F2	50	50	0	2:5
F3	25	75	0	2:5
F4	0	100	0	1:3
F5	50	25	25	1:3
F6	25	50	25	2:7
F7	25	25	50	2:7

[a]*The ratio of rice and water was based on experimentation by the author, considering the maturity level of the rice, since brown and black rice need more water to cook. Unpublished work.*



(A) (B) (C)

FIGURE 10.2 Fresh cooked rice mixtures. (A) 75% white rice and 25% brown rice. (B) 100% brown rice. (C) 25% white rice, 25% brown rice, and 50% black rice.

cooking methods to make them comparable to the sensory expectations of white rice [56]. Third, brown and black rice are known for their advantages for diabetic patients. Therefore consumers might consider this rice suitable only for sick people. Our study among young adults found that the campaign to increase brown and black rice consumption without the intervention from the government is hard to achieve. Although they know its health benefits and are interested in trying this rice, they still have difficulties to afford and find brown and black rice.

In our research, we tried to modify seven rice mixtures consisting of white, brown, and black rice and evaluate the preference of some panelists (Table 10.3). The assessment was based on the preference of the color, aroma, taste, texture, appearance, and as a whole. It was interesting that none of the mixtures had the highest value of preference but all ranged from 4 (dislike slightly) to 6 (like slightly). This finding suggested the potential of the rice mixture to lower the consumption of white rice. However, the preference and acceptance could differ according to culture and tradition, since not all people are used to hard rice but may prefer to eat soft rice. Fresh cooked white rice is generally considered softer than brown and black rice (Fig. 10.2).

A longitudinal study among Japanese adults tried to identify whether there was a shifting of rice consumption behavior and the related factors. The study showed that of more than 5000 participants, 9.9% of women and 8.7% of men were more likely to change their behavior from white rice to brown rice consumption. The reasons for their change were mostly related to preclinical laboratory conditions of hyperlipidemia and diabetes. Another factor was increasing income, which made them able to afford brown rice [81].

Literature about the empirical benefits of black rice are more limited than that of brown rice. Few studies are available about trials to substitute black rice for white rice consumption. Kumar and Murali [82] suggested the role of black rice as a substitute ingredient in other food products. As an example, cake or bread can be made incorporating black rice flour, which can also be used as one of the ingredients in the composition of noodles and pasta. Additionally, the anthocyanin pigment of black rice can be extracted as a natural food colorant for use in yogurt.

In conclusion, on the basis of the literature, it seems that the best substitute for white rice is colored rice. Specifically, for metabolic syndrome prevention, colored rice is better for lowering insulin demand and preventing complications from cardiovascular diseases. Many studies, policies, and programs are focused on reducing the rate of white rice consumption to prevent an epidemic of metabolic syndrome in the future. Our research contributes to the growing evidence that these dietary options can be both delicious and healthy alternative foods that can prevent unhealthy complications and better manage metabolic syndrome.

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Section 3

Fatty acids in the diet as functional foods

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Chapter 11

Effects of polyunsaturated fatty acid–rich diets and risk of non-communicable diseases

Ram B. Singh[1], Shaw Watanabe[2], Duo Li[3], Teiji Nakamura[4], Lekh Raj Juneja[5], Toru Takahashi[6], Sanit Wichansawakun[7], Agnieszka Wilczynska[8], Ibrahim Jantan[9], Ahmad Sulaeman[10], Hardinsyah Ridwan[11], Kshitij Bharadwaj[12], Viliam Mojto[13], Kumar Kartikey[14], Somansh Rawal[14] and Manal M.A. Smail[15]

[1]Halberg Hospital and Research Center, Civil Lines, Moradabad, India, [2]Clinical & Functional Nutriology, Life Science, Tokyo, Japan, [3]Institute of Nutrition & Health, Qingdao University, Qingdao, P.R. China, [4]Kanagawa University of Human Services, Yokohama, Japan, [5]The Rohto Pharmaceutical Co., Ltd., Osaka, Japan, [6]Graduate School of Human Environment Science, Fukuoka Women's University, Fukuoka, Japan, [7]Department of Internal Medicine, Faculty of Medicine, Thammasat University, Bangkok, Thailand, [8]The Tsim Tsoum Institute, Krakow, Poland, [9]Faculty of Health and Medical Sciences, Taylor's University, Subang Jaya, Malaysia, [10]Department of Community Nutrition, Faculty of Human Ecology, Bogor Agricultural University, Bogor, Indonesia, [11]Southeast Asia Probiotics Scientific and Regulatory Experts Network (SEA PROBIOTICS SREN), Indonesia, [12]Department of Physiology, KG Medical University, Lucknow, India, [13]3rd Department of Internal Medicine, Faculty of Medicine, Comenius University, Bratislava, Russia, [14]Halberg Hospital and Research Institute, Moradabad, India, [15]University of Central Lancashire, Preston, United Kingdom

Introduction

The United Nations Food and Agriculture Organization (FAO) and the World Health Organization (WHO) policy action for high-quality diets proposed that eating more of the nutrient-rich foods that are already being produced would result in savings in land, water, and energy consumption [1–3]. If this concept is tied to food production and resources used in industrial food fortification, it may lead to a marked increase in functional foods for health promotion [4,5]. Many agencies and experts have been emphasizing that malnutrition, including overnutrition and undernutrition, is a global challenge that needs to be addressed by all countries of the world [6,7]. It seems that malnutrition contributes to double burden of diseases and needs to be tackled via multiple perspectives to combat multiple manifestations [6–9]. Despite the production of 1.3 billion metric tons of food in 2018, more than 149 million children had stunted growth. However, overweight and obesity in childhood are also increasing in all countries [3,6]. It is clear that the world is not on track to meet the goals agreed upon by the FAO and WHO, because deaths due to non-communicable diseases (NCDs) continue to increase [1–4]. In April 2016 the U.N. member states proclaimed 2016–25 the U.N. Decade of Action on Nutrition (Nutrition Decade) [1–3].

The double burden of malnutrition is characterized by the coexistence of undernutrition along with overweight and obesity, leading to diet-related NCDs within individuals, households, and populations and across the life course [4–9]. The dynamics of this double burden may differ by socioeconomic level as well as by food and nutrition policies at the country level [6–9]. Most experts agree that the double burden of malnutrition is increasing in lower- and middle-income countries, mainly owing to increases in overweight and obesity on account of scarcity in health education, despite sufficient income and the ability of advertising [6–9]. Economic determinants of health are incomplete because people may be rich but not health educated. Apart from health education, motivation to eat and convenient foods are other confounders that decrease the influence of economic development on health promotion. These factors have been commonly observed in India, China, and Indonesia, which are the largest countries with a severe double or triple burden of diseases [8,9]. Other Asian and sub-Saharan African countries are on track to face the same problems. Apart from the increased availability of cheap ultraprocessed food and beverages, there are other factors that contribute to increased consumption of unhealthy diets along with marked reductions in physical activity at work, transportation, home, and even leisure due to the introduction of activity-saving technologies.

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Reviews of food intakes from *Homo erectus* to *Homo sapiens* and from hunter-gatherers to modern Asian and Western populations indicate that there have been marked changes in the diets during human evolution. Rapid increases in industrialization and urbanization have been associated with increased availability of manufactured refined foods, which are high in sugar, salt, and trans fat and low in phytochemicals, essential fatty acids, and essential amino acids. It seems that suboptimal diets, characterized by deficiencies in polyunsaturated fatty acids (PUFA) and flavonoids due to increased intake of manufactured foods, are responsible for approximately one-half of deaths due to NCDs [1,2]. However, the food for this century may be different, with improved food quality and food diversity. Now the aim is to achieve the global nutrition and diet-related NCD targets by 2025 and contribute to realization of the sustainable development goals by 2030 [1–3]. The FAO guidelines emphasize making full use of available food biodiversity to enhance the nutritional status of populations, for which a better understanding of food biodiversity information in dietary intake is required [2,3]. Only a few national and regional food consumption surveys exist that report food biodiversity, particularly at the cultivar or breed level.

Polyunsaturated fatty acids in modern diets

Recent studies indicate that the fatty acid composition of diets appears to be an important determinant of increased risk of morbidity and mortality due to NCDs [5,10–12]. Since linoleic acid (omega-6), linolenic acid (omega-3), and arachidonic acid (AA) are not synthesized by the body; hence these three are called as essential fatty acids [10–12]. These fatty acids must be obtained from the diet because they are not synthesized by the body, owing to the lack of endogenous enzymes for omega-3 desaturation [10–12]. The dietary sources of omega-6 fatty acids are vegetable oils: sunflower oil, soybean oil, rice bran oil, peanut oil, and walnut oil, Flaxseed oil, rape seed oil, mustard oil, and walnuts are rich omega-3 fatty acids as well as in omega-6 fatty acids. Omega-6 and omega-3 fatty acids are PUFA, indicating the presence of more than one cis double bond in the chemical formula [10]. The first double bond is located between the sixth and seventh carbon atoms from the methyl end of the fatty acid in all omega-6 fatty acids. However, omega-3 fatty acids show one double bond between the third and fourth carbon atoms counting from the methyl end of the fatty acid. Table 11.1 shows the types of fatty acids that are available for human consumption.

Table 11.1 also shows the abbreviation for alpha-linolenic acid (ALA), which is 18:3n-3. The first component (18:3) indicates that ALA is an 18-carbon fatty acid with three double bonds, while the second component (n-3) indicates that the first double bond is in the n-3 position. It defines this fatty acid as an omega-3 (Fig. 11.1). The kinks in the chain of hydrocarbon influence the structure and physical properties of the fatty acid molecule, which is introduced by the double bond (Fig. 11.1).

There is evidence that the carbon groups from carbohydrates and proteins are used by humans and other mammals to synthesize monounsaturated fatty acids and saturated fatty acids [10]. The parent fatty acid of the omega-6 series is linoleic acid (LA) (18:2n-6), and the parent fatty acid of the omega-3 series is ALA (Figs. 11.2 and 11.3). Humans lack the delta-12 and delta-15 desaturase enzymes that are needed to insert a cis double bond at the n-6 or n-3 position of a fatty acid [13–15]. Thus both omega-6 and omega-3 fatty acids are considered essential nutrients. Humans can also synthesize long-chain (20 carbons or more) omega-6 fatty acids, such as dihomo-γ-linolenic acid (DGLA) (20:3n-6) and AA (20:4n-6), from LA and long-chain omega-3 fatty acids, from ALA, such as eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3).

TABLE 11.1 Types of omega-6 fatty acids and omega-3 fatty acids.

Omega-6 fatty acids		Omega-3 fatty acids	
Linoleic acid	18:2n-6	Alpha-linolenic acid	18:3n-3
Gamma-linolenic acid	18:3n-6	Stearidonic acid	18:4n-3
Dihomo-γ-linolenic acid	20:3n-6	Eicosatetraenoic acid	20:4n-3
Arachidonic acid	20:4n-6	Eicosapentaenoic acid	20:5n-3
Adrenic acid	22:4n-6	Docosapentaenoic acid (DPA), n-3	22:5n-3
Tetracosatetraenoic acid	24:4n-6	Tetracosapentaenoic acid	24:5n-3
Tetracosapentaenoic acid	24:5n-6	Tetracosahexaenoic acid	24:6n-3
DPA, n-6	22:5n-6	Docosahexaenoic acid	22:6n-3

Source: Modified from Linus Pauling Institute. Micronutrient Information Center, Essential Fatty Acids, https://lpi.oregonstate.edu/mic/other-nutrients/essential-fatty-acids; 2020 [accessed 30.05.20].

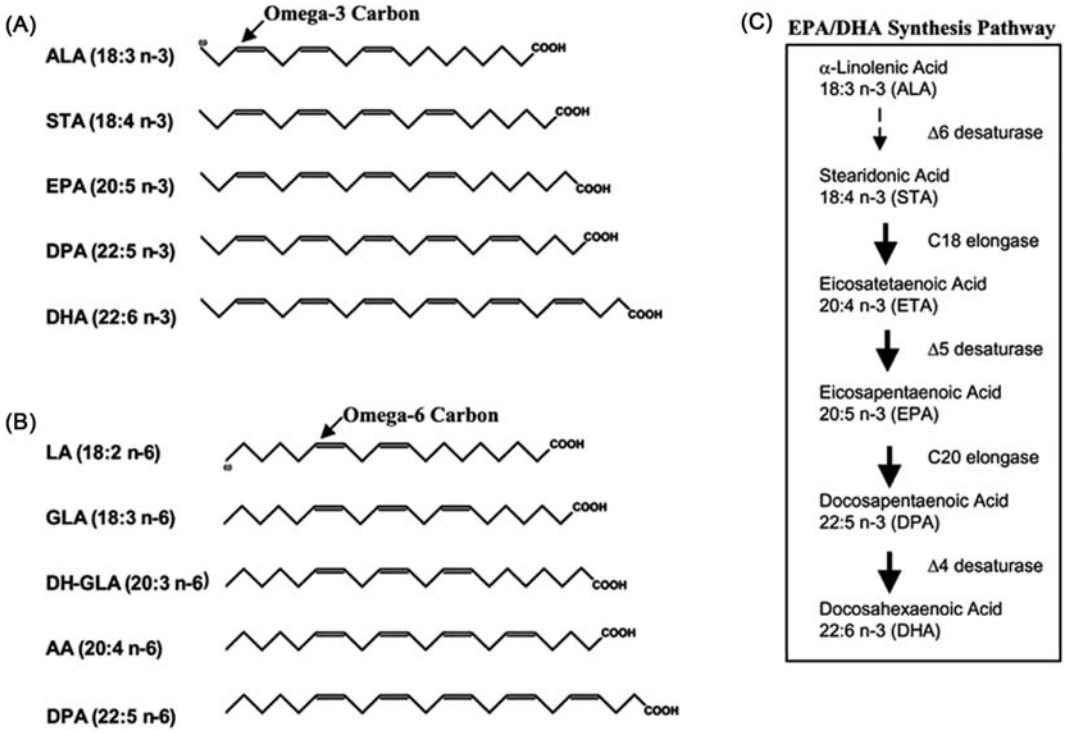
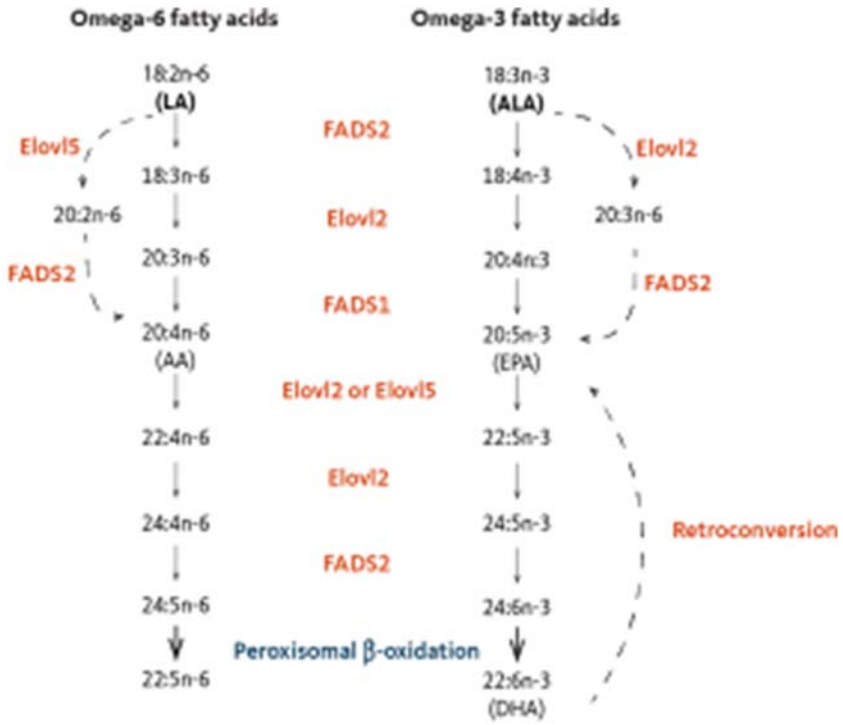


FIGURE 11.1 Chemical structures of fatty acids. *Modified from Google.*



Omega-6 (n-6) and omega-3 (n-3) fatty acids comprise the two classes of essential fatty acids (EFA). The parent compounds of each class, linoleic acid (LA) and α-linolenic acid (ALA) (bold font), give rise to longer chain derivatives inside the body. Due to low efficiency of conversion of ALA to the long-chain omega-3 PUFA, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), it is recommended to obtain EPA and DHA from additional sources. Dietary sources of the different long-chain PUFA are listed in the colored boxes (25).

FIGURE 11.2 Classes of essential fatty acids. *Modified from Linus Pauling Institute. Micronutrient Information Center, Essential Fatty Acids, https://lpi.oregonstate.edu/mic/other-nutrients/essential-fatty-acids; 2020 [accessed 30.05.20].*



Humans can synthesize longer omega-6 and omega-3 fatty acids from the essential fatty acids LA and ALA through a series of desaturation (addition of a double bond) and elongation (addition of two carbon atoms) reactions that occur in microsomes. Delta-6 desaturase (FADS2) is considered the rate-limiting enzyme in this metabolic pathway. Retroconversion of DHA to EPA in peroxisomes occurs at low basal rates and following DHA supplementation (4, 5). *FADS2, delta-6 desaturase; FADS1, delta-5 desaturase; Elovl2, Elovl5, elongases.*

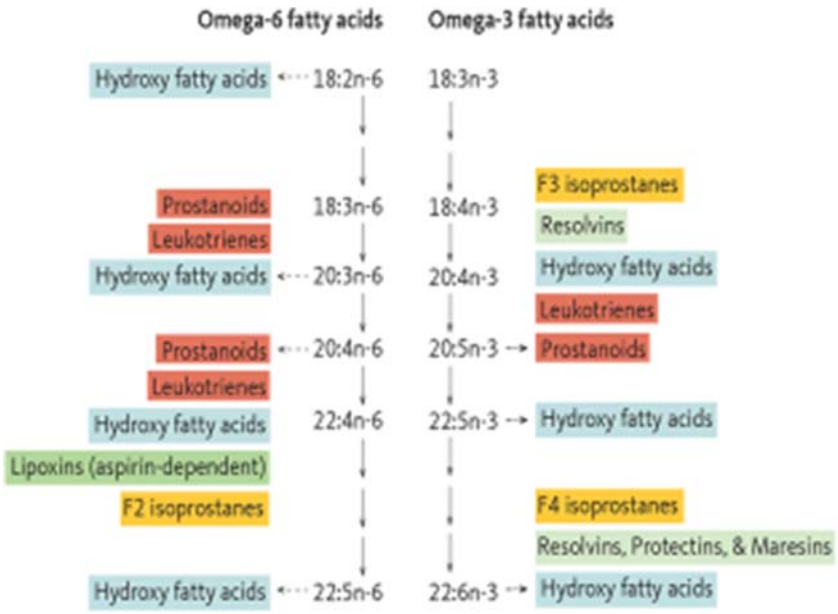
FIGURE 11.3 Desaturation and elongation of essential fatty acids. *Modified from Linus Pauling Institute. Micronutrient Information Center, Essential Fatty Acids, https://lpi.oregonstate.edu/mic/other-nutrients/essential-fatty-acids; 2020 [accessed 30.05.20].*

The fatty acids are hydrolyzed by pancreatic enzymes with the help of bile salts in the small intestine, where up to 85%−95% of them is absorbed. The levels of fatty acids in the blood—whole blood, plasma, serum, and red blood cells—are indicators of both dietary intake and biological processes [10]. In humans, through a series of desaturation (addition of a double bond between two carbon atoms) and elongation (addition of two carbon atoms) reactions, fatty acids can be synthesized as mentioned above (Fig. 11.3). However, LA and ALA compete for the same elongase and desaturase enzymes in the synthesis of long-chain PUFA: EPA, DHA, and AA [10−12].

In healthy young men, approximately 8% of dietary ALA may be converted to EPA, and 0%−4% may be converted to DHA [13]. However, in women, approximately 21% of dietary ALA can be converted to EPA, and 9% to DHA, which may be to the result of estrogens [10,13−15]. It seems that genetic variability in enzymes delta-6 desaturase (FADS2) and delta-5 desaturase (FADS1) is involved in fatty acid metabolism, which influences one's ability to generate long-chain PUFA [15] (Fig. 11.3). There is a difference in the FADS genes' capability to produce long-chain PUFA. Haplotype D is associated with increased FADS activity of both FADS1 and FADS2 genes along with greater conversion rate of precursors of fatty acids, LA and ALA, to long-chain PUFA: EPA, gamma-linolenic acid (GLA), DHA, and AA [16] (Table 11.1). DHA can also be retroconverted to EPA and docosapentaenoic acid (DPA) at a low basal rate and on its supplementation (Fig. 11.3) [17]. Dietary supplementation to omnivores ($N = 8$) and vegetarians ($N = 12$) for six weeks with an EPA-free preparation of DHA (1.62 g/day), was associated with increases in EPA, DPA, and DHA levels in serum and platelet phospholipids [18].

Synthesis of lipid mediators

Oxylipins are potent chemical messengers and lipid mediators derived from PUFA. The most common oxylipins are eicosanoids, which encompass numerous bioactive lipid mediators derived from 20-carbon AA. It would be an oversimplification to label all AA-derived eicosanoids as proinflammatory because they produce prostaglandins (PGs) that are



Dietary intake can alter the fatty acid composition of cell membranes and influence the local production of bioactive lipid mediators. Each PUFA precursor gives rise to a variety of molecules with a range of immune-modulating activities: inflammatory (red), anti-inflammatory (blue), and pro-resolving (green). Isoprostanes (yellow) are markers of oxidative stress (16, 24, 27).

FIGURE 11.4 Bioactive lipid mediators. *Modified from Linus Pauling Institute. Micronutrient Information Center, Essential Fatty Acids, https://lpi.oregonstate.edu/mic/other-nutrients/essential-fatty-acids; 2020 [accessed 30.05.20].*

known to induce inflammation. However, they also inhibit proinflammatory leukotrienes and cytokines and induce anti-inflammatory lipoxins, thereby modulating the intensity and duration of the inflammatory response via negative feedback [19] (Fig. 11.4).

It seems that physiological responses to AA-derived eicosanoids differ from responses to EPA-derived eicosanoids. EPA-derived eicosanoids are less potent inducers of inflammation, blood vessel constriction, and coagulation than eicosanoids derived from AA [20,21]. Oxylipin synthesis relies primarily on three families of enzymes: cyclooxygenases (COX), lipoxygenases (LOX), and cytochrome p450 monooxygenases (P450s). From C_{18}–C_{22} precursors, COX enzymes produce prostanoids: PGs, prostacyclins, and thromboxanes (TXs); LOX produces leukotrienes and hydroxy fatty acids; and P450s produce hydroxyeicosatetraenoic acids and epoxides (Fig. 11.4). Since oxylipins have a critical role in the development of immunity and inflammatory responses and are derived from PUFA, it becomes clear that PUFA can influence immunity and inflammation [22–24]. PUFA bound to membrane phospholipids are released from cell membranes on stimulation by hormones, cytokines, and other stimuli and become substrates for production of dodecanoid, eicosanoids, and docosanoids [24–26].

Deficiency in polyunsaturated fatty acids

The manifestation of deficiency of essential fatty acid are a dry scaly rash, decreased growth in infants and children, increased susceptibility to infection, and poor wound healing [27]. There is evidence that omega-3, omega-6, and omega-9 fatty acids compete for the same desaturase enzymes. These enzymes indicate preferences for the different series of fatty acids in the following order: omega-3 > omega-6 > omega-9. The synthesis of the omega-9 fatty acid eicosatrienoic acid (20:3n-9), also known as mead acid or 5,8,11-eicosatrienoic acid, increases only when dietary intakes of omega-3 and omega-6 fatty acids are very low. Thus mead acid is one indicator of a deficiency of essential fatty acid [10,27]. It has been agreed that a plasma eicosatrienoic acid:AA (triene:tetraene) ratio greater than 0.2 may be considered an indicator of a deficiency of essential fatty acid [27]. Total parenteral nutrition containing fat-free, glucose–amino acid mixtures may cause biochemical signs of deficiency of essential fatty acids, which may develop in as little as 7–10 days [10]. Continuous glucose infusion may cause a high level of circulating insulin, which inhibits the release of essential fatty acids stored in adipose tissue. However, amino acid infusion does not have these adverse

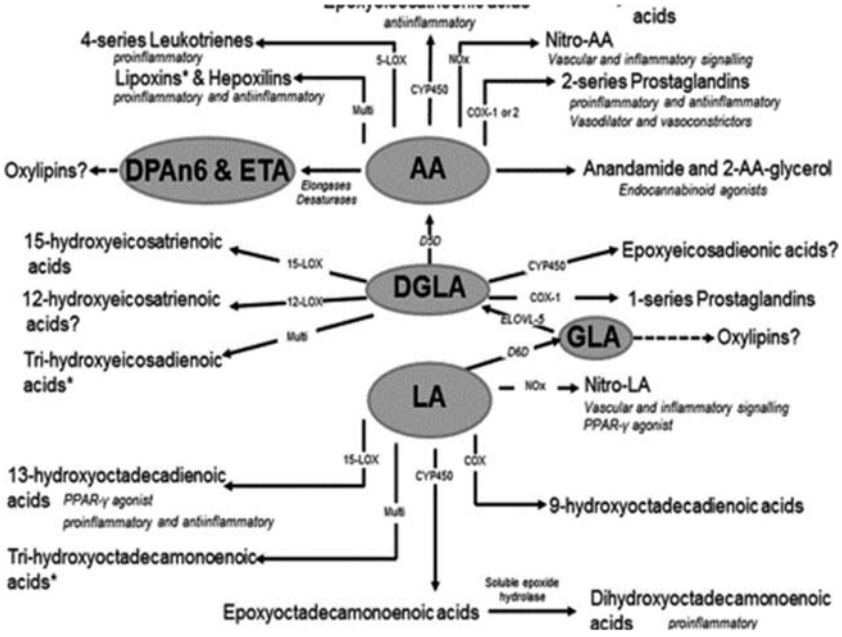


FIGURE 11.5 Mechanisms of interactions of fatty acids. *Modified from Linus Pauling Institute. Micronutrient Information Center, Essential Fatty Acids, https://lpi.oregonstate.edu/mic/other-nutrients/essential-fatty-acids; 2020 [accessed 30.05.20].*

effects. Chronic malabsorption, such as in cystic fibrosis and protein energy malnutrition, may also produce essential fatty acid deficiency [10,27] (see Fig. 11.5).

Isolated deficiency of omega-3 fatty acid has been reported in a young girl who received intravenous lipid emulsions with very little ALA and developed visual problems and sensory neuropathy that were repaired on treatment with omega-3 fatty acid [28]. If omega-3 fatty acid intake is insufficient, plasma DHA concentrations decrease, and there may be visual or memory impairment, but no accepted plasma omega-3 fatty acid or eicosanoid concentrations indicative of impaired health status have been defined [10]. If the amount of EPA plus DHA in red blood cell membranes is expressed as the percent of total red blood cell membrane fatty acids, it may be defined as omega-3 index [29]. The omega-3 index may be used as a biomarker with suggested cutoffs as follows: high risk, $<4\%$; intermediate risk, $4\%-8\%$; and low risk, $>8\%$ [30]. In 115 healthy adults aged 20−45 years, treatment with EPA plus DHA from fish oil capsules for approximately five months showed a dose-dependent increase in the omega-3 index, validating the use of the omega-3 index as a biomarker of EPA plus DHA intake [31]. In a large study, aging has been associated with an increase in omega-3 fatty acids and a decrease in LA [32]. It is possible that a balanced omega-6/omega-3 fatty acid ratio and/or a balanced PUFA/flavonoid ratio may be useful in the pathogenesis and prevention of NCDs. The lack of effectiveness of fish oil in the prevention of morbidity and mortality in some of the metaanalyses of studies may be due to these confounders. It is possible that a balanced ratio of EPA and DHA with omega-6 fatty acids and flavonoids is important to achieve beneficial effects from these fatty acids (Fig. 11.6).

Effect of polyunsaturated fatty acids on pregnancy and its outcome

Randomized, controlled trials concerning pregnancy indicate that omega-3 PUFA therapy does not appear to decrease the incidence of gestational diabetes and preeclampsia and may alter the duration of pregnancy, which has been controversial [34]. In a metaanalysis of trials, omega-3 PUFA supplementation during pregnancy reduced the overall risk of prematurity and the risk of early premature births, increased gestational age at delivery and birth weight, and had no effect on the risks of perinatal death and low Apgar scores at 1 minute post birth [35]. There was a dose−response effect; with continuous reduction of the risks of early premature birth (birth before 34 weeks gestation) and very low birth weight (<1500 g) with daily doses of DHA supplement up to at least 600 mg during pregnancy [36]. In a meta-analysis of 17 trials, only a little evidence was noted to indicate that supplementing preterm infants with long-chain PUFA (primarily EPA and DHA) improved measures of visual acuity, neurodevelopment, and physical growth during infancy [37]. It is possible that a balanced omega-6/omega-3 fatty acid ratio and/or a balanced PUFA/flavonoid ratio may be useful in the pathogenesis and prevention of these problems.

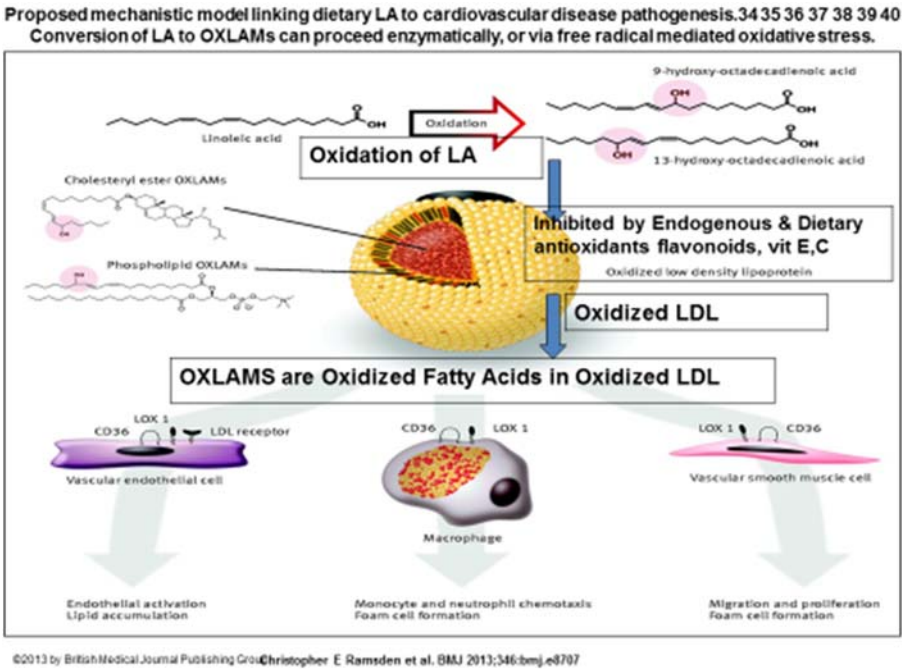


FIGURE 11.6 Role of dietary linoleic acids in the oxidation of low-density lipoprotein predisposing CVDs [33] CVDs, Cardiovascular diseases. *Modified from Ramsden CE, Zamora D, Leelarthaepin B, et al. Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. BMJ 2013;346:e8707*

Effects of polyunsaturated fatty acids on non-communicable diseases

There is evidence that omega-3 fatty acids such as ALA, EPA, and DHA as well as omega-6 fatty acids such as LA and AA may have a protective role in the pathogenesis and prevention of NCDs [10–12]. There is some evidence that monounsaturated fatty acids and stearic acid may also have a protective role by increasing high-density lipoprotein cholesterol and antiplatelet effects.

Effects of linoleic acids on cardiovascular disease

The U.S. Department of Agriculture has reported nutrient intakes from food indicating that LA is the most abundant dietary PUFA, accounting for approximately 90% of dietary intake of omega-6 PUFA [38]. A metaanalysis of 13 prospective cohort studies, comprising 310,602 subjects and 12,479 events due to coronary artery disease (CAD), included 5882 deaths due to CAD [39]. After a follow-up of 5.3–30 years, a greater intake of LA was significantly associated with a 15% lower risk of events due to CAD and a 21% lower risk of deaths due to CAD [39]. Further analysis revealed that replacement of 5% of energy from saturated fatty acids with LA was associated with a 9% decline in the risk of coronary events and a 13% lower risk of deaths due to CAD [39].

In a consortium of 30 observational cohort studies from 13 countries, among 68,659 subjects, with medians of follow-up ranging from 2.5 to 31.9 years, 15,198 incident cardiovascular events occurred [40]. Increased concentrations of LA were significantly associated with lower risks of total CVD [hazard ratio (HR): 0.93], cardiovascular mortality (HR: 0.78), and ischemic stroke, (HR: 0.88) per interquintile range. No association was found between concentrations of LA in tissues and the risks of CAD. These relationships were similar for LA evaluated across quintiles. Higher levels of AA were associated with lower risk of total CVD (0.92; 0.86–0.99) indicating a modest association. It is clear that in pooled global analyses, higher in vivo circulating and tissue levels of LA and possibly AA were associated with a lower risk of major cardiovascular events [40] (Fig. 11.7).

In a systemic review of 44 prospective cohorts including 811,069 participants, dietary intakes were assessed [41]. Of 170,076 all-cause, 50,786 CVD, and 59,684 cancer deaths and 65,411 participants with biomarker measurements (9758 all-cause, 6492 CVD, and 1719 cancer deaths), relation with LA was examined. Pooled relative risks (RRs) comparing extreme categories of dietary intake of LA (high vs low) were 0.87 ($I^2 = 67.9\%$) for total mortality, 0.87 ($I^2 = 3.7\%$) for CVD mortality, and 0.89 ($I^2 = 0\%$) for cancer mortality. Pooled RRs for each standard deviation increment in LA concentrations in adipose tissue/blood compartments were 0.91 ($I^2 = 64.1\%$) for total mortality, 0.89

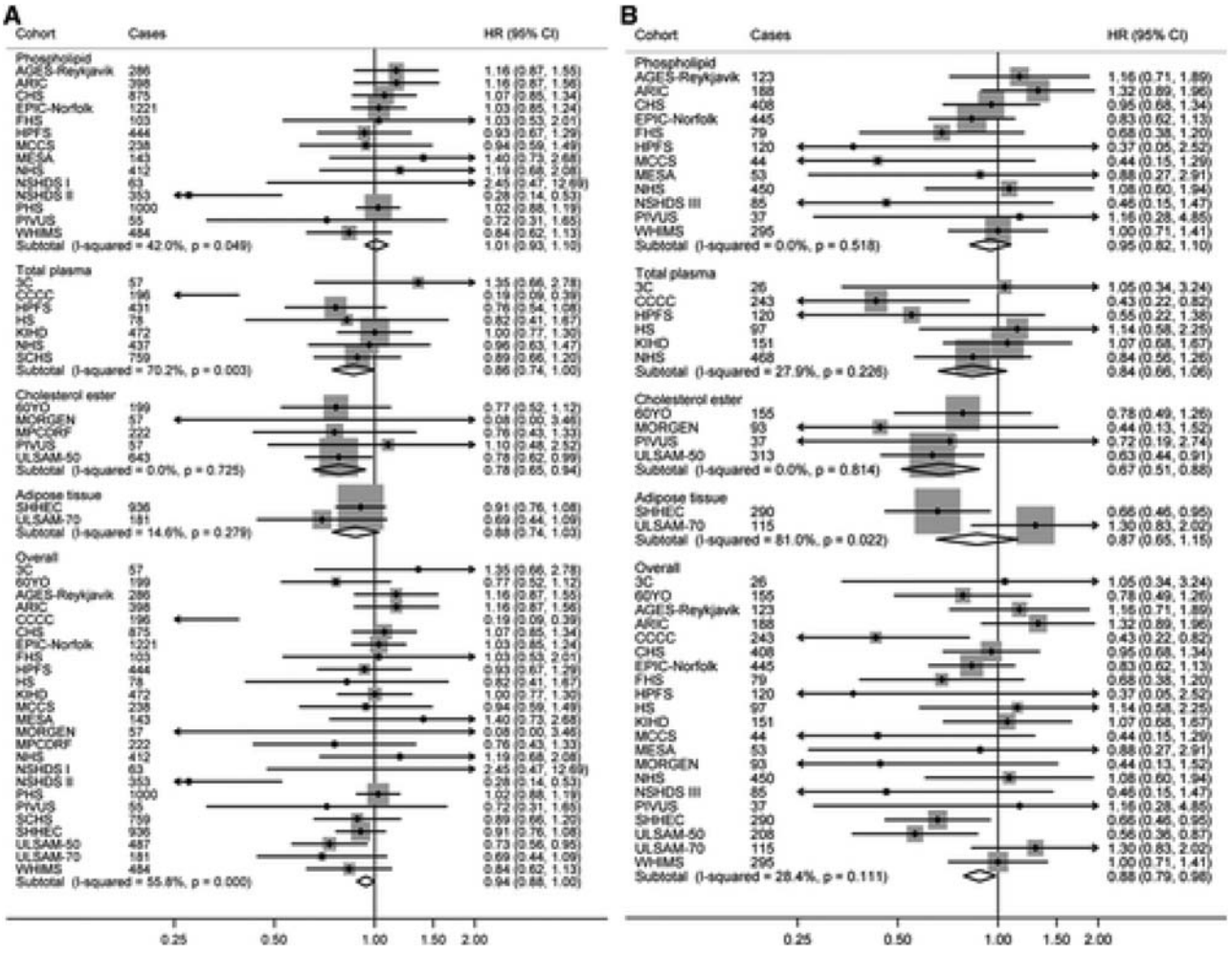


FIGURE 11.7 Association of biomarkers of omega-6 fatty acids with risk of incident CVDs and mortality. CVDs, Cardiovascular diseases. *Modified from Marklund M, Wu JHY, Imamura F, et al. Biomarkers of dietary omega-6 fatty acids and incident cardiovascular disease and mortality: an individual-level pooled analysis of 30 cohort studies. Circulation 2019;139(21):2422–436.*

($I^2 = 28.9\%$) for CVD mortality, and 0.91 ($I^2 = 26.3\%$) for cancer mortality [41]. It is possible that in prospective cohort studies, a higher intake of LA, assessed by dietary surveys or biomarkers, was associated with a modestly lower risk of mortality from all causes, CVD, and cancer. The findings support the potential long-term benefits of PUFA intake in lowering the risk of CVD and premature death.

The Kuopio Ischaemic Heart Disease Risk Factor Study, including 2480 men, age 42–60 years at baseline, the stratified analyses by baseline disease status included 1019 men with a history of CVD, cancer, or diabetes and 1461 men without a history of disease [42]. During the mean follow-up of 22.4 years, of total 1143 deaths, 575 were due to CVD, 317 to cancer, and 251 to other causes. High serum levels of LA were associated with a lower risk of death from any cause; 0.57 ($P < .001$) and with deaths due to CVD, 0.54 ($P < .001$) and non-CVD or noncancer causes, 0.48 ($P = .001$). Interestingly, serum levels of AA had similar, although weaker, inverse associations. Serum GLA and DGLA were not associated with risk of death, and none of the fatty acids were associated with cancer mortality [42]. It is possible that there is an inverse association of a higher biomarker of intake of LA with total and CVD mortality and little concern for risk, thus supporting the current dietary recommendations to increase intake of LA for CVD prevention. It is possible that the inverse association of serum AA with the risk of death needs further proof in other populations. In another study, circulating GLA, DGLA, and AA were not significantly associated with total or cause-specific mortality [e.g., for AA and deaths due to CAD, the extreme-quintile HR was 0.97 ($P = .87$)] [43]. However, LA had graded inverse associations with total mortality ($P = .005$). There was little evidence that associations of n-6 PUFA with total mortality varied by age, sex, race, or plasma n-3 PUFA. When both n-6 and n-3 PUFA were evaluated, the

lowest risk was evident with the highest levels of both. It is clear that high circulating LA but not other n-6 PUFA was inversely associated with total and CAD mortality in older adults.

In another study 306 patients (mean age: 66.4 ± 15.0 years) were analyzed after a follow-up period of 2.4 ± 1.2 years, during which 50 patients (16.3%) died [44]. The DGLA levels, AA levels, and DGLA/AA ratio were significantly lower in the nonsurvivor group than in the survivor group (DGLA: 23.2 ± 9.8 vs 31.5 ± 12.0 μg/mL, AA: 151.1 ± 41.6 vs 173.3 ± 51.6 μg/mL, and DGLA/AA: 0.16 ± 0.05 vs 0.19 ± 0.06, all $P < .01$). Kaplan–Meier curves showed that survival rates were significantly higher in the higher DGLA, AA, and DGLA/AA groups than in their lower counterparts (DGLA and AA; $P < .01$, DGLA/AA; $P = .01$), although omega-3 PUFA were not associated with prognosis. Interestingly, in patients with acute decompensated heart failure (ADHF), survival rates were significantly higher in the higher DGLA, AA, and DGLA/AA groups than in their lower counterparts (DGLA and AA; $P < .01$, DGLA/AA; $P = .04$). Among patients with ADHF, DGLA, and DGLA/AA were associated with long-term mortality. For DGLA, the HR was 0.94 ($P = .01$) and for DGLA/AA, the HR was 0.87 ($P < .01$), whereas AA was not associated with prognosis. It is possible that low omega-6 PUFA levels, particularly DGLA, and a low DGLA/AA ratio predict long-term mortality in patients with acute cardiovascular disease (CVD) and ADHF. Now diabetes is considered a CVD because its main complications begin with cardiovascular inflammation predisposing to CVDs. In the prospective Kuopio Ischaemic Heart Disease Risk Factor Study, 417 out of 2189 men developed diabetes mellitus [45].

Randomized controlled trials

In a metaanalysis, four randomized, controlled trials (five papers) included 660 participants [46]. Three trials examined the effect of increased omega-6 intake on lipid levels, and two trials reported triglycerides and diastolic and systolic blood pressure. The results reported no statistically significant effects of either increased or decreased omega-6 intake on CVD risk factors such as blood lipids and blood pressures [46]. The results from four randomized controlled trials [47–51] compared the effects of diets high in either saturated fatty acids or PUFA over at least two years, and a 2016 systematic review and presidential advisory from the American Heart Association concluded that lowering saturated fat intake and replacing it with vegetable oil rich in PUFA (primarily soybean oil) could reduce the risk of CAD by 29% [52]. However, these clinical trials were conducted in the 1960s and 1970s, when the use of the cholesterol-lowering drug statin was not common and the intake of saturated fat content in diets was higher. Also, all trials except one were in men with diagnosed CVD [50,51]. The Oslo Diet-Heart Study [49] increased both omega-3 and omega-6 PUFA intake, and the Finnish Mental Hospital Study [50,51] used a crossover design.

In a Cochrane systematic review of 19 randomized controlled trials that examined the effect of increasing omega-6 PUFA intake on CVD outcomes, the above two trials were excluded from the analysis [53]. Of these 19 trials, seven assessed the effect of supplemental GLA, and 12 assessed the effect of substituting dietary LA for saturated fat or monounsaturated fatty acids. This analysis of studies showed no effect of increasing omega-6 intake on the risks of CAD or CVD events, major adverse cardiac events, and stroke, myocardial infarction, and cerebrovascular events and CVD mortality, or all-cause mortality (low-quality evidence) [53]. It seems that many trials that examined the effect of replacing saturated fatty acids with mostly omega-6 PUFA may not have been adequately controlled. In some trials, only the high omega-6 PUFA group received dietary advice for prudent food intake, for example, to avoid dietary sources of sugar and sweets, trans fatty acids, and processed foods, to consume more whole-plant foods and to increase consumption of fish and shellfish, which could have biased the results [54]. Apart from this, a recent metaanalysis of trials with low risk of bias, showed no evidence of an effect of substituting omega-6 PUFA for saturated fatty acids on the risks of major coronary events (MI and sudden death), total CAD events, CAD mortality, and all-cause mortality [54]. This assessment was free of differences between intervention and control groups other than those under examination.

However, replacing dietary saturated fatty acids with omega-6 PUFA was consistently found to lower total blood cholesterol levels [33,53]. In a metaanalysis, LA has been reported to be the highly potent fatty acid for decreasing total cholesterol when substituted for dietary saturated fatty acids [33,55]. In the metaanalysis of four trials by Ramsden et al., intervention with combined omega-3/omega-6 showed significant decline in deaths due to CAD, whereas LA alone showed no beneficial effects (Fig. 11.8). However, this metaanalysis is open to bias because it is based on very old studies and moreover other positive studies using mustard oil and rape seed oil providing high content of ALA were ignored.

The potential mechanisms by which LA decreases blood cholesterol are the upregulation of low-density lipoprotein (LDL) receptor and redistribution of LDL cholesterol from plasma to tissue, the rise in the production of bile acid and cholesterol catabolism, and the decreased VLDL-to-LDL conversion [56,57]. In an experimental study, PUFA with double bonds closer to the carboxyl head group showed greater apparent affinity for certain channels and increased certain current [58]. An increase in shifting the bonds farther away from the head group reduced the apparent binding affinity

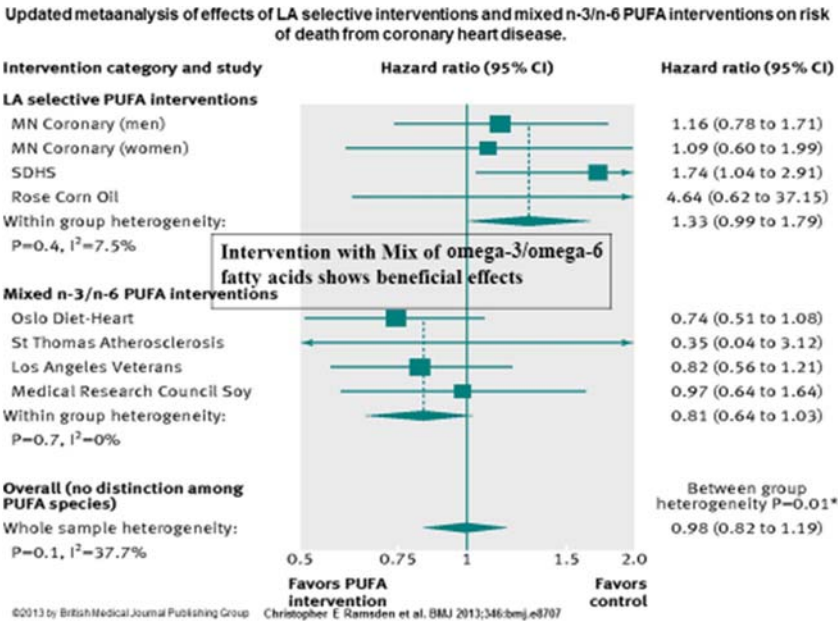


FIGURE 11.8 Metaanalysis of trial showing role of intervention with mix of omega-3/omega-6 fatty acid–rich oils on risk of death from coronary disease. *Modified from Ramsden CE, Zamora D, Leelarthaepin B, et al. Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. BMJ 2013;346: e8707.*

for and effects on these currents [58]. Interestingly, it has been found that omega-6 and omega-9 PUFA with the first double bond closer to the head group left-shifted the voltage dependence of activation the most. These results allow for informed design of new therapeutics targeting certain channels in long QT syndrome.

As was mentioned earlier in the chapter, substituting omega-6 PUFA for saturated fatty acids can reduce blood cholesterol, but some of the systematic reviews and metaanalyses have failed to find evidence of clinical cardiovascular benefits [53,54,56,57,59]. The 12th Congress of the International Society for the Study of Fatty Acids and Lipids advocated that nutritional guidelines on fat intake need a proper scientific basis in which randomized controlled trials with clinical endpoints and their metaanalyses are essential and decisive [60]. The recommendations on dietary fat intake should always be based on the totality of the evidence, including physiological and biochemical findings and associations from observational epidemiological studies. Clinical trials and metaanalyses have their own disadvantages, but well-conducted systematic reviews and metaanalyses support a transparent process for developing dietary fat guidelines [60]. It seems that there is an unmet need to consider all important nutrients in the diet while advising a particular food or diet for health promotion and diseases prevention. In view of these controversies, it is prudent to suggest increased intake foods that are rich in PUFA, such as fish and other seafood, vegetable oils, and other foods, along with Indo-Mediterranean-style foods, which can provide adequate amounts of PUFA in the diet [59,61–67].

Effects of arachidonic acid in non-communicable diseases

AA (20:4n-6) is one of the most important PUFA after omega-3 fatty acids and is a constituent of cell membranes [64,65]. It is available in very small amounts in the human diet. The AA content of human milk is significantly greater than that in cow's milk, in which it is present only in small amounts, indicating that it may have a potential role in the health of the newborn. Rich sources of AA are meat, shrimps, egg yolks, human milk, and some seaweeds. The mean daily intake of AA is in the range of 50–300 mg/day which accounts for the total daily production of various PGs, estimated to be about 1 mg/day [64,65]. AA modulates the fluidity of the cell membrane. It is metabolized by LOX, COX, and cytochrome P450 enzymes leading to formation of several metabolites that have important biological actions.

There is evidence that AA and its metabolites especially, lipoxin A4 (LXA4) and epoxyeicosatrienoic acids (EETs) have potent antiinflammatory effects, which have a crucial role in the pathogenesis of obesity, hypertension, CAD, and diabetes mellitus [64,65]. AA as well as its metabolites LXA4 and EETs can regulate cell membrane fluidity, smooth muscle function and proliferation, voltage-gated ion channels, membrane receptors, G-coupled receptors, peroxisome proliferator–activated receptors, free radical generation, and production of nitric oxide. These beneficial effects can decrease inflammation and suppressive immune responses, and this, in turn, has beneficial effects in the regulation blood pressure, inhibition of atherosclerosis, and beta cell dysfunction leading to decline in CVDs and diabetes mellitus. In view of new evidence related to inflammation and immune function, the role of AA appears to be interesting in

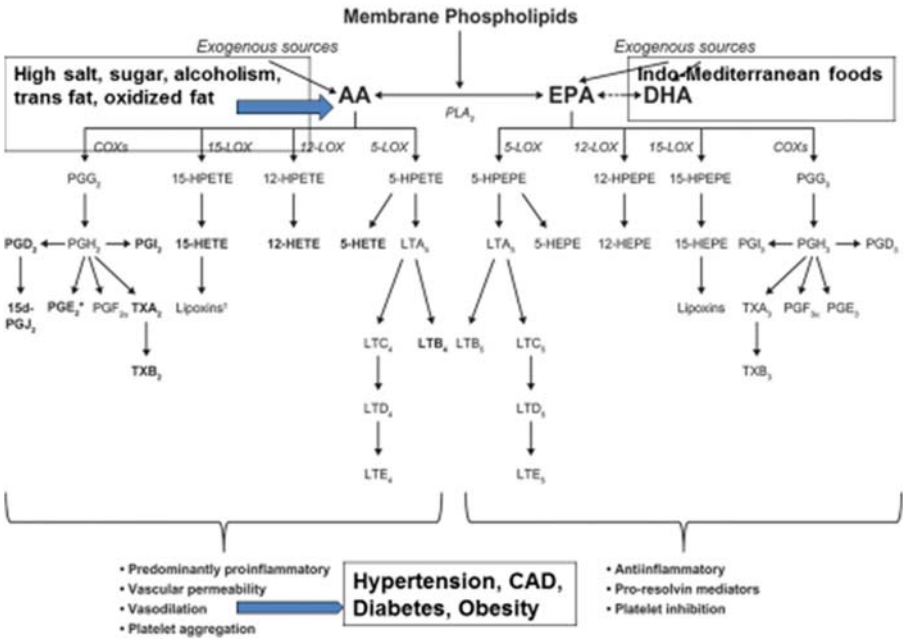


FIGURE 11.9 Effects of nutritional factors on arachidonic acid metabolism leading to development of cardiometabolic diseases. *Modified from Sonnweber T, Pizzini A, Nairz M, Weiss G, Tancevski I. Arachidonic acid metabolites in cardiovascular and metabolic diseases. Int J Mol Sci 2018;19(11):3285. Published 2018 Oct 23. https://doi.org/10.3390/ijms19113285.*

TABLE 11.2 Formation of various omega-fatty acid metabolites from dietary fatty acids.

- The omega-3 series derived from alpha-linolenic acid (18:3, omega-3).
- The omega-6 series derived from cis-linoleic acid (18:2, omega-6).
- The omega-9 series derived from oleic acid (18:1, omega-9).
- The omega-7 series derived from palmitoleic acid (16:1, omega-7).

regard to the regulation of blood pressure and its ability to prevent both type 1 and type 2 diabetes mellitus. Das has proposed that a combination of AA and aspirin could be of benefit in the prevention and management of hypertension, preeclampsia, and diabetes mellitus [64] (Fig. 11.9).

Western-type diets may be deficient in AA, owing to decreased intake of dairy products, poultry, and seafoods and increased consumption of refined carbohydrates and processed and preserved red meats, a combination that is rich in trans fat, saturated, fat and sugar. The amount of AA is likely to be insufficient for human requirements, since it may be destroyed or degraded during storing, processing, and cooking [64,65]. It seems that there is an unmet need for endogenous production of AA through its precursor, LA (18:2n-6). There are two essential fatty acids, LA and ALA (18; 3n-3), which are widely distributed in our diet, and hence their deficiency is least likely. Although both of these fatty acids are essential for life, many of their functions are brought about by their metabolites, namely, long-chain compounds such as GLA (18:3n-6), DGLA (20:3n-6) and AA from LA and EPA (20:5n-3) and DHA (22:6n-3). These fatty acids—GLA, DGLA, and AA from LA and EPA and DHA from ALA—are regulated by the actions of desaturase and elongase enzymes, as shown in Fig. 11.1. Interestingly, DGLA, AA, EPA, and DHA are further metabolized to form a variety of metabolites by the actions of COX-1, COX-2, and LOX enzymes as described in Table 11.2.

Both LA and ALA are converted to their respective long-chain fatty acids by the action of enzymes: delta-6 and delta-5 desaturases, leading to formation of GLA (18:3), DGLA (20:3), and AA (20:4) from LA. However, ALA is converted to form EPA (20:5) and DHA (22:6), respectively. DGLA forms precursor to series 1 PGs, whereas AA is helpful in the formation of the precursor of PGs 2, TXs, and leukotrienes 4 (LTs-4) and antiinflammatory molecules: lipoxins. Interestingly, EPA derived from ALA induces the formation of the precursor to the 3 series of PGs, TXs, and the 5 series of LTs and antiinflammatory compounds: resolvins. Thus EPA can be elongated to form DHA, the precursor of antiinflammatory compounds: protectins, resolvins, and maresins.

It seems that LA, AA, GLA, DGLA, ALA, EPA, and DHA are all PUFA, whereas only LA and ALA are essential fatty acids that need to be supplied from the diet. In general, PGs, TXs, and LTs formed from AA and EPA have

proinflammatory actions. However, eicosanoids derived from EPA have the least proinflammatory effects compared to those formed from AA and play a significant role in the pathogenesis of atherosclerosis, asthma, inflammatory bowel disease, rheumatoid arthritis, lupus, sepsis, cancer, and other diseases. Interestingly, all the essential fatty acids are PUFA, but not all PUFA are essential fatty acids [64–66]. PUFA are abundantly present in phospholipids of cell membranes and in lipid droplets in immune cells. In fact, AA refers to all-cis-5,8,11,14-eicosatetraenoic acid, which is an omega-6 PUFA, having 20 carbon chains and four cis double bonds. Owing to the 20 carbon units of length, AA and its metabolites as well as various omega-3 PUFA are also called eicosanoids, which are known to have antiinflammatory effects.

EPA is a major antiinflammatory and antiaggregatory long-chain polyunsaturated omega-3 fatty acid [64,65]. As was mentioned earlier, AA is a precursor to a number of proinflammatory and proaggregatory mediators, and EPA acts competitively with AA for the key COX and LOX enzymes to form less proinflammatory products [65]. Therefore the EPA:AA ratio could be a marker of chronic inflammation, with a lower ratio corresponding to higher levels of inflammation [65]. Epidemiological studies indicate that a decline in the EPA:AA ratio may be associated with an increased risk of CAD, including acute coronary syndromes, stroke, chronic heart failure (HF), peripheral artery disease, and vascular disease. It is possible that the EPA:AA ratio is a valuable predictor of cardiovascular risk. Results from ongoing clinical trials will help to define thresholds for EPA treatment associated with better clinical outcomes. The highest content of AA is present in the brain, muscle, liver, spleen, and retina, whereas concentrations of free AA in the circulation are typically very low, owing to albumin binding and trafficking to cells [66]. There is evidence that lipid mediators and immune pathways may be crucial in the development of cardiometabolic diseases [66]. AA and its metabolites may have a link with nutrient metabolism in relation to immunity and inflammation. Therefore AA may have a major role in the emergence and progression of obesity, diabetes, nonalcoholic fatty liver disease, and CVDs as well as neuropsychiatric diseases. In previous clinical trials with diets, the role of AA was not examined, although evidence is emerging for the role of fatty acids in CVDs and diabetes [68,69]. Supplementation of purified EPA increases the EPA:AA ratio, leading to primary and secondary prevention of CVDs as well as reducing the risk of cardiovascular events following percutaneous coronary intervention [70]. The role of AA in the prevention of CVDs and diabetes has also been supported by animal studies [71,72].

Effects of omega-3 fatty acids and a balanced omega-6/omega-3 fatty acid ratio in non-communicable diseases

Some studies and metaanalyses also question the role of fish oil supplements and AA in the prevention of CVDs. In two of the metaanalyses, all studies on the role of omega-3 supplements were not included in the analysis [59,73]. In a randomized, controlled trial among 8179 patients, 70.7% had cardiovascular events and were followed for a median of 4.9 years [70]. A primary endpoint event was significantly lower in icosapent ethyl group compared with placebo group [17.2% vs 22.0%; HR: 0.75; 95% confidence interval (CI): 0.68–0.83; $P < .001$]. The corresponding rates of the key secondary endpoint were 11.2% versus 14.8% (HR: 0.74; 95% CI: 0.65–0.83; $P < .001$). The rates of additional ischemic endpoints, as assessed according to a prespecified hierarchical schema, were significantly lower in the icosapent ethyl group than in the placebo group, including the rate of cardiovascular death (4.3% vs 5.2%; HR: 0.80; 95% CI: 0.66–0.98; $P = .03$) [70]. A larger percentage of patients in the icosapent ethyl group than in the placebo group were hospitalized for atrial fibrillation or flutter (3.1% vs 2.1%, $P = .004$). It is possible that among patients with elevated triglyceride levels despite the use of statins, the risk of ischemic events, including cardiovascular death, was significantly lower among those who received 2 g of icosapent ethyl twice daily than among those who received placebo. This trial confirmed that the use of purified EPA in patients after myocardial infarction can cause a significant decline in cardiovascular events.

Previous studies and recent metaanalyses indicate that there may be confounders due to the presence or absence of flavonoid and ALA contents in the diets of the two groups, giving negative results in these studies [59,67,73–75]. It should also be emphasized that the majority of the studies on fish intake and risk of CVDs have found a beneficial effect of fish consumption on risk of CVDs [61–63]. This shows that there is something in the fish, such as fish peptides or selenium, that is not in the fish oil, resulting in no benefits in the fish oil group [59,73]. Other confounders may be flavonoid and polyphenolics in other components of diets, which can also influence the findings, giving positive or negative results. Despite the questionable evidence on the benefits of omega-3 supplements in the prevention of CVDs, the recommendation of the American Heart Association (AHA) for patients with prevalent CAD such as a recent myocardial infarction remains essentially unchanged [59]. It has been suggested that treatment with supplements of omega-3 PUFA is reasonable for benefits in these patients because of the evidence of benefits in patients with acute myocardial infarction [76]. In the secondary prevention of CAD, even a potential modest reduction in mortality (10%) would justify treatment with a relatively safe therapy. The AHA recommends this treatment for patients with prevalent HF without

preserved left ventricular function to reduce mortality and hospitalizations (9%) on the basis of a single, large controlled trial. The AHA also expressed its inability to recommend treatment for patients with diabetes mellitus and prediabetes to prevent CAD, owing to a lack of consensus on the recommendation for patients who are at high risk of CVDs [59].

Since previous studies show inconsistent associations between ALA and risk of CAD, another metaanalysis examined an aggregate association between ALA intake and risk of CAD and assessed for any dose–response relationship [75]. Of 14 studies included in this metaanalysis, the pooled findings revealed that a higher intake of ALA was associated with a modestly reduced risk of composite CAD [risk ratios (RR) = 0.91] and fatal CAD (RR = 0.85). Interestingly, this analysis revealed a J-shaped relationship between intake of ALA and relative risk of composite CAD ($\chi^2 = 21.95$, $P < .001$). Only subjects with an ALA intake less than 1.4 g/day showed a reduced risk of composite CAD, compared with subjects without an ALA intake. ALA intake was linearly associated with fatal CAD; every 1 g/day increase in ALA intake was associated with a 12% decline in the risk of fatal CAD (95% CI: −0.21, −0.04). Surprisingly, a higher dietary intake of ALA was associated with a reduced risk of composite and fatal CAD [75]. A greater composite CAD risk at higher ALA intakes warrants further investigation, especially through randomized controlled trials, although it may be explained as a result of the lack of other protective nutrients, such as flavonoids, which are known to inhibit the free radical stress that can be produced by a higher intake of all PUFA.

A metaanalysis of ten trials involving 77, 917 subjects also found that supplementation with marine-derived omega-3 fatty acids for a mean of 4.4 years had no significant association with reductions in fatal or nonfatal CAD or any major vascular events [73]. A Cochrane-based metaanalysis included 86 randomized trials ($N = 162,796$ participants), of which 28 were at low summary risk of bias [77]. The duration of trials were 12–88 months among adults at varying cardiovascular risk with supplementation of capsules, but some used long-chain omega-3 or ALA-rich or enriched foods or dietary advice compared to placebo or optimal diet. The doses of omega-3 fatty acids ranged from 0.5 g/day to more than 5 g/day. This metaanalysis and its sensitivity analyses suggested little or no effect of increasing omega-3 fatty acids on all-cause mortality [risk ratio (RR): 0.97], 143,693 participants, 11,297 deaths in 45 controlled trials (high-class evidence); cardiovascular mortality (RR: 0.92), 117,837 participants, 5658 deaths in 29 controlled trials (moderate-class evidence); cardiovascular events (RR: 0.96), 140,482 participants, 17,619 people experienced events in 43 controlled trials (high-class evidence); stroke (RR: 1.02), 138,888 participants, 2850 strokes in 31 controlled trials (moderate-class evidence); arrhythmia (RR: 0.99), 77,990 participants, 4586 people experienced arrhythmia in 30 controlled trials (low-class evidence) [77]. Increasing consumption of omega-3 fatty acids may slightly reduce mortality due to CAD [number needed to treat for an additional beneficial outcome (NNTB): 334, RR: 0.90]; 127,378 participants; 3598 deaths due to CAD in 24 controlled trials (low-class evidence); and coronary events (NNTB: 167, RR: 0.91), 134,116 participants, 8791 subjects developing events due to CAD in 32 controlled trials (low-class evidence). Only a little evidence of benefits was observed of the effects of eating fish.

This analysis also revealed that increasing the intake of ALA probably makes little or no difference in all-cause mortality (RR: 1.01), 19,327 participants, 459 deaths in five controlled trials (moderate-class evidence); cardiovascular mortality (RR: 0.96), 18,619 participants, 219 deaths due to CVDs in four controlled trials (moderate-class evidence); CAD mortality (RR: 0.95), 18,353 participants, 193 CAD deaths in three controlled trials (moderate-class evidence); and CAD events (RR: 1.00), 19,061 participants, 397 CAD events in four controlled trials (low-class evidence) [77]. Despite these findings, increased ALA may possibly slightly reduce the risk of CVDs (NNTB: 500, RR: 0.95); but RR = 0.9 in controlled trials at low summary risk of bias, 19,327 participants, 884 CVD events in five controlled trials (low-class evidence), and probably slightly reduces the risk of arrhythmia (NNTB: 91, RR: 0.73), 4912 participants, 173 events in two controlled trials (moderate-class evidence). The effects on stroke were not very clear. This analysis showed that increasing omega-3 fatty acids, including ALA, revealed little or no effect on serious adverse events, adiposity, lipids, and blood pressure. However, increasing omega-3 fatty acids reduced triglycerides by approximately 15% in a dose-dependent way (high-class evidence).

A more recent metaanalysis included data from three randomized, controlled single-blind trials, published earlier, on the role of Indo-Mediterranean-style foods and nutrients in the prevention of CVDs, including HF [67]. The intervention and control groups were compared for behavioral risk factors, food intake, fatty acid intake, and on the ratio of PUFA to flavonoid intake in the two groups ($N = 1446$ vs 1320). At baseline, all the parameters of HF showed no significant differences between the intervention and control group. However, during a follow-up of two years, left ventricular strain [odds ratio (OR): 0.57, $P < .01$], left ventricular hypertrophy (OR: 0.69, $P < .01$), and NYHA class II–IV HF (OR: 0.59, $P < .05$) were significantly reduced in the intervention group compared to the control group. The incidence of cardiac arrhythmias also significantly declined in the intervention group compared to the control group (OR: 0.49, $P < .01$) [67]. Total mortality due to CVDs was significantly lower in the intervention group compared to the control group. It is clear that eating an Indo-Mediterranean-style diet, which includes rich sources of omega-3 fatty acids, flavonoids, and

polyphenolics, can cause a significant decline in pre-HF symptoms as well as in arrhythmias, possibly owing to the anti-inflammatory effects of such diets. In most controlled trials and in metaanalyses of studies of micronutrients such as omega-3 fatty acids, many confounders are not considered, leading to negative results [59,73,77]. This may be an important cause of variations in the reduction in cardiovascular morbidity and mortality in patients with acute CAD and among subjects at high risk of CVDs, who often change their diets.

Randomized, controlled clinical trials using Mediterranean-style diets, which are characterized by a low omega-6/omega-3 fatty acid ratio, revealed that treatment with such diets caused a significant decline in cardiovascular events in all the three trials [78–82]. Epidemiological studies also indicate that a high omega-6/omega-3 fatty acid ratio in the diet decreases the risk of cardiovascular events [83,84]. The role of omega-3 fatty acids along with a high omega-6/omega-3 fatty acid ratio has been emphasized by many experts for health promotion [85–87]. A diet with a high omega-6/omega-3 ratio may be associated with greater mortality due to NCDs (Tables 11.3 and 11.4) [84].

Effects of omega-6 and omega-3 polyunsaturated fatty acids in diabetes mellitus

The prospective Kuopio Ischaemic Heart Disease Risk Factor Study of 2189 men was undertaken for an average follow-up of 19.3 years, during which 417 men developed diabetes mellitus [45]. Those with higher estimated delta-5 desaturase

TABLE 11.3 Food intakes and omega-6/omega-3 fatty acid ratio in the diet in relation to causes of death due to non-communicable diseases (NCDs).

Cause of death	Prudent diet	Western-type diet	Total foods	Score	Omega-6/omega-3 ratio
N = 1385	Men (Mean ± SD) (g/day)				
Injury—accidents (*N* = 215)	892 ± 252	202 ± 22	1094 ± 302	7.93 ± 2.8	31.3 ± 5.3
Communicable diseases (*N* = 372)	806 ± 237	256 ± 28	1062 ± 198	7.26 ± 2.7	38.2 ± 6.6
NCDs					
Malignant (*N* = 77)	715 ± 241	412 ± 53	1127 ± 311	6.44 ± 2.5	42.2 ± 6.8
Circulatory (*N* = 406)	757 ± 245	437 ± 47	1194 ± 318	6.81 ± 2.6	45.3 ± 8.3
Chronic lung diseases (97)	705 ± 202	405 ± 41	1110 ± 302	6.25 ± 2.2	42.0 ± 7.4
Kidney diseases (*N* = 163)	617 ± 188	505 ± 55	1122 ± 325	5.72 ± 1.8	41.8 ± 6.1
Diabetes (*N* = 23)	605 ± 175	522 ± 61	1127 ± 334	5.65 ± 1.7	41.6 ± 5.7
Kendall's Γ	0.045*	0.048**	0.025	0.041*	0.042*
N = 837	Women (Mean ± SD) (g/day)				
Injury-accidents (*N* = 139)	822 ± 234	186 ± 23	1008 ± 224	8.40 ± 2.2	25.5 ± 5.7
Communicable diseases (*N* = 194)	736 ± 237	218 ± 33	954 ± 201	7.51 ± 1.9	34.5 ± 5.6
NCDs (*N* = 502)					
Malignant (*N* = 54)	657 ± 197	186 ± 23	962 ± 221	6.70 ± 1.8	41.6 ± 6.8
Circulatory (*N* = 240)	655 ± 205	218 ± 33	987 ± 218	6.68 ± 1.7	44.5 ± 7.5
Chronic lung diseases (*N* = 95)	660 ± 180	305 ± 35	1029 ± 180	6.12 ± 1.3	40.0 ± 6.5
Renal diseases (*N* = 87)	565 ± 155	382 ± 48	995 ± 165	5.57 ± 1.1	39.7 ± 6.8
Diabetes (*N* = 26)	553 ± 146	380 ± 130	940 ± 153	5.53 ± 1.1	40.0 ± 6.5
Kendall's Γ	0.041*	387 ± 135	0.024	0.043*	0.041*

*$P < .01$; **$P < .001$. *SD*, Standard deviation.
Source: Modified from Fedacko J, Vargova V, Singh RB, Anjum B, Takahashi T, Tongnuka M, et al. Association of high ω-6/ω-3 fatty acid ratio diet with causes of death due to non-communicable diseases among urban decedents in North India. Open Nutraceuticals J 2012;5:113–23.

TABLE 11.4 Multivariate logistic regression analysis for association of food and nutrient intakes with risk of death from non-communicable diseases, after adjustment of age and body mass index among men and women.

Risk factor	Odds ratio (95% confidence interval)	
	Men	Women
Prudent foods	1.11 (1.06–1.18)**	1.09 (1.04–1.16)**
Fruit, vegetables, legumes, and nuts	1.07 (1.02–1.12)**	1.05 (0.99–1.11)**
Western-type foods	1.02 (0.95–1.09)*	1.00 (0.94–1.06)*
Meat and eggs	1.00 (0.94–1.06)*	0.98 (0.93–1.04)*
Refined foods	0.98 (0.91–1.05)*	0.95 (0.89–1.02)*
Omega-6/omega-3 fat ratio	1.12 (1.01–1.19)**	1.11 (1.00–1.18)**

*$P < .01$; **$P < .001$.
Modified from Fedacko J, Vargova V, Singh RB, Anjum B, Takahashi T, Tongnuka M, et al. Association of high ω-6/ω-3 fatty acid ratio diet with causes of death due to non-communicable diseases among urban decedents in North India. Open Nutraceuticals J 2012;5:113–23.

activity (extreme-quartile HR: 0.55, $P < .001$) and higher concentrations of total n-6 PUFA (HR: 0.54, $P < .001$), LA (HR: 0.52, $P < .001$), and AA (HR: 0.62, $P = .007$) had a lower risk, and those with higher concentrations of GLA (HR: 1.28, $P = .021$) and DGLA (HR: 1.38, $P = .005$) and higher delta-6 desaturase activity had a higher (HR: 1.50, $P < .001$) multivariate-adjusted risk of diabetes. Zinc levels were the main modifier of the association with GLA in terms of diabetes risk, with a higher risk observed among those with serum zinc levels above the median ($P = .04$). It is possible that higher serum total n-6 PUFA, LA, and AA levels and estimated delta-5 desaturase activity were associated with a lower risk of incident diabetes and that higher GLA and DGLA concentrations and estimated delta-6 desaturase activity were also associated with a higher risk. A higher serum zinc concentration modified the association of GLA with the risk of diabetes [45]. Omega-3 fatty acids have also been found to be useful among patients with impaired glucose metabolism, insulin resistance with dyslipidemia, and gestational diabetes [88–92]. The effects of omega-3 fatty acids on glucose metabolism and lipid levels was improved in combination with vitamin D in patients with gestational diabetes [93]. In a metaanalysis, plant-derived PUFA did not significantly affect fasting glucose (−0.01 mmol/L) but lowered fasting insulin by 2.6 pmol/L and lowered homeostatic model assessment-insulin resistance (HOMA-IR) by 0.12 unit [94]. A 5% increase in energy from PUFA significantly reduced insulin by 5.8 pmol/L but did not reduce glucose or HOMA-IR. Evidence from randomized controlled trials indicated that plant-derived PUFA as an isocaloric replacement for saturated fatty acids or carbohydrates probably reduces fasting insulin and HOMA-IR in populations without diabetes [94]. In most studies, a mixture of omega-3 and omega-6 fatty acids in the form of plant-derived oils was used; thus that potential differences in effect between them could not be examined. Another metaanalysis involving 20 prospective cohort studies, including 39,740 adults, revealed that omega-6 fatty acid and its biomarkers were associated with incident type 2 diabetes [95]. The levels of LA ranged from 8.3% of total fatty acids in erythrocyte phospholipids to 54.5% in plasma cholesterol esters. The highest percentage of AA was found in erythrocyte phospholipids (17.0%), and the lowest percentage was found in the adipose tissue (0.3%). The highest versus lowest level of LA markers in each compartment (phospholipids, plasma or serum, cholesterol esters) except adipose tissue was associated with a 35% lower risk of type 2 diabetes. In contrast, only AA in plasma or serum was inversely associated with the risk of type 2 diabetes. In a recent metaanalysis including 13 studies consisting of 36,542 subjects, higher omega-3 PUFA levels in diets or blood were associated with a 26% reduction in the risk of metabolic syndrome (OR: 0.74), which was more clear among Asians (OR: 0.69) than in other populations [96]. It seems that higher intakes of omega-3 PUFA but not omega-6 PUFA was associated with a lower risk of metabolic syndrome; this adds to the current body of evidence on the metabolic health effects of circulating and dietary omega-3 fatty acids that may be due to other confounders. It is possible that if the LA level in blood and adipose tissue can provide an objective assessment of dietary intake of this fatty acid, the dietary content of LA may be important for glycemic control and prevention of type 2 diabetes.

Effects of fatty acids in dementia

The WHO estimate of the number of people living with dementia worldwide is approximately 50 million, which is projected to increase to 75 million by 2030 [97]. Epidemiological studies report a close correlation of cognitive impairment and development of dementia with diet and lifestyle factors, such as physical inactivity, unhealthy diet, short sleep,

night shift work, tobacco use, and harmful use of alcohol [97–99]. Apart from these risk factors, cardiometabolic diseases—obesity, hypertension, diabetes, stroke, and hypercholesterolemia—as well as depression are also associated with an increased risk of dementia. The risk of dementia can also increase if the person does not get adequate sleep, enough physical activity, and Mediterranean-style foods in the diets. Recently, caloric restriction or intermittent fasting, circadian restricted eating, supplementation of cocoa and probiotics, yoga therapy, and moderation in alcohol intake have been found to have protective effects against dementia. Previous studies indicate that omega-3 fatty acids, AA, vitamin E, B vitamins, magnesium, vitamin D, flavonoids, and amino acids may also protect from dementia [12,97]. However, sweets, syrups, sugary foods, rapidly absorbed refined fast foods, saturated fat, trans fat, and red and preserved meats may increase the risk of dementia [12,97].

In a cohort study during 22,288 person-years of follow-up (1992–2015), 1164 subjects with dementia were identified, 530 with Alzheimer's disease, and 256 with vascular dementias [100]. After adjustment for demographic, lifestyle and dietary factors, higher concentrations of AA were significantly associated with a lower risk of total dementia and Alzheimer's disease. Omega-3 PUFA or LA showed no such association with incident dementia. It is possible that among elderly adults, higher circulating levels of AA may be inversely associated with the risk of total dementia [100]. These results highlight the need to identify mechanisms influencing circulating AA levels that could be effective for the prevention of dementia later in life. In a metaanalysis, all studies that reported on the association between the n-6/n-3 ratio and dementia or cognitive decline were selected [101]. In the 13 animal studies that we examined, the dietary n-6/n-3 ratio was shown to affect brain composition, Alzheimer's disease pathology, and behavior. The 14 studies in humans that fulfilled the selection criteria (seven prospective studies, three cross-sectional studies, one controlled trial, and three case-control studies) provided some limited evidence of an association between the n-6/n-3 ratio and cognitive decline and incidence of dementia.

There appears to be growing evidence of a positive association between dietary AA, the n-6/n-3 ratio, and the risk of Alzheimer's disease [100,101]. Alzheimer's disease is characterized by formation of amyloid plaque in the neurons with neuronal degeneration and is the most common cause of dementia in older adults [97]. Previous cohort studies indicate that increased intake of fish and PUFA may reduce the risk of cognitive impairment, dementia, and Alzheimer's disease [102–104]. Neither apo-lipoprotein E (APOE) genotype nor polymorphisms in 11 other genes associated with Alzheimer's disease were found to modify the inverse relationship between fish intake and risk of cognitive decline in the pooled analysis of the five cohorts [105]. The pooled analysis of five large prospective cohort studies (Three-City Study, Nurses' Health Study, Women's Health Study, Chicago Health and Aging Project, and Rush Memory and Aging Project) that followed a total of 23,688 older (ages ≥ 65 years) participants (88% women) for 3.9–9.1 years found slower rates of decline in episodic memory and global cognition with increasing fish intakes [105]. Previous studies have also indicated that the effect of fish or PUFA consumption on cognition may be dependent on APOE genotype [102,103] Of three common APOE alleles (epsilon 2 [ε2], ε3, and ε4), the presence of the APOE ε4 (E4) allele has been associated with increased risk and earlier onset of Alzheimer's disease [104]. It was found that long-chain omega-3 PUFA supplementation did not increase plasma omega-3 concentrations to the same extent in E4 carriers as in noncarriers [106] and that DHA metabolism differs in E4 carriers compared to noncarriers, with greater oxidation and lower plasma concentrations in E4 carriers. However, preclinical studies suggest that long-chain omega-3 fatty acids may have neuroprotective effects, potentially through mitigating neuroinflammation, improving cerebral blood flow, and/or decreasing aggregation of amyloid [107]. In a recent metaanalysis of cohort studies, each one-serving increase in fish intake per week was found to be associated with a 5% lower risk of dementia and a 7% lower risk of Alzheimer's disease [102]. This study found that a 100-mg/day increase in dietary DHA intake was associated with a lower risk of dementia (−14%) and Alzheimer's disease (−37%). Results from two large cohort studies published after this dose–response metaanalysis showed blood DHA concentration to be positively associated with cognitive performance in adults [103,104].

There have been three randomized, controlled trials that examined the effect of omega-3 supplementation on the risk of cognitive decline in elderly adults [108]. There was no evidence of any benefits of omega-3 fatty acids on measures of cognitive functions in these clinical trials. However, in a more recent metaanalysis, including seven trials conducted in healthy participants, there were positive effects of long-chain omega-3 supplementation on measures of cognitive outcomes in all studies but the second longest and the two largest trials [109]. Effects of long-chain omega-3 supplementation in individuals with mild cognitive impairment were also examined in another seven trials, in which all but three trials showed a significant benefit on measures of cognitive function or specific memory tasks [109]. It seems that the data favor a role for diets that are rich in long-chain omega-3 fatty acids in slowing cognitive decline. However, larger trials with longer follow-up periods may be necessary to determine whether there is a consistent beneficial effect of omega-3 supplementation in older individuals with normal or declining cognitive functions. Omega-3

fatty acids have also been tried with possible beneficial effects among patients with fatty liver diseases, rheumatoid arthritis, autism, depression, bipolar disorder, schizophrenia, and anxiety symptoms in depression and psychosis [107,110–116]. The role of the omega-6/omega-3 fatty acid ratio has also been described in regard to various NCDs: cancer, chronic pulmonary diseases, bone and joint diseases, kidney diseases, ophthalmological disorders, neuromuscular diseases, and gut health [12].

In brief, oxidative stress and inflammation appear to be basic factors in the pathogenesis of CVDs and other chronic diseases. It is possible that increased intake of PUFA, omega-3 fatty acids (EPA, DHA, and ALA), as well as omega-6 fatty acids (LA and AA) may decrease inflammation, thus providing benefits in many NCDs. Therefore the balance of omega-6 and omega-3 fatty acids in conjunction with AA, polyphenolics, and flavonoids could be important for primary and secondary prevention of NCDs. A more practical approach would be to consume functional foods that are rich in these nutrients, such as vegetables, fruits, whole grains, nuts, seeds, fish, and poultry in conjunction with blended oils, such as mustard oil or rape seed oil or canola oil and flaxseed oil, along with oils that contain polyphenolics (olive oil, palm oil) to achieve added health benefits that were found prevalent in evolutionary diets. It is the tissue that is mainly involved in the mechanism of inflammation; hence it is the main issue in the pathogenesis and prevention of NCDs. In view of epigenetic and genetic variations the optimal omega-6/omega-3 ratio would vary with the disease and the population under consideration. If the tissue concentration of the omega-6/omega-3 fatty acid ratio is 1:1 along with other nutrients, such as AA and flavonoids, that are in the proper ratios, high LDL cholesterol (unoxidized) may be neutral without any evidence of endothelial dysfunction. The Indo-Mediterranean-style diets, which contain pulses and spices along with millets, may prove to be even more beneficial and considerably healthier in combating the obesogenic environment and in decreasing the risks of the NCDs than conventional, modern dietary recommendations.

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Chapter 12

Nutritional modulators of preconceptional and perinatal factors for primordial prevention of non-communicable diseases: the role of a millet-based diet rich in functional foods

Ram B. Singh[1], Jan Fedacko[2], Viliam Mojto[3], Rie Horiuchi[4], Mira Dewi[5], Shaw Watanabe[6], Poonam Tiwari[7], Mukta Singh[8], Divyank Sharma[9] and Ahmad Sulaeman[5]

[1]Halberg Hospital and Research Center, Civil Lines, Moradabad, India, [2]Department of Internal Medicine, PJ Safaric University, Kosice, Slovakia, [3]3rd Department of Internal Medicine, Faculty of Medicine, Comenius University, Bratislava, Russia, [4]Department of Food Sciences and Nutrition, School of Food Science and Nutrition, Mukogawa Women's University, Nishinomiya, Japan, [5]Department of Community Nutrition, Faculty of Human Ecology, IPB University, Bogor, Indonesia, [6]Clinical & Functional Nutriology, Life Science, Tokyo, Japan, [7]Division of Nutrition, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India, [8]Department of Home Science, Mahila Maha Vidyalaya, Banaras Hindu University, Varanasi, India, [9]Halberg Hospital and Research Institute, Moradabad, India

Introduction

The United Nations (UN) "Decade of Action on Nutrition" is an initiative covering the years 2016−25 to eradicate hunger, end malnutrition in all its forms—undernutrition, micronutrient deficiencies, overweight, and obesity—and reduce the burden of diet-related NCDs in all age groups [1]. In most developing countries, including India, undernutrition is still common, and one-third of children and women have iron, calcium, and protein deficiencies [1−3]. According to the World Health Organization (WHO), malnutrition involves deficiencies, excesses, or imbalances in a person's intake of energy and/or nutrients [2]. The term *malnutrition* addresses three broad groups of undernutrition: wasting (low weight-for-height), stunting (low height-for-age), and underweight (low weight-for-age) [2]. The modern pandemic of micronutrient-related malnutrition includes deficiencies in micronutrients—essential fatty acids, amino acid, vitamins, and minerals or excess of micronutrient—and overweight, obesity, and diet-related non-communicable diseases (NCDs), including heart disease, stroke, diabetes, and some cancers [2−4]. Cardiovascular diseases (CVDs) combined with obesity and diabetes are considered to be cardiometabolic diseases (CMDs).

Malnutrition in all its forms, including undernutrition and inadequate micronutrients with overweight and obesity results in diet-related NCDs [5−10]. A systematic analysis of global, regional, and national levels and trends in maternal mortality between 1990 and 2015, with projections to 2030, have also been reported by the UN Maternal Mortality Estimation [7]. The double burden of diseases related to undernutrition and overnutrition is a challenge for the WHO as well as for the Food and Agriculture Organization (FAO), because despite adequate food availability, the burden is increasing [2,10−20]. It should be emphasized that 1.9 billion adults are overweight or obese, while 462 million are underweight [2]. The WHO recommendations on calcium supplementation before pregnancy for the prevention of preeclampsia and its complications and use of ferritin concentrations to assess iron status in individuals and populations are quite efficient [2,10]. Considering that 38.3 million children are overweight or obese, whereas 47 million children under 5 years of age are wasted, 14.3 million are severely wasted, and 144 million are stunted [1,2,10], undernutrition could be the underlying cause of around 45% of deaths among children under 5 years of age. These deaths occur mostly

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in low- and middle-income countries; at the same time, these countries, have high rates of childhood overweight and obesity [1−6]. The developmental, economic, social, and medical impacts of the global burden of malnutrition are serious and lasting for individuals and their families, for communities, and for countries [7−20]. However, prevention goals are unlikely to be achieved unless preconception factors and perinatal nutrition are given due consideration in prevention programs [18−30]. Prevention of malnutrition should begin at its origin, during the preconception period as well as during pregnancy, for prevention of malnutrition in offspring and in pregnant women for primordial prevention of NCDs [21,22]. This review aims to highlight the role of malnutrition in the pathogenesis and prevention of NCDs with emphasis on preconception factors and nutrition of mother and fetus.

Preconception nutrition of the father and mother

There is an emerging consensus that the period around conception is critical in the development of health or emergence of NCDs [21,22,29−31]. This idea has evolved from both animal and human studies ranging across different environmental exposures from the quality of maternal and paternal nutrition to assisted reproductive technology [29−31]. The stages of the periconceptional period may be defined as (1) gamete maturation, (2) fertilization, and (3) development of early embryo to fetus. In view of the WHO advice on a "life-course approach" to preconception and perinatal factors, these risk factors appear to be important for achieving population health goals [21,22,29−31]. The studies indicate that nutrient and energy supplementations to parents may counteract malnutrition via genetic and epigenetic alterations, which may increase immunity and health and may be helpful in the prevention of CVDs and diabetes in adult life [21,22]. WHO experts have also declared a life-course approach to be essential for achieving the population health goals of the UN 2030 Agenda for Sustainable Development [21].

Most of the CMDs have a family component that depends on the interaction of genes and the internal and external nutritional environment to which the individual is exposed, especially during fetal life [23−29]. Recent experiments in mice and rats indicate that diet and other lifestyle factors of the father and mother during and before conception can influence the health and behavior of the offspring [22,29,30]. A maternal high-fat diet fed to mice caused a significant increase in body length and a reduction in insulin resistance [30,31]. It seems that diets that are high in saturated fat and have a high glycemic index have adverse effects on mother and fetus, predisposing to adverse effects with a future risk of CMDs [32−35]. It is proposed that during spermatogenesis or oogenesis, apart from in vitro environmental factors, reprogramming of methylation profiles by environmental factors such as diet, activity, mental stress, tobacco, alcohol, and/or pollutants can affect imprinted genes during or before conception, resulting in physiological and metabolic alterations in the fertilized egg and later in the offspring [36−39]. The function of human spermatozoa depends upon the availability of progesterone release by cumulus cells surrounding the egg, which attracts the spermatozoa toward the egg and helps them penetrate the egg's protective coating [38]. Progesterone induces Ca^{2+} influx into spermatozoa and triggers multiple Ca^{2+}-dependent physiological responses that are essential for successful fertilization [38]. In this context, the fatty acid and antioxidant content composition of the sperm's flagellum and of coating of the oocyte appear to be important to allow penetration of the oocyte by the sperm, resulting in fertilization [37−41]. The antioxidant activity of tea, herbs, and nutrients has been demonstrated by many experts [42−44]. Unhealthy lifestyle features such as tobacco smoke and stress may produce oxidative stress, damaging the sperm in the father and ova in the mother, producing an unhealthy embryo [45,46]. Therefore unhealthy diet and lifestyle of the father and mother may predispose the offspring to cardiometabolic risk [37−46] (Fig. 12.1).

A chronic high-fat diet in rat fathers programs beta cell dysfunction in female offspring and induces obesity and insulin resistance among offspring relative to controls [30]. This diet altered the expression of 642 pancreatic islet genes in adult offspring ($P < .01$). Genes belonged to 13 functional clusters, including cation and ATP binding, cytoskeleton, and intracellular transport. A pathway analysis of 2492 genes, broadly differentially expressed, demonstrated the involvement of Ca-MAPK and MnT signaling pathways, apoptosis, and cell cycle. Hypomethylation of the *Il13ra2* gene showed the highest (1.76-fold) difference in expression along with a nongenetic, intergenerational transmission of metabolic sequelae of a high-fat diet from father to offspring for the first time [30]. However, the effects of Mediterranean style diets and healthy lifestyle on genome and epigenome have not been well studied, although beneficial effects of such diets and lifestyle have been observed in clinical studies [45−50]. Such studies are desirable in humans to have healthy fetuses and therefore a healthy infant and possibly healthy adult for primordial prevention of NCDs.

Further studies have revealed that maternal diet and other lifestyle factors can strongly influence embryonic development and fetal outcomes, including altering the molecular biological responses of the embryo and biasing the offspring sex ratio within the placenta [51]. Alterations in the nutritional environment of the uterus may also lead to profound developmental origin of health promotion and disease outcomes into adulthood. It also includes increased risk

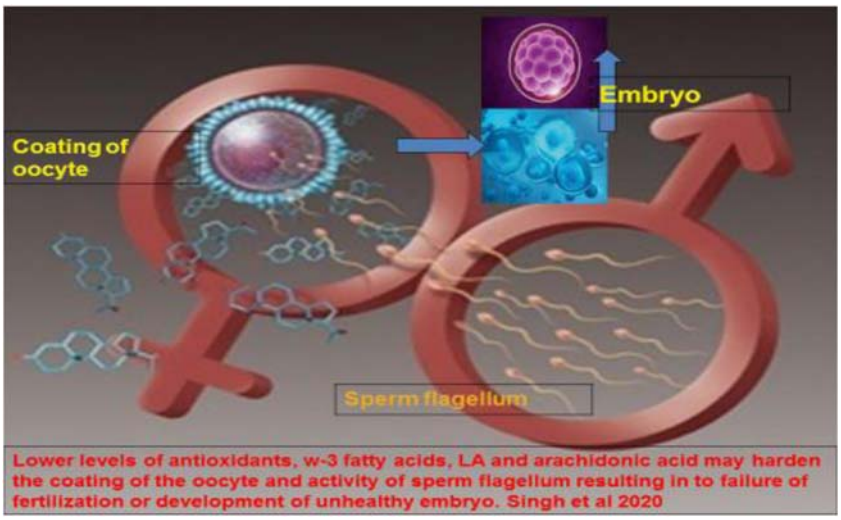


FIGURE 12.1 Ova of female showing liberation of progesterone to attract the sperm during fertilization. Progesterone release by cumulus cells surrounding the egg attracts the spermatozoa toward the egg and helps them penetrate the egg's protective coating. Omega-3 fatty acids, linoleic acid, arachidonic acid, and antioxidants may maintain the cell membrane integrity of the egg and the motility and total health of the sperm, producing healthy fertilization of the ovum [37–44].

of NCDs, more among males in general than among females. Experimental studies have shown that female mice maintained on a very high-fat diet produce more sons than those on a chow-based and low-fat, high-carbohydrate diet, with the latter group producing more daughters [51]. However, neither the underlying mechanisms that contribute to this shift in offspring sex ratio nor when they occur during pregnancy have been determined. It is known that maternal diet and other factors influence the secondary sex ratio in a variety of species, including humans [51,52]. It seems that fetal sex and maternal diet influence patterns of gene expression in the mouse placenta, which serves as the primary nutrient acquisition and communication organ between the mother and her developing fetus [30,31,51,52]. These adaptations to diet that are observed as changes in gene expression and epigenome are likely to provide insight into how the placenta reacts in relation to health or diseases [51,52]. It is possible that the fetus is susceptible to environmental alterations in nutrient availability during pregnancy and that the response of male and female embryos may be in different mechanisms in regard to the environmental factors. Thus the period around conception, embracing gamete maturation and early embryogenesis, may be the most vulnerable period for development of future health or diseases [51,52].

It is possible that paternal diet and lifestyle, maternal overnutrition and obesity, maternal undernutrition, and assisted reproductive technology are important determinants of future outcome. These environmental exposures and paternal lifestyles can change the epigenome of the sperm and may influence both the development of the embryonic program and the health of future generations. There are diverse epigenetic, cellular, and physiological mechanisms that mediate to alter gene expression and cellular signaling and function in the conceptus, affecting offspring growth and metabolism and leading to increased risk for cardiometabolic and neurological disease in later life [51,52].

The parental genomes are superseded by the new embryonic genome and the establishment and differentiation of early cell lineages from a pluripotent cellular stock required for the development of the new organism and new offspring [52–54]. These processes may involve significant epigenetic, cellular, and metabolic activity related to fertilization [53–55]. The maternal oviduct and uterine lumens can facilitate the stepwise progression in gamete and embryo maturation, culminating in implantation [56]. The molecular processes that ensure this silent transcription remain under development because the genomes of the sperm and egg are hypermethylated. The genome may gradually become transcriptionally activated during the union in the prepared environment of the egg, initiating their epigenetic genomic reprogramming into a totipotent zygote [51–53]. The sex-specific processes result in sperm and eggs with disparate epigenomes during gametogenesis, both of which require drastic reprogramming to establish the totipotent genome of the zygote and the pluripotent inner cell mass of the blastocyst. It is clear that the DNA and histone modifications, activation and repression of retrotransposons, and cytoplasmic localizations, are known to influence the activation of the mammalian genome at the initiation of new life.

It has also been found that restricting the food intake of male rodents reduced their body weight and fertility, increased sperm oxidative DNA lesions, and reduced global sperm methylation [54]. During undernutrition, increased paternal supplementation of vitamin and antioxidants repaired the deficit, normalized preexisting oxidative sperm DNA lesions in fathers, and prevented early growth restriction, fat accumulation, and dyslipidemia in offspring. It is clear that paternal undernutrition reduces postnatal growth but increases the risk of obesity and metabolic disease in the next generation. However, repairing the micronutrient deficit, during this period of undernutrition restores the metabolic

health of the offspring [54]. However, humans adapt in such a way that despite undernutrition and unhealthy sperm, they continue to fertilize the women's ovum to evolve and continue generation without any decline in rates of fertility, which is apparent from the population status in developing countries.

Paternal or maternal diet and lifestyle factors, such as nutritional quality, can influence parental physiology and metabolism as well as outcome in different ways [54–56]. It seems that diet can modify oviduct and uterine transport activities and thereby alter the nutrient composition of luminal compartments and the environment experienced by early embryos [57]. Unhealthy diets in the father can predispose a similar defect in the seminal tubule and sperm microenvironment [58]. In view of the biological and the clinical implications observed for the health of the next generation, there is a need for public awareness because most women do not know when they are going to get pregnant. It is possible that these findings related to environmental susceptibility of periconceptional stages have contributed to the call for consideration of the preconception health of both partners before pregnancy [59–61]. There is a need to determine diet and lifestyle factors for both father and mother in planning pregnancy to prevent malnutrition in the fetus and newborn [11,12,61–64].

It has become apparent that these periconceptional stages in reproduction are vulnerable to environmental risk factors that may cause changes in the fetus either through perturbation or via adaptive compensatory responses. These complications may persist beyond the periconceptional period and may influence the phenotype across the lifespan as the result of overnutrition and undernutrition and of assisted reproductive treatment in human and animal models [11,12,59–61]. Fleming et al. have proposed that environmental factors, including diet, physical activity, stress, body composition, and metabolism of both father and mother, can influence the health and chronic disease risk of people throughout their lives [61]. Experimental, epidemiological, and clinical studies have identified the period around conception as being crucial for the processes that mediate parental influences on the health of the next generation. It is possible that the maturation of gametes during the early embryonic development is strongly influenced by parental diets and lifestyle that can influence long-term risks in offspring for cardiovascular, metabolic, immune, and neurological morbidities, often termed developmental programming [65]. It seems that induction of a disease during the periconceptional period increases risk arising from four broad exposures: maternal undernutrition, maternal overnutrition and obesity, related paternal factors, and the use of assisted reproductive treatment [61]. Studies in both humans and animal models have demonstrated the underlying biological mechanisms, including epigenetic, cellular, physiological, and metabolic processes. The evidence for periconceptional effects on lifetime health seems quite compelling. This calls for new guidance on preparation and planning of pregnancy, beginning before conception, to protect the health of the fetus, infant, and child [11,12].

It is well known that maternal overnutrition and obesity induced by a Western style diet have been associated with reduced fertility and a greater risk of obesity in children, mediated by increases in maternal metabolites, such as those arising in hyperglycemia and hyperinsulinemia, leading to increased placental transport of macronutrients and a subsequent increase in fetal growth in late gestation [66–68]. However, choline prevented fetal overgrowth and normalized placental fatty acid and glucose metabolism in a mouse model of maternal obesity [68]. Therefore the periconceptional period is critical in the transmission of disease risk from obese mothers to offspring. Robker et al. demonstrated that obese women transfer excess metabolites and hormones such as insulin, triglycerides, leptin, and lactate from the circulation into ovarian tissue and especially the follicular fluid of maturing follicles [69]. These metabolites subsequently accumulate within oocytes and influence their metabolic function, leading to decline in embryonal developmental potential after fertilization [70]. Within human follicular fluid, an increase in accumulation of lipids coincides with increased inflammatory mediators, which may contribute to the decline in potential of embryos from obese mothers [71]. A high body mass index in the mother causes a reduction in human oocytes, which may lead to poorer-quality embryos with excess triglycerides and diminished glucose consumption [72].

Malnutrition during pregnancy

The WHO and UNICEF currently recommend that pregnant women take iron supplements to reduce their risk of anemia, and the role of maternal multiple micronutrient therapy for protecting the fetus has been confirmed [18]. Early life nutritional exposures combined with even modest changes in lifestyle in adult life can result in increased risk of chronic diseases [23]. Although much of the focus on the developmental origins of disease has been on birth size and growth in postnatal life, the availability of energy and protein during these critical developmental periods and micronutrient deficiencies may also play an important role in fetal growth and development [21–25]. Apart from energy, micronutrient status in fetal and early life may alter metabolism, vasculature, and organ growth and function, leading to increased risk of CMDs, including adiposity, altered kidney function, and, ultimately, type 2 diabetes and CVDs.

All the metabolic activities that regulate tissue growth, function, and homeostasis, including cell signaling, proliferation, differentiation, and apoptosis, need essential vitamins and minerals, which are dietary components that are required in small quantities [73]. These fundamental physiological functions in early life enable the fetus to develop and mature into a healthy neonate. Minerals, antioxidants, and vitamins provide support at all the stages of maternal, placental, and fetal interaction to enable a healthy gestation. These micronutrients, accessible from the diet, are essential for physiological activity [21–25,73]. Micronutrient status varies widely throughout pregnancy and across communities and populations as well as in countries. Women in lower-income countries and also possibly in middle-income countries often enter pregnancy malnourished, and the demands of gestation can exacerbate micronutrient deficiencies with health consequences for the fetus [21–25,73]. Examples of efficacious single-micronutrient interventions include folic acid to prevent neural tube defects, iodine to prevent cretinism, zinc to reduce preterm birth, and iron to reduce the risk of low birth weight. Folic acid and vitamin D might also increase birth weight.

Apart from these findings, there is more conclusive evidence that energy, iron, folic acid, calcium, iodine, zinc, and vitamin D deficiencies coexist with pregnancy, leading to complications and deaths of mothers, fetuses, and newborns [18–23,73]. The results of cohort studies on the association between exposure to famine and risk of CMDs in later life have been confirmed [74–79]. A recent meta-analysis included 39 studies with a total of 81,504 participants [74]. Total famine exposure in 14 studies from 10 articles for fetal famine exposure, 20 studies from 7 articles for childhood famine exposure, and 5 studies from 3 articles for adolescent and adult famine exposure were included in this meta-analysis. The results showed that famine exposure significantly increased the risk of metabolic syndrome for early life famine exposure [odds ratio (OR): 1.27], fetal famine exposure (OR: 1.27), and childhood famine exposure (OR: 1.29) compared to nonexposed group [74]. Subgroup analyses showed that the result was consistent regardless of the study designs, definitions of metabolic syndrome, and causes of famine with or without adjustment for age, smoking, drinking, and physical activity. The results revealed that exposure to famine causing energy and nutrient deficiencies in early life can predispose individuals to metabolic syndrome in adult life [74]. Thus fetal exposure to famine may have long-term consequences in adulthood (Fig. 12.2).

Another cohort study included 8054 subjects (3422 males, 4632 females) from the cross-sectional China National Nutrition and Health Survey [75]. The results showed that as compared to the unexposed group, the female subjects had a significantly higher prevalence of obesity and central obesity, with ORs of 1.34 ($P = .022$) and 1.28 ($P = .008$), respectively. It is possible that fetal exposure to the Chinese famine increased obesity risk in adulthood, and the association was stronger in female and urban subjects [75]. A previous meta-analysis included 16 studies from 14 articles for early life famine exposure, 11 studies from 10 articles for fetal famine exposure, and 10 studies from 8 articles for childhood famine exposure [76]. Compared with unexposed group, the pooled RRs were 1.26, 1.27, and 1.32 for early life famine exposure, fetal famine exposure, and childhood famine exposure, respectively (Not given in the table but observed.). In subgroup analyses these mentioned associations were consistent in cohort studies, and studies conducted in Asia. This meta-analysis also confirmed the association between exposure to famine in early life and increased risk of hypertension in adulthood.

A more recent study found that both fetal exposure (OR: 1.249) and early-childhood exposure (OR: 1.360) were risk factors for hypertension in adulthood [77]. Meanwhile, in rural area, compared with the unexposed group, fetal exposure (OR: 1.401) and early-childhood exposure (OR: 1.460) were also associated with a greater risk of hypertension in adulthood. Apart from this, fetal exposure and early-childhood exposure to famine in women were associated with 36.0% and 31.9% increased risks for hypertension, respectively, according to the stratified analysis [77]. It is possible that fetal exposure to famine increases the risk for hypertension in adulthood. In another study, the prevalence of dyslipidemia among subjects in an unexposed group, a fetal-exposed group, a childhood-exposed group, and an adolescence-exposed group was 56.40%, 64.00%, 63.90%, and 63.90%, respectively [78]. Subjects who were exposed to famine in the fetal period (OR: 1.34), during childhood (OR: 1.44), or in adolescence had higher risks of dyslipidemia as adults after adjustment for potential confounders than the unexposed group. It seems that exposure to the Chinese famine in early life was associated with an increased risk of dyslipidemia in adulthood. It is possible that prevention of undernutrition in early life may be an appropriate recommendation to reduce the prevalence of later obesity, metabolic syndrome, diabetes mellitus, dyslipidemia, and hypertension [74–79].

Inadequate weight gain during pregnancy often results in low birth weight, which increases an infant's risk of dying [21–25]. Pregnant women also require more protein, iron, iodine, vitamin A, folate, and other nutrients [21–23]. Deficiencies in certain nutrients are associated with maternal complications and death, fetal and newborn death, birth defects, and decreased physical and mental potential of the child. It has been proposed that deficiencies in omega-3 fatty acids and flavonoids during pregnancy can decrease the performance of the arcuate nucleus and POMC (Pro-opiomelanocortin) neurons in the brain, resulting in greater appetite, excessive eating, and obesity [11,16]. Adequate energy intake and a

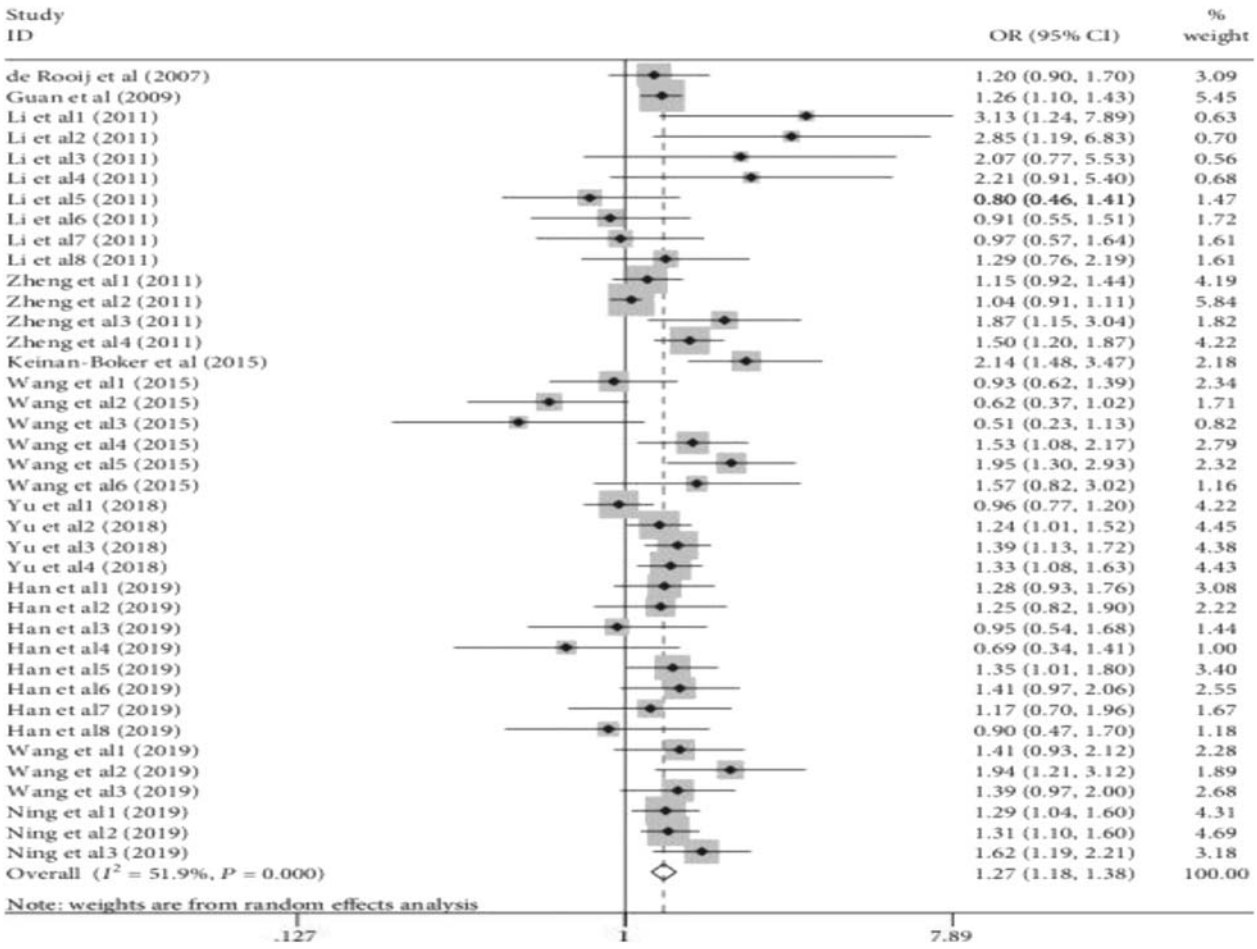


FIGURE 12.2 Forest plot showing exposure to famine and risk of metabolic syndrome in adult life.

diversified diet that includes fruit, vegetables, and animal products throughout the life cycle help to ensure that women enter pregnancy and lactation without deficiencies and obtain adequate nutrients during periods of heightened demand [21–25]. Some nutrient requirements, particularly of iron, folic acid, and vitamin A, are more difficult to achieve than others through food sources. Supplements with these nutrients are recommended in addition to improved diets. It may be prudent to promote fortified foods through counseling and social marketing in countries where foods fortified with iron, iodine, folic acid, or vitamin A are available and affordable. However, fish and nuts, the components of a Mediterranean style diet which is rich in amino acids, omega-3 fatty acids, vitamin A, and vitamin D (fish) could be helpful during the preconception and perinatal periods to provide multiple nutrients to the fetus and mother as well as the father to possess healthy sperm and ovum for physiological fertilization [25–27].

While diets with a high glycemic index predispose consumers to oxidative stress and inflammation, which may have adverse effects on the mother and fetus, Mediterranean style diets may provide an excess of micronutrients, which may be protective against micronutrient and macronutrient deficiency, oxidative stress, and inflammation and risk of CMDs [24–35]. Some of the longest life expectancies come from the Mediterranean Sea region. Additionally, countries such as those of Scandinavia (culinary cultures rich in seafood) have some of the lowest prematurity rates in the world (2%–6%). Women in these countries who do not consume fish-rich diets (i.e., they consume fewer than two servings of fish weekly) have premature birth rates that are comparable to those in fish-deficient countries [79]. In Norway, investigators compared Norwegian women with high and low fish consumption rates. The women who ate fish at least twice weekly had lower prematurity rates. Similar findings were reported in a study of Danish women. In this study, women who consumed fish as well as a healthful diet that was rich in olive oil or rapeseed oil and five or more services of fruits and vegetables daily had lower rates of both preterm and early preterm births. Fish oil is rich in antioxidants, omega-3 fatty acid, vitamin A, and vitamin D in particular, but there is clearly more benefit from fish in our diet, regardless of pregnancy [1–3].

Micronutrient deficiency as well as fat and protein deficiency have become a public health problem [10−12]. Epidemiological studies indicate a causal associations between micronutrient and energy deficiencies during fetal and early infancy with increased risk of CMDs, CVDs, and type 2 diabetes in later adult life [74−79]. Some investigators have raised concerns that micronutrient supplementation during pregnancy may increase perinatal mortality and cause adverse effects on the fetus [18−21]. However, there is a scarcity of studies examining the effects of micronutrient-rich diets on the fetus, mother, newborn, and infant [26].

Effects of dietary supplementation on health of mothers

Epidemiological studies indicate that dietary deficiencies during the preconception and perinatal period, can increase the risk of complications and maternal mortality among women [7,12,18]. The UN estimation for 171 of 183 countries revealed that global maternal mortality rate decreased from 385 deaths per 100,000 live births [80% uncertainty interval (UI): 359−427] in 1990 to 216 (80% UI: 207−249) in 2015, corresponding to a relative decline of 43.9% (80% UI: 34.0−48.7), with 303,000 (80% UI: 291,000−349,000) maternal deaths worldwide in 2015 [7]. The annual rate of reduction in mortality since 1990 ranged from 1.8% (80% UI: 0.0−3.1) in the Caribbean to 5.0% (80% UI: 4.0−6.0) in eastern Asia. For 2015, mortality ranged from 12 deaths per 100,000 live births (80% UI: 11−14) for high-income regions to 546 (80% UI: 511−652) for sub-Saharan Africa. There would be a need for accelerated progress in the improvement of diet and lifestyle of women to eliminate preventable maternal mortality to achieve the sustainable development goals (SDGs) in most countries to meet the ambitious SDG 2030 target of United Nations of Organization (UNO) [7]. The majority of these complications and deaths during pregnancy occur as a result of malnutrition and infections as well as intake of Western-type foods, and they can be prevented via increased intake of Mediterranean-type foods, such as fish, pulses, fruits, leafy vegetables, nuts, and seeds [10−21,80−87]. Apart from adverse outcomes for the fetus and newborn, perinatal nutrition has adverse effects on the health of pregnant mothers [7,25,26,80,81]. Although the father's diet and lifestyle have been found to influence the health of the fetus and newborn, the husband's diet and lifestyle have no known adverse effects on the health of pregnant women.

Mediterranean style diets are rich in vegetables, whole grains, fruits, walnuts, olive oil, poultry, and fish with low amounts of red meat and butter [84,85]. Indo-Mediterranean diets are characterized by an excess of whole grains (millets, beans, wheat porridge), spices, and mustard oil along with vegetables, fruits, peanuts, and poultry, which may be more economical and nutritious for pregnant women [82,83]. There is a need for further clinical trials among pregnant women to determine the effects of such diets on complications of pregnancy as well as on the health of the fetus and newborn [25,86−93]. Since Western-type diets predispose consumers to adverse effects, such diets are important in the physiopathogenesis of malnutrition in the fetus and pregnant mother [94]. The role of nutrition in the health of fetuses and pregnant mothers has been emphasized by several experts [95−97]. Increased supplementation of flavonoids, essential fatty acids, and essential amino acids as well as other micronutrients during the perinatal period may decrease the nutritional risk factors and provide beneficial effects on the placenta, fetal development, and pregnancy [25,88−93,96,97]. It has been suggested that these diets and nutrients can also protect against obesity and metabolic syndrome, eclampsia, high blood pressure, and gestational diabetes as well as undernutrition in mothers and newborns if consumed before and during pregnancy [96,97].

In Japan, Horiuchi et al. have reported the nutritional impact of okara leaves on the nutritional status and health of children [98−100]. Okara leaves could be protective against high-sugar diets among patients with CVDs. They are rich in nutrients and contain nonsoluble and soluble fiber, calcium, protein. and minerals. Owing to high content of fiber, okara leaves are more nutritious than tofu and soy milk [99]. It is possible that okara leaves may also be mixed in the modified Mediterranean style diets to develop healthful diets for pregnant women, infants, and children [99]. There are only a few studies showing role of Mediterranean style diets in the prevention of complications of pregnancy. Of 7950 screened women, 1252 were randomized, and baseline data were available for 593 women in the intervention (93.3% follow-up: 553/593) and 612 in the control (95.6% follow-up: 585/612) groups [48]. The pregnant women in the intervention arm consumed more nuts [70.1% vs 22.9%; adjusted odds ratio (aOR): 6.8, $P \leq .001$] and extra-virgin olive oil (93.2% vs 49.0%; aOR: 32.2, $P \leq .001$) than controls; increased their intake of fish ($P < .001$), white meat ($P < .001$), and pulses ($P = .05$); and reduced their intake of red meat ($P < .001$), butter, margarine, and cream ($P < .001$). The results revealed that there was no significant decline in the composite maternal (22.8% vs 28.6%; aOR: 0.76, $P = .08$) or composite offspring (17.3% vs 20.9%; aOR: 0.79, $P = .14$) outcomes. However, there was a significant reduction in the odds of gestational diabetes by 35% (aOR: 0.65, $P = .01$) but not in other individual components of the composite outcomes. The weight gain in mothers was significantly lower (mean: 6.8 vs 8.3 kg; adjusted difference: −1.2 kg, $P = .03$) in the intervention group in comparison to the control group. There was no difference in any of the other maternal and offspring complications between both groups. When findings were pooled from the Effect of Simple,

Targeted Diet in Pregnant Women With Metabolic Risk Factors on Pregnancy Outcomes (ESTEEM) trial with similar trials using random effects meta-analysis, we observed a significant reduction in gestational diabetes [odds ratio (OR): 0.67, 95% CI: 0.53−0.84, $I^2 = 0\%$], with no heterogeneity (two trials, 2397 women). It is possible that a simple, individualized, Mediterranean style diet in pregnancy does not reduce the overall risk of adverse maternal and offspring complications but has the potential to reduce gestational weight gain and the risk of gestational diabetes [48]. However, in this study, the intervention diet did not stop the intake of Western-type foods, and the control group also received Mediterranean-type foods as general advice from the dietitians during antenatal follow-up.

Effects of a millet-based Indo-Mediterranean style diet on cardiometabolic disorders

A millet-based Indo-Mediterranean style diet could be most suitable for pregnant women to prevent CMDs such as eclampsia, hypertension, and gestational diabetes as well as undernutrition. The nutrient content in this designer's diet are given in Tables 12.1 and 12.2.

In a recent real-world clinical trial involving 60 subjects with type 2 diabetes mellitus, 400−500 g/day of whole grains, including 200−250 g/day of millets, were administered along with fruits, vegetables, and mustard oil for a period of 12 weeks [101]. All the patients received an 11-fold greater amount of a millet-based intervention diet, which increased from a mean of 21.36 ± 3.8 to 235.20 ± 23.6 g/day ($P < .001$) [101] (Table 12.3).

Treatment with a millet-based intervention diet for 12 weeks was associated with a significant reduction in fasting and 2-hour postprandial blood glucose and HbA1c indicating, that this diet can prevent diabetes. Mean levels of total cholesterol, very-low-density lipoprotein cholesterol, and triglycerides showed significant reduction compared to baseline levels. Proinflammatory cytokines; C-reactive proteins—tumor necrosis factor-alpha, and interleukin-6—also showed significant reduction after treatment with the intervention diet compared to baseline levels [101] (Table 12.4).

Apart from these benefits, systolic (127.33 ± 10.66 mm Hg vs 122.25 ± 5.07 mm Hg, $P < .001$) and diastolic blood pressures (87.83 ± 9.61 mm Hg vs 82.52 ± 8.03 mm Hg, $P < .001$) showed significant decline after 12 weeks compared to baseline levels [101]. In terms of parameters of oxidative stress, TBARS (thiobarbituric acid reactive substance), MDA (malondialdehyde), and diene conjugate levels decreased, and antioxidant vitamins A, E, and C and beta-carotene levels increased (Table 12.5).

Of 60 subjects with diabetes mellitus, 33 were females whose baseline levels of hemoglobin and serum calcium were lower than normal values. Interestingly, there was a significant increase in hemoglobin, iron, and magnesium levels after 12 week of the intervention diet compared to baselines levels. No significant changes were observed in these parameters among men and among total subjects, indicating that a millet-based diet can also prevent undernutrition (Table 12.6).

TABLE 12.1 Energy and macronutrient value of foods in the millet-based diet.

Ingredient	Amount (g)	Energy	Carbohydrate (g)	Fats (g)	Protein (g)
Millets	50	189	30.4	2.1	6.1
	100	378	60.8	4.3	12.3
Soy flour	30	130.2	9	6.6	11.4
	100	434	30	22	38
Brown rice	10	37	7.7	0.29	0.8
	100	370	77	2.9	8
Crushed peanuts	9	54.6	1.55	3.5	2.1
	100	607.14	17.72	39.63	23.65
Flax seeds	1	5.34	0.29	0.42	0.18
	100	534	29	42	18
Total in mentioned amounts		416.14	48.94	12.91	20.58
Total per 100 g		2323.1	214.5	110.8	99.95

TABLE 12.2 Micronutrient value of foods in the millet-based diet.

Ingredient	Amount (g)	Fiber (g)	Iron (mg)	Calcium (mg)	Magnesium (mg)	Zinc (mg)	Beta-carotene (μg)	Polyphenols (mg)	Flavonoids (mg)
Millets	50	4	1.4	15.5	40.5	1.2	16	136.5	0
	100	8	2.8	31	81	2.4	32	273	0
Soy flour	30	2.9	1.7	56.4	110.7	1.07	21.9	1.83	0.657
	100	9.7	5.82	188	369	3.58	73	6.13	2.19
Brown rice	10	0.38	0.056	0.3	3.9	0.071	0	1.84	0
	100	3.8	0.56	3	39	0.71	0	18.47	0
Crushed peanuts	9	0.93	0.27	6.93	0	0	0	38.5	13.7
	100	10.38	3.1	77	0	0	0	428.1	152.6
Flax seeds	1	0.27	0.05	2.55	3.92	0.043	0	0	0
	100	27.3	5.73	255	392	4.34	0	0	0
Total in mentioned amounts		8.48	3.4	81.68	159.02	2.38	37.9	178.6	14.3
Total per 100 g		59.1	18.01	554	881	11.03	105	725.7	154.7

TABLE 12.3 Food and nutrient intakes and physical activity scores before and after treatment with designer's diet.

Food and nutrient intake	Baseline	After 12 weeks	*P* value
Total fatty acids (g/day)	220 ± 11.05	218 ± 11.55	.145
Total visible fat (g/day)	24.66 ± 2.64	23.76 ± 2.54	.244
Total trans fat (g/day)	5.1 ± 0.63	3.6 ± 0.33	.105
Meats and eggs (g/day)	15.1 ± 2.23	12.1 ± 3.23	.052
Fruits and vegetables (g/day)	211.7 ± 10.83	215.7 ± 14.83	.721
Whole grains (g/day)	231.5 ± 15.82	422.5 ± 25.82**	.001
Millet (g/day)	4.32 ± 0.64	124.36 ± 20.14**	.001
Soybeans (g/day)	5.36 ± 1.04	47.36 ± 6.04**	.001
Flax seeds (g/day)	0.36 ± 0.04	8.36 ± 0.04**	.001
Brown rice (g/day)	4.16 ± 1.04	17.76 ± 3.04**	.001
Nuts (g/day)	7.16 ± 1.34	37.36 ± 6.045**	.001
Total designer foods (g/day)	21.36 ± 3.8	235.20 ± 23.6**	.001
Roots (g/day)	247 ± 9.85	235 ± 9.26	.062
Refined foods (g/day)	216.833 ± 12.93	15.33 ± 3.29*	.001
Milk and curd (g/day)	114.66 ± 8.78	112.166 ± 6.73	.321
Sweets (g/day)	47.36 ± 5.045	23.36 ± 3.04*	.015
Salt (g/day)	7.36 ± 5.045	6.45 ± 5.045	.143
Total energy, (kcal/day)	2078.76 ± 54.32	2066.666 ± 56.27	.467
Physical activity scores	3.87 ± 0.29	3.86 ± 0.2649	.241

*$P < .05$; **$P < .01$.
Source: Modified from Singh RB, Fedacko J, Mojto V, Isaza A, Dewi M, Watanabe S, et al. Effects of millet based functional food rich diet on coronary risk factors among subjects with diabetes mellitus a single arm, real world observation from hospital registry. MOJ Public Health 2020;9(1):18–25 [101].

TABLE 12.4 Laboratory data before and after treatment among subjects receiving designer foods.

Laboratory data	Before treatment	After 12 weeks	*P* value
Total cholesterol, mg/dL	187.67 ± 32.420	169.226 ± 26.056	.0183 (S)
LDL cholesterol, mg/dL	109.0233 ± 34.447	102.4733 ± 28.005	.4223 (NS)
HDL cholesterol, mg/dL	39.726 ± 4.203	41.379 ± 1.776	.1113 (NS)
VLDL cholesterol, mg/dL	37.336 ± 17.881	27.993 ± 11.313	.0187 (S)
Triglycerides, mg/dL	189.8 ± 93.257	142.396 ± 65.033	.0261 (S)
Fasting blood glucose, mg/dL	138.503 ± 40.97	100.066 ± 23.13	.001 (S)
Postprandial glucose, mg/dL	226.54 ± 47.2033	160.49 ± 30.14	.0028 (S)
hs-C-reactive proteins, mmol (0–1.0)	1.548 ± 0.2033	1.476 ± 0.1487	.262 (S)
HbA1c, %	6.866 ± 0.8891	5.073 ± 0.1799	.0001 (S)
TNF-alpha, mmol/L (0–8.1)	7.810 ± 1.221	3.9 ± 0.649	.0007 (S)
Interleukin-6, mmol/L (0–5.0)	4.933 ± 0.7024	1.606 ± 0.541	.01667 (S)

HbA1c, Hemoglobin A1c; *HDL*, high-density lipoprotein; *hs*, high sensitivity; *LDL*, low-density lipoprotein; *NS*, nonsignificant; *S*, significant; *TNF-alpha*, tumor necrosis factor-alpha; *VLDL*, very-low-density lipoprotein.
Source: Modified from Singh RB, Fedacko J, Mojto V, Isaza A, Dewi M, Watanabe S, et al. Effects of millet based functional food rich diet on coronary risk factors among subjects with diabetes mellitus a single arm, real world observation from hospital registry. MOJ Public Health 2020;9(1):18–25 [101].

TABLE 12.5 Antioxidant vitamins and oxidative stress among subjects receiving designer foods.

Data	Before treatment	After 12 weeks	*P* value
TBARS (mmol//L)	2.454 ± 0.2822	1.596 ± 0.3250	<.0001 (S)
MDA (mmol/L)	3.396 ± 0.1968	2.605 ± 0.1848	<.0001 (S)
Diene conjugates (OD)	27.756 ± 0.9947	24.663 ± 0.4767	<.0001 (S)
Vitamin E (mmol/L)	23.033 ± 2.312	28.766 ± 1.906	<.0001 (S)
Vitamin C (mmol/L)	20.7 ± 2.466	24.2 ± 1.846	<.0001 (S)
Nitrite (μmol/L)	0.628 ± 0.058	0.676 ± 0.06100	.0034 (S)
ACE (μmol/L)	85.233 ± 7.176	75.233 ± 7.319	.0293 (NS)

MDA, Malondialdehyde; *NS*, nonsignificant; *S*, significant; *TBARS*, thiobarbituric acid reactive substance.
Source: Modified from Singh RB, Fedacko J, Mojto V, Isaza A, Dewi M, Watanabe S, et al. Effects of millet based functional food rich diet on coronary risk factors among subjects with diabetes mellitus a single arm, real world observation from hospital registry. MOJ Public Health 2020;9(1):18–25 [101].

TABLE 12.6 Biochemical data among women subjects receiving designer foods.

Data	Before treatment (*N* = 33)	After 12 weeks (*N* = 33)	*P* value
Hemoglobin (g%)	10.554 ± 04.28	13.59 ± 4.42	<.040 (S)
Serum proteins (g/dL)	4.39 ± 1.19	5.605 ± 1.58	<.060 (NS)
Serum calcium (mg/dL)	8.75 ± 3.89	9.2 ± 3.07	<.050 (S)
Serum magnesium (mg/dL)	1.53 ± 0.33	1.76 ± 0.45	<.040 (S)
Serum iron (mmol/L)	15.23 ± 3.17	22.33 ± 4.32	<.0293 (S)

NS, Nonsignificant; *S*, Significant.
Source: Modified from Singh RB, Fedacko J, Mojto V, Isaza A, Dewi M, Watanabe S, et al. Effects of millet based functional food rich diet on coronary risk factors among subjects with diabetes mellitus a single arm, real world observation from hospital registry. MOJ Public Health 2020;9(1):18–25 [101].

Cohort studies have demonstrated that control of undernutrition and hunger by increased supplementation with Western-type foods has been associated with a decrease in undernutrition but rapid emergence of NCDs [1–3,95,96]. It is possible that a millet-based intervention diet can cause significant decreases in blood glucose, HbA1c, oxidative stress, blood pressure, blood lipoproteins, and proinflammatory cytokines with increases in antioxidant vitamins, magnesium, calcium, and hemoglobin. It is proposed that such a diet may be most suitable for pregnant women who have undernutrition or overnutrition because the diet has all the possible nutrients, including folic acid, required by the pregnant women as well as for the development of the fetus and newborn [102]. Such diets are rich in essential and nonessential amino acids as well as folic acids that are important for fetal development and for the prevention of undernutrition in infants and children [101–104]. In a clinical trial involving 20 infants and children with undernutrition, increased supplementation with ovolipid milk (100 g/day) as daily infant milk intake has been found to possibly cause a greater increase in body weight with a possible decrease in waist circumference and a significant decline in postprandial blood glucose, which are indicators of metabolic syndrome [103]. This is an important finding because low birth weight and undernutrition during infancy have been found to predispose people to CMDs in later adult life [80,95,96]. This diet is also rich in flavonoids and polyphenolics as well as polyunsaturated fatty acids (mustard oil), which have recently been found to have potential antiinflammatory effects, and these are important markers of CMDs [105–109]. Recently, diet quality has been found to be protective against mortality due to CMDs [110–114]. It is proposed that the designer diet composed of millet, soybeans, brown rice, nuts, and flax seeds, a portfolio of nutrients, may also be protective against morbidity and mortality due to CMDs [115–121].

The WHO has suggested that maintaining good nutrition and a healthy diet during pregnancy is critical for the health of the mother and fetus [80,96]. Nutrition education and counseling is a widely used strategy to improve the nutritional status of women during pregnancy [80]. It is prudent to advise pregnant women to consume adequate macronutrients such as proteins, complex carbohydrates, fats, and fatty acids in relatively large quantities compared to the

TABLE 12.7 WHO and UNO guidelines for nutritional therapy for health promotion.

1. Create sustainable, resilient food systems for healthy diets.
2. Provide social protection and nutrition-related education for all.
3. Align health systems to nutrition needs, and provide universal coverage of essential nutrition interventions.
4. Ensure that trade and investment policies improve nutrition.
5. Build safe and supportive environments for nutrition at all ages.
6. Strengthen and promote nutrition governance and accountability everywhere.

amounts required for normal women. Micronutrients—vitamins and minerals—are consumed in relatively small quantities but are essential to body processes. Increased intake of Western-type diets, which are rich in salt, sugar, and trans fat and deficient in calcium, magnesium, and vitamin D, may predispose women to hypertension and gestational diabetes during pregnancy, and Mediterranean style diets may be protective [80–86]. Vitamin D supplementation during pregnancy can significantly reduce fasting blood glucose levels and regulate HOMA-IR (homeostasis model assessment as an index of insulin resistance) [81]. This study also reported that magnesium supplementation was superior in decreasing serum insulin than supplementation with other nutrients [81]. It is possible that nutrient supplementation may have an effect on glucose homeostasis maintenance in patients with gestational diabetes and may be considered an adjunctive therapy and preventive therapy for gestational diabetes during pregnancy.

Normally, during early pregnancy, blood pressure falls and then slowly rises until the end of pregnancy [80]. However, increased intake of a Western style diet along with sedentary behavior may predispose the pregnant woman to obesity, diabetes, twin pregnancy, or teenage pregnancy. Lower calcium consumption during pregnancy may alter the equilibrium and increase the risk of developing preeclampsia and hypertension. Calcium supplementation improves calcium intake and consequently reduces the risk of hypertensive disorders during pregnancy [80]. In populations with low dietary calcium intake, daily calcium supplementation (1.5–2.0 g oral elemental calcium) is recommended for pregnant women to reduce the risk of preeclampsia. Hypertensive disorders of pregnancy are a significant cause of severe morbidity and mortality and account for approximately 14% of all maternal deaths [80]. Among the hypertensive disorders that complicate pregnancy, preeclampsia and eclampsia stand out as major causes of maternal and perinatal mortality and morbidity. Improving care for women during pregnancy and around the time of childbirth to prevent and treat obesity, gestational diabetes, preeclampsia, and eclampsia are necessary steps toward achievement of the health targets of the SDGs. Efforts to prevent and reduce morbidity and mortality due to these conditions can help to address the profound inequities in maternal and perinatal health globally. The WHO and UNO have advised several guidelines for SDGs (see Table 12.7).

In brief, the idea of preconception and perinatal origins of cardiometabolic health disparities across the life course is trending and in agreement with other experts as well as the WHO. Paternal characteristics in humans have been found to have an impact on birth weight of their offspring. It seems that the strategy should be to advise Indo-Mediterranean style diets, characterized by more whole grains, such as millet, as well as spices, vegetables, fruits, nuts, fish, and olive oil, to both mother and father before conception to prevent complications during pregnancy in the mother and fetus via inhibiting epigenetic inheritance of cardiometabolic risk, resulting in reduction in complications in mothers and fetuses, leading to healthy newborns and infants. These diets may also reduce the complications of pregnancy. The role of a designer diet containing millet, soybeans, brown rice, peanuts, and flax seeds needs randomized, controlled trials involving pregnant women to establish whether this diet may be healthful for pregnant women as well as fetuses. Cohort studies and large-scale, long-term intervention trials during the preconception period and during pregnancy would be necessary to confirm the role of these factors in primordial prevention of CMDs. The role of a modified Mediterranean style diets with rapeseed oil and Indian spices during pregnancy is unknown.

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Chapter 13

Olive fruit and olive oil bioactive polyphenols in the promotion of health

Nancy B. Ray[1], Kyle D. Hilsabeck[1], Eleni Pitsillou[2], Abella Mann[2], Tom C. Karagiannis[2] and D. Elizabeth McCord[1]
[1]*McCord Research, Coralville, IA, United States,* [2]*Epigenomic Medicine Program, Department of Diabetes, Central Clinical School, Monash University, Prahan, VIC, Australia*

Introduction

Olives are the fruits produced by trees from the family Oleaceae. They can be utilized for consumption (table olives) or to produce olive oil. The most common olive tree cultivated to produce table olives and olive oil is known as *Olea europaea*, which is grown throughout the Mediterranean region and other areas [1,2]. Olives contain nutrients such as lipids, sugars, minerals, and proteins [1]. They contain many interesting chemical compounds; however, phenolic compounds, which are the focus of this chapter, account for only up to 3% of the olives fresh weight and approximately up to 2% of the total weight of olive oil [1,3,4]. The specific concentration of polyphenols in olives and olive oil depends on the olive tree variety (cultivar), fruit ripening and irrigation and extraction processes, storage conditions, and other variables [1,4–7].

Virgin olive oil (VOO) and extra-virgin olive oil (EVOO) are mechanically processed (olives are pressed to extract oil) and are known to have higher concentrations of polyphenols than nonvirgin olive oils [8,9]. A substantial quantity of evidence exists concerning olive polyphenols in relation to human health. This chapter will focus specifically on the olive polyphenol oleuropein, which is the major phenolic constituent of the unripe fruit, which tends to be bitter tasting; it will also focus on the olive polyphenol hydroxytyrosol (HT), which increases in concentration during the olive fruit ripening process due to hydrolysis of oleuropein (OL) [1,10]. It follows that fresh olives contain more OL, whereas table olives that have been treated to remove any bitter taste have more HT [2,11]. In addition, OL is hydrolyzed during olive oil production [6]. The relative presence of HT or OL in olives and olive oil is shown in Table 13.1, where a plus sign represents detectable amounts of the polyphenols, a minus sign represents no detectable amounts, and the number of pluses or minuses shown corresponds to relative amounts of the polyphenols in olives or olive oil on the basis of relevant studies [2,6,10–12]. Varying amounts (relative) of the polyphenols depending upon different parameters as described are also indicated.

Olive oil is a main component of the Mediterranean diet, which includes olives and has been shown to have various positive health effects [13]. Olive polyphenols, including HT and OL, are associated with many of the beneficial effects of olive oil on health, including antioxidant, antiinflammatory, and enhanced wound healing effects as well as effects

TABLE 13.1 Relative presence of hydroxytyrosol or oleuropein found in olives and olive oil.

Hydroxytyrosol	Oleuropein	Olive or olive oil
+	+ or + +	Fresh olives (untreated)
+ or ++	− or +	Table olives
+	−	Olive oil
+ or ++	− or +	Virgin olive oil and extra-virgin olive oil

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against diabetes, cardiovascular disease (CVD), neurological disease, depression, and nonalcoholic fatty liver disease (NAFLD) [7,13–17] (Fig. 13.1). In addition, olive polyphenols have been shown to have beneficial effects against other important diseases, including cancer, as reviewed elsewhere [18,19]. In fact, EVOO fits the definition of a functional food, owing to its "clinically proven and documented health benefits for the prevention, management or treatment of chronic disease" [20].

Absorption and oral bioavailability of olive polyphenols

Absorption and bioavailability studies on olive polyphenols are limited and often complicated by the fact that some of the most biochemically significant olive polyphenols have metabolites that are naturally and endogenously produced in the human body as a part of normal dopamine metabolism [19]. Studies are further complicated because there appear to be significant differences in absorption, metabolism, and excretion between humans and animal models, including a 25-fold increase in metabolite excretion seen in rats compared to humans [21]. Olive polyphenols are also subject to acid hydrolysis in the low-pH environment of the stomach, however a significant portion does appear to survive into the small intestine where they are absorbed into the bloodstream and subject to first-pass intestinal hepatic metabolism, predominately via glucuronidation [21,22].

Despite all of the factors complicating absorption and bioavailability studies, it is clear that there is significant absorption of olive polyphenols when obtained naturally in the diet as well as in concentrated oral preparations [21–23]. Intestinal absorption was confirmed in studies comparing absorption and excretion in persons with and without an ileostomy, with results confirming the intestines as the primary site of systemic absorption as there was little to no systemic absorption in persons with an ileostomy [23]. In general, pharmacodynamic and pharmacokinetic studies on olive polyphenols have found relatively high absorption and bioavailability characteristics of therapeutically significant compounds [21–24].

Safety or toxicity of olive polyphenols

Olive polyphenols and their metabolites appear to have a favorable safety profile; in vivo and in vitro toxicity studies indicate no toxic effects at relatively high doses. For example, hydroxytyrosol (DOPET) exhibited no toxicity on cultured intestinal Caco-2 cells at doses as high as 900 μM, and oral gavage doses of 2 g/kg in Sprague-Dawley rats exhibited no observable toxic effects after two weeks [25]. Some small studies have suggested exercising caution with prolonged use of high doses of olive leaf extract, owing to some changes in hepatic and renal tissues and function, including changes in bilirubin and serum alkaline phosphatase levels [26]. Aside from the few studies showing some possible negative hepatic effects, the majority of research overwhelmingly identifies olive extracts and purified polyphenols as safe with little risk of significant toxicity, even with extended use at relatively high doses. In fact, many studies highlight the hepatoprotective effects of olive polyphenols (discussed later in this chapter), but as with all things, it is still good practice to exercise caution and good judgment.

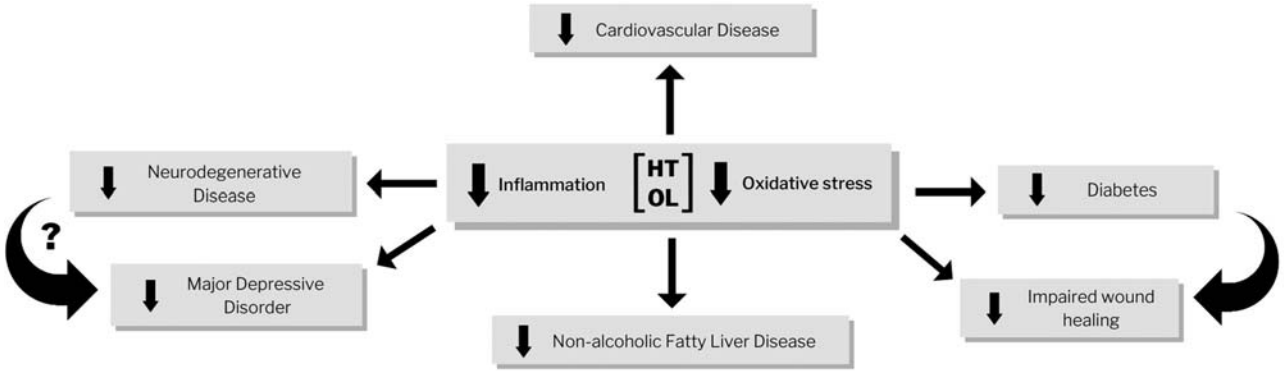


FIGURE 13.1 The olive polyphenols hydroxytyrosol and oleuropein are associated with decreased inflammation, oxidative stress, and diseases.

Effects against oxidative stress and inflammation

Many polyphenols, including HT and OL, possess antioxidant and antiinflammatory activities that contribute to their beneficial effects against diseases. Notably, various chronic diseases, including diabetes, CVD, neurodegenerative diseases, and NAFLD, are associated with inflammation and/or oxidative stress [27–29]. Oxidative stress occurs when cells are incapable of eliminating free radicals known as reactive oxygen species (ROS) using the natural antioxidant defense system, which includes glutathione and defense enzymes such as superoxide dismutase (SOD) and heme oxygenase (HO)-1 [30,31]. During oxidative stress, cells express genes that encode detoxifying enzymes found in the cytoplasm that are regulated by nuclear factor erythroid-2-related factor 2(Nrf2), including glutathione-S-transferase and HO-1 [31].

The mitochondria are the powerhouses of cells and produce ROS during metabolism, which can contribute to oxidative stress, especially when mitochondria are damaged or dysfunctional [32]. On the other hand, excessive ROS can lead to oxidative stress, which can damage mitochondria so that they become dysfunctional [33]. The mitochondrial antioxidant system is under the control of the forkhead box O (FOXO) transcription factor FOXO3a, which turns on the antioxidant defense enzyme, manganese superoxide dismutase (MnSOD) [31]. HT has been shown to activate FOXO3a and MnSOD and to decrease mitochondrial dysfunction [31,34–36]. OL has also been shown to activate MnSOD [37]. In addition, HT and OL have been found to upregulate Nrf2 and activate HO-1 [38–41].

Inflammation is the body's response to infection and wounding. Interestingly, ROS can activate signaling pathways and transcription factors that contribute to inflammatory cascades, including nuclear factor kappa light-chain enhancer of activated B cells (NF-κB), an important transcription factor that plays a key role in inflammation regulation, which also upregulates the production of many inflammatory cytokines [42,43]. Importantly, VOO was found to inhibit NF-κB activation in a study of obesity, and an olive oil phenolic extract was reported to inhibit NF-κB activity in cancer cells [44,45]. Moreover, HT and OL have both been shown to inhibit activation of NF-κB [46–48].

Chronic inflammation can be tracked by measuring biomarkers, such as the acute phase protein C-reactive protein (CRP), that can be detected in the blood. Higher CRP levels have been associated with CVD and diabetes [49,50]. In an important randomized, crossover, controlled trial with 28 patients having stable coronary disease, VOO was found to significantly reduce CRP levels [51]. Furthermore, a systematic review and metaanalysis reported that olive oil interventions (having daily consumption that ranged between approximately 1 and 50 mg) resulted in significantly greater decreases in CRP as compared to controls [52]. Interestingly, HT treatment reduced levels of CRP in different models of diabetes [53].

As mentioned, the diseases that are highlighted in this chapter are associated with harmful inflammation and/or oxidative stress, and olive polyphenols have been shown to inhibit these processes, reducing the effects of these diseases in many cases (Fig. 13.1). Other deleterious disease processes or aspects (influenced by inflammation and oxidative stress) that HT or OL inhibit include endothelial dysfunction, mitochondrial dysfunction, protein aggregate toxicity, insulin resistance, and impaired wound healing (Table 13.2), as this chapter will illustrate.

Endothelial dysfunction and impaired wound healing

The inflammatory response is the first step in a number of overlapping processes that result in wound healing. However, inflammation (especially chronic inflammation) has also been shown to delay or impair wound healing [54]. During normal healing, microvascular endothelial cells migrate to form new blood vessels (angiogenesis) in response to wounds. Here, we discuss the effects of endothelial dysfunction on wound healing, particularly in relation to diabetes, and the impacts of olive oil, HT, and OL on these processes.

Notably, the intrinsic abnormalities associated with diabetes, including hyperglycemia and circulatory and vascular deficiencies, contribute to endothelial dysfunction and impaired wound healing [55]. Delayed or impaired wound healing also occurs with aging and is associated with impaired angiogenesis, decreased endothelial cell proliferation, and excessive ROS production [56,57]. Vascular cells and endothelium are major sources of ROS during hyperglycemia, seen even with mild glucose elevations. In fact, oxidative stress induced by hyperglycemia plays an important role in endothelial cell dysfunction and wound-healing impairment [58,59].

Endothelial dysfunction involves the dysregulation of endothelial cell functions, including vasodilation, proliferation, and migration as well as angiogenic properties [57]. It is involved in the pathology of CVD and diabetes mellitus, contributing substantially to impaired wound healing in the latter case. The endothelium plays a major role in the regulation of vascular tone through the production and release of vascular modulators, such as nitric oxide (NO) and endothelin-1, that must be balanced for proper endothelial functioning [60]. In addition, NO plays a key role in wound repair, and decreased levels of cutaneous NO have been associated with impaired wound healing under disease conditions, including diabetes [61].

TABLE 13.2 Diseases and processes or aspects affected by hydroxytyrosol or oleuropein.

Disease	Process or aspect
Diabetes	Neuropathy
	Endothelial dysfunction
	Impaired wound healing
Cardiovascular disease	Hypertension
	Lipid oxidation
	Endothelial dysfunction
Neurodegenerative disease	Mitochondrial dysfunction
	Protein misfolding
	Protein aggregate toxicity
Major depressive disorder	Monoamine deficiency
	Epigenetics
	Neurodegeneration (?)
Nonalcoholic fatty liver disease	Insulin resistance
	Decreased Intestinal barrier function
	Endoplasmic reticulum stress

In an important study, a polyphenol fraction and a HT extract of EVOO protected against endothelial dysfunction induced by high glucose and free fatty acid levels. The authors concluded that the protection was due to the modulation of NO and endothelin-1 and possibly a decrease of ROS levels [60]. Notably, olive oil was found to promote wound healing in model studies in which it reduced oxidative damage and accelerated NO synthesis or in which it was shown to restore redox equilibrium [62,63].

In an interesting study of an aging population, daily adherence to the Mediterranean diet, which included olive oil, resulted in higher levels of endothelial progenitor and circulating progenitor cells than in subjects that had no daily consumption or lower consumption of the Mediterranean diet, suggesting that a diet incorporating olive oil may protect against endothelial dysfunction by increasing endothelial progenitor and circulating progenitor cells in old age [64]. In addition, OL has been shown to restore function in endothelial progenitor cells [65].

As noted, a HT extract was demonstrated to protect against endothelial dysfunction [60]. In addition, HT alone has been shown to decrease endothelial dysfunction by reducing ROS levels in vascular endothelial cells and by decreasing mitochondrial dysfunction [66]. HT was also demonstrated to prevent endothelial dysfunction induced by oxidative stress by upregulating HO-1 expression that promoted wound repair [38]. Remarkably, OL was found to promote wound healing in a model of aging [15]. Furthermore, HT and OL have been shown to promote wound healing even under conditions of hyperglycemia [67].

Diabetes mellitus

As was mentioned previously, diabetes mellitus is a metabolic disease associated with hyperglycemia (excess blood glucose). Hyperglycemia results from insulin resistance, inadequate insulin secretion, or the secretion of excessive amounts of glucagon. Diabetes is a major health problem and one of the major causes of morbidity and mortality worldwide [68]. Type 2 diabetes, the most common form of the disease, is characterized by an impaired response to insulin along with dysfunctional pancreatic beta cells [69,70]. Oxidative stress plays an important role in type 1 diabetes. Type 2 diabetes is also linked with oxidative stress as well as chronic inflammation and is known to increase the risk of other inflammatory diseases, including CVD and Alzheimer's disease [58,71,72].

Hyperglycemia can lead to advanced glycation end products (AGEs), which are highly stable cross-linked complexes of protein and glucose. The interactions between AGEs and their receptors are thought to produce oxidative stress [73]. Interestingly, a metaanalysis of cohort studies and intervention trials reported that patients who consumed

olive oil had a lower production of AGEs. Olive oil supplementation also resulted in a significant reduction in hyperglycemia measurements (HbA1c and fasting plasma glucose) in patients with type 2 diabetes compared to control groups [74].

A recent model study found that streptozotocin-induced diabetic rats treated with olive oil had pancreatic beta cells with a normal appearance and had increased liver functions in contrast to the diabetic control rats, which had massive pathological changes [75]. Remarkably, a model study of high-fat lard diet-induced diabetic mice found that diabetic mice that were fed EVOO for 24 weeks following the lard diet (12 weeks) had significantly improved measurements of glycemia, insulinemia, glucose tolerance, insulin sensitivity, and insulin degradation. Furthermore, mice that consumed EVOO had increased beta cell numbers, normalized glucose metabolism, and glucose-induced insulin secretion [76].

Hyperglycemia can result in the production of excessive ROS and endothelial dysfunction associated with impaired vascular relaxation as well as the impaired wound healing that is commonly found in patients with type 2 diabetes [58–60]. In an in vitro model that simulated the conditions of type 2 diabetes, a protective effect of olive oil polyphenols, including HT, was found against endothelial dysfunction that was induced by hyperglycemia and free fatty acids [60]. In addition, as alluded to previously, HT and OL have been found to substantially increase wound closure in an in vitro model of diabetic wound healing that included hyperglycemia [67].

In a model study of alloxan monohydrate–induced diabetes that included hyperglycemia, purified HT from olive mill waste was administered intraperitoneally to Wistar rats for two months, resulting in significantly decreased glucose levels and attenuation of alloxan-induced effects in pancreatic beta bells [77]. In another model study, diabetes including hyperglycemia was induced in rats by intraperitoneal streptozotocin or streptozotocin and high-dose nicotinamide, and the rats were then treated with purified HT. After two months of treatment, increased levels of antioxidant enzymes were found in the pancreas, including SOD as well as decreased formation of AGEs [78]. Another interesting study using streptozotocin-induced diabetes in rats found that HT could attenuate peripheral neuropathy that has been linked with hyperglycemia and oxidative stress [79]. Likewise, a neuroprotective effect (on retina) was recently revealed in another model study of streptozotocin-induced diabetes in rats following oral treatment with HT [80].

Remarkably, a model study of alloxan-induced diabetic rats indicated that OL was able to restore blood glucose levels to the same levels as those of control rabbits [81]. A recent study revealed that OL can promote beta cell insulin secretion and protect cells from amylin amyloid–induced toxicity. Amylin is a peptide hormone that is cosecreted with insulin from beta cells, and insulin resistance frequently results in toxic amylin amyloid deposits in the pancreas of type 2 diabetes patients [82]. Notably, an important study indicated that OL induced insulin sensitivity in C2C12 muscle cells, and another study found that OL prevented palmitic acid–induced insulin resistance in C2C12 cells [83,84]. Further, in a recent study involving 20 healthy subjects, OL was found to improve postprandial glycemia by reducing glucose and increasing insulin levels via an oxidative stress–mediated mechanism, providing further evidence for OL-induced antidiabetic effects [85].

Cardiovascular disease

CVD has been and continues to be a leading cause of death worldwide. Olives and olive oil have both been associated with improved cardiovascular health for decades, especially as part of the Mediterranean diet [86]. Moreover clinical trials that have examined the effects of olive oil on CVD and related health problems have indicated that the consumption of olive oil can provide protection against various aspects of CVD [5,7]. Some of the cardiovascular benefits have been attributed to the lipid profile of olives and olive oils [87–89]. However, other minor constituents are increasingly being implicated and considered for the health benefits of olives, including those related to cardiovascular health [5,89,90]. In fact, several studies have identified that more robust health benefits are observed from using olive oils with higher phenolic content and/or preparations of concentrated or purified olive polyphenols, including HT and OL [19,90].

CVD can manifest itself in many ways, yet there are central commonalities that contribute to cardiovascular and other disease processes. Hypertension, dyslipidemia, endothelial dysfunction, atherosclerosis, venous/arterial insufficiency, inflammation, and oxidative damage are all so closely related and interdependent that it is difficult to talk about any single component without the others [19,91,92]. The shared theme of free radical damage and inflammation is one reason that potent antioxidants such as those found in olives have shown so much potential in all these aspects of CVD [91–93].

OL and HT have both direct and indirect antioxidant effects throughout the cell, including but not limited to regulation of superoxide dismutase enzymes, FOXO3a expression and activation, Nrf-2/Keap-1 activation, glutathione-acting enzymes (GSH reductase, GSH peroxidase), catalase, and heme oxygenase-1 [19,24,94]. Moreover, OL and HT exhibit

cardioprotective effects against doxorubicin-induced cardiotoxicity through a combination of factors, including antioxidant activity and mitochondrial protection [24,95]. Studies of OL in diabetic animal models have highlighted its potential role in cardiovascular protection by way of favorable impacts on cholesterol levels and lipid oxidation plus restoration of normal antioxidant enzymatic activity [26].

In fact, the antioxidant properties of OL appear to contribute to the antithrombotic and antiatherogenic properties of OL, which have also been shown to have beneficial effects in dyslipidemia and preventing low-density lipoprotein oxidation [10]. Moreover, the antiinflammatory effects of OL are attributed to a combination of antioxidant activity, inhibition of lipoxygenase activity, and induction of leukotriene B4 [95]. HT has also demonstrated potent antiinflammatory activity through regulation of several inflammatory prostaglandins (PGE2), cytokines (IL-1α, IL-1β, IL-6, IL-12, and TNF-α), and chemokines (CXCL10/IP-10, CCL2/MPC-1) and decreased expression of proinflammatory genes [24]. Elevated CRP levels are also associated with increased inflammation and risk of CVD-related mortality, and the CRP-lowering effects of both HT and OL have been previously highlighted in this chapter [51−53].

In addition to properties related to its antioxidant activity, OL has been shown to exhibit antiatherosclerotic effects and to address endothelial dysfunction by increasing high-density lipoprotein levels, neutrophil modulation, NO regulation, and the inhibition of thromboxane and leukotriene B4 production [24,89,90,95]. HT has also been shown to inhibit endothelial dysfunction [66]. In fact, HT conveyed a protective effect against endothelial dysfunction in human aortic endothelial cells [96]. Additionally, olive polyphenols, including OL, have been shown to have antiplatelet effects by way of inhibition of cAMP-PDE and platelet ATP−mediated platelet aggregation as well as decreased collagen-induced thromboxane production [89,95].

Further, OL exhibits antihypertensive effects through increased expression of intercellular inducible nitric oxide synthase (iNOS) and resultant vasodilatory effects [24,95]. In vitro and in vivo studies have also shown that HT exerts cardioprotective effects in hypoxic conditions used to simulate myocardial infarction through direct action within the endoplasmic reticulum as indicated by inhibition of GRP78 and CHOP expression [97]. In addition, OL and HT have been found to protect against ischemic injury and reperfusion injury through antieicosanoid and antioxidant effects [95].

While the body of evidence in support of the positive effects of olive polyphenols against CVD continues to expand, there is an increased call for larger clinical trials in humans to confirm the therapeutic significance of the robust evidence highlighted in the current literature and supported by in vitro and in vivo studies in both animal and human models. HT and OL continue to show promise in both nutraceutical and pharmacological approaches to preventing and treating several aspects contributing to CVD.

Neurodegenerative disease

Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disease and the most common cause of dementia, accounting for an estimated 60%−80% of dementia cases [98,99]. Common symptoms include persistent and frequent memory difficulties, cognitive impairment, deterioration of social skills, and changes in mood and behavior [100]. Although there is a small proportion of genetically inherited early-onset cases of the disease, AD is predominantly associated with old age, and age is the most prominent biological risk factor [101,102].

The current and most widely accepted hypothesis for the pathogenesis of the disease is the amyloid cascade hypothesis. This hypothesis proposes that the original pathological event in the disease is the deposition of extracellular beta-amyloid (Aβ), leading to the accumulation of soluble Aβ oligomers and the formation of senile plaques. This in turn activates inflammation and accelerates the aggregation of intracellular hyperphosphorylated tau as neurofibrillary tangles, a combination that causes neuronal cell death [103,104].

Tau is a microtubule-associated protein that acts to stabilize the microtubules in the cytoskeleton of neurons in the brain [105]. However, in AD its ability to keep the cytoskeleton stabilized is lost as a result of hyperphosphorylation and integration into neurofibrillary tangles, rendering tau proteins incapable of binding to microtubules, decreasing their stability and resulting in disrupted cellular trafficking as well as synapse dysfunction and loss [106,107]. While the normal function of Aβ is not entirely known, $A\beta_{1-42}$ monomers were shown to be neuroprotective by contributing to the survival of developing neurons and protecting mature neurons against excitotoxic death [108]. In contrast, $A\beta_{1-42}$ aggregation is strongly implicated in the neurotoxic effects found with Alzheimer's disease [109].

Studies have shown that adherence to the Mediterranean diet is associated with a lower risk for AD [110]. This has been further supported by a metaanalysis and systemic review [111]. It was concluded from the results of their analysis

that higher adherence to the Mediterranean diet was associated with a reduced risk of developing AD. Olive oil is a major component of the Mediterranean diet that has a significant role in delaying cognitive decline [112].

In an important study that included 6947 participants, associations between olive oil and cognitive outcomes were examined. Individuals who had moderate or intensive use of olive oil (compared to those who did not use olive oil) had lower odds of cognitive deficit for verbal fluency and visual memory [113]. In a study utilizing a mouse transgenic model known to exhibit both amyloid plaques and neurofibrillary tangles, an EVOO-supplemented diet had a beneficial effect on behavioral deficits, synaptic pathology, and Aβ and tau neuropathology [114]. A more recent study concluded that patients with mild cognitive impairment treated for one year with EVOO showed decreased tau protein levels in comparison to control groups [115].

Many animal models have shown that EVOO conveys protection against AD-related neurotoxicity, as was recently reviewed [112]. Importantly, EVOO administration improved learning and memory in SAMP8 mice that have age-related decreases in learning and memory resulting from an age-related increase in Aβ protein [116]. In another interesting study, feeding TgSwDI mice (that start accumulating Aβ protein at the age of 2−3 months) an EVOO-enriched diet beginning before Aβ accumulation started significantly decreased the total Aβ and tau levels in the brain and significantly improved cognitive behavior [117].

In a study utilizing another transgenic model (3xTg) known to exhibit both amyloid plaques and neurofibrillary tangles, an EVOO supplemented diet had a beneficial effect on behavioral deficits, synaptic pathology, and Aβ and tau neuropathology [114]. Moreover, a recent study with a model of tauopathology in which human transgenic mice (hTau) were administered chronic supplementation of EVOO revealed that mice that received EVOO had improved memory and cognition that was associated with increased basal synaptic activity and short-term plasticity [118].

Evidence from some studies suggests that OL may protect against amyloid plaque formation and deposition. Remarkably, OL was discovered to noncovalently bind to $A\beta_{1-40}$ peptide at a site critical for Aβ peptide polymerization and fibril formation [10,119,120]. In addition, OL conveyed an antiamyloidogenic effect in HEK293 cells [121]. Moreover, OL and HT were reported to inhibit tau aggregation and fibrillization in vitro [107]. An interesting model study of colchicine-induced cognitive dysfunction in Wistar rats indicated that OL pretreatment significantly improved learning and memory [122].

In cultured murine neuroblastoma N2a cells treated with $A\beta_{25-35}$ to induce cytotoxicity, HT decreased cell death, suggesting that HT is neuroprotective [47]. Another recent study found that HT interfered with $A\beta_{1-42}$ aggregation in human neuroblastoma cells [109]. Furthermore, in a model of Aβ deposition, it was discovered that transgenic mice (TgCRND8) given HT supplementation had improved cognitive functions and significantly reduced plaque areas and numbers [123]. Additionally, DOPET decreased cognitive impulsivity that is associated with Alzheimer's disease in an $A\beta_{1-42}$ plus ibotenic acid−induced mouse model [124]. Another interesting study revealed that HT had an important role in preventing $A\beta_{25-35}$-induced cytotoxicity in astrocytes along with the restoration of proper insulin signaling, strengthening the link between Alzheimer's disease and diabetes [72].

Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease [125,126]. PD results from a complex interaction of the environment with the genetics of the affected individual that involves the processes of oxidative stress and inflammation [126−128]. The main characteristics of the disease are the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) area of the brain and the presence of alpha-synuclein deposits in neuronal cell bodies (Lewy bodies) in various regions of the brain [126,129]. However, Lewy bodies can also be found in the spinal cord and peripheral nervous system, including the vagus nerve [126].

Along with oxidative stress and inflammation, impairment of mitochondrial function, alterations in protein processing, and dysfunction of protein degradation have been identified as important mechanisms in the pathogenesis of PD [125,126,129,130]. Oxidative stress is thought to result from the enzymatic breakdown of dopamine in the dying SNpc neurons (where dopamine is produced), mitochondrial dysfunction, and aging [128,131]. SNpc neurons are thought to be especially susceptible to higher levels of oxidative stress from mitochondria due to elevated levels of intracellular calcium in these cells that results in higher mitochondrial activity [126].

In addition, evidence suggests that SNpc neurons that contain high amounts of the pigment neuromelanin (NM) are particularly prone to PD-associated neurodegeneration, which may be related to the association of NM with sequestered toxic metals, pesticides, and ROS in affected neurons. In fact, NM-rich cells have been found to display high levels of oxidative stress and mitochondrial dysfunction that may lead to neuronal cell death [128]. Oxidative stress can result in

endoplasmic reticulum (ER) stress, which can affect protein folding. The aggregation of misfolded proteins, including alpha-synuclein, is directly related to neurodegeneration that occurs in PD [131].

In support of oxidative stress as a major mechanism in PD pathogenesis, high levels of lipid peroxidation and glutathione depletion are found in the SNpc of PD brains [130]. Interestingly, it has been reported that HT can protect differentiated PC12 dopaminergic cells from cell damage caused by hydrogen peroxide−induced oxidative stress [132]. Recently, it was also reported that HT has a strong protective effect against dopamine- and 6-hydroxydopamine (6-OHDA)-induced dopaminergic cell death. Another recent study indicated that OL protected neurons from 6-OHDA-induced neurotoxicity. Protection was attributed to the regulation of mitochondrial functions and control of persistent protein misfolding [130,131].

In another important study, utilizing a neuronal dopaminergic cellular model that involved exposing PC12 cells to 6-OHDA, OL significantly decreased neuronal death and reduced mitochondrial production of ROS [133]. Notably, HT has been found to convey protection against in vivo neurotoxicity induced by 1-methyl-4-phenylpyridinium, and this protection correlated with the preservation of dopamine and the inhibition of monoamine oxidase (MAO), an enzyme that is known to catabolize dopamine with resultant increased ROS production [134]. Additionally, HT was shown to decrease oxidation of dopamine during MAO inhibition in PC12 cells [135]. Another interesting study found that OL could inhibit glutamate-induced neuronal cell death by attenuating mitochondrial dysfunction [136]. In fact, impaired mitochondrial function is thought to make SNpc neurons highly susceptible to the effects of the neurotransmitter glutamate, which acts as a neurotoxin during impaired cellular energy metabolism, as with PD [137].

Remarkably, HT has been found to be protective against alpha-synuclein toxicity and fibril formation in PC12 cells [138]. Another study reported HT-induced protection against alpha-synuclein toxicity and fibril formation with concurrent increased expression of vitagenes. Evidence from this study suggests that modulation of the vitagenes system [sirtuin-1 (SIRT-1), sirtuin-2 (SIRT-2), heme oxygenase-1 (HO-1), and heat shock protein 70 (Hsp-70)] leads to the reduction of alpha-synuclein misfolding and oxidative stress. In this study, HT increased the expression of SIRT-2, HO-1, and Hsp70, which contributed to the neuroprotective effect [139]. Surprisingly, alpha-synuclein aggregates have been detected in the gastrointestinal tract years before the onset of motor-related Parkinson's disease symptoms [140].

It has been proposed that alpha-synuclein aggregation may occur in the enteric neurons and propagate from the gut to the brain via the vagus nerve [141]. In fact, evidence for this route has recently been reported. It has also been shown that gut inflammation and increased intestinal permeability can induce the leakage of gut microbes and metabolites to the rest of the body, stimulating the production of pathologic alpha-synuclein or proinflammatory cytokines [140,141]. In an in vitro model of the intestinal barrier, damage was induced by tert-butyl hydroperoxide, and it was shown that a phenolic extract of table olives counteracted alterations in cell monolayer integrity [142]. In addition, olive oil has been found to improve intestinal integrity [143]. Moreover, in a model of obesity, HT was shown to improve integrity of the intestinal wall, and in another study, HT restored intestinal integrity in a model of NAFLD [144,145].

Activated brain macrophage−like cells known as microglia that produce ROS have been found with PD [128]. Remarkably, a recent study involving 6-OHDA toxin indicated rapid neurodegeneration accompanied by microglial activation [146]. Moreover, it has been demonstrated that the neuroinflammation that occurs with PD is mainly due to activated microglia [147]. In fact, it has been shown that with ongoing neurodegeneration there are increases in the numbers of activated microglia that are "primed" such that systemic inflammation results in increased synthesis of proinflammatory cytokines [148]. Notably, in vitro studies have shown that HT and OL have demonstrated antiinflammatory effects on microglial cells [147].

Levodopa is used in PD treatment, since it can be converted to dopamine by the enzyme catechol-O-methyl transferase (COMT), however some levodopa is converted in the peripheral area of the brain before reaching its target. Therefore COMT inhibitors are commonly used along with levodopa [149]. An interesting rodent study in which HT-induced inhibition of COMT was investigated demonstrated that HT treatment (especially chronic) led to increased intracellular levels of dopamine in corpus striatum brain cells [150]. Finally, olive oil has been associated with a reduced rate of progression in PD, and phenol-rich extracts of olive oil have been shown to inhibit MAO enzymes in a dose-dependent manner [151,152].

Major depressive disorder

Major depressive disorder (MDD) is a major health problem worldwide that is characterized by depressed mood, decreased interests, impaired cognitive function, and symptoms that include disrupted sleep and/or appetite [153,154]. Currently available psychiatric drugs are only moderately effective, and only certain individuals respond to existing antidepressants [155]. MDD is a complex disorder that is linked with numerous major molecular pathways, including

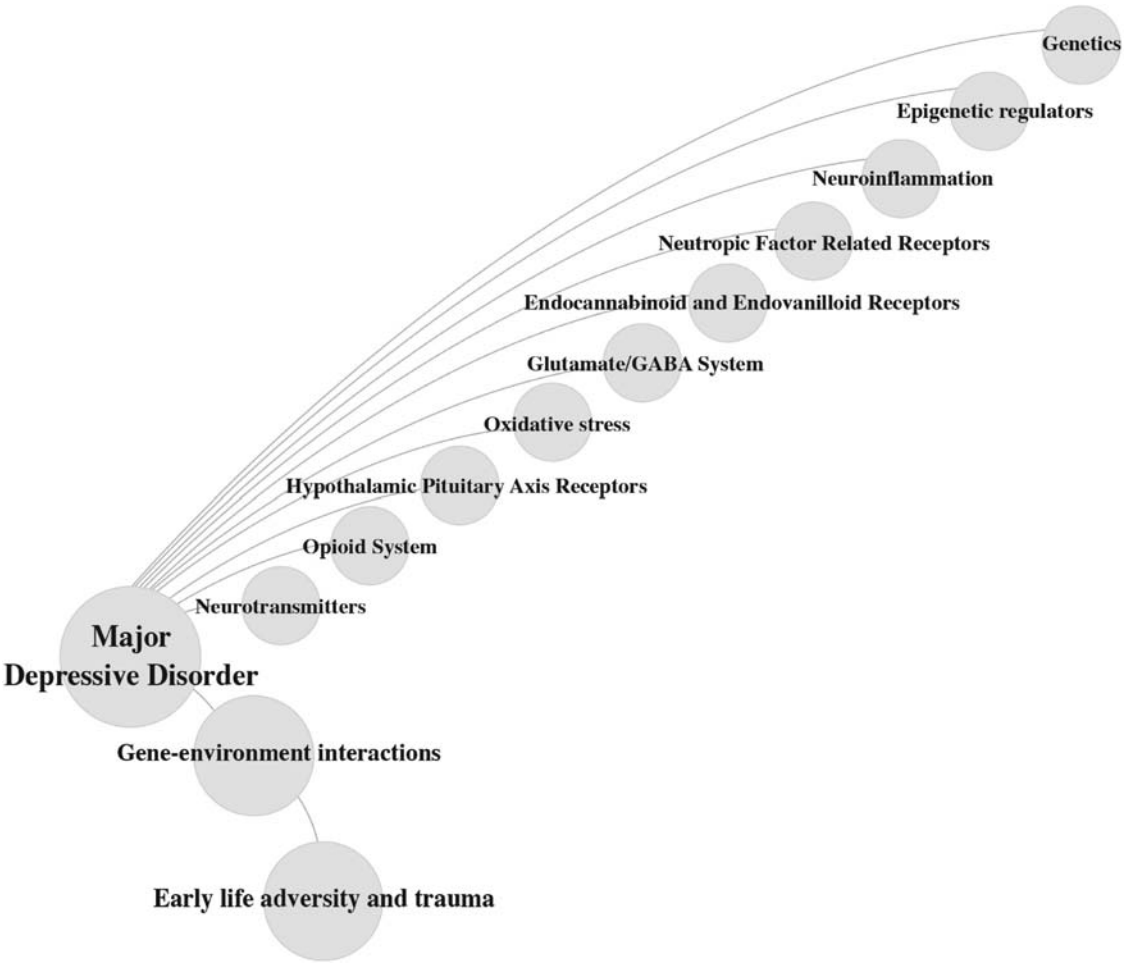


FIGURE 13.2 Major depressive disorder is a complex disorder associated with genetic and environmental components, early life adversity, and numerous molecular pathways.

those involving various neurotransmitters, the opioid system, and the hypothalamic-pituitary axis (Fig. 13.2), as has been reviewed [156].

Depression is frequently preceded by anxiety and is also associated with inflammation as well as neurodegenerative disease [153,157]. Indeed, increasing evidence suggests that inflammation plays a significant role in the etiology of depression. This evidence includes the observation that depressed individuals or individuals with depressive symptoms often have increased levels of proinflammatory chemical messengers known as cytokines as well as increased levels of inflammatory markers including CRP [158].

Despite the significant socioeconomic impact of depression, studies are just beginning to reveal the causes and processes that are involved. Evidence suggests that depression is a multifactorial disease with both environmental and genetic components [159]. Stress is one widely studied environmental component that is believed to contribute significantly to depression and anxiety as well as cognitive impairment [160]. In fact, early life adversity, such as exposure to child abuse, has been found to contribute to the development of depression [161].

Additionally, oxidative stress has been linked with depression. ROS have been shown to impair brain function by modulating the activity of neurotransmitter systems involved in the neurobiology of depression. Clinical studies have also revealed that depression is associated with increased levels of oxidative stress markers and reduced levels of antioxidants and antioxidant enzymes, including glutathione, glutathione peroxidase, and SOD [162,163]. Notably, depression and neurodegenerative diseases, including AD and PD, share many common mechanisms, and increasing evidence suggests that depression may correspond with neurodegeneration [164,165].

For many years, the monoamine hypothesis has been accepted as a key pathophysiological explanation for MDD and has resulted in the synthesis of antidepressants that are widely used. This hypothesis postulates that some or all

forms of depression are associated with a deficiency in the monoamines, particularly norepinephrine, dopamine, and serotonin [166]. The selective serotonin reuptake inhibitors are commonly used to increase the availability of serotonin, which is also known as 5-hydroxtyptamine (5-HT), through selectively inhibiting the serotonin transporter and preventing serotonin reabsorption into the presynaptic neuron [167]. On the other hand, monoamine oxidase inhibitors target the monoamine oxidase enzymes and were one of the first antidepressants to be marketed.

The mitochondrial monoamine oxidase enzyme is predominantly responsible for degrading amine neurotransmitters, including serotonin, norepinephrine, and dopamine [168,169]. Because the monoamine system, neuroinflammation, and oxidative stress are involved in the pathophysiology of MDD, various compounds in olive oil have the potential to produce an antidepressant effect and be used as therapeutic substances. This is supported further by the fact that some phenolic compounds and their metabolites, including HT, have the ability to cross the blood-brain-barrier and may also be found endogenously [25,170].

In a randomized control trial known as Supporting the Modification of Lifestyle in Lowered Emotional States, participants with moderate to severe depression were recruited. They were separated into two groups; those in the dietary support group adhered to the Mediterranean diet, and those in the control group received social support. Interestingly, 32.3% of the dietary support group achieved remission criteria of a score less than 10 on the Montgomery-Åsberg Depression Rating Scale (MADRS) at 12 weeks. In contrast, 8.0% of the social support group achieved remission criteria of a score less than 10 on the MADRS. Although this was a preliminary study, it suggests that dietary improvement that includes olive oil can be beneficial to health and may even improve depressive symptoms [171]. Moreover, other studies have found an inverse relationship between following the Mediterranean diet and the risk of developing depression [172−174].

An interesting model study revealed that repeated administration of olive oil induced antidepressant and anxiolytic effects in rats that corresponded with decreased levels of brain 5-HT and dopamine [175]. In another recent model study, long-term administration of a low dose of olive oil resulted in antianxiety effects that corresponded with increased levels of serotonin [176]. Importantly, HT has been identified as a potent inhibitor of lysine-specific demethylase 1A (LSD1), an epigenetic modifying protein that regulates histone demethylation [67]. LSD1 shares sequence homology with FAD-dependent amine oxidases, including the MAO enzymes, and is an important constituent of genetic and epigenetic regulatory complexes [177−179].

Nonalcoholic fatty liver disease

NAFLD is regarded as the most common liver disease worldwide, as might be expected with increasing rates of contributing factors such as obesity and type 2 diabetes mellitus [180]. In fact, fatty liver resulting from overnutrition and insulin resistance combine to produce NAFLD [181]. NAFLD is likened to the hepatic manifestation of metabolic syndrome; consequently, it has many of the same risk factors, causes, and underlying etiology with related conditions, including CVD, obesity, and type 2 diabetes mellitus [182].

The pathogenesis of NAFLD appears complex, involving a combination of dietary, metabolic, and environmental factors that contribute to intestinal microbiome composition, altered metabolism, oxidative stress, and inflammation [180]. While there have been several hypotheses concerning the pathogenesis of NAFLD, mitochondrial dysfunction leading to imbalances in prooxidant/antioxidants systems and subsequent impairment of fatty acid beta oxidation is increasingly implicated [28]. NAFLD often begins as hepatic steatosis, which can advance to nonalcoholic steatohepatitis (NASH) and eventually NAFLD, potentially progressing to fibrosis, cirrhosis, and hepatocellular carcinoma [10,28]. Approaches to mitigate risk, slow progression, reverse damage, and even cure NAFLD should focus on all aspects related to its pathogenesis, including oxidative stress and mitochondrial dysfunction.

The Western diet is a well-known dietary pattern that is associated with metabolic syndrome and NAFLD [181]. In contrast, epidemiological studies have indicated that adherence to the Mediterranean diet has beneficial effects on NAFLD and metabolic syndrome, leading researchers to investigate specific components of the Mediterranean diet, including olive polyphenols, for their potential roles in the disease processes associated with NAFLD including oxidative stress, mitochondrial dysfunction, inflammation, insulin resistance, and endothelial dysfunction [182]. In fact, a major component of the Mediterranean diet, olive oil has been shown to significantly decrease fatty liver grade, weight, waist circumference and blood pressure in a randomized clinical trial [183].

In vitro studies in both rat and human hepatic and endothelial cells have shown that olive polyphenols can decrease hepatic accumulation of lipids and stabilize lipid-dependent oxidative imbalances in as little as 24 hours [184]. Studies in rats have demonstrated the therapeutic effects of polyphenol-enriched olive oils, HT, and OL in models representing insulin resistance and NAFLD showing lowering of serum AST, ALT, and cholesterol levels, plus improved glucose

tolerance and insulin sensitivity, reductions in hepatic inflammation and lipid accumulation, corrections of metabolic imbalances, and improved intestinal barrier function [10,145,185]. In addition, HT has been shown to prevent steatosis and ameliorate insulin resistance by modulating endoplasmic reticulum stress in diet-induced obese mice [186]. Further, OL has also been found to attenuate steatosis induced by a high-fat diet in mice [187].

In summary, the net result of these hepatoprotective effects includes reduced hepatic steatosis and possible slowed or halted development and/or progression of NASH and NAFLD [10,145,185]. The findings of these studies highlight the ability of the olive oil and olive-derived polyphenols HT and OL to affect several aspects of the disease and processes that lead to development and progression of NASH and eventually NAFLD through a variety of mechanisms, indicating that further studies, particularly in humans, should be done.

Conclusion

Many studies have shown that olive oil and two important polyphenols found in olives and olive oil, HT and OL, have various positive health effects including against diabetes, CVD, neurodegenerative disease, depression, and NAFLD. There are many other important diseases and studies that were not reviewed in this chapter. Although evidence is rapidly accumulating to support the positive health effects of olives, olive oil, and olive polyphenols, including studies concerning the Mediterranean diet, more studies are needed to persuade the general public that olives and/or olive oil should be incorporated into their diet. Therefore the alternative of olive polyphenol supplementation is important.

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Chapter 14

Do modern eggs, but not wild-type eggs, increase the risk of cardiovascular disease, diabetes, and cancer?

Dominic Pella[1], Jan Fedacko[2], Daniel Pella[2], Viola Vargova[2], Viliam Mojto[3], Ram B. Singh[4] and Manal M.A. Smail[5]

[1]*Department of Cardiology, Eastern Slovak Institute of Cardiovascular Diseases,* [2]*Faculty of Medicine, PJ Safaric University, Kosice, Slovakia,* [3]*3rd Department of Internal Medicine, Faculty of Medicine, Comenius University, Bratislava, Russia,* [4]*The Tsim Tsoum Institute, Krakow, Poland,* [5]*University of Central Lancashire, Preston, United Kingdom*

Introduction

The yolk of a chicken egg is particularly rich in cholesterol but, unlike dairy products and meat, does not contain saturated fatty acids [1,2]. Dietary cholesterol appears to have only marginal effects on plasma cholesterol levels. Cohort studies indicating an association of dietary cholesterol intake from egg with blood lipids and cardiovascular diseases (CVD) are contradictory [3,4]. There is no human requirement for dietary cholesterol, and it is advisable to keep intake as low as possible. If intake of dairy fat and meat is limited, there may not be any need to restrict egg intake, although some limitation remains prudent [2]. A cohort study from the United States indicate that egg intake may increase morbidity and mortality due to CVDs, whereas other studies involving subjects from 50 countries reported no significant association of egg intake with morbidity and mortality due to CVDs [3,4]. These studies do not mention the intake of wild-type eggs, which are considered to be more healthy [5–7]. Wild-type eggs have been developed by feeding the hen flax seeds and tea leaves to increase the content of polyunsaturated fatty acids, in particular alpha-linolenic acid and flavonoids [7–13], in the eggs. Although wild-type eggs, appear to be more protective, owing to increased content of omega-3 fatty acids and flavonoids, if modern farm eggs are consumed along with a healthy dietary pattern, such as a Mediterranean-type diet that includes fruits, vegetables, nuts, olive oil, and fish, the cholesterol in the diet may remain unoxidized, owing to high amounts of antioxidants, flavonoids and polyphenolics, vitamins, and minerals in the diets. Dietary plant sterols, especially sitostanol, reduce serum cholesterol by inhibiting cholesterol absorption [1,2,5,6]. The cholesterol-lowering effects of plant sterols has also been well documented, and commercial products made of these compounds are widely available, but their long-term effects remain to be seen. One major cause of controversies involving egg intake and health may be due to intake of wild-type eggs or modern eggs from farms where hens are kept in feedlots and given artificial feeds to increase the size of the eggs without consideration of micronutrients [10–13]. This review aims to highlight the role of wild-type eggs, compared to modern eggs from poultry farms, in health promotion and prevention of diseases.

Composition of eggs

It is important to emphasize the composition of a chicken egg because health agencies such as the International College of Cardiology, International College of Nutrition, World Health Organization, and American Heart Association (AHA) advise restricting intake of eggs to one per day, owing to the bioactive nutrient content of eggs [3–5]. Each chicken egg has 78 calories and is an efficient, rich source of high-quality protein, monounsaturated fatty acids, and micronutrients, including minerals, B vitamins, folate, and fat-soluble vitamins [1,6,7] (see Table 14.1). A large egg contains about 6 g of protein, as well as vitamin D, which is protective to bone health and the immune system, and choline, which improves metabolism, liver function, and fetal brain development [1,6]. Egg yolks may also be good for the vision, owing to a high

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TABLE 14.1 Nutrients contents in eggs.

Nutrient	White	Yolk	% Total in white	% Total in yolk
Protein	3.6 g	2.7 g	57%	43%
Fat	0.05 g	4.5 g	1%	99%
Calcium	2.3 mg	21.9 mg	9.5%	90.5%
Magnesium	3.6 mg	0.85 mg	80.8%	19.2%
Iron	0.03 mg	0.4 mg	6.2%	93.8%
Phosphorus	5 mg	66.3 mg	7%	93%
Potassium	53.8 mg	18.5 mg	74.4%	25.6%
Sodium	54.8 mg	8.2 mg	87%	13%
Zinc	0.01 mg	0.4 mg	0.2%	99.8%
Copper	0.008 mg	0.013 mg	38%	62%
Manganese	0.004 mg	0.009 mg	30.8%	69.2%
Selenium	6.6 μg	9.5 μg	41%	59%
Thiamin	0.01 mg	0.03 mg	3.2%	96.8%
Riboflavin	0.145 mg	0.09 mg	61.7%	48.3%
Niacin	0.035 mg	0.004 mg	89.7%	9.3%
Pantothenic acid	0.63 mg	0.51 mg	11%	89%
B6	0.002 mg	0.059 mg	3.3%	96.7%
Folate	1.3 μg	24.8 μg	5%	95%
B12	0.03 μg	0.331 μg	8.3%	91.7%
Vitamin A	0 IU	245 IU	0%	100%
Vitamin E	0 mg	0.684 mg	0%	100%
Vitamin D	0 IU	18.3 IU	0%	100%
Vitamin K	0 IU	0.119 IU	0%	100%
DHA and AA	0	94 mg	0%	100%
Carotenoids	0 μg	21 μg	0%	100%

content of lutein and zeaxanthin, which are known to decrease the risk of macular degeneration and cataracts. However, egg yolks are also known for their cholesterol content; a typical large egg contains 186 mg of cholesterol. The egg cholesterol may be unoxidized by feeding flax seeds and tea leaves to the hen [1,6–8], Eggs are widely available and inexpensive, and their production has low environmental impact compared with other animal sources of protein-rich foods [7].

Nutrition in transition and risk of non-communicable diseases

It is known that the diets of hunter-gatherers during the Paleolithic period comprised mainly fruits, vegetables, seeds, whole grains, eggs, fish, and wild animal meat, which were low in omega-6 fatty acids and high in omega-3 fatty acids along with antioxidants polyphenols and flavonoids, vitamins and minerals, and essential and nonessential amino acids [13–16]. Dietary intakes and lifestyle have changed rapidly in the last century with the modernization of the world. Modern diets are characterized by increased intake of Western-type foods; these include bread, syrups, cakes, biscuits, red meat, dairy products, and poultry, and they are rich in cholesterol, saturated fat, and trans fat. These diets involve lower intake of typical Indo-Mediterranean foods, such as whole grains, vegetables, fruits, and nuts, which are rich in fiber, omega-3 fatty acids, and flavonoids [15–17]. It is clear from the cohort studies that Mediterranean-style diets may be protective against deaths due to NCDs. Therefore it is important to know the composition of such diets (Table 14.2).

TABLE 14.2 Components of the Mediterranean style foods.

- Eating plant-based foods: fruits and vegetables, whole grains, legumes and nuts
- Replacing butter and clarified butter or lard with healthy fats, such as olive oil
- Using herbs and spices instead of salt to flavor foods
- Eating fish and poultry at least twice a week
- Drinking red wine in moderation (optional)
- No advice for red meat, which may not exceed a few times a month

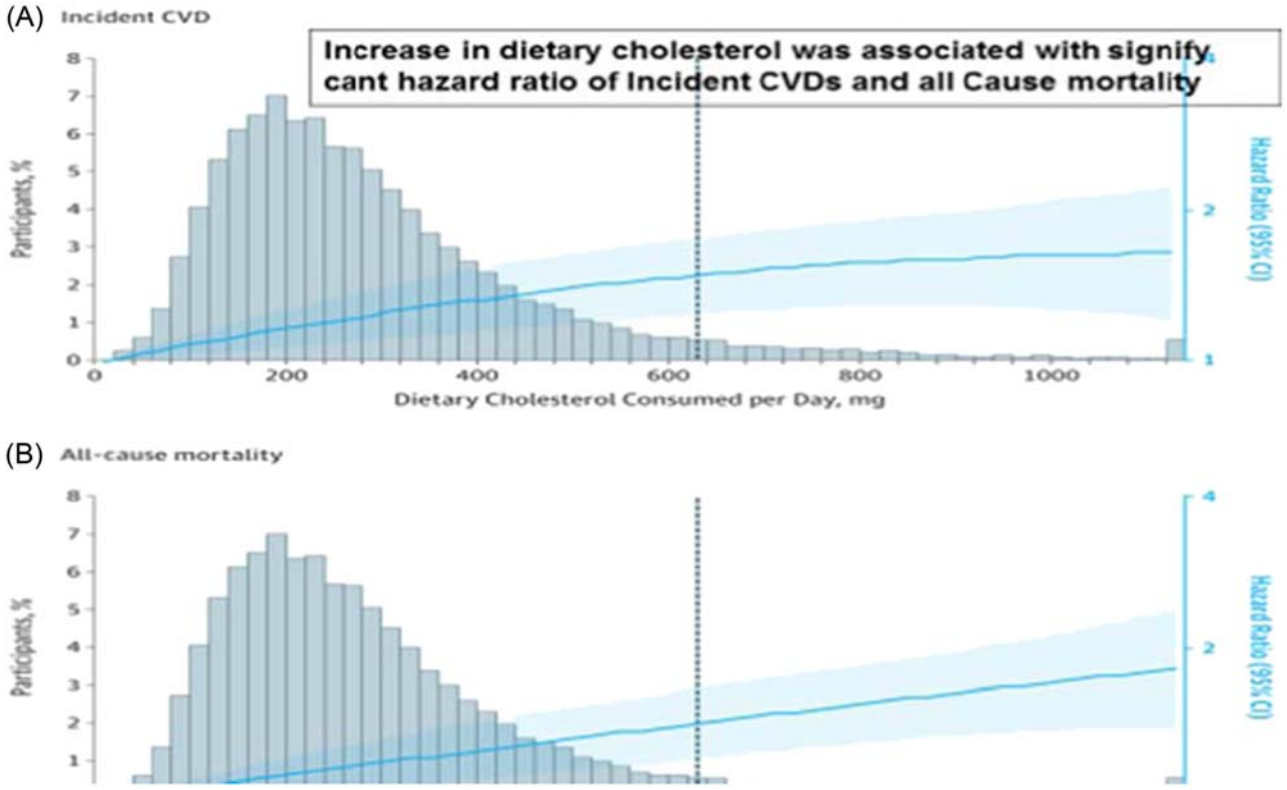


FIGURE 14.1 Association of egg cholesterol with risk of cardiovascular diseases and mortality. *Modified from reference Zhong VW, Van Horn L, Cornelis MC, et al. Associations of dietary cholesterol or egg consumption with incident cardiovascular disease and mortality. JAMA 2019;321 (11):1081–1095. doi:10.1001/jama.2019.1572.*

Economic development in middle- and high-income countries during transitions from poverty to affluence has been associated with industrialization and urbanization, raising of animals in feedlots, and development of feeds for animals in factories. The majority of the deaths (80%) occur in low- and middle-income countries, possibly due to rapid nutritional transition due to change in dietary habits from traditional diets to Western-type diets that are deficient in micronutrients (Table 14.3) [16,17,19,20]. The key ingredients of Mediterranean-type diets include olive oil, fresh fruits and vegetables, protein-rich legumes, fish, poultry including eggs, and whole grains with moderate amounts of wine and red meat. Poultry is one important component of a Mediterranean-style diet; hence it is important to reemphasize the nutrient content of eggs. The composition of a chicken egg, given in Table 14.1, shows that that it is quite rich in proteins, vitamins, and minerals with a few antioxidants and cholesterol. The eggs and red meat from free-range animals may be healthy partly because of favorable changes in the fatty acid composition of tissues in comparison to those from animals that are kept in domesticated at farm houses and artificial feeds made by the industry, may have adverse effects on meat, eggs, and milk due to lipid peroxidation [7–15]. Egg intake appears to increase during nutritional transitions from poverty to affluence.

Poultry is considered a type of white meat and includes chicken meat and eggs, which are components of healthy dietary patterns such as the Mediterranean-style diet or the Dietary Approaches to Stop Hypertension (DASH). Only a

few studies have evaluated the relationship between changes in diet quality over time and the risk of death [20]. In a cohort study of 47,994 women in the Nurses' Health Study and 25,745 men in the Health Professionals Follow-up Study, changes in diet quality were assessed over the preceding 12 years with the use of the Alternate Healthy Eating Index−2010 score, the Alternate Mediterranean Diet score, and the DASH diet score. For all-cause mortality among participants who had the greatest improvement in diet quality (0%−3% vs 13%−33% improvement), as compared with those who had a relatively stable diet quality, the hazard ratios (HR) in the 12-year period were 0.91, according to changes in the Alternate Healthy Eating Index score; 0.84, according to changes in the Alternate Mediterranean Diet score; and 0.89, according to changes in the DASH score (4). A 20-percentile increase in diet scores for improved quality of diet was significantly associated with a reduction in total mortality of 8%−17% with the use of the three diet indexes and a 7%−15% reduction in the risk of death from CVDs with the use of the Alternate Healthy Eating Index and Alternate Mediterranean Diet. For subjects with a high-quality diet over a 12-year period, the risk of death from any cause was 14%, when assessed with the Alternate Healthy Eating Index score, 11%, when assessed with the Alternate Mediterranean Diet score, and 9%, when assessed with the DASH score compared to subjects with consistently low diet scores over time. A majority of the cohort studies support an association between healthy dietary patterns identical with DASH diet or Mediterranean-style diets, and a decreased risk of death [17,19,20]. Diet appears to be an important factor in the pathogenesis of NCDs.

Egg intake and risk of non-communicable diseases

Since poultry is considered to be a component of a prudent diet, there is an unmet need to assess its safety in relation to health promotion [17,19,20]. All prudent diets are similar to the Mediterranean-style diet, which traditionally includes fruits, vegetables, whole grains, nuts, olive oil, fish, and poultry with lower intake of red meats and butter [20]. The Indo-Mediterranean-style diet also gives due consideration to wild-type meat and eggs, which are rich in omega-3 fatty acids and flavonoids, as well as spices and increased amounts of whole grains [5,10]. Consideration of micronutrient content of chicken eggs, in particular omega-3 fatty acids and flavonoids, can explain the cause of recent controversy on the role of egg intake, on risk of CVDs and mortality [3,4]. In a recent metaanalysis, including 29,615 participants, mean age 51.6 years, data were pooled from six prospective U.S. cohorts to determine the associations of dietary cholesterol or egg consumption with incidence of CVDs and all-cause mortality (Fig. 14.1) [3]. Eggs are a major source of cholesterol in the diet and a common nutrient in the diets consumed by all the subjects. There were 5400 cardiovascular events and 6132 deaths due to all causes during the follow-up of 17.5 years. The findings revealed that each additional 300 mg per day intake of dietary cholesterol had a significant association with a higher risk of CVDs (adjusted HR: 1.17) and all-cause mortality (adjusted HR: 1.18). Most interestingly, each additional half an egg consumed per day was significantly associated with a higher risk of incident CVD (adjusted HR: 1.06) and all-cause mortality (adjusted HR: 1.08). Surprisingly, the associations between egg consumption and incident CVD were no longer significant after adjusting for dietary cholesterol consumption [3]. It is possible that among adults in the United States, increased intake of dietary cholesterol from eggs was associated with significantly higher risk of incident CVD and deaths due to all the causes in a dose-dependent manner. These results should be considered important in developing dietary guidelines for prevention of CVDs.

Many guidelines recommend limiting egg consumption for prevention of CVDs, especially in middle- and high-income countries [1,2,5]. A more recent analysis was conducted to assess the association of egg intake with blood lipids, CVD, and mortality in large global studies involving 177,000 subjects from 21 low-, middle-, and high-income countries [4]. The PURE study recorded 14,700 composite events (8932 deaths and 8477 CVD events). In the PURE study, after excluding subjects with history of CVD, higher intake of egg (7 or more eggs per week compared with less than 1 egg per week) was not significantly associated with blood lipids, composite outcome (HR: 0.96), total mortality (HR: 1.04; 95%), or major CVD (HR: 0.92). Similar findings were observed in ONTARGET/TRANSCEND studies for composite outcomes [4]. It is clear from this synthesis from three large international prospective studies including approximately 177,000 individuals, 12,701 deaths, and 13,658 CVD events from 50 countries on six continents that there was no significant association between egg intake and blood lipids, mortality, or major CVD events [4]. The most important weakness of this multicenter study is that the food frequency questionnaires were answered by populations with various socioeconomic and educational status, making the results open to bias. Second, some of the investigators were already biased to report that saturated fatty acids are not unhealthy, and now they reported that dietary cholesterol is also unhealthy. This issue is clear from a comparison of the results of the study conducted in the United States [3] with those reported by the authors of the ONTARGET/ TRANSCEND studies [4]. Finally, in patients with undernutrition, related mortality may be reduced by increasing the intake of eggs, which may influence the results, giving the impression that egg cholesterol has no adverse effects on morbidity and mortality.

TABLE 14.3 Nutrition in transition and emergence of non-communicable diseases in developing countries [18].

Homo sapiens diet patterns	Pattern 1: Hunter-gatherers	Pattern 2: Food scarcity, poverty	Pattern 3: Receding food scarcity and poverty	Pattern 4: More food, less exercise: *Homo economicus*	Pattern 5: Healthy behavior: *Homo modestis*
Nutrition profile/diet	Plants, low-fat wild animals, diet diversity by collecting foods	Cereals predominate, diet less varied	Fewer starchy staples; more fruit, vegetables, animal protein; low variety continues	More fat (animal products, trans fat, omega-6 fatty acid), sugar, processed foods; less fiber, less omega-3 fatty acid and flavonoids	Higher-quality fats, reduced refined carbohydrates, more whole grains, fruit, vegetables rich in omega-3 fatty acid and flavonoids
Nutritional status	Robust, lean population; few nutritional deficiencies	Children and women suffer most from low fat intake, nutritional deficiency diseases emerge, stature declines	Continued maternal and child health nutrition problems, many deficiencies disappear, weaning diseases emerge, stature grows	Obesity, problems for elderly (osteoporosis, fractures, etc.), type 2 diabetes, hypertension, stroke, heart attack, brain degeneration, psychological disorders, cancer	Reduction in body fat and obesity, reduction in NCDs, improvement in bone health; epigenetic modulation and transgenerational epigenetic inheritance, natural selection.
Economy	Hunter-gatherers	Agriculture, animal husbandry, homemaking begin; shift to monocultures	Second agricultural revolution (crop rotation, fertilizer), Industrial Revolution, women join paid labor force	Fewer jobs with heavy physical activity, service sector and mechanization, household technology revolution	Service sector mechanization and industrial robotization dominate, increase in leisure exercise offsets sedentary jobs
Household	Primitive, onset of fire	Labor-intensive, primitive technology begins (clay cooking vessels)	Primitive water systems, clay stoves, cooking technology advances	Household technology mechanizes and proliferates	Significant reduction in food preparation costs as a result of technological change
Income and assets	Subsistence, primitive stone tools	Subsistence, few tools	Increases in income disparity and agricultural tools industrialization	Rapid growth in income and income disparities, technology proliferation	Decrease in income growth, increase in home and leisure technologies
Professional skill/ education	Hunting	Stock breeding, cultivation	Industry, intensive agriculture	Processed unhealthy foods increased	Functional foods availability increases
Demographic profile/ mortality	Low fertility, high mortality, low life expectancy	Age of Malthus; high natural fertility, short life expectancy, high infant and maternal mortality	Mortality declines slowly, then rapidly; fertility static, then declines; small, cumulative population growth, which later explodes	Life expectancy hits unique levels (ages 60–70), huge decline and fluctuations in fertility (e.g., postwar baby boom)	Life expectancy extends to ages of 70 and 90 years, disability-free period increases
Age structure	Young population	Young, very few elderly	Chiefly young, shift to older population begins	Rapid decline in fertility, rapid increase in proportion of elderly person	Increases in the proportion of elderly >75 years of age
Housing	Rural, low density	Rural, a few small, crowded cities	Chiefly rural, move to cities increases, international migration begins, megacities develop	Dispersal of urban population decrease in rural green space	Lower-density cities rejuvenate, increase in urbanization of rural areas encircling cities
Food processing	Nonexistent	Food storage begins	Storage processes (drying, salting) begin, canning and processing technologies emerge, food refining and milling	Numerous food-transforming technologies	Technologies create functional foods and food constituent substitutes (e.g., macronutrient substitutes)

Source: As modified from Popkin et al. (2006), Salas-Salvadó J, Bulló M, Babio N, et al. PREDIMED Study Investigators. Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus nutrition intervention randomized trial. Diabetes Care. 2011 Jan;34(1):14 – 19. doi:10.2337/dc10-1288. Epub 2010 Oct 7. Erratum in: Diabetes Care. 2018 Oct;41(10):2259 – 2260. PMID: 20929998; PMCID: PMC3005482.

Some guidelines and many independent experts also recommend that intake of eggs and dietary cholesterol be limited among subjects with type 2 diabetes mellitus [21]. A previous study followed the published weight maintenance study and assessed the effects of high-egg diets compared with low-egg diets as part of a 3-month weight loss period followed by a 6-month follow-up period for a total duration of 12 months. The weight loss was similar (-3.1 ± 6.3 with high-egg diets compared with -3.1 ± 5.2 with low-egg diets; $P = .48$) from 3 to 12 months. No differences between groups were observed in traditional serum lipids, glycemia (plasma glucose, glycated hemoglobin, 1,5-anhydroglucitol), markers of inflammation [high-sensitivity C-reactive protein, interleukin 6, soluble E-selectin, oxidative stress (F2-isoprostanes), or adiponectin] from 3 to 12 months or from 0 to 12 months. It is possible that subjects with prediabetes or type 2 diabetes who consumed a 3-month, high-egg weight loss diet with a 6-month follow-up exhibited no adverse changes in metabolic markers compared with those who consume a low-egg weight loss diet. A healthy diet based on population guidelines advising more eggs than currently recommended by some countries may be safe.

The AHA has developed a new advisory after a review of these and other cohort studies on the association of dietary cholesterol with blood lipids, lipoproteins, and risk of CVDs [10]. Evidence from cohort studies conducted in several other countries does not indicate a significant association of dietary cholesterol intake with risk of CVDs [10]. The findings differ in the metaanalyses of intervention studies, but most studies found that intakes of cholesterol that exceed current average levels with elevated total or low-density lipoprotein (LDL) cholesterol levels need further observation. In the light of these controversies, the AHA experts advise that dietary guidance should focus on healthy dietary patterns, in particular, Mediterranean-style and DASH-style diets, which are inherently relatively low in cholesterol with typical levels similar to the intake in most developed countries. These dietary patterns emphasize vegetables, fruits, whole grains, low-fat or fat-free dairy products, lean protein sources, nuts, seeds, and liquid vegetable oils. A specific dietary cholesterol target within the context of food-based advice is challenging for clinicians and consumers to implement [10]. Therefore guidance focused on dietary patterns is more likely to improve diet quality and to promote cardiovascular health. However, none of the guidelines should be considered final. There is still an unmet need to explore additional mechanisms by which eggs and egg cholesterol or any other cholesterol-containing food can predispose consumers to CVDs [22–24].

Effects of animal foods on trimethylamine-N-oxide

There is evidence that increased intake of animal foods—egg, meats, and fish—may be associated with higher concentration of trimethylamine-N-oxide (TMAO) which has proinflammatory effects on body tissues [22–24]. TMAO is formed as a result of the presence of choline, which is a nutrient found in red meat, eggs, fish, and poultry. Eggs are rich in lecithin (phosphatidylcholine), which is a precursor of choline. Since gut bacteria feast on the choline, they produce a substance called trimethylamine (TMA), which is metabolized in the liver into TMAO [22]. A plant-based diet that is rich in fiber can decrease TMAO as a result of its probiotic effects. TMAO is produced in a microbial-mammalian cometabolic pathway mainly from the digestion of meat-containing food and dietary quaternary amines such as phosphatidylcholine, choline, betaine, or L-carnitine [22–24]. Increased intake of red meat can cause increased production of meat-eating bacteria in the gut, altering the gut flora. The gut has to essentially grow more microbes that can metabolize meat. Subjects who eat vegetarian diets for a long time may not have high levels of these microbes in their body. Hence if they eat red meat, they will not initially be able to synthesize TMA in the gut or convert it to TMAO in the liver.

The plasma level of TMAO is determined by several factors, including diet, gut microbial flora, drug administration, and liver flavin monooxygenase activity [23,24]. The metabolism of macronutrients and micronutrients is a complex and highly regulated biological process [24]. The effects of micronutrient deficiency, carbohydrate or calorie restriction, protein malnutrition, and lipid emulsions on metabolic health can induce or inhibit inflammation [22–24]. The role of amino acid starvation and lipemia, which modulate new age diseases such as inflammatory bowel disease and atherosclerosis, and various markers of diseases, such as FGF21-β-hydroxybutryate-NLRP3 axis, the GCN2-eIF2α-ATF4 pathway, the von Hippel-Lindau/hypoxia -inducible transcription factor pathway, and the TMAO-PERK-FoxO1 axis, are quite interesting. The gut microbiota responds to altered nutrient status and also antimicrobial peptides generated from nutrient-based signaling pathways that in turn can modulate the gut microbiota [24]. It must be emphasized that metabolic starvation and inflammation are strongly regulated by both environmental (i.e., nutrition, gut microbiome) and nonenvironmental (i.e., genetics) factors, which can influence a person's susceptibility to inflammatory disorders [24]. Recent clinical studies indicate a positive correlation between elevated plasma levels of TMAO and an increased risk for major adverse CVDs [23–26].

A cross-sectional, multicohort study was conducted among 1663 subjects aged 60–77 years to examine the associations of TMAO and its precursors (choline, carnitine, and betaine) with inflammatory and cardiometabolic risk biomarkers and to identify fecal microbiome profiles associated with TMAO [23]. The composition of the fecal microbiome

was evaluated by sequencing the 16S ribosomal RNA gene V1−V3 region. Multivariate linear regression analysis was conducted to assess the associations of TMAO and its precursors with disease risk biomarkers, and associations between TMAO and the fecal microbiome were assessed by using the negative binomial distribution via permutational multivariate ANOVA and hurdle regression models. The findings revealed that median (interquartile range) concentration of plasma TMAO was 3.05 μmol/L (2.10−4.60 μmol/L). Insulin resistance was significantly greater in association with higher levels of TMAO and carnitine and lower concentrations of betaine (all $P < .02$). Interestingly, plasma choline level was associated with higher levels of systolic blood pressure, triglycerides, lipopolysaccharide-binding protein, and lower high-density lipoprotein cholesterol (P ranging from less than .001−.03), reflecting an adverse cardiometabolic risk profile [23]. An abundance of 13 genera (false discovery rate < 0.05), including Prevotella, Mitsuokella, Fusobacterium, Desulfovibrio, and bacteria belonging to the families Ruminococcaceae and Lachnospiraceae as well as the methanogen *Methanobrevibacter smithii*, were significantly associated with higher TMAO [23]. It is possible that higher plasma TMAO levels were associated with a number of trimethylamine-producing bacterial taxa and, along with its precursors, may contribute to proinflammatory and cardiometabolic risk markers.

In a recent study of 1463 subjects with a mean age of 65 years, an association between higher TMAO concentrations and increased risk of major acute cardiovascular events and all-cause mortality was reported during the mean 85 months follow-up [26]. This prospective study also confirmed the presence of some avenues for the role of dysbiosis in patients with cardiovascular risk and type 2 diabetes. Another recent study among 1653 subjects, aged 60−77 years, also revealed that plasma TMAO levels were significantly associated with a number of trimethylamine-producing bacterial taxa, and that, along with its precursors, may contribute to inflammatory and cardiometabolic risk pathways [23]. A previous systematic review and metaanalysis of 19 prospective studies comprising 19,256, subjects, including 3315 incident CVD cases, concluded that elevated TMAO levels were associated with a 62% greater risk for all-cause mortality [27]. However, subjects who had elevated levels of precursors of TMAO (L-carnitine, choline, or betaine) had only a 1.3−1.4 times higher risk for major adverse cardiovascular disease events compared to subjects with low concentrations [27]. Another metaanalysis of 11 prospective studies comprising 10,245 patients reported that increased circulating TMAO was associated with a 23% greater risk of CVD events and a 55% higher risk of all-cause mortality [28]. Mean elevated TMAO levels ranged from 4.1 to 72.2 μM. Control subjects with the lowest risk had levels ranging from 2.3 to 32.2 μM [28]. Interestingly, after exclusion of the studies without values in the control group and those with unusually high control values (27.5 and 32.2 μM), the levels of TMAO in the remaining 5799 patients ranged between 4.1and 12.0 μM (mean: 6.8 μM) for high-risk patients and between 2.3and 2.9 μM (mean: 2.6 μM) for low-risk patients. A further prospective study investigated the relationship between 10-year changes in plasma TMAO levels and incidence of coronary artery disease (CAD) among 760 healthy women [29]. Rising levels of TMAO during the follow-up 10 years were significantly associated with greater risk of CAD. This relationship was strengthened by unhealthy dietary patterns and attenuated by healthy dietary patterns, which again indicates an effect of the microbiome independent from TMAO metabolism.

The association of dietary factors with proinflammatory activity of TMAO can also explain the cardiorenal involvement in the pathogenesis of CVDs and chronic kidney disease presenting with microalbuminuria [30−33]. There is evidence that metabolic syndrome and diabetes mellitus can produce chronic low-grade inflammation which is a risk factors for CAD, myocardial infarction, stroke, heart failure, atrial fibrillation, and chronic kidney disease, as well atherosclerosis [30,31]. The prevalence of chronic kidney disease is 5%−15% in the adult population (13.6% in the U.S. population [33]) which further increases with age, making it one of the major contributors to the disease network around metabolic syndrome and CVD [34,35]. The AHA has reiterated that diabetes mellitus and atherosclerosis can also lead to the development of kidney disease, possibly due to a gut dysbiosis−induced dual burden of inflammation [32,33]. This hypothesis is also emphasized by bridging the gap between gut microbial dysbiosis and CVDs by other experts [36−39]. A news article published on June 11, 2019, in *JAMA* emphasized three recent analyses that linked high blood levels of TMAO with a higher risk for both CVDs and early death from any cause [3]. The researchers in one of the studies found that people with higher levels of plasma TMAO may have more than twice the risk of heart attack, stroke, or other serious CVDs compared with people who have lower levels. Other studies have found links between high TMAO levels and heart failure and chronic kidney disease [30−33].

Mechanisms

The mechanism by which animal foods or highly refined foods predispose consumers to chronic inflammatory diseases may be related to the adverse effects of diet on gut microbiota or its direct effects on inflammation in the body tissues. The imbalance between Western diets and Mediterranean diets appears to have a major role in causing dysbiosis and producing or inhibiting the induction of TMAO which is proinflammatory [30]. While unhealthy diet can directly

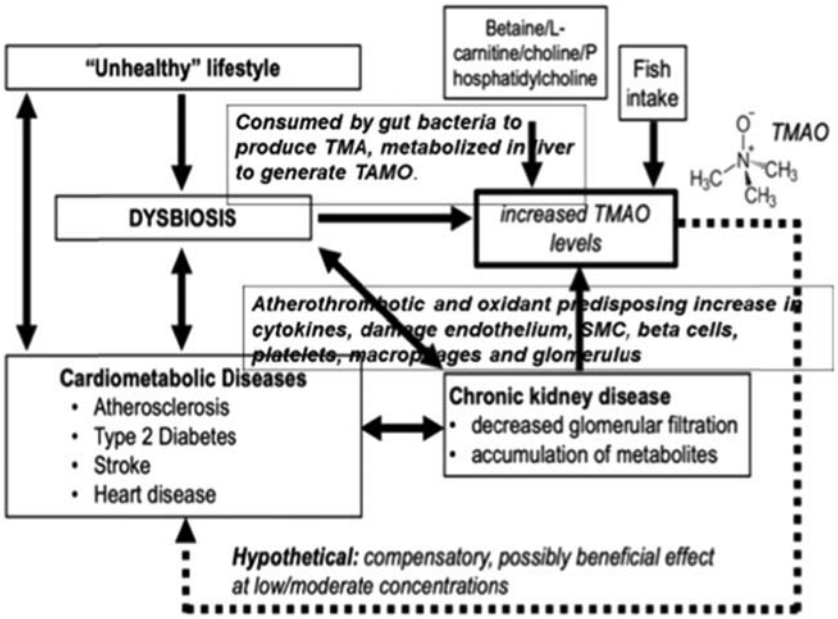


FIGURE 14.2 Effects of animal foods on trimethyleamine-N-oxide (TMAO) levels leading to risk of chronic diseases. *Modified from reference Papandreou C, Moré M, Bellamine A. Trimethylamine N-Oxide in relation to cardiometa- bolic health-cause or effect? Nutrients 2020;12(5):1330. doi:10.3390/nu12051330.*

predispose CVDs, dysbiosis appears to be unifying mechanism for the development of CVDs as well as chronic kidney disease which may present with microalbuminuria [30–33]. Animal foods or a Western-type diet provides excess of choline, which is a food for gut bacteria to produce TMA, which is metabolized by the liver to produce TMAO. Increased levels of TMAO may damage the glomerulus in the kidneys as well as endothelial cells, smooth muscle cells, and cardiomyocyte and beta cells of the pancreas, predisposing the person to CVDs and diabetes in conjunction with chronic kidney disease [32]. Chronic kidney disease, CVDs, and diabetes further increase each other by activating proinflammatory molecules, which worsen as a result of continued dysbiosis-induced TMAO levels.

The mechanisms by which dietary factors interact and predispose a person to CVDs and chronic kidney disease may be associated with inflammation, which may cause dysfunction of both the heart and kidneys, leading to rapid development of each of these problems, as shown in Fig. 14.2. The consumption of fish may also increase TMAO and inflammation, but the antiinflammatory effects of omega-3 fatty acids, fish peptides, and selenium as well as vitamins A, E, and D present in the fish may counteract the overall adverse effects of TMAO (Fig. 14.2).

Effects of changes in feed on the composition of eggs and meat

There is an unmet need to understand the role of livestock or feed of the animal in altering the nutrient content of eggs [7–9,11]. There is further evidence that soil chemistry such as mineral content in the soil can influence the nutrient content of livestock [40]. Animal feed is the food that is grown or developed for feeding large animals and poultry. Modern feeds are produced by carefully selecting and blending ingredients to provide highly nutritional diets. The objective is to maintain the health of the animals and increase the quality of such end products as meat, milk, or eggs. It seems that farm animals eating unhealthy foods would provide unhealthy meat and eggs, which may be peroxidized and proinflammatory.

Western types of foods, such as bread, biscuits, candies, syrups, preserved foods, and animal foods such as eggs and red meat from domesticated animals, are considered unhealthy. Increased intake of such foods may also inhibit the growth of gut microbiota of the host, resulting in an increased risk of NCDs [3,5,6].

Use of natural and synthetic estrogen, progesterone, and testosterone hormones by agribusiness, although not permitted, causes a rapid increase in animals' weight, increased size of eggs, and increased amounts of milk. These drugs boost production of growth-stimulating hormones, which help the animal convert feed into muscle, fat, and other tissues more efficiently than they would naturally. This artificial plumping process boosts the amount of meat, eggs, and milk that farmers can sell per animal. The consumption of meat, eggs, and milk from these animals may cause inflammation among human populations, leading to greater risk of obesity and NCDs much more rapidly compared to food from normally fed animals. (http://www.businessinsider.com/farmers-fatten-cattle-hormone-implants-2016-4?IR = T). The hunter-gatherer diets were paradoxical, being meat based but nonatherogenic because animal meat was from free-

ranging animals who ate what they found in the natural environment [5,14−16]. Feeding experiments have demonstrated that using flax seed and tea leaves as animal feed can increase the content of omega-3 fatty acids in egg, milk and meat [7−9]. As a matter of fact, no hormones have been allowed in poultry production for more than 50 years. Hormone use in poultry production was banned in the United States in the 1950s. Thus animal feeds are primarily made up of macroingredients such as cereal grains such as wheat, barley, and sorghum; oilseed meals, such as soybean or canola meal; and animal by-product meals. Cereal grains make up between 60% and 70% of the animals' diet and are the major source of energy in the feeds. Feed making for laying hens starts by mixing whole maize meal, soya, fish meal, maize bran, and limestone powder into a large bucket or barrel, which is stirred with a shovel until the feed is well mixed so that the chickens get nutrients from all the ingredients at once. However, if the hens are fed natural healthy food products, such as flax seeds and leaves from tea and other flavonoid-rich leaves, the milk may contain increased amount of omega-3 fatty acids, carotenoids, catechin, and beta-carotene [7−9].

Can a prudent diet improve gut microbiota and health?

Commonly used prudent foods are fruits, vegetables, whole grains, nuts, fish oil, olive oil, and mustard oil or canola oil. Eggs, chicken meat, and seafood are also considered prudent foods by most of the experts [5−7]. For example, residents of Greece average six or more servings a day of antioxidant-rich fruits and vegetables [28−30,41−43]. In the Mediterranean region, grains are typically whole grains and usually contain very few unhealthy trans fats or saturated fat, and bread is an important part of the diet [44]. However, throughout the Mediterranean region, bread is eaten plain or dipped in olive oil; hence its adverse effects if any are neutralized by flavonoids present in olive oil. Eating bread with butter or margarine, which contains saturated or trans fats, may have adverse effects on glycemia, free fatty acids, and lipoproteins. Nuts are another part of healthy Mediterranean-style diets, which are high in fat, but most of the fat is healthy monounsaturated fat, and there is a high content of omega-3 fatty acids in walnuts consumed in the Mediterranean region [44,45]. Since nuts are high in calories, they may be eaten in large amounts to avoid other energy-rich foods such as red meat and refined carbohydrates, which are considered unhealthy.

In a metaanalysis of the role of diet in metabolic syndrome, the authors conducted a systematic review and random effects of epidemiological studies and randomized controlled trials, including 50 original research studies (35 clinical trials, 2 prospective studies, and 13 cross-sectional studies) with 534,906 participants, were included in the analysis [44]. The combined effect of prospective studies and clinical trials showed that adherence to the Mediterranean diet was associated with a reduced risk of metabolic syndrome (log HR: 0.69, 95% confidence interval [CI]: 1.24−1.16). Additionally, results from clinical studies (mean difference, 95% CI) revealed the protective role of the Mediterranean diet on components of metabolic syndrome, such as waist circumference, diastolic blood pressure, and blood glucose. The results from epidemiological studies confirmed those of clinical trials. It is possible that this dietary pattern can be easily adopted by all population groups and various cultures and cost-effectively serve for primary and secondary prevention of the CVDs and other chronic diseases. Sofi et al. conducted a metaanalysis of cohort prospective studies that investigated the effects on diseases of adherence to the Mediterranean diet [41]. The study showed that a two-point increase in adherence to the Mediterranean-style diet was associated with a significant reduction in overall mortality [relative risk (RR) = 0.92; 95% CI: 0.90, 0.94], incidence or mortality from CVDs (RR = 0.90; 95% CI: 0.87, 0.93), cancer incidence or mortality (RR = 0.94; 95% CI: 0.92, 0.96), and incidence of neurodegenerative diseases (RR = 0.87; 95% CI: 0.81, 0.94). This updated metaanalysis confirmed, in a larger number of subjects and studies, the significant and consistent protection provided by adherence to the Mediterranean diet in relation to the occurrence of major chronic degenerative diseases.

In the PrediMed study, a multicenter randomized, controlled trial in Spain, 7447 participants (55−80 years of age, 57% women) who were at high risk of CVDs but with no CVDs at enrollment, were administered one of three diets: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet [42]. There were 288 incident cases; 96 (3.8%) of these occurred in the group assigned to a Mediterranean diet with extra-virgin olive oil, 83(3.4%) occurred in the group assigned to a Mediterranean diet with nuts, and 109 (4.4%) occurred in the control group [42]. In the intention-to-treat analysis including all the participants and adjusting for baseline characteristics and propensity scores, the HR was 0.69 for a Mediterranean diet with extra-virgin olive oil and 0.72 for a Mediterranean diet with nuts as compared with the control diet. In another component of PrediMed study, of 418 subjects, aged 55−80 years, after a median follow-up of 4.0 years, the incidence of diabetes was 10.1%, 11.0%, and 17.9% in the MedDiet with olive oil group, the MedDiet with nuts group, and the control group, respectively [18]. The PrediMed study, of 4282 women aged 60−80 years and at high risk of CVDs, were recruited and randomly allocated to a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed

nuts, or a control low-fat diet [43]. After a median follow-up of 4.8 years, there were 35 confirmed incident cases of breast cancer. Observed rates (per 1000 person-years) were 1.1 for the Mediterranean diet with extra-virgin olive oil group, 1.8 for the Mediterranean diet with nuts group, and 2.9 for the control group. The multivariable-adjusted HRs versus the control group were 0.32 for the Mediterranean diet with extra-virgin olive oil group and 0.59 for the Mediterranean diet with nuts group. In analyses with yearly cumulative updated dietary exposures, the HR for each additional 5% of calories from extra-virgin olive oil was 0.72 [43]. This randomized trial revealed for the first time that a long-term dietary intervention can prevent the risk of breast cancer incidence. There was a significant beneficial effect of a Mediterranean diet supplemented with extra-virgin olive oil in the primary prevention of breast cancer [43]. Since the results come from a secondary analysis of a previous trial involving a small number of patients with a few incident cases, they need to be confirmed by longer-term and larger studies. In most of the clinical trials involving persons at high cardiovascular risk, such as the PrediMed study, the comparison is made to determine differences in the incidence of major cardiovascular events, which is lower among those assigned to a Mediterranean diet supplemented with extra-virgin olive oil or nuts than among those assigned to a reduced-fat diet. This does not mean that this is the perfect intervention diet; further improvement in the diet may be associated with a greater increase in benefits.

Although poultry is an important part of Mediterranean-style diets, there was a significant decline in CVDs, diabetes mellitus, and cancer in the intervention group consuming eggs and chicken meat along with other Mediterranean foods. However, many patients in the intervention group as well as in the control group continued to suffer from these diseases, which may be due to continuation of egg consumption [18,42,43]. Previous cohort studies, such as the Northern Manhattan Study of 2568 participants (mean ± standard deviation age: 69 ± 10 years; 64% women; 55% Hispanic, 21% white, and 24% black) [46], the Nurses Health Study involving 72,113 female nurses [47], and the Greek Epic Prospective cohort study with the Greek segment comprising 23,349 men and women [48], reported similar results on follow-up of 10−15 years. It is possible that moderate consumption of ethanol, low consumption of meat and meat products and poultry including eggs, and high consumption of vegetables, fruits and nuts, olive oil, and legumes were highly protective in all these studies. A comparison of the highest and lowest quintiles of adherence showed that consumption of the Western diet was associated with increased total mortality, CVD mortality, cancer mortality, and mortality from non-CVD, noncancer causes, whereas an increased score for the Mediterranean diet was associated with beneficial effects on all these parameters.

The INTERHEART study, involving participants from 52 countries, examined the relationship between dietary patterns and risk of heart attack [49]. No association of Oriental diets with risk of heart attack was reported. A dietary risk score based on seven food items on the food frequency questionnaire (Western: meat, salty snacks, fried foods; prudent: fruits, green leafy vegetables, cooked vegetables, other raw vegetables) was constructed by the authors. A higher score, indicating a poor diet including poultry, was strongly associated with heart attack risk, and the subjects in the highest quartile of the score had a nearly twofold increased risk even after adjustment for established risk factors [49]. On the basis of an arbitrary cut point of the score (the top three quartiles versus the bottom quartile), the investigators estimated that 30% of heart attacks worldwide could be explained by unhealthy diets. Analysis of diet-quality indexes was based on prevailing dietary recommendations or healthful traditional diets, for example, the Mediterranean diet, the Japanese diet, and the Indo-Mediterranean diet. The Lyon Heart study, using a Mediterranean-style diet high in omega-3 fatty acids, included poultry in the diet, but the Indo-Mediterranean diet heart study did not include poultry as a healthy component of a diet [50,51]. The Diet and Reinfarction Trial, using 50−75 g of fish twice weekly, and the Lyon Heart Study were the first to demonstrate that total mortality can be reduced without reduction in LDL cholesterol [50,52]. In all these studies except the Indian experiment of Infarct Survival and the Indo-Mediterranean Diet Heart study, poultry, eggs, and chicken were considered prudent. However, in both trials, heart attack patients were advised to eat only fruits, vegetables, nuts, whole grains, soybean curd, and mustard oil, which resulted in a significant decline in total cardiovascular events [52,53]. It is possible that if poultry had been excluded from the prudent food category, the results of above studies would have been much better. The role of wild-type poultry in the evolutionary diet has also been appreciated by other investigators [14−16].

Comments

Eggs, chicken, and seafood have been considered components of prudent diets by most of the experts. Eggs, fish, other seafood, and meat from free-range animals are also component of Paleolithic diets [13−16]. However, the eggs and chickens that are produced today appear to be different from those that were consumed by the hunter-gatherers. Cohort studies on the association between egg consumption and risk of type 2 diabetes mellitus, CVDs, and cancer have been

inconsistent [41,44,45]. Since chicken eggs are a good source of protein and micronutrients and are inexpensive, it is important to clarify their role in the risk of diabetes, CVDs, and cancer.

The EAT-Lancet Commission report emphasizes diet quality to decrease morbidity and mortality due to NCDs [7]. However, this report is open to bias because there is less focus on reduction in energy consumption [54]. Since new and previous metaanalyses provide support to the connection between diet quality and risk of morbidity and mortality due to CVDs, diabetes, and cancer and since obesity is also associated with greater risk of NCDs, there is an unmet need to modify total diet and lifestyle for prevention of NCDs [7,54–67]. A metaanalysis involving 13 cohort studies showed that egg consumption was associated with increased breast cancer risk (RR: 1.04) [56]. Subgroup analyses showed that egg consumption was also associated with increased breast cancer risk based on cohort studies (RR: 1.04) among a European population (RR: 1.05), an Asian population (RR: 1.09), a postmenopausal population (RR: 1.06), and those who consumed 2–5/week (RR: 1.10) but not in case-control studies (RR: 1.06) [56]. There is evidence that egg intake may be implicated in the etiology of sex hormone–related cancers, but the dose-response association is not clear [57]. Previous cohort studies also support the hypothesis that egg intake may be associated with increased risk of morbidity and mortality due to CVDs and diabetes as well as cancer [57–64].

While studies conducted in the United States showed a positive association between increased intake and risk of CVDs and diabetes, the PURE study found no such association, which may be explained by differences in the baseline nutritional status of the subjects in the two studies [3,4]. However, in determining associations between egg intake and cardiometabolic diseases, principal components analysis is a commonly used method to define dietary patterns using food consumption information to identify common underlying dimensions (factors or patterns) of food intake. Earlier validation studies found that two major patterns (the prudent and Western patterns) identified through analysis of food consumption data assessed by food frequency questionnaires were reproducible over time and correlated reasonably well with the patterns identified from diet records. The consistent association observed between the Western or unhealthy dietary pattern (high in animal products, particularly red meat and preserved meat as well as eggs, salty snacks, refined starches and sugar, and fried foods and low in fruits and vegetables) and risk of acute coronary syndrome in different regions of the world from the INTERHEART study and other studies provides evidence of the adverse effects of globalization on human nutrition and risk of NCDs. However, the risk of diet varies from one population to another depending on variations in the susceptibility of the populations due to periconception factors and nutritional status during infancy and childhood that may be important determinants of morbidity and mortality in later life. The adverse effects of increased intake of meat and eggs as well as of total dietary cholesterol may vary depending on these factors, which can influence overall long-term health. A metaanalysis of new-onset heart failure following exposure to egg consumption was conducted among four prospective cohorts for a total of 105,999 subjects and 5059 cases of new-onset heart failure [64]. Comparing the highest (1 or more per day) to the lowest category of egg consumption, pooled RR of heart failure was 1.25 (95% CI = 1.12–1.39; $P = .00$). The findings suggest an elevated risk of incident heart failure with frequent egg consumption, which may be due to an increase in inflammation produced by egg intake in tissues that are already inflamed as a result of heart failure.

Despite a few weaknesses, most recent studies suggest that the current trend of dietary convergence toward a typical Western diet rich in eggs and red meat characterized by a high ratio of omega-6 to omega-3 acids and low in flavonoids, fruits, vegetables, and nuts is likely to play a role in the globalization of obesity, diabetes, CVDs, and cancers [3,57–67]. It is possible that adding nuts, whole grains, vegetables, and fruits as well as fish may provide increased intake of omega-3 fatty acids, fiber, and flavonoids as well as protein peptides and other micronutrients to modern diets, which might prevent the adverse effects of eggs, meats, and other unhealthy foods [18,41–44,46–53]. In a recent metaanalysis, 12 studies were included, involving 9513 cases and 181,906 controls [61]. The risk of breast cancer was significantly decreased in women with high intake of flavonols (RR = 0.88, 95% CI: 0.80–0.98) and flavones (RR = 0.83, 95% CI: 0.76–0.91) compared with the risk in women with low intake of flavonols and flavones [61]. Furthermore, summary RRs of three case-control studies stratified by menopausal status suggested that intake of flavonols, flavones, or flavan-3-ols is associated with a significantly reduced risk of breast cancer in postmenopausal women but not in premenopausal women. It seems that the intake of flavonols and flavones but not of other flavonoid subclasses or total flavonoids is associated with a decreased risk of breast cancer, especially among postmenopausal women. It is suggested that feeding tea leaves to animals such as hens may increase flavanols levels in the eggs and meat of the animals, which may be protective against diseases when such animals and their eggs are consumed as food.

Among 85,013 women and 46,329 men from the Nurses' Health Study (1980–2012) and Health Professionals Follow-up Study, increased intake of animal protein was positively associated with mortality, whereas increased intake of plant protein was inversely associated with mortality, especially among individuals with at least one lifestyle risk factor [65]. Substitution of plant protein for animal protein (especially from processed red meat) was associated with lower

mortality rates, suggesting the importance of plant protein for good health. In a cohort study from France, egg intake was positively and significantly associated with hypertension [67]. It is clear from more recent analysis that apart from egg cholesterol, egg protein may also have adverse effects on all-cause mortality [65]. Similar observation were made in a large prospective cohort; higher plant protein intake was associated with small reductions in risk of overall and cardiovascular disease mortality [66].

In brief, it is possible that eating three or more eggs per week can increase the risk of CVDs and diabetes in populations living in developed countries such as the United States. However, diabetic subjects and populations at high risk for diabetes may have greater risk of CVDs on eating three or more eggs per week. The findings also revealed that egg consumption is not associated with the risk of CVD and cardiac mortality in some populations, possibly owing to improvements in undernutrition-related problems and other confounders. A high egg intake may be associated with a modestly elevated risk of breast cancer, and a positive association between egg intake and ovarian and fatal prostate cancers cannot be ruled out. Feeding of flax seeds and tea leaves to hens may provide wild-type eggs and meat, which may be healthy, but long-term cohort studies and controlled trials are needed to confirm this hypothesis.

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Further reading

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Chapter 15

Effects of nutritional factors on immunity

Ram B. Singh[1], Sanjay Mishra[2], Somansh Rawal[2], Hardinsyah Hardinsyah[3,4], Ahmad Sulaeman[4] and Yasuo Kagawa[5]

[1]*Halberg Hospital and Research Center, Civil Lines, Moradabad, India,* [2]*School of Biotechnology, IFTM University, Moradabad, India,* [3]*Southeast Asia Probiotics Scientific and Regulatory Experts Network (SEA PROBIOTICS SREN), Bogor, Indonesia,* [4]*Department of Community Nutrition, Faculty of Human Ecology, Bogor Agricultural University, Bogor, Indonesia,* [5]*Kagawa Nutrition University Toshimaku, Tokyo, Japan*

Introduction

Diet and lifestyle factors appear to have a definite influence on innate and adaptive immunity, which may influence the development of non-communicable diseases (NCDs) [1−5]. Essential fatty acid (EFA) deficiency is known to enhance the susceptibility to infection because both alpha-linolenic acid and arachidonic acid are involved in maintaining immune function [2−5]. Oxylipins, which are derivatives of EFA, have a critical role in the development of immunity and inflammatory responses and are derived from polyunsaturated fatty acids (PUFA). Thus it becomes clear that PUFA can influence immunity and inflammation [1,2]. PUFA bound to membrane phospholipids are released on stimulation by hormones, cytokines, and other stimuli, such as viral infection, from cell membranes and become substrates for production of dodecanoids, eicosanoids, and docosanoids. Deficiency of PUFA and other micronutrients in Western-type diets may decrease these eicosanoids, resulting in a decline in T lymphocyte function and immune protection, predisposing the individual to infection [1−3]. Apart from diet, other factors, including tobacco intake, alcoholism, mental stress, pollutants, viral infections, and chronic diseases such diabetes, heart failure, chronic kidney diseases, and lung disease, are known to reduce immunity, predisposing the individual to infections and other NCDs [4−9]. However, there is an unmet need to determine the role of protective factors, which may be immunogenic and may alter the course of the disease, resulting in the suppression of viral infection and its complications. There is evidence that regular yoga practice, meditation, and mindfulness such as active prayer, moderate physical activity, optimal sleep, Indo-Mediterranean-style diets, omega-3 fatty acids, flavonoids, and herbs as well as a moderate intake of alcohol may have beneficial effects and ultimately act as immune modulators [10−20]. This review aims to emphasize that diet is the most important nutritional modulator of immunological function and may provide protection from diseases [1−3,12].

Risk factors and immunity

It is known that tobacco intake, alcoholism, and pollution are important toxicants that decrease immunity and protective immunological responses of the immune system [4−6]. These risk factors are significantly more common among patients with COVID-19 compared to the control group, which may contribute to increased risk of coronavirus infection and complications. This study also reveals that subjects who performed moderate physical activity were significantly lower in the COVID-19 group compared to the control group 25 (17.0%) versus 55 (36.66%), indicating that lack of moderate physical activity may have caused reduced immunity and increased susceptibility to COVID-19 (RBS: personal communication).

Apart from the above risk factors, physicochemical stress results from environmental factors, such as food/nutrition, toxins, metabolic disorders, infections, and inflammation as well as psychological stress, which may also decrease immunity [7]. It seems that if the immune system is compromised and cannot properly cope with stresses, or if the stress exceeds the regular adaptability of the immune system, this may lead to disease states or fatal conditions. On the other hand, the effects of psychological stress on the body and the immune system are well known [7,8]. Long-term and chronic stress leads to persistently high cortisol and corticosteroid levels, which cause resistance to cortisol and

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impaired antiinflammatory effects on the immune system. Such effects result in chronic infection, chronic inflammatory autoimmune diseases, or cancers as well as other physiological disorders. Chronic stress also inhibits the cross-talk of immune cells and signaling networks [7,8]. The immune system may be mounting adaptive responses to chronic stressors [9]. Immunological research involving cancer, rheumatoid arthritis, inflammatory bowel disease, asthma, multiple sclerosis, diabetes, heart diseases, and others has not only enabled an understanding of the mechanisms that underlie these diseases but also suggested new therapies that may positively affect patients, minimizing morbidity and mortality [9]. This chapter is aimed at presenting and discussing the advancement of research and innovative therapies involving chronic diseases, which have a high impact on society.

Evidence shows that purinergic signaling is involved in processes associated with the immune system in health and disease, including cardiovascular, neurological, and degenerative diseases [10]. These diseases may occur at any time from childhood and infancy to old age and are generally characterized by progressive deterioration of cells, eventually leading to tissue or organ degeneration. These pathological conditions can be associated with disturbance in the signaling mediated by nucleotides and nucleosides of adenine, in expression or activity of extracellular ectonucleotidases, and in activation of P2X and P2Y receptors [10,11]. Among these diseases the best known are atherosclerosis, hypertension, cancer, epilepsy, Alzheimer's disease, Parkinson's disease, and multiple sclerosis. The currently available treatments have limited effectiveness and are mostly palliative. Bagatini and collaborators reviewed the role of purinergic signaling, highlighting the ectonucleotidases E-NTPDase, E-NPP, E-5-nucleotidase, and adenosine deaminase in CVDs and other chronic diseases, neurological and degenerative diseases, and cancer [10,11].

Diet and immunity

There is evidence that a Western diet reduces immunity, whereas Mediterranean, Indo-Mediterranean, and Japanese diets may protect and modulate immune functions [1−5]. An Indo-Mediterranean-type diet includes a combination of Indian foods such as whole grains (red beans, green beans, black beans, kidney beans, gram, millet, and peas) and spices (coriander, cumin, fenugreek, turmeric, and mustard oil) along with Mediterranean foods (vegetables, fruits, nuts, olive oil, poultry, and fish with small quantities of red meat). These foods are rich in flavonoids and polyphenolics, vitamins, A, E, C, and D, and beta-carotene as well as the minerals zinc, copper, magnesium, selenium, and chromium, which possess potential antioxidant and immune-modulating action [1−3,15,16]. These foods and nutrients can prevent the decline in immune cell activation that has a protective effect on development of immunity and prevention of NCDs.

A Western diet is characterized by high energy and low levels of micronutrients and is known to generate free radical−induced oxidative stress, leading to systemic inflammation [1−3]. The effect of a Western diet is largely blunted by dietary changes, but myeloid cell−induced innate immune responses remain augmented and could predispose the individual to proinflammatory NCDs, if prevented measures are not undertaken [1−3]. Western diet triggers innate immunity, the nucleotide-binding oligomerization NLRs, and interferon-signaling pathways. Thus a Western diet induces long-lasting trained immunity in myeloid cells and alters the lipopolysaccharide responses of cyclic dimeric guanosine monophosphate and regulate hematopoietic stem cells. It is important to understand the mechanisms regarding the role of diet and lifestyle factors in the development of immunity to explain their role in the pathogenesis and prevention of COVID-19. It is proposed that diet- and lifestyle-induced immunological protection provided to a host should be recognized as trained immunity. It is an emerging new concept highlighting long-term hyperactivation of the innate immune system after exposure to certain antigenic stimulations. These antigens may be; infection, pollutants, or any oxidants, leading to an augmented immune response to a secondary stimulus. The nucleotide-like receptor precursor 3 can identify a Western diet rich in sugar, saturated fat. and salt and can mediate trained immunity. The trained immunity has evolved innate and adaptive immune systems. The adaptive immunity arm induces antigen-specific memory formation on encounter with any pathogen. The innate immunity arm rapidly evolves nonantigen-specific protective mechanisms against the pathogens. However, if the energy-rich, nutrient-deficient diet is continued, there may be immunosuppression. predisposing the individual to increased susceptibility from free radical−induced damage to tissues (Fig. 15.1).

It seems that several protective counteractive innate immune responses are evoked by the activation of a series of innate immune signaling receptors, such as Toll-like receptors (TLRs) and the NLRs. However, these receptors can further recognize "sterile" danger signals, which are thought to trigger inflammation in NCDs. These observations provide a link for activation of innate immune receptors with the development of rapid inflammation, leading to dysfunction of the body systems, similar to what occurs in COVID-19 infection. Trained immunity may exert beneficial effects for the host defense against invading pathogens by providing adaptations [1−3]. However, uncontrolled persistent innate immune activation causes chronic inflammatory diseases or acute inflammatory reaction, resulting from acute reactants,

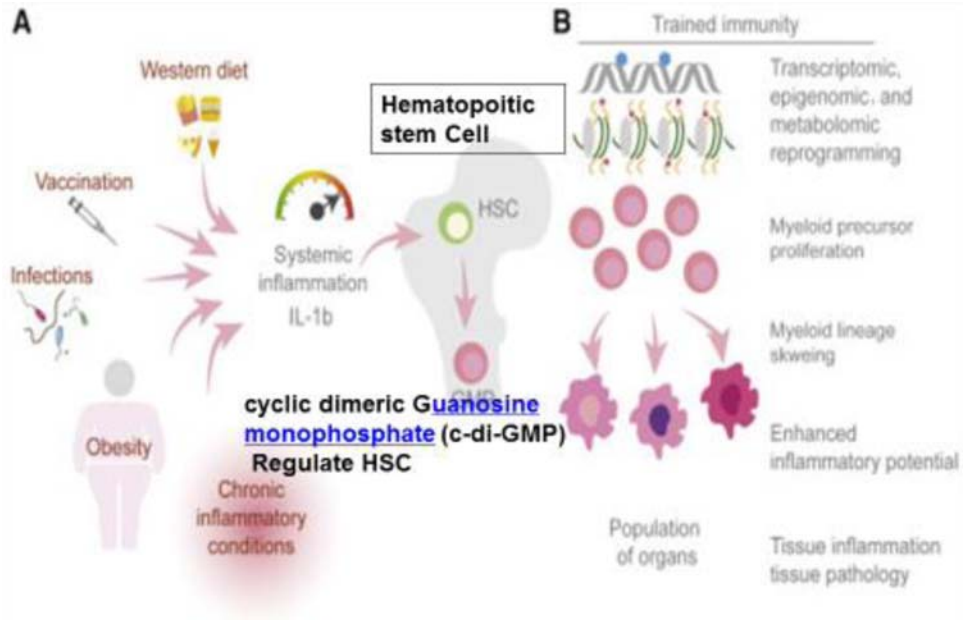


FIGURE 15.1 Effects of a Western diet on the immune system. *Modified from Christ A, Lauterbach M, Latz E. Western diet and the immune system: an inflammatory connection. Immunity 2019;51 (5):794–811. doi: 10.1016/j.immuni.2019.09.020; Yamaguchi NH. Smoking, immunity, and DNA damage. Transl Lung Cancer Res 2019;8 (Suppl 1):S3–S6. doi:10.21037/tlcr.2019.03.02.*

leading to thrombosis, in vascular cells and fibrosis-sepsis in alveoli, possibly causing consolidation leading to acute respiratory distress syndrome. The progression of disease is associated with inflammatory processes involving cells of the innate immune system, mainly monocyte-derived macrophages. Hence it is of fundamental and translational importance to understand explicitly the mechanisms that link to the consumption of energy-rich diets to increase in inflammation. In view of these considerations it is possible that Indo-Mediterranean-type diets can inhibit inflammation by reducing oxidative stress produced by COVID-19.

Effects of polyphenols and flavonoids on immunity

Among dietary factors, flavonoids have specific immunomodulatory effects that might be of importance in the development of many diseases in which immunity is reduced [15,16]. Among several types of immune cells, T lymphocytes play a critical role in protecting the immune system as well as in the pathogenesis of specific autoimmune diseases. In the immune system, mTOR, particularly in T lymphocytes, is an important mediator of metabolism. Polyphenolics and flavonoids can suppress mTOR activity and may induce the T regulatory subset [15]. There is evidence that several of the dietary flavonoids, including quercetin, naringin, hesperetin, and catechin, can influence virulence and replication of herpes simplex virus type 1 (HSV-1), poliovirus type 1, parainfluenza virus type 3, and respiratory syncytial virus (RSV) [16]. In cell culture monolayers, quercetin produced a concentration-dependent reduction in the infectivity of each virus. It also decreased intracellular replication of each virus when monolayers were infected and subsequently cultured in medium containing quercetin. Use of quercetin in the preincubation of tissue culture cell monolayers showed a marked decline in the ability of the viruses to infect or replicate in the tissue culture monolayers. Reduced intracellular replication of each of the viruses was observed on treatment with hesperetin. However, catechin inhibited the infectivity without any effects on replication of RSV and HSV-1 and had negligible effects on the other viruses. Naringin showed no effect on either the infectivity or the replication of any of the viruses studied. It seems that dietary flavonoids may have a variable spectrum of antiviral activity against certain RNA and DNA viruses, which may inhibit infectivity and/or replication, indicating that flavonoids might also inhibit these markers in COVID-19.

Effects of fatty acids on immunity

PUFA are known to exhibit a range of immunomodulatory functions that progress through T cell–mediated events, although the molecular mechanisms of these actions have not yet been fully elucidated [17,18]. It seems that some of these immune functions are linked to PUFA-induced alteration of the composition of cellular membranes and the consequent changes in signaling pathways linked to membrane raft-associated proteins. Some experts have suggested that significant aspects of the PUFA bioactivities are mediated through their transformation to specific lipid mediators,

products of cyclooxygenase, lipoxygenase, or cytochrome P450 enzymatic reactions [17,18]. It is possible that fatty acid–induced bioactive metabolites, including prostaglandins, leukotrienes, and endocannabinoids, are produced by and/or act upon T leukocytes through cell surface receptors and have been shown to alter T cell activation and differentiation, proliferation, cytokine production, motility, and homing events [17]. It is possible that appreciation of the mode of action of these lipids presents opportunities for the design and development of therapeutic strategies aimed at regulating T cell function. It is clear that fatty acids are involved in T cell biology both as nutrients that are important for energy production and as signaling molecules [14,17,18].

Omega-3 fatty acids induce an immune response apart from a decrease in inflammation. Long-chain omega-3 fatty acids may help to boost the immune system by enhancing the functioning of immune cells [18]. There is evidence that omega-3- and omega-6-derived metabolites have important immune regulatory functions. These metabolites are generally known as proresolving mediators. These mediators may be classified as prostaglandins, leukotrienes, thromboxanes, maresins, protectins, and resolvins. The synthesis of these molecules is orchestrated by certain enzymes: lipoxygenase, cyclooxygenase, or cytochrome P450. [14]. Omega-3 and omega-6 substrates compete for these enzymes as well as for the above-mentioned elongases and elastases. In the presence of omega-3 fatty acids the competition for the enzymes reduces the synthesis of omega-6-derived metabolites, which also have effects on immune cells (see Fig. 15.2).

There have been significant advances in understanding the mechanisms of action of *n*-3 fatty acids over the last ten years [18]. These include the identification of new actions of lipid mediators that were already described and of novel interactions among those mediators and the description of an entirely new family of lipid mediators, resolvins and protectins, that have antiinflammatory actions and are critical to the resolution of inflammation [18]. More recently, effects on signal transduction pathways and on gene expression profiles have been identified. It is also recognized that eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can inhibit the activation of the prototypical inflammatory transcription factor NF-κB. Recent studies suggest three alternative mechanisms by which *n*-3 fatty acids might have this effect. Within T cells as well as other cells of relevance to immune and inflammatory responses, EPA and DHA act to disrupt very early events involving formation of structures termed *lipid rafts*, which bring together various proteins to form an effective signaling platform [18]. Several effects of the *n*-3 fatty acids EPA and DHA on functional responses of cells involved in inflammation and immunity have been described. Fatty acid–induced modifications in membrane order and in the availability of substrates for eicosanoid synthesis are long-standing mechanisms that are considered important.

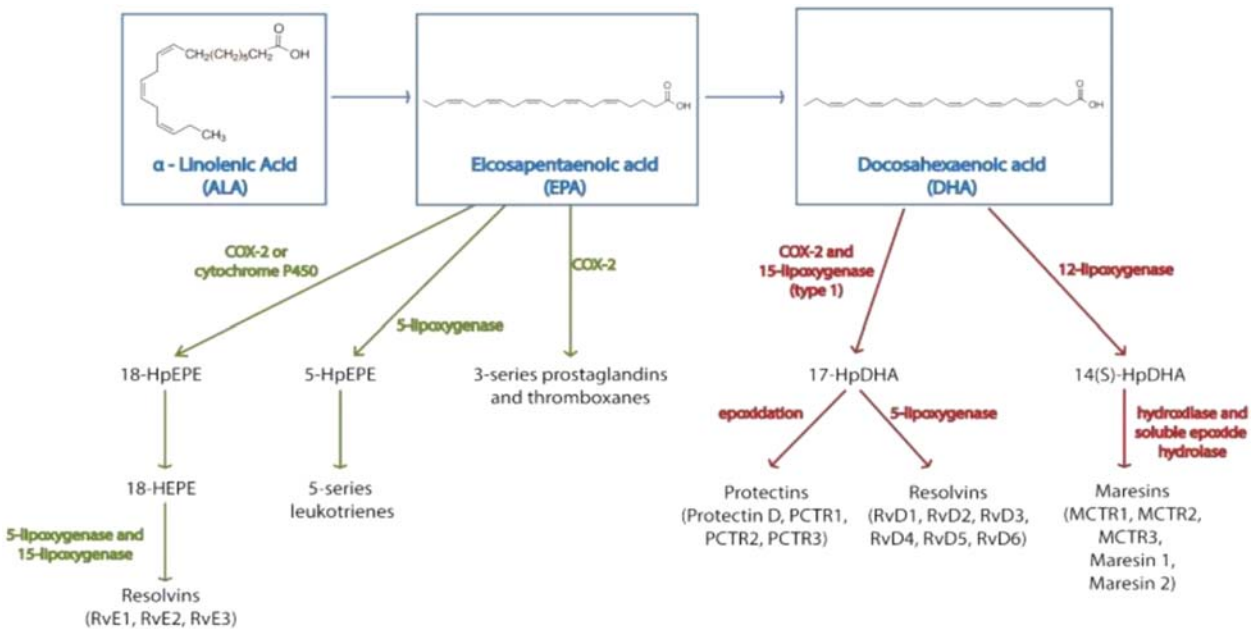


FIGURE 15.2 Main biochemical pathways for the synthesis of omega-3-derived metabolites. The figure shows the omega-3 fatty acids alpha-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid; their downstream metabolites; and the enzymes regulating their synthesis. *Modified from Gutiérrez S, Svahn SL, Johansson ME. Effects of omega-3 fatty acids on immune cells. Int J Mol Sci 2019;20(20):5028. doi:10.3390/ijms20205028.*

Arachidonic acid

Arachidonic acid is found in muscle and eggs acts as a chemical messenger first released by the muscles during intense weight training, controlling the core physiological response to exercise and regulating the intensity of all growth signals. If there is any tissue injury, inflammation is involved in healing of the wound as mediated by arachidonic acid present in cell membranes that produces eicosanoids. T cells, also called T lymphocytes, are a type of leukocyte that is an essential component of the immune system. The T cells are one of two primary types of lymphocytes—B cells being the second type—that determine the specificity of immune response to antigens in the body that may be under the influence of an inflammatory reaction in the tissues [13]. The eicosanoids may be proinflammatory and antiinflammatory and compete with each other. Of two prostaglandins, arachidonic acid is the substrate to PGE2 and PGF2a. The first one is generally thought to be proinflammatory, while the second is antiinflammatory [13]. There is evidence that PGF2a specifically is the prostaglandin that is most closely tied to increased synthesis of protein in the skeletal muscle. Skeletal muscle tissue has no capacity to actually store prostaglandins, so the only local source for PGF2a is the arachidonic acid that is retained in the outer phospholipids layer of each cell [13]. It is the stretching of muscle fibers during intense physical exercise that causes arachidonic acid to be released and metabolized to active prostaglandins.

The intake of *n*-6 PUFA greatly exceeds that of *n*-3 PUFA in most dietary patterns [13]. Arachidonic acid, a type of *n*-6 PUFA that is present in eggs, meat, and fish, gives rise to the eicosanoid family of inflammatory mediators, such as prostaglandins, leukotrienes, and related metabolites. It is possible that these mediators regulate the activities of inflammatory cells, the production of cytokines, and the various balances within the immune system [13]. It is possible that increased intake of fish oil and oily fish provides a good source of long chain *n*-3 PUFA as well as arachidonic acid, which is found in fish. Consumption of these fatty acids liberates the amount of arachidonic acid from cell membranes, increasing its availability for eicosanoid production. Thus one important mechanism of action of *n*-3 PUFA may be that it act as arachidonic acid antagonists. Components of both natural and acquired immunity, including the production of key inflammatory cytokines, may be under the influence of *n*-3 PUFA. Although some of the effects of *n*-3 fatty acids may be brought about by modulation of the amount and types of eicosanoids that are made, these fatty acids might elicit some of their effects by eicosanoid-independent mechanisms. Such *n*-3 fatty acid−induced effects may be of use as a therapy for acute and chronic inflammation and for disorders that involve an inappropriately activated immune response [13,14].

Effects of herbs on immunity

The benefit of most of herbs that have built-in immune-stimulating and inflammation-modulating effects means that they can help to prevent immune overreaction (cytokine storm) to a viral respiratory infection (VRI) while still helping the immune system to cope better with the infection. The scientific basis supporting these contentions has been discussed [19]. Major herbs with clinical trial evidence that they help to resolve VRI that have been reviewed in detail include *Sambucusnigra* (black elder) fruit, BNO 1016 (Sinupret) formula, *Andrographis paniculata* (kalmegh), *Pelargonium sidoides* (African geranium), máhuángtāng (maō-tō, ephedra decoction), and antiwei formula. The failure of research on *Echinacea angustifolia* (narrow-leaved purple coneflower), particularly by using doses that were far too low, is reviewed. An individualized approach to formulating for VRI patients is presented, followed by a review of the evidence that various herbs, notably *Panax ginseng* (Asian red ginseng), *Panaxquinquefolius* (American ginseng), *Camellia sinensis* (green tea), and *Allium sativum* (garlic), can prevent VRI [19].

The occurrence of coronavirus infection has become a public health problem in India, according to the government of India's Ministry of Health [21]. Half of the deaths occur among subjects above 60 years and one-third of deaths have occurred among subjects between 34 to 60 years, in India. The death rates are greatest among people with comorbidities, including diabetes mellitus, heart failure, coronary artery disease, and chronic kidney disease (78%). The death rate is lower (14%) among subjects younger than 45 years. COVID-19 has been declared a pandemic, having infected people in well over 200 countries around the globe [21−23]. Since COVID-19 infection is associated with marked decline in immunity, it poses the possibility that diet and lifestyle factors related to immune function may influence rates of infection, complications, and deaths.

Increasing evidence suggests that light to moderate amounts of polyphenol-rich alcoholic beverages such as wine or beer could have health benefits [20]. Scientists have long debated the effects of alcohol on immune function, showing, on the one hand, that high doses of alcohol consumption can directly suppress a wide range of immune responses and that alcohol abuse is associated with an increased incidence of a number of infectious diseases. On the other hand, moderate alcohol consumption seems to have a beneficial impact on the immune system compared to alcohol abuse or

abstinence [20]. Therefore the link between alcohol consumption, immune response, and infectious and inflammatory processes remains incompletely understood. With this in mind, it is important to realize that other factors, unrelated or indirectly related to immune function, such as drinking patterns, beverage type, amount of alcohol, or gender differences, will affect the influence that alcohol consumption may have on the immune system. It is possible that light to moderate amounts of polyphenol-rich beverages such as wine or beer may have beneficial effects [12].

There is evidence that sleep can also influence immunity which is bidirectionally linked [24]. Immune system activation appears to alter sleep, and sleep in turn affects the innate and adaptive arm of the body's defense system. A short sleep of less than 6 hours in 24 hours may reduce immunity, whereas a normal sleep of 6−8 hours in 24 hours may modulate immune functions. Stimulation of the immune system by environmental factors, such as microbial challenges, triggers an inflammatory response that, depending on its magnitude and time course, can induce an increase in sleep duration and intensity but also a disruption of sleep. Enhancement of sleep during an infection is assumed to feed back to the immune system to promote host defense. However, sleep affects various immune parameters and may be associated with a reduced infection risk, and it can improve infection outcome and vaccination responses [24]. Absence of an infectious challenge may induce hormonal changes to promote inflammatory homeostasis through effects on several inflammatory mediators, such as cytokines. Prolonged sleep deficiency, such as short sleep duration or sleep disturbance, can predispose a person to chronic, systemic, low-grade inflammation and may be associated with NCDs. It is possible that the induction of a hormonal constellation supporting immune functions is one likely mechanism underlying the immune-supporting effects of sleep.

In brief, Mediterranean-type diets, which are rich in polyphemols and flavonoids, omega-3 fatty acids, and arachidonic acids, may be important immune modulators, as may moderate alcohol intake, physical activity, and sufficient sleep. It is possible that vitamins A, E, C, and D and beta-carotene and the minerals zinc, copper, selenium, chromium, and magnesium may have beneficial effects on immunity. However, Western-type diets that contain sugar, excessive amounts of salt, trans fat, refined foods, and processed and red meat may have adverse effects on immunity, as may tobacco use, excessive intake of alcohol, short sleep, and infections.

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Chapter 16

Fish, fish oil, and fish peptides and other seafood

Ram B. Singh[1], Kumar Kartikey[2], Adrian Isaza[3], Kazuyoshi Yazawa[4], Shaw Watanabe[5], Lekh Juneja[4] and Manal M.A. Smail[6]

[1]*Halberg Hospital and Research Center, Civil Lines, Moradabad, India,* [2]*Halberg Hospital and Research Institute, Moradabad, India,* [3]*Alternative Medicine, Everglades University, Tampa, FL, United States,* [4]*Lifescience Association, Tokyo, Japan,* [5]*Clinical & Functional Nutriology, Life Science, Tokyo, Japan,* [6]*University of Central Lancashire, Preston, United Kingdom*

Introduction

Cardiovascular diseases (CVDs) are major components of non-communicable diseases (NCDs), which are the leading cause of death and disability worldwide. The major NCDs are CVDs, diabetes, cancers and respiratory diseases, which have devastating impact. It seems that fatty acid composition of the diets appears to be important determinant of increased risk of morbidity and mortality due to CVDs and other chronic diseases [1−5]. Therefore novel prevention and treatment strategies, including marine organisms, are considered as an important source of therapy due to the presence of bioactive peptides that can exert biological functions to prevent and treat NCDs [1,2]. Since linoleic acid (omega-6 fatty acid), linolenic acid (omega-3 fatty acid) and arachidonic acid (AA) are not synthesized by the body, these three are called essential fatty acids, which must be obtained from the diet. The cause of lack of synthesis of these fatty acids may be the absence of endogenous enzymes for omega-3 desaturation [1−4]. In an epidemiological study, blood fatty acid levels of 2480 men aged 42 and 60 years were examined [5]. After 22 years, 1143 men had died from NCDs, including CVDs. The risk of premature death due to CVDs was 43% lower in the group with the highest level of linoleic acid when compared to the group with the lowest level of linoleic acid [5].

The American Heart Association has advised that one to two servings of seafood per week be included in the diet to decrease the risk of coronary artery disease (CAD), heart failure, ischemic stroke, and sudden cardiac death, especially when seafood replaces a less healthy food [6,7]. This advisory from the AHA reviewed the evidence and made the suggestion in the context of the *2015−2020 Dietary Guidelines for Americans* and in consideration of other constituents of seafood and the impact on sustainability. Seafood appear to have antiinflammatory, antiarrhythmic, hematological, and endothelial benefits, which may be due to the high content of omega-3 fatty acids and AA in seafood. However, longer-term dietary trials of seafood are warranted to substantiate the benefit of seafood as a replacement for other healthy foods [6,7]. This review aims to highlight the role of fish oil, fish, and fish peptides in the prevention of CVDs and diabetes.

The fish oil debate

The American Heart Association (AHA) continues to recommend marine omega-3 fatty acid supplementation for patients with prevalent CAD for reduction of mortality [6,7], However, there is insufficient evidence for its use in prevention among patients at high risk of CVDs but without CAD and stroke [7]. There is an intense debate on the use of fish oil or long-chain omega-3 fatty acid supplementation regarding its beneficial effects in reducing risk of CVD [8]. Hu et al. emphasized that consistent results are available from observational studies, reporting inverse associations between higher fish consumption and lower risk of heart disease [4,9,10], Surprisingly, controlled clinical trials examining the role of marine omega-3 supplementation, usually a moderate-dose combination of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) compared with placebo, have reported negative results [11,12]. These studies cast suspicion on a causal relationship between fish oil intake and prevention of CVD [13]. A previous metaanalysis

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including ten randomized, trials, reported no significant favorable effects of marine omega-3 fatty acid supplementation on fatal or nonfatal CAD or any major vascular events during the one year of follow-up [14]. Similar conclusions were drawn in another expanded metaanalysis that included smaller trials with fish oil as well as dietary intervention trials [15].

The AHA has recommended that people with CAD consume omega-3 fatty acids from fish oil to prevent another heart attack [6,7]. This recommendation was based on early randomized, controlled trials, which found that fish oil supplementation was associated with lower rates of stroke, heart attack, and death in people who already had heart disease [3,4]. Recently, large trials were conducted to examine the relationship between fish oil and heart disease, but they produced mixed and confusing results [8]. Clinical studies in humans have not consistently supported the protective benefits of fish oil supplementation in the prevention of CVDs [8]. The ASCEND and VITAL trials were published later, reporting mixed results [16,17]. The ASCEND trial included patients with diabetes mellitus but without known CAD, and supplementation of fish oil intervention failed to cause significant decline in myocardial infarction (MI) or strokes, but did significantly lower risk of death from heart MI and stroke [16]. The VITAL trial, which was designed to determine the effects of fish oil supplementation in primary prevention, also failed to find a significant decline in all major CVD events [17]. Among subjects who did not eat fish, there was a significant decline in MI in study subjects who took fish oil supplements. The REDUCE-IT trial examined the effect of high-dose fish oil supplements on people with high blood triglyceride levels who were at elevated risk for CVD [18]. Surprisingly, REDUCE-IT, using 4 g/day of EPA alone, demonstrated a significant decline in cardiovascular events among subjects in the intervention group, who were taking high-dose fish oil supplements. In the Indian Experiment of Infarct Survival, 1.08 g/day of EPA + 0.72 g of DHA in fish oil were administered to patients with acute MI was associated with significant decline in cardiovascular events in the intervention group compared to control group after one year [3]. The REDUCE-IT used Vascepa, a version of the EPA fish oil supplement, which is FDA-approved, to treat triglyceride levels of 500 mg/dL or higher [18]. Recently, an FDA advisory panel unanimously voted in favor of expanding approved use of Vascepa in patients with hypertriglyceridemia to reduce the risk of cardiovascular events.

In October 2019 a repeat of the earlier metaanalysis [14], but now including 13 trials instead of the original 10, was published [4]. The addition of these three trials increased the sample size by almost 65%, from 77,917 study participants to 127,477 participants. This large metaanalysis demonstrated that fish oil omega-3 supplementation can cause significant reduction in the risk of MI and CAD [4]. However, no significant benefit was observed for stroke. The reductions in risk was linearly related to doses of omega-3 fatty acid, indicating the higher the dose, the greater the decline in risk. It is clear that results and conclusions observed in earlier trials, such as Indian Experiment of Infarct Survival [3] and the GISSI-Prevenzione trial [19], should have been duly trusted regarding beneficial effects of fish oil in the prevention of CVDs, including deaths. This scientific proof has also been provided by the most extensive systematic metaanalysis of effects of omega-3 fatty acids on cardiovascular health to date [20]. There is significant moderate- and low-certainty evidence suggesting that increasing long-chain omega-3 fatty acid intake causes at least a slight but definite reduction in the risk of CAD mortality and events. Fish oil supplements also reduce serum triglycerides [18,20]. However, this analysis found only slight benefit from the use of alpha-linolenic acid (ALA) in decreasing the risk of cardiovascular events and arrhythmia.

Singh et al. were the first to conduct a randomized, placebo-controlled trial comparing the effects of treatment with fish oil (EPA, 1.08 g/day) and mustard oil (ALA, 2.9 g/day) for one year in the management of 122 patients (fish oil, group A), 120 patients (mustard oil, group B), and 118 patients (placebo, group C) with suspected acute MI (AMI) [3]. After one year, the numbers of total cardiac events were significantly lower in the fish oil and mustard oil groups compared with the placebo group (24.5% and 28% vs 34.7%, $P < .01$). The numbers of nonfatal infarctions were also significantly lower in the fish oil and mustard oil groups compared with the placebo group (13.0% and 15.0% vs 25.4%, $P < .05$). The number of total cardiac deaths showed no significant reduction in the mustard oil group; however, the fish oil group had significantly fewer cardiac deaths compared with the placebo group (11.4% vs 22.0%, $P < .05$). Apart from the decrease in the cardiac event rate, the fish oil and mustard oil groups also showed a significant reduction in total cardiac arrhythmias, left ventricular enlargement, and angina pectoris compared with the placebo group. Reductions in blood lipoproteins in the two intervention groups were modest and do not appear to be the cause of the benefit in the two groups. Diene conjugates showed a significant reduction in the fish oil and mustard oil groups, indicating that part of the benefit may be derived from the reduction in oxidative stress. The findings of this study suggest that fish oil and mustard oil, possibly owing to the presence of n-3 fatty acids, may provide rapid protective effects in patients with AMI [3].

It should be noted that the majority of metaanalyses are conducted by experts who have received funds from rival food and drug companies that have vested commercial interests in results that will safeguard their business. After

publication of the Lyon Diet Heart Study in 1994, the Indian Experiment of Infarct Survival-3 in 1997, and the Indo-Mediterranean diet heart study in 2002, showing that increased intake of rape seed oil containing ALA can cause significant decline in CVDs, there was an epidemic of metaanalyses supported by the corn oil and sunflower oil industry to provide evidence that omega-3 fatty acids are not that healthful [3,21,22]. A similar situation may have occurred with regard to the drug industry when results on the intake of fish in the Diet and Re-infarction trial in 1989 and the intake of fish oil in earlier studies were published [3,19,23]. The Diet and Re-infarction Trial (DART), a randomized, controlled trial with a factorial design, was done to examine the effects of dietary intervention in the secondary prevention of MI [23]. The DART study included 2033 men who had recovered from MI and who were randomized to receive or not receive advice on each of three dietary factors: a reduction in fat intake and an increase in the ratio of polyunsaturated to saturated fat, an increase in fatty fish intake, and an increase in cereal fiber intake. The patients eating fatty fish showed a 29% reduction in two-year all-cause mortality, which was significant and was not altered by adjusting for ten potential confounding factors. The two-year incidence of re-infarction plus death from CAD was not significantly affected by any of the dietary regimens. A modest intake of fatty fish (two or three portions per week) may reduce mortality in men who have recovered from MI. However, in this study, increased intake of peptides was not considered to be a protective factor for providing benefits. The advice on fat was not associated with any difference in mortality. However, patients who were given fiber advice had a slightly higher nonsignificant mortality than other subjects [23].

The GISSI-Prevenzione trial including 11,324 patients surviving recent ($\leq$3 months) MI were randomly assigned to receive supplements of n-3 polyunsaturated fatty acids (PUFAs) (1 g daily, $N = 2836$), vitamin E (300 mg daily, $N = 2830$), both ($N = 2830$), or none (control, $N = 2828$) for 3.5 years [19]. Treatment with n-3 PUFA, but not with vitamin E, significantly reduced the risk of the primary endpoint [relative-risk (RR) decrease by 10%, 95% confidence interval (CI): 1−18] by two-way analysis and 15% (95% CI: 2−26) by four-way analysis. Benefit was attributable to a decrease in the risk of death (14%, 95% CI: 3−24, two-way analysis; 20%, 95% CI: 6−33, four-way analysis) and cardiovascular death (17%, 95% CI: 3−29, two-way analysis; 30%, 95% CI: 13−44, four-way analysis). The effect of the combined treatment was similar to that for n-3 PUFA for the primary endpoint (14%, 95% CI: 1−26) and for fatal events (20%, 95% CI: 5−33) [19]. Dietary supplementation with n-3 PUFA led to a clinically important and statistically significant benefit. Vitamin E had no benefit. Its effects on fatal cardiovascular events require further exploration.

These conclusions are also confirmed in the metaanalysis of studies published in 2020 on intake of fish oil [20] and fish [23]. In this metaanalysis a total of 427,678 men and women aged between 40 and 69 years who had no CVD or cancer at baseline were enrolled and followed up to the end of 2018 [20]. At baseline, 133,438 (31.2%) of the participants were habitually taking fish oil supplements. The multivariable adjusted hazard ratios for habitual users of fish oil versus nonusers were highly significant: 0.87 for all-cause mortality, 0.84 for CVD mortality, and 0.93 for incident CVD events. The association appeared to be stronger for cardiovascular events among those with prevalent hypertension ($P = .005$). This large metaanalysis has proven that habitual use of fish oil seems to be associated with a lower risk of all-cause and CVD mortality and to provide a marginal benefit against CVD events among the general population [20]. It is possible that incorporating new data from the large trials and metaanalysis, with and without inclusion of REDUCE-IT, is important to provide the most up-to-date evidence. The dose−response relationships between marine omega-3 supplementation and CVD risks is also an important subject that has not been addressed by previous metaanalyses [4]. The possible biochemical mechanisms that have been proposed for beneficial effects of omega-3 fatty acids are supported by animal and clinical research [24] (Table 16.1).

However, before we all start reaching for supplements, it may be worth following a heart-healthy diet full of fresh fruits and vegetables with lean protein such as fish, as recommended by the AHA and all other stakeholders [6,7,21−23]. It seems that it is worth administering high-dose EPA fish oil supplements to the subjects who are at highest risk, especially those with elevated levels of triglyceride. The current Scientific Advisory from the AHA addressed some of the important points emphasizing fish and fish oil intake [6,7]. The experts stated that fish oil supplements

TABLE 16.1 Mechanisms of beneficial effects of omega-3 fatty acids.

Stabilizing blood flow in and around the heart
Reducing inflammation by reducing cytokines and by producing lipid mediators
Preventing blood clots by antiplatelet effects
Lowering blood pressure by vasodilation due to increased NO release
Reduction in triglycerides
Antiarrhythmic effects

may help in the prevention of mortality associated with MI. However, guidelines might now change because there is some evidence of cardiovascular benefit even for the general population [20,25−27]. Apart from omega-3 fatty acids, fish also contain AA and peptides, which may be protective against CVDs and diabetes [28−32]. In view the several beneficial effects of fish and fatty acids, seafood should be included as a most beneficial component of healthy dietary pattern [28−36].

Fish peptides and fish in the diets

Most physicians and scientists are aware of the potential cardiovascular benefits of fish fatty acids and fish, but they may not be aware of some important details regarding peptides, owing to technical ignorance [1,24−27]. The PUFAs as well as peptides are most commonly found in fish, such as salmon, herring, anchovies, mackerel, and tuna. Lower levels are found in shellfish, tilapia, and cod [1]. The average seafood consumption in the United States in 2012 was 1.3 servings per week, a figure that was just slightly higher than average seafood consumption in 1999 [6,7]. The most common sources of seafood were shrimp, salmon, and canned tuna [25,26]. Several guidelines have recommended consumption of at least one to two servings of fish per week, preferably an oily fish that is substituted for another animal protein [25−27]. In fact, one serving per week of a fatty fish such as salmon could deliver the PUFAs as well as peptides necessary to maintain health and prevent CVDs [1].

Recent studies have reported antioxidant, antiobesity, cardioprotective, anticancer, and antidiabetic effects of marine-derived bioactive peptides based on consistent scientific evidence supporting the utilization of marine organisms and their bioactive peptides to prevent NCDs [1,38,39]. Marine-derived bioactive peptides are alternative sources for synthetic ingredients that contribute to good health as part of nutraceuticals and functional foods that can be measured [38,39]. Omega-3 fatty acids may have greater beneficial effects on cardiometabolic diseases when combined with omega-6 fatty acids at a ratio of less than 5 [40]. Fish peptides were not popular during the publication of earlier studies on fish intake and CVDs. Therefore most studies examined the association of higher omega-6/omega-3 fatty acids in the diet and reported a higher prevalence of metabolic syndrome and CVDs in earlier studies [36,40].

Many food scientists advise that fish and fish side streams are valuable sources of high-value components, including peptides [37]. Algae and other marine by-products, such as fish, have been recognized as rich sources of structurally diverse bioactive peptides [1]. After ingestion and digestion by the gut enzymes, proteins are absorbed as amino acids and peptides from the gut and may act as therapeutic agents [1]. The structural characteristics, including unique amino acid residues in these peptides, may be responsible for their biological activity [41]. Various species of marine origin show multifunctional bioactivities that are useful for new discoveries and/or reinvention of biologically active ingredients, nutraceuticals, and/or pharmaceuticals. Furthermore, a wider spectrum of bioactive peptides can be produced through proteolytic-assisted hydrolysis of various marine resources under controlled physicochemical (pH and temperature of the reaction media) conditions. Owing to their numerous health-related beneficial effects and therapeutic potential in the treatment and/or prevention of many diseases, such marine-derived bioactive peptides exhibit a wider spectrum of biological activities, including anticancer, antiproliferative, anticoagulant, antibacterial, antifungal, and antitumor activities [41]. On the basis of emerging evidence of marine-derived peptide mining, the above-mentioned marine resources contain noteworthy levels of high-value protein.

Proteins from different fish species and different raw materials, such as fish fillets and by-products, have shown promising cardioprotective effects, including cholesterol metabolism in rodents and humans [37,42]. Blue whiting (*Micromesistius poutassou*) is used mainly to produce fish meal for the feed industry. During this production, a water-soluble protein fraction is isolated that contains small peptides that are easily absorbed and may hold bioactive properties. In an experimental study, the effects of water-soluble fish protein on cholesterol metabolism were investigated in twelve male obese Zucker fa/fa rats [42]. Rats were fed diets with water-soluble protein from blue whiting as one-third of the total protein and the remaining two-thirds as casein (blue whiting group) or with casein as the sole protein source (control group). After a five-week intervention, the blue whiting group had lower total serum cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol concentrations and lower cholesteryl ester concentration compared to controls. Hepatic concentrations of cholesterol, 3-hydroxy-3-methylglutaryl coenzyme A reductase, and LDL receptors were also lower in the intervention group. The blue whiting diet led to lower concentrations of serum and liver cholesterol in obese Zucker fa/fa rats, probably owing to lower hepatic cholesterol synthesis [42].

Blue whiting is used primarily to produce fish meal for the aquaculture industry and is utilized only to a limited extent for human consumption [42]. Proteins from this component may be upgraded to products suitable for human consumption, thereby leading to products with higher value. Fish meal can be produced from either the whole fish or fish

by-products, such as heads, guts, and bones [37,42]. During the production process, the aqueous fraction containing water-soluble protein (stick water) is separated from the solid parts of the fish material. Small peptides, free amino acids, and low molecular−weight compounds, such as taurine, are found in the water-soluble fish protein fraction. Unlike large proteins, short peptides (mainly dipeptides and tripeptides) can produce local effects in the digestive tract or enter the circulatory system without prior digestion and thus exert effects as bioactive compounds [37,42]. The effects of water-soluble proteins from blue whiting may lead to improved utilization of this source of proteins and promote the development of dietary supplements targeting risk factors for CVDs [37,42].

Effects of fish proteins on coronary risk factors

Epidemiological studies have strongly indicated an association between fish consumption and reduced risk of CVD, but data from randomized controlled trials have been inconclusive [6,7,25,26]. The effects of fish consumption on plasma lipids and lipoproteins have been well described in studies that have generally been conducted with fatty fish and fish oil capsules. The popularity of high-protein diets for weight reduction is immense. However, there is an unmet need to examine the potential benefits from altering the source of dietary protein rather than the amount, which show several benefits [43−46]. In a parallel intervention trial, 276 overweight subjects were following a diet designed for weight loss [43]. The subjects were randomized to four groups and followed a diet plan with either lean meat, lean meat supplemented with omega-3 fatty acids, cod, or salmon during eight weeks. After the intervention period of eight weeks, the amount of the oxidation product was significantly reduced in the group that followed the cod-based diet (from 1.81 to 1.72 nM). At the same time, the antioxidant capacity in this group increased significantly (from 0.62 to 0.71 nM) and was significantly higher than that in the individuals who followed the lean meat diet and the lean meat with omega-3 capsules diet [43]. The authors suggested that the specific protein characteristics of cod or the high amount of taurine may have contributed to this effect.

In another study, the effects of fish protein supplement on glucose and lipid metabolism in 34 overweight adults were examined [44]. The adult subjects were randomized to eight-week supplementation with fish protein or placebo tablets (controls). The intake of fish protein supplement was 3 g/day for the first four weeks and 6 g/day for the last four weeks. In this study, eight weeks of fish protein supplementation resulted in lower values of fasting glucose ($P < .05$), two-hour postprandial glucose ($P < .05$), and glucose-area under the curve (AUC) (five measurements over two hours, $P < .05$) after fish protein supplementation compared to controls. Glucose-AUC was decreased after eight weeks of fish protein supplement compared to reference (start) ($P < .05$), concomitant with increased 30-minute and decreased 90-minute and two-hour insulin C-peptide concentration ($P < .05$) and reduced LDL cholesterol ($P < .05$). Percentage of body muscle was increased ($P < .05$) and percentage of body fat was reduced ($P < .05$) after four weeks of supplementation. Physical activity and energy and macronutrient intake did not change during the course of the study. Short-term daily supplementation with a low dose of fish protein may have beneficial effects on blood concentrations of glucose and LDL cholesterol as well as glucose tolerance and body composition in overweight adults [44]. The long-term effects of fish protein supplementation is of interest in the context of using more fish as a protein source in the diet, and the effects of inclusion of fish in the diet of individuals with low glucose tolerance should be evaluated. However, not all studies have reported significant beneficial effects. In a clinical study of 126 overweight subjects, a comparison of eight-week interventions consisting of 150 g cod, 300 g cod, or no cod per week, showed no difference among the three groups and hence no benefit [45]. Fish intake can also reduce other coronary risk factors, such as blood pressures and inflammation, and may also cause a significant decline in mortality due to CVDs [10,46−49].

Many studies have examined the role of peptides obtained from salmon, tuna, or bigeye tuna, protein-derived hydrolysates, and fatty acids from lean fish, on coronary risk factors from various countries [50−55]. Angiotensin I−converting enzyme (ACE) inhibitory peptides derived from salmon muscle has also been found to have antihypertensive effects [56].

A previous study showed that, in comparison with a cholesterol-free diet, both lean fish and beef diets raised plasma LDL cholesterol concentrations, but the fish diet resulted in lower concentrations of plasma total cholesterol, triglycerides, and very low-density lipoprotein (VLDL) cholesterol [57]. The beef diet also resulted in higher plasma HDL concentrations. These findings can help practitioners to extend their dietary recommendations to incorporate significant quantities of low-fat fish to reduce triglyceride concentrations. The primary outcome in a randomized, controlled trial with a crossover design was to elucidate the potentials of the two main dietary protein sources, lean seafood and nonseafood, in reducing fasting and postprandial lipid levels in healthy subjects [58]. After a three-week run-in period and separated by a five-week washout period, 20 healthy subjects (7 men and 13 women) consumed two balanced diets that varied in main protein sources (60% of total dietary proteins from lean seafood or nonseafood sources) for four weeks.

Compared to the nonseafood intervention, the lean seafood intervention reduced fasting (relative difference by diets: 0.31 mmol/L; $P = .03$) and postprandial ($P = .01$) serum triacylglycerol concentrations [58]. The lower serum triacylglycerol concentration was associated with reduced fasting triacylglycerol in chylomicrons and VLDL ($P = .004$), reduced fasting VLDL particle size ($P = .04$), and a reduced postprandial concentration of medium-sized VLDL particles ($P = .02$) [58]. The lean seafood intervention prevented the elevated ratio of total cholesterol to HDL cholesterol in the fasted serum ($P = .03$) and postprandial serum ($P = .01$) that was observed after the nonseafood intervention [58]. The dietary protein source may determine fasting and postprandial lipids in healthy individuals in a manner that may have an effect on the long-term development of CVDs.

In a randomized, double-blind, and parallel trial among 80 healthy volunteers, one group ($N = 39$) received fish pâté (36 g/day) enriched in n-3 (1.1 g EPA + DHA/day) and the second group ($N = 41$) received an identical pâté enriched both in n-3 and taurine (425 mg/day) [59]. Total cholesterol (−5%, $P < .001$), LDL cholesterol (−8%, $P < .001$), and apolipoprotein B (−4%, $P < .001$) decreased more in the n-3 + taurine group compared to the n-3 group. A significant within-group enhancement of HDL cholesterol was demonstrated in the n-3 + taurine group (6%, $P < .0001$). Reductions in triacylglycerol (−16%, $P < .05$ in n-3; −14%, $P < .05$ in n-3 + taurine), thromboxane B(2) (−21%, $P < .001$ in n-3; −15%, $P < .05$ in n-3 + taurine), tumor necrosis factor alpha (TNF-α) (−24%, $P < .001$ in n-3; −12%, $P < .05$ in n-3 + taurine), and monocyte chemotactic protein (−12%, $P < .05$ in n-3; −6%, $P < .0001$ in n-3 + taurine) were evident in both groups [59]. Reductions in interleukin-6 (−16%, $P < .05$) and leukotriene B4 (−18%, $P < .05$) were significant only in the n-3 group. The beneficial effects on blood lipids of combining n-3 PUFAs and taurine were superior to those of n-3 alone. Since fish peptides have antiinflammatory activity, they can be administered to subjects with insulin resistance and type 2 diabetes, which are associated with chronic low-grade inflammation [60]. Cod protein, administered to 19 subjects, aged 40−65 years, who had a body mass index greater than 25 kg/m^2, was shown to improve insulin sensitivity in insulin-resistant subjects [60]. The subjects were rotated in a crossover design and consumed either a cod protein diet or a similar diet containing lean beef, pork, veal, eggs, milk, and milk products (BPVEM) for four weeks each. Diets differed only in the protein source and thus provided equivalent amounts of dietary fibers, monounsaturated fat, PUFAs (including [n-3] fatty acids), and saturated fat. The consumption of a cod protein diet reduced high-sensitivity C-reactive protein ($P = .021$), whereas the BPVEM diet tended to increase it ($P = .063$), leading to a significant difference between diets ($P = .041$) [60]. Changes in plasma interleukin-6, TNF-α, and adiponectin concentrations did not differ between diets. Plasma total cholesterol ($P = .0007$), LDL cholesterol ($P = .014$), and apolipoprotein B ($P = .005$) were reduced only by the BPVEM diet. Thus changes in total cholesterol differed between diets ($P = .040$), whereas changes in LDL cholesterol ($P = .052$) and apolipoprotein B ($P = .075$) tended to differ. A cod protein diet may lower high-sensitivity C-reactive protein, a marker of inflammation that is associated with insulin resistance and type 2 diabetes [60].

Effect of fish protein in coronary artery disease

In patients with MI, fatty fish intake was associated with an increase in the proportion of EPA and DHA in serum lipids in the fatty fish group only ($P < .05$) [46,54]. Therefore both omega-3 fatty acids and fish proteins may provide independent beneficial effects in patients with CVDs. In a previous study of 33 patients, aged 61.0 ± 5.8 (mean ± standard deviation) years, the effect of fatty acid and lean fish intake on the lipoprotein subclasses was examined in patients with CAD [54]. The subjects were randomly assigned to a fatty fish ($N = 11$), lean fish ($N = 12$), or control ($N = 10$) diet for eight weeks. Fish diets included at least four servings of fish per week. Subjects in the control group consumed lean beef, pork, and chicken. Concentrations of n-3 fatty acids and DHA increased in the fatty fish group. The concentrations of cholesterol, cholesterol esters, and total lipids in very large HDLs increased in the fatty fish group (overall difference $P = .005$, $P = .002$, and $P = 0$ 0.007, respectively; false discovery rate $P = .04$, $P = .04$, and $P = .05$, respectively). The mean size of HDL particles increased in the fatty fish group (9.8 ± 0.3 nm at start and 9.9 ± 0.4 nm at the end of the study; overall difference $P = .004$, false discovery rate $P = .04$). Intake of fatty fish at least four times per week increases HDL particle size, which might have a beneficial effect in patients with CAD [54].

The association of fish protein intake with the risk of CAD was examined in a cohort study [61]. The Nurses' Health Study followed 84,136 women aged 30−55 years with no known cancer, diabetes mellitus, angina, MI, stroke, or other CVD. During a follow-up of 26 years, there were 2210 incident nonfatal infarctions and 952 deaths from CAD. In multivariable analyses, including age, smoking, and other risk factors, higher intakes of red meat, red meat excluding processed meat, and high-fat dairy were significantly associated with an elevated risk of CAD. Higher intakes of poultry, fish, and nuts were significantly associated with a lower risk. In a model controlling statistically for energy intake, one serving per day of nuts was associated with a 30% (95% CI: 17%−42%) lower risk of CAD, compared with one serving per day of

red meat. Similarly, compared with one serving per day of red meat, a lower risk was associated with one serving per day of low-fat dairy (13%; 95% CI: 6%−19%), poultry (19%; 95% CI: 3%−33%), and fish (24%; 95% CI: 6%−39%) [61]. These results indicate that high red meat intake increases the risk of CAD and that the risk of CAD may be reduced significantly by shifting sources of protein in the diet. These studies indicate that a metaanalysis of the association of fish intake, showing an inverse association with CVD and all-cause mortality, may be relevant [10,49].

Effects of fish peptides in hypertension

There is evidence of a small beneficial effect of protein and fatty acids on blood pressure, [46,55,62]. This pilot study examined the effects of fatty fish and lean (white) fish on fatty acid composition of serum lipids, blood pressures and other risk factors in subjects with CAD [46]. After a follow-up of eight weeks, the reported fish meals per week were 4.3 ± 0.4 (mean $\pm$ SD), 4.7 ± 1.1, and 0.6 ± 0.4 kg in the groups, respectively. The proportions of EPA and DHA in serum lipids increased in the fatty fish group only ($P < .05$). There was a significant decline in systolic and diastolic blood pressure in the lean fish group (0 vs 8 weeks: 3.5 ± 3.2 and $4.6 \pm 3.6\%$, respectively; $P < .05$). The HDL cholesterol level change differed among groups but without significant post hoc differences and no decrease in levels of triglycerides. The apolipoprotein A-1 level declined in the control group (0 vs 8 weeks, $P < .05$) [46]. Coagulation factors, 25-hydroxy vitamin D levels, and heart rate variability (24-hour Holter) did not change among the groups. The findings suggest that intake of lean fish at least four times per week may reduce blood pressure levels in patients with CAD.

In recent clinical observations, increased intake of lean fish was found to cause a significant decline in blood pressure, possibly owing to proteins with amino acids [1]. A blood pressure−lowering effect of protein may have important public health implications. However, this warrants further investigation in randomized controlled trials. It seems that more data are needed on protein from specific sources in relation to blood pressure.

Table 16.2 shows results from 32 cases with prehypertension and 22 with mild hypertension. Subjects were give 200 g of fish daily or every other day for about four weeks. The decline in blood pressure was noted after 3−7 days of treatment with fish, and the decline continued for up to four weeks. The most common fish eaten by patients was catfish (singhara fish in Hindi).

Recently, several studies carried out to isolate and identify bioactive hydrolysates and peptides indicated that most of the peptides may have ACE inhibitory activity and antihypertensive effect [53−56]. These peptides are obtained from animal, marine, microbial, and plant food proteins. It is important to know the effects of food processing and conditions of hydrolyzation as well as other impacts on formation, activity, and stability of these hydrolysates and peptides that are prepared for human use.

Taurine, the most abundant, semiessential, sulfur-containing amino acid, is well known to lower blood pressure in hypertensive animal models [55]. However, no rigorous clinical trial has validated whether this beneficial effect of taurine occurs in human hypertension or prehypertension. In a randomized, double-blind, placebo-controlled study, the effects of taurine intervention were examined in patients with prehypertension [55]. There were 120 eligible prehypertensives, who received either taurine supplementation (1.6 g/day) or a placebo for 12 weeks. Taurine supplementation significantly

TABLE 16.2 Effect of fish proteins on blood pressure.

Data	Prehypertension (<140/90 mmHg) ($N = 32$)		Mild hypertension (<150/100 mmHg) ($N = 22$)	
Sex, male, *N* (%)	21		15	
Mean age (years)	54.5 ± 9.6		56.7 ± 10.2	
Mean body weight (kg)	68.8 ± 11.3		67.5 ± 9.6	
BMI (kg/m^2)	25.4 ± 3.1		25.2 ± 3.2	
Blood pressure (mmHg)	Baseline	After 4 weeks	Baseline	After 4 weeks
Systolic	136.3 ± 6.5	131.2 ± 5.5*	148.6 ± 10.3	140.2 ± 8.9*
Diastolic	88.8 ± 4.5	82.4 ± 3.3*	95.7 ± 6.1	90.0 ± 4.7*

Values are mean and standard deviation. *$P < .01$.

decreased clinic and 24-hour ambulatory blood pressure, especially in patients with high-normal blood pressure. The mean clinic systolic blood pressure reduction for taurine versus placebo was 7.2 versus 2.6 mmHg, and the mean clinic diastolic blood pressure was 4.7 versus 1.3 mmHg. The mean ambulatory systolic BP reduction for taurine versus placebo was 3.8 versus 0.3 mmHg, and the mean ambulatory diastolic blood pressure was 3.5 versus 0.6 mmHg. Treatment with taurine also significantly improved endothelium-dependent and endothelium-independent vasodilation and increased plasma H_2S and taurine concentrations. The changes in blood pressure were negatively correlated with both the plasma H_2S and taurine concentrations in taurine-treated prehypertensive subjects [55]. A double-blind, placebo-controlled, parallel-group study showed the efficacy of salmon peptide in mildly hypertensive subjects [56]. The systolic blood pressure, after intake of 1.0 g of salmon peptide was significantly reduced at four weeks after the intake and two weeks after the intake, compared to the value before ingestion. After a single intravenous administration of salmon peptide at a dose of 30 mg/kg body weight, the systolic blood pressure was significantly reduced compared to the control.

In a metaanalysis published in 2010, 46 papers met the inclusion criteria [62]. Most observational studies showed no association or an inverse association between total dietary protein and blood pressures or incident hypertension. Results of randomized controlled trials indicated a beneficial effect of protein on systolic and diastolic blood pressures. This beneficial effect may be mainly driven by plant protein, according to the results of observational studies. Data on protein from specific sources (e.g., fish, dairy, grain, soy, and nuts) were scarce. There was some indication that patients with hypertension and older age showed a decline in blood pressure on increased protein consumption [62]. In conclusion the findings indicate a small beneficial effect of protein on blood pressures, especially for plant protein. A blood pressure−lowering effect of protein may have important public health implications. However, this warrants further investigation in randomized controlled trials. Furthermore, more data are needed on protein from specific sources in relation to blood pressure and on the relationship between protein and blood pressure in population subgroups

There is increasing interest in utilizing nutritionally exorbitant fish proteins, which has instigated research activities in the utilization of fish waste. The development of newer technologies to utilize fish waste has fostered the use of bioactive value-added products for specific health benefits. Enzymatically obtained fish protein hydrolysate is a rich source of biologically active peptides that have antioxidant, anticancer, antimicrobial, and antihypertensive activity [63]. Isolating natural remedies to combat alarming negative consequences of synthetic drugs has been the new trend in current research promoting identification of antihypertensive peptides from fish hydrolysate. The purified peptides are known to be rich in arginine, valine, and leucine. Reports reveal that peptides with low molecular weight (<1 kDa) and shorter chain length (<20 amino acids) exhibited higher antihypertensive activity. As these peptides have proven (ACE) inhibitory activity in vitro and in vivo, they have the potential to be used as antihypertensive drugs. However, a focus on research in the field of molecular docking is necessary to improve understanding of the interaction of the peptides with the enzyme.

Fish intake and all-cause morbidity and mortality

Although fish consumption has an influence on mortality due to major chronic diseases, findings on the relationship between fish consumption and all-cause morbidity and mortality have been inconsistent [10,49,64]. In a metaanalysis, 17 cohorts with 315,812 participants and an average follow-up period of 15.9 years were identified [10]. The results showed that compared with the lowest fish intake (<1 serving/month or 1−3 servings/month), the pooled RR of fish intake on CAD mortality was 0.84 for low fish intake (1 serving/week), 0.79 for moderate fish intake (2−4 servings/week) and 0.83 for high fish intake (>5 servings/week) [10]. The dose−response analysis indicated that every 15-g/day increment of fish intake decreased the risk of CAD mortality by 6% (RR: 0.94). The results indicate that either low (1 serving/week) or moderate fish consumption (2−4 servings/week) has a significantly beneficial effect on the prevention of CAD mortality. High fish consumption (>5 servings/week) has only a marginally protective effect on CAD mortality, possibly owing to the limited studies included in this group.

In a more recent metaanalysis, the RR for the highest versus lowest category of fish intake on risk of all-cause mortality was calculated by using a random-effects model [49]. This metaanalysis included 12 prospective cohort studies with 672,389 participants and 57,641 deaths occurring during the follow-up. Compared with the lowest category, the highest category of fish intake was associated with about a 6% significantly lower risk of all-cause mortality (RR: 0.94, $I^2 = 39.1\%$, $P = .06$). The dose−response analysis indicated a nonlinear relationship between fish consumption and all-cause mortality. Compared with never consumers, intake of 60 g of fish per day was associated with a 12% reduction RR: 0.88, in risk of total death [49]. These results indicate that fish intake may be associated with a reduced risk of all-cause mortality (Fig. 16.1).

A comprehensive review of published metaanalyses of prospective cohort studies on the association of fish consumption and the risk of chronic disease was undertaken [64]. The quality of methodology of included metaanalyses

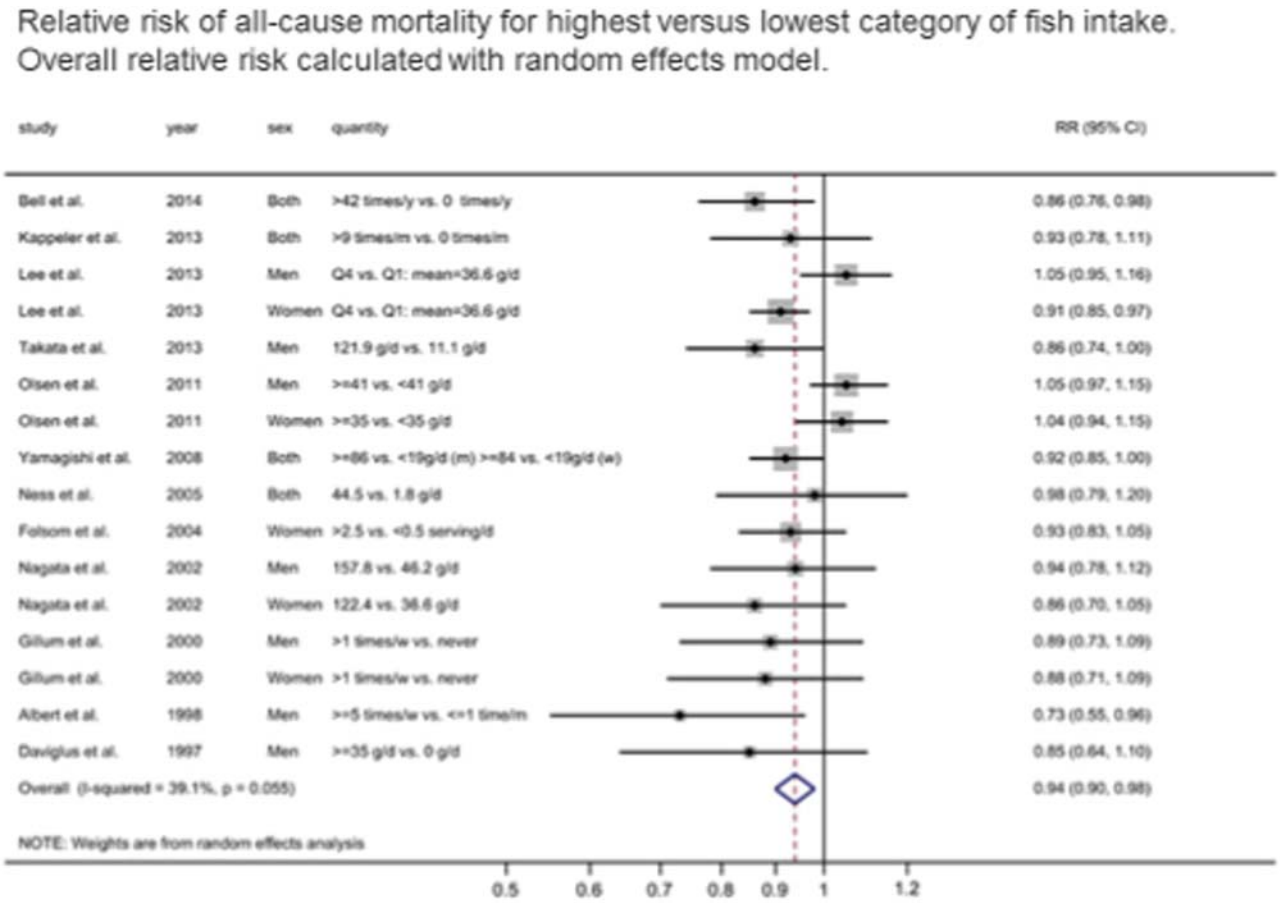


FIGURE 16.1 Relative risk of all-cause mortality for highest versus lowest category of fish intake showing lower risk of mortality with higher intake of fish. *Modified from Zhao LG, Sun JW, Yang Y, Ma X, Wang YY, Xiang YB. Fish consumption and all-cause mortality: a meta-analysis of cohort studies. Eur J Clin Nutr 2016;70:155–61. https://doi.org/10.1038/ejcn.2015.72.*

($N = 34$), and the quality of the evidence was assessed by the AMSTAR and Nutri-Grade tools, respectively, from 298 primary prospective cohort studies. Each 100-g/day increment in fish consumption was associated with a lower risk of all-cause mortality (SRR: 0.92); cardiovascular mortality (SRR: 0.75), CAD (SRR: 0.88), MI (SRR: 0.75), stroke (SRR: 0.86), heart failure (SRR: 0.80), depression (SRR: 0.88), and liver cancer (SRR: 0.65; 95%), indicating moderate-quality evidence [64]. There was no significant association, and the quality of the evidence was rated low and very low for cancers. It seems that fish consumption is associated with a lower risk of CVDs, depression, and mortality and therefore can be considered to be a healthy animal-based dietary source of protein. Further studies are urgently needed for outcomes for which the quality of the evidence was rated low and very low, considering methods of cooking, types of fish eaten, and all potential factors responsible for confounding.

Mechanisms of action of fish proteins and peptides

The beneficial effects of fish proteins appear to be due to the presence of amino acids and peptides, although fish also has vitamin D and selenium. If amino acids are linked together, they form chains of amino acids and are called peptides. These chains can be short or long. If the peptides form longer chains of amino acids, they become the building blocks of proteins. The results of experimental work show that taurine treatment upregulates the expression of hydrogen sulfide-synthesizing enzymes and reduces agonist-induced vascular reactivity through the inhibition of transient receptor potential channel subtype 3–mediated calcium influx in human and mouse mesenteric arteries. The antihypertensive effect of chronic taurine supplementation shows promise in the treatment of prehypertension through improvement of vascular function.

Omega-3 fatty acids and amino acids as well as peptides and other nutrients may interact in cellular function in providing the benefits, because both can enhance nitric oxide release, leading to vasodilatation [62,65–67]. Terpenes are

aromatic organic compounds that possess the flavor and fragrance oils and can modulate the amino acids in the blood. A clinical study examined the effects of terpenes on plasma-free amino acids in healthy humans [47]. In this open-label, single-arm acute trial, 17 healthy male volunteers were administered mastiha, a naturally occurring product of known terpenes, after overnight fasting. A total of 24 free amino acids were quantified. Branched-chain valine significantly decreased 4 hours post ingestion, whereas proline decreased at 6 hours and ornithine at 2 hours, compared to 0 hour. These novel findings demonstrate that free amino acids concentrations are modulated in response to the intake of terpenes in healthy subjects. Another study was conducted to elucidate how two diets that varied in main protein sources affected the fasting and postprandial serum metabolites and lipid species [48]. In this randomized, controlled trial with a crossover design, healthy adults ($N = 20$) underwent a four-week intervention with two balanced diets that varied mainly in their protein source (lean seafood vs nonseafood proteins). In the fasting state, the lean seafood diet, in contrast to the nonseafood diet, significantly decreased the serum concentrations of isoleucine and valine, and during the postprandial state, a decreased concentration of lactate and increased concentrations of citrate and trimethylamine *N*-oxide were observed. The nonseafood diet significantly increased the fasting concentration of 26 lipid species, including ceramides 18:1/14:0 and 18:1/23:0 and lysophosphatidylcholines 20:4 and 22:5, in comparison to the lean seafood diet. Thus the lean seafood diet decreased circulating isoleucine and valine concentrations, whereas the nonseafood diet elevated the concentrations of certain ceramides, metabolites that are associated with insulin resistance [48]. A nonseafood diet may increase the concentrations of ceramides, which have adverse effects on beta cell function of the pancreas, leading to insulin resistance and diabetes.

In another study, bioassay-guided separation of the salmon peptide, using a combination of column chromatographic techniques led to the identification of 20 active dipeptides and tripeptides, including Ile-Val-Phe and Phe-Ile-Ala as two new ACE inhibitory tripeptides [27]. Ile-Trp had the strongest ACE inhibitory activity ($IC_{50} = 1.2\ \mu M$) in vitro and contributed 5.2% to the total ACE inhibitory activity. The salmon peptide and Ile-Trp showed a digestive resistance by in vitro assay, which mimicked the digestive organ, and had no affinity for factors related to blood pressure regulation except for the ACE inhibitory activity [56]. An experimental study of fish peptide digested from salmon muscle also showed a strong inhibitory activity against ACE [56].

Proteins can be converted to protein hydrolysates to increase their activity. These hydrolysates are water soluble and hence are rapidly absorbed from the gut. Salmon by-product protein was hydrolyzed with six proteases, and the antioxidant activities of salmon by-product protein hydrolysates (PHs) were examined [50]. Salmon PH fraction 1 (PHF1) contained 1000- to 2000-Da molecular-weight peptides and antioxidant amino acids, such as tyrosine, phenylalanine, proline, alanine, histidine, and leucine, which accounted for 28.62% of the total amino acids. The peptic hydrolysates from salmon PHs showed the highest antioxidant activity compared to that of the other protease hydrolysates and were further fractionated into four fractions by size exclusion chromatography. The salmon PHFs showed 2,2-diphenyl-1-picrylhydrazyl− and hydrogen peroxide−scavenging activity; salmon PHF1 exhibited the highest antioxidant activity. Additionally, salmon PHF1 showed antiinflammatory activity by inhibiting nitric oxide production and proinflammatory cytokines, including TNF-α, interleukin-6, and interleukin-1β in RAW264.7 macrophage cells [50]. In another study, mackerel (*Scomber austriasicus*) hydrolysates were prepared by an autolytic process and accelerated hydrolysis with a commercial enzyme, protease N. Changes in the concentrations and compositions of free amino acids and small peptides during hydrolysis were examined to determine their relationships with antioxidant activities [51]. Increased concentrations of free amino acids, anserine, carnosine, and other peptides of the hydrolysates obtained with protease were much higher than those by autolysis alone. Similarly, a purification of bigeye tuna (*Thunnus obesus*) for its antioxidant properties of dark muscle peptide showed a potential free radical−scavenging activity on free radical−mediated oxidative systems [52]. The protein intake during the Paleolithic period has been estimated to be 2.5-fold greater than current recommendations. Hydrogen, nitrogen, oxygen, and carbon atoms are important components of essential and nonessential amino acids, which are components of proteins.

These simple molecules play an important role in the human body. The 22 known amino acids, essential and nonessential (see Table 16.3), affect a broad range of physical and mental processes.

Recent studies indicate that amino acids are cell-signaling molecules as well as being regulators of gene expression and the protein phosphorylation cascade. Most neurotransmitters are composed of amino acids and can influence biological functions related to brain-body interactions. Amino acids are key precursors for syntheses of hormones and low molecular−weight nitrogenous substances, each having enormous biological importance. Physiological concentrations of amino acids and their metabolites—nitric oxide, polyamines, glutathione, taurine, thyroid hormones, and serotonin—are required for the biological functions in the human body. These metabolites are known to be protective against CVDs and degenerative diseases of the brain. However, increased concentrations of amino acids and their products (e.g., ammonia, homocysteine, and asymmetric dimethylarginine) are pathogenic factors for neurological disorders, oxidative stress, and

TABLE 16.3 Essential and nonessential amino acids.

Number	Nonessential amino acids that can be synthesized in the body	Essential amino acids that cannot be synthesized in the body
1.	Alanine	Histidine
2.	Tyrosine	Isoleucine
3.	Asparagine	Leucine
4.	Aspartate	Lysine
5.	Cystine	Methionine
6.	Glutamine	Phenylalanine
7.	Glycine	Threonine
8.	Ornithine	Tryptophan
9.	Proline	Valine
10.	Serine	Arginine
11.	Taurine	

CVD. Glutamate is a nonessential amino acid that is present in many foods that is considered protective against obesity and CVDs. Therefore a balance between amino acids and other nutrients appears to be important for normal physiological functions without any adverse effects. A recent study demonstrated the effect of the simultaneous dietary administration of fish protein and fish oil, two macronutrients that are found in fish meat, on cholesterol metabolism in rats [56]. Male Wistar rats were divided into four groups and fed an AIN-93G modified hypercholesterolemic diet with (1) 20% casein + 7% soybean oil, (2) 10% casein + 10% fish protein + 7% soybean oil, (3) 20% casein + 5% soybean oil + 2% fish oil, and (4) 10% casein +10% fish protein + 5% soybean oil + 2% fish oil for four weeks. Cholesterol metabolism was measured through serum and liver cholesterol assay, fecal cholesterol and bile acid excretion levels, and liver mRNA expression levels of enzymes and nuclear receptors involved in cholesterol homeostasis. Dietary fish protein decreased serum and liver cholesterol contents, perhaps through increasing fecal cholesterol and bile acid excretion and liver cholesterol-7-alphahydroxylase expression level. Dietary fish oil, by contrast, decreased liver cholesterol content, perhaps owing to the suppression of cholesterol synthesis through a decrease in the 3-hydroxy-3-methylglutaryl-coenzyme A reductase expression level. The serum cholesterol content was unchanged. This study found that the simultaneous dietary administration of fish protein and fish oil, which is achieved by the intake of intact fish muscle, has hypocholesterolemic effects that help to prevent hyperlipidemia and atherosclerosis. In another study, the existence of an insulin-stimulated glucose and nonessential but not essential amino acid substrate interaction was observed in diabetic pigs [67].

American Heart Association advisory

In an updated scientific advisory the AHA reaffirms advice that adults consume fish twice a week to help reduce the risk for congestive heart failure, coronary heart disease, sudden cardiac arrest, and ischemic stroke [6,7,25,26]. The AHA recommendation is to eat two 3.5-ounce servings of nonfried fish (or about three-fourths of a cup of flaked fish) per week, preferably oily fish such as salmon, mackerel, herring, lake trout, sardines, or albacore tuna, which are all high in omega-3 fatty acids. One serving per week of fatty fish, such as salmon, provides the recommended approximately 250 mg daily intake of long-chain n-3 PUFAs, whereas multiple servings of lean fish, such as cod, are required to achieve the recommended intake.

Several studies have further established the beneficial effects of eating seafood that is rich in omega-3 fatty acids, especially when it replaces less healthy foods such as red meats and refined foods. The advisory notes that in 2012 the average seafood intake in the United States was about 1.3 servings per week, up modestly from 1.1 servings per week in 1999 but still well below the current recommendations. The most common sources of seafood were shrimp, salmon, and canned tuna. The advice is consistent with a beneficial role of dietary long-chain PUFAs on triglycerides, cardiac

electrophysiology, endothelial function, and possibly blood pressure and inflammation, although the evidence for each of these endpoints is more limited for dietary sources as opposed to supplement sources.

The advisory also addresses concerns about mercury in fish. Mercury is present in most seafood, but it is found in higher concentrations in large fish, such as shark, swordfish, tilefish, king mackerel, bigeye tuna, marlin, and orange roughy. Although mercury contamination may be associated with serious neurologic problems in newborns, existing evidence shows that mercury contamination does not have harmful effects on heart disease risk in adults, and the benefits of eating fish outweigh the risks associated with mercury contamination, especially if a variety of seafood is consumed. The new advisory is consistent with the AHA 2020 Impact Goals, which recommend including seafood as part of the healthy dietary pattern goals, as well as the 2015 AHA diet and lifestyle recommendations. As for fish oil supplements, a 2017 AHA science advisory recommended against omega-3 fish oil supplements for the general public to prevent clinical CVD because of a lack of scientific evidence of any effect on cardiovascular risk [25,26]. However, the advisory noted that fish oil supplements may help to prevent death from heart disease in patients with recent MI and may prevent death and hospitalization in patients with heart failure.

Seafood-derived light chain n-3 PUFAs have been associated with a slower heart rate, slower atrioventricular conduction, and reduced rates of abnormal polarization, which together should suppress arrhythmia. These same PUFAs are associated with improved endothelial function and lower rates of atherosclerotic plaques. Fish oil supplements are associated with lower blood pressure in adults with and without hypertension. However, seafood consumption itself has not been established as a means to reduce blood pressure. In contrast, diets that are rich in seafood have been associated with a lower risk for coronary heart disease events, sudden cardiac death in particular. There appears to be a threshold effect with approximately 50% reduction in the risk for sudden cardiac death with one or two servings of fatty fish per week versus no fish consumption. There is little additional benefit to consuming more fish per week, and fried fish was not associated with a lower rate of sudden cardiac death. Only a few studies have evaluated the association between fish consumption and incident heart failure, with mixed results. An AHA report suggests that PUFA supplementation may reduce the risk for hospitalization and death associated with established heart failure. In a systematic review, participants who reported seafood consumption four or more times per week experienced a 22% reduction in the risk for CAD events compared with participants who consumed seafood less than once per month. Even infrequent fish consumption was associated with a CAD benefit in this study.

Metaanalyses may underestimate the effect of fish consumption that replaces the consumption of other, less healthy forms of protein, such as processed meats. A metaanalysis of cohort studies found that consuming seafood once per week was associated with a 14% reduction in the risk for ischemic stroke compared with little or no consumption of seafood. There is no strong evidence that seafood consumption can reduce the risk for hemorrhagic stroke. Seafood-derived PUFAs have generally had a nonsignificant effect in the secondary prevention of cardiovascular events but can decrease infarct size [68]. There has been concern that increased consumption of n-6 PUFAs may obviate the positive effects of n-3 long-chain PUFAs, but this hypothesis has not been supported in prospective trials. Farm-raised salmon and trout have higher PUFA concentrations in comparison to wild-caught fish. The authors conclude by endorsing recommendations for one to two servings of seafood per week, especially if seafood replaces less healthy choices. In a prospective study, comprising 70,696 subjects aged 45–74 years from Japan, higher plant protein intake was associated with lower total and CVD-related mortality [69]. Although animal protein intake was not associated with mortality outcomes, replacement of red meat protein or processed meat protein with plant protein was associated with lower total, cancer-related, and CVD-related mortality. It is possible that fish protein is as safe as vegetable protein with reference to all-cause mortality.

In conclusion, recent literature provided evidence that marine-derived bioactive peptides may play a critical role in human health along with many possibilities of designing new functional nutraceuticals and/or pharmaceuticals to clarify potent mechanisms of action for a wider spectrum of diseases. Fish intake and fish oil intake may be inversely associated with all-cause mortality as well as morbidity due to CVDs and other chronic diseases, such as depression. EPA and DHA are most commonly found in fish such as salmon, herring, anchovies, mackerel, and tuna. Lower levels are found in shellfish, tilapia, and cod, which can be used to administer peptides. The current science advisory recommends one to two servings of seafood per week for cardiovascular health. Moderate consumption of seafood appears particularly beneficial in the prevention of sudden cardiac death, incident CAD, and ischemic stroke.

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Section 4

Functional foods and micronutrients

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Chapter 17

Sumac: a functional food and herbal remedy in traditional herbal medicine in the Asia

Mehdi Khoshkharam[1], Mohamad Hesam Shahrajabian[2,3,7], Ram B. Singh[4], Wenli Sun[2,3], Anathi Magadlela[5], Mozhgan Khatibi[6] and Qi Cheng[1,2]

[1]*Department of Agronomy and Plant Breeding, Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, Iran,* [2]*Biotechnology Research Institute, Chinese Academy of Agricultural Sciences, Beijing, P.R. China,* [3]*Nitrogen Fixation Laboratory, Qi Institute, Jiaxing, P.R. China,* [4]*Halberg Hospital and Research Center, Civil Lines, Moradabad, India,* [5]*School of Life Sciences, University of KwaZulu-Natal, Pietermaritzburg, South Africa,* [6]*Endocrinology and Metabolism Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran,* [7]*Department of Agronomy and Plant Breeding, Faculty of Agriculture, Islamic Azad University, Isfahan (Khorasgan) Branch, Isfahan, Iran*

Introduction

Spice and herbal remedies have been used since ancient times to treat a variety of disorders [1−8]. Sumac is a very popular flavoring spice in Iran and other areas of the Middle East. Sumac comes from *Rhus coriaria* L., a shrub that is native to the Mediterranean, and its history dates to ancient times [9]. The Romans used sumac berries as a souring agent and flavoring before citrus fruits reached the region. Sumac still grows wild around the Mediterranean; major sources today include Turkey and the Middle East. There are many varieties of the shrub, some of which are poisonous. However, Native Americans traditionally used sumac to make a refreshing drink, and they also used both leaves and berries in tobacco mixtures [10]. Sumac is widely used in cooking in Turkey and the Middle East, especially in Lebanon, Iran, and Iraq [11,12]. The dried whole berries must be soaked or ground before use; occasionally, the berries are soaked to soften them and then are strained and pressed to release all their juices, and the liquid used as part of the cooking medium for a stew or other dish. A simple salad of sliced onions seasoned with ground sumac is popular throughout the Middle East. Sumac flavors kebabs and grilled meats, fish, and chicken, and it is added to marinades for foods that will be roasted or grilled. It can be stirred into yogurt to make a marinade, or the seasoned yogurt can be served on its own as a dip or a condiment. Sumac is also sprinkled over rice, hummus, or baba ghanoush, along with a drizzle of olive oil, as a garnish and flavoring [13]. Native Americans used the split bark and stems in basket making and the roots for a yellow dye. In Iran, sumac is grown in Mazandaran, Azadbayegan, Khorasan, Shiraz, Ghazvin, Ghom, and Hamedan. This study showed that the water extracts of sumac could inhibit the microbial growth in ground beef meat during refrigerated storage [39]. Because sumac is commonly used as a seasoning ingredients in muscle foods (kebabs, chicken meat meal, etc.), the application of their extracts in these foods not only can improve sensory characteristics but also extend the shelf life of the food. Meanwhile, these extracts might have health-promoting effects on the consumers, owing to their potential antimicrobial activities [14]. Studies on sumac fruit and leaf oil have determined that the sumac fruit contains flavanols, phenolic acid, anthocyanins, and organic acids. The sour taste is due to the presence of organic, acids such as malic acid, citric acid, and tartaric acid [15,16]. Syrian sumac (*R. coriaria* L.) is famously used in Mediterranean region and the Middle East as a spice, in sauces, and in drinks, and Chinese sumac (*R. typhina* L.) is indigenous to the eastern area of North America and is now extensively cultivated in the north and northwest of China and many other regions, such as Lanzhou, Beijing, Hebei, and Shanxi, where it is usually called *huojushu* [17]. The plant is used in traditional medicine as a pharmacological blood purifier, diuretic, stomachic, and tonic [12]. Citric acid is a hydroxy acid that is used in the beverage, juice, cosmetics, and pharmaceutical industries and flavoring and to regulate pH.

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Sumac as a medicinal plant

Sumac has been used as a medicinal plant or a spice for hundreds of years. It contains a wide range of medicinally active components, including organic acids, phenolic acids, flavonoids, anthocyanins, hydrolysable tannins, and terpenoids [18]. Its scientific name is *Rhus glabra* L. of the Anacardiaceae family, commonly known as the cashew family or sumac family. Its common names are blue glabrum, dwarf sumac, mountain sumac, Indian salt (the powder on the berries), Pennsylvania sumach, scarlet sumac, sleek sumach, smooth sumac, and upland sumach.

Identified metabolites of sumac fruit

All parts of the plant, including its fruit, contain significant amounts of tannin (glutamine). In a general study of compounds found in sumac fruit, anthocyanins and fats have been identified as major constituents of sumac fruit [19].

Botany

Anacardiaceae (the sumac family) includes flowering plants, with about 80 genera and about 870 species [20]. Several species are economically important fruit and nut crops. The fruits are commonly fleshy drupes. Sumac (genus *Rhus*) grows as shrubs and small trees and is native to temperate and subtropical areas of the world. Sumac leaves are characteristically arranged in spirals and are usually compound, though some species have simple leaves. The minute flowers have five petals and occur in dense panicles or spikes. The fruits are red drupes that are borne in dense upright clusters. All sumacs have a milky or resinous sap. Many species can spread asexually by rhizomes. The smooth, or scarlet, sumac (*R. glabra*), which is native to the eastern and central United States, is a common species. It grows to a height of 6 m (20 ft.), with an open, flattened crown and a few stout spreading branches. A cultivated variety has dissected fern-like leaves. Sumac (*R. typhina*), grow up to 9 m (29.5 ft.), and its fall foliage is orange-red to purple. It also has a variety of finely cut leaves [20]. Edible sumac varieties include smooth sumac (*R. glabra*), staghorn sumac (*R, typhina*), sweet sumac (*R. aromatica*), dwarf or winged sumac (*R. copallina*), lemonade berry (*R. integrifolia*), southwestern sumac (*R. microphylla*), sugar bush (*R. ovata*), and squaw berry (*R. trilobata*). All nonpoisonous species contain red berries when ripe and are sometimes inaccurately and collectively called red sumac. *R. coriaria*, the only species of the *Rhus* genus that is prevalent in Iran, is a large shrub or small tree (1−3 m high), with pinnately compound leaves, greenish-white flowers, and brown to red fruits. Sumac fruit consists of pulp (outcrop and shortcut), the endocarp, and the nuclei; the nuclei reportedly have the highest percentage of oil, and the endocarp has the lowest oil content [21]. In China, millions of tons of sumac are produced annually. Sumac fruit contains12%−20.8% oil, and linoleic acid is the predominant fatty acid (47.4%). Linoleic acid is an unsaturated fatty acid and can reduce cholesterol and the risks associated with heart disease. In Turkey the oil content of the sumac fruit has been reported to be in the range of 10%−15%, but in other studies, oleic acid has been identified as the dominant fatty acid, with a content of 34%−40%. Oleic acid (omega-9) is an essential fatty acid in the body that forms a major part of the body's fatty acids, but it is low in the liver and neurons.

Sumac chemical component

Studies have mentioned that a high degree of variation was found in the chemical characteristics of sumac, and the results revealed significant differences among the accessions in sumac. Titratable acidity ranged from 2.01% to 7.84%, and pH ranged from 2.66 to 3.90 ($r = 0.56$). Ascorbic acid ranged from 10.00 to 45.00 mg per gram of dry weight, phenolic content varied from 77.54 to 389.30 mg gallic acid equivalents per gram of dry weight ($r = 0.32$). the flavonoid content ranged from 2.19 to 7.54 mg quercetin equivalents per gram of dry weight, and tannin content ranged from 52.00 to 189.80 mg gallic acid equivalents per gram of dry weight. Free amino acid content ranged from 25.01 to 166.38 mg glycine equivalents per gram of dry weight, while anthocyanin content varied from 3.57 to 66.14 mg cyanidin-3-glucoside equivalents per gram of dry weight. The antioxidant capacity ranged from 1.55 to 11.09 mg ascorbic acid equivalents per gram of dry weight [22]. The aqueous and aqua-methanol extracts of sumac parts were analyzed by high-performance liquid chromatography to unfold the deferent tannins derivatives, gallotannins methyl gallate, digallic acid, trigallic acid, and ellagic acid, and dodecagallolyl glycoside derivatives as representative tannins present in *R. coriaria* [23]. The components of sumac ethanolic extract gained by gas chromatography−mass spectrometry is shown in Table 17.1.

TABLE 17.1 The components of sumac ethanolic extract gained by gas chromatography–mass spectrometry.

Name of component	Percent of total	Retention time (min)
trans-Caryophyllene	7.84	12.858
Butanedioic acid, diethyl ester	22.01	13.87
1,7-Nonadien-4-ol,4,8-dimethyl	1.06	15.869
Malate	39.7	17.873
Tricyclo[6.3.1.02,5]dodecane-8-ol	1.18	17.941
Cembrene	5.84	19.198
Palmitate	7.64	19.808
9-Octadecenoic acid	2.61	21.78
Ethyl linoleic acid	4.04	22.187
Ethyl linoleolate	6.32	22.743
Phytol	1.76	22.858

Sumac as a spice

Sumac has long been used as a pure spice, sometimes in combination with other spices, in drinks and sauces and as a natural stimulant in food recipes [24]. Sumac is also of particular economic importance because of its use in the cosmetics, dyeing, food preservation, and animal skin processing industries [25]. Sumac oil can be mixed with vinegar or olive or sesame oil, depending on the type of recipe. Nowadays, the most common use of sumac is as an additive to food as a spice or water [15].

Traditionally care

A vast proportion of the important metabolites for nutrients and pharmacology (e.g., tannins, phenolic acids, anthocyanins, organic acids, proteins, essential oils, fatty acids, fiber, and minerals) have already been identified in various parts of sumac [26]. Based on the *Canon of Medicine* of Avicenna (Ibn-Sina), compiled in the Middle Ages, sumac was used as a remedy plant in the treatment of stroke. Sumac has been utilized in traditional medicine for the treatment of blood disease, diabetes diuresis, stroke, cancer, gastrointestinal diseases (e.g., ulcer, diarrhea), stomachache, hemorrhoids, anorexia, measles, smallpox, hyperglycemia, atherosclerosis, hypertension, conjunctiva, hematosis, hemoptysis, leukorrhea, dermatitis, and ocular and liver diseases [27]. Other medicinal uses have also been studied, including weight loss, skin treatment, hair, burns, digestive tract disorders, headache, and temperature reduction [28]. In traditional Iranian medicine, sumac has been used as a hemostasis factor and for antidiarrhea, anti-pus, and trachea treatment, as well as for prevention of ocular complications of smallpox [29]. Studies have shown the effects of the hyperglycemic and uric acid–lowering effects of sumac [29,30]. Sumac inhibits the alpha-amylase enzyme significantly. Alpha-amylase is responsible for breaking down starch into simpler sugars, and inhibiting this enzyme increases glucose tolerance in diabetic patients [29]. In addition, the sumac can indirectly inhibit xanthine oxidase, which is one of the ways to reduce blood uric acid levels in patients with gout [30]. In recent years, owing to the emergence of microbial resistance, the global tendency to investigate the antimicrobial effects of biological materials has been increasing, and sumac has been no exception [31]. Sumac reduces blood sugar and uric acid [32].

Modern pharmaceutical science

The methanol extract of sumac fruits is a rich source of natural antioxidant phenols and tannins, which have an inhibitory function on vascular smooth muscle cell migration. Studies have shown that tannins have anticarcinogenic effects. Sumac has been utilized for its antibacterial, antifungal, antioxidant, antiinflammatory, antidiabetic, and anticholinergic effects and to inhibit vascular smooth muscle cell migration [33]; it also has hypoglycemic and hypolipidemic activities and acts as a tumor growth inhibitor on breast cancer [34]. Ahmadi et al. [35] showed that the water extract of sumac

TABLE 17.2 The most important health benefits of sumac.

Balances blood sugar levels
Reduces cholesterol
Is rich in antioxidants
Reduces the chance of bone depletion
Calms muscle aches
Can help in the fight against cancer

has retention effect against *Bacillus cereus* in soup and can be considered as a natural preservative in some foods. Shidfar et al. [36] found that sumac consumption had a significant effect on serum glycemic status and on the apolipoprotein B, apolipoprotein A-I, and tacrolimus levels in patients with type 2 diabetes. The sumac ethanolic extract showed a high antioxidant effect, and the predominant compounds in the essential oil were malate (39.7%), Butanedioic acid, and diethyl ester (22.01%). On the basis of these findings, the possibility of using the fruit of *R. coriaria* L. as a novel source of natural antimicrobial and antioxidant agents for the food and pharmaceutical industries has been suggested. Abdallah et al. [37] concluded that *R. coriaria* extract could potentially induce its anticancer effects, and *R. coriaria* may have promise as a therapeutic drug candidate for uterine and cervical cancer. The most important health benefits of sumac are presented in Table 17.2.

Industry

In the past, the leaves, skin, roots, and branches of the sumac were used as natural dyes. In the food industry, antioxidants are used to prevent oxidative degradation of fats by inhibiting the formation of free radicals. Synthetic antioxidants, such as butylated hydroxy anisole, butylated hydroxy toluene, and propyl gallate, are widely used. However, the use of synthetic antioxidants in food products has been abused [38]. On the basis of the finding of fumaric acid in sumac. Tohma et al. [29] suggested that sumac may have health-enhancing effects and may inhibit certain enzymes or interfere with some cellular pathways.

Conclusion

Sumac is a famous spice in the Middle East. It is made from berries from a bush of the same name. To produce the spice from the plant, its fruit is dried and crushed into a fine red-purple powder. The red berries are tangy and delicious, containing malic acid, which is found in apples. As a spice, sumac is delicious on meat and in salad dressings, and it makes a delicious infused vinegar if the fruit is macerated in apple cider vinegar. The most important phenolic acids and flavonoids found in sumac are catechin, ferulic acid, gallic acid, apigenin, gentisic acid, chlorogenic acid, P-coumaric acid, caffeic acid, isorhamnetin, quercetin, cinnamic acid, taxifolin, epicatechin, kaempferol, P-hydroxybenzoic acid, vanillic acid, vanillin, anisic acid, pyrogallol, sinapic acid, syringaldehyde, syringic acid, and benzoic acid. The organic acids in sumac are malic acid, citric acid, tartaric acid, and fumaric acid. The fatty acid components of sumac fruits are myristic acid, palmitic acid, palmitoleic acid, stearic acid, oleic acid, linoleic acid, and linolenic acid. The vitamin contents of sumac fruits are thiamin, riboflavin, pyridoxine, cyanocobalamin, nicotinamide, biotin, and ascorbic acid. The most important health benefits of sumac are as follows: As an anticancer agent, sumac is a superantioxidant, packed with vitamin C, which means that it can help to ward off diseases such as diabetes, cardiovascular diseases, and cancer. Inflammation is thought to be the cause of most diseases, and sumac is an antiinflammatory spice that helps to fight various disorders, including colds and influenza. Sumac has been found to be effective in regulating cholesterol levels and treating diabetes by reducing blood sugar. Sumac has antimicrobial and antifungal properties, making it useful in treating skin inflammation and disorders. It has also been found to be effective in fighting bacteria such as *Salmonella* and can be used to safely disinfect fruits and vegetables. Sumac can increase breast milk production and ease menstrual cramps. Sumac is a diuretic, which means that it helps to remove toxins from the body via the urine, and it has been used traditionally to treat urinary tract infections and digestive problems.

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Chapter 18

Quark cheese: characteristics, preparation, and health effects as a functional food

Anil K. Chauhan, PhD[1], Poonam Yadav[1], Ram B. Singh, MD[2], Raj K. Singh[3], Rajesh K. Singh[3], Wiriya On-Saard[4] and Ekasit On-Saard[4,*]

[1]*Department of Dairy Science and Food Technology, Institute of Agricultural Sciences, Banaras Hindu University, Varanasi, India,* [2]*Helburg Hospital and Research Center, Civil Lines, Moradabad, India,* [3]*Biochemistry Department, Era's Lucknow Medical College and Hospital, Lucknow, India,* [4]*Department of Agro-Industry, Faculty of Agriculture, Ubon Ratchathani University, Ubon Ratchathani, Thailand*

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Introduction

Quark cheese, also known as quarg cheese, is a fresh cheese with a smooth texture and a mild, slightly sour flavor. It is a protein-rich, milky white or faintly yellowish, acid- and rennet-coagulated cheese (Fig. 18.1). Quark is a natural unripened, fresh cheese and is very popular in many countries (Table 18.1). It is generally prepared from pasteurized skim milk or whole milk by using *Streptococcus cremoris* and *Leuconostoc citrovorum* as a starter culture along with a small quantity of rennet enzyme [1]. Acidification occurs until the pH is lowered to 4.6, which causes precipitation of the casein proteins. A very small amount of rennet is included with the cheese-milk, and it functions to make the curd firmer. The presence of viable culture organisms and beta-galactosidase activity in quark prevents the problem of lactose intolerance. Quark cheese has a high nutritional value, owing to its high concentration of proteins. It has a high moisture content (~82%, w/w) (Table 18.2) and low dry matter and hence is low in fat, and shelf-life is limited to two to four weeks at less than 8°C. Odor and taste, that is, the flavor, of quark cheese is mildly acidic [1,2].

There are several advanced methods of quark cheese preparation in which the whey protein content increases, which may have beneficial effects on health. Probiotic microorganisms have good potential for health benefits, so when these microorganisms are introduced into quark at a therapeutic dose, there may be health benefits as well as increased shelf life of the product. Using potassium sorbate and sorbic acid in quark preparation reduces contamination and increases



FIGURE 18.1 (A) Freshly prepared quark cheese. (B, C) Quark cheeses available in the market.

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TABLE 18.1 Top 15 cheese-producing countries.

Country	Production in 2008 (metric tons)	Production in 2016 (metric tons)	Change (%)
United States	3746	4950	32
Germany	1686	2430	44
France	1612	1842	14
Italy	927	985	6
Netherlands	684	762	11
Egypt	380	720	89
Poland	404	718	77
Brazil	445	415	57
Turkey	250	202	80
Argentina	443	564	27
Russia	221	410	85
United Kingdom	302	398	32
New Zealand	289	354	22
Canada	292	345	18
Australia	376	346	–

Source: PM Foods & Dairy Consulting, Denmark.

TABLE 18.2 Typical composition of skim milk quark cheese.

Compounds	Percentage
Moisture	82%
Protein	12%
Fat	0.2%
Carbohydrate	3%
Ash	1%

Source: National Dairy Research Institute, Karnal, India.

the product's shelf life. The thermization process has improved the quality of cold-stored quark and reduced proteolysis. Quark produced from milk that has not been thermized can stored up to five weeks only. Economists, nutritionists, dieticians, and many medical practitioners have actively recommended quark consumption and will undoubtedly continue to do so for its health benefits. Quark cheese is relatively unknown in the United States, but in one of the projects at the NASA Space Center in Houston, quark was included in the daily breakfast of the astronauts. Further possibilities in quark research and development involve various drying process and direct acidification technique. The food service industry will undoubtedly also work with quark and incorporate it into the wide spectrum of Indian cuisine. Chakka shrikhand is the product related to quark that is most popular in India. However, quark products might not be healthy, owing to the addition of fat and salt and the peroxidation of fatty acids in the cheese.

Beneficial and adverse effects of quark cheese

Like other dairy products quark is high in calcium, which is protective against diseases of the bones and joints. Quark cheese also a rich source of vitamin A and vitamin B, which may have additional beneficial effects [3–5]. However,

cheese may have adverse effects on health. For example, 1 ounce of cheddar cheese contains around 120 calories and 6 g of saturated fat [3]. A high intake of saturated fat and total fat may increase the risk of obesity, diabetes, metabolic syndrome, and cardiovascular diseases. Cottage cheese is high in sodium (696 mg/cup), which may have adverse effects on the positive balance of calcium on blood pressure.

Excess intake of calcium itself may be unhealthy, according to some experts. For example, high dairy or calcium intake may increase the risk of prostate cancer, although the results on this topic are mixed. In several epidemiological studies, the association between cheese intake and risk for major health endpoints has been examined, but the findings are inconsistent [3]. Therefore a metaanalysis was conducted involving nine prospective cohort studies comprising 21,365 deaths to investigate the long-term association of cheese consumption with all-cause mortality [3]. The relative risk (RR) of all-cause mortality for the highest compared with the lowest cheese consumption was 1.02. Interestingly, there was no dose-response relationship between cheese consumption and risk of all-cause mortality (RR per 43 g/day = 1.03). The results suggested that long-term cheese intake was not associated with an increased risk of all-cause mortality nor a beneficial effect (Figs. 18.2 and 18.3).

Recent studies of dairy products have suggested that fermented rather than nonfermented dairy products might provide benefits for cardiovascular health, but the evidence is inconclusive [4]. The present study comprised a total of 1981 men, aged 42−60 years, from the Kuopio Ischemic Heart Disease Risk Factor Study, with absence of coronary artery disease (CAD) at baseline. During a mean follow-up of 20.1 years, 472 CAD events were recorded. Median intakes were 105 g/d for fermented dairy products (87% low-fat products) and 466 g/d for nonfermented dairy products (60% low-fat products). The findings revealed that those in the highest (vs lowest) intake quartile of fermented dairy products showed a 27% (P-trend = .02) lower risk of CAD. However, those in the highest intake quartile of nonfermented dairy products had a 52% (P-trend = .003) higher risk of CAD [4]. The analysis of data, based on fat content, found that low-fat (<3.5% fat) fermented dairy product intake was associated with lower risk [hazard ratio in the highest quartile = 0.74 (P-trend = .03)], but high-fat fermented dairy products and low-fat or high-fat nonfermented dairy

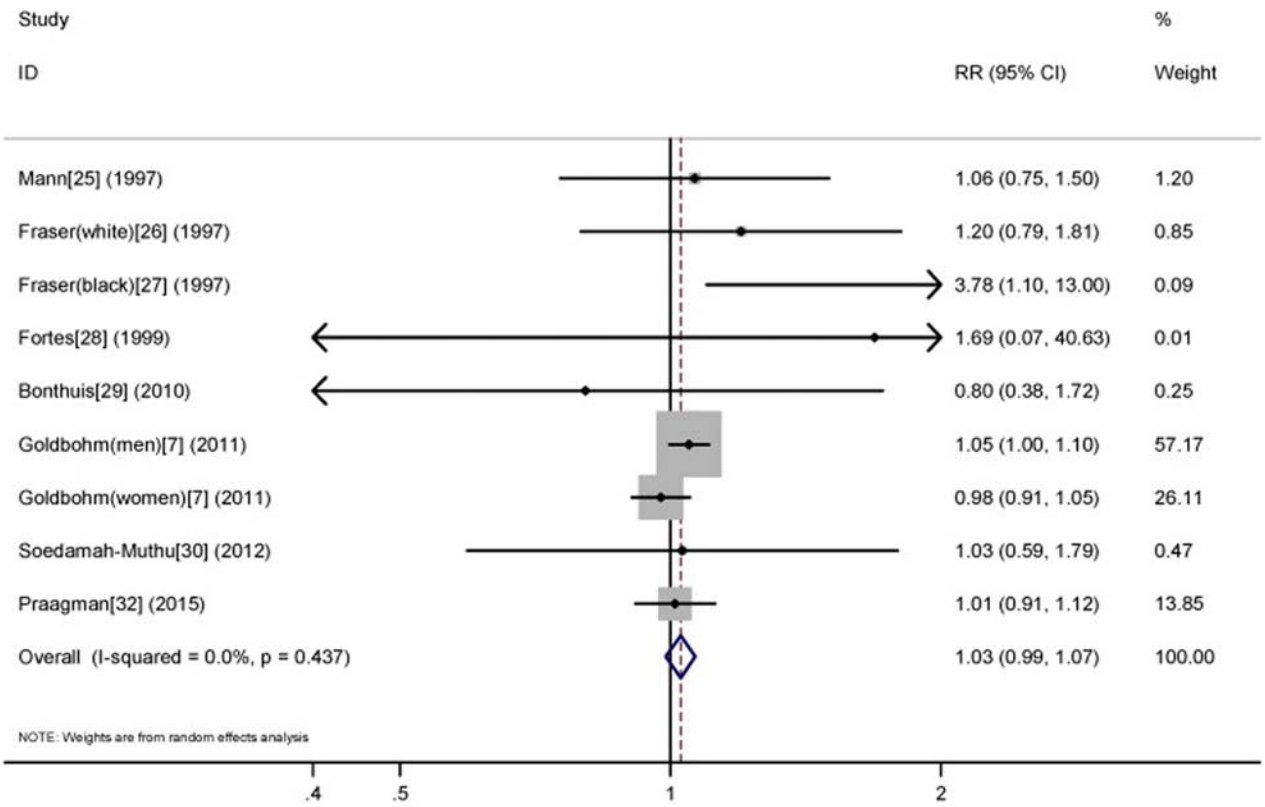


FIGURE 18.2 Metaanalysis of prospective studies on cheese consumption (high vs low) and risk of all-cause mortality. *Modified from reference Schulz D, Senge B. Acid and acid/rennate curd cheeses, part A: quarg, cream cheese and related varieties. Berlin, Germany: Department of Food Rheology; 1999.*

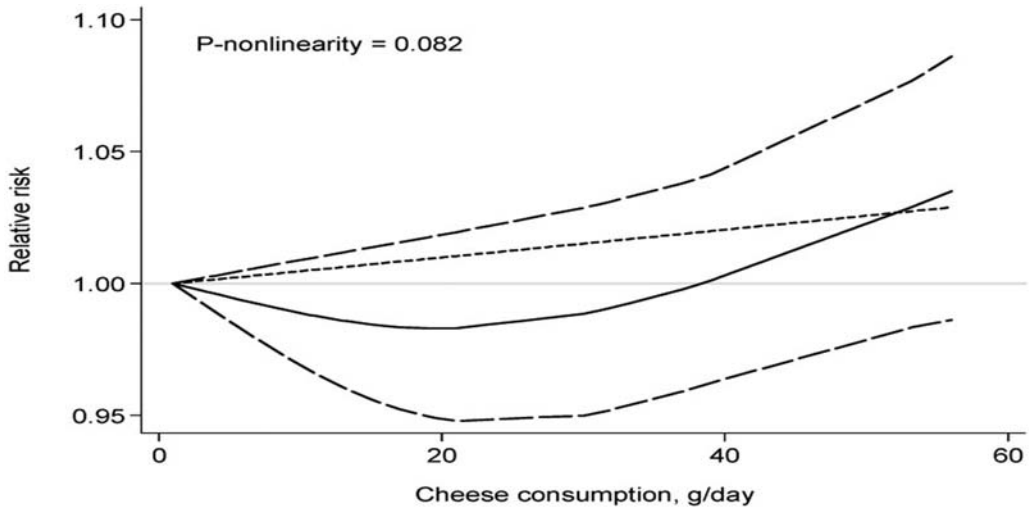


FIGURE 18.3 Relative risk with 95% confidence interval for the relationship between cheese intake and risk of all-cause mortality in a restricted cubic spline random-effects metaanalysis. *Modified from reference Schulz D, Senge B. Acid and acid/rennate curd cheeses, part A: quarg, cream cheese and related varieties. Berlin, Germany: Department of Food Rheology; 1999.*

products had no association. It is possible that fermented and nonfermented dairy products can have opposite associations with the risk of CAD [4].

In a further study, the physicochemical and sensory properties, texture profile, and antioxidant activity of ginseng extract−supplemented quark cheese as a new cheese product were examined [5]. There was a significant decline in the moisture content of the cheese on addition of less than 1.0% ginseng extract, while fat and protein levels increased, although microbial counts and lactose and ash contents showed no effect ($P < .05$). The texture profiling found that cohesiveness and springiness were unaffected, whereas hardness, gumminess, and chewiness increased significantly. Interestingly, the 2,2′-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid radical-scavenging activities of the cheese fortified with 0%, 0.5%, or 1.0% of the ginseng extract were $4.22\% \pm 0.12\%$, $20.14\% \pm 1.34\%$, and $56.32\% \pm 1.54\%$, respectively. There was a significant improvement in bitterness, ginseng odor, and aftertaste with increasing concentration of ginseng extract ($P < .05$). The overall quality attributes of quark cheese between the no-supplement control and samples with less than 0.5% of the ginseng extract ($P > .05$) revealed no significant differences. It is possible that these products may promote public health as functional foods [5]. It is well known that quark cheese is a fermented soft fresh cheese categorized as an acid-rennet coagulated cheese [6]. This study examined whether use of alternative raw materials such as kefir and yayik buttermilk can produce quark cheese in comparison with the cheese produced by the acidification of skim milk with mesophilic lactic culture [6]. The cheese products were evaluated in terms of physicochemical, microbiological, and sensorial properties in addition to the volatile and peptide profiles [6]. The results revealed that quark produced from kefir and buttermilk had preferred properties that may directly influence the cheese characteristics as well as its health effects [6].

Characteristics of quark cheese

Quark is a fresh unripened cheese prepared from pasteurized milk. It is unripened, fresh, and very smooth in texture. It is produced on a large scale in Germany. Quark is milky white in color or faintly yellowish. It has a high moisture content (82% w/w) and a relatively short shelf life (2−3 weeks). During the manufacture of quark the curd is not washed (as in cottage cheese manufacture), so it has a relatively high lactose content. Quark cheese can be prepared from skim milk, partially skim milk, or whole milk. There should be no appearance of water or whey, dryness or graininess, bacteriological deterioration, overacidification, or bitter flavor during storage [7−9]. The odor and taste, that is, the flavor of quark, are mildly acidic. Quark is prepared from milk by acid coagulation and/or rennet coagulation and then separation of whey. It contains a low percentage of dry matter in comparison with other ripened cheeses; hence it is low in fat and protein and high in lactose and lactate. Most of the calcium is solubilized during acid coagulation and removed with the whey, so the quark has less calcium [1].

Quark cheese as a probiotic

A starter culture is a microbiological culture that is used to initiate the fermentation process. The starter culture that is used for the preparation of quark cheese is a mixture of mesophilic bacteria, mainly *S. cremoris* and *L. citrovorum*. Milk, starter culture, and any rennet are mixed directly in a cheese vat, and the mixture is left unstirred until it curdles. Probiotic organisms are live microorganisms that are thought to be beneficial to the host organism. According to the Food and Agriculture Organization and the World Health Organization, probiotics are "live microorganisms which when administered in adequate amounts confer a health benefit on the host." Lactic acid bacteria and *Bifidobacteria* are the most common types of microbes used as probiotics.

Quark cheese enhanced with a therapeutic dose of probiotics has been said to have health benefits and to increase the shelf life of the product. Cheese has good potential for delivery of Probiotic microorganisms into the human intestine [10]. For probiotic culture, three types of bacteria are commonly used: *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum*. Other species of probiotics that are also used as starter culture are *L. ruterii*, *L. johnsonii*, *B. lactis*, *L. plantarum*, and *B. longum*, [10]. A study compared traditional starter culture with probiotic starter cultures such as *L. acidophilus* culture and *Bifidobacterium* culture in the manufacture of quark cheese and concluded that probiotic starter cultures give a product with superior quality in terms of protein, fat, minerals, sensory characteristics, and shelf life [11].

Functional properties of quark cheese

- Quark cheese has a mild, slightly sour flavor that complements many other ingredients.
- Quark cheese can serve as a flavor carrier.
- Quark cheese has a relatively light, soft texture. This texture is good on its own, for example as a pasta filling, or quark can be used in place of other cheeses to give a lighter texture, for example as a replacement for cream cheese in cheesecake.
- Quark cheese has a smooth texture and can be used to add viscosity to a variety of products.
- Quark cheese has a high moisture content. Incorporating quark into baked goods will help keep the product moist.

Preparation methods of quark cheese

General methods of quark preparation

A better quality of quark can be prepared from high-quality milk. Therefore several laboratory test have bee performed to determine the taste, acidulating, and fermenting qualities of the skim milk [8]. For the manufacturing of quark cheese, milk is pasteurized at 72°C for 40 seconds. After the milk has cooled to 28°C−30°C, it is coagulated with a mesophilic culture of *S. cremoris* and *L. citrovorum*, and a small quantity of rennet also added. Rennet (∼2−20 mL standard strength rennet/1000 L of milk) is usually added approximately 90 minutes after culture addition at a pH of around 6.3.

The coagulated skim milk is then stirred continuously for approximately 10−15 minutes and is then passed through a tubular strainer to remove curd particles. After separation the quark is cooled and optimally blended with cream and other food additives. The remaining whey removed from the separator still contains nearly about 0.65%, whey proteins and 0.2%, w/w, nonprotein nitrogen [12].

Whey proteins in their native state do not gel under the heating and acidification conditions used in standard separator quark production. Various methods have been developed to increase the whey protein content of quark and reduce losses in the whey (Table 18.3):

1. Westfalia thermoprocess: In this method, milk was pasteurized at 95°C−98°C for 2−3 minutes to denature and coprecipitate the whey proteins onto the casein. After addition of rennet enzyme, the resulting finer milk coagulum was heated at around 60°C for 3 minutes. This process is known as thermization. Thermization is done to enhance the aggregation and sedimentation characteristics. After that the stirred curd is cooled to 25°C. This process enables recovery of 50%−60% of the whey proteins in the cheese [13].
2. Centriwhey process: In this process, quark whey is heated at 95°C to precipitate the whey proteins. The denatured whey protein is removed by centrifugation, which contains solid 12%−14%, and it is used in the next batch of quark production [7,13,14].

TABLE 18.3 Yield of quark and whey protein recovery using various production methods for quark cheese.

Method	Principle	Typical quark yield (kg skim milk/kg)	Whey protein recovery in quark (%)	Flavor and texture
Westfalia standard separator process	Separation of acidified milk	4.50–4.70	~ 15	Firm and sour
Westfalia thermocompressor	Separation of acidified milk	4.08–4.30	50–70	Firm, smooth and mild
Centriwhey/westfalia-lactal/meggle-alcor	Separation/decanting/ ultrafiltration of whey	3.98	50–100	Whey taste possible
Ultrafiltration (UF)	Full UF of milk	~ 3.8	~ 100	Bitter taste
Ultrafiltration	Full UF of acidified milk	3.60–3.98	~ 100	Smooth

Source: Kroger M. The manufacture of quarg cheese. Cult Dairy Prod J 1980;15:11–14.

3. Westfalia lactal process: In this process, whey is heated at 95°C to precipitate the whey proteins, which are allowed to settle. By partial decantation of the serum, concentrated whey of 7%–8% solid was obtained. For more concentration a quark separator is used [14].
4. Ultrafiltration: This method is used for large-scale production of quark cheese and other varieties of fresh cheese. For ultrafiltrated (UF) quark, acidified skim milk (pH 4.6) is heated to around 40°C and then cooled, if required, then homogenized and packed. This method allows complete recovery of whey proteins in the cheese. However, the nonprotein nitrogen, which amounts to 0.2%–0.3% w/w of the milk, is lost in permeate. Thermization of the curd (at 60°C for 5 minutes) before ultrafiltration considerably reduces the development of stale, bitter, and metallic flavors and increases shelf life. Ultrafiltration is carried out at around 40°C–45°C to maintain good calcium solubility so as to remove calcium in permeate. Cheese milk was enriched with 25% sweet whey UF retentate containing 12% w/w dry matter and 4% w/w [15].
5. FML process (Forschungsinstitute fur Milch und Lebensmittel, Weihenstephan): In this process, the skim milk is nanofiltered to obtain 7% w/w protein and then fermented. The coagulum is stirred and concentrated by ultrafiltration. A separator is needed to obtain higher viscosity of the retentate coagulum. The texture of the final product of UF fresh cheese is similar to that of quark made with the thermoprocess [16].
6. Aubios process: In this process, the skim milk is preconcentrated 1.7-fold to 5.4% w/w and protein using microfiltration. By using this technique, a product was reported that was similar to that produced by the thermoprocess. A special combination of starter cultures is needed for the fermentation of retentates, as more lactic acid must be formed than in unconcentrated milk.

Production of quark cheese by using a two-stage continuous fermenter

A two-stage continuous fermentation process may be used for the production quark cheese from skim milk. The first stage is a stirred pH-stat fermenter, operated at pH 5.4, 5.6, 5.8, and 6.0, in which the operating pH was maintained by inflowing fresh milk. The remaining fermentation down to pH 4.7 is carried out by a procedure that simulates a second-stage plug flow fermenter in which forward velocity is as constant as possible at all points of the cross section. This two-stage continuous fermentation has a total residence time of about 5 hours, which represents a rate of production 4.8 times that obtainable in 24 hour in a batch fermenter of the same fluid capacity filled once daily with the same reconstituted milk [16].

Preparation of quark cheese by the National Dairy Research Institute method

Steps involved in modern manufacture of quark cheese

To obtain the desired level of dry matter (17%–20%) content and a protein content of a 12.5%–13.5% (for low-fat quark), the following processes are used:

- Batch separation by pressing or drainage by using filter cloth or filter bags.

- Continuous centrifugation using quark separators.
- Continuous concentration or separation by ultrafiltration.

At the National Dairy Research Institute for preparation of quark cheese, good-quality buffalo milk contained in a vat is pasteurized at 85°C for 15 minutes. The milk is then cooled and inoculated with NCDC culture at approximately 1.0% and incubated at 37°C. Two and half hours after the addition of starter culture, when the pH reaches 6.3, Meito rennet enzymes are added and mixed thoroughly. After that the vat content is left undisturbed for curd setting, which takes around 14−16 hours starting from culturing. The coagulum is then cut by using cheese knives and then left undisturbed for about 10−15 minutes. Then the temperature of the content is slowly increased to 55°C−60°C (10°C/minutes). For the manufacturing of thermoquark the curd is kept at 60°C for 10 minutes. After that the curd is cooled to room temperature and placed in muslin cloth for 3.5−4 hours [Total Solid (TS) around 28%−30%] for dewheying. In the last step, fibers, plant sterol esters, and salt are added to the curd, and homogenization of the total mass is carried out in a Hobart mixer. The quark is then put into PS cups and stored at 6°C.

Factor affecting the preparation of quark cheese

Heating affects the physical properties of quark cheese

Heat treatment at 82°C for 5 minutes is mostly preferred for quark cheese production. It has been seen that heat treatment affects the microstructure and physical properties of quark cheese. Three levels of time-temperature combination were used: 72°C for 16 seconds, 82°C for 5 minutes, and 90°C for 5 minutes. Rheological properties were studied by means of frequency sweep experiment with the measurement of elastic modulus (G′), and microstructures of samples were observed by scanning electron microscopy. Maximum and minimum elastic modulus (G′) and cheese yield were obtained at 90°C and 72°C, respectively ($P < .05$). Yield at 82°C and 90°C was higher than that at 72°C. This study showed that heat treatments at 82°C and 90°C were more suitable for quark cheese making than that at 72°C. Quark cheese is one of the most popular acid-coagulated cheeses. Contribution of denatured whey proteins in the gel network led to higher cheese-making yield as well as high nutritional value [17].

Lactose hydrolysis in high heated milk affects the physical properties of quark cheese

The recovery of whey proteins in quark from high heated milk is 40.5% in unhydrolyzed milk and 42.7% in hydrolyzed milk. Quark is produced from homogenized milk with or without lactose hydrolysis or before heating to 95°C for 15 minutes. The yield obtained was 9.2% and 13.3% for unhydrolyzed and hydrolyzed high heated milk, respectively, in comparison to the corresponding unheated milk. No effect of lactose hydrolysis on yield was observed. The time required to attain the desired pH 4.5 in the quark fermentation was reduced in lactose-hydrolyzed milk by 7.1% and 4.6% for the unheated and high heated milk, respectively. The results of sensory evaluation indicated that heating resulted in graininess and hydrolysis, and high heating induced an unclean flavor in the quark. In a nutritional evaluation by bioassay methods, no differences were found in protein digestibility among any of the quark cheeses studied; however, protein efficiency ratio, biological value, and net protein utilization values indicated that lactose hydrolysis plus high heating had a negative effect on the nutritional value of milk. Amino acid analysis of quark samples indicated a possible lowering of lysine content in the hydrolyzed quark [18].

Preparation of quark cheese by adding honey and its effects

Quark cheese can be manufactured by using different concentrations of honey with partially skim milk (1.5% fat, 9% solid nonfat). The physicochemical, microbiological, and organoleptic characteristics of quark cheese with 15% honey concentration were superior to those of the control quark cheese.

L. casei was used as a starter culture in the preparation of quark cheese with honey. Different honey concentration (5%, 10%, 15%, and 20%) were used to determine the physicochemical, rheological, microbial, and sensory effects of honey on quark cheese. Quark cheeses that contained 20% honey had the highest amount of carbohydrates as compared to the other samples. Texture analysis was also done to determine different properties of quark, such as hardness, cohesiveness, adhesiveness, springiness, and gumminess. The highest probiotic bacterial count was found in the quark that contained 15% honey, and less growth of yeast and molds was found in quark containing 15% and 20% honey. Honey had a positive impact on sensory attributes such as appearance, color, flavor, and consistency. The study concluded that

the physicochemical, microbiological, and organoleptic characteristics of quark cheese with 15% honey concentration were superior to those in the control quark cheese.

Quark filtration technology

Filtration technology can be used at different stages during the manufacture of quark-type products, for example, filtration of the acid whey (partial) filtration of the sweet milk or filtration of (partially) acidified milk. UF quark is generally softer, smoother and creamier than conventional quark. When full filtration to final cheese solids was carried out before acidification, the sensory attributes of the resulting products were described as impaired due to bitterness contributed by the slower rate of acidification, failure to reach the desired pH and the high calcium content. This problem has been overcome by UF of partially (pH 5.7−5.95) or fully (pH 4.8−4.6) acidified milk [13].

Preconcentration of cheese milk by nanofiltration

In a study, the preconcentration of milk was done by nanofiltration for production of quark-type cheese that is sweeter and has a higher calcium content than conventional quark. In the nanofiltration process, transmembrane pressure and flow velocity have an effect on both permeation flux and lactose retention. When the temperature increased, there was an increase in permeate flux and a decrease in lactose retention. The milk was concentrated 2−3 times by nanofiltration. The quark obtained by using milk nanofiltration is naturally sweeter than traditional fresh cheese and has a high calcium content and no bitter taste. The whey has a higher TSs and lactose content and therefore required an easier treatment than normal quark acid whey [15,16].

Application based on end use of quark cheese

- The mild flavor and smooth texture of quark make it excellent as a topping or filling for a variety of dishes.
- Quark cheese can often be substituted in place of sour cream, cottage cheese, or ricotta cheese.
- Quark cheese can be blended with seasonings and used as a topping. For example, it may be blended with chives and used to top potatoes. The creamy texture of quark cheese gives it the desired mouth feel and viscosity for this application. The mild flavor and flavor-carrying properties of the cheese are also important.
- Quark cheese can be blended with seasonings and used as a dip. Again, the texture and flavor/flavor-carrying ability are the important factors.
- Quark can be used as the filling in a variety of pasta dishes. The lightness of the cheese provides a pleasant texture, and the mild flavor of the cheese complements the flavor of the pasta sauce. Furthermore, the white color of the quark as a pasta filling or as a layer in lasagna provides an attractive contrast to dark pasta sauces.
- Quark cheese can be blended into a sauce or dressing to provide viscosity. Quark can be mixed with fruit. The mild flavor of the cheese complements the sweetness of the fruit. The light, creamy texture of the cheese is also important.
- Quark cheese can be used in making baked goods such as cakes or brownies. The high moisture content of the quark helps to keep the product moist. The cheese also contributes to the browning when the product is baked.
- Quark cheese can be used as a cheesecake filling. The creaminess of the quark makes it suitable for this application, and it can be used to replace cream cheese to provide a lower fat level and a lighter texture.

Recent advances in the preparation of quark cheese

Enhancement of functional attributes in quark cheese

Functional foods have developed to enhance the health attributes of widely consumed foods by fortification with functional ingredients. Studies have found that plant sterols and stanols lower blood cholesterol levels by partly blocking absorption of cholesterol in the gut.

Enrichment with dietary fiber

Dietary fiber, especially soluble fiber associated with carbohydrate and lipid metabolism, has shown to have hypercholesterolemia properties. After addition of fiber at the level 1.0% in curd, sensory scores of all attributes studied increased and were very close to those of the control. But after addition of 2%−3% oat fiber there was a substantial

decrease in the sensory scores. Oat fiber, when it was mixed in 1.0% concentration, showed the highest overall acceptability; this may be because of reduced free whey, whitish to creamy color, and good body and textural attributes. Further increasing the fiber level to 3.0% along with inulin resulted in significant lowering of the sensory scores. Inulin acts as a fat mimetic and improves textural characteristics of the product. It can effectively bind water in a system with a high moisture content and can prevent phase separation. It also makes the product slightly sweetish [17,18].

Enrichment of quark cheese with prebiotic and probiotic attributes

By using recent technology, probiotic quark cheese are being developed with enhanced therapeutic dose for claimed health benefits increase the shelf life of product. For Probiotic culture, mainly three types of bacteria are commonly used, that is, *L. acidophilus*, *L. casei*, and *B. bifidum*. Probiotic starter cultures such as *L acidophilus* culture and *Bifidobacterium* culture are used in the manufacturing of quark cheese. Thus probiotic starter culture gives a product with superior quality in terms of protein, fat, minerals, sensory characteristics, and shelf life [10].

Preservation of quark cheese by using chemicals

In the preparation of quark cheese by using chemicals, a temperature of 8°C acts as a means of preservation that eliminates mold contamination, but owing to the presence of potassium sorbate, mold contamination is also inhibited at room temperature. Thus chemical treatments help in the preservation of cheese. In this method, natural cheeses are dipped in 25% potassium sorbate solution before being packaged. A processed cheese sample was manufactured with 0. l% sorbic acid added with the emulsifying salt, and untreated cheeses were used as controls. The cheeses were stored at 10°C and 20°C, at 60% relative humidity. Potassium sorbate reduced mold contamination approximately 3% on brick cheese and 10% for controls after 14 weeks of storage, whereas sorbic acid in the processed cheddar cheese reduced mold contamination approximately 30% and 100% for controls after 10 weeks of storage. The effect of the sorbate dip on the cheese during the seven-week ripening period was also studied [19]. Nonpasteurized skim milk quark was treated with 0%, 0.015%, 0.022%, 0.033%, and 0.050% potassium sorbate and stored for 40 days at 8°C as well as room temperature. Thus chemical treatments help in the preservation of cheese.

Effect of rennet enzyme on proteolysis and bitterness in quark cheese during storage

The role of rennet enzyme, starter culture, and plasmin was studied to determine the effect of proteolysis on acid-coagulated quark cheese during storage. In the experiment design, each agent was used in separate treatments that excluded rennet and replaced it with a proteolysis substitute (glucono-δ-lactone) or alternatively either increased by the addition of exogenous enzyme or decreased by addition of a specific inhibitor (plasmin). In the experiment, milk was heated at 90°C for 10 minutes prior to acidification. After that, all quark samples were thermized to reduce the levels of adventitious microflora and extend shelf life. The experimental treatments had little effect on composition or yield of quark. After exclusion of rennet during manufacturing of quark, reduced proteolysis was observed. This has been confirmed by urea-polyacrylamide gel electrophoresis and reversed-phase high-performance liquid chromatography (HPLC). It was also observed that omission of starter had a considerably lesser effect. The role of plasmin was also minor, resulting in production of large, water-insoluble gamma-caseins. The principal ripening agent in thermized quark appeared to be rennet, while starter enzymes and plasmin played a lesser role [20].

The effects of rennet level, culture composition, strain, and microbial contamination have been evaluated to determine the potential cause of bitterness in quark cheese. In one study, rennet was decreased from 3876 to 388 units/1000 kg of milk, bitterness was reduced, and an acceptable product with an extended shelf life was obtained. The microbiological results indicated low psychrotroph, coliform, and yeast and mold counts during the six-week storage trial, suggesting that bitterness was not the result of microbial contaminants. The nature of the starters that were tested (mixed cultures of *S. lactis* and *S. cremoris* with and without *S. diacetilactis*, or single strains of *S. cremoris* 134 and 584) did not play an important role in bitterness development during storage. Thus rennet is the main cause of bitterness development in quark cheese [21].

Nonstarter lactobacilli-enhanced flavor of quark

In this experiment, one of two strains (*L. plantarum* I91 or *L. casei* I90) was added to the starter composed of *S. thermophilus*. During ripening, cheeses containing the added lactobacilli showed an increased content of total free amino

acids, but this increase was significant only in cheeses inoculated with *L. plantarum* I91. Cheeses inoculated with *L. plantarum* I91 or *L. casei* I90 were also characterized by a significantly higher concentration of diacetyl, a key flavor compound, and an increased content of acetoin. Results suggest an increase in the catabolism of either citrate or aspartate, with the production of the derived aroma compounds. Thus aspartate content increased in both lactobacilli-enhanced cheeses, whereas citrate was more or less constant, suggesting that aspartate could be the source of increased diacetyl and acetoin. A triangle aroma test showed that the addition of the lactobacilli strains significantly changed the sensory attributes of cheeses. Sensory analysis was performed by 11 of 12 panelists, and they commented that the aroma of cheeses with adjuncts was more buttery than that of control cheeses, which is desirable in most soft cheeses. Both *L. plantarum* I91 and *L. casei* I90 performed well as adjunct cultures by influencing cheese aroma development and cheese proteolysis [19,20].

Physiological effects and dietary application of quark cheese produced with enzyme transglutaminase in growing rats

In a study, 24 rats were divided in three groups, which were given specific diets for 35 days. One group was provided with a diet in which casein was the sole protein source; the two experimental diets included quark produced with or without the use of transglutaminase as a protein source. The dietary application of quark produced with transglutaminase was found to significantly decrease fecal ammonia and putrefactive short-chain fatty acid concentrations, increase calcium and phosphorus utilization in the body, and reduce the total cholesterol level in the serum. Incorporating whey proteins into the quark with the aid of transglutaminase more favorably modified the serum cholesterol level, the calcium and phosphorus utilization, and measurements of fermentation in distal sections of the rat's gastrointestinal tract compared with the dietary quark produced without transglutaminase [22].

Cathepsin D activity in quark

In a study to investigate the cathepsin D activity in quark, the cheese was produced from raw skim milk with pepstatin added at curd cutting and from ultrafiltration retentate of raw milk with added pepstatin. No starter bacteria were used for the reduction of pH because it was achieved by the addition of glucono-δ-lactone. After the addition of glucono-δ-lactone, yields ranged between 20.25% and 23.5%, with protein levels of 13.6%−15.7%. Quark cheese was also produced from raw skim milk, pasteurized skim milk, and raw skim milk with rennet added and UF raw skim milk. Proteolysis in the quark occurred during storage of all experimental cheese samples for three months at 8°C. By immunoblotting using antibodies against bovine cathepsin D, immunoreactive procathepsin D was identified in all cheese samples. The presence of cathepsin D or procathepsin D−derived activity was confirmed by a specific enzyme assay in all samples except those that contained pepstatin. Inhibition of cathepsin D−catalyzed proteolysis by pepstatin was observed in chromatograms of water-soluble extracts analyzed by reverse-phase HPLC. Peptides produced as a result of cathepsin D activity were observed in cheese made from both raw and pasteurized milk, suggesting that the activity at least partially survived pasteurization [23].

Lactose absorption by postweaning rats from yogurt, quark, and quark whey

Lactose intolerance was studied by providing diets including yogurt, quark cheeses prepared from yogurt culture and buttermilk culture, and two types of whey obtained from quark processing to postweaning rats. After feeding each diet for a period of 7 days, absence of blood glucose elevation and occurrence of diarrhea were used as indicators of lactose absorption. After that, blood glucose assays were performed, and the absence of diarrhea indicated that yogurt and quark cheeses prepared from yogurt and buttermilk culture were well tolerated by the rats, whereas the whey protein containing the same levels of viable organisms and lactose as the quark cheeses caused severe symptoms of diarrhea and poor lactose absorption, as indicated by no changes in blood glucose levels. Plate counts and enzyme assays of gastrointestinal contents were performed to confirm the presence of viable culture organisms and beta-galactosidase activity after feeding the two types of quark cheese. The availability of viable organisms, the exogenous lactase activity, and especially the slow gastric emptying may all have contributed to more efficient hydrolysis and digestion of lactose from quark cheeses and yogurt than from the whey protein [24].

Food consistency effects of quark in lactose malabsorption

Food consistency effects of quark in lactose malabsorption were observed by providing quark prepared with yogurt (QY) or buttermilk (QBM) cultures, pasteurized quark (QP), and quark whey (WY) in comparison to a semisolid

yogurt. After an overnight fast, the subjects consumed 250 g of each product, which contained 15 g lactose. The blood glucose level of each subject was measured at 15-minute intervals for 90 minutes and symptoms of lactose intolerance were noted for 6 hours following consumption of the food. All the quark products (QY, QBM, or QP) were tolerated as well as the yogurt. The whey (WY), which showed levels of lactose and viable yogurt organisms similar to those of the quark products or the yogurt, caused symptoms of lactose malabsorption. The blood glucose level was increased by each product. Yogurt (QY) and buttermilk (QBM) culture and, pasteurized quark (QP) caused smaller rises in blood glucose level but higher total blood glucose accumulation over a 90-minute period compared to the quark whey (WY). Food consistency seemed to be the common factor related to lack of lactose malabsorption effects with all the quark products, while microbial enzyme activity or the presence of viable yogurt culture organisms appeared insignificant [25].

Effect of thermization on the quality of quark

Quark cheese prepared from thermized cultured milk, pH 4.5, had better keeping quality at 7°C than quark produced without thermization. Thermization also improved the quality of cold-stored quark, and it reduced proteolysis. Thermization also helped in the reduction of proteolysis in quark produced from milk containing 5 ng/mL of proteinase from *Pseudomonas fluorescens*. Quark produced without thermization from milk contained 5 ng/mL of proteinase P1 and could be stored up to five weeks but had average flavor scores that were significantly lower than those of quark produced from control milk, which did not contain this enzyme. Quark cheese that was thermized with proteinase at a concentration of 30% had a better capability to react to antibodies specific for proteinase than quark produced without thermization. Only a little immunoreactive material was found in wheys separated from thermized cultured milks as compared with nonthermized controls. This study indicates that during thermization of cultured milk, proteinase is inactivated by association with the casein and self-digestion and increased shelf life of quark cheese [26].

Conclusion

Quark cheese is very smooth, similar to cottage cheese, which consists of distinct curds. Quark cheese is incorporated into different food products to add sensory appeal, mild flavor, and nutritional value. Quark cheese can be prepared from skim milk, partially skim milk, or whole milk. When the quark cheese is enriched with fat, it imparts flavor and smoothness to the cheese. However, an increase in fat content may cause adverse effects on the consumer's health. Quark cheese is perishable, owing to its relatively high moisture content. Since the curd is not washed (as in cottage cheese manufacture), quark cheese has a relatively high lactose content.

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Chapter 19

Cocoa and chocolate consumption and prevention of cardiovascular diseases and other chronic diseases

Reema Singh[1], Ram B. Singh[3], Viliam Mojto[2], Dominik Pella[4], Jan Fedacko[9], Viola Vargova[10], Krasimira Hristova[5], Agnieszka Wilczynska[6], Maria Mojtova[1,7] and Anna Gvozdjáková[1,8]

[1]Centre of Nutrition and Heart, Medical Hospital and Research Centre, Moradabad, India, [2]3rd Department of Internal Medicine, Faculty of Medicine, Comenius University, Bratislava, Russia, [3]Halberg Hospital And Research Center, Civil Lines, Moradabad, India, [4]School of Public Health and Community Medicine, Hebrew University Hadassah Medical School, Jerusalem, 91120 Israel and Safaric University, Kosice, Slovakia, [5]University National Heart Hospital, Sofia, Bulgaria, [6]Institute of Psychology, Silesian University, Katowice, Poland, [7]University in Nitra, Slovakia - Univerzita Konštantína Filozofa v Nitre, [8]Pharmacobiochemical Laboratory of 3rd Department of Internal Medicine, Faculty of Medicine, Comenius University in Bratislava, Bratislava, Slovakia, [9]Department of Internal Medicine, PJ Safaric University, Kosice, Slovakia, [10]Faculty of Medicine, PJ Safaric University, Kosice, Slovakia

Introduction

Cardiovascular diseases (CVDs), coronary artery disease (CAD), stroke, diabetes mellitus, cancer, and neuropsychiatric diseases are major non-communicable diseases (NCDs), which remain the leading causes of morbidity and mortality worldwide [1]. The global prevalence of CVDs and diabetes is rising progressively and is forecast to increase twofold by the year 2030. These cardiometabolic diseases (CMDs), that is, obesity, metabolic syndrome, and diabetes, along with CVDs need effective prevention guidelines to improve public health in which nutritional and other lifestyle behaviors have major a role. Chocolate, a popular food item, is rich in cocoa, which is a potential antioxidant used by the food industry to provide flavor to a variety of foods throughout the world. Recently, cocoa and chocolates that contain cocoa have gained increasing attention for their potential benefits in CMDs [2−9]. A number of experimental and clinical studies have indicated a protective role of chocolate against oxidative stress, inflammation, and endothelial dysfunction [4,5]. In recent metaanalyses of feeding trials, the beneficial effects of cocoa and cocoa-containing foods have been emphasized, supporting the favorable impact of cocoa consumption on blood pressure, lipid profiles, flow-mediated dilation (FMD), and insulin sensitivity and diabetes [2,5−9]. There is consistent evidence that cocoa consumption can improve vascular function, but the evidence showing reduced risk of CMDs is weaker. The overall results on the role of cocoa in CMDs remain inconclusive. The beneficial effects of hot chocolate on health and NCDs are considered secondary, although these have recently been reported in world-class journals [2−8]. However, chocolate is consumed mainly for taste and flavor in most countries of the world. This review aims to highlight pertinent studies to comprehensively evaluate the role of chocolate in the prevention of CMDs.

Historical view of cocoa

Cocoa was admired by the 16th century Aztec emperor Montezuma II, who named it a divine drink. According to Montezuma, cocoa "builds up resistance and fights fatigue. A cup of this precious drink permits a man to walk for a whole day without food" [10]. The botanical name of the cocoa tree, *Theobroma cacao*, is derived from the Greek words *theo* (god) and *broma* (drink), and the Incas considered it the drink of gods [11]. In Honduras, archeologists have uncovered elaborately designed bowls that are believed to have been used by the Aztecs to drink liquid cocoa thousands of years ago [11−13]. In the language of the Aztecs (Nahuatl) this drink was called *xocolatl* (comprising "*xococ*," meaning sour or

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bitter, and "*atl*," meaning water or drink from the cocoa tree). However, *T. cacao* was known much earlier, perhaps originally consumed as an infusate by the Paleo-Indian gatherers of Mesoamerica, who became hunter-gatherers. The evidence regarding cocoa consumption by the Incas, Aztecs, and Mayans is abundant, and early consumption can be traced to the Mokaya and other pre-Olmec people. Cacao beverages date back even earlier (1900 BCE) [11–13]. Recent studies indicate that they have beneficial biochemical and clinical effects as well as being enjoyable drinks.

In the 19th century, chocolate was considered, a luxury item, and its consumption was considered to have adverse effects on health because it was sweetened with sugar, which is a part of Western diets and lifestyles [10]. A Western diet in conjunction with ordinary white chocolate intake may be associated with dental caries, obesity, high blood pressure, and diabetes; hence many physicians tend to warn patients about the potential health hazards of consuming large amounts of chocolate-based, energy-rich foods [10,14]. Native Indians were consuming it in an unsweetened drink of raw and dried cocoa powder, which is rich in polyphenolic flavonoids [10–13]. As it became commercialized in European countries, the product was sweetened. Other processing methods were used by the food industry to decrease its bitterness and to achieve taste and flavor that were pleasing to Europeans. The flavanol content of cocoa, which is most likely polyphenolic, having potential antioxidant effects, was reduced as a result of this modification. It seems that not all chocolates with cocoa are equal in bioactivity. The high cocoa consumption of the native Mesoamericans could be difficult with currently available chocolate products. The products should be duly fortified and their bioactivity examined to achieve more effective highly bioavailable cocoa-containing chocolate. Further studies are needed on plant epidemiology and manufacturing to determine whether there are any interactions with coingredients. In a native population of Kuna Indians, living on islands off the coast of Panama, cocoa is consumed for its protective effects. The Kuna belong to one of the few cultures that are protected against the age-dependent increase in blood pressure and the development of arterial hypertension.

Biochemistry and pharmakokinetics

The main contents of cocoa are biologically active phenolic compounds, which have stimulated research into the effects of cocoa on various biological markers, oxidative stress, blood lipids, insulin resistance, endothelial cells, atherosclerosis, and aging (Table 19.1) [15–23]. Polyphenolics, including flavonoids, have a common chemical structure: C6-C3-C6 (Figs. 19.1 and 19.2). Flavonoids can be classified into flavonols, flavones, isoflavones, flavanones, anthocyanidins, and flavanols [15–38]. Fruits and vegetables are also rich sources of flavanols (also called flavan-3-ols), which are well known to provide protective effects against death due to NCDs [14]. Cocoa is consumed as chocolate, cakes, and other baked goods, but the highest content is present in bread (Table 19.2). Flavanols occur as the monomers epicatechin and catechin, which are the main flavanols in fruits [35–37]. These monomers can form links between C4 and C8, allowing them to assemble as dimers, oligomers, and polymers of catechins, the so-called procyanidins [27]. Procyanidins are also known as condensed tannins, which, through the formation of complexes with salivary proteins, are responsible for the bitterness of cocoa [35]. Major sources of flavonols are certain teas, grape juice, wine, various berries, and especially cocoa.

The flavanol content and the total antioxidant capacity in plasma increase after oral consumption of flavonol or cocoa products [25,26]. However, if cocoa is consumed with milk or if cocoa is ingested as milk chocolate, these effects appear to be markedly reduced; but the finding is controversial [28–30]. The highest plasma peak concentrations of

TABLE 19.1 Nutrient composition of cocoa and chocolates.

Nutrient	Cocoa	Chocolates
Flavonoids (g/g)	200–1055 (dry powder)	
Flavanols + procyanidins (g/g)	1400 (cocoa liquor)	700–1700
Flavanols (catechin, epicatechin) (g/g)	336–956 (dry powder)	460–610
Antioxidant activity (ORAC) (mmol Trolox equivalents)	40 (cocoa liquor)	6.7–13
Total fat (g/g)	0.045 (dry powder)	0.326
Total carbohydrates (g/g)	0.070 (dry powder)	0.587
Total proteins (g/g)	0.080 (dry powder)	0.004
Total cholesterol (mg/g)	<3 (dry powder)	0.1

ORAC Oxygen radical absorbance capacity.
Data from Refs. [8–11].

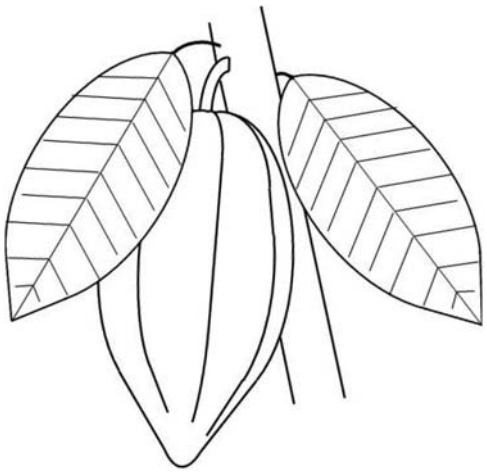


FIGURE 19.1 Cocoa fruit and leaves.

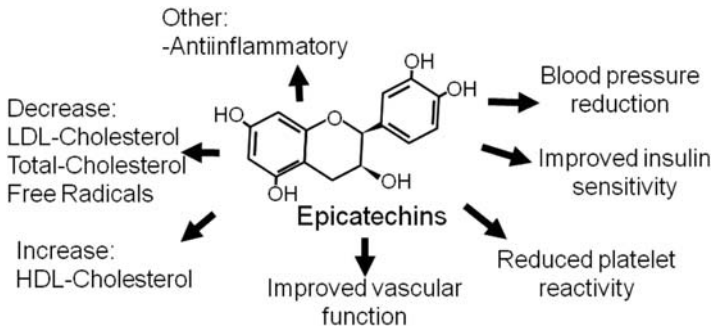


FIGURE 19.2 Effects of cocoa epicatechin on biomarkers of health and disease.

TABLE 19.2 Flavonoid contents in various foods.

Foods	Flavanol content (mg/kg or mg/L)
Beans	350–550
Apricots	100–250
Cherries	50–220
Peaches	50–140
Blackberries	130
Apples	20–120
Green tea	100–800
Black tea	60–500
Red wine	80–300
Cider	40
Chocolate	460–610

flavanols are obtained 2–3 hours after ingestion in a dose-dependent manner and are still measurable after 8 hours [28,31,32]. The smaller the polyphenol is, the higher the concentration in blood, so it is the molecular size of the flavonol that matters. A single measurement of plasma levels at 2 hours may be a check for compliance [33]. This measure

has limited usefulness in determining the bioavailability and bioactivity of flavonols. The metabolic conversion of flavonols in the intestinal cells, liver, and other tissues; their binding to proteins; their accumulation in cells; and the urinary elimination rate are important in determining bioactivity [33,34]. The quantity of flavanols markedly decreases during the conventional chocolate manufacturing process from fresh cocoa seeds to the final product [35]. Roasting and fermentation may also reduce the final flavanol content of foods, and the flavanol concentrations may depend on the soil in which the plant is grown [36]. It should be noted that milk chocolate has the lowest flavanol content compared with cocoa powder and dark chocolate [37].

Mechanisms of action

The potential mechanisms of actions of cocoa flavanols on various body systems for providing benefits on CMDs have been explored (Fig. 19.3). Inhibition of free radical stress, activation of nitric oxide (NO), and antiplatelet and antiinflammatory effects are important mechanisms of actions of cocoa flavonols [15–23]. These actions may improve endothelial function, lipid levels, blood pressure, and insulin resistance, resulting in better clinical outcomes [39]. Among these beneficial effects of cocoa, improvement in endothelial function, characterized by a continuous, smooth, nonthrombogenic surface of all blood vessels that exhibit a highly selective permeability in its healthy state, appears to be most important. The endothelium synthesizes and releases a broad range of vasoactive substances. The structural atherosclerotic changes may develop long after functional impairment of the vascular endothelium in response to injury by oxidants and toxicants that impair the release of NO, synthesized by endothelial NO synthase (eNOS) from L-arginine in the presence of the cofactor the trahydrobiopterin [40]. The circulating blood or receptor ligand substances, such as acetylcholine, bradykinin, or serotonin, induce shear stress, which is responsible for the release of NO from the endothelial cells [41]. NO causes vasodilation and inhibits adhesion of leukocyte and migration, smooth muscle cell proliferation, and platelet dysfunction. Decrease in eNOS expression and/or NO bioavailability may result in dysfunction of the endothelium, predisposing the person to atherothrombosis [42] (Fig. 19.4). After diffusion from endothelial to vascular smooth muscle cells, within a few seconds it augments intracellular cGMP levels and leading to relaxation of vascular smooth muscle cells [43]. Epidemiological studies indicate that forearm endothelial dysfunction is predictive of coronary vascular dysfunction and predispose future coronary events [44–46].

There is evidence that increased consumption of flavanol-rich red wine, black tea, and green tea can enhance endothelial function among patients with CAD [47–50]. An experimental study in rats indicated that cocoa can induce NO-dependent vasodilation [51]. Cocoa can also cause vasodilation in the finger or forearm circulation of healthy subjects [52–54] and among patients with coronary risk factors, including diabetes mellitus [55–59] (Table 19.3). Long-term consumption of a high-flavanol diet may cause an increased release of NO metabolites, consistent with an augmented NO production, or diminish its degradation [54]. Epicatechins are known to closely mimic the vascular effects of flavanol-rich cocoa in humans, indicating that these antioxidants represent the primary mediator of the beneficial effect of cocoa flavanols on vascular function [54]. In vitro experiments in cultured endothelial cells and rat aorta indicate

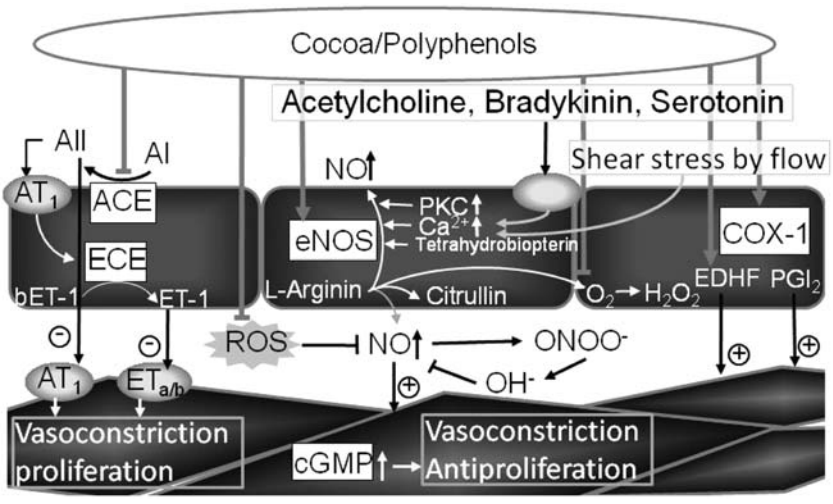


FIGURE 19.3 Mechanism of action of cocoa-epicatechin showing release of nitric oxide.

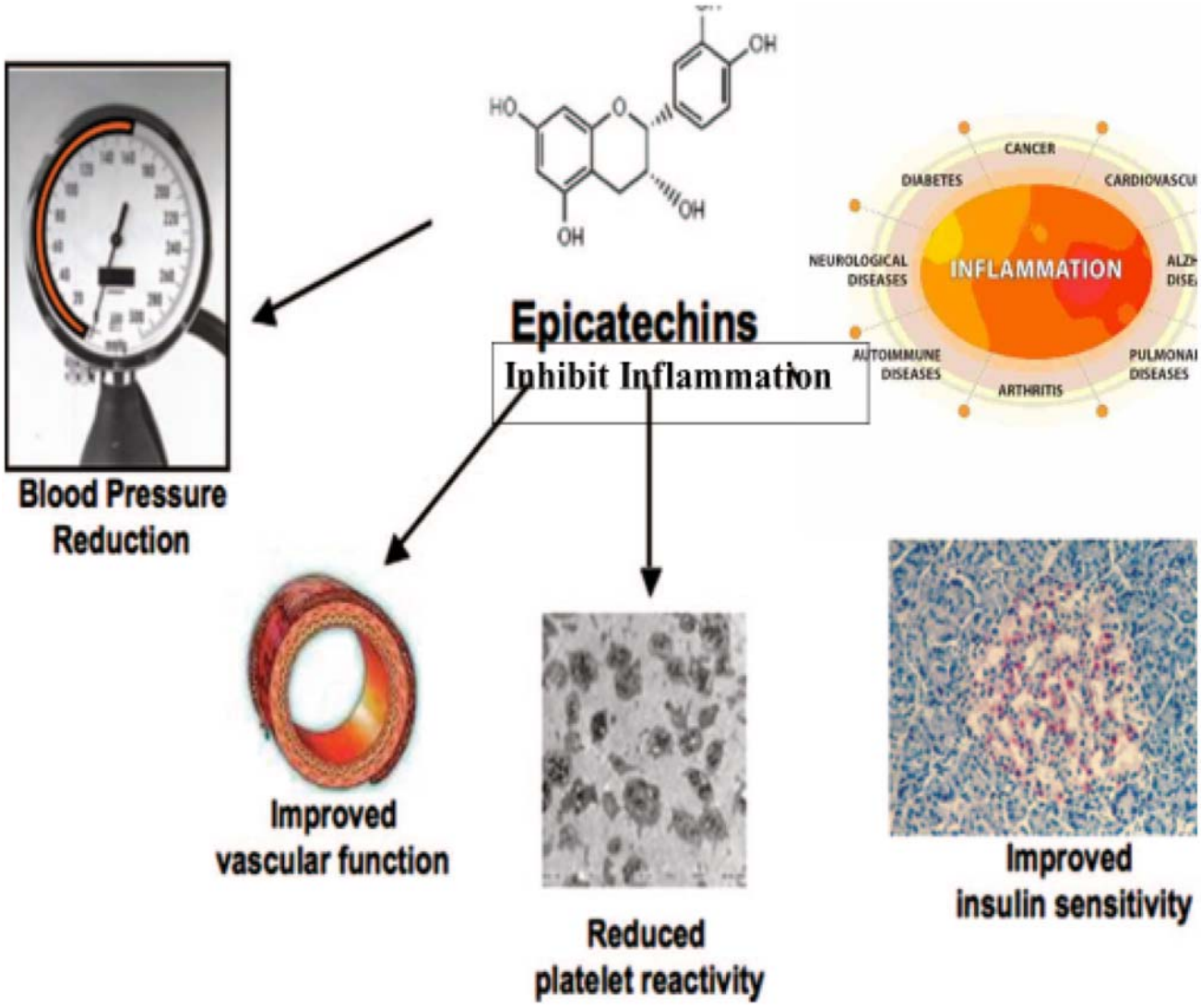


FIGURE 19.4 Effects of epicatechin on clinical and biochemical risk factors.

that plant extracts that are rich in flavanoids enhance eNOS activity [72–74]. Further study showed that incubation of endothelial cells with flavonoid-rich red wine upregulates eNOS mRNA and protein expression, most likely via stabilization of eNOS mRNA [75]. It is known that endothelial cells can produce up to threefold more bioactive NO compared to control cells [75]. Similarly, cocoa flavanols can induce NOS in vitro and can lower vascular arginase activity in human endothelial cells in vitro, thus augmenting the local levels of L-arginine [76,77]. Further studies indicate that epicatechin elevates NO in endothelial cells via inhibition of NADPH oxidase [78], and the pure dietary flavonoids quercetin and epicatechin augment NO products and reduce endothelin-1 acutely in healthy men [79].

A recent study Ref. [32] indicates that low-dose epicatechin, which does not have significant antioxidant activity, may be protective. The mechanism by which low-dose epicatechin induces this effect is unknown. It is possible that low-dose epicatechin mediates cardiac protection via opioid receptor activation. In this experimental study among C57BL/6 mice, there were 10 groups with a control group. Administration of epicatechin (1 mg/kg) or other inhibitors (5 mg/kg) was done by oral gavage or intraperitoneal injection, respectively, daily for 10 days. In the experiment, coronary artery occlusion was induced for 30 minutes followed by 2 hours of reperfusion, and infarct size was determined via planimetry. Compared with control mice, there was a significant decrease in infarct size in epicatechin-treated and epicatechin + nor-BNI-treated mice. Naloxone, naltrindole, and 5-HD were able to block this protection. Epicatechin and epicatechin + nor-BNI increased the phosphorylation of Src, Akt, and IκBα. There was a concurrent decreasing effect on the expression of c-Jun NH_2-terminal kinase, and caspase-activated DNase. These results are consistent with

TABLE 19.3 Effects of cocoa on memory dysfunction, dementia, endothelial function.

Authors	Year	*N*	Animals/ patients	Duration	Intervention	Outcome
Karim et al. [60]	2000	5	Aortic rings from rats	Immediately	Procyanidins derived from cocoa	Endothelium-derived relaxation mediated by activation of NOS
Fisher et al. [61]	2003	27	Healthy people	5 days	Flavanol-rich cocoa (821 mg/day)	Peripheral vasodilation, improvement in vasodilator response to ischemia assessed by pulse-wave amplitude on the finger
Engeler et al. [62]	2004	21	Healthy subjects	2 weeks	High-flavonoid chocolates (213 mg procyanidins, 46 mg epicatechin) versus low-flavonoid chocolate	Improvement in flow-mediated vasodilation of the brachial artery, increase in epicatechin concentrations
Schroeter et al. [63]	2006	16	Healthy subjects, isolated rabbit rings		Drink with high flavonoid content	Improvement in flow-mediated vasodilation paralleled the appearance of flavanols in plasma; enough to mediate ex vivo vasodilation; pure epicatechins mimic vascular effects of cocoa; high-flavanol diet causes high urinary excretion of NO metabolites
Heiss et al. [64]	2003	26	Patients with at least one cardiovascular risk factor	2 hours (crossover)	Flavanol-rich cocoa drink (100 mL)	Improvement in flow-mediated vasodilation, increase in levels of nitrosated and nitrosylated species
Hermann et al. [65]	2006	20	Healthy smokers	2 hours	40 g commercially available dark chocolate versus white chocolate	Increase in flow-mediated vasodilation of the brachial artery, improvement in antioxidant status and platelet function
Grassi et al. [66]	2005	20	Patients with untreated essential hypertension	15 days (crossover)	100 g dark chocolate (21.91 mg catechin, 65.97 mg epicatechins) versus flavanol-free white chocolate	Increase in flow-mediated vasodilation of the brachial artery, decrease in blood pressure and LDL cholesterol, increase in insulin sensitivity
Heiss et al. [67]	2005	11	Smokers	2 hours (crossover)	100 ml cocoa drink with high (176−18 mg) or low (<11 mg) flavanol content	Increase in flow-mediated vasodilation and circulating NO pool, increase in flavanol metabolites
Balzer et al. [68]	2008	41	Diabetes	4 weeks	Drink with high flavanol content	Improvement in flow-mediated vasodilation (acute and chronic)
Flammer et al. [45]	2007	22	Heart transplant recipients	2 hours	40 g commercially available dark chocolate versus flavonoid-free placebo chocolate	Induction of coronary vasodilation, improvement in coronary endothelial function and platelet function
Grassi et al. [84]	2008	19	Hypertensives, impaired glucose tolerance patients	2 weeks	Flavanol-rich dark chocolate	Improvement in flow-mediated vasodilation, insulin sensitivity, beta cell function, and blood pressure
Shina et al. [70]	2009	39	Healthy subjects	2 weeks		

(*Continued*)

TABLE 19.3 (Continued)

Authors	Year	*N*	Animals/ patients	Duration	Intervention	Outcome
					45 g commercially available dark chocolate versus white chocolate	Improvement in coronary circulation as measured by coronary velocity flow reserve
Grassi et al. [71]	2012	12	Healthy volunteers	3 days	100 g/day dark chocolate	Improved flow-mediated dilation, wave reflections, and endothelin-1

opioid receptor stimulation and subsequent cardiac protection. The effects were attenuated by naloxone, naltrindole, and 5-HD. It is clear that the action of epicatechin is mediated by the opioid receptors, possibly through the δ-opioid receptor, to produce cardiac protection from ischemia-reperfusion injury. These beneficial effects of cocoa and dark chocolate have also been observed in the epidemiological studies [60−66].

Platelet dysfunction

Platelet dysfunction may predispose individuals to atherothrombotic vascular disease. Apart from providing micronutrients, certain fruits and vegetables and legumes that are rich in polyphenolics and flavonoids may also protect against thrombosis [4,14]. The antiplatelet effects of cocoa have been demonstrated in many studies [67−69]. Within hours of ingestion, cocoa decreases ADP/collagen-activated, platelet-related primary hemostasis. The antiplatelet effects may be explained, at least in part, by a reduction in the ADP-induced expression of the activated conformation of glycoprotein IIb/IIIa surface proteins. In vitro experimentation has indicated that catechin and epicatechin reduce glycoprotein IIb/IIIa expression, thereby exerting antiplatelet effects [79]. In a clinical study among healthy volunteers, 100-g intake of dark chocolate reduced platelet aggregation [70]. This effect was not observed among subjects who ate white chocolate or milk chocolate [70]. Cocoa decreases platelet aggregation as well as platelet adhesion [70,71,80,81]. Dark chocolate intake among young healthy smokers may decrease platelet adhesion as assessed by a shear stress−dependent platelet test [81]. Stearic acid, a saturated fat that is found in Indian clarified butter as well as in chocolate, reduces mean platelet volume, an index of platelet activation, in humans [71,80].

Clinical studies on the effect of cocoa on cardiometabolic diseases

Previous studies reported beneficial effects of cocoa or chocolate on insulin resistance, oxidative stress, and inflammation, which are important risk factors of type 2 diabetes mellitus and hypertension [3−6]. However, it is unclear whether chocolate consumption is associated with risk of diabetes mellitus. In the Physicians Health Study, involving 18,235 participants, aged 66.3 ± 9.2 years who were free of diabetes at baseline, 1123 men (6.2%) developed diabetes mellitus during a follow-up of 9.2 years [3]. For self-reported chocolate consumption of none, 1−3 servings/month, 1 serving/week, and 2 or more servings/week, multivariable-adjusted hazard ratios (HRs) [95% confidence intervals (CIs)] of diabetes adjusted for lifestyle, clinical, and dietary risk factors, including total energy intake, were 1.00 (referent), 0.93, 0.86, and 0.83, respectively (P-trend = .047). In secondary analyses the inverse association of chocolate consumption and risk of diabetes was slightly stronger in subjects without a history of CVDs or heart failure (P-trend = .023) [3]. The results support an inverse relationship between chocolate intake and incident diabetes, which appears to apply only in younger and normal-body-weight men after controlling for comprehensive lifestyle factors, including total energy intake. The effect of cocoa intake on blood pressure is not consistent. A metaanalysis published in 2017, included studies with 2- to 18-week interventions involving 1804 subjects, who were administered 30−1218 mg of flavanols (mean: 670 mg) in 1.4−105 g/day cocoa products in the intervention group [4]. The results revealed a small but statistically significant decrease in blood pressure (systolic and diastolic) of 1.8 mmHg. This small reduction in blood pressure might complement other treatment options and might contribute to a decline in the risk of

CVDs. It seems that large and longer-term trials are needed to establish whether regularly eating flavanol-rich cocoa products has a blood pressure−lowering effect and an effect on cardiovascular complications during follow-up [4].

Many epidemiological studies that have examined the role of chocolate intake in the prevention of CVDs and diabetes show inconsistent findings. In an earlier metaanalysis published in 2011 [21], in which the association between chocolate consumption and the risk of outcomes related to cardiometabolic disorders were reported, the primary outcomes were CAD, stroke, type 2 diabetes, and metabolic syndrome [21]. (Fig. 19.5). This metaanalysis assessed the risk of developing these disorders by comparing the highest and lowest levels of chocolate consumption. Only seven studies met the inclusion criteria, comprising 114,009 participants. None of the studies was a randomized trial, six were cohort studies, and one was a cross-sectional study. Large variations were observed among these seven studies for measurement of chocolate consumption, methods, and outcomes evaluated. Five of the seven studies reported a beneficial association between higher levels of chocolate consumption and the risk of cardiometabolic disorders. The highest levels of chocolate consumption were associated with a 37% reduction in cardiovascular disease [relative risk (RR): 0.63 (95% CI: 0.44−0.90)] and a 29% reduction in stroke compared with the lowest levels (see Fig. 19.1). It is possible that chocolate consumption may be associated with a substantial reduction in the risk of cardiometabolic disorders.

A metaanalysis of prospective studies examined the association between chocolate intake and risk of CAD, stroke, and diabetes [5]. In this large metaanalysis, including 14 prospective studies among 508,705 subjects, the follow-up period ranged from 5 to 16 years. The RRs for the highest versus lowest chocolate consumption were 0.90 (95% CI: 0.82−0.97; $N = 6$) for CAD, 0.84 (95% CI: 0.78−0.90; $N = 7$) for stroke, and 0.82 (95% CI: 0.70−0.96; $N = 5$) for diabetes. A dose-response metaanalysis suggested a nonlinear association of chocolate consumption with all outcomes [5]. Interestingly, in case of both CAD and stroke, there was little additional risk reduction in consuming chocolate 3 or more servings of chocolate per week (one serving was defined as 30 g of chocolate). For diabetes, the peak protective effect of chocolate emerged at 2 servings/week (RR: 0.75, 95% CI: 0.63−0.89), with no benefit observed when consumption increased above 6 servings/week. It clear that chocolate intake is associated with decreased risks of CAD, stroke, and diabetes, but consuming chocolate in moderation (≤6 servings/week) may be optimal for preventing these disorders [5].

Evidence for the association between chocolate intake and risk of chronic diseases is not very strong. Therefore there is an unmet need to evaluate the credibility of evidence on the dose-response association between chocolate consumption and risks of all-cause mortality, CAD, stroke, heart failure, type 2 diabetes, colorectal cancer, and hypertension [6]. This metaanalysis identified 27 studies, including 2 for all-cause mortality, 9 for CAD, 8 for stroke, 6 for heart failure, 6 for diabetes, and 2 each for hypertension and colorectal cancer. In the linear dose-response metaanalyses, no associations were observed with heart failure (RR: 0.99, 95% CI: 0.94−1.04) or diabetes (RR: 0.94, 95% CI: 0.88−1.01) per each 10-g/day increase in the intake of chocolate [6]. However, minor inverse associations for the risk of CAD (RR: 0.96, 95% CI: 0.93−0.99) and stroke (RR: 0.90, 95% CI: 0.82−0.98) were observed for each 10-g/day increase in chocolate intake. The quality of evidence was considered either very low (all-cause mortality, heart failure,

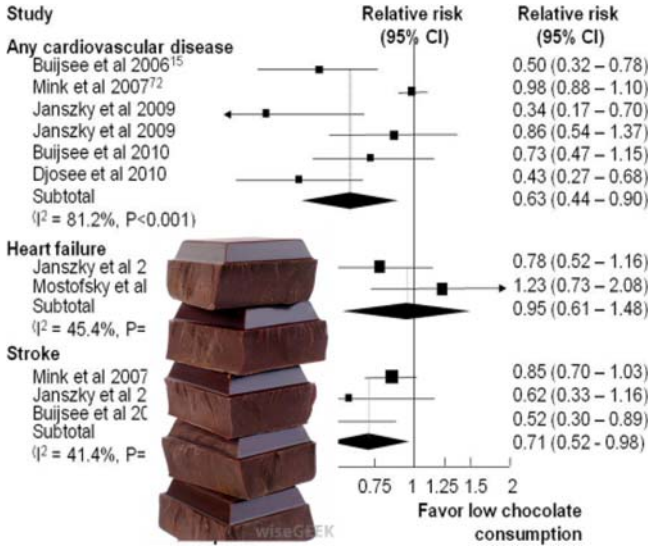


FIGURE 19.5 Relative risks for cardiovascular disease, heart failure, and stroke in adults with higher levels of chocolate consumption compared with lower levels. *Modified from Buitrago-Lopez A, Sanderson J, Johnson L, Warnakula S, Wood A, Di Angelantonio E, et al. Chocolate consumption and cardiometabolic disorders: systematic review and meta-analysis. BMJ 2011;343:d4488. doi: 10.1136/bmj.d4488.2012 [21].*

type 2 diabetes, colorectal cancer, or hypertension) or low (CAD, stroke). It is possible that intake of chocolate is not related to risk for several chronic diseases but may have a minor inverse association with CAD and stroke [6].

In a previous study, the association between chocolate consumption, severity of coronary lesions, risk factors, and severity of the first infarction were examined in 350 patients with myocardial infarction [2]. The results revealed a lower prevalence of hypertension (43.2%% versus 62.3%, $P = .003$), diabetes mellitus (13.5% versus 25.7%, $P = .027$), and smoking (24.3% versus 37.7%, $P = .032$) among the patients who consumed chocolate. There was a negative correlation between amount of chocolate consumed and SYNTAX score ($r = -0.296$, $P = .019$) among the patients. There was no association between amount of chocolate consumed and postinfarction ventricular function and TIMI frame count [2]. There was association between chocolate consumption and lower prevalence of hypertension, diabetes, and smoking.

A Swedish prospective study involving 67,640 women and men from the Cohort of Swedish Men and the Swedish Mammography Cohort examined the association between chocolate consumption and risk of CAD [7]. After 12 years of follow-up (1998−2010), 4417 myocardial infarction cases were ascertained in the Swedish study. Chocolate consumption was inversely associated with risk of myocardial infarction. Compared with nonconsumers, the multivariable relative risk for those who consumed 3−4 or more servings/week of chocolate was 0.87 (P for trend = .04) compared with those subjects who did not eat chocolate. The metaanalysis included six studies with a total of 6851 cases of CAD. The overall relative risk for the highest versus lowest category of chocolate consumption was 0.90 (95% CI: 0.82−0.97), with little heterogeneity among studies ($I^2 = 24.3\%$). It is possible that chocolate consumption may be associated with lower risk of myocardial infarction and CAD [7]. The prospective Women's Health Initiative cohort involving 83,310 postmenopausal women free of baseline preexisting major chronic disease was assessed for association chocolate intake and risk of CVDs [8]. After exclusions there were 3246 CAD and 2624 stroke events or deaths, representing incidence rates of 3.9% and 3.2% during 1,098,091 and 1,101,022 person-years (13.4 years), respectively. No associations between consumption of chocolate and risk of CAD (P for linear trend = .94) or risk of stroke ($P = .24$) were observed. However, the results for CAD and stroke combined were similar ($P = .30$) but were significantly modified by age (P for interaction = .02) [8]. Epidemiological studies have shown inconsistent findings on the association between chocolate consumption and risk of heart failure [9]. A metaanalysis of prospective studies was conducted to determine the role of chocolate intake in the prevention of heart failure. This metaanalysis included five prospective studies including 106,109 subjects. Compared to no consumption of chocolate, the pooled HRs (95% CIs) of heart failure were 0.86 (0.82−0.91) for low-to-moderate consumption of chocolate [9].

Epidemiological studies, in particular observations of native Kuna Indians living on Central American islands, suggest that cocoa-rich products reduce cardiovascular mortality [14,60−62]. The Kunas consume enormous amounts of cocoa daily, which may be rich in salt, similar to rural populations in India with enormously physically demanding occupations. Clinical studies revealed that the Kunas indeed have lower blood pressure values and no age-dependent decline in kidney function [61,62]. Randomized controlled trials and cohort studies further confirm that polyphenolic antioxidant flavonoid consumption can be beneficial in CMDs and degenerative diseases of the brain. It is believed that the high content of polyphenolic antioxidants in some fruits, vegetables, whole grains, nuts, dark chocolate, and tea may contribute to their cardioprotective effects. In a recent study [14], death records of 2222 decedents (1385 men and 837 women), aged 25−64 years, were examined. Causes of death, clinical data, and food intakes were assessed by using data from verbal autopsy questionnaires. Compared to deaths due to NCD, the scores for intake of prudent foods (fruits, vegetables, whole grains, nuts, chocolate) were significantly higher and the ratio of omega-6/omega-3 fatty acids of the diet significantly lower for deaths due to accidents. After adjustment for age, regression analysis revealed that Western-type foods (1.02; 0.95−1.09 men; 1.00; 0.94−1.06 women), meat and eggs (1.00−0.94−1.06 men; 0.98; 0.93−1.04 women), refined carbohydrates (0.98; 0.91−1.05 men, 0.95; 0.89−1.02 women), and high omega-6/omega-3 ratio of fatty acids were positively associated, whereas total prudent foods (OR, CI: 1.11; 1.06−1.18 men; 1.09; 1.04−1.16 women) as well as fruits, vegetables, legumes, and nuts (1.07; 1.02−1.12 men; 1.05; 1.99−1.11 women) were independently inversely associated with deaths due to NCDs. The findings indicated that polyphenolic flavanoids and omega-3 fatty acids may be protective against deaths due to NCDs. In a cross-sectional analysis, the Zutphen Elderly Study [24] reported that cocoa consumption was inversely related to blood pressure. In a prospective analysis the study showed that intake of cocoa was associated with a reduction in cardiovascular and all-cause mortality [24]. Among 470 elderly men free of chronic diseases, this report highlighted the protective effects of cocoa intake. After adjustment for age, body mass index, lifestyle factors, drug use, food, and caloric intake, the risk of cardiovascular mortality for men in the highest tertile of cocoa intake was reduced by 50% compared with the lowest tertile ($P = .004$). The adjusted relative risk for all-cause mortality was 0.53 (95% CI: 0.39−0.72; $P = .001$). In the native population, mortality resulting from cardiovascular events is significantly lower compared with other Pan-American citizens (9.2−3.1 vs 83.4−0.7 age-

adjusted deaths per 100,000) [73]. It is possible that the factors involved are environmental rather than genetic because this protection is lost on migration to urban Panama City, where other cocoa products with a lower flavanol content are used [61]. In the Iowa Women's Health Study [64], 34,489 postmenopausal women who were free of CVDs were examined. After 16 years of follow-up, foods rich in flavonoids were associated with a decreased risk of death caused by CAD. After multivariate adjustment, there was a significant inverse association between chocolate consumption and CVD mortality.

Cocoa is highly rich in flavonoids (catechin, epicatechin, and procyanidins), which predominate in antioxidant activity [65]. The tricyclic structure of the flavonoids determines antioxidant effects that scavenge reactive oxygen species (ROS), chelate $Fe2^{+}$ and Cu^{+}, inhibit enzymes, and upregulate antioxidant defenses. The epicatechin content of cocoa upregulates NO production; this is primarily responsible for its favorable impact on the vascular endothelium. Other beneficial effects are mediated through the antiinflammatory effects of cocoa polyphenols and modulated through the activity of NF-κB.

Cocoa can stimulate changes in redox-sensitive signaling pathways involved in gene expression and the immune response. It may also protect neurons from injury and inflammation and protect the skin from oxidative damage from UV radiation in topical preparations. Cocoa consumption has beneficial effects on satiety, cognitive function, and mood, and regular intake has been found to improve cognitive function in elderly subjects with mild memory dysfunction, which is mostly due to microvascular dysfunction [10,33].

Obesity

Commercially available chocolates have a high fat content, which may enhance dietary energy intake, leading to obesity and dyslipidemia [30,31]. An excess intake of energy via such chocolate (about 500 kcal/100 g) may predispose individuals to weight gain, which is a risk factor for hypertension, stroke, dyslipidemia, CAD, and diabetes. However, a study in 49 healthy women showed no weight gain after daily consumption of 41 g of chocolate, 60 g of almonds, or almonds and chocolate together for 6 weeks [30]. It is possible that weight gain may occur only with higher amounts of daily chocolate intake with very high fat content. In this study, the primary objective was to identify potentially synergistic or additive effects of combining consumption of dark chocolate with almonds as part of a low-fat diet on serum lipids and proinflammatory biomarkers of obesity and atherosclerosis. The biomarkers were intercellular adhesion molecule (ICAM), vascular adhesion molecule, and high-sensitivity C-reactive protein. The duration of the study was 6 weeks among 49 women with normal serum cholesterol, and a four-armed parallel design was used. Women were randomized to one of three treatments: chocolate (41 g/day), almonds (60 g/day), chocolate and almonds, or control (no chocolate or almonds). All women improved dietary intakes in accordance with guidelines, and no subjects gained or lost weight. Serum cholesterol concentrations showed no changes after 6 weeks; however, triacylglycerol levels were reduced by approximately 21%, 13%, 19%, and 11% ($P < .05$), in the chocolate, almond, chocolate and almond, and control groups, respectively. Circulating ICAM levels decreased significantly by 10% in the treatment group that consumed chocolate only ($P = .027$). Vascular adhesion molecule and high-sensitivity C-reactive protein levels showed no abnormality in any treatment group. It seems that the consumption of chocolate and almonds as part of the Therapeutic Lifestyle Changes diet for 6 weeks showed no harmful effects in healthy women; all dietary modifications improved serum triacylglycerol levels, and consumption of chocolate reduced the levels of circulating ICAM.

Insulin resistance, diabetes mellitus, and vascular disease

The antioxidant activity of cocoa may directly influence insulin resistance by protecting the beta cells of the pancreas against free radicals, resulting in increased insulin release. A decrease in insulin resistance in turn reduces the risk for type 2 diabetes mellitus. However, because cocoa is predominantly consumed as energy-dense chocolate, potential detrimental effects of overconsumption exist, including increased risk of weight gain. Overall, research to date suggests that the benefits of moderate dark chocolate consumption or cocoa intake are likely to outweigh the risks of increased energy intake and sugar-induced hyperglycemia, oxidative stress, hypertriglyceridemia, and free fatty acids. It seems that chocolate's potential benefits should be explored in outcome studies looking at these biomarkers and NCDs, including diabetes mellitus, dementia, heart attack, stroke, cancer, and death [11–18].

The overall prognosis among patients with diabetes mellitus is unfavorable, owing to deteriorated cardiovascular function, despite optimal control of hyperglycemia by optimal drug therapy [59]. Epidemiological data indicate that diets rich in flavanols are associated with a reduced cardiovascular risk. This study examined the feasibility and efficacy of a dietary intervention based on daily intake of flavanol-containing cocoa for improving vascular function of patients with type 2 diabetes patients on optimal drug therapy [59]. The study included 10 diabetic patients, in whom vascular function was

assessed by FMD of the brachial artery, plasma levels of flavanol metabolites, and tolerability after an acute, single-dose ingestion of cocoa containing increasing concentrations of flavanols (75, 371, and 963 mg). In a subsequent efficacy study, changes in vascular function in 41 medicated diabetic patients were assessed after a 30-day, thrice-daily dietary intervention with either flavanol-rich cocoa (321 mg flavanols per dose) or a nutrient-matched control (25 mg flavanols per dose). Both studies were undertaken in a randomized, double-blind fashion. Primary and secondary outcome measures included changes in FMD and plasma flavanol metabolites, respectively. A single ingestion of flavanol-containing cocoa was dose-dependently associated with significant acute increases in circulating flavanols and FMD (at 2 hours: from 3.7%−0.2% to 5.5%−0.4%, $P = .001$). A 30-day, thrice-daily consumption of flavanol-containing cocoa increased baseline FMD by 30% ($P = .0001$), while acute increases of FMD upon ingestion of flavanol-containing cocoa continued to be manifest throughout the study. Treatment was well tolerated without evidence of tachyphylaxia. Endothelium-independent responses, blood pressure, heart rate, and glycemic control were unaffected.

In hypertensive patients with impaired glucose tolerance (IGT), the effects of flavanol-rich dark chocolate on endothelial function, insulin sensitivity, beta cell function, and blood pressure (BP) were examined [56,57]. After a run-in phase, 19 patients with hypertension with IGT (11 males, 8 females; 44.8 ± 8.0 years) were randomized to receive isocalorically either dark or flavanol-free white chocolate at 100 g/day for 15 days. After a washout period, patients were switched to the other treatment. Clinical and 24-hour ambulatory BP was determined by sphygmomanometry and oscillometry, respectively. FMD, oral glucose tolerance test, serum cholesterol and C-reactive protein, and plasma homocysteine were evaluated after each treatment phase. Dark chocolate intake but not white chocolate intake reduced insulin resistance (homeostasis model assessment of insulin resistance; $P = .0001$) and increased insulin sensitivity (quantitative insulin sensitivity check index, insulin sensitivity index (ISI), ISI(0); $P < .05$) and beta cell function (corrected insulin response CIR(120); $P = .035$). Systolic (S) and diastolic (D) BP decreased ($P = .0001$) after dark chocolate (SBP, −3.82 ± 2.40 mmHg; DBP, −3.92 ± 1.98 mmHg; 24-hour SBP, −4.52 ± 3.94 mmHg; 24-hour DBP, −4.17 ± 3.29 mmHg) but not after white chocolate. Dark chocolate also increased FMD ($P = .0001$) and decreased total cholesterol (−6.5%; $P < .0001$) and low-density lipoprotein (LDL) cholesterol (−7.5%; $P < .0001$). Changes in insulin sensitivity (Delta ISI; Delta FMD: $r = 0.510$, $P = .001$; Delta QUICK1; Delta FMD: $r = 0.502$, $P = .001$) and beta cell function (D CIR(120); Delta FMD: $r = 0.400$, $P = .012$) were directly correlated with increases in FMD and inversely correlated with decreases in BP (Delta ISI; Delta 24-hour SBP: $r = -0.368$, $P = .022$; Delta ISI; Delta 24-hour DBP: $r = -0.384$, $P = .017$). Thus dark chocolate ameliorated insulin sensitivity and beta cell function, decreased blood pressures, and increased FMD in IGT hypertensive patients. These findings indicate that flavanol-rich, low-energy cocoa food products may have a positive impact on CVD risk factors. Another study aimed to test the hypothesis that consumption of cocoa may simultaneously lower blood pressure, improve endothelial dysfunction, and ameliorate insulin resistance in subjects with essential hypertension [58]. This randomized, placebo-controlled, double-blind, crossover trial examined the effects of a flavanol-rich cocoa drink (150 mL twice a day, 900 mg flavanols/day) in 20 individuals with essential hypertension. Antihypertensive medications were discontinued before study enrollment. After a 7-day cocoa-free run-in period, treatment with cocoa or a flavanol-poor placebo (28 mg flavanols/day) for 2 weeks was followed by a 1-week washout and then crossover to the other treatment arm. Blood pressure was measured thrice weekly. At baseline and after each treatment period, the authors [58] assessed insulin sensitivity (hyperinsulinemic-isoglycemic glucose clamp) and insulin-stimulated changes in brachial artery diameter and forearm skeletal muscle capillary recruitment (Doppler ultrasound with or without microbubble contrast). Cocoa treatment for 2 weeks increased insulin-stimulated changes in brachial artery diameter when compared with placebo (median percentage increase from baseline (25th−75th percentile): 8.3 (4.2−11.3) compared with 5.9 (−0.3 to 9.6); $P = .04$). Nevertheless, cocoa treatment did not significantly reduce blood pressure or improve insulin resistance and had no significant effects on skeletal muscle capillary recruitment, circulating plasma concentrations of adipocytokines, or endothelial adhesion molecules. Daily consumption of flavanol-rich cocoa for 2 weeks was not sufficient to reduce blood pressure or improve insulin resistance in human subjects with essential hypertension. It is clear that there is a controversy about the role of cocoa flavanol in the treatment of hypertension and insulin resistance. Therefore a metaanalysis of studies is conducted to determine the cumulative results of epidemiological studies and controlled trials.

A more recent metaanalysis, published in 2012, included 42 acute or short-term chronic (≤18 weeks) randomized, controlled trials that comprised 1297 participants [16]. Insulin resistance (HOMA-IR: −0.67; 95% CI: −0.98, −0.36) was improved by chocolate or cocoa due to significant reductions in serum insulin. FMD improved after chronic (1.34%; 95% CI: 1.00%−1.68%) and acute (3.19%; 95% CI: 2.04%−4.33%) intakes. Effects on HOMA-IR and FMD remained stable to sensitivity analyses. The investigators observed reductions in diastolic blood pressure (−1.60 mmHg; 95% CI: −2.77, −0.43 mmHg) and mean arterial pressure (−1.64 mmHg; 95% CI: −3.27, −0.01 mmHg) and marginally significant effects on LDL (−0.07 mmol/L; 95% CI: −0.13, 0.00 mmol/L) and high-density lipoprotein (HDL) (0.03 mmol/L; 95% CI: 0.00, 0.06 mmol/L) cholesterol. Chocolate or cocoa improved FMD regardless of the dose consumed, whereas doses of

epicatechin greater than 50 mg/day resulted in greater effects on systolic and diastolic BP. GRADE (Grading of Recommendations, Assessment, Development and Evaluation, a tool to assess quality of evidence and strength of recommendations) suggested low- to moderate-quality evidence of beneficial effects with no suggestion of negative effects [16]. The strength of evidence was lowered, owing to unclear reporting for allocation concealment, dropouts, missing data on outcomes, and heterogeneity in biomarker results in some studies. There was a consistent acute and chronic benefit of chocolate or cocoa on FMD and previously unreported promising effects on insulin and HOMA-IR.

The effects of cocoa or chocolate on the augmentation index (AI), a measure of vascular stiffness and vascular tone in the peripheral arterioles, are not well known [66]. In a randomized, placebo-controlled, 4-week, crossover study among 30 middle-aged, overweight subjects, the effects of cocoa were examined. During the active treatment (cocoa) period, the participants consumed 37 g/day of dark chocolate and a sugar-free cocoa beverage (total cocoa = 22 g/day, total flavanols = 814 mg/day). The cocoa treatment significantly increased the basal diameter and peak diameter of the brachial artery by 6% (+2 mm) and basal blood flow volume by 22%. In women, substantial reduction in the augmentation index, a measure of arterial stiffness, was observed. The consumption of cocoa had no effect on fasting blood measures, while the control treatment increased fasting insulin concentration and insulin resistance ($P = .01$). The high-flavanol cocoa and dark chocolate treatment was associated with enhanced vasodilation in both conduit and resistance arteries and was accompanied by significant reductions in arterial stiffness.

Hypertension

High blood pressure is an important risk factor for cardiovascular disease, contributing to about 50% of cardiovascular events worldwide and 37% of cardiovascular-related deaths in Western populations [4]. Epidemiological studies suggest that cocoa-rich products reduce the risk of CVDs. Flavanols found in cocoa have been shown to increase the formation of endothelial NO, which promotes vasodilation and therefore blood pressure reduction. Here, we update previous metaanalyses on the effect of cocoa on blood pressure.

The Cochran metaanalysis of randomized controlled trials investigated the effects of chocolate or cocoa products on systolic and diastolic blood pressure in adults by including studies in which the intervention was of a minimum of 2 weeks' duration [4]. Thirty-five trials provided participants with 30−1218 mg of flavanols (mean: 670 mg) in 1.4−105 g of cocoa products per day in the active intervention group. The control group received either a flavanol-free product ($N = 26$ treatment comparisons) or a low-flavanol-containing cocoa powder (range: 6.4−88 mg) flavanols (mean: 55 mg, 13 treatment comparisons; 259 mg, 1 trial). Metaanalyses of the 40 treatment comparisons involving 1804 mainly healthy participants revealed a small but statistically significant blood pressure−reducing effect of flavanol-rich cocoa products compared with control in trials of 2−18 weeks' duration. The mean difference in systolic blood pressure (SBP) was −1.76 mmHg (95% CI: −3.09 to −0.43 mmHg, $P = .009$, $N = 40$ treatment comparisons, 1804 participants). The mean difference in diastolic blood pressure (DBP) was −1.76 mmHg (95% CI: −2.57 to −0.94 mmHg, $P < .001$, $N = 39$ treatment comparisons, 1772 participants).

The systolic blood pressure was reduced significantly by 4 mmHg in hypertensive people ($N = 9$ treatment comparisons, $N = 401$) and tended to be lowered in prehypertensive people ($N = 8$ treatment comparisons, 340 participants), there was no significant difference in normotensive people ($N = 23$ treatment comparisons, $N = 1063$); however, the test for subgroup differences was of borderline significance ($P = .08$; $I^2 = 60\%$), requiring further research to confirm the findings. Sensitivity analysis excluding trials with authors employed by trial-sponsoring industry (33 trials, 1482 participants) revealed a small reduction in effect size, indicating some reporting bias. Cocoa products appear to be highly tolerable, with adverse effects including gastrointestinal complaints and nausea being reported by 1% of participants in the active cocoa intervention group and 0.4% of participants in the control groups (moderate-quality evidence).

This review provides moderate-quality evidence that flavanol-rich chocolate and cocoa products cause a small (2 mmHg) blood pressure-lowering effect in mainly healthy adults in the short term [4]. However, baseline blood pressure may play a role in the effect of cocoa on blood pressure; subgroup analysis of trials with prehypertensive participants revealed a greater blood pressure−reducing effect of cocoa compared to normotensive participants with borderline significance. Long-term trials investigating the effect of cocoa on clinical outcomes are also needed to assess whether cocoa has an effect on cardiovascular events and to assess potential adverse effects associated with chronic ingestion of cocoa products. It is possible that cocoa exerts a beneficial impact on cardiovascular health through the reduction of BP, improvement of vascular function, modulation of lipid and glucose metabolism, and reduction of platelet aggregation [80]. These potentially beneficial effects have been shown in healthy subjects as well as in patients with hypertension, diabetes, and smoking or established CVDs, such as coronary heart disease or heart failure.

As was mentioned earlier, one study [57] reported a decline in daytime and nighttime blood pressures, recorded by ambulatory 24-hour measurements, after intake of 100 g of flavonoid-rich dark chocolate daily for 2 weeks. This study found a decline in systolic blood pressure by 12 mmHg after consumption of dark chocolate, whereas white chocolate had no such effect. Another study found decreases in systolic and diastolic blood pressures in hypertensive elderly subjects [25]. Earlier metaanalyses revealed that foods rich in cocoa may reduce blood pressure. Recently, several additional trials have been conducted with conflicting results. Therefore a random effects metaanalysis of all studies was necessary, fitting the inclusion criteria, as well as a subgroup analysis by baseline blood pressure among patients with hypertension and normotension [26]. In this metaanalysis, current evidence on the effect of flavanol-rich cocoa products on blood pressure in hypertensive and normotensive individuals was reported [26]. Only randomized controlled trials investigating the effect of cocoa as food or drink compared with placebo on systolic and diastolic blood pressure for a minimum duration of 2 weeks were included in this study. Only nine clinical trials used chocolate with 50%−70% cocoa that were compared with cocoa-free chocolate or other control foods, while six trials compared high-flavanol cocoa products with low-flavanol cocoa products. The daily dosages of flavanol ranged from 30 to 1000 mg in the active treatment groups and with a follow-up for 2−18 weeks. There was a significant decline in blood pressure due to cocoa-chocolate compared with control (mean BP change ± SE: SBP: -3.2 ± 1.9 mmHg, $P = .001$; DBP: -2.0 ± 1.3 mmHg, $P = .003$) as revealed in the pooled analysis. The subgroup metaanalysis reported significant results only for the hypertensive or prehypertensive subgroups (SBP: -5.0 ± 3.0 mmHg; $P = .0009$; DBP: -2.7 ± 2.2 mmHg, $P = .01$). The decline in BP among subjects with normal blood pressures was not significant. It is clear that cocoa-rich chocolate can reduce blood pressures compared to placebo in subjects with hypertension. Also in 2010, another meta-analysis of randomized controlled trials examined the blood pressure−lowering effects of flavanol-rich cocoa products [27]. The primary outcome measure was the change in systolic and diastolic BP between intervention and control groups. In total, 10 randomized controlled trials comprising 297 individuals were included in the analysis. The populations that were studied were either healthy normotensive adults or patients with prehypertension or stage 1 hypertension. There are potential mechanisms that may be responsible for the positive effect of cocoa; among these are activation of NO synthase, increased bioavailability of NO as well as antioxidant, and antiinflammatory properties.

Reduction in blood lipids

All chocolates contain saturated fat and are a major source of dietary calories. Cocoa butter is derived from cocoa plants and is found predominantly in dark chocolate, which contains an average of 33% monounsaturated oleic acid and 33% stearic acid. In general, plant stearic acid neither lowers HDL nor increases LDL or total cholesterol but can increase platelet volume and function. As was mentioned in the studies discussed earlier [30,31], it is important to determine whether consumption of dark chocolate adversely affects the blood lipid profile. Tokede et al. [15] reported that cocoa products, which are rich sources of flavonoids, can reduce blood lipid levels and the risk of CVDs. The primary effect measure was the difference in means of the final measurements between the intervention and control groups. In the clinical studies that were included in this analysis, there were 320 subjects and the duration of treatment was 2−12 weeks. Treatment with dark chocolate or cocoa products was associated with a significant reduction in serum LDL and total cholesterol levels. The means (95% CI) were −5.90 mg/dL (−10.47, −1.32 mg/dL) and −6.23 mg/dL (−11.60, −0.85 mg/dL), respectively. HDL (difference in means (95% CI): −0.76 mg/dL (−3.02 to 1.51 mg/dL)) and triglyceride (TG) (−5.06 mg/dL (−13.45 to 3.32 mg/dL)) did not show significant effects. The findings suggest that cocoa and its products may have beneficial effects on total and LDL cholesterol levels and no major effects on HDL and TG levels in short-term intervention trials. However, one earlier study found that dark chocolate consumption increases HDL cholesterol concentration, and chocolate fatty acids may inhibit lipid peroxidation in healthy humans [18].

Dysfunction of the endothelium

Endothelial function and dysfunction as well as smooth muscle function are important in the pathogenesis of vascular diseases, including hypertension, stroke, and atherothrombosis. There is evidence that endothelial function is impaired during hyperglycemia which may be due to increase in ROS, free fatty acids and decreased NO release [16,22,56−59]. The effects of pretreatment with dark chocolate on endothelial function and other vascular responses to hyperglycemia need further studies (Table 19.3). It is known that cocoa-rich chocolate increases FMD in healthy and hypertensive subjects with and without glucose intolerance. Grassi et al. [82] sought to test the effect of flavanol-rich dark chocolate (FRDC) on endothelial function, insulin sensitivity, beta cell function, and blood pressure in hypertensive patients with IGT. After a run-in phase, 19 hypertensives with IGT (11 males, 8 females; 44.8 ± 8.0 years) were randomized to receive isocalorically either

FRDC or flavanol-free white chocolate (FFWC) at 100 g/day for 15 days. After a washout period, patients were switched to the other treatment. FRDC ingestion but not FFWC ingestion decreased insulin resistance (homeostasis model assessment of insulin resistance; $P < .0001$) and increased insulin sensitivity (quantitative insulin sensitivity check index, insulin sensitivity index (ISI), ISI (0); $P < .05$), and beta cell function (corrected insulin response CIR(120); $P = .035$). Systolic and diastolic BP decreased ($P < .0001$) after FRDC (SBP: -3.82 ± 2.40 mmHg; DBP: -3.92 ± 1.98 mmHg; 24-hour SB: -4.52 ± 3.94 mmHg; 24-hour DBP: -4.17 ± 3.29 mmHg) but not after FFWC. Further, FRDC increased FMD ($P < .0001$) and decreased total cholesterol (-6.5%; $P < .0001$) and LDL cholesterol (-7.5%; $P < .0001$). Changes in insulin sensitivity (Delta ISI; Delta FMD: $r = 0.510$, $P = .001$; Delta QUICKI; Delta FMD: $r = 0.502$, $P = .001$) and beta cell function (Delta CIR(120); Delta FMD: $r = 0.400$, $P = .012$) were directly correlated with increases in FMD and inversely correlated with decreases in BP (Delta ISI; Delta 24-hour SBP: $r = -0.368$, $P = .022$; Delta ISI; Delta 24-hour DBP: $r = -0.384$, $P = .017$). Thus FRDC ameliorated insulin sensitivity and beta cell function, decreased BP, and increased FMD in IGT hypertensive patients. These findings suggest that flavanol-rich, low-energy cocoa food products may have a positive impact on endothelial function and other CVD risk factors. Shiina et al. [83] assessed the effects of the oral intake of flavonoid-rich dark chocolate on coronary circulation by measuring coronary flow velocity reserve (CFVR) by noninvasive transthoracic Doppler echocardiography in healthy adult subjects in a randomized, single-blind design. After a follow-up for 2 weeks in 39 healthy men (mean age: 29.7 ± 3.9 years, range: 23–40 years), subjects were randomly assigned a daily intake of either 45 g of flavonoid-rich dark chocolate (including 550 mg/day cacao polyphenol, 200 kcal) or 35 g of nonflavonoid white chocolate (including 0 mg/day cacao polyphenol, 140 kcal) as a control. After a follow-up of 2 weeks, flavonoid-rich dark chocolate consumption significantly improved CFVR (3.38 ± 0.49 before intake, 4.28 ± 0.85 after intake; $P < .01$), whereas nonflavonoid white chocolate consumption did not (3.28 ± 0.49 before intake, 3.16 ± 0.49 after intake; $P = .44$). All predictor variables were used as dependent variables in a multiple regression model of the incremental change in CFVR after 2 weeks of chocolate intake. Intake of dark (but not white) chocolate, MDA-LDL, TG, and heart rate significantly influenced the change of CFVR after 2 weeks of intake ($P < 0.01$) according to the multiple regression formula $Y = 1.01X(1) - 0.005X(2) - 0.003X(3) - 0.017X4$ (Y = change in CFVR after 2 weeks of chocolate intake, X1 = intake of dark (but not white) chocolate, X2 = MDA-LDL, X3 = TG, X4 = heart rate).

A more recent study examined the effects of flavanol-rich chocolate intake on blood pressures and FMD and wave reflections as well as on endothelin-1 and oxidative stress, before and after an oral glucose tolerance test (OGTT) [22]. There were only 12 (5 males, aged 28.2–2.7 years) volunteers, who were randomized to take either 100 g/day of dark chocolate or white chocolate free of flavanols for 3 days. The volunteers were switched to the other treatment after a washout period of 7 days. After each treatment phase and OGTT, the FMD, stiffness index, reflection index, peak-to-peak time, blood pressure, endothelin-1 and 8-iso-PGF2 were evaluated. The consumption of dark chocolate caused significant improvement in FMD ($P = .03$), wave reflections, endothelin-1, and 8-iso-PGF2 ($P = .05$) as compared to white chocolate ingestion. The ingestion of white chocolate also showed a decline in FMD after OGTT from 7.88–0.68 to 6.07–0.76 ($P = .027$) and 6.74–0.51 ($P = .046$) at 1 and 2 hours, respectively, after the glucose load. Similarly, blood pressures, wave reflections, and endothelin-1 and 8-iso-PGF2- increased after OGTT on ingestion of white chocolate but not after dark chocolate. OGTT induces an acute, transient impairment of endothelial function and oxidative stress, whereas flavanol-rich dark chocolate suppresses it. The findings indicate that flavanols found in cocoa may improve vascular health by reducing the blood glucose–induced decrease in arterial function that is associated with the mechanism of atherothrombosis and cerebral blood flow response among healthy elderly humans [22]. Hooper et al. [16] reviewed the effects of chocolate, cocoa, and flavan-3-ols on major CVD risk factors by studying the databases for randomized controlled trials of chocolate, cocoa, or flavan-3-ols. The metaanalysis included 42 acute or short-term chronic ($\leq$18 weeks) trials that comprised 1297 participants. Insulin resistance (HOMA-IR: -0.67; 95% CI: -0.98, -0.36) was improved by chocolate or cocoa as a result of significant reductions in serum insulin. FMD improved after chronic (1.34%; 95% CI: 1.00%, 1.68%) and acute (3.19%; 95% CI: 2.04%, 4.33%) intakes. Effects on HOMA-IR and FMD remained stable to sensitivity analyses. Reductions in diastolic blood pressure (BP: -1.60 mmHg; 95% CI: -2.77, -0.43 mmHg) and mean arterial pressure (-1.64 mmHg; 95% CI: -3.27, -0.01 mmHg) and marginally significant effects on LDL (-0.07 mmol/L; 95% CI: -0.13, 0.00 mmol/L) and HDL (0.03 mmol/L; 95% CI: 0.00, 0.06 mmol/L) cholesterol were also observed. Chocolate or cocoa improved FMD regardless of the dose consumed, whereas doses of epicatechin greater than 50 mg/day resulted in greater effects on systolic and diastolic BP. GRADE suggested low- to moderate-quality evidence of beneficial effects. The findings showed consistent acute and chronic benefits of chocolate or cocoa on FMD and previously unreported promising effects on insulin and HOMA-IR. However, larger, longer-duration, and independently funded trials are required to confirm the potential cardiovascular benefits of cocoa flavan-3-ols. Table 19.3 shows the studies indicating the role of cocoa in endothelial function, memory dysfunction, dementia, and other chronic diseases [51–59,63,81–89].

Stroke

Epidemiological studies on the role of chocolate in preventing stroke remain inconsistent [9]. Recent studies indicate that cerebral ischemia is a common, morbid condition accompanied by cognitive decline leading to stroke [33–37,90]. Studies on the vascular health benefits of flavanol-containing foods signify a promising approach to the treatment of cerebral ischemia by improving endothelial function [32,33]. A metaanalysis of prospective studies was conducted to determine the association between chocolate intake and risk of CAD, stroke, and diabetes [9].

This metaanalysis included 14 prospective studies of primary prevention with 508,705 participants, with follow-up durations ranging from 5 to 16 years. Relative risks (RRs) for the highest versus lowest chocolate consumption were 0.90 (95% CI: 0.82–0.97; $N = 6$) for CHD, 0.84 (95% CI: 0.78–0.90; $N = 7$) for stroke, and 0.82 (95% CI: 0.70–0.96; $N = 5$) for diabetes. A dose-response metaanalysis suggested a nonlinear association of chocolate consumption with all outcomes [9]. There was little additional risk reduction when consuming 3 or more servings of chocolate per week for CAD and stroke (1 serving was defined as 30 g of chocolate). The peak protective effect of chocolate emerged at 2 servings/week (RR: 0.75, 95% CI: 0.63–0.89) in diabetes, with no benefit observed when increasing consumption above 6 servings/week. In conclusion, chocolate intake was associated with decreased risks of CHD, stroke, and diabetes. Consuming chocolate in moderation (≤6 servings/week) may be optimal for preventing these disorders. In another study, mean blood flow velocity (MFV) was measured by transcranial Doppler ultrasound in the middle cerebral artery (MCA) among 34 healthy elderly volunteers, aged 72–76 years, after cocoa consumption or flavanol-poor cocoa ingestion [33]. After follow-up of 2 weeks on cocoa intake, MFV increased by 8% and 4% at 1 week ($P = .01$) and 10% and 4% ($P = .04$) at 2 weeks. Cocoa administration for 1 week showed increases in MFV($P = .05$) in a greater number of subjects in the high-cocoa group as compared with the low-cocoa group. It is possible that regular ingestion of high cocoa can cause a significant increase in cerebral blood flow velocity in the MCA. The findings indicate an important role for regular ingestion of cocoa flavanols for prevention of stroke and transient ischemic attacks, which may also protect against future occurrence of dementia and cognitive dysfunction [32–37].

The effects of chocolate consumption on risk of stroke were examined by Larsson and coworkers in men by conducting a cohort study [27]. They prospectively followed a cohort of 37,103 Swedish men; a food frequency questionnaire (FFQ) was used to assess baseline chocolate consumption. During a follow-up of 10.2 years, the authors reported 1995 incident cases of stroke, including 1511 cerebral infarctions, 321 hemorrhagic strokes, and 163 unspecified strokes. A lower risk of stroke was reported in association with greater intake of chocolate. The association did not differ by stroke subtypes. In a metaanalysis of five studies, with a total of 4260 stroke cases, the overall relative risk of stroke for the highest versus lowest category of chocolate consumption was 0.81 (95% CI: 0.73–0.90) without heterogeneity among studies ($P = .47$). The multivariable RR of stroke comparing the highest quartile of chocolate consumption (median 62.9 g/week) with the lowest quartile (median 0 g/week) was 0.83 (95% CI: 0.70–0.99). It seems that ingestion of cocoa chocolate in moderation can reduce the risk of stroke. However, more studies are required that include decreasing fat and sugar content of chocolates for improvement of therapeutic efficacy as well as long-term safety [27–30].

Memory dysfunction and dementia

Dietary flavonoids, which are abundant in plant-based foods, can improve cognitive function, particularly including a reduction in the risk of dementia, enhanced performance on some cognitive tests, and improved cognitive function in elderly patients [23,84–86]. Improved cognitive performance with the administration of a cocoa polyphenolic extract has also even been reported in aged Wistar-Unilever rats [33]. There is evidence that dietary flavanols might improve cognitive function in subjects with mild cognitive impairment. The memory functions are under the influence of microcirculation of the neurons as well as NO release which may be impaired as a result of hyperglycemia, oxidative stress, atherosclerosis and inflammation. Since regular consumption of cocoa flavanols might be effective in improving cognitive function in subjects with mild cognitive impairment, it is possible that flavonol can protect the neurons from dementia and neurodegeneration. This effect appears to be mediated in part by an improvement in insulin sensitivity and NO release [23] A cross-sectional study in Norway of 2031 elderly subjects, aged 70–74 years (55% women), examined the relationship between intake of three common foodstuffs that contain flavonoids (chocolate, wine, and tea) and cognition [84]. Cognitive performance was examined via a cognitive test battery including the Kendrick Object Learning Test, the Trail Making Test, Part A (TMT-A), modified versions of the Digit Symbol Test, Block Design, the Mini Mental State Examination, and the Controlled Oral Word Association Test. Poor cognitive performance was defined as a score in the highest decile for the TMT-A and in the lowest decile for all the other tests. A self-reported FFQ was used to assess habitual food intake. Subjects who consumed chocolate,

wine, or tea had significantly better mean test scores and lower prevalence of poor cognitive performance than those who were not consuming flavonoid-rich foods. The subjects who consumed all three studied items had the best test scores and the lowest risks for poor test performance. The associations between intake of these foodstuffs and cognition were dose dependent. The effect was approximately linear for tea with the maximum effect at intakes of approximately 10 g/day for chocolate and approximately 75−100 mL/day for wine. All cognitive functions tested were influenced by intake of these three foodstuffs. The effect was most pronounced for wine and modestly weaker for chocolate intake. It seems that in the elderly subjects, a diet high in some flavonoid-rich foods was associated with better performance in several cognitive abilities in a dose-dependent manner.

Desideri et al. conducted a double-blind, parallel arm study involving 90 elderly individuals with mild cognitive impairment who were randomized to consume a drink containing approximately 990 mg (high flavanols), approximately 520 mg (intermediate flavanols), or approximately 45 mg (low flavanols) of cocoa flavanols once per day for 8 weeks [23]. The Mini Mental State Examination, the Trail Making Test, Parts A and B, and a verbal fluency test were the instruments for the study of cognitive function. After the follow-up period, results of the Mini Mental State Examination was similar in the three treatment groups ($P = .13$). There were significant decreases in insulin resistance, blood pressure, and lipid peroxidation among subjects in the high-flavanol and intermediate-flavanol groups compared to the low-flavanol group. Alteration in insulin resistance explained approximately 40% of composite z-score variability through the study period (partial $r^2 = 0.4013$; $P < .0001$). The time required to complete and Trail Making Test, Parts A and B, was significantly ($P < .05$) lower in subjects assigned to high flavanols (38.10 ± 10.94 and 104.10 ± 28.73 seconds, respectively) and intermediate flavanols (40.20 ± 11.35 and 115.97 ± 28.35 seconds, respectively) in comparison with those assigned to low flavanols (52.60 ± 17.97 and 139.23 ± 43.02 seconds, respectively). Similarly, verbal fluency test scores were significantly ($P < .05$) better in subjects assigned to high flavanols in comparison with those assigned to low flavanols (27.50 ± 6.75 vs 22.30 ± 8.09 words per 60 seconds, respectively).

Of all flavonoids and/or polyphenolics, there is a subclass known as flavanols, which are quite rich in cocoa; they are also in abundance in red wine, green tea, and some fruits These agents have potential antioxidant activity which may slow down or even reverse the decline in memory dysfunction that occur among elderly subjects with aging. However, it is possible that flavonols can improve memory function at any age, including among children. There appear to be only nine published studies in the scientific literature that have examined the effects of cocoa- and chocolate-related products on neurocognitive functioning [86]. Seven of nine studies examined the clinical value of cocoa products on memory dysfunction. The findings revealed that these agents have a positive influence on improvement and/or preserved aspects of cognitive functioning. Cocoa and chocolate consumption could hypothetically improve cognitive function in individuals as well as in communities [84,86]. It has been proposed to study a country's level of chocolate consumption and cognitive function of the populations. It is likely that by studying the total number of Nobel laureates per capita as a surrogate end point reflecting the proportion with superior cognitive function and influence of chocolate consumption may be interesting. It might give some measure of the overall cognitive function of a given country showing association of chocolate consumption and number of Nobel laureates in a country [85]. In 2012, Messerli reported a significant linear correlation ($r = 0.791$, $P < .0001$) between chocolate consumption per capita and the number of Nobel laureates per 10 million persons in 23 countries [85]. Switzerland was the top performer in terms of both the number of Nobel laureates and chocolate consumption. The slope of the regression line allows us to estimate that it would take about 0.4 kg of chocolate per capita per year to increase the number of Nobel laureates in a given country by 1. For the United States, that would amount to 125 million kg/year. The minimally effective chocolate dose seems to hover around 2 kg/year, and the dose−response curve reveals no apparent ceiling on the number of Nobel laureates at the highest chocolate-dose level of 11 kg/year. Calculation with the exclusion of Sweden revealed that the correlation coefficient increased to 0.862, which may be due to general behavior. American Indians and Kuna Indians, who traditionally consume chocolate, have not receive any Nobel Prize so far, indicating, of course, that many confounders may exist apart from memory function. Further evidence suggests that flavonoids and methylxanthines, such as those commonly found in cocoa and chocolate products, may provide neuroprotective, neuroenhancing, neurostimulating, and cardioprotective effects [35−38]. The addition of omega-3 fatty acids to dark chocolates, which is rich in the cell membranes of neurons, can enhance its capability in enhancing memory function and perhaps even in getting the Nobel Prize as well as in the prevention of CMDs and other chronic diseases [14].

Other chronic diseases

Chocolate that is rich in cocoa has been known for its good taste and also for its proposed health effects on all other body systems related to NCDs [10−29,63,87−89]. The health effects of cocoa include improvement in cardiovascular

function and relief of angina pectoris, stimulation of the nervous system, facilitated digestion, and improved kidney and bowel function. In addition, cocoa has been used to treat anemia, mental fatigue, tuberculosis, fever, gout, kidney stones, and even poor sexual appetite. Substantial data suggest that flavonoid-rich foods could help to prevent CVDs, CAD, stroke, hypertension, hyperlipidemia, insulin resistance, diabetes mellitus, and cancer [63,87–89]. Cocoa is one of the richest sources of flavonoids, but current processing reduces the content substantially. The Kuna who live on the San Blas Islands of the Caribbean drink a flavanol-rich cocoa as their main beverage, contributing more than 900 mg/day, and thus probably have the most flavonoid-rich diet than any other population.

In a recent study, diagnoses on death certificates for comparison of cause-specific death rates from the years 2000 to 2004 on the mainland of Panama and the San Blas Islands, where only Kuna live, were studied [63]. It is possible that high flavanoid intake and consequent NO system activation would be considered important if the result indicated a reduction in the frequency of CAD, stroke, diabetes mellitus, and cancer, which are all NO-sensitive processes. The study included 77,375 deaths on mainland Panama and 558 deaths on the San Blas Islands. On mainland Panama, as anticipated, CVD was the leading cause of death (83.4 ± 0.70 age-adjusted deaths/100,000), and cancer was second (68.4 ± 1.6). In contrast, the rates of CVD and cancer among island-dwelling Kuna were much lower (9.2 ± 3.1 vs 4.4 ± 4.4, respectively). Similarly, deaths due to diabetes mellitus were much more common on the mainland than on the islands (24.1 ± 0.74 vs 6.6 ± 1.94). This comparatively lower risk of NCDs among the Kuna on the San Blas Islands from the most common causes of morbidity and mortality in most of the world possibly reflects a very high flavanol intake and sustained NO synthesis activation. However, there are many risk factors, and an observational study cannot provide definitive evidence. Controlled trials among high-risk populations would be necessary to provide causal proof regarding the role of cocoa flavanol in the prevention of NCDs.

Drug development

The activation of NO, antioxidant, antiinflammatory, and antiplatelet effects, of cocoa appear to be important, which in turn might improve endothelial function, lipid levels, blood pressure, insulin resistance, hyperglycemia, and atherothrombosis and eventually clinical outcome in CVDs, diabetes, dementia, and early carcinogenesis [11–16,20–24]. The blood-pressure lowering effect is small (2–3 mmHg) but significant. There is a need to develop concentrated forms of flavanol-rich cocoa that can be used as soft capsules for conducting double-blind randomized, controlled trials to determine the potential beneficial effects of cocoa on CVDs and metabolic syndrome, memory dysfunction, and dementia. Such studies may also clarify both dose-response relationships and drug development as well as addressing the optimal processing method of raw cocoa beans to optimize antihypertensive actions and other actions having beneficial effects on obesity, diabetes, insulin resistance, blood lipids, hypertension and atherothrombosis, brain degeneration, and carcinogenesis. Cocoa itself, unlike chocolate, can be recommended without hesitation because it is low in sugar and fat. Current evidence suggests that the beneficial effects of cocoa are attributed mainly to its flavanol content, especially epicatechin. Therefore direct dietary supplementation with flavanols instead of chocolate consumption deserves further study. Protocols using epicatechin or other flavanoids specifically are now feasible and should clarify this question. Recommending dietary supplementation with flavanols, similar to vitamins, appears problematic because potential prooxidative effects of large quantities cannot be excluded [87].

Functional food development

It is important to assess the adverse effects of daily chocolate intake for a long period to find out whether cocoa can predispose people to obesity, dental caries, and type 2 diabetes. The energy density of cocoa chocolate, which is due to high fat and sugar content, may be decreased by incorporation of fruit juice or water acidified with ascorbic acid without affecting mouth-feel [28]. Cocoa flavanols are potential antioxidants that may also upregulate endogenous antioxidant enzymes and thereby lower ROS levels, apart from increased endothelial NO release [91]. ROS interfere with NO's bioavailability [19], which may indirectly increase NO levels and its actions. Nitrate-rich vegetables, such as beetroot, also reduce blood pressure in hypertensive individuals in a NO-dependent manner, which may be incorporated into the cocoa powder to dilute its bitterness [20]. It may be possible to have beetroot or dietary nitrate (generating NO) with cocoa (increasing NO's bioavailability) and thus move from the adverse effect of fat- and sugar-containing chocolate to NO-containing chocolate. The addition of flax seeds or flax seed oil may also decrease the need for saturated fat in cocoa, which would enhance the omega-3 fatty acid content, which is known to be protective against NCDs [14].

Agricultural policy

Cocoa farming should be encouraged in all the developing and developed countries. Since the protective effects of cocoa are due to the flavanol contents (catechin and epicatechin), these antioxidants need to be enhanced in the cocoa seeds by plant breeding and genetic modification. Efforts should be made to decrease the bitterness of cocoa by genetic manipulation or by other methods so that use of milk, saturated fat, and sugar can be avoided in cocoa-based dishes.

In view of the limited data, future studies should provide detailed information about the chocolate product that is used in each study. The exact content of polyphenols, especially flavanols, and, most important, the flavanol plasma concentrations achieved would be important. It has to be taken into account that cocoa contains many other potentially active substances, such as theobromine or magnesium, which may be responsible for a significant part of the benefits. In brief, the available evidence indicates that increased consumption of dark chocolate or cocoa (300−1000 mg/day) can protect against CVDs and other chronic diseases, including metabolic syndrome and memory dysfunction.

The recent metaanalyses suggest that chocolate consumption provides reduced risks of CAD, stroke, and diabetes. Increased intake of chocolate in moderation (1−6 servings/week) may be protective for the prevention of CMDs. Large prospective studies are required to confirm the observed benefits of chocolate in populations with different characteristics and to establish the optimum frequency of chocolate intake for prevention of CMDs.

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Chapter 20

A survey of biological nitrogen fixation in adzuki beans, soybeans, and mung beans, three legumes in traditional Chinese medicine

Mohamad Hesam Shahrajabian[1,2], Wenli Sun[1,2] and Qi Cheng[1,2]

[1]*Biotechnology Research Institute, Chinese Academy of Agricultural Sciences, Beijing, P.R. China,* [2]*Nitrogen Fixation Laboratory, Qi Institute, Jiaxing, P.R. China*

Introduction

Adzuki beans

Adzuki beans: a unique traditional Chinese food for sustainable agriculture

Among the species of medicinal plants, some are mainly confined to folk medicine, and some are used as occasional or local substitutes for the main species listed in the *Materia Medica* [1−12]. Hu Shiuying [13] listed 60 genera of legumes, with nearly 100 species, in her extensive book *An Enumeration of Chinese Materia Medica*. Grain legumes are known for their nutritional richness, especially protein and amino acids, which are often lacking in human diets, leading to malnutrition [14]. The economic and environmental importance of legume crops is largely due to their ability to fix atmospheric dinitrogen in symbiosis with rhizobia [15−22]. The adzuki bean (*Vigna angularis*) is a small bean that has an inherently sweet, nutty taste. It is one of the 12 most important grain legume crops in the world [23−25]. In Chin, it is called *xiaodou*, *hondou*, and *chidou*. Adzuki bean sprouts are consumed as food and in herb medicine in traditional Chinese medicine (TCM) [26]. Globally, China ranks number one in adzuki bean production and export. The major production regions are located in northeast China, Huabei, and the Huanghe River and Haihe River valleys, including Heilongjiang, Inner Mongolia, Jilin, Liaonin, Hebei, Shaanxi, Shanxi, and Jiangsu provinces. As an herbal medicine, the bean has been used since the Tang Dynasty of China to maintain health and control weight [27]. The chief countries of adzuki bean production are China, Japan, Taiwan, and South Korean. Adzuki beans were most likely developed in China and introduced into Japan around AD 1000 [28]. Adzuki beans cultivars showed different antioxidant activities and cytoprotective effects according to the concentration and composition of phenolic compounds. Gohara et al. [29] found that all adzuki bean cultivars showed polyunsaturated fatty acids prevalence and nutritional indices and ratios considered adequate for biological system maintenance of a healthy organism. The province of origin and frequency of accessions of adzuki bean from each province in China are shown in Table 20.1. A list of elite varieties of adzuki bean in China is shown in Table 20.2. The chemical composition of the whole adzuki bean is presented. The essential amino acid content of adzuki bean is shown in Table 20.3. The flavonoid and saponin contents in adzuki bean extracts are presented in Table 20.4. The health benefits of the adzuki bean are shown in Table 20.5.

Adzuki cultivation in different parts of China

The lowland regions of the southern provinces of China are not major production areas for adzuki beans, having complex terrain and various cropping system, including intercropping, relay intercropping, and multiple cropping.

There are rice + adzuki bean multiple cropping systems and maize + adzuki bean relay intercropping systems.

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TABLE 20.1 Province of origin and frequency of accessions of adzuki bean from each province in China [30].

Province (Region)	Frequency	Percentage	Province No.
Shanxi	64	27.7	8
Hebei	34	14.7	7
Henan	27	11.7	11
Jilin	21	9.0	3
Shandong	17	7.4	9
Heilongjiang	15	6.5	2
Shaanxi	11	4.8	10
Hubei	9	3.9	15
Liaoning	8	3.5	4
Beijing	7	3.0	5
Anhui	6	2.6	12
Neimenggu (North)	4	1.7	1
Sichuan	2	0.9	14
Jiangsu	2	0.9	13
Taiwan (Coast)	1	0.4	18
Tianjin	1	0.4	6
Guizhou	1	0.4	17
Yunnan	1	0.4	16
Total	231	100.0	

TABLE 20.2 A list of elite varieties of adzuki bean in China [31].

Jihongxiaodou 2
Jihongxiaodou 4
Jihnog 9218
Jibaohongxiaodou 2
Bao 876-16
Zhonghong 2
Baochong 947
Baihong 2
Baihong 3
Jihong 6
Jingnong 5
Jingnong 8
Liaoxiaodou 1
Jinlinghongdou
Ehongxiaodou 1

TABLE 20.3 Essential amino acid content of adzuki bean.

Amino acid	Content (g/16 g N)
Isoleucine	4.5
Leucine	7.8
Lysine	7.0
Methionine	1.8
Cystine	1.1
Phenylalanine	5.4
Tyrosine	3.4
Threonine	3.8
Valine	5.4

TABLE 20.4 Flavonoid and saponin contents in adzuki bean extracts [27].

Peak No.	Compound	Contents (mg/g ABTE)	Contents (mg/g ABF)	Contents (mg/g ABS)
2	Catechin	12.37	49.39	ND
7	Quercetin-3-O-rutinoside	225.99	404.73	ND
8	Quercetin-3-glucoside	21.37	90.08	ND
9	Vitexin-4″-O-glucoside	36.66	74.60	ND
10	Azukisaponin IV	6.63	ND	11.40
11	Azukisaponin VI	20.04	ND	206.35
12	Azukisaponin V	165.99	ND	283.21
13	Azukisaponin II	186.99	ND	389.73
14	Azukisaponin I	8.90	ND	5.42
15	Azukisaponin III	79.03	ND	27.58

ABF, Adzuki bean flavonoids; *ABS*, adzuki bean saponins; *ABTE*, adzuki bean total extract; *ND*, not detected.

TABLE 20.5 Health benefits of adzuki beans.

Cholesterol-free
Good source of folate
Easy to cook with
Incredible delicious
Good for weight loss
Decrease the blood glucose level and protect against diabetes
Easy to digest
Good source of magnesium, potassium, phosphorus, manganese, and iron
Fantastic source of protein
Good source of fiber

The areas in Inner Mongolia and the north part of Hebei, Shanxi, and Shaanxi have the following main cropping patterns (one crop per year):

1. Adzuki bean, maize (sorghum), −millet
2. Adzuki bean, maize, sorghum
3. Adzuki bean, spring wheat, maize (flax), maize
4. Adzuki bean, wheat, wheat
5. Adzuki bean, millet, maize, wheat

The areas in Shandong, Henen, and the southern part of Hebei have the following main cropping patterns (two crops per year):

1. Winter wheat (barley), adzuki bean, winter wheat (barley), adzuki
2. Winter wheat (barley), adzuki bean, cotton (maize, sorghum, or millet)
3. Winter wheat (barley), summer maize intercropping with adzuki bean, spring maize intercropped with soybean
4. Spring wheat, millet (broomcorn millet), adzuki bean
5. Winter wheat (barley), maize intercropped with adzuki bean, winter wheat (barley), maize intercropped with adzuki

Adzuki beans and nitrogen fixation

Kimura et al. [32] reported that the adzuki bean has a remarkable peak of N accumulation in the early reproductive stage. This is mainly due to N_2 fixation, although the soil nitrate level is high. They concluded that adzuki beans absorb N mainly for a short period and depended more on symbiotically fixed N_2 and, in contrast to common beans, leave a high level of NO_3-N remaining in the soil. Delic et al. [33] reported that strains of *Bradyrhizobium japonicum* showed a high potential for N_2 fixation, particularly strains 525 and 542. *B. japonicum* strains resulted in 65%−71% shoot dry weight and 99%−138% total N content uninoculated control with full N content (100%). No significant difference was found between the plants inoculated with *Bradyrhizobium* spp. strains and uninoculated control plants without N (40%−42% and 42% shoot dry weight, respectively), which indicated symbiotic N_2 fixation inactivity of the *Bradyrhizobium* spp. strains. The Knj strain had the middle position (56% shoot dry weight). These data showed that *B. japonicum* strains 525 and 542 could be used in further investigations in order to apply them as inoculants in microbiological N fertilizers. Da Silva et al. [34] indicated that inoculation with *Rhizobium* strains and a supply of molybdenum effectively contributed to biological nitrogen fixation and improved grain production. Abd-Alla [35] noticed that isoflavonoid analysis from root extracts of grafted plants showed that NOD1−3 shoots had markedly higher root isoflavonoid concentrations in the roots of both NOD1−3 and common bean cv. adzuki compared with self-grafts of common bean adzuki. Exogenous application of daidzein, genistein, coumestrol, and glycitein alone and in combination at concentration of 10 μmol to the nutrient solution significantly increased the nodule numbers of common bean cv. adzuki. Kimura et al. [32] concluded that adzuki beans absorb N mainly for a short period and depend more on symbiotically fixed N_2 and, in contrast to the common bean, left a high level of NO_3-N in the soil after being harvested. Various sources of nitrogen fixation are shown in Table 20.6. Average shoot dry weight, total

TABLE 20.6 Various sources of nitrogen fixation [36].

No.	Source of nitrogen fixation	Nitrogen fixed (10^6 tons per year)
1	Land	153
2	Legume	39
3	Nonlegume	10
4	Others	104
5	Sea	40
6	Total biological	193
7	Lightning	9
8	Industry	85
9	Total nonbiological	94

TABLE 20.7 Average shoot dry weight, total N content, and fixed N content of nodulated adzuki beans (*Vigna angularis*) to potential nitrogen fixation activity of *Bradyrhizobium* strains.

	Shoot dry weight			Shoot total nitrogen content			
Treatment inoculated and uninoculated[a]	(mg/plant)	Symbiotic effectiveness (%)	% N	(mg/plant)	Symbiotic effectiveness (%)	Shoot fixed N content (mg/plant[1])	Active groups of strains[b]
525	320b	71	1.77	5.73ab	122	4.90ab	
532	310bc	69	1.68	5.37bc	114	4.54bc	
542	300bc	67	2.16	6.52a	138	5.71a	I
526	290bc	65	1.27	4.64bc	99	3.81c	
Knj	250cd	56	1.27	3.17d	67	2.34d	II
2001	210de	47	0.67	1.40e	30	0.63e	
2801	190e	42	0.56	1.08e	23	0.32e	III
5388	180e	40	0.71	1.26e	27	0.46e	
N	450a	100	1.04	4.71bc	100	—	Controls
	190e	42	0.45	0.83e	18	—	
LSD 0.05	47.9			0.870		0.867	
U0.01	63.0			1.150		1.147	

[a]*Uninoculated controls; N: with N, : without N.*
[b]*I:* B. japonicum, *II: Knj, III:* B. *spp. a–e: Means in a column followed by the same letter are not significantly different by Duncan's multiple range test at the 5% level (P ≤ .05).*

TABLE 20.8 Nodulation and nitrogenase activity of adzuki inoculated with *Rhizobium legumiosarum* biovar *phaseoli* strain RCR 3622 and TAL 1383 [35].

Plant species	Bacterial strain	Number of nodules per plant	C_2H_4 (μmol/plant/hectare)
Adzuki	RCR 3622	19	0.92
	TAL 1384	15	0.71

Means followed by the same letter in each column were not significantly different at the 5% level using the least significant difference test.

N content, and fixed of nodulated adzuki bean are shown in Table 20.7. The average nodule number, nodule dry weight, shoot and root length, root dry weight, and total root N content of nodulated adzuki beans are presented. The nodulation and nitrogenase activity of adzuki is shown in Table 20.8.

Soybeans

Soybeans in traditional Chinese medicine

Nutrition therapy on the basis of TCM is quite effective at treating common diseases. China is the home of the soybean. It was domesticated in the eastern half of north China around the 11th century BCE. In TCM, soybeans are known for their ability to tonify *qi* and blood. They also help to clear heat and eliminate toxins from the body [37–43]. In TCM, soybeans have long been known as an herb that is capable of healing many diseases including edema, the common cold, skin sores, diarrhea, habitual constipation, iron-deficiency anemia, leg ulcers, complications of pregnancy (e.g.,

TABLE 20.9 Some key nutrients currently under investigation in soybeans.

Nutrient	
Flavonoids and isoflavonoids	1. Daidzein
	2. Genistein
	3. Malonylgenistin
	4. Malonyldaidzin
Phenolic acids	1. Caffeic acid
	2. Coumaric acid
	3. Ferulic acid
	4. Gallic acid
	5. Sinapic acid
Phytoalexins	1. Glyceollin I
	2. Glyceollin II
	3. Glyceollin III
Phytosterols	1. Beta-sitosterol
	2. Beta-stigmasterol
	3. Campestrol
Proteins and peptides	1. Defensins
	2. Glycinin
	3. Conglycinin
	4. Lunacin
Saponins	1. Soyasaponins (groups A and B)
	2. Soyasapogenols

vomiting), atrophy of the liver, and renal failure. Chinese farmers feed soybeans to cow to promote lactation, and humans may benefit from frying soybeans and then steaming them with turnips and fresh ginger to promote lactation [44]. In TCM, fermented soybeans are plants that belong to the "Cool/Acrid Herbs That Release the Exterior" category. Herbs that release the exterior aim to treat the early stages of diseases that affect the upper respiratory tract, eyes, ears, nose, throat, or skin. TCM believes that external diseases such as colds or allergies can invade the body only if the external environment overwhelms our *wei qi* (the TCM version of the immune system). To counteract this invasion, cool/acrid herbs aim to induce sweating by dilating the capillary pores so that they release more sweat. The belief is that this will expel the disease from the body and stop it from invading further [45]. A list of some key nutrients that are under investigation in soybeans is shown in Table 20.9. The most important health benefits of soybeans are presented in Table 20.10. The most important health benefits of soybean milk are shown in Table 20.11.

Nitrogen fixation in soybeans

Greater amounts of potassium, nitrogen, and phosphorus were taken up from intercropping soil than from monoculture [46–52]. Gao et al. [53] reported that soil nitrification was the main method of N_2O emission in intercropped field in the experimental zone. Nitrogen is one of the primary limiting nutrients for plant growth in agriculture, and the productivity of many agricultural ecosystems is controlled by nitrogen availability. The value of fixed nitrogen depends on its capacity to generate farm profits, the economic value of the fixation agent (typically a legume) and its place in the farming system, the proportion of fixed and applied nitrogen in the system, and the bioeconomic interactions between the two forms of nitrogen. Soil type and climate also affect the value of nitrogen, as do fertilizer and crop and animal prices as well as their seasonal variability [54] (Figs. 20.1 and 20.2).

TABLE 20.10 The most important health benefits of soybeans.

1. Improve metabolic activity
2. Promote healthy weight gain
3. Anticancer potential
4. Boost heart health
5. Relieve menopausal symptoms
6. Boost digestion
7. Improve bone health
8. Prevent birth defects
9. Improve circulation
10. Control diabetes
11. Relieve sleep disorders

TABLE 20.11 The most important health benefits of soybean milk.

1. Helps to lower serum cholesterol levels
2. Beneficial in providing relief from osteoporosis
3. Helps to prevent liver damage caused by oxidative stress
4. Provides relief from many postmenopausal health issues
5. Aids in maintaining optimal blood pressure in diabetic patients
6. Helps in maintaining optimal estrogen levels in menopausal women
7. Good remedy for managing weight and improving cardiovascular health

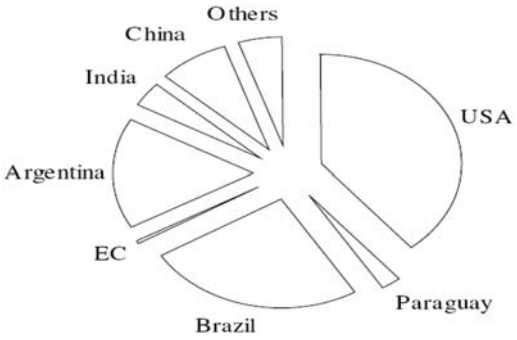


FIGURE 20.1 Contribution of different countries to world soybean production (estimated as 183.28 teragrams) in 2002/2003 [55].

The soybean nodule is classified as a determinate type nodule, which has a spherical form. The cell divisions and nodule development are completed at the initial stage of nodule growth, when the nodule is as small as about 1 mm in diameter, and the nodule growth thereafter is mainly due to cell expansion. The soybean nodule has the symbiotic region (infected region) in the center, which consists of the mosaic of large infected cells and small uninfected cells. The nitrogenase, an enzyme to fix N_2 in bacteroids, is very susceptible to free O_2 and irreversibly destroyed by O_2. Therefore the free O_2 concentration should be kept at very low levels in a symbiotic region of nodules. On the other

hand, nitrogen fixation and its assimilation processes require a large amount of energy and reductant produced through O_2 respiration. Therefore nodule respiration is about four times higher than that of roots based on dry weight. To support active respiration, an abundant supply of O_2 is essential (Figs. 20.3–20.7).

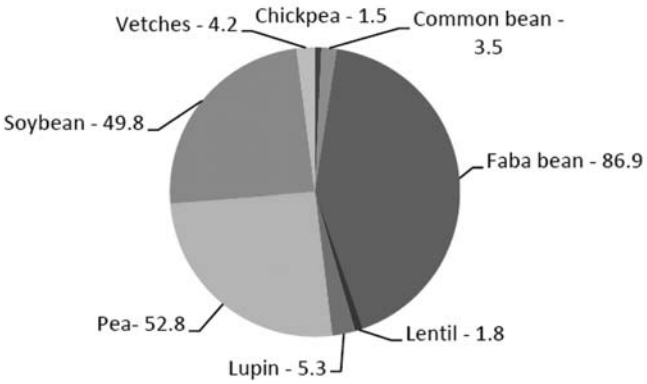


FIGURE 20.2 Total N fixed (10^3 tons) by grain legume crops in Europe (EU27 countries in 2009) [56].

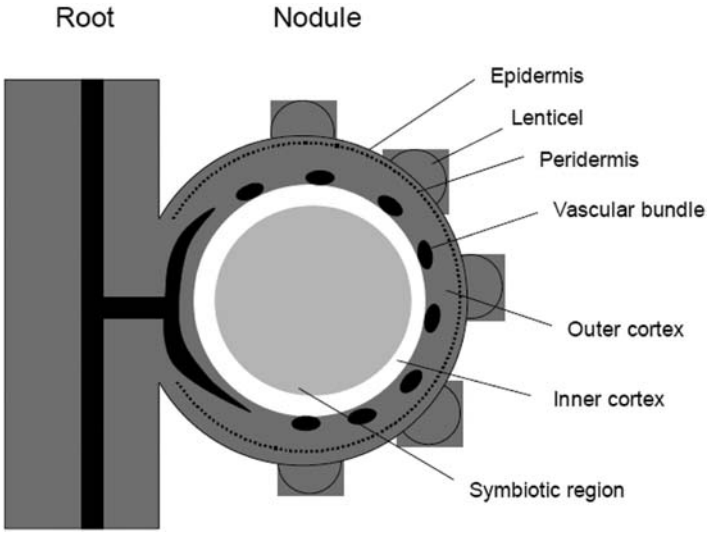


FIGURE 20.3 Structure of a soybean root nodule.

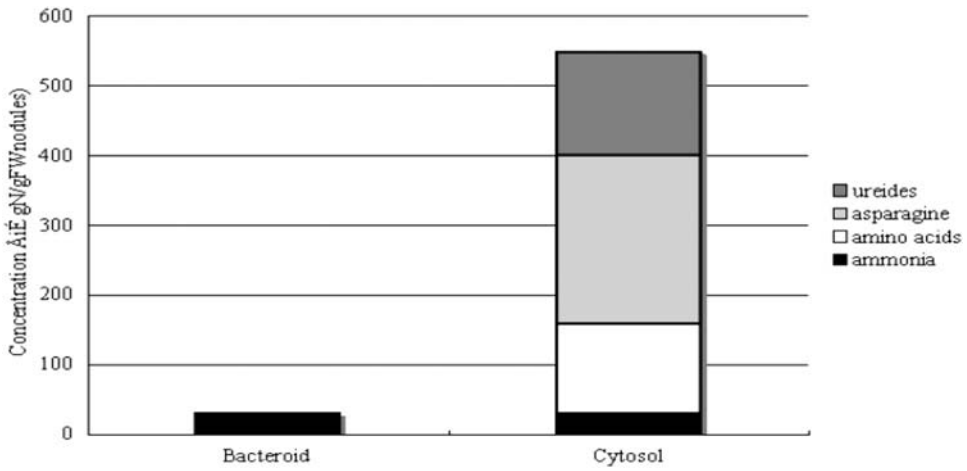


FIGURE 20.4 Major nitrogen constituents in bacteroids and cytosol fractions of soybean nodules.

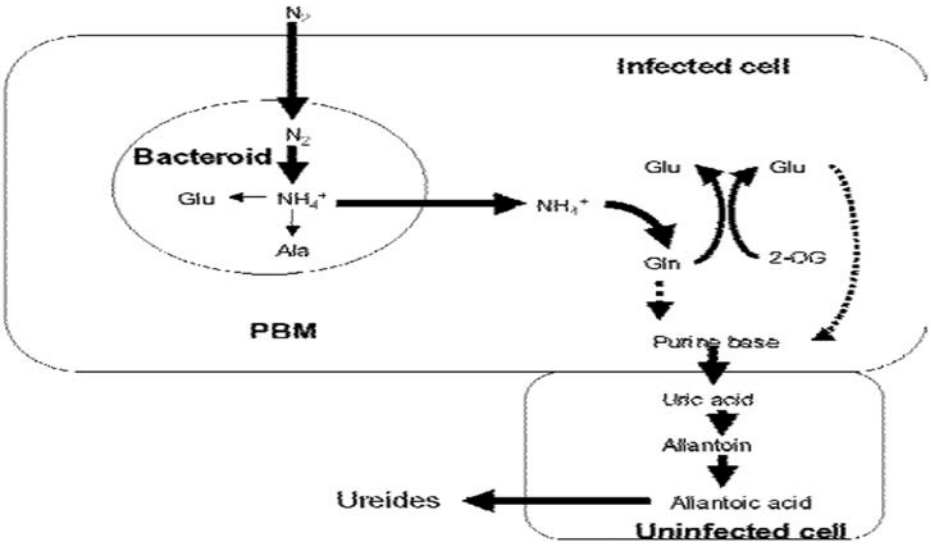


FIGURE 20.5 A model of nitrogen metabolism and transport in a soybean nodule.

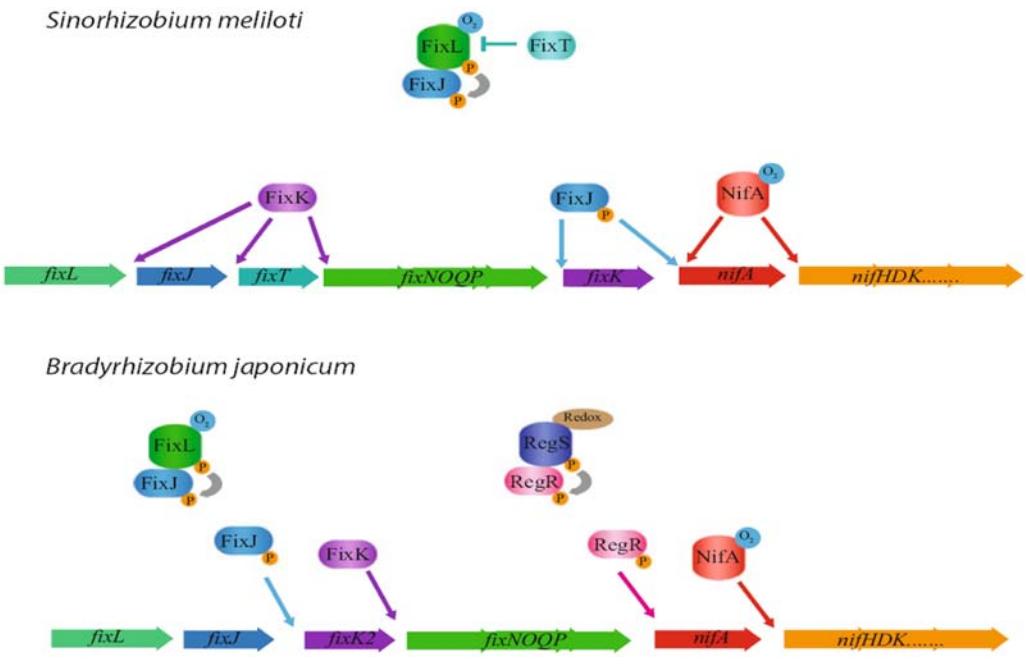


FIGURE 20.6 The mechanism of symbiotic nitrogen fixation.

Ohyama et al. [58] indicated that the major part of fixed ammonia in bacteroid (a symbiotic state of rhizobia) is rapidly excreted into the cytosol of infected cells in nodules; then the ammonia is assimilated into amino acids via the glutamine synthetase/glutamate synthase pathway. The fixed nitrogen is then assimilated into ureides, allantoin, and allantoate through de novo purine synthesis and degradation, followed by transport of the ureides to the shoots via xylem vessels. The combined nitrogen, especially nitrate, rapidly and reversibly inhibits the nodule growth and nitrogen fixation activity, possible owing to changes in the photoassimilate supply to the nodules. In soybeans, atmospheric nitrogen (N_2) fixation happens in the nodules, which grow in the roots that are produced by N2-fixing rhizobial bacteria. Most of these bacteria belong to the genera *Bradyrhizobium*, *Mesorhizobium*, *Rhizobium*, and *Sinorhizobium*. Santachiara et al. [59] found that the atmospheric N concentration curve might indicate an upper benchmark for evaluating symbiosis performance during crop development. Second, the concentration pattern that is observed for biological nitrogen fixation could potentially help to reverse the decline in seed

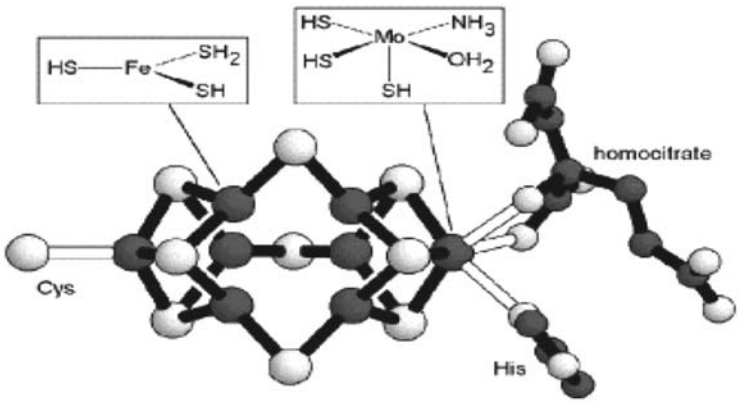


FIGURE 20.7 Structure of nitrogenase enzyme [57].

protein concentration in modern soybean cultivars. Furthermore, the N concentration and dilution curves for the individual nitrogen sources could be incorporated into crop models for estimating nitrogen biological fixation at different crop biomass levels during soybean development. Schipanski et al. [60] mentioned that soil N availability is often considered to be a central factor affecting biological nitrogen fixation. They have found that soil N uptake by N_2-fixing soybeans relative to the nonnodulating isoline increased as soil N decreased, suggesting that N_2 fixation increased soil N scavenging in low-fertility fields.

Mung beans

Mung beans in traditional Chinese medicine

In the Chinese tradition a meal is not just an accumulation of calories but an opportunity to supply our organs with a balance of yin and yang. TCM, which is an essential part of the healthcare system in most Asian countries, relies on natural products and has been playing a very important and significant role in health protection and disease control for thousands of years. The Mung beans (*Vigna radiata*) are widely consumed as a nutritional food in the forms of cooked whole beans, flour, or sprouts [61]. In China the mung bean has also been used as a medicinal herb for dissipating fever and detoxifying the body since the 1050s [62]. Interestingly, in line with the ancient description, recent studies have shown that mung bean extract and/or components such as vitexin and isovitexin can alleviate pathogenic heat and oxidative stresses [63,64]. Drinking a bowl of cold, sweet mung bean soup everyday is a Chinese habit in summer, and it is a delicious dessert and a cold (yin energy) treat to cool down the body system in the heat. According to TCM, the tiny green mung beans (*lu dou*) eaten as soup or congee can expel toxins. Furthermore, since mung beans are cold (yin), they help to dispel internal heat, clear away toxins, promote urination, and relieve hot weather ailments and rashes. From an energy perspective, mung beans are a surefire way to support the entire body while relieving itchy skin rashes and detoxifying and strengthening the stomach and liver. Most illnesses are related, on an energetic level, to poor liver function, so it is especially important to give this organ a boost. Even though spring is the season of the liver, mung beans can be used throughout the year, with the added side effect of beautiful, glowing skin. Zhu et al. [65] suggested that mung bean proteins and their hydrolysates hold great promise as sources of compounds with significant nutritional, functional, and bioactive potential uses in foods, pharmaceuticals, and other products and processes. The species and common names of the two important species of *Vigna radiata* are shown in Table 20.12. The macronutrient composition of mung beans is presented in Table 20.13. The most important pharmacological effects of mung beans are shown in Table 20.14. Selected mung bean recipes for herbal remedies are presented in Table 20.15. Biological activities and compounds of mung beans are shown in Table 20.16. Amino acids in mung bean protein isolates with levels comparing the ones adapted from the U.N. Food and Agriculture Organization (FAO) and the World Health Organization (WHO) are presented in Table 20.17.

Mung beans and nitrogen fixation

Greater amounts of potassium, nitrogen, and phosphorus are taken up from intercropping soil than from monoculture [67]. Soil nitrification was the main way of N_2O emission in intercropped field in the experimental zone. Nitrogen is one of the primary limiting nutrients for plant growth in agriculture, and the productivity of many agricultural ecosystems is controlled by nitrogen availability. As a consequence of the persistent energy crises, which have resulted in

TABLE 20.12 Species and common names of the two important species of *Vigna radiata*.

Species	Synonyms	Common names
Vigna radiata var. *aureus*	*Vigna radiata* (L.) Wilczek	Mung bean, green gram, golden gram
	Phaseolus radiatus (L.)	Oregon pea, moong, Jerusalem pea
	Phaseolus aureus Roxb.	Newman pea
Vigna radiata var. *mungo*	*Vigna mungo* (L.) Hepper	Urd bean, black gram
	Phaseolus mungo (L.)	Mash, mungo bean, woolly pyrol, black matpe

TABLE 20.13 Macronutrient composition of mung beans.

Macronutrient	Average[a]	Minimum	Maximum
Moisture (g/100 g)	9.80	4.10	15.20
Crude protein (g/100 g) dm	23.8	14.6	32.6
Crude lipid (g/100 g) dm	1.22	0.71	1.85
Crude fiber (g/100 g) dm	4.57	3.8	6.15
Ash (g/100 g) dm	3.51	0.17	5.87
Carbohydrate (g/100 g) dm	61.0	53.3	67.1
Energy (kcal/100 g) dm	344	338	347

[a]*Mean value of all collected data.*

TABLE 20.14 The most important pharmacological effects of mung beans.

1. Protein and phospholipids can excite the nerves and increase appetite, which is necessary to increase the nutrition of many important organs.
2. Polysaccharide can enhance the activity of the serum lipoprotein lipase (LPL) and in turn promote the triglyceride hydrolysis in lipoprotein to give it a lipid-lowering effect, which thus can prevent coronary heart disease and angina pectoris.
3. Antimicrobial ingredients such as tannin can accelerate local hemostasis and promote wound healing.
4. It is a good raw source for extracting superoxide dismutase, which has very good antiaging effects.
5. It has inhibiting effects on staphylococci and certain viruses; that is, it can clear heat and detoxify, which is useful on treating acne caused by inflammation or endogenous heat.
6. One type of globulin and polysaccharide can promote an animal's cholesterol to break down into cholic acid in the liver, accelerate the secretion of bile salt in bile, and reduce the intestinal absorption of cholesterol.
7. According to clinical trials, its active ingredients have antiallergic effects, which can be useful in treating hives and other diseases.
8. It is rich in trypsin inhibitors, which can protect the liver, reduce protein breakdown, and thereby protect the kidneys.
9. Experiments found that it has certain preventive effects in morphine + nitrate induced mouse lung and liver cancer.
10. It is so rich in protein that fresh mung bean milk can protect the gastrointestinal mucosa if taken orally. In addition, its proteins, tannins, and flavonoids can combine with organophosphorus pesticides, mercury, arsenic, and lead compounds to form precipitates and thus reduce or totally get rid of their toxicity, since they interfere with gastrointestinal absorption.

TABLE 20.15 Selected mung bean recipes for herbal remedies.

1. San Dou Yin from *Shi Yi De Xiao Fang* (*Effective Formulas from Generations of Physicians*). It is mixed with *chi xiao dou* (adzuki beans), *hei dou* (black soybean), and *gan cao* (licorice root) to prevent smallpox and measles.
2. Lu Dou Yin from *Jing Yue Quan Shu* (*Jingyue's Collected Writings*). It is used alone to cook and make cold drink for the treatment of polydipsia, dark urine, and other ailments due to hot summer weather.
3. Lu Dou Yin from *Zheng Zhi Zhun Sheng* (*The Level-line of Patterns & Treatment*). It is used with *huang lian* (coptis root), *ge gen* (kudzu root), and licorice to detoxify people suffering from food poisoning or poisoning induced by aconite, croton, arsenic, and other toxins.
4. Tuo Li Tang from *Sheng Ji Zong Lu* (*Complete Record of Holy Benevolence*). It is mixed with *ru xiang* (frankincense) to treat carbuncles on the back and vomiting and pain due to a number of pathogens attacking the heart.
5. Lu Dou Yin from *Huo You Xin Shu* (*The Heart Book of Pediatrics*). It is formulated with coptis, kudzu, and licorice to cure irritability, nausea, vomiting, or thirst due to eating a medicine of hot nature by mistake.

TABLE 20.16 Biological activities and compounds of mung beans [66].

Biological activities	Biological compounds
Antioxidant effects	Proteins, polypeptides, polysaccharides, polyphenols
Antimicrobial activity	Enzymes, peptides, polyphenols
Antiinflammatory activity	Polyphenols
Antidiabetic effects	Polyphenols
Lipid metabolism accommodation	Phytosterol
Antihypertensive effects	Proteins, amino acids
Antitumor effects	Polyphenols, mung bean trypsin inhibitor fragments
Antisepsis effects	Polyphenols, aqueous extracts from mung bean coat

TABLE 20.17 Amino acids in mung bean protein isolates with levels comparing the ones adapted from the FAO and WHO.

MBPI levels	Amino acids	MBPI (mg/g)	FAO/WHO (mg/g)
Overview	Total amino acids	800.2	
	Total essential amino acids	348.2 (43.51%)[a]	
	Total aromatic amino acids	96.7 (12.08%)[a]	
	Total sulfur amino acids	13.0 (1.63%)[a]	
Higher levels	Phenylalanine + tyrosine	90.3	63
	Leucine	74	66
	Lysine	62.4	58
	Valine	46.3	35
	Isoleucine	39.1	28
	Histidine	27.9	19

(*Continued*)

TABLE 20.17 (Continued)

MBPI levels	Amino acids	MBPI (mg/g)	FAO/WHO (mg/g)
Lower levels	Theronine	28.4	34
	Methionine + cysteine	13	25
	Tryptophan	6.4	11
Not mentioned by the FAO/WHO	Glutamic acid/glutamine	125.4	
	Aspartic acid/asparagines	85.3	
	Arginine	64.4	
	Serine	38.5	
	Alanine	36.6	
	Glycine	32.2	
	Proline	30	

MBPI, Mung bean protein isolates.
[a]*Percent of amino acids relative to total amino acids in MBPI.*

higher fertilizer costs, biological N_2 fixation has become one of the most attractive strategies for the development of sustainable agricultural systems. The factors that determine the symbiotic process are the genetic constitution of the host plant and the bacteria, the environment, and technological inputs such as inocula, fertilizers, and pesticides. Balasubramanian and Sinha [68] concluded that there was a considerable decrease in the nitrogen fixation efficiency of mung beans in a saline environment. Inoculation with *Bradyrhizobium* enhanced the nodulation, shoot biomass, and grain yield of mung bean. The legume residues can supply more mineral nitrogen to the succeeding crops than cereal residues can, owing to the relatively high nitrogen content of legume residues. Anwar et al. [69] concluded that the application of organic poultry manure at the rate of 5 tons per hectare improved growth, yield, and yield components of mung beans. They recommend that farmers use 30 kg per hectare nitrogen with 5 tons per hectare poultry manure. Htwe et al. [70] concluded that *B. japonicum* SAY3−7 plus *B. elkanii* BLY3−8 and *Streptomyces griseoflavus* are effective bacteria that can be used together as biofertilizer for the production of economically important leguminous crops, especially mung beans and soybeans. The N_2 fixation capacity of mung beans and mash beans was enhanced by the application of phosphorus fertilization. A legume-cereal sequence also enhanced the biomass and grain yield of subsequent wheat.

Conclusion

Legumes help to build soil fertility, and their nitrogen fixation has other advantages in the agricultural ecosystem, including improved soil structure, deep rooting, erosion protection, and contributing to greater biological activity and sustainability. Growing of leguminous plants can also benefit both the plants and soils by yielding nitrogen in the compound form. Adzuki beans fix atmospheric nitrogen by working symbiotically with special bacteria, known as rhizobia, that live in the root nodules. Rhizobia infect the root hairs of the leguminous plants and produce the nodules. Adzuki beans are consumed in many Asian countries, such as China, Japan, Korea, Taiwan, Singapore, Indonesia, Malaysia, Thailand, Vietnam, India, and the Philippines. In China and Japan, they are consumed daily as a dessert or snack, especially during traditional Chinese festivals such as Chinese New Year. Adzuki beans are a rich source of carbohydrates, protein, vitamins, minerals, and fiber and also contain antinutritional factors. Adzuki beans have various pharmacological activities related to different extracts or individual compounds. One of the most important role of adzuki beans is balancing yield, which gives a better economic return with environmental and agronomic benefits.

TCM is a system of healing that is thousands of years old. When used in TCM, fermented soybeans are affiliated with the stomach and lung meridians and are used to aid digestion and relieve stuffiness and congestion in the chest. Fermented soybeans are used in the treatment of cancer-related symptoms, including reducing the risk of prostate, stomach, and breast cancer, and for counteracting the effects of chemotherapy and radiation therapy. They are also used as a calming agent and help to treat restlessness, irritability, and vexation. Fermented soybeans are used to help improve sleep. Other conditions

that are treated with fermented soybeans include fevers and menopausal symptoms. Biological nitrogen fixation is mediated by diazotrophic microorganisms that are capable of fixing atmospheric nitrogen using the enzyme nitrogenase. Nitrogenase catalyzes the reduction of N_2 to ammonia (NH_3) in the energetically expensive reaction $N_2 + 8\ H^+ + 8\ e^- + 16\ ATP \rightarrow 2\ NH_3 + H_2 + 16\ ADP + 16\ P_i$. In soybeans, atmospheric nitrogen (N_2) fixation happens in the nodules, nodules grow in the roots that are produced by N_2-fixing rhizobial bacteria, and most of these bacteria belong to the genera *Bradyrhizobium*, *Mesorhizobium*, *Rhizobium*, and *Sinorhizobium*. The natural process of symbiotic nitrogen fixation, whereby plants such as legumes fix atmospheric nitrogen gas to ammonia, which is usable by plants, can have a substantial impact as it is found in nature, has low environmental and economic costs, and is broadly established. Nitrogen is the nutrient that is in most demand by crops and most expensive in the process of industrial production. Next to plant photosynthesis, biological fixation is probably the most important biochemical process for life on the earth. Biological nitrogen fixation occurs mainly through the symbiotic association of legumes and some woody species with certain N_2 fixing microorganisms that convert elemental nitrogen into ammonia. The ability of legumes to fix atmospheric nitrogen, their nodulated roots, and plant residues left after harvesting represent a valuable source of organic N. As a consequence of the persistent energy crises, which result in higher fertilizer costs, biological N_2 fixation has become one of the most attractive strategies for the development of sustainable agricultural systems. Inoculation with *Bradyrhizobium* enhanced nodulation and increased the shoot biomass and grain yield of mung beans. The legume residues can supply more mineral nitrogen to the succeeding crops than cereal residues can, owing to the relatively high nitrogen content of legume residues. Mung beans are rich is easily digestible protein and contain vitamin A, iron, calcium, zinc, and folate. Mung beans are also high in vitamins B1, B2, and C and niacin. Antinutrients are phytic acid, tannins, hemagglutinins, and polyphenols. In TCM, mung beans are cool in nature and sweet in taste. They act on the heart and stomach and have many healing properties. Mung beans can clear heat, promote urination, lower blood pressure and cholesterol, treat pesticide poisoning and lead poisoning, and treat burns, alcoholism, and food poisoning. In Chinese cuisine, whole mung beans are used to make dessert, which is served either warm or chilled. Shelled mung beans and mung bean paste are made into ice cream or frozen ice pops. Mung bean paste is commonly used as a common for mooncakes in China. Also in China the boiled and shelled beans are used as filling in the glutinous rice dumplings that are eaten during the dragon boat festival. The beans may also be cooked until soft, blended into a liquid, sweetened, and served as a beverage, which is popular in many parts of China. The benefits of legumes, especially mung beans, have also been said to include control of cereal diseases and insect pests and improvements in soil structure. The factors that determine the symbiotic process are the genetic constitution of the host plant and the bacteria, the environment, and technological inputs such as inocula, fertilizers, and pesticides.

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Chapter 21

Functional food and organic farming for sustainable development with a vision for sustainable food and farming

Wenli Sun[1,2,3,*], Mohamad Hesam Shahrajabian[1,2,3,*] and Qi Cheng[1,2,3]

[1]*Biotechnology Research Institute, Chinese Academy of Agricultural Sciences, Beijing, P.R. China,* [2]*College of Life Sciences, Hebei Agricultural University, Baoding, P.R. China,* [3]*Global Alliance of HeBAU-CLS&HeQis for BioAl-Manufacturing, Baoding, P.R. China*

Introduction

Organic agriculture and functional food

The term *organic* refers to specific ways in which agricultural products are grown and processed [1−7]. Each country has its own regulation for organic food production, but organic crops should be grown without the use of synthetic pesticides, bioengineered genes, petroleum-based fertilizers, and sewage sludge-based fertilizers [8−13]. Different agricultural management systems may have an impact on the sustainability of food systems, as they may affect human health as well as animal well-being, food security, and environmental sustainability [14−23]. Ensuring the sustainable production of healthy food and ecofriendly products has been of interest to researchers of agricultural sciences and ecology, as well as politicians and practitioners, because of high demands by consumers in various countries in the world [24,25]. Consumers are increasingly concerned with purchasing products that not only have good nutritional quality and enjoyable sensory properties, but also provide diverse health benefits [26−32]. The reasons that lead consumers to choose to purchase organic and functional foods are related to quality, taste, food safety, healthy lifestyle, and concerns about the environment and animal welfare [33,34]. However, high prices, difficulty of access, and irregular supply and availability are highlighted as the main limiting factors for not consuming organic food [35]. The human health benefits of organic food are associated with the application of organic methods of production within conventional agriculture management [36−38]. Organic farming is one of the agri-environmental schemes aimed at enhancing biodiversity [39]. The development of organic worldwide is shown in Table 21.1.

The summary of prohibited activities in organic agriculture are the use synthetic fertilizer, the use of chemical pesticides, the use of genetically modified organisms (GMOs), the use of sewage sludge, the use of growth hormones, the prophylactic administration of antibiotics, and the use of GMOs. The most important required activities in organic farming are the use of organic seeds and locally adapted varieties; the use of measures to improve soil fertility, such crop

TABLE 21.1 The development of organic farming worldwide.

Stage of emergence (1924−70)
Stage of expansion (1970−90)
Stage of growth (since 1990)

*The authors contributed equally to this research.

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rotation, organic fertilizer, and soil erosion; pest and weed control only through mechanical and biological measures; animal housing that allows for natural behavior with natural light and sufficient space; the use of organic fodder; and access to pasture areas. The differences between organic and nonorganic production are presented in Table 21.2. The most important benefits of organic food production are shown in Table 21.3. The characteristics of organic agriculture are presented in Table 21.4. The most important parameters of effective social factors of marketing of agricultural

TABLE 21.2 Organic versus nonorganic.

Organic production	Conventionally grown production
Grown with natural fertilizers (manure, compost)	Grown with synthetic or chemical fertilizers
Weeds are controlled naturally (the organic practices include crop rotation, hand weeding, mulching, and tilling)	Weeds are controlled with chemical herbicides
Pests are controlled by using natural methods (birds, insects, traps) and naturally derived pesticides	Pests are controlled with synthetic pesticides
Livestock are given all organic, hormone- and genetically modified organism (GMO)-free feed	Livestock are given growth hormones for faster growth, as well as nonorganic, GMO feed
Disease is prevented with natural methods such as clean housing, rotational grazing, and a healthy diet	Antibiotics and medications are used to prevent livestock disease
Livestock must have access to the outdoors	Livestock may or may not have access to the outdoors

TABLE 21.3 The most important benefits of organic food production.

1. Organic produce contains fewer pesticides.
2. Organic food is often fresher.
3. Organic farming is better for the environment.
4. Organically raised animals are not given antibiotic or, growth hormones and are not fed animal byproducts.
5. Organic meat and milk are richer in certain nutrients.
6. Organic food is genetically modified organisms-free.

TABLE 21.4 Characteristics of organic food production.

The food has a better appearance.
The food has better taste, color, and smell.
The food has higher nutritional value.
The food is safer than the products produced with the chemicals.
The food has more durability and higher resistance.
Smaller amounts of hormones are used in poultry production.
Sustaining chemical are not used in the production of the livestock products.
Chemical fertilizers are not used for the production of food.
Chemical pesticides are not used in the production of food.

products are shown in Table 21.5. The theoretical framework of variables influencing attitudes toward organic farming is shown in Fig. 21.1. The supply of ecosystem services by agriculture is shown in Fig. 21.2.

The Chinese organic agriculture movement started from ecological agriculture, which emerged in the 1980s. The demands of the international market for organic products directly promoted the start of Chinese organic agriculture. Consumption of organic products can reduce a person's exposure to synthetic pesticides. However, the health benefits of an organic diet remain largely unproven because of the presence of other contaminants and to the difficulties in separating the potential effects of organic food from other lifestyle factors [40]. The regulation and policy for organic agriculture, including organic farming regulations, support for the regulation and policy for organic farming, and national organic farming guidelines, need to be improved in order to ensure that Chinese green foods are in harmony with

TABLE 21.5 The most important parameters of effective social factors of marketing of agricultural products.

Notification about the benefits of organic products.
Providing the information about the quality of organic products to consumers.
Training to change the consumption behavior of consumers.
Instructing consumers in the principles of producing high-quality products.
Learning how to package organic products.
Learning how to provide a profile of organic products.
Increasing consumer awareness of the nutritional value of organic products.
Explaining how to improve the supply of organic products.
Education about the prices of organic products.

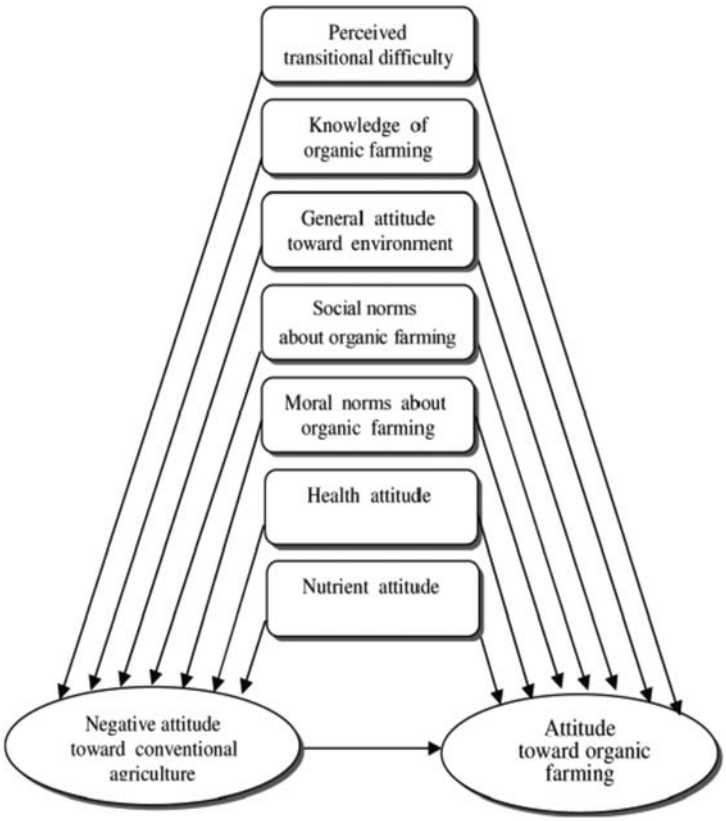


FIGURE 21.1 Theoretical framework of variables influencing attitudes toward organic farming.

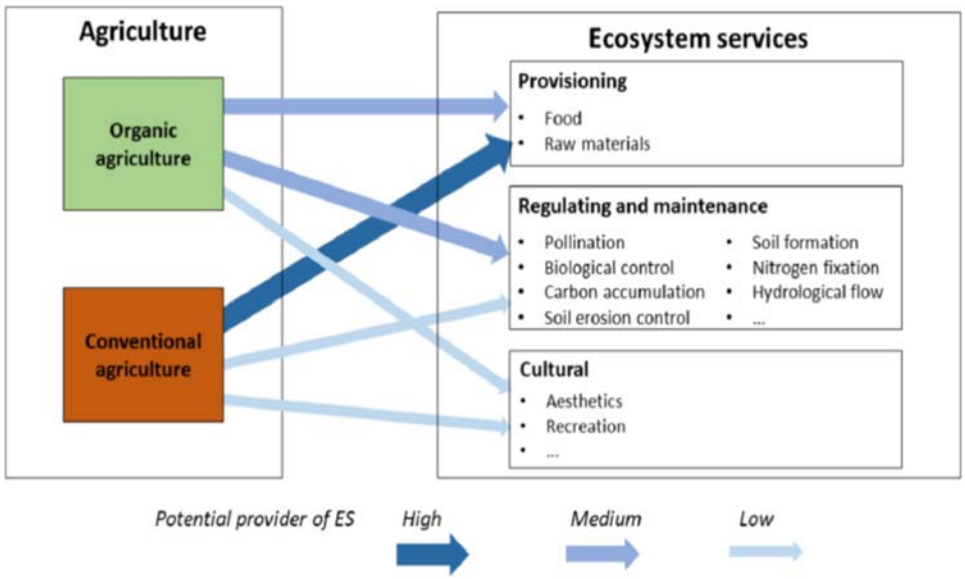


FIGURE 21.2 Supply of ecosystem services by agriculture.

international standards to promote the development of market-oriented organic agriculture in the direction of standardization, industrialization, and internationalization and to sharpen the ability of Chinese organic products to compete in the international market [41]. Hu et al. [42] reported that because China is in the course of a nutrition transition toward animal-based foods, promoting healthy food consumption to increase public awareness of nutrition and avoid overconsumption of meat is important for public health in China. Some farmers in China are abandoning the industrial paradigm of monocrops with high chemical input and livestock factory farms and adopting more sustainable methods, such as organic poultry farming. The principles of organic farming make it obvious that environmental friendliness or benefits for the environments are a key concept of organic farming [43]. Zhang et al. [43] noted that organic farming practices in China are experiencing challenges on many levels. For example, they conflict with China's food safety strategy, they often involve small-scale operations, the farmers may lack knowledge of best production practices, and they have a bad reputation with the credit system. In Chinese culture, foods have traditionally been considered to be the most important materials from the same origins as medicines [44]. Beliefs about foods are closely related to the concept of functional foods, which are purposely designed to provide added benefit beyond nutritional values to improve health and reduce risks of disease [45]. The active components of many functional products derive from foods also pertain to Chinese herbal medicines [46]. Highlight the uncertainty with which conventional farmers initially tend to view organic farming, and they found that the experience gained by organic farmers over time helps them to increase and maintain their environmental efficiency. Marchand and Guo also warn against the rapid expansion of organic farming and recommend more technical support and strict nutrient regulation to foster the environmental efficiency of organic farming. With the passage of time, the perception of food has changed from something to be consumed just to fill the stomach to something that is eaten so that the consumer may benefit from the nutrition, which enhances the physiological functioning of the system [47]. Sibbel [48] stated that in times of climate change, increasing world populations, and clear evidence of the depletion or damage being done to critical resources, it is imperative to take action to sustain and develop the capacity of agricultural and manufacturing systems to continue to provide sustainable food production. Functional food is defined as food containing health-promoting components, and these foods have been enriched with active components such as prebiotics and probiotics [47]. Li et al. [49] emphasized medical functional foods in China, divided these into four categories, and clarified the importance and practical significance of clinical nutritional support for patients, especially in cases of diabetes, cancer, and other non-communicable diseases. Functional foods must remain foods and should not be pills or capsules. Functional foods include fruits, beverages, vegetables, cereals, nuts, milk, and milk-based products, and they must show their effects in amounts that can be expected for normal consumption patterns [50]. The concept of functional foods is a new idea that involves a food or a constituent that has more positive effect on health than a regular food [51]. Organic food covers the entire manner of production [52], while functional foods have nutrition- and health-related product attributes [53,54]. Organic food has positive effects on health, the environment, and animal welfare [55,56], although only the production process is regulated, not the effects. Functional foods offer human health-specific benefits, while organic food promotes not only the health of the consumer, but also the health of

the environment, animals, and society [57]. Do et al. [58] stated that knowledge of functional foods and traditional medicinal crops and fruits has a specific contribution to improving our health and has grown immensely in recent years. The use of medicinal plants could help to reduce current healthcare costs by improving health and disease prevention.

Conclusion

Organic farming is an alternative system for the production of healthy foods that are free of synthetic substances. In recent decades the world has experienced an increase in the cost of health care and people are searching for ways to stay healthy in order to avoid excessive spending on health care. The rapidly growing demand for organic, functional, and ecological foods has been seen in the megacities of China, despite the country's economic and financial crisis. The most important required activities in organic farming are the use of organic seeds and locally adapted varieties; the use of measures to improve soil fertility such crop rotation, organic fertilizer, and soil erosion; pest and weed control only through mechanical and biological measures; animal housing that allows for natural behavior with natural light and sufficient space; the use of organic fodder; and access to pasture areas. Organic and functional foods offer high-quality products to consumers with added value related to health. Organic farming is also concerned with protecting the environment and working in harmony with existing ecosystems, including conserving water, soil, and energy, and using renewable resources and natural farming cycles. Organic food derived from nature by a naturally sound agricultural system already contains all substances needed for human health and respects the health of the environment and society along the food chain. In other words, organic foods promote healthier and more sustainable use of natural resources. Organic agricultural production also has as a big goal the minimization of damage to the environment by using physical weed control and animal and green fertilizers. Functional foods offer human health-specific targets, while organic food promotes not only the health of the consumer, but also the health of the environment, animals, and society. A functional food is any food that has at least one specific nutrient added to it for a specific functional purpose. Improving the sustainability of animal and crop farming and production is important for all countries, especially China, to promote healthy food consumption, which improves public health and reduces the associated environmental and public health risks. Both organic and functional foods have a perceived health-promoting or disease-preventing property beyond the basic function of supplying nutrients. It is accepted that the first priority of producers, especially those who think about sustainability, is to improve the general functionality of food. Improving the healthy diet of the people has become an important public policy goal in the food industry in China.

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Chapter 22

Organic acids: microbial sources, production, and applications

Poonam Yadav[1], Anil K. Chauhan[1], Ram B. Singh[2], Shairy Khan[3] and Ghazi Halabi[4]

[1]*Centre of Food Science and Technology, Institute of Agricultural Sciences, Banaras Hindu University, Varanasi, India,* [2]*Halburg Hospital and Research Center, Civil Lines, Moradabad, India,* [3]*Halburg Hospital and Research Institute, Moradabad, India,* [4]*Halberg Chronomedicine and Cardiology Center, Aley, Lebanon*

Introduction

Organic acids are broadly distributed in nature, and humans have used them in their natural forms since prehistoric times. Fermentation processes that involve the production of acetic acid and lactic acid have been used in food preparation for centuries. Industrial production via the microbiological route was started when the acids were identified as the main product in known fermentation processes. During the first half of the 20th century, advances in chemical synthesis offered new manufacturing procedures that became economically competitive and replaced many fermentation processes. The situation changed in the 1990s, when further developments in the biotechnology field, environmental pressures, and the vertical integration of the fermentation and corn-processing industries resulted in much improved economics for the biological route.

Organic acids are traditional products of food technology and biotechnology. However, organic acids have recently become more interesting for the chemical industry as building blocks. A wide variety of organic acids are of use for polymer and solvent production but also as starting compounds or cosubstrates for pharmaceuticals.

This chapter will focus on organic acids for food use. Furthermore, we will focus on biotechnology and not on traditional food technology. Consequently, the bulk production of acetic acid and lactic acid will not be covered. Acetic acid for industrial use is produced chemically from petroleum-derived resources. Acetic acid for food use (about 10% of the annual world production) is produced by microbial processes, as many food purity laws require that vinegar used in foods must be of biological origin (the production processes were reviewed by Raspor et al., 2008). Lactic acid for food use is a traditional product, in most cases directly produced by fermentation of the food with lactic acid bacteria. The industrially relevant production of purified lactic acid as a starting material for polymer production is predominantly based on yeast as production host (Sauer et al., 2010 and Miller et al., 2011) (Fig. 22.1).

Microbial sources for organic acid production

A large number of microorganisms, including bacteria, such as *Arthrobacter paraffinens*, *Bacillus licheniformis*, *Corynebacterium* sp., *Lactobacillus casei*, *L. helveticus*, *L. paracasei*, and *Streptococcus thermophilus*; fungi, such as *Aspergillus niger*, *A. aculeatus*, *A. carbonarius*, *A. awamori*, *A. foetidus*, *A. fonsecaeus*, *A. phoenicis*, *Rhizopus oryzae*, and *Penicillium janthinellum*; and yeasts, such as *Candida tropicalis*, *C. oleophila*, *C. guilliermondii*, *C. citroformans*, *Hansenula anamola*, and *Yarrowia lipolytica*, have been employed for the production of organic acids [1]. Among these strains, *A. niger* has remained the organism of choice for commercial production because it produces higher levels of citric acid per time unit. The main advantages of using *A. niger* are its ease of handling, ability to ferment a variety of cheap raw materials, and high yields. The problem associated with the production of citric acid by the yeasts is the simultaneous formation of isocitric acid.

Efforts have been made to develop microbial strains that could produce high yields of organic acids. The most commonly employed technique has been inducing mutations in parental strains by using mutagens [1,2]. Among mutagens, gamma radiation, ultraviolet (UV) radiation, and chemical mutagens are often used. Among different approaches, one

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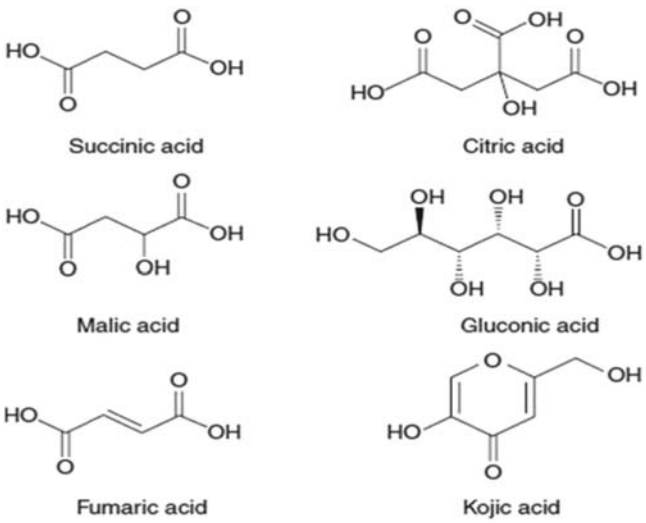


FIGURE 22.1 Chemical structures of food-related organic acids.

has been to combine the UV treatment with some chemical mutagens. The single-spore technique and the passage method are generally the principal methods of selecting strains. The single-spore technique has the disadvantage that mineral acid and organic acids (gluconic and oxalic acids) simulate the presence of citric acid [1,2].

Citric acid

Citric acid ($C_6H_8O_7$, 2-hydroxy−1,2,3-propane tricarboxylic acid), a natural constituent and common metabolite of plants and animals, is the most versatile and widely used organic acid in the fields of food (60%) and pharmaceuticals (10%). It also has several other applications in various other fields. Citric acid is a tricarboxylic acid with a molecular weight of 210.14 g/mol and contains three carboxylic functional groups with three different pK_a values (3.1, 4.7, and 6.4). Citric acid is a primary metabolic product that is formed in the tricarboxylic acid (Krebs) cycle and is found in small quantities in virtually all plants and animals. Citric acid was first isolated by Karls Scheels in 1874 in England from lemon juice imported from Italy. The main application of citric acid (70%) is in the food and beverage industry, as the most versatile and widely used acidulant. Its pleasant taste, high water solubility, and property of enhancing flavors have affirmed its application in this market, which has been largely responsible for the increases in demand for citric acid. A buffering capacity and the ability to form complexes with heavy metals have driven the application of citric acid and several of its salts in the pharmaceutical and chemical-processing industries as sequestering agents.

Microorganisms used for citric acid production

A large number of microorganisms, including bacteria, fungi, and yeasts, have been reported to produce citric acid. Table 22.1 shows the microorganisms that are used to produce citric acid. Among these, only *A. niger* and certain yeasts, such as *Saccharomycopsis* sp., are employed for commercial production.

Metabolic pathway for citric acid synthesis

The excretion of citric acid is not a normal phenomenon for microorganisms, but it can accumulate in very large quantities when certain bacteria, yeast, and fungi are grown under specific constraints. Appreciable accumulation is the result of severe irregularities in the metabolism caused by genetic deficiencies or by metabolic imbalances. The definition of the appropriate conditions to maximize citric acid yield and concentration varies widely depending on the strain in use and the main carbon source. The basic metabolic sequences related to citrate metabolism are well established, as shown in Fig. 22.2.

The regulation of the metabolic pathway and the main points that control citrate accumulation are still subject to debate because different conclusions have been reached in numerous studies. Among the reasons for this are the facts that many studies have used different strains and conditions and that there is evidence indicating that more than one set of conditions can lead to citric acid accumulation.

TABLE 22.1 Microorganisms used for citric acid production.

Microorganism	References
Fungi	
Aspergillus niger	[3–6],
A. aculeatus	[7]
A. awamori	[8]
A. carbonarius	[7]
A. wentii	[9]
A. foetidus	[10]; Tran et al., 1998
Penicillium janthinelum	[8]
Yeast	
Saccahromicopsis lipolytica	[11,12]
Candida tropicalis	[13]
C. oleophila	[14]
C. guilliermondii	Miall & Parker, 1975; [15]
C. parapsilosis	[16]
C. citroformans	[17]
Hansenula anamola	[18]
Bacteria	
Bacillus licheniformis	[19]
Arthrobacter paraffinens	[20]
Corynebacterium sp.	[21]

Aspergillus niger forms citric acid from glucose via glycolytic catabolism to 2 mol of pyruvate and their subsequent conversion to oxaloacetate. Citrate synthase then condenses oxaloacetate with acetyl-CoA to form citrate. The presence of the enzymes of the tricarboxylic acid cycle has been demonstrated in this organism under various conditions. For citric acid to accumulate, an imbalance between the metabolic flux in the glycolytic pathway and the tricarboxylic cycle must occur [22]. This imbalance has been detected as an increase in the flux through glycolysis with high activity of the glycolytic enzymes due to culture conditions. A key step in the process is the synthesis of oxaloacetate by an anaplerotic carbon dioxide fixation catalyzed by pyruvate carboxylase, which is induced in the presence of high carbohydrate concentrations. This enzyme and citrate synthase produce an accumulation in the cellular concentration of citric acid. When yeasts produce citric acid from alkanes, these compounds are converted by beta-oxidation to acetyl-CoA, which combines with oxaloacetate to produce citrate. The anaplerotic glyoxylate cycle replenishes oxaloacetate [23].

Even though a large number of microorganisms can produce citric acid, the fungus *A. niger* has remained the organism of choice for commercial production. In the last few years, production with the yeast *Yarrowia lipolytica* (asexual form *Saccharomycopsis*, formerly *Candida*) has increased significantly. Some other organisms include *A. wentii*, *A. carbonarius*, *A. aculeatus*, *A. awamori*, *Candida tropicalis*, *C. oleophila*, *C. guilliermondii*, and *C. citroformans*. A significant effort has been devoted to obtaining strains with higher yields and better production efficiency, but the strains that are actually used in manufacture and the selection methods for strain improvements have been kept secret, and information about them is not generally available [24].

Fermentation processes

Different fermentation processes have been developed for the different strains and carbon sources. *A. niger* and *Y. lipolytica* are used for commercial production of citric acid. Surface and submerged methods have been used with *A. niger*,

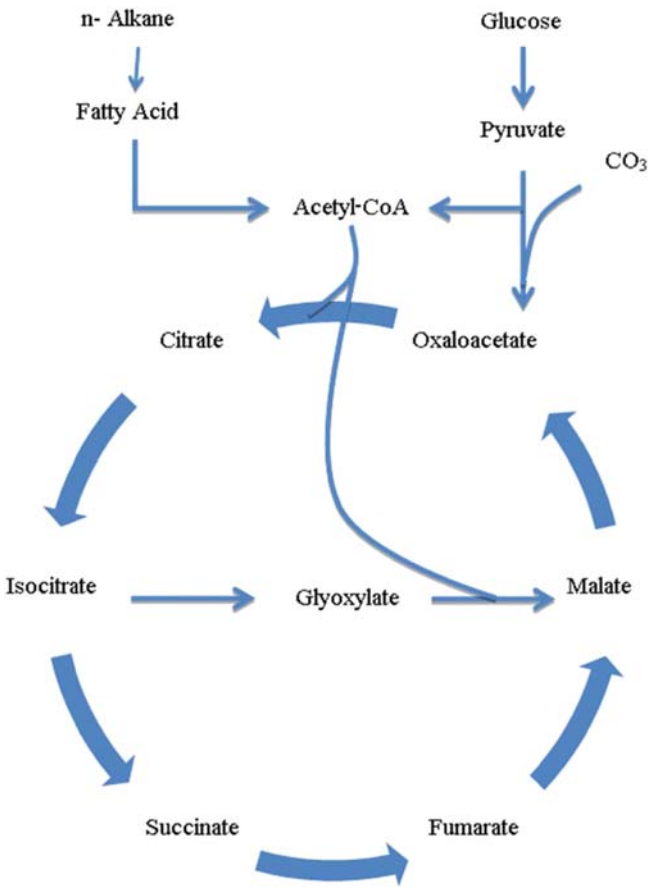


FIGURE 22.2 Metabolic relationships of citrate metabolism from carbohydrate or n-alkane.

and either carbohydrates or n-alkanes can be the carbon source in processes using yeast. About 99% of world production of citric acid occurs via microbial processes, which can be carried out by using surface or submerged cultures. The product is sold as an anhydrous or monohydrate acid, and about 70% of total production of 1.5 million tons per year is used in the food and beverage industries, 20% in the pharmaceutical industry, and the remaining 10% in the chemical industry [25].

Surface fermentation

In the classical process for citric acid manufacture, the culture solution is held in shallow trays (with a capacity of 50−100 L), and the fungus develops as a mycelial mat on the surface of the medium. The trays are made of high-purity aluminum or special-grade steel and are mounted one over another in stable racks. The fermentation chambers are provided with effective air circulation to control temperature and humidity. Fermentation chambers are always in aseptic conditions, which might be conserved principally during the first two days when spores germinate. Frequent contamination is caused mainly by *Penicillia*, other *Aspergilli*, yeast, and lactic bacteria (Rohr et al., 1983; Morgant, 1988). Refined or crude sucrose, cane syrup, or beet molasses is generally used as a source of carbon.

Submerged fermentation

The submerged fermentation (SmF) process is the most commonly employed technique for citric acid production. It is estimated that about 80% of world production is obtained by SmF. Several advantages, such as higher yields and productivity and lower labor costs, are the main reasons for this. Two types of fermenters are employed: conventional stirred fermenters and tower fermenters [26]. Preferentially, fermenters are made of high-grade steel and require provision of an aeration system, which can maintain a high dissolved oxygen level. Fermenters for citric acid production do not have to be built as pressure vessels, since sterilization is performed by simply steaming without applying pressure. Cooling can be done by an external water film over the entire outside wall of the fermenter.

In SmF, different kinds of media are used, such as sugar- and starch-based media. Inoculation is performed by adding a suspension of either spores or precultivated mycelia. When spores are used, a surfactant is added to disperse them in the medium. For precultivated mycelia an inoculum size of 10% of fresh medium is generally required. Normally, submerged fermentation is concluded in 5−10 days depending on the process conditions. It can be carried out in batch, continuous, or fed-batch systems, although the batch mode is most frequently used.

Solid-state fermentation

Solid-state fermentation (SSF) has been termed an alternative method to produce citric acid from agroindustrial residues [27]. Citric acid production by SSF (the Koji process) was first developed in Japan and is the simplest method for its production. SSF can be carried out by using several raw materials of agroindustrial waste, such as orange peel, lemon peel, sugar cane bagasse, and coconut coir. Generally, the substrate is moistened to about 70% moisture depending on the substrate absorption capacity. The initial pH is normally adjusted to 4.5−6.0, and the temperature of incubation can vary from 28°C to 30°C. The most commonly used organism is *A. niger*. However, there also have been reports with yeasts [28]. One of the important advantages of SSF process is that the presence of trace elements may not affect citric acid production as harmfully as it does in SmF. Consequently, substrate pretreatment is not required.

Citric acid recovery

The recovery of citric acid from liquid fermentation is generally accomplished by three basic procedures: precipitation, extraction, and adsorption and absorption (mainly using ion exchange resins). The first step of citric acid recovery involves the precipitation of oxalic acid, possibly in the form of calcium oxalate at low pH, and subsequent separation from the medium containing the mycelium through rotating filters or centrifuges. Citric acid is then precipitated at pH 7.2 and 70°C−90°C and recovered by filtration and drying. If a purer product is desired, it is dissolved with sulfuric acid, treated with charcoal or ion exchange resins, and again crystallized as anhydrous citric acid (above 40°C) or as a monohydrate (below 36.5°C) [29]. In surface processes, the mycelium is sometimes squeezed to increase the recovery yield. Pinacci and Radaelli [30] have proposed a process of electrodialysis with bipolar membranes for the recovery of citric acid from fermentation media.

Applications of citric acid

Citric acid is mainly used in the food industry because of its pleasant acid taste and its high solubility in water. It is worldwide accepted as “GRAS” (generally recognized as safe) and has been approved by the Joint U.N. Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives. Table 22.2 presents the main applications of citric acid.

Gluconic acid

Gluconic acid (pentahydroxycaproic acid) is produced from glucose through a simple dehydrogenation reaction catalyzed by glucose oxidase. Oxidation of the aldehyde group on the C-1 of beta-D-glucose to a carboxyl group results in the production of glucono-δ-lactone ($C_6H_{10}O_6$) and hydrogen peroxide. Glucono-δ-lactone is further hydrolyzed to gluconic acid either spontaneously or by a lactone-hydrolyzing enzyme, while hydrogen peroxide is decomposed to water and oxygen by peroxidase. The gluconate pathway is detailed in Fig. 22.3. Gluconic acid is used in the food, beverage, and pharmaceutical industries. It imparts a refreshing sour taste in many foods items, such as wine and fruit juices. Sodium gluconate has a high sequestering power. It is a good chelator at alkaline pH; its action is comparatively better than that of EDTA chelator. The actual main product is sodium gluconate, which makes up about 80% of the gluconic acid market [31]. Aqueous solutions of sodium gluconate are resistant to oxidation and reduction at high temperatures. It is an efficient plasticizer and a highly efficient set retarder. It is easily biodegradable (98% at 48 hours). It has an interesting property of inhibiting bitterness in foodstuffs. The US Food and Drug Administration (FDA) has assigned sodium gluconate a GRAS status, and its use in foodstuff is permitted without limitation [32].

TABLE 22.2 Applications of citric acid [1].

Industry	Applications
Beverages	Provides tartness and complements fruit and berry flavors. Increases the effectiveness of antimicrobial preservatives. Used in pH adjustment to provide uniform acidity
Jellies, jams and preserves	Provides tartness. pH adjustment
Candy	Provides tartness. Minimizes sucrose inversion. Produces dark color in hard candies. Acts as an acidulant
Frozen fruit	Lowers pH to inactivate oxidative enzymes. Protects ascorbic acid by inactivating trace metals
Fruit and vegetable juices	Acts as stabilizer in commercially prepared juices of fruits and vegetables
Dairy products	Used as an emulsifier in ice creams and processed cheese; used as an acidifying agent in many cheese products and as an antioxidant
Gelatin desserts	Adjusts pH to the desired levels and helps in setting of gelatin desserts
Fats and oils	Synergist for other antioxidants, as a sequestrant
Pharmaceuticals	Used as an effervescent in powders and tablets in combination with bicarbonatesProvides rapid dissolution of active ingredients. Acts as an acidulant in mild astringent formulations. Acts as an anticoagulant
Cosmetics and toiletries	Used for pH adjustment, as an antioxidant as a metallic ion chelator, and as a buffering agent
Industrial applications	Used as a sequestrant of metal ions, neutralizer, buffer agent
Metal cleaning	Removes metal oxides from the surface of ferrous and nonferrous metals and for preparational and operational cleaning of iron and copper oxides
Others	Used in electroplating, copper plating, metal cleaning, leather tanning, printing inks, bottle-washing compounds, floor cement, textiles, photographic reagents, concrete, plaster, refractories and molds, adhesives, paper, polymers, tobacco, and waste treatment

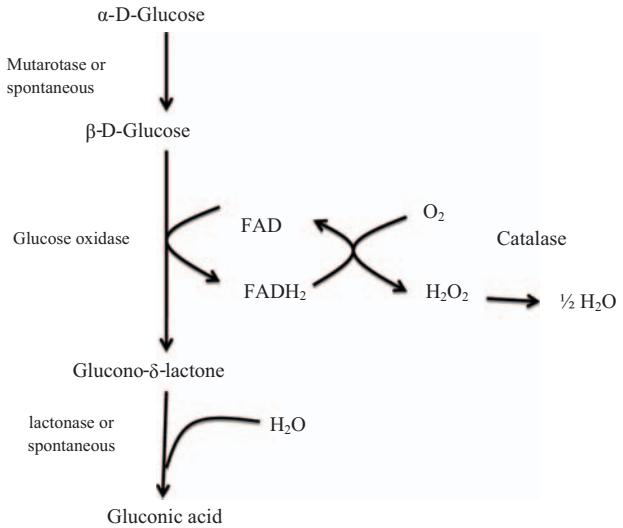


FIGURE 22.3 Fungal gluconic acid biosynthetic pathway.

Properties of gluconic acid

Gluconic acid is a noncorrosive, nonvolatile, nontoxic, mild organic acid. It imparts a refreshing sour taste in many food items such as wine, fruit juices, etc. Sodium gluconate has a high sequestering power. Concentrated gluconic acid solution contains certain lactone structures (neutral cyclic ester) showing antiseptic property (Table 22.3).

TABLE 22.3 General characteristics of gluconic acid [32].

Gluconic acid	
Nature	Noncorrosive, mildly acidic, not very irritating, nonodorous, nontoxic, easily biodegradable, nonvolatile organic acid
Relative molecular mass	196.16
Chemical formula	$C_6H_{12}O_7$
Melting point (50% solution)	Lower than 12°C
Boiling point (50% solution)	Higher than 100°C
Density	1.24 g/mL
Appearance	Clear to brown
Sourness	Mild, soft, refreshing taste
Solubility	Soluble in water
Degree of sourness (sourness of citric acid is regarded as 100)	29–35

Production of gluconic acid by *Aspergillus niger*

A. niger produces all the enzymes required for the conversion of glucose into gluconic acid, which include glucose oxidase, catalase, lactonase, and mutarotase. Crystalline glucose monohydrate, which is in the alpha form, is converted spontaneously into the beta form in the solution with the help of the enzyme mutarotase produced by *A. niger*, which serves to accelerate the reaction [33].

The production parameters are defined by the enzyme properties of glucose oxidase. The enzyme is rapidly inactivated at low pH; therefore the pH of the culture has to be kept between 4.5 and 6.5 for efficient gluconic acid production. There are two key parameters that influence gluconic acid production: oxygen availability and pH of the culture medium. Oxygen is one of the key substrates in the oxidation of glucose, as glucose oxidase uses molecular oxygen in the bioconversion of glucose. The concentration of oxygen gradient and the volumetric oxygen transfer coefficient are the critical factors, which monitor the availability of oxygen in the medium [34].

Current commercial production of gluconic acid as sodium gluconate uses submerged state fermentation with *A. niger*. It involves fed-batch cultivation with intermittent glucose feedings and the use of sodium hydroxide as a neutralizing agent, pH is held at 6.0–6.5, and the temperature is held at about 34°C. The productivity of the process is very high, since glucose is converted at a rate of 15 g/L/hour. The gluconic acid can be produced by a synthetic medium by surface and submerged fermentation. Agricultural and industrial residues such as molasses [35], grape must [36], whey, and Jerusalem artichoke [37] have been used as the source of glucose.

There are only a few reports available for the production of gluconic acid by SSF. Roukas [38] reported a maximal gluconic acid concentration of 490 g/kg of dry fig with a 63% yield obtained at an initial moisture of 75% and a pH of 7.0 after nine days of fermentation. The addition of 6% methanol into the substrate helped to increase the production of gluconic acid from 490 to 685 g/kg. Singh et al. [39] performed SSF by using HC1 pretreated sugar cane bagasse, and the highest level of gluconic acid (107 g/L) with 95% yield was obtained. In comparison with the submerged culture, the degree of conversion was higher in SSF.

Recovery of gluconic acid

The recovery process depends on the method of broth neutralization and the nature of carbon sources used. Generally, the downstream process is similar for the fermentation processes using fungal and bacterial species. Gluconic acid, glucono-δ-lactone, calcium gluconate, and sodium gluconate are some of the important products, and their extraction process is briefly described as follows.

For the recovery of free gluconic acid from calcium gluconate, the broth is clarified, decolorized, concentrated, and exposed to −10°C in the presence or absence of alcohol. Thus the calcium salt of gluconic acid crystallizes and then is recovered and further purified [32].

For obtaining calcium gluconate as a product, calcium hydroxide or calcium carbonate is used as the neutralizing agent. It is added to the nutritive broth accompanied by heating and vigorous stirring. The broth is concentrated to a hot supersaturated solution of calcium gluconate, followed by cooling at 20°C, and water-miscible solvents are added, which crystallizes the compound. A treatment with activated carbon facilitates the crystallization process. Finally, the crystals are centrifuged, washed several times, and dried at 80°C [40].

Sodium gluconate, the principal manufactured form of gluconic acid, is prepared by ion exchange. In the process developed by Blom et al. in [41] the sodium gluconate from the filtered fermented broth is concentrated to 45% (mass per volume), followed by the addition of sodium hydroxide solution, raising the pH to 7.5, and drum drying. Carbon treatment of the hot solution before drying process is done to obtain a refined product.

Application of gluconic acid

Gluconic acid is a mild organic acid that has applications in the food industry. As was stated earlier in the chapter, gluconic acid is a natural constituent of fruit juices and honey and is used in the pickling of foods. Its inner ester, glucono-δ-lactone, imparts an initially sweet taste, which later becomes slightly acidic. It is used in meat and dairy products, particularly in baked goods as a component of a leavening agent for preleavened products. It is used as a flavoring agent (e.g., in sherbets), and it also finds application in reducing fat absorption in doughnuts and cones. Foods that contain D-glucono-d-lactone include bean curd, yogurt, cottage cheese, bread, confectioneries, and meat. Generally speaking, gluconic acid and its salts are used in the formulation of food, pharmaceutical, and hygienic products (Table 22.4). They are also used as mineral supplements to prevent deficiencies of calcium and iron and as buffer salts. Different salts of gluconic acid find various applications based on their properties. Sodium salt of gluconic acid has the outstanding property of chelating calcium and other divalent and trivalent metal ions [32].

Ramachandran et al. [32] explained how the property of gluconic acid for sequestering iron over a wide pH range is exploited in the textile industry, where it prevents the deposition of iron and for desizing polyester and polyamide fabrics. Gluconic acid is also used in metallurgy for alkaline derusting and in the washing of painted walls and removal of metal carbonate precipitates without causing corrosion. Calcium gluconate is used in the pharmaceutical industry as a source of calcium for treating calcium deficiency by oral or intravenous administration. It also has a place in animal nutrition. Iron gluconate and iron phosphogluconate are used in iron therapy. Zinc gluconate is used as an ingredient for treating the common cold, in wound healing, and in treatment of various diseases caused by zinc deficiencies, such as delayed sexual maturation, mental lethargy, skin changes, and susceptibility to infections.

TABLE 22.4 Applications of gluconic acid and its derivatives [32].

Component	Applications
Gluconic acid	Prevention of milkstone in the dairy industryCleaning of aluminum cans
Glucono-δ-lactone	Latent acid in baking powders for use in dry cakes and instantly leavened bread mixesSlow-acting acidulant in meat processing, such as sausagesCoagulation of soybean protein in the manufacture of tofuCheese curd formation and improvement of heat stability of milk in the dairy industry
Sodium salt of gluconic acid	Detergent in bottle-washingMetallurgy (alkaline derusting)Additive in cementDerusting agentTextile (iron deposit prevention)Paper industry
Calcium salt of gluconic acid	Calcium therapyAnimal nutrition
Iron salt of gluconic acid	Treatment of anemiaFoliar feed formulations in horticulture

Fumaric acid

Fumaric acid is used as a food acidulant in beverages and baking powders. Furthermore, fumaric acid is a pharmaceutically active substance that is used to treat psoriasis or multiple sclerosis [42]. Originally, fumaric acid was isolated from plants belonging to the genus *Fumaria*, from which its name is derived. Fumaric acid is an intermediate of the tricarboxylic acid cycle.

Fumaric acid is a useful intermediate in several chemical syntheses, including esterification and polymerization, and in the manufacture of sizing resins for the paper industry [43]. It can easily be produced from *Rhizopus arrhizus* on an industrial scale. Similar to the other fungal acid fermentation processes, the culture conditions are crucial to obtain the correct cellular morphology, which promotes efficient production. Factors that affect fungal growth morphology and fumaric acid production by *R. arrhizus* include the initial pH value and concentrations of trace metals, such as zinc, magnesium, iron, and manganese [44]. A lower initial pH value in the cultivation medium appears to be inhibitory to fungal growth and promotion of fumaric acid productivity. A higher initial pH value leads to fast growth and the formation of large pellets or filamentous forms, which remain unproductive. The importance of pellet morphology for fumarate productivity has also been shown for *R. delemar* [45].

Lactic acid

Lactic acid (2-hydroxypropanoic acid) was discovered and isolated in 1780 by the Swedish chemist Scheele from sour milk, and the first organic acid was produced microbiologically in 1881 by Charles E. Avery at Littleton, Massachusetts, United States. Lactic acid is present in plants and microorganisms. Lactic acid has two enantiomers: L-(+) and D-(-)-lactic acid (Fig. 22.4). It is classified as GRAS by the US FDA [46].

There are two groups of lactic acid bacteria: heterofermentative and homofermentative. The heterofermentative lactic acid bacteria (e.g., *Luconostoc mesenteroides*) produce many byproducts other than lactic acid and are not suitable for commercial processes. In the case of homofermentative bacteria (*Lactobacillus* sp.), very little substrate is used for producing cell mass and other metabolites, and the majority of the carbon source is converted to lactic acid; the percent conversion of sugars to lactic acid is virtually equivalent to the theoretical yield of 2 mol of lactic acid per mole of hexose sugar utilized. Some *Lactobacillus* species and their preferred carbon sources are listed in Table 22.5. The homofermentative lactic acid bacteria are facultative anaerobes that can be grown at a low oxygen concentration and are used for industrial production of lactic acid [47].

Lactic acid production

The lactic acid is an anaerobic fermentation end product of glycolysis, in which pyruvate is reduced to lactic acid by lactate dehydrogenase generating nicotinamide adenine dinucleotide for glycolysis (Fig. 22.5). The lactic acid bacteria are able to produce either D(-)-lactic acid, L(+)-lactic acid or the racemic mixture of both D and L isomers (Fig. 22.4). Two stereospecific lactate dehydrogenases are present in organisms synthesizing the L(+) or D(-)-lactic acid. Semirefined corn sugar (dextrose), molasses, and whey are some commonly used carbon sources for the industrial production of lactic acid [49]. The typical medium employed in the fermentation process consists of 10%−15% dextrose, 10% calcium carbonate, and small amounts of nitrogen. The presence of calcium carbonate neutralizes the free lactic acid, which is toxic to the bacteria and maintains the pH of the medium between 5.5 and 6.5. The medium is also supplemented with B vitamins for proper growth of the organism. Lactic acid fermentation with *Lactobacillus delbrueckii* is carried out at 45°C−50°C. No aeration is required during fermentation, as lactic acid fermentation is anaerobic, but for proper mixing of the calcium carbonate to react with lactic acid produced, agitation is essential. The fermentation is

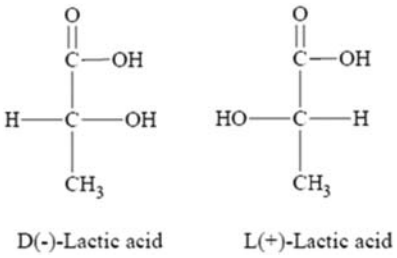


FIGURE 22.4 D and L enantiomers of lactic acid.

TABLE 22.5 Some homofermentative lactic acid bacteria and their preferred carbon sources [47].

Organism	Carbon source
Lactobacillus delbrueckii	Glucose
Lactobacillus leichmannnii	Glucose
Lactobacillus bulgaricus	Lactose
Lactobacillus helviticus	Lactose and galactose
Lactobacillus amylophyllus	Starch
Lactobacillus amylovirus	Starch
Lactobacillus lactis	Glucose, sucrose, and galactose
Lactobacillus pentosus	Pentoses of sulfite waste liquor

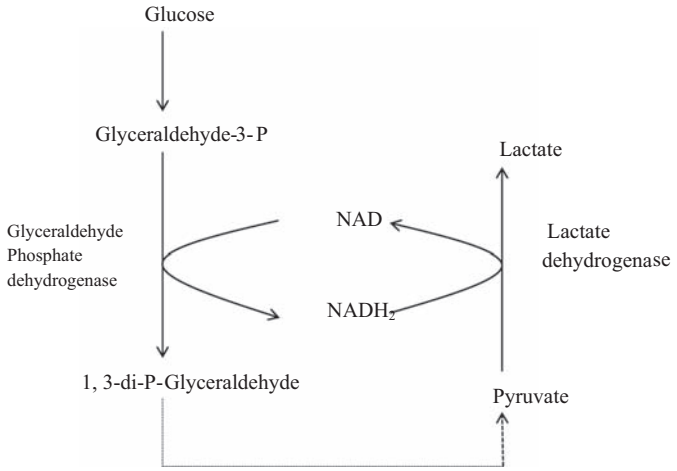


FIGURE 22.5 Lactic acid biosynthesis from glucose [48].

continued for six days or less until complete all the sugar in the medium has been used [50]. The lactic acid yield is 80%−90%, which is very near to the theoretical value. The temperature during fermentation in case of *L. pentoses*, *L. casei*, or *Streptococcus lactis* is kept relatively low, around 30°C [51].

A high yield of lactic acid is obtained either by the continuous cell recycle fermentation process or by fed-batch fermentation. The inhibitory effect of lactic acid has also been overcome by using the electrodialysis fermentation method, which continuously removes lactic acid from the fermentation broth, resulting in continuation of fermentation activity.

Recovery of lactic acid

A number of methods can be applied for the separation of lactate salt from fermented medium; they involve extraction by solvents or separation by ion exchange, adsorption, vacuum distillation, or membrane filtration [52]. The medium after completion of fermentation consists of either pure lactic acid or its salt or a mixture of the two. Earlier methods used the addition of excess of calcium carbonate to the medium at the end of the fermentation, the pH is adjusted to 10, and the mixture is heated and filtered. In this procedure all the lactic acid is converted to calcium lactate, the bacteria are killed, and the protein in the medium gets coagulated. A number of other methods have been developed to recover and purify lactic acid. In one such method the filtrate is concentrated to crystallize calcium lactate, following which sulfuric acid is added to precipitate calcium as calcium sulfate and removed by filtration. Lactic acid is again recrystallized as calcium lactate and is passed through activated carbon to remove colored impurities [52].

TABLE 22.6 Applications of lactic acid in different industries.

Industry	Applications
Food	Preservative, acidulant, buffering agent, pickling agent, and dough conditioner
Meat	Prolongs the shelf life of poultry and fish during packaging
Textile	Finishing, antimony lactate as a mordant during dyeing
Metal	Electroplating bath, plasticizer, and corrosion inhibitor
Leather	Acidulant
Pharmaceuticals	Ointments, lotions, antiacne solutions, humectants, parenteral solutions, calcium lactate (anticaries agent), and biodegradable polymers for sutures in medicine
Medical	Orthopedic implants, controlled drug release
Chemical	Ethyl lactate and butyl lactate are used as green solvents

Applications of lactic acid

Lactic acid is used in the food, pharmaceutical, cosmetic, and textile industries. The free acid is used as an acidulant and preservative in several food products, such as cheese, meat, beer, and jellies. Ammonium lactate is used as a source of nonprotein nitrogen in feeds; sodium and calcium stearoyl lactylates are used as emulsifiers and dough conditioners. Only the L(+) form of the lactic acid is metabolized in animal and human cells because these cells can synthesize only L(+)-lactate dehydrogenase enzyme for metabolism. Therefore consumption of a large quantity of D(-)-lactic acid results in its accumulation in the blood in unmetabolized form. As a result of D(-)-lactic acid accumulation, hyperacidity of urine and decalcification may occur (Datta et al., 1995).

Lactic acid is a good solvent and provides acidity in foods and beverages. Ethyl and butyl lactates are used as flavoring ingredients. Lactic acid has some important applications in the food industry, such as for the production of fermented foods; in the pickling process for gherkins, dill pickles, pickled olives, sauerkraut, pickled carrots, and some leafy vegetables; and in the processing of Oriental foods. Lactic acid has applications for the production of dairy products, such as yogurt, buttermilk, acidophilus milk, cottage cheese, cream cheese, and fermented cheese etc [51].

Recently, there has been increased interest in lactic acid because of its application in the synthesis of biodegradable, biocompatible plastics and coatings. L(+)-lactic acid can be polymerized to form polylactic acid. This polymer can be used in the manufacture of new biodegradable plastics. Biodegradable plastics could play an increasing role in industry by replacing nondegradable ordinary plastics or minimizing their use to solve environmental pollution problems. Lactic acid has been used in the manufacture of cellophane, resins, and some herbicides and pesticides. Another important application of lactic acid is in the textile and tanning industries [53] (Table 22.6).

Conclusion

It is clear that filamentous fungi are established natural producers of a variety of organic acids. First, they evolved to overproduce these acids naturally under certain conditions. This includes the fact that they also tolerate these acids in high concentrations, which is a prerequisite for an industrial process. The efficient production of organic acids is otherwise connected to precise culture conditions, such as pH, a defined carbon and nitrogen ratio, or concentration of metal ions. The productivity of filamentous fungi is furthermore strongly connected to morphology. With a growing demand, the production of citric acid is expected to increase. Its production has now reached 1.4 million tons per year and continues to increase more each year. The main reason for this constant increase is the large number of applications that can be found for citric acid, mainly in the food and pharmaceutical industries. Traditional processes, such as submerged fermentation using the fungus *A. niger*, dominate global production. However, different techniques of production, such as continuous fermentation and solid-state fermentation, are continuously being studied, showing new perspectives for the production of organic acids.

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Further reading

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Section 5

Fruits, vegetables, legumes and whole grains

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Chapter 23

Role of millets in disease prevention and health promotion

Ashwani Kumar[1], Pooja Kumari[2] and Mukul Kumar[1]

[1]*Department of Food Technology and Nutrition, Lovely Professional University, Phagwara, India,* [2]*Department of Pharmaceutical Sciences, Lovely Professional University, Phagwara, India*

Introduction

The advancements in nutrition science have adopted the mantra that a healthy life resides in healthy food. People have become aware of the effects of the nutritional and phytochemical composition of food on human health, and hence an increase in the demand for functional foods has been observed [1,2]. A trend has been also observed among health professionals of studying the nutritional and phytochemical profiles of nonconventional and underutilized food sources. Millets have become the grains of choice, owing to their high nutritional profile and ability to grow on the less fertile soils [3]. They belong to the group of small-seeded species of cereal crops belonging to the family Poaceae. The most widely grown millets are pearl millet (*Pennisetum glacum*), finger millet (*Eleusine corcana*), foxtail millet (*Setaria italica*), proso millet (*Panicum miliaceum*), barnyard millet (*Echinochloa crusgalli*), kodo millet (*Paspalum scrobiculatum*), and little millet (*Panicum sumatrense*). All of these are rich in macronutrients and micronutrients such as carbohydrates, proteins, minerals, and vitamins [3,4]. The fat content varies by millet type. Millet carbohydrates contain less starch in comparison to the staple cereals and are a rich source of dietary fiber [3]. Dietary fiber slows down the absorption of glucose in the small intestine and lowers the glycemic index (GI) of the food [5]. It also controls the gastric emptying and absorption of fat and has been found to be effective against stomach ulcers [6]. Dietary fiber also acts as prebiotics, which makes millet a suitable substrate for the development ofsynbiotic foods [2]. Millet protein contains all eight essential amino acids and is particularly high in cysteine and methionine. Millets are also free from gluten and can be consumed by celiac patients as a substitute for wheat [3]. Millet lipids are high in healthy unsaturated fatty acids [7]. Millets are a rich source of essential minerals, such as calcium, phosphorus, iron, and zinc. They can help to combat mineral deficiencies in developing countries such as India. They are also a good source of B-vitamins. Millets are also rich in phytochemicals, such as phenolics, flavonoids, and tannins. These phytochemicals exhibit strong antioxidant activity and reduce the chances of tumor growth [8]. The cholesterol-lowering properties of millet phytochemicals are also reported [9]. In this chapter we will discuss in detail the role of millets in disease prevention and health promotion.

Proximate composition and calorific value

Like all cereal grains, millets are composed of moisture, carbohydrates, proteins, lipids, and inorganic matter, such as ash. The proximate composition of millets is shown in Table 23.1 [3,10]. The moisture content in all the millets is reported to be in the range of 8%−14%. The carbohydrate content of millets is less than that of rice and comparable to that of whole wheat and whole maize. However, carbohydrate content as low as 49% and 56.1% has been also reported in some varieties of barnyard millet and kodo millet, respectively [3]. The protein content of millets is more than that of rice and maize and equivalent to or greater than that in whole wheat [7]. The fat content in the millets varies a lot; the highest fat content, 4.8%−5%, is found in pearl millet, while the least fat content, 1.3%−1.5%, is found in finger millet [11]. By contrast, among the staple cereals, rice and wheat are low in fats: 1.24% and 1.47%, respectively. Maize is a good source of fat, at 3.77%. The ash content of millets is 1.9%−4.5%, that is, several times higher than that of

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TABLE 23.1 Proximate composition and calorific value of millets.

Millet type	Moisture (%)	Carbohydrates (%)	Protein (%)	Fat (%)	Ash (%)	Calorific value (calories)
Pearl millet	8–12	67–70.4	10.6–12.6	4.8–5.0	1.9–2.3	363–412
Finger millet	9–12	66.5–75.0	6–8.2	1.3–1.5	2.6–2.7	332–376
Proso millet	9–11	62.3–72.2	10.6–12.5	1.76–4.0	1.9–3.2	341–364
Foxtail millet	9–12	61.6–72.4	9.9–12.3	2.5–4.0	3.3–3.5	351–353
Barnyard millet	8–12	49–65.5	8.9–11.9	2.2–4.5	4–4.5	300–310
Kodo millet	8–10	56.1–74.0	8.3–11.6	1.3–4.2	2.6–3.3	346–353
Little millet	13.5–15	64.2–67	7.6–10	2.4–2.8	1.5–1.9	325–336
Rice (brown rice)	8–10	72.8–75.8	8.5–9.90	1.12–1.30	0.9–1.2	325–340
Wheat	8–12	61.2–66.8	10–12	1.42–152	1.20–1.64	310–334
Maize	8.5–10	63.2–66.42	8–9.5	3.60–4.12	1.02–1.34	328–338

Source: From Kumar A, Tomer V, Kaur A, Kumar V, Gupta K. Millets: a solution to agrarian and nutritional challenges. Agric Food Secur 2018;7(1):31; Dayakar RB, Bhaskarachary K, Arlene Christina GD, Sudha Devi G, Tonapi A. Nutritional and health benefits of millets. ICAR. Indian Institute of Millets Research (IIMR), Hyderabad; 2017, p. 112.

rice, wheat, and maize (1.04%–1.64%) [3,11]. Ash content is an indicator of the mineral content of grains. Millets are a good source of energy and provide calories equivalent to the major cereals.

Health benefit of the millets

All the millet components, that is, carbohydrates, proteins, lipids, minerals, and phenolic compounds, possess health properties. The major health benefits of the millets in a nutshell are shown in Fig. 23.1.

Carbohydrates

The millets carbohydrate consists of sugars, starch, and dietary fiber. Free sugar content ranges between 1% and 1.4% in different millets [12,13]; sucrose is the predominant free sugar with a content of 0.3%–1.2% [14]. Starch (49%–70%) is the main source of energy; however, part of the starch, known as resistant starch, cannot be digested by the human body. The resistant starch has functions similar to those of dietary fiber [7]. Dietary fiber (8%–37%) is the non-digestible component. Millet dietary fiber has two major classifications: soluble dietary fiber (SDF) and crude fiber or insoluble dietary fiber (IDF). Examples of SDF are pectins, gums, glucans, and some hemicelluloses. They are partly soluble in water. IDF is insoluble in water and is composed of cellulose, lignin, and most hemicelluloses. Neither SDF nor IDF can be digested or absorbed by the human body. The dietary fiber content of the millets is several times higher than that of the staple cereals such as rice, wheat, and maize (Table 23.2) [3,10,15–22].

Among the millets the highest dietary fiber content has been reported in kodo millet (6.8%–37.8%), finger millet (15%–20%), and foxtail millet (19.11%) [3,10]. The crude fiber content of millets is higher than that of rice and equal to or more than that of wheat and maize. Millets are a good source of soluble fiber (1.5%–3%) in comparison to the staple cereals. Their SDF content is comparable to that of barley (3%–11%) and oats (3%–7%) [21]. Dietary fiber plays several functions in the human body and is believed to impart several health benefits. It is not decomposed in the gut and controls the rate of water absorption in the human gut [23]. It adds bulk to the diet and gives a feeling of fullness that helps to control the appetite.

The dietary fiber of the millets also reduces the GI of the food. The GI is the scale that ranks foods on the basis of increase in blood glucose levels in comparison to the consumption of the same amount of standard food [24]. The maximum GI value for a food is 100, and on the basis of GI, foods can be classified into three categories: high GI (GI value of 70 and above), medium GI (GI value of 56–69), and low GI (GI value of 55 or less) [19]. Dietary fiber forms a gel during digestion, which entraps the carbohydrates and slows down the absorption of glucose, reduces the GI of the

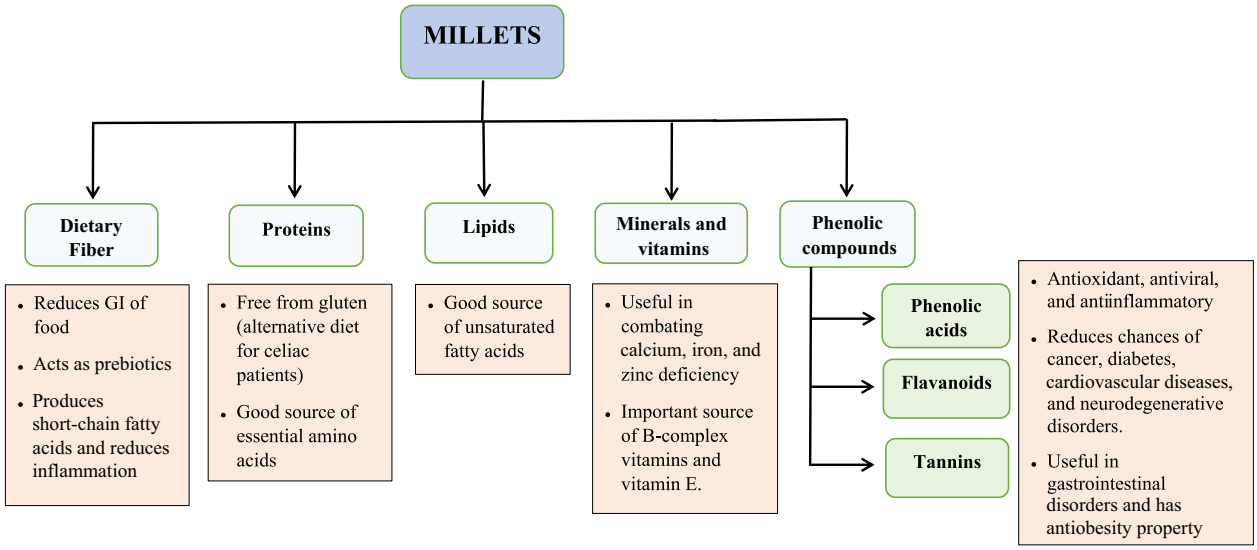


FIGURE 23.1 Major health components in millets and their health benefits.

TABLE 23.2 Comparison of dietary fiber content of millets with staple cereals.

Millet type	Total dietary fiber (%)	Insoluble dietary fiber (%)	Soluble fiber (%)	Glycemic index
Pearl millet	8.0–13.5	5–8	2–3	55
Finger millet	15.0–20.0	3.6–19.7	2.5–3	55–65
Proso millet	8.5–14.2	7–12	1.5–2	50.2–64.7
Foxtail millet	19.11	7–17.80	1.31	33
Barnyard millet	13.6	4.0–14.7	4.2	41.7–50
Kodo millet	6.8–37.8	4–6	2–3	49.5
Little millet	6.4–12.2	5–7	2–3	41.50–61.80
Rice (brown rice)	0.7–6.0	0.6–4.25	0.70–1.0	65–81
Wheat	2.8–12.1	2–10	1–2	44–60
Maize	3.9–13.4	2.32–12.4	0.80–1.24	78.5–86.3

Source: From Kumar A, Tomer V, Kaur A, Kumar V, Gupta K. Millets: a solution to agrarian and nutritional challenges. Agric Food Secur 2018;7(1):31; Dayakar RB, Bhaskarachary K, Arlene Christina GD, Sudha Devi G, Tonapi A. Nutritional and health benefits of millets. ICAR. Indian Institute of Millets Research (IIMR), Hyderabad; 2017. p. 112; Shobana S, Lakshmipriya N, Bai MR, Gayathri R, Ruchi V, Sudha V, et al. Even minimal polishing of an Indian parboiled brown rice variety leads to increased glycemic responses. Asia Pac J Clin Nutr 2017;26(5):829–36; Chapagai MK, Bakar NA, Jalil RA, et al. Glycaemic index values and physicochemical properties of five brown rice varieties cooked by different domestic cooking methods. Funct Foods Health Dis 2016;6(8):506–18; McSweeney M. Proso millet as an ingredient in foods common to North Americans (Doctoral dissertation); 2014; Ugare R, Chimmad B, Naik R, Bharati P, Itagi S. Glycemic index and significance of barnyard millet (*Echinochloa frumentacae*) in type II diabetics. J Food Sci Technol 2014;51 (2):392–5; Urooj A, Rupashri K, Puttaraj S. Glycaemic responses to finger millet based Indian preparations in non-insulin dependent diabetic and healthy subjects. J Food Sci Technol Mysore 2006;43(6):620–5; Dhingra D, Michael M, Rajput H, Patil RT. Dietary fibre in foods: a review. J Food Sci Technol 2012;49(3):255–66; Stevenson L, Phillips F, O'sullivan K, Walton J. Wheat bran: its composition and benefits to health, a European perspective. Int J Food Sci Nutr 2012;63(8):1001–13; Radhika G, Sumathi C, Ganesan A, Sudha V, Henry CJ, Mohan V. Glycaemic index of Indian flatbreads (rotis) prepared using whole wheat flour and 'atta mix'-added whole wheat flour. Br J Nutr 2010;103(11):1642–7.

food, and helps to control diabetes [20]. The GI value for millets ranges from 33 to 65 (Table 23.2) and is much lower than that of rice and corn. Among the millets, foxtail millet has the lowest GI. The GI of millets varies with the variety and the method of processing. In a study conducted by Urooj et al. [19], finger millet was found to have no beneficial effect compared to other cereals in reducing the GI. Dietary fibre also entraps the low-density lipoprotein (LDL) cholesterol, removes it from the body and controls the cholesterol level. It adds bulk to the stool and alleviates constipation

by speeding up the passage of the stool. Dietary fiber is also used as a food by the gut microbiota and is broken down to short-chain fatty acids, which maintain the pH of the intestine [25]. Such fibers are known as prebiotics. The prebiotic components of the millets are shown in Table 23.3.

The major prebiotics in the millets are arabinoxylans, beta-glucans, fructooligosaccharides, inulin, and hemicelluloses. They inhibit the growth of pathogens and remove carcinogens from the body. They also enhance the rate of nutrient absorption and immunity [37]. Being a food source for probiotics, they stimulate the growth of probiotic microorganisms and increase the number of healthy microbiota in the gut. Probiotics are live microorganisms of health significance that, when administered in adequate amounts, confer health benefits on the host [38]. Prebiotics are selective in their action and support the growth of selective microorganisms. In an in vivo humanized rat study, the long-chain arabinoxylans were found to stimulate the growth of bifidobacteria by 60-fold [39]. Fructooligosaccharides results in the largest increase in the population of *Lactobacillus* spp. Fructooligosaccharides at a dosage of 5 g/day have also been reported to enhance the number of *Bifidobacteria* by 1 log cycle [40]. Prebiotics also protect the prebiotics from bile acid stress [41]. Pearl millet fibers have been found to have a prebiotic effect in the growth of *Lactobacillus rhamnosus* and *Bifidobacterium bifidum* [42]. A linear increase in the growth of *L. acidophilus* was observed by Mridula et al. [30] with a linear increase in the quantity of pearl millet flour. Inulin extracted from pearl millet has been found to have a positive effect on the growth of *Lactobacillus casei* [43]. An increase in *L. rhamnosus* and *Streptococcus thermophilus* on the addition of pearl millet flour has been reported by Stefano et al. [44]. A high number of probiotics (*Lactobacillus* spp.) in comparison to control (milk) was reported by Kumar [45] in a finger millet and oat based synbiotic drink. A high count of *Lactobacillus helvecticus* and *S. thermophilus* was found in a beverage prepared by using finger millet malt and milk in comparison to the probiotic drink prepared by using milk [46]. Kodo millet bran residue hydrolysate had a predominant effect on the growth of *Lactobacillus delbrueckii* [47].

Proteins

The average protein content of the millets is 10%−11% and is comparable to the major cereals [3]. Grain proteins are classified in four categories on the basis of solubility: (1) water-soluble albumins, (2) dilute salt solution−soluble globulins, (3) alcohol-soluble prolamins, and (4) dilute alkali- or acid-soluble glutelins. The millet proteins have three major fractions: albumin + globulin fraction, prolamin + prolamin-like fraction and true glutelin + glutelin-like fraction. The glutelin fraction has the highest (45%−55%) share in millet proteins, followed by prolamins (15%−30%) and albumin and globulin (8.5%−16.26%). The exceptions are foxtail millet and finger millet, which have a higher prolamin content: 60% and 36%, respectively, of total protein [4,17]. The nutritional and health properties of the millet proteins depend on their essential amino acid composition and protein digestibility. The amino acid composition of the millets is shown in Table 23.4 [26,48].

Lysine is the most limiting amino acid in the millets, as in all other cereals. The lysine content of millets is less than that of whole rice but is comparable to or more than that of wheat (Table 23.4) except foxtail millet and little millet. The contents of other essential amino acids, such as cysteine, leucine, isoleucine, methionine, valine, threonine, and tryptophan, are higher in millet in comparison to the staple cereals. The essential amino acids constitute 44.7% of the total amino acids in finger millet [49]. In foxtail millet, lysine is the only limiting amino acid [50]. According to Kalinova [33], the most limiting amino acid in proso millet is lysine, but the content is still more than that in wheat.

TABLE 23.3 Prebiotic components of millets and their health benefits.

Millet type	Prebiotic components	References
Pearl millet	Arabinoxylans, arabinogalactan, beta-glucan, inulin, fructooligosaccharides	[26−30]
Finger millet	Arabinoxylans, beta-glucans, fructans, inulin, xylooligosaccharides	[31,32]
Proso millet	Arabinoxylans, arabinogalactan, beta-glucan	[33]
Foxtail millet	Arabinoxylans (pentosans), beta-glucan	[34,35]
Barnyard millet	Arabinoxylans, beta-glucan, hemicelluloses	[4,34]
Kodo millet	Arabinoxylans, beta-glucan, inulin, hemicelluloses	[34−36]
Little millet	Hemicelluloses	[4]

TABLE 23.4 Essential amino acid composition of millets (g/100 g protein).

Millet	Cysteine	Isoleusine	Leusine	Lysine	Methionine	Phenylalanine	Threonine	Tryptophan	Valine
Pearl millet	1.5–1.8	4.1–4.4	9.6–10.7	3.1–3.4	1.1–2.5	4.4–4.8	3.1–4.0	1.4–2.0	4.9–5.5
Finger millet	2.2	4.4	9.5	2.9	3.1	5.2	3.8	1.6	6.6
Foxtail millet	1.6	7.6	16.7	2.2	2.8	6.7	2.7	1.0	6.9
Proso millet	1.0	8.1	12.2	3.0	2.6	4.9	3.2	0.8	6.5
Barnyard millet	2.8	8.8	16.6	2.9	1.9	2.2	2.2	1.0	6.4
Kodo millet	2.6	3.0	6.7	3.0	1.5	6.0	3.2	0.8	6.6
Little millet	1.85	4.14	8.08	1.86–2.48	2.21	6.14	4.24	0.14–0.32	5.31
Rice	1.4–1.8	3.8–4.1	8.2	3.5–3.8	2.3–2.4	5.2–5.3	3.5–4.1	1.2–1.4	5.5–5.8
Wheat	2.0–2.2	3.3	6.7–6.8	2.7–2.8	1.5–1.7	4.5–5.2	2.8	1.3–1.5	4.4–4.9
Maize	1.6–1.8	3.6–3.7	12.3–12.5	2.7–2.8	1.9–2.1	4.9	3.6–3.8	0.7	4.9–5.1

Source: From Dias-Martins AM, Pessanha KL, Pacheco S, Rodrigues JA, Carvalho CW. Potential use of pearl millet (*Pennisetum glaucum* (L.) R. Br. in Brazil: food security, processing, health benefits and nutritional products. Food Res Int 2018;109:175–86; Kaur KD, Jha A, Sabikhi L, Singh AK. Significance of coarse cereals in health and nutrition: a review. J Food Sci Technol 2014;51(8):1429–41.

The other marginal amino acid in proso millet is threonine. The essential amino acid index of proso millet is higher than that of wheat [51]. The finger millet proteins are better balanced than those in common millet and foxtail millet in terms of essential amino acid content [52].

Another major factor that determines the quality of protein is its digestibility, which can be defined as the level of release and the availability of the amino acids for absorption in the small intestine. Many in vitro and in vivo methods are available to determine protein digestibility. To determine the in vitro protein digestibility (IVPD), the enzyme pepsin or other peptidases are used to digest the protein, while the in vivo protein digestibility is determined by using animal models. The various in vivo methods to determine protein digestibility are biological value (BV), chemical score, net protein utilization (NPU), protein efficiency ratio (PER), true digestibility, protein digestibility−corrected amino acid score, and digestible indispensable amino acid score.

The IVPD has been reported to be in the range 58.3%−58.9% for pearl millet [53] and 47.29%−88.1% for finger millet [11,54]. In the pearl millet variety *Dhanshakti,* an IVPD of 95.36 ± 6.26 has been reported by Anitha et al. [54]. The IVPD value of foxtail millet is 77.3 [52], that for proso millet is 71.3% [33], and that for barnyard millet is in the range 74.9%−84.7% [55]. Data on the IVPD of kodo millet and little millet are scarce. However, data on the in vivo protein digestibility of most of millets are available. The PER for pearl millet flour is 1.74, and the BV is 65.6% [56]. The PER for finger millet is 1.40, and the NPU is 35% [11]. Proso millet has a PER of 1.2 and a BV of 42%−56%. The BV values for barnyard millet, kodo millet, and little millet are 54.79%, 56.51%, and 53.0%, respectively, and the NPU values are 52.20%, 54.20%, and 51.53%, respectively [57].

Millet proteins are free from gluten and hence can be a good alternative to wheat in the diets of celiac patients [3,4].

Lipids

Millets as a whole are not good source of lipids and their lipid content varies from 1.3% to 5%. But millets are a good source of unsaturated fatty acids. Of the total lipids present in finger millet, 74.4% are unsaturated fatty acids [11]. Proso millet contains 86%−89% of total fats as unsaturated fatty acids. Of these unsaturated fatty acids, 42% are polyunsaturated fatty acids (PUFAs) [33]. The major unsaturated fatty acids in millets are linoleic acid and oleic acid. Small quantities of linolenic acid and palmitoleic acid are also present. The unsaturated fatty acid composition of millets is shown in Fig. 23.2 [33,58−61].

The consumption of monounsaturated fatty acids (MUFAs) and PUFAs has been reported to reduce LDL cholesterol levels and to decrease the risk of developing cardiovascular diseases. MUFAs and linoleic acid also increase the level of high-density lipoprotein (HDL) cholesterol, which aids in removing triacylglycerols from the bloodstream. The presence of PUFAs may also influence cognitive function and behavior [62].

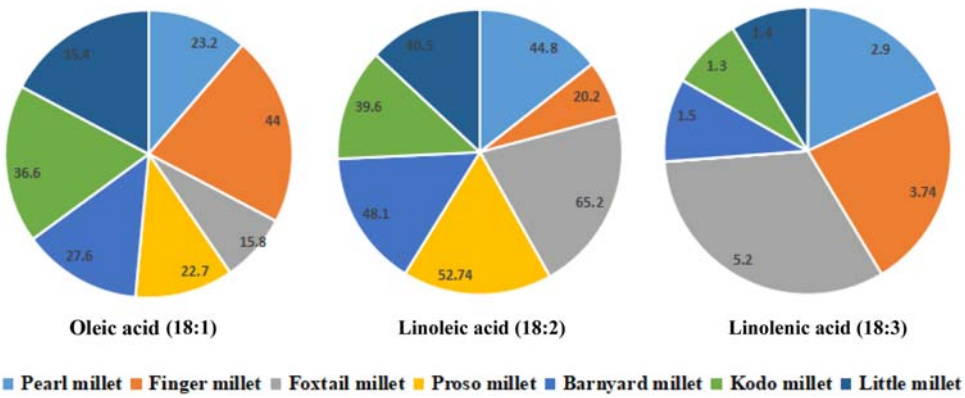


FIGURE 23.2 Unsaturated fatty acid composition of millets (% of total fat). *From Kalinová J. Nutritionally important components of proso millet (*Panicum miliaceum *L.). Food 2007;1:91−100; Sawaya WN, Khalil JK, Safi WJ. Nutritional quality of pearl millet flour and bread. Plant Foods Hum Nutr 1984;34(2):117−25; Glew RS, Chuang LT, Roberts JL, Glew RH. Amino acid, fatty acid and mineral content of black finger millet (*Eleusine coracana*) cultivated on the Jos Plateau of Nigeria. Food 2008;2(2):115−8; Kim SM, Zhang QY, Yu XZ, Yoon ST, Ji SJ, Kim JB. Fatty acids composition of foxtail millet (*Setaria italica *BEAUVOIS) seeds collected in South Korea. Korean J Med Crop Sci 2010;18(6):405−8; Sridhar R, Lakshminarayana G. Lipid class contents and fatty acid composition of small millets: little (*Panicum sumatrense*), kodo (*Paspalum scrobiculatum*), and barnyard (*Echinochloa colona*). J Agric Food Chem 1992;40(11):2131−4.*

Minerals and vitamins

Millets are a rich source of many minerals and vitamins. The major minerals and vitamins present in the millets are listed in Table 23.5 [3,10,48,63–65].

Millets can play a crucial role in combating the existing calcium, iron, and zinc deficiencies in India. Among the millets, finger millet is the highest source of calcium. Its calcium content varies from 162 to 487 mg/100 g [11]. The consumption of 100 g of finger millet provides about half of the recommended dietary allowance (RDA) for calcium [66]. The phosphorus content of millets range between 200 and 339 mg/100 g. This is about 50% of the phosphorus content recommended by the Indian Council of Medical Research [67]. The highest phosphorus content is found in pearl millet, while lowest is found in proso millet. The zinc content is highest in foxtail millet (60.6 mg) and barnyard millet (55–60 mg). The zinc content of finger millet, kodo millet, and little millet is also higher than the RDA value of 12 mg/day. The highest iron content, 15–19 mg/100 g, is found in barnyard millet. A daily intake of 100 g of barnyard millet can provide 100% of the RDA for iron. All other millets are also good sources of iron, and 100 g of these millets provide about 10%–25% of the RDA for iron. Substantial amounts of other minerals, such as magnesium, potassium, sodium, and sulfur, and traces of copper, manganese, and selenium are also present.

Minerals perform a wide array of functions in the body, such as building and health maintenance of bones, cell energy production, oxygen transportation, signaling and proper working of the neuron system, maintenance of heart health, metabolism and synthesis of proteins and fats, and enhancing immunity [68]. Calcium and phosphorus are the main components of bones and teeth and play an important role in bone and tooth health. Regular intake of the recommended amount of calcium can prevent the osteoporosis. Calcium also plays an important role in muscle function. Low calcium intake can also result in lactase deficiency and can lead to lactose intolerance. Therefore a proper intake of calcium is crucial for a healthy life [69]. In addition to bone formation, phosphorus is involved in many important reactions, such as formation of cell membrane and nucleic acids, production of ATPs, cell signaling, and urinary buffering [70]. Most of the phosphorus in plant-based sources is present in the phytate form; hence it is advised to germinate or ferment millet to increase the availability of phosphorus. The iron content of millets can help to eradicate the prevailing iron deficiency anemia in India. Iron is also essential for a number of metabolic processes, such as oxygen transportation, synthesis of DNA and transportation of electrons [71]. Zinc intake enhances immunity and supports growth. It plays an important role in the synthesis of DNA and controls the enzymes that renew the cells in the body. It is also used in the treatment of pneumonia and enhances wound healing [72].

The major vitamins that are present in the millets are the B-complex vitamins and vitamin E; 100 g of millet provides about 10%–20% of the daily requirement of B-complex vitamins. Millets also contains carotenoids, but the quantity of beta-carotene is very low. Among the millets the highest contents of thiamine, riboflavin, niacin, and total carotenoids are found in proso millet, and the highest tocopherol content is found in finger millet (Table 23.5). Vitamins, especially the water-soluble vitamins, play an important role in energy metabolism, while the carotenoids and vitamin E act as antioxidants and provides immunity to the body and prevent several diseases. The derivative of thiamine, that is, thiamine pyrophosphate, serves as a coenzyme in the energy metabolism. Thiamine also aids in the synthesis of hemoglobin and red blood cells. A deficiency in thiamine results in impaired oxidative metabolism and decreased adenosine triphosphate production. A decrease in energy production leads to impaired brain functioning, oxidative stress, and lactic acidosis [73]. The various diseases caused by thiamine deficiency are Korsakoff syndrome, optic neuropathy, and beri-beri [74]. Riboflavin is the precursor of coenzymes flavin mononucleotide and flavin adenine dinucleotide. These coenzymes play an important role in energy metabolism. A deficiency in riboflavin can also affect the beta-oxidation of fatty acids. A deficiency in riboflavin also results in abnormal fetal development and increases the risk of cancer [75]. Niacin has two coenzymatic forms: nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate. These coenzymes are crucial for energy production. Niacin also performs other functions, such as cell signaling, gene expression, cell cycle progression, and DNA repair [76]. Millets are also good source of folic acid; 100 g of millet provide 10%–20% of the recommended dosage of folates to adults, that is, 200 μg/day. Folate plays an important role in keeping the blood healthy by helping red blood cells to form and grow. Folic acid also protects unborn children against serious neural tube defects [77]. The major carotenoids present in the millets are zeaxanthin and lutein. These carotenoids prevent vision disorders and have anticancerous properties [65,78]. In a comparative study on the tocopherol content of millets, the highest content of total tocopherols was found in brown finger millet (4 mg/100 g) followed by white finger millet and proso millet (~3.6 mg/100 g). Foxtail millet and little millet were reported to contain low quantities of tocopherols: 1.3 mg/100 g [65]. Vitamin E is a strong antioxidant and helps in the prevention of cancer, aging, arthritis, and cataracts. Vitamin E also reduces the production of prostaglandin and thromboxane, which prevent platelet hyperaggregation and hence control atherosclerosis [79].

TABLE 23.5 Micronutrient composition of millets.

Millet type	Calcium (mg/100 g)	Phosphorus (mg/100 g)	Zinc (mg/100 g)	Iron (mg/100 g)	Thiamine (mg/100 g)	Riboflavin (mg/100 g)	Niacin (mg/100 g)	Folic acid (μg/100 g)	Total carotenoids (μg/100 g)	Vitamin E (mg/100 g)
Pearl millet	27–43	339	3.1	6–17	0.3–0.4	0.09–4.0	1–3	45.5	–	1.0
Finger millet	335–352	250	32–41	4–6	0.3–0.5	0.02–0.19	0.8–2.0	18.3	45–199	4.1
Foxtail millet	20–42	300	60.6	3–5	0.6	0.05–0.16	0.5–3.2	15	173	1.2
Proso millet	7–13.5	200–206	2.36–3.7	2.2–4.8	0.41	0.28	4.54	–	366	3.6
Barnyard millet	12–25	280	55–60	15–19	0.33	0.1	4.2	–	–	–
Kodo millet	27–37	300	30–35	1.8–4.0	0.15	0.09	0.09–1.16	23.1	–	0.53
Little millet	15–17	220	32.20–35.1	1.2–1.7	0.28	0.05–0.09	1.29–3.2	9.0	78	1.3

Source From Kumar A, Tomer V, Kaur A, Kumar V, Gupta K. Millets: a solution to agrarian and nutritional challenges. Agric Food Secur 2018;7(1):31; Dayakar RB, Bhaskarachary K, Arlene Christina GD, Sudha Devi G, Tonapi A. Nutritional and health beneftis of millets. ICAR. Indian Institute of Millets Research (IIMR), Hyderabad; 2017. p. 112; Kaur KD, Jha A, Sabikhi L, Singh AK. Significance of coarse cereals in health and nutrition: a review. J Food Sci Technol 2014;51(8):1429–41; Deshpande SS, Mohapatra D, Tripathi MK, Sadvatha RH. Kodo millet: nutritional value and utilization in Indian foods. J Grain Process Storage 2015;2(2):16–23; Nambiar VS, Dhaduk JJ, Sareen N, Shahu T, Desai R. Potential functional implications of pearl millet (*Pennisetum glaucum*) in health and disease. J Appl Pharm Sci 2011;1(10):62; Asharani VT, Jayadeep A, Malleshi NG. Natural antioxidants in edible flours of selected small millets. Int J Food Prop 2010;13(1):41–50.

Phenolic compounds

Phenolic compounds are a large group of compounds that are characterized by the presence of an aromatic ring consisting of one or more hydroxyl groups as the fundamental component. Phenolic compounds can be broadly classified as phenolic acids, flavonoids, and tannins. The phenol content of millets as a whole is more than that of the staple cereals. However, the content of phenol in millets varies according to the type of millet, variety, fraction of the millet, and agroclimatic conditions [80]. A wide variation in phenolic compound concentration and antioxidant activity has been reported for the soluble and bound fractions of millets [81,82]. The soluble phenolic compounds are extractable in aqueous media and are present mostly in the outer layers of the grain. The bound phenolics are present within the cell wall and are found in the residue left after the extraction of the soluble fractions [83]. The highest contribution to the total phenol content is in the form of the insoluble bound phenolics attached to the cell wall. Phenolic acids are further subclassified as benzoic acid derivatives, cinnamic acid derivatives, hydroxyphenylacetic acids, and hydroxyphenylpropanoic acids. The concentrations of various phenolic compounds present in the millets are shown in Table 23.6 [3,7,11,80–85].

Among the millets, the highest content of phenolic compounds is found in finger millet. Hydroxycinnamic acids are the major phenolic acids found in proso millet, finger millet, and foxtail millet [86]. However, in a study conducted by Chandrasekara and Shahidi [82] the highest amounts of hydroxybenzoic acid derivatives (62.2 μg/g) were reported in the soluble fraction of finger millet. In the same study, the highest amount of cinnamic acid derivatives were reported in the soluble fractions of little millet (173 μg/g) and foxtail millet (171 μg/g).

The phenolic compounds have antioxidant, antiinflammatory, and antiviral effects along with activity against mutations, tumors, and platelet aggregation [7]. The anticataractogenic, anticancerous, and blood pressure–reducing properties of the millets have been attributed to their phenolics [32,87]. The polyphenols of finger millet have been reported to have inhibitory effects on cataract formation [88]. Phenolic extracts from finger millet seed coat partially inhibit the activity of pancreatic amylase and alpha-glucosidase in the carbohydrate metabolism, and slow down glucose absorption, and help in the management of postprandial hyperglycemia [80]. They are also beneficial in treating stomach ulcers. Chethan [89] has reported that phenolics extracted from finger millet inhibit aldolase reductase and snake venom phospholipases. Gallic acid exhibit antioxidant, antiinflammatory, and antineoplastic properties and have therapeutic activities in gastrointestinal, neuropsychological, metabolic, and cardiovascular disorders [90]. p-Hydroxybenzoic acid has direct action on the hemoglobin molecule and is used in the management of sickle-cell disease. It also prevents acetic acid–induced edema. Cholorogenic acid plays an important role in the regulation of glucose and lipid metabolism and has antidiabetic, anticarcinogenic, antiinflammatory, and antiobesity properties [91]. Ferulic acid has strong antioxidant activities, syringic acid has protective effect on liver health, and caffeic acid selectively blocks the biosynthesis of leukotrienes. Flavonoids are more prevalent in free form. The highest contents of flavonoids and tannins are found in the brown varieties of finger millet [11]. The major flavonoids in the millets are catechin, myricetin, dizein, luteolin, quercetin, apigenin, naringenin, and kaempferol (Table 23.7) [81,82]. Flavonoids and tannins have strong antioxidant activities, and their regular consumption reduces the incidences of cancer, diabetes, cardiovascular diseases, and neurodegenerative disorders.

Catechin and epicatechin have antioxidant properties and have been reported to be effective in the prevention of various cancers, cardiovascular disorders, and neurodegenerative diseases [92]. Ghayur et al. [93] reported calcium channel–inhibiting and relaxant effects of catechins on smooth muscles, suggesting their efficacy against gastrointestinal, respiratory, and vascular disorders. Myricetin is a strong antioxidant, but some studies have also shown the prooxidative properties of myricetin [94]. Asif and Khodadadi [95] have reported its anticarcinogenic and antimutagenic properties. Luteolin has antiinflammatory and anticarcinogenic activity that can be attributed to its antioxidant and free radical–scavenging properties. Luteolin prevents the growth and proliferation of tumor cells by inhibiting the cell cycle [96]. Qurecetin has anticarcinogenic, antiinflammatory, and antiatherosclerotic properties, owing to its potent antioxidant effect [95]. Apigenin has antioxidant, antiinflammatory, antibacterial, and antiviral properties. It also possesses efficacy against various cardiovascular disorders. Kaempferol and some of its glycosides have been reported to possess antioxidant, antimicrobial, antitumor, cardioprotective, neuroprotective, antiosteoporotic, and antiulcer properties and to have inhibitory action on HIV protease [95,97].

The role of millets in the management of various diseases

Diabetes

Diabetes mellitus is a metabolic disorder characterized by increased blood glucose levels due to abnormalities in insulin secretion or action [98]. This disease does not have a permanent cure, but it can be managed by consuming a diet that

TABLE 23.6 Major phenolic compounds in different millets.

Millet type	Total phenols	Benzoic acid derivatives (μg/g)						Cinnamic acid derivatives (μg/g)					Total flavonoids	Tannins
		Gallic acid	p-Hydroxybenzoic acid	Vanillic acid	Methyl vanillate	Protocatechuic acid	Syringic acid	Caffeic acid	Chlorogenic acid	Ferulic acid	Sinapic acid	p-Coumaric acid		
Pearl millet	268.43[W] mg GAE/100 g	–	22	16.3[W], 7.08	19.8	11.8	17.3	21.3[W]	–	718.5	–	268.9[W], 53.5	9.60[W] mg CE/100 g	0–2800[W] mg CE/100 g
Finger millet	190–3370[W] mg CE/100 g	–	8.9[W], 1.7	15.2[W]	–	23.1[W], 48.2	7.7[W]	16.6[W], 11	–	396.3	–	36	2.5–12.5[W] mg CE/100 g	40–3740[W] mg CE/100 g
Foxtail millet	72.70[W] mg FAE/100 g	6.57	8.27	44.41	–	10.2	93.6[W]	14.76	25.99	225.09	15.12	45.41	87.63[W] mg CE/100 g	39.95[W] mg CE/100 g
Proso millet	295[W], 74.43 mg FAE/100 g	9.37[W], 4.19	9.11[W], 34.18	84.71	–	69.7	11.27[W]	15.97	8.71	68.63[W], 165.70	9.32[W], 2.66	12.43	51.62[W] mg CE/100 g, 183 mg RU/100 g	84.48[W], 82.49 mg CE/100 g
Barnyard millet	80.14[W] mg FAE/100 g	4.25	10.48	119.03	–	–	–	7.69	19.61	211.63	31.90	27.37	58.42[W] mg CE/100 g	76.09[W] mg CE/100 g
Kodo millet	54.54[w] mg GAE/100 g		10.5	40.1	–	39.7	–	276	–	1944	–	767	52.95[w] mg RU/g	1.60[w] mg CE/100 g
Little millet	23.95–24.12[w] μmol FAE/g	1.7–8.28	2.88–11.88	15.59–39.07	–	–	–	26.96–83.04	17.8–51.45	128.25–146.64	15.5–61.99	39.87–174.7	11.33–15.09[W] μmol CE/g	89.12–107.56[W] mg CE/100 g

CE, Catechin equivalent; *FAE*, ferulic acid equivalent; *GAE*, gallic acid equivalent; *RU*, rutin equivalent; *W*, whole grain.

Source: From Kumar A, Tomer V, Kaur A, Kumar V, Gupta K. Millets: a solution to agrarian and nutritional challenges. Agric Food Secur 2018;7(1):31; Devi PB, Vijayabharathi R, Sathyabama S, Malleshi NG, Priyadarisini VB. Health benefits of finger millet (*Eleusine coracana* L.) polyphenols and dietary fiber: a review. J Food Sci Technol 2014;51(6):1021–40; Singh P, Raghuvanshi RS. Finger millet for food and nutritional security. Afr J Food Sci 2012;6(4):77–84; Pradeep PM, Sreerama YN. Impact of processing on the phenolic profiles of small millets: evaluation of their antioxidant and enzyme inhibitory properties associated with hyperglycemia. Food Chem 2015;169:455–63; Pradeep PM, Sreerama YN. Phenolic antioxidants of foxtail and little millet cultivars and their inhibitory effects on α-amylase and α-glucosidase activities. Food Chem 2018;247:46–55; Chandrasekara A, Shahidi F. Determination of antioxidant activity in free and hydrolyzed fractions of millet grains and characterization of their phenolic profiles by HPLC-DAD-ESI-MSn. J Funct Foods 2011;3(3):144–58; Kalam Azad MO, Jeong DI, Adnan M, et al. Effect of different processing methods on the accumulation of the phenolic compounds and antioxidant profile of broomcorn millet (*Panicum miliaceum* L.) flour. Foods 2019;8(7):230; Kumar H, Kaur C. A comprehensive evaluation of total phenolics, flavonoids content and in-vitro antioxidant capacity of selected 18 cereal crops. Int J Pure Appl Biosci 2017;5(2):569–74; Badau MH, Nkama I, Ajalla CO. Physico-chemical characteristics of pearl millet cultivars grown in northern Nigeria. Int J Food Prop 2002;5(1):37–47.

TABLE 23.7 Major flavonoids in different millets.

Millet type	Catechin (μg/g)	Epicatechin (μg/g)	Myricetin (μg/g)	Luteolin (μg/g)	Quercetin (μg/g)	Apigenin (μg/g)	Kaempferol (μg/g)
Flavonoids in soluble bound fraction							
Pearl millet	–	–	–	–	–	4.13	–
Finger millet	1611	134	11.7	–	–	–	–
Foxtail millet	12.75	–	4.57	37.28	20.02	59.29	29.33
Proso millet	–	–	–	–	–	1.9	–
Kodo millet	–	–	–	46.2	–	1.52	–
Little millet	5.84	–	29.50	54.97	17.03	10.64	86.34
Flavonoids in insoluble bound fraction							
Pearl millet	–	–	–	–	–	–	–
Finger millet	–	–	–	–	1.73	–	–
Foxtail millet	18.76	–	7.14	20.32	42.94	50.85	17.66
Proso millet	–	–	–	–	–	–	–
Kodo millet	–	–	–	–	–	–	8.06
Little millet	10.74	–	4.25	25.32	52.23	8.19	69.81

Source: From Pradeep PM, Sreerama YN. Phenolic antioxidants of foxtail and little millet cultivars and their inhibitory effects on α-amylase and α-glucosidase activities. Food Chem 2018;247:46–55; Chandrasekara A, Shahidi F. Determination of antioxidant activity in free and hydrolyzed fractions of millet grains and characterization of their phenolic profiles by HPLC-DAD-ESI-MSn. J Funct Foods 2011;3(3):144–58.

is rich in dietary fiber and polyphenols. Millets are naturally rich in dietary fiber and polyphenols, have a low GI, and exhibit antidiabetic properties. The antidiabetic properties of the millets have been established in animal and human studies. In a study conducted by Singh et al. [99], 60 patients with type 2 diabetes mellitus were given a millet-based functional food intervention diet containing 60% millet, 20% soybeans, 10% brown rice, 8% peanuts, and 2% flax seeds, and its effect on fasting and postprandial blood glucose levels was studied. The authors reported that administration of the intervention diet for 12 weeks resulted in a significant decline in fasting and 2 hours postprandial blood glucose. The millet-based diet also reduced the level of total cholesterol and very low-density lipoprotein (VLDL) cholesterol and triglycerides. Okoyomoh et al. [100] reported a 45% reduction in the blood glucose level in streptozotocin-induced diabetic rats after feeding them on a diet containing 40% seed coat matter (SCM) of finger millet. An improvement in the body weight of the experimental group of diabetic rats fed with 40% SCM was also observed. In a similar study, Shobana et al. [101] reported a decrease in fasting blood glucose levels in streptozotocin-induced diabetic rats when they were given a diet containing 20% SCM of finger millet for 6 weeks. Sireesha et al. [102] evaluated the antidiabetic potential of different doses of aqueous extract of seeds of *S. italica* (foxtail millet) in streptozotocin-induced diabetic rats. The study revealed that after 6 hours of the administration of a dose of 300 mg/kg body weight resulted in a 70% decrease in blood glucose in diabetic rats. Administration of a dose of 300 mg/kg body weight per day for 30 days decreased the levels of HbA1c in diabetic rats and lowered fasting glucose levels and improved glycemic control. Kumari and Sumathi [103] studied the effect of diets containing finger millet on hyperglycemia in six subjects with type 2 diabetes mellitus. The subjects in the study were fed diets having a carbohydrate load equivalent to 75 g, and the glycemic response of the diets was compared with that of 75 g of glucose. The diets containing finger millet resulted in a significant decrease in blood glucose levels. The authors attributed the high fiber content and antinutritional factors of the millet for the decrease in blood glucose level, as they decrease the rate of digestion and absorption of carbohydrates.

Cancer

Shi et al. [104] studied the effect of bound polyphenols of the inner shell (BPIS) of foxtail millet bran on human colorectal cancer cell line HCT-116. The study concluded that foxtail bran extracted BPIS could induce apoptosis in human colorectal cancer HCT-116 cells. The anti−colon cancer activities of foxtail millet bran−derived BPIS was attributed to the prooxidant activity in the HCT-116 cells, which resulted in the activation of mitochondria-mediated intrinsic pathways and the blockage of the nuclear factor-kappa B (NF-κB) signaling pathway of the downstream of reactive oxygen species (ROS). Zhang et al. [105] studied the antiproliferative activity of three proso millet varieties (Gumi 20, Mizao 52, and Mi2504-6) against MDA human breast cancer and HepG2 human liver cancer cells. Extracts from all three varieties showed significant antiproliferative activity in a dose-dependent manner. The greatest antiproliferative activity was observed in the free extracts of Mizao 52 (EC50 value: 46.47 mg/mL) and Gumi 20 (EC50 value: 51.37 mg/mL) against MDA human breast cancer cells and HepG2 human liver cancer, respectively. Shan et al. [106] extracted and purified a novel protein called foxtail millet bran protein (FMBP). It was found in the study that FMBP was homologous to peroxidase and had the ability to suppress the xenografted tumor growth in nude mice. The protein was reported to cause induction of G_1 phase arrest and initiation of caspase-dependent apoptosis of cancer cells in the colon, which was attributed to its targeted ability against colon cancer. Chandrasekara and Shahidi [82] studied the anticancerous properties of phenolic extracts in seven millet varieties—kodo millet, finger millet (ragi), finger millet (local), proso millet, foxtail millet, little millet, and pearl millet—for their activities against proliferation of HT-29 cells. The authors reported a 28%−100% inhibition of cell proliferation after four days of administration of millet extracts, showing the effectiveness of millet phenolics against cancer cells.

Cardiovascular diseases

Hou et al. [107] studied the antihypertensive potential of whole foxtail millet diets in 45 human subjects with untreated mild hypertension. The regular diet of the participants was replaced with 50 g of millet daily for 12 weeks. The study revealed a significant reduction in the systolic and diastolic blood pressure of participants after 12 weeks. Sireesha et al. [102] demonstrated the hypolipidemic property of the aqueous extracts of the seeds of foxtail millet. The treatment of diabetic rats with 300 mg/kg of body weight per day with aqueous extract of seeds decreased triglyceride, LDL cholesterol, and VLDL cholesterol levels and increased HDL cholesterol levels. The hypolipidemic action of seed aqueous extract may be attributed to alkaloids or glycosides present in the seeds. Lee et al. [108] studied the beneficial effects of consumption of whole grains of millets (foxtail millet and proso millet) on the lipid profiles of hyperlipidemic

rats. In this study, different groups of hyperlipidemic Sprague-Dawley rats were fed diets containing white rice, sorghum, foxtail millet, and proso millet for five weeks. The serum triglyceride level was reported to decrease significantly with foxtail millet and proso millet, which may be effective in maintaining cardiovascular health. Choi et al. [109] studied the effect of consumption of Korean foxtail millet protein (FMP) on the plasma lipid profiles and levels of adiponectin in KK-A^y mice having type 2 diabetes genetically. The mice that were fed a simple FMP diet or an FMP diet rich in fat and sugar for three weeks showed increased levels of HDL cholesterol and adiponectin in comparison to the group that was fed a normal casein diet. Increases in adiponectin concentrations improved the insulin sensitivity and cholesterol metabolism; hence FMP consumption may have beneficial effects in type 2 diabetes and cardiovascular diseases.

Ulcer

In a study conducted by Tovey et al. [110] protection against mucosal ulceration was observed in female Wistar albino rats on feeding with finger millet incorporated stock diet for 2 weeks.

Antimicrobial properties

Bisht et al. [111] extracted proteins from the seeds of finger millet (PRM I and PRM II), barnyard millet, and porso millet and evaluated their antibacterial activity against certain pathogens: *Bacillus subtilis* (MTCC 441), *Pseudomonas aeruginosa* (MTCC 424), *Escherichia coli* (MTCC 733), and *Salmonella enterica* (MTCC 739). The study observed that the seed extract of PRM I variety of finger millet had the highest efficacy against *P. aeruginosa* and *S. enterica* among the studied millet varieties with a zone of inhibition of 22.6 $\pm$ 1.18 and 22.3 $\pm$ 0.98, respectively. Singh et al. [112] studied the antimicrobial activity of phenolic acids isolated from finger millet and pearl millet using the Kirby Bauer well diffusion technique. The study revealed the inhibitory effects of the phenolic extracts against *E. coli*, *Streptococcus aureus*, *Proteus mirabilis*, *P. aeruginosa*, *Serratia marcescens*, *Klebsiella pneumoniae*, *Shigella dysenteriae*, *Enterococcus* sp., and *Salmonella* sp. Banerjee et al. [113] studied the antibacterial activity of polyphenolics of finger millet against *E. coli*, *Bacillus cereus*, *Staphylococcus aureus*, *Listeria monocytogenes*, *Streptococcus pyogenes*, *Proteus mirabilis*, *P. aeruginosa*, *Serratia marcescens*, *Klebsiella pneumonia*, and *Yersinia enterocolitica*. Quercetin, a flavonoid compound in finger millet, showed significant inhibition of these pathogens. Vishwanath et al. [88] reported significant inhibitory activity of the acidic methanol (1% HCl in 100 mL methanol) extract of seed coat of finger millet against *B. cereus* and *Aspergillus flavus*.

Inflammation and wound healing

In a study conducted by Shi et al. [114] the antiinflammatory property of foxtail millet bran−derived bound polyphenols of inner shell (BPIS) was studied in LPS-induced HT-29 cells. The concentration of proinflammatory cytokines IL-1β, IL-6, and IL-8 decreased while that of antiinflammatory cytokine IL-10 increased with BPIS. This antiinflammatory action of BPIS may be attributed to the ROS/miR-149/Akt/NF-κB signaling pathway, where BPIS-induced ROS enhances the expression of miR-149, targeting Akt expression blocking the nuclear translocation of NF-κB. Hegde et al. [115] investigated the effect of finger millet and kodo millet on dermal wound healing of rats. An aqueous paste of 300 mg of finger millet or kodo millet flour was applied topically once daily on a 4 cm^2 wound on the back of the rat for 16 days. The granulation tissue on 4th, 8th, and 12th days was assessed, and significant increases in protein and collagen levels with a reduction in lipid peroxides were observed. Rats treated with finger millet and kodo millet showed an 88%−90% rate of contraction compared to 75% in the control group. The study reported that the rats treated with finger millet and kodo millet showed accelerated wound healing within 13 and 14 days, respectively, compared to 16 days in untreated rats. Rajasekaran et al. [116] conducted a study on the wound-healing property of finger millet in alloxan-induced diabetic rats. The rats were fed 50 g of finger millet per 100 g of feed, and the diet containing finger millet was started 2 weeks prior to induction of diabetes. The control groups (diabetic and nondiabetic) were given a nutritious balanced diet. The rats were then given skin wounds, and various parameters, such as rate of wound contraction, collagen content, skin antioxidant status, and lipid peroxide concentration, were monitored during the study. Diabetic rats that were fed finger millet showed an increased antioxidant profile of skin and enhanced speed of dermal wound healing.

Conclusion

Millets are rich in nutrients and provide all the essential nutrients, such as essential amino acids, essential fatty acids, minerals, and vitamins. Detailed studies of the total phenolic compounds that is, phenolic acids, flavonoids, and tannins, are available. Many studies have been also reported in the literature that demonstrate the health properties of the millets. However, large variations in the data on nutrients and phytochemicals reported by various researchers have been observed. Hence there is a need to conduct more variety-specific studies and to identify and promote the varieties that have the best potential for disease prevention and health promotion.

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Chapter 24

Potential health benefits of selected fruits: apples, blueberries, grapes, guavas, mangos, pomegranates, and tomatoes

Poonam Jaglan[1], Harpal S. Buttar[2], O.A. Al-bawareed[3] and Sergey Chibisov[4]

[1]Department of Food Science and Technology, School of Agriculture, Lovely Professional University, Phagwara, India, [2]Department of Pathology & Laboratory Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada, [3]People's Friendship University of Russia, Moscow, Russia, [4]Faculty of Medicine, People's Friendship University of Russia, Moscow, Russia

Introduction

India is blessed with great amounts of flora and fauna as well as a diversity of medicinal plants and fruit trees. Since ancient times, many traditional medicines used in the Indian Ayurveda system of medicine have originated from fruits and medicinal plants for curing chronic diseases in children and adults. There exists a wonderful opportunity to discover cost-effective and affordable therapies and nutraceuticals from medicinal plants, fruit components, and fruit juices. The edible fruits and fruit-based nutraceuticals possess both disease-curing and health-promoting properties. It is well known that through photosynthesis, plants can make highly complex molecules that are difficult to synthesize in the laboratory in a cost-effective manner. More than 50% of modern medicines have been discovered from plant materials. Through the use sophisticated modern analytical and characterization techniques for the chemical identification of bioactive molecules and the application of pharmacometabolomics, there are emerging trends for the discovery of new, affordable phytomedicines. By using innovative chemical techniques and biotechnology methods, researchers can discover new commercial compounds and nutraceuticals from fruits, fruit juices, peels, and seeds.

In 2015 the Nobel Prize in Physiology and Medicine was awarded to William Campbell, Satoshi Omura, and Youyou Tu for the discovery of two major natural products: avermectin and its derivative ivermectin, isolated from the soil microorganism *Streptomyces avermitilis*, and artemisinin, isolated from the plant *Artemisia annua* L. (Asteraceae). Both these drugs have proven highly useful: artemisinin for treating malaria and avermectin for treating lymphatic filariasis and onchocerciasis. Having the Nobel Prize awarded in the field of phytotherapy not only put phytomedicines in the limelight, but also recognized the importance of medicinal systems that have been practiced in India, China, and other countries of the world for thousands of years [1].

India is among the largest producer of different varieties of fruits [2], and fruit products have been an integral part of the Indian diet for ages. Consumption of fresh fruits, juices, and fruit products contribute to food security on the basis of the caloric value of food ingredients such as proteins, lipids, carbohydrates, and micronutrients. In addition, the bioactive components of fruits help in the prevention of multiple age-related chronic diseases, such as cardiovascular disease, neurodegenerative disease, diabetes, obesity, and certain types of cancer [3]. There is emerging evidence that the bioactive phytochemicals present in fruits can modulate biochemical pathways and downregulate the genetic expression and synthesis of inflammatory cytokines involved in causing inflammation and inflammation-related disorders. The fruit-derived nutraceuticals retain the bioactive ingredients in a natural state to act as nutrients and pharmaceuticals. There is robust evidence from preclinical and clinical studies of the potential health benefits of plant-based nutraceuticals. The oils extracted from pomegranate and orange peels and seeds are used for aromatherapy. Potential health benefits of major bioactive compounds present in different fruits and fruits products are summarized in Table 24.1.

The diverse geographic regions of India are conducive for growing different varieties of fruits, such as apples, grapes, guavas, mangos, pomegranates, blueberries, and tomatoes for human consumption as well as cash crops. Unfortunately, the fruit-processing and preservation industries are lacking in India, and ample amounts of fruits decay,

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TABLE 24.1 Potential health benefits of major bioactive compounds present in different fruits and fruits products.

Fruit and fruit component	Major bioactive compounds	Amount	Health benefits	References
Apple pomace	Chlorogenic acid, phloridzin, quercetin glycosides, amygdalin	4.22–8.67 mg/g	Improvement in serum triglycerides, HDL, total cholesterol, insulin, and adiponectin	[4,5]
Apple peel	Phloretin glycosides, quercetin glycosides, catechins, procyanidins, cyanidin glycosides, chlorogenic acid, phloridzin, caffeic acid	33.42 mg/g	Antioxidant, weight loss, increased gut health	[6,7]
Apple seed	Amygdalin, phloridzin	2.17 mg/g	Weight reduction, increase in protein digestibility, increased serum HDL	[5,8]
Blueberries	Cyanidin-3-*O*-glucoside, gallic acid, quercetin-3-*O*-glucoside, protocatechuic acid	21.7–47.4 mg/g	Antioxidant, antiinflammatory, cardioprotective, neuroprotective	[9,10]
Citrus peel	Hesperidin, nobiletin, narirutin, hydroxycinnamic acid, naringin, eriocitrin, and their glycosides	24 mg/g	Antioxidant, reduces oxidative stress	[11,12]
Citrus fruits	Naringin, nobiletin, hesperidin, neohesperidin, narirutin, and tangeretin	19.2 and 16.2 mg/g	Antioxidant, anticancer, good for the skin	[13,14]
Grape pomace	Anthocyanins, catechins, trans-resveratrol, flavonol glycosides, phenolic acids	107.12–376.71 mg/g	Increase in glucose tolerance, insulin sensitivity	[15–17]
Grape pomace	Anthocyanins, catechins, trans-resveratrol, flavonol glycosides, phenolic acids	107.12–376.71 mg/g	Increase in glucose tolerance, insulin sensitivity	[15–17]
Grape pomace	Anthocyanins, catechins, trans-resveratrol, flavonol glycosides, phenolic acids	107.12–376.71 mg/g	Increase in glucose tolerance, insulin sensitivity	[15–17]
Grape skin	Epicatechin gallate, catechin, epicatechin, epigallocatechin, resveratrol	–	Cardioprotectivity; curing neurological disorders such as Alzheimer's disease, Parkinson's disease, and Huntington's disease; longevity and antiaging properties	[18]
Grape seeds	Epicatechin-3-*O*-gallate, catechin, epicatechin, dimeric procyanidins B2 and B3	325.37–811.95 mg/g	Antioxidants, inhibit inflammation and allergies	[17,19]
Guava	Myricetin, quercetin, isorhamnetin, quercitrin, 1-*O*-trans-cinnamoyl-β-D-glucopyranose, and ellagic acid	391.93 ± 15.08 mg/kg	Lowers risk of cancer, healthy for diabetics, treats constipation, improves immunity, antioxidant	[8,20]
Mango peel	Xanthone-*C*-glycosides, flavonol-*O*-glycosides, mangiferin, lupeol	55–110 mg/g (GAE)	Antioxidant, weight loss, antidiabetic	[21,22]
Mango seed	Ellagic acid, gallic acid, gallates	117 mg/g (GAE)	Cardioprotective, weight reduction, antidiabetic, cures acne	[23]
Mango fruit	Chlorogenic acid, gallic acid, kaempferol, mangiferin, vanillic acid, quercetin	31.2 ± 7.8 mg GAE/100 g	Anticarcinogenic, antioxidant, antiinflammatory	[24]

(*Continued*)

TABLE 24.1 (Continued)

Fruit and fruit component	Major bioactive compounds	Amount	Health benefits	References
Pomegranate peel	Punicalagin, punicalin, ellagic acid, gallagic acid, quercetin, kaempferol, myricetin	364 mg/g	Reduced adipogenecity, reduction of weight	[11,25]
Pomegranate seed	Ellagic acid, 3,3′,4′-Tri-*O*-methylellagic acid, 3,3′-Di-*O*-methylellagic acid	117.0–177.4 mg GAE/L	Helpful in metabolic and chronic inflammatory diseases	[26,27]
Pomegranate juice	Catechin, epicatechin, rutin, quercetin, epigallocatechin-3-gallate	784.4–1551.5 mg GAE/L	antiinflammatory and antiatherosclerotic activity against heart disease, osteoarthritis, prostate cancer, and HIV-I	[26]
Tomato skin	Quercetin, kaempferol, rutin, phenolic acids, naringenin	0.29 mg/g	Antioxidant, cancer prevention, reduction of LDL levels, reduced risk of kidney stones	[28,29]

Note: Gallic acid equivalent (GAE) or gallic acid is used as a standard in the pharmaceutical industries for the determination of phenol content by Folin–Ciocalteu assay. The results are reported in terms of GAE. One gallic has four hydrogens to reduce, so one gallic is equal to four phenols.



FIGURE 24.1 *Source: https://paintwithdiamonds.art/products/vegetables-fruits.*

decompose, and are wasted in India during the harvest season. There is an urgent need for the development of fruit-processing industries in India. The focus of this chapter is on the potential health benefits of eating fruits and promising possibility of making nutraceuticals from diverse phytochemicals present in various fruits, peels, and seeds and extracting natural antioxidant polyphenolic by-products from the leftover waste from the fruit-processing industry. It is now well recognized that leftover waste from the fruit- and food-processing industries contains valuable bioactive chemicals, micronutrients, and soluble and insoluble fibrous ingredients that can be incorporated into pastry and bakery products as well as into animal feed (Fig. 24.1) [30].

Unique characteristics of various fruits

1. The nutritional composition of fruits can provide almost all the recommended daily allowances of essential nutrients to children and adults.

2. Fruits have unique flavors and aromas, which are also important aspects of human nutrition.
3. Phytochemicals in fruits (e.g., flavonoids, carotenoids, antioxidants) are beneficial in maintaining good health and well-being and in the prevention of non-communicable diseases.
4. Some useful by-products can be extracted from nonedible fruit peels, seeds, and discarded waste after fruit processing. For instance, phenolic compounds have been extracted as by-products from the leftover waste of grapes after winemaking, and nobiletin has been extracted from citrus fruit peels (Fig. 24.2).

Apples

Apples (*Malus domestica*) are extensively consumed all over the globe. They are a good source of antioxidants and phenolic compounds, such as catechins, chlorogenic acids, and quercetin [3,31]. However, the amount of bioactive phenolic compounds differs among various varieties of apples and between the flesh and peel of the apple [6,32−35]. Apple peel contains ample amounts of catechins, caffeic acid, proanthocyanidins, and chlorogenic acid [7,32,36−42]. Apple seeds are also a valuable source of polyphenols, amygdalin, and phloridzin [33,43−46] in the amount of roughly more than 2 g/kg [33,46].

The apple pomace, which is waste left over after the extraction of apple juice, is also a rich source of polyphenols, dietary fiber, and minerals. Analytical studies showed that water is a good solvent for the extraction of hydroxycinnamic acids, flavonols, flavanols, dihydrochalcones, and flavones present in apple pomace.

The major polyphenols of apple pomace are chlorogenic acid, quercetin, hydroxycinnamic acids, and phloridzin [47]. Because of the high occurrence of bioactive polyphenolic compounds as well as the antioxidant and antiinflammatory properties of various bioactive dietary components present in apples, it is worth quoting Benjamin Franklin, who said that "an apple a day keeps the doctor away."

The results of a 10.2-year follow-up cohort prospective study done in Swedish men ($N = 40{,}271$) and women ($N = 34{,}670$) showed an inverse association for the risk of stroke following the consumption of apples and pears (RR (relative risk): 0.89, 95% CI (confidence interval): 0.80−0.98, P for trend = .02) and green leafy vegetables (RR: 0.89, 95% CI: 0.80−0.98, P for trend = .02) [48]. To evaluate the effects of dietary flavonols and flavones on the risk of coronary heart diseases, a 12-year follow-up prospective Nurses' Health Study was conducted among 66,360 American women. It was found that long-term intake of dietary flavonols and flavones did not decrease the risks of nonfatal myocardial infarction and fatal coronary heart disease [49].

A study in rats showed that 7% addition of apple pectin in the diet can modify the microbiota composition in the intestine. After four weeks, consumption of a pectin-rich diet increased the number of *Clostridium coccoides* and lowered the number of the *Bacteroides* species in the rat intestine. Consumption of whole apples, apple juice, or pomace did not cause similar changes in the population of gut microbiota. In contrast to the control animals, the activity of beta-glucuronidase and butyrate production were significantly increased ($P < .01$) in the cecal contents of pectin-fed rats [49]. In view of these observations, consumption of fiber-rich pectin could possibly confer potential health benefits in humans. Apple pectin may be used for making nutraceuticals.

Blueberries

Blueberries (*Cyanococcus* genus *Vaccinium*) are well known for their antioxidant properties and for the abundant amounts of polyphenolic compounds and anthocyanins. Maximal health benefits are derived from anthocyanins. The amount of anthocyanins dramatically increases as the blueberries ripen and gives them a vibrant dark blue color when they ripen. Anthocyanins account for about 60% of the total polyphenols in ripened blueberries, and the amount of anthocyanins is around 487 mg/100 g of blueberries.

The skin of both high-bush and low-bush blueberries contains the highest amount of phenolic compounds. The total phenolic content of blueberries ranges from 21.7 to 47.4 mg/g of dry matter [48]. The anthocyanins that are present in blueberries have shown cardioprotective, neuroprotective, antidiabetic, and vision-improving properties [50]. A limited number of clinical trials have shown short- and long-term multiple health benefits of blueberries [51], but information about the optimal daily amounts of blueberries required for health promotion in humans is lacking and warrants further studies.

A double-blind, parallel, randomized, controlled trial was conducted in adult men and women ($N = 115$, age 63 ± 7 years), who were given dietary blueberry intakes equivalent to 1/2 cup (75 g) or 1 cup per day (150 g) per day for six months. Statin ($N = 71$) was used as a comparator drug. Daily intake of 1 cup of blueberries significantly elevated HDL levels and apolipoprotein A-1 concentration, improved endothelial function and nitric oxide bioactivity, and reduced blood

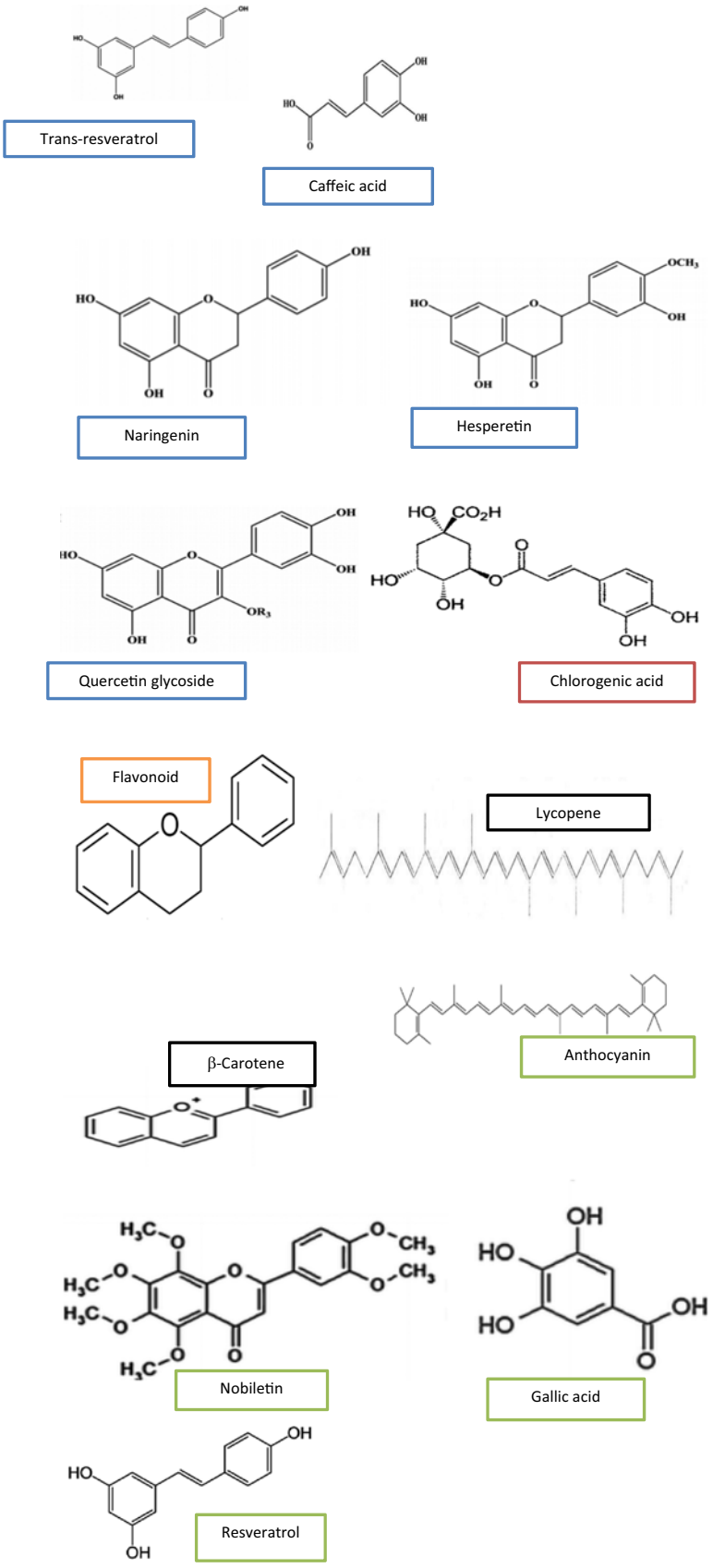


FIGURE 24.2 Chemical structures of major bioactive compounds present in different fruits.

pressure. A half-cup per day had no effect on any biomarkers. It was concluded that 1 cup per day of anthocyanin-rich blueberries is associated with a markedly reduced risk of cardiovascular and cardiometabolic diseases [52].

Supplementation of freeze-dried blueberries powder (2% wt/wt) along with a low-fat diet (10% of kcl (potassium chloride)) reduced triglyceride, fasting insulin, and glucose levels in Zucker fatty rats [52]. Prior et al. [53] reported that supplementation of blueberry juice (0.2 or 1.0 mg/mL) in drinking water reduced peritoneal fat and epididymis adipose tissue in male C57BL/6J mice that were fed a high-fat diet (45%). In comparison with the controls, serum leptin was elevated in mice that were fed a high-fat diet, whereas drinking of blueberry juice lowered serum leptin to the control level. It was concluded that anthocyanins present in blueberry juice alters the development of obesity in mice that are fed an obesogenic high-fat diet.

Grapes

Grapes (*Vitis vinifera*) are among the ancient fruits linked to human history. The major bioactive component of red grapes is resveratrol, which is present in the skin and seeds of muscadine grapes [54]. Red wine produced from red grapes also contains resveratrol. It is often reported that moderate consumption of red wine has beneficial effects in patients with neurodegenerative diseases [54]. Resveratrol is also found in peanuts and berries. Administration of resveratrol (100 mg) to mice decreased high blood pressure and heart failure, improved diastolic pressure, improved vascular function. and reduced cardiac fibrosis. These cardiovascular benefits of resveratrol have not yet been confirmed in humans [55].

The skin of white grapes lacks the myricetin glycosides that are abundantly present in the skin of red grapes [56]. Also, the content of resveratrol is far higher in red grapes than in the white grapes. The amount of resveratrol in fresh red grapes ranges from 0.15 to 0.78 mg/100 g [57]. Resveratrol is considered cardioprotective, neuroprotective, and antiaging and is thought to cure neurological disorders such as Parkinson's disease, Alzheimer's disease, and Huntington's disease. Another compound that is present in the grapes is melatonin [58], which has strong antioxidant properties. Researchers have reported that the phenolic compounds extracted as by-products from the leftover waste after winemaking have greater potential to reduce low-density lipoprotein (LDL) cholesterol and triglyceride levels than does red wine. Shahidi and De Camargo [59] used the enzymes pronase and viscozyme, which improved the extraction of by-product phenolic compounds from the leftover waste during winemaking. The addition of these enzymes increased the content of soluble phenolics but lowered the amount of insoluble phenolics.

Zhang et al. [60] performed a metaanalysis of 16 randomized, controlled trials consisting of 810 hypertensive subjects who were treated with grape seed extract at doses ranging from 100 to 2000 mg/day for periods of 4, 6, 8, and 12 weeks. The researchers found significant reductions ($P < .001$) in both systolic and diastolic blood pressures in obese and metabolic syndrome patients in contrast to their baseline blood pressures. Well-designed, randomized, placebo-controlled, multicenter, long-term studies with large number of subjects are needed to establish the long-term safety, efficacy, and doses of grape seed extract in hypertensive and obese patients.

Guava

Guava (*Psidium guajava*) is cultivated mostly in tropical and subtropical regions. It is also known as apple of common man. Guava contains almost 74%−87% moisture and is rich in ascorbic acid (vitamin C). Guava has been promoted for multiple uses in India and other countries. For instance, it has been used for treating various ailments, such as childbirth, convulsions, epilepsy, jaundice, nephritis, anorexia, and cerebral diseases. Guava is rich in dietary fiber, vitamin C, copper, iron, manganese, sodium, potassium, and phosphorus [61]. The vitamin C content of guava is almost four times greater than that of orange [62]. Among the varieties of guava, *Psidium littorale* contains the largest amount of vitamin C [63]. It also contains antioxidant polyphenols and carotenoids. Guava fruits that are red inside have more polyphenols and pro-vitamin A [64]. The antioxidants of guava are useful for several health promotion functions in humans, such as anticancer, antidiabetic, neuroprotective, and cardioprotective effects. Owing to the beneficial health effects and medicinal properties, guava therapy has been recommended in the Ayurveda system of medicine.

Singh et al. [65] conducted a randomized, single-blind, controlled trial to examine the effects of guava fruit on blood lipids and blood pressure in hypertensive patients. Seventy-two patients were given a diet rich in soluble fiber and potassium containing 0.5−1.0 kg of guava daily (group A), and 73 patients received their usual diet (group B). After four weeks of follow-up, group A patients showed mean reductions of 7.5 mmHg in systolic blood pressure and 8.5 mmHg in diastolic blood pressure compared with group B. Guava fruit caused a minor increase in HDL cholesterol

(4.6%) in group A patients compared with group B. It was concluded that guava fruit causes a marked reductions in both systolic and diastolic blood pressures but has an insignificant effect on the blood lipid profile.

Rats were fed guava pulp juice and a diet supplemented with guava seeds ad libitum for 40 days. Significant reductions were observed in the levels of blood glucose, triglycerides, and total cholesterol, and the concentration of HDL cholesterol was elevated in animals that were fed guava juice and a seed-supplemented diet, in contrast to the control group. Further, the liver enzymes alanine transaminase and aspartate transaminase were markedly reduced in the guava-treated groups in comparison with their control counterparts. The authors concluded that the carotenoids, lycopene, polyphenols, and vitamin C present in the guava fruit and guava-related agroindustrial waste (pulp, skin, and seeds) can be useful food ingredients for the prevention of chronic degenerative diseases [66].

Mango

Mango (*Magnifera indica*) is a delicious tropical fruit that is grown worldwide. The main producers of mango fruit are Brazil, Nigeria, Egypt, Indonesia, India, and Pakistan [67]. Mangos are a rich source of macronutrients, such as amino acids, carbohydrates, and organic acids. Phenolic compounds, polyphenols, volatile compounds, and carotenoids are also present in mangos as micronutrients. Mangos contain vitamins B and E, and their composition changes from immature to mature during the ripening process [68]. About 20% of the total production of mangos is used for pickles, jams, jellies, and chutneys [69]. After the mango pulp is processed, the peel and seeds are used as by-products (about 35%–60% of total weight) by the industries. Both peel and seeds are good source of phenolic compounds [5]. However, the phenolic content of mango peel is higher than that of the pulp [70]. The major phenolic compounds of mango seeds are ellagic acid, gallic acid, and gallates [23], whereas the mango peel contains xanthone-*c*-glycosides and flavonol-*O*-glycosides [21]. Being a polyphenolic-rich fruit, the mango has antioxidant, antiinflammation, hypotensive, immunomodulation, cardioprotective, hepatoprotective, and gastroprotective properties. The bark of the mango tree contains tannins, which are used for dyeing [71]. Overall, the mango fruit is a rich source of macronutrients and micronutrients and is called “the king of all fruits” [72].

Mangiferin a bioactive compound found in mango fruit that has been proved to reduce triglyceride levels along with plasma glucose levels when administered at a dose of 15, 30, or 60 mg/kg body weight for a period of eight weeks. There are other health benefits as well, such as hepatoprotective, cardioprotective, and gastroprotective effects. Bioactive compounds present in the peel of mango fruit acts as antioxidant, weight loss, and antidiabetic agents [73].

Pomegranate

The pomegranate (*Punica granatum*) is one of the ancient fruits associated with human history. The health benefits of pomegranate are even mentioned in the Bible and the Quran. Pomegranate leaves, flowers, root, peel, and seeds have been used as prophylaxis and to cure a wide array of diseases. Most cultivars of pomegranate exist in tropical and subtropical countries, such as Egypt, Turkey, Spain, Iran, China, India, Mexico, and the American state of California [74]. Pomegranate juice is a rich source of bioactive polyphenolic compounds and glycosides [75]. This fruit is widely consumed fresh as well as in the form of jam, jellies, and juices. Pomegranate seeds, carpellary membrane, and peel are by-products of the food-processing industries. Pomegranate seeds are a rich source of phenolic acids, flavonoid glycosides, tannins, and flavol-3-ols [76] (Fig. 24.3).

In comparison with other fruits, such as apples, bananas, and oranges, pomegranates contain the highest amount of polyphenolic compounds [11]. Pomegranate leaves possess abundant amount of tannin, ellagitannins, and ellagic acid and about 30% of total proanthocyanidins. Pomegranate peel contains about 364 mg/g dry weight. In comparison with seeds and pulp, pomegranate peel exhibits more antioxidant and phenolic compounds [75]. Ambigaipalan et al. reported that pomegranate seeds contain more phenolic compounds than does the juice [77]. Pomegranate exhibits antioxidant, antimicrobial, antibacterial, antiinflammatory, and anticarcinogenic properties. The fruit has also been used in the Ayurveda and Siddha systems of medicine in India. According to Liu et al., the pomegranate polyphenolic compounds ameliorate hydrogen peroxide ($H_2O_2^-$) induced oxidative stress and cytotoxicity in human keratinocytes by reducing the population of apoptotic cells and downregulating the levels of apoptosis-related enzymes caspases-3/7 and 8 in $H_2O_2^-$-exposed cells [28]. Pomegranate seed oil is rich in punicic acid, which has a chemopreventive potential as a natural topical agent against skin cancer [78]. Inhibition of skin cancer promotion is mediated via inhibiting prostaglandin biosynthesis, specifically the activities of cyclooxygenase (COX-1 and COX-2), lipoxygenase, and ornithine decarboxylase [79]. Pomegranates contain ample amounts of micronutrients and macronutrients along with antioxidant bioactive compounds that promote good health and well-being. The anthocyanins in pomegranates are found mostly in the peel

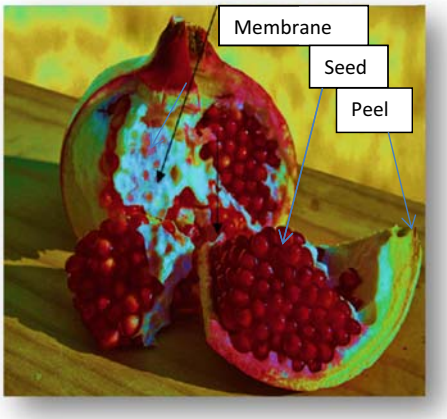


FIGURE 24.3 Schematic representation of pomegranate parts.

and juice, which are well known for their probiotic, antimicrobial, antiobesity, and dental health benefits [80]. Since pomegranate fruit or juice is well known for its multiple nutritional benefits and as a potent antioxidant and antiinflammatory substance, the regular consumption of pomegranate products may be a powerful tool for combating inflammation-associated disorders such as atherosclerosis, rheumatoid arthritis, dementia, and cognitive decline as well as some cancers, just to name a few. Well-designed, randomized, placebo-controlled, double-blind, and multicenter clinical trials should be done to determine the safety, efficacy and optimal doses of pomegranate extract and/or products for human use.

Tomato

The tomato (*Solanum lycopersicum*) is a versatile fruit, often considered to be a vegetable, that can be consumed either raw or after processing in the form of sauce, juice, or soup [81]. Tomatoes have multiple uses, and some people consume the whole raw fruit in salads, while some remove the skin and seeds of the tomatoes before consumption. Unfortunately, about 25% of tomatoes get wasted all around the world in the making of soups, tomato paste, and sauces because the skin and seeds are removed during these processes. Tomatoes are highly rich source of antioxidant phenolic compounds (e.g., phenolic acids and flavonoids) as well as carotenes, carotenoids, and lycopene. The amount of phenolic compounds is greater in skin than that of seeds and pulp. About 83% of the flavonols are present in the tomatoes skin [82]. The amount of flavonoid compounds depends on the agronomical conditions, season, country, and variety of the tomatoes [83]. Tomatoes contain about 90−180 mg/kg of the lycopene (carotenoids), and the accumulation of the lycopene starts in the final stage of ripening, and it is also responsible for the red color of the tomatoes. The amount of lycopene is highest in skin and less in the pulp and seeds [81].

Lycopene is a fat-soluble pigment that gives the red color to tomatoes, guavas, pink grapefruit, watermelon, and some other red-colored fruits. It is a type of hydrocarbon carotenoid that has proven effective in preventing prostate, lung, uterine, and breast cancer as well as cardiovascular diseases in humans. Among the majority of the carotenoids, lycopene is one of the most powerful antioxidants, with cardiovascular benefits that include effects on cardiac, endothelial, and vascular functions [84,85]. The antioxidative mechanisms of lycopene result from its ability to scavenge free radicals by effectively removing the singlet oxygen radicals. In terms of antioxidant-scavenging capacity, lycopene is ten times more potent than alpha-tocopherol and two times more potent than beta-carotene The singlet oxygen (O^{-}) quenching property of lycopene is due to the increased number of double bonds present in the lycopene molecule, thus making it a potentially powerful antioxidant. It has also been shown to modulate the action of nicotinamide adenine dinucleotide phosphate oxidase, COX-2, nitric oxide synthase, and 5-lipoxygenase, the enzymes that are responsible for the formation of free radicals [86,87]. When ingested through food, lycopene gets absorbed from the gut and is transported into the liver through the subepithelial lymphatic vessels, leading to the formation of lipoprotein LDL and VLDL (very low density lipoprotein) complexes. These complexes transfer lycopene to various body organs and tissues through systemic circulation, where it gets absorbed via the LDL receptors present in these organs. The consumption of lycopene prevents lipid formation, LDL lipoprotein segmentation, and protein and DNA oxidation, thus protecting the body against myocardial infarction, coronary insufficiency, and angina pectoris. Humans cannot produce lycopene

endogenously; therefore dietary consumption of lycopene is necessary. Several studies have shown that a higher dietary intake of lycopene increases its serum concentration, which considerably reduces the risk of major cardiovascular incidents [87,88].

A metaanalysis of 12 studies (13 trial arms) showed that in a subgroup of trial using more than 25 mg/day doses, lycopene significantly lowered serum LDL cholesterol levels. The lycopene-induced LDL reduction was comparable to the low doses of statins prescribed to patients with slightly elevated cholesterol levels. In addition, lycopene caused marked reduction in systolic blood pressure in all trials [89]. Daily intake of lycopene (30 mg/day) for three weeks by prostate cancer patients caused marked a reduction in prostate-specific antigen (PSA) from 10.9 to 8.7 μg/L. Lycopene also decreased oxidative DNA damage in the enrolled patients [90]. Several epidemiological studies suggest that tomato consumption may reduce the risk or the progression of prostate cancer.

In a human study done on patients with prostate cancer, the patients consumed lycopene in an amount of 30 mg/day for a period of three weeks, and reduced PSA levels in the serum of patients from 10.9 to 8.7 μg/L were observed. It acted as an antioxidant and reduced the amount of oxidative DNA damage in the patients. [90].

Summary and conclusion

This review has provided an overview of many promising health benefits of major bioactive compounds present in different commonly consumed fruits and fruits products as well as the clinical evidence obtained regarding the prevention of non-communicable diseases with fruits and fruit products from the published literature. This review has also highlighted the extraction of valuable bioactive ingredients from fruit peels, seeds, and pulp, thus harnessing the potentials of leftover waste by the fruit-processing industry.

Self-medication with natural remedies such as herbs, spices, fruits, and vegetables is becoming more popular these days because these substances provide great benefits in promoting health and well-being and are useful in reducing the risk of non-communicable diseases. The fruits described in this review contain potent antioxidants and antiinflammation and immune function−boosting substances. The ingestion of fruits produces healthy gut microbiota and causes immunomodulatory benefits through the microorganisms present in the gastrointestinal system. The antioxidants that are present in fruits have the ability to capture overly produced free radicals by oxidative stress. Fruits also reduce the risks of inflammation-related non-communicable diseases, namely, cardiovascular diseases, neurological disorders, eye problems, dementia and cognitive disorders, obesity, diabetes mellitus, musculoskeletal abnormalities, rheumatoid arthritis, and some cancers. Fruits and fruit juices as well as the fiber content and natural ingredients that are present in peels and seeds not only act as antiaging agents prophylactically, but also alleviate the incidence of non-communicable diseases. The enrichment of vegetarian cereal-based foods with fruit matrix or fruit extracts would be a good strategy to formulate healthier diets and alternative therapies for treating non-communicable diseases. The intake of fruits and fruit products may not cure all non-communicable diseases but can help to slow the pathogenesis process.

Significant reductions in both systolic and diastolic blood pressures have been observed in obese and metabolic syndrome patients treated with grape seed extracts. The in vitro investigations that have been done with different cancer cell lines and in vivo animal studies have provided useful insights about the anticancer mechanisms and prevention of cancer with the bioactive ingredients in pomegranates. The importance of synergistic effects of pomegranate phytotherapies with chemotherapeutic drugs is under scrutiny and is being evaluated by a large number of cancer experts. Several studies have demonstrated that resveratrol and quercetin, two structurally related flavonoids, have beneficial effects against diabetes and diabetic complications, owing to their strong antioxidant and antiinflammation properties as well as hyperglycemia-modulating capabilities. It is hypothesized that a nutraceutical developed from the combination of resveratrol and quercetin would be a promising cost-effective and safe alternative therapy for treating diabetes and diabetes-related pathological conditions such as insulin resistance, nephropathy, retinopathy, dyslipidemia, nonalcoholic fatty liver disease, cardiovascular disease, and neurodegenerative disorders.

The leftover waste of the fruit- and food-processing industries contains valuable bioactive ingredients, micronutrients, and soluble and insoluble fibrous materials that can be developed as nutraceuticals or added to baked goods such as bread, cake, biscuits, cookies, and crackers. Such products are consumed daily in large quantities, and the addition of by-products from the fruit- and food-processing industries would enhance their functional profile for human nutrition.

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Chapter 25

Bioactive ingredients of legumes

Wenli Sun[1,2,3,*], **Mohamad Hesam Shahrajabian**[1,2,3,*] **and Qi Cheng**[1,2,3]

[1]Biotechnology Research Institute, Chinese Academy of Agricultural Sciences, Beijing, P.R. China, [2]College of Life Sciences, Hebei Agricultural University, Baoding, P.R. China, [3]Global Alliance of HeBAU-CLS&HeQis for BioAl-Manufacturing, Baoding, P.R. China

Introduction

Legumes are indispensable for the human diet with respect to their valuable and nutritive bioactive molecules [1−7]. Among the species of medicinal plants, some are mainly confined to folk medicine, and some are used as occasional or local substitutes for the main species listed in the *Materia Medica* [8−13]. Traditional Chinese medicine has a history of thousands of years and developed through the accumulation of the precious experience of understanding life, maintaining health, and fighting diseases as experienced in daily life, production, and medical practice [14−21]. The soybean (*Glycine Max*. (L.) *Merrill*) is a legume that originated in China and has been cultivated for more than 5000 years. It has been suggested to have many health benefits, such as the healthy functioning of bowels, heart, kidney, and liver; lowering of serum cholesterol levels; reduction in the risk for coronary heart disease; and reduction in the risk for breast cancer and osteoporosis in women; and alleviation of the disturbances caused by menopause [22,23]. Peanuts, also known as groundnuts, are used mainly for oil production. But the by-products of peanut oil production contain many other functional compounds, such as proteins, fibers, polyphenols, antioxidants, vitamins, and minerals, which can be added as functional ingredients to many processed foods [24−26]. Cowpeas are commonly cultivated as a nutritious and highly palatable food source in Asia, the Middle East, and the United States and throughout the tropics and subtropics. It can be used as forage, hay, and silage [27]. Forage crop production is very important for successful animal production [28−31]. Alfalfa is a perennial flowering herb plant in the pea family Fabaceae, botanically known as *Medicago sativa*. Clovers are in the tribe Trifolieae of the subfamily Papilionoideae, family Fabaceae, *Trifolium* L. [32]. The genus contains approximately 230−250 species, and clovers are used for forage, pasture, soil improvement, and silage [33]. Clovers are an important source of nutrients for livestock and are grown throughout the world [34]. Clovers included arrowleaf clover, ball clover, berseem clover, crimson clover, red clover, white clover, and subterranean clover. Because clovers are basic to ruminant livestock production, it is necessary to produce clovers cultivars that continue to be high in quality and possess a minimum of antiquality components.

Soybeans, peanuts, and cowpeas

Sitohy and Osman [35] reported on glycinin its basic subunit, and beta-conglycinin isolated from soybean protein. Their results suggest that a soy protein fraction containing mainly beta-conglycinin can be used as an effective environmentally friendly fungicidal agent against postharvest fungal infections. Soybeans have various bioactive compounds such as saponins, protease inhibitors, phytic acid, and isoflavones [36]. The most important isoflavone in soy is genistein; others are daidzein and glycitein, and the metabolism of isoflavones is different from that of the parent compounds [37]. Filho et al. [38] stated that the conversion of isoflavone was influenced directly by the characteristics of each sample, inhibiting or promoting the action of the enzyme. Silva and Perrone [39] concluded that soybean meals presented 43% higher protein content, 29%−101% higher bioactive compounds contents, and 52% higher antioxidant capacity than soybeans. Vernaza et al. [40] reported that consumption of soybeans has been linked to cholesterol reduction and prevention of cardiovascular and gastrointestinal diseases, cancer, diabetes, and obesity. They have found that the health

*The authors contributed equally to this research.

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benefits of soy are attributed to the presence of bioactive compounds such as isoflavones, saponins, and lunasin. Lokuruka [41] concluded that many of the chemical reactions affecting amino acid residues are often accompanied by protein−protein interactions involving the formation of covalent bonds, which may reduce their bioavailability. Excessive thermal denaturation and heat-induced interactions may form mutagenic and toxic compounds. Hydrogenation results in the formation of the hypercholesterolemic trans-fatty acid isomers, implying potential loss of the unsaturated essential fatty acids. Chatterjee et al. [42] showed that some soy peptides, such as lunasin and soy morphins, possess more than one of the properties and play a role in the prevention of multiple chronic diseases. Meghwal and Sahu [43] revealed that isoflavones are the most abundant phytoestrogen in soybeans, which are structurally similar with 17-beta-estradiol. The antioxidant properties of genistein and daidzein have been well established in different experimental and clinical models. Isoflavone compounds have been found to be effective in the management of diabetes. They reduce low-density lipoprotein and triglycerides and hence minimize the risk of coronary heart disease. Soy isoflavones were found to be useful for treatment of osteoporosis by inhibiting tyrosine kinase. In soy isoflavones, genistein is effective in the treatment of cancer by acting on androgen receptors and inhibiting tyrosine kinases. Many nutraceutical and medicinal uses and applications of soy isoflavones have been investigated, such as treatment and prevention of cardiovascular diseases, cholesterol lowering, osteoporosis, diabetes, cancer, cognitive decline, and menopausal symptoms. The sterol profiles of the bioactive compounds loaded in the lipid nanoparticles are shown in Table 25.1. The functional components of soy and their impacts are presented in Table 25.2. The structures of genistein, daidzein, and glycitein are shown in Fig. 25.1, and the structure of glyceollins is presented in Fig. 25.2.

The peanut is one of the most widely used legumes, owing to its nutrition and taste, and it has been recognized recently as a functional food [47]. The peanut industry's by-products, such as peanut hulls and shells, skins, and even leaves and roots, have also been identified as possible sources of bioactive compounds [47]. Peanuts are also a source of helpful biologically active components found in plant foods, such as phytochemicals. Some of the phytochemicals in peanuts include flavonoids and phenolic compounds. The most important bioactive compounds in peanut shells are as follows: (1) Arginine, an amino acid found in high levels in peanuts, is a precursor to nitric oxide, which helps to expand the blood vessels and decrease blood pressure. (2) Resveratrol, also found in grapes and wine, improves longevity and performance and reduces inflammation. (3) Phytosterols are well known for their ability to reduce cholesterol levels, and research shows that they have cancer-preventing qualities. (4) Phenolic acids are found in plants and act as a defense mechanism against environmental stress and pest attacks. They may also defend our bodies and keep them

TABLE 25.1 Sterols profile of the bioactive compounds loaded in the lipid nanoparticles [44].

Composition of free phytosterols	Percentage[a]
Cholesterol	0.60 ± 0.02
Brassicasterol	0.30 ± 0.01
Campesterol	23.56 ± 0.23
Campestanol	0.66 ± 0.11
Stigmasterol	26.77 ± 0.22
Delta-7-campesterol	0.78 ± 0.04
Delta-5,23-stigmastadienol	0.48 ± 0.01
Beta-sitosterol	44.05 ± 0.15
Sitostanol	1.18 ± 0.08
Delta-5-avenasterol	0.84 ± 0.04
Delta-5,24-stigmastadienol	0.14 ± 0.01
Delta-stigmastenol	0.47 ± 0.02
Delta-7-avenasterol	0.68 ± 0.01
Total of phytosterols	98.00

[a]*Average of three replicates ± standard deviation.*

TABLE 25.2 Functional components of soy and their impact [45].

Alpha-linolenic acid	Essential fatty acid, hypertriglyceridemic, improves heart health
Isoflavones	Estrogenic, hypocholesterolemic activities; improve digestive tract function; prevent breast, prostate, and colon cancer; bone health; improve lipid metabolism
Lecithins	Improve lipid metabolism, improve memory and learning abilities
Lectins	Anticarcinogenic, immunostimulator
Linoleic acid	Essential fatty acid, hypocholesterolemic
Peptides	Readily absorbed, reduce body fat, anticancer
Phytosterols	Hypocholesterolemic, improve prostate cancer
Protein	Hypocholesterolemic, antiatherogenic, reduces body fat
Saponin	Regulates lipid metabolism, antioxidant

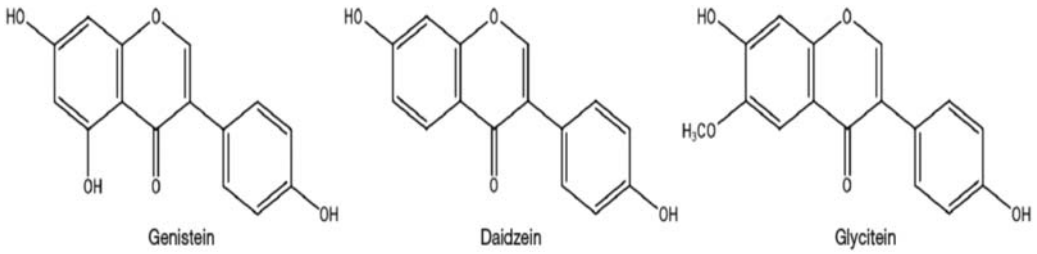


FIGURE 25.1 Structures of genistein, daidzein, and glycitein [46].

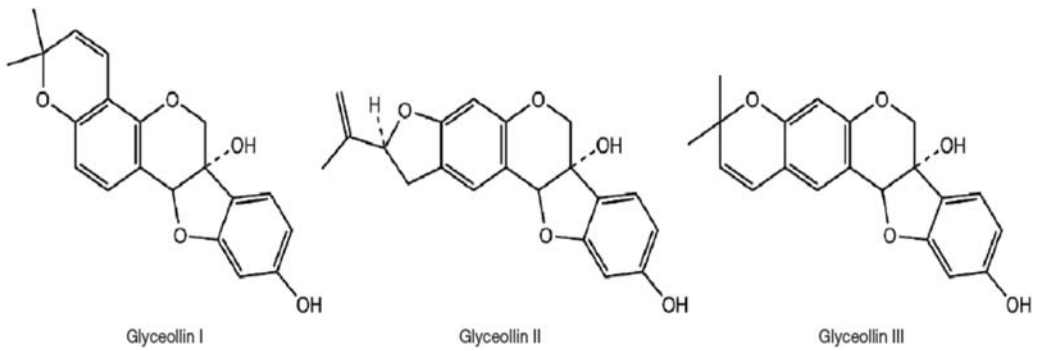


FIGURE 25.2 Structure of glyceollins [46].

healthy. (5) Flavonoids are a class of compounds found in peanuts that reduce inflammation and inhibit platelets from sticking to arteries. Bhat et al. [48] reported that the peanut consists of different functional components, such as coenzyme Q10, which secures the heart amid absence of oxygen, for example, at high altitudes, and in cases of clogged veins. Peanuts also possess various health benefits beyond basic nutrition. Peanuts act as efficiency source of dietary fiber, and other essential nutrients, including some B-complex vitamins; vitamin E; minerals such as iron, zinc, potassium, and magnesium; and antioxidant minerals such as selenium, manganese, and copper. The antioxidant activity of peanut is because of vitamin E, caffeic, coumaric acid, flavonoids, and stilbenes, and these bioactive compounds possess preventive properties [49]. Akl et al. [50] observed that the analysis of soluble and insoluble peanut meal proteins by native and SDS−PAGE showed peptide bands at low molecular weight in a range up to 25 kDa, which were extracted by acid and base treatments. These peptides were easily digested and were recommended as components of

the diets of babies, athletes, and older adults. Velu et al. [51] noted that phytochemical screening of the peel extract of *Arachis hypogaea* showed the presence of bioactive compounds such as tannins, saponin, flavonoids, alkaloids, glycosides, beta-cyanin, coumarins, quinines, and steroids. Silva et al. [52] concluded that the bioactive compounds are found in larger amounts in peanut powder extract with skin. The peanut powder extracts are classified as nonhygroscopic, have poor fluidity, and have intermediate cohesiveness in samples with skin and high cohesiveness in samples without skin. The peanut powder extracts have a significant percentage of minerals, such as potassium, phosphorus, magnesium, and calcium, and are composed mainly of oleic and linoleic fatty acids. Groundnut, nutritional values of peanuts are shown in Table 25.3. Components in peanuts that are thought to be beneficial are listed in Table 25.4. The chemical structures of trans-resveratrol and trans-piceatannol are shown in Fig. 25.3.

TABLE 25.3 Nutritional values of peanuts per 100 g [53].

Principle	Nutrient value	Percentage of recommended daily allowance
Energy	567 kcal	12
Carbohydrates	16.13 g	12
Protein	25.80 g	46
Total Fat	49.24 g	165
Cholesterol	0 mg	0
Dietary fiber	8.5 g	22
Vitamins		
Folates	240 μg	60
Niacin	12.066 mg	75
Pantothenic acid	1.767 mg	35
Pyridoxine	0.348 mg	27
Riboflavin	0.135 mg	10
Thiamin	0.640 mg	53
Vitamin A	0 IU	0
Vitamin C	0	0
Vitamin E	8.33 mg	55.5
Electrolytes		
Sodium	18 mg	1
Potassium	705 mg	15
Minerals		
Calcium	92 mg	9
Copper	1.144 mg	127
Iron	4.58 mg	57
Magnesium	168 mg	42
Manganese	1.934 mg	84
Phosphorus	76 mg	54
Selenium	7.2 μg	13
Zinc	3.27 mg	30

Source: U.S. Department of Agriculture National Nutrient database.

TABLE 25.4 Components in peanuts that are thought to be beneficial [54].

n-6 and *n*-3 Monounsaturated and polyunsaturated fatty acids
Fiber
Micronutrients
Vitamin E
Folic acid
Copper
Magnesium
Plant protein (arginine)
Phytochemicals
Plant sterols

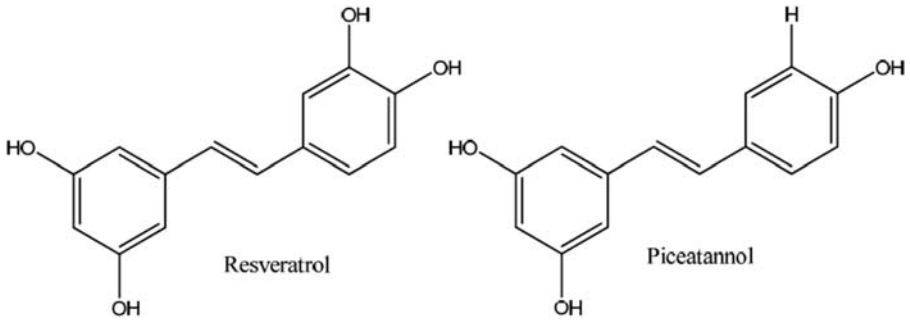


FIGURE 25.3 The chemical structures of trans-resveratrol and trans-piceatannol [53].

Lee et al. [55] evaluated the antiinflammatory effects of methanol extract and solvent fractions of cowpea (*Vigna sinensis* L.) seeds and the isolated compounds. In their experiment, ethyl acetate and n-butanol fractions of *V. sinensis* L. seeds were found to strongly inhibit nitric oxide production and inducible nitric oxide synthase mRNA and protein expressions in lipopolysacharide-stimulated RAW 264.7 macrophage cells. Among the isolated compounds, linolenic acid and linoleic acid were found to inhibit nitric oxide production significantly. Contents of linolenic acid and linoleic acid in *V. sinensis* L. seeds were 2.034 and 1.162 mg/g, respectively, on a dry weight basis. Linoleic acid suppressed the production of proinflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor alpha in lipopolysaccharide-induced macrophage cells. Cai et al. [56] reported that the amount of protocatechuic acid increased from a trace amount to 9.3−92.7 mg/100 g of flour in the 17 varieties of cowpeas after hydrolysis. Six other phenolic acids—*p*-hydroxybenzoic acid, caffeic acid, *p*-coumaric acid, ferulic acids, 2,4-dimethoxybenzoic acid, and cinnamic acid—were also identified. The cowpea is an important food crop in tropical countries, especially in West Africa, where it is a cheap source of dietary protein. The dry seed consists of about 25% protein and 67% carbohydrate, and it is also a good source of calcium, iron, vitamins, and carotene. Dalaram [57] stated that cowpeas contain phenolic compounds, which are believed to works synergistically to promote human health through their antioxidant properties and ability to modulate the activity of various enzymes. These phenolics are also potent inhibitors of alpha-amylase and alpha-glucosidase, the two important enzymes involved in the regulation of glucose homeostasis. Cowpeas are low in fat and high in protein; thus they can help to prevent cardiovascular and metabolic diseases associated with high fats. Furthermore, cowpeas are rich in thiamine, riboflavin, vitamins A and C, niacin, calcium, potassium, magnesium, and carbohydrates [58]. The major polyphenols common to all cowpea varieties are phenolic acids derivatives (148−1176 μg/g) and flavanol glycosides (27−1060 μg/g). Some varieties also contain anthocyanins (875−3860 μg/g), and flavan-3-ols (2155−6297 μg/g). The flava-3-ols (tannins) are dominated by monomers, mostly catechin-7-*O*-glucoside. Cowpeas also contain beneficial bioactive peptides. Sombie et al. [59] noticed that cowpea genotypes with colored seed coats showed the highest phenolic content, ferric reduction ability, and antilipid peroxidation activities. They found that nitric oxide scavenging potential was found not be related to its total phenolic and total flavonoids content. 2,2-

Compounds	Cowpea	Sorghum	Sorghum/ cowpea	Sorghum /cowpea porridge	Gastric digest	Intestinal digest
Gallic acid	378.0c	96.8ab	242.6bc	193.9ab	61.7a	226.7c
Protocatechuic acid	493.6d	132.4b	179.0c	122.7b	39.6a	92.2b
4-hydroxybenzoic acid	81.6d	74.5d	73.2d	59.6c	17.5a	42.2b
Vanillic acid	13.394a	150.604e	99.850d	77.035c	21.715a	44.0b
Caffeic acid	11.9c	42.6f	27.1e	18.1d	1.7a	6.3b
Syringic acid	920.4d	2011.8e	794.1cd	684.9c	402.7b	178.0a
p-coumaric acid	5.2b	13.3d	7.1bc	12.9d	1.7a	10.3cd
Ferulic acid	3.8b	16.1f	12.2d	13.9e	2.2a	9.5c
Quercetin dihydrate 380 nm	442.8c	606.3f	555.3e	489.6d	58.2a	218.1b
Hesperidin 380 nm	ND	ND	ND	ND	ND	ND
Naringin 280 nm	617.4c	690.5d	815.9e	486.0b	190.5a	558.9c
Fisetin 380 nm	403.3b	ND	ND	ND	ND	191.2a
Kaempferol 380 nm	ND	939.6e	719.2d	612.2c	38.2a	144.7b
Kaemferol glucoside 380 nm	184.8d	ND	68.7c	ND	9.4a	30.0b
Taxifolin 280 nm	430.3b	549.6c	632.0d	876.2e	290.9a	575.4c
Catechin 280 nm	8799.0d	3045.2ab	3590.2bc	4188.3c	1957.4a	2760.0ab
Epicatechin 280 nm	1545.2ab	2593.1ab	3324.9b	3417.9b	1049.9a	3007.7b
Tannic acid 280 nm	7031.9e	5368.3d	4935.1d	2935.0c	1942.1a	2420.9b

Values are means of two determinations
Values with the same letter in the same row are not significantly different ($P < 0.05$)
ND: Not detected

FIGURE 25.4 Compound detected in the extracts of flours, porridges, and digested porridge (μg/g) [60].

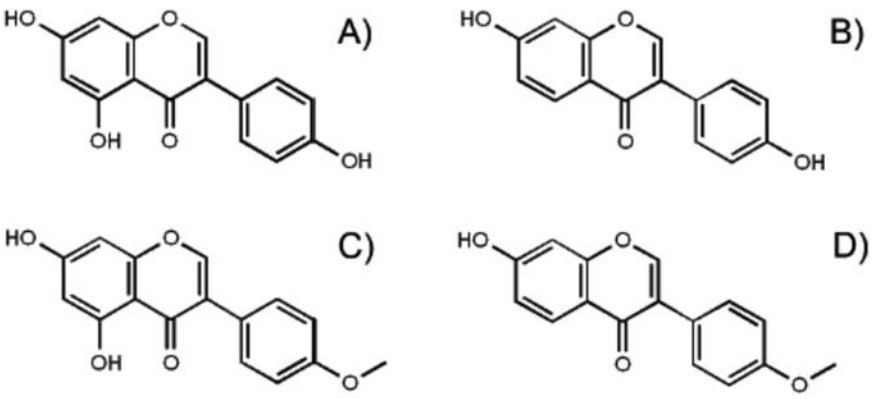


FIGURE 25.5 Chemical structures of (A) genistein, (B) daidzein, (C) biochanin A, and (D) formononetin [66].

Diphenyl-1-picrylhydrazyl and hydroxyl radical scavenging potentials were not correlated with the total flavonoids content. Compounds detected in the extracts of flours, porridge, and digested porridge are shown in Fig. 25.4.

Clover

Three classes of phytoestrogens are found in red clover: isoflavones, coumestrols, and lignans. Since the amounts of coumestrols and lignans are small, they do not contribute greatly to the effects of red clover [61]. Isoflavones are found in physiologically significant amounts in legumes, mainly soy and red clover [62,63]. Isoflavones are a subclass of flavonoids [64], and the key structural elements that are essential for the estrogenic effects of isoflavones are the phenolic ring and 2-4 hydroxyl groups in certain positions [65]. Sazdanic et al. [66] reported that the isoflavone content in red clover is primarily a result of genetic factors but is also influenced by many other complex environmental influences. Usually, these compounds are accumulated in red clover leaves, and their content fluctuates during different

TABLE 25.5 The names of selected phenolics in examined *Trifolium pretense* MeOH extracts [75].

Compound
Phenolic acids
Hinic acid
Gallic acid
Protocatechuic acid
Chlorogenic acid
2,5-Dihydroxybenzoic acid
p-Hydroxybenzoic acid
Caffeic acid
Vanillic acid
Syringic acid
p-Coumaric acids
Ferulic acid
Sinapic acid
o-Coumaric acid
3,4-Dimethoxycinnamic acid
Cinnamic acid
Flavonoids
Apigenin
Apigenin 7-*O*-glucoside
Apigein
Vitexin
Amentoflavone
Baicalein
Baicalin
Daidzein
Genistein
Isorhamnetin
Kaempferol
Kaempferol 3-*O*-glucoside
Chrysoeriol
Luteolin
Luteolin 7-*O*-glucoside
Quercetin
Quercetin 3-*O*-glucoside
Quercitrin
Hyperoside
Rutin
Myricetin

(*Continued*)

TABLE 25.5 (Continued)

Compound
Naringenin
Epicatechin
Catechin
Epigallocatechin gallate
Coumarins
Umbelliferone
Aesculetin
Scopoletin
Lignans
Matairesinol
Secoisolariciresinol

phenophases. In their research, an increase in biosynthesis of isoflavones as a response to different abiotic factors is also considered. The highest yield of isoflavones is obtained by the vacuum-drying method, and the isoflavone composition depends on the ensiling process. The estrogenic properties of red clovers are commonly listed as their main pharmacological activity, even though the efficacy of estrogenic action of plant-derived preparations is still widely discussed [67]. The distribution of isoflavones in red clover is dependent on various factors, such as genotype, environment, and climate [68]. Hoffman et al. [69] reported that when cows were fed alfalfa and red clover with similar acid detergent fiber (ADF) content, the milk yield of cows that were fed red clover was lower than that of cows that were fed alfalfa in first year, and milk yields were similar between cows that were fed alfalfa and red clover in second year. The researchers reported that intake of ADF and neutral detergent fiber was lower for cows that were fed red clover in both years of the experiment. They concluded that when red clover contained the same ADF content as did alfalfa, cows that were fed red clover ate less ADF, neutral detergent fiber, and dry matter (DM), resulting in lower milk yield potential. Winters et al. [70] stated that a relationship between nitrogen and protein levels in white clover herbage and the ensiling process had been demonstrated. In their experiment, the extent of protein degradation during ensilage was influenced by the initial nitrogen content of the fresh herbage. They concluded that a higher initial protein content results in a higher proportion of protein degradation during ensiling. Butkute et al. [71] noted that red clover may supply food with many of the bioactive compounds that are required in the human diet and could be used as an ingredient in functional food, but the nutritional, mineral, and phytochemical value varies within and among species. Sharaf et al. [72] reported that the ethanolic extract of the seeds of *Trifolium alexandrium* afforded a new, naturally occurring compound that was identified as methyl-α-glucose. The known compounds quercetin, kaempferol, and apigenin 7-*O*-β-D-glucoside and the nucleoside xanthoside were also isolated in their experiment. Tava et al. [73] revealed that red clover was characterized by the presence of quercetin, formononetin, and biochanin A derivatives as the most abundant flavonoids, whereas snow clover was characterized by higher amounts of quercetin and prunetin derivatives. Moreover, the higher amount of prunetin in snow clover suggests a possible role of this isoflavone as a chemotaxonomic marker for this subspecies. Lemeziene et al. [74] found that red clover accumulated the highest concentrations of formononetin (51%) and biochanin A (40%) at the flowering stage, and the concentrations of formononetin, biochanin A, daidzein, and genistein at the flowering stage were 2.61−4.40, 1.79−3.32, 0.06−0.14, and 0.36−0.59 mg/g DM, respectively. The ravage formononetin concentration of 11 genotypes was 3.02 mg/g DM, that of biochanin A was 2.70 mg/g DM, that of daidzein was 0.10 mg/g DM, and that of genistein was 0.45 mg/g DM. The average concentration of all four isoflavones at the flowering stage during the two experimental years was 6.66 mg/g DM and ranged from 5.4 to 8.09 mg/g DM. The chemical structures of (A) genistein, (B) daidzein, (C) biochanin A, and (D) formononetin are shown in Fig. 25.5. The names of selected phenolics in examined *T. pretense* MeOH extracts are listed in Table 25.5. Some of the compounds isolated from *Trifolium* species are shown in Fig. 25.6.

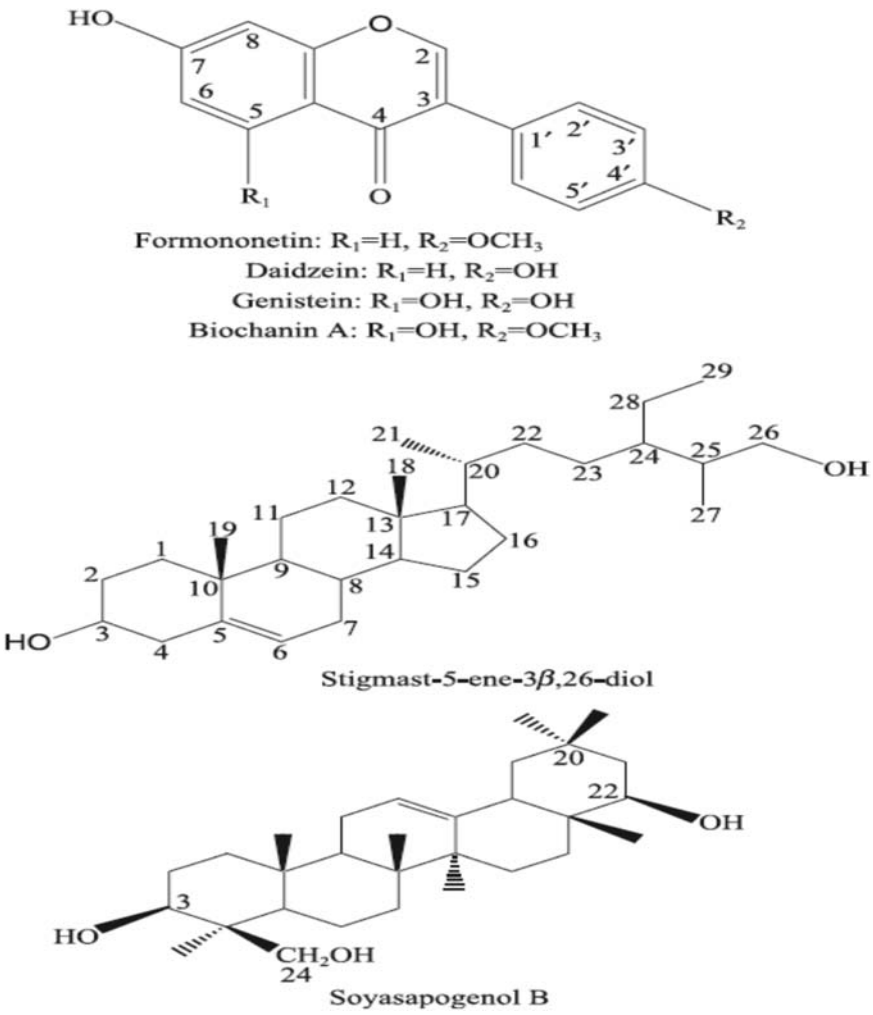


FIGURE 25.6 Some of the compounds isolated from *Trifolium* species [67].

Conclusion

Legumes play a key role in traditional medicine. In most countries, especially in Iran and China, Western medicine and traditional medicine have been practiced side by side. Soybeans have been one of the most important sources of vegetable-sourced proteins. The soybean itself is composed of approximately 40% protein, 20% oil, 35% carbohydrates, and 5% trace minerals and other compounds. The most important functional components of soy are alpha-linolenic acid, isoflavones, lecithins, lectins, linoleic acid, peptides, phytosterols, protein, and saponin. Peanuts are important source of oil, folate, antioxidants, protein, and essential fatty acids (linoleic), and peanuts ranked fourth in oilseed crops in the world after soybeans, rapeseed, and cotton. Peanuts contain flavonoids, tannins, terpenoids, saponins, steroids, and alkaloids, as shown by positive reactions to the respective test reagents. Cowpeas are valuable source of protein, carbohydrate, mineral and vitamins, and it also contain biologically active components including phenols, phytic acid, saponin, oligosaccharides, fiber, etc. *Trifolium* (Leguminosae or Fabaceae) is one of the most important genera of the Leguminosae family, in terms of both its agricultural value and the number of species. The genus *Trifolium* is found in temperate and subtropical regions of both hemispheres. Plants from the genus *Trifolium* have been used in traditional medicine by many cultures. In Asian traditional medicinal practices, some *Trifolium* species are used for their expectorant, analgesic, and antiseptic properties and to treat rheumatic aches. The high concentrations of quercetin and soyasaponin make the seeds of some *Trifolium* species a potential source of health-promoting phytochemicals for use in human nutrition. Cultivation of leguminous plants can benefit both the plants and soils by yielding nitrogen in compound form. Legumes are often used in traditional medicine, which are natural and organic health care systems that view the body as a complex network of interconnected parts.

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Chapter 26

Effects of nuts consumption on cardiovascular diseases and other chronic diseases

Viola Vargova[1], Ram B. Singh[1,2], Jan Fedacko[1], Dominik Pella[1], Daniel Pella[1], Agnieszka Wilczynska[3], Viliam Mojto[4], O.A. Al-bawareed[5] and V.I. Torshin[6]

[1]Faculty of Medicine, PJ Safaric University, Kosice, Slovakia, [2]Halberg Hospital and Research Center, Civil Lines, Moradabad, India, [3]The Tsim Tsoum Institute, Krakow, Poland, [4]3rd Department of Internal Medicine, Faculty of Medicine, Comenius University, Bratislava, Russia, [5]Peoples's Friendship University of Russia, Moscow, Russia, [6]Department of Physiology, RUDN University, Moscow, Russia

Introduction

Nuts may be an important functional food to help ensure food security. The U.N. Decade of Action on Nutrition 2016−25 is an initiative that calls on the U.S. Food and Agriculture Administration and the World Health Organization to take action to accelerate its implementation [1]. The purposes of the initiative are to achieve the global nutrition and diet-related non-communicable disease (NCD) targets by 2025 and to contribute to the realization of the sustainable development goals by 2030. Both the agencies emphasize making full use of available food biodiversity and nutrient density, which includes nuts, as well as fruits, vegetables and whole grains, to enhance the nutritional status of populations. To achieve this, a better understanding of food biodiversity in dietary intake is required [1]. Nuts are concentrated sources of food energy and nutrients in a package built to promote good health and ward off disease [2,3]. Most physicians and dietitians avoid advising nuts to patients with obesity, diabetes, and hypertension because of the high caloric value of nuts. However, epidemiological studies suggest that nut eating is associated with diminished risk of cardiovascular diseases (CVDs), including coronary artery disease (CAD), stroke, and hypertension [1,4]. Nuts have been an indispensable component of the human diet for thousands of years because of their unique nutrient composition and are thought to play a beneficial role in the prevention of CVDs and diabetes [2−4]. Although nut consumption has been associated with a reduced risk of diabetes and CVDs as well as all-cause mortality, data on less common causes of death have not been systematically assessed [4−6]. Previous reviews missed several studies, after which many more studies have been published [4].

Recent cohort studies have shown that increased consumption of nuts can decrease total mortality and mortality due to many NCDs [6−9]. Only limited information is available on the connection between nut intake and all-cause mortality; hence a systematic review and metaanalysis of nut consumption and risk of CVDs, total cancer, and all-cause and cause-specific mortality have been presented [5−10]. In the systematically reviewed prospective studies that explored the effects of nut consumption on all-cause, CVD, and cancer mortality and quantified the size effect through a meta-analysis, there is no mention of confounding factors associated with nut consumption to assess potential clustering with other covariates [9]. Recent findings also indicate that use of peanuts in peanut butter may reduce its protective quality, leading to no beneficial effect on risk of cardiometabolic diseases [4]. This review aims to illuminate the association of nut consumption with risk of NCDs in all social groups with due consideration of mortality risk due to NCDs.

Nut consumption and risk of all-cause mortality

Previous studies on nut consumption and risk of NCDs, provided inconsistent results [11−15]. Recently several important reviews have been published demonstrating the role of nuts in decreasing cause-specific and all-cause risk of

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mortality. However, the associations between intake of nuts and peanuts (which are actually legumes) and less common causes of mortality have not been investigated. Moreover, approximately, 50% of peanut consumption in the United States is via peanut butter but the association between peanut butter consumption and mortality has not been thoroughly examined. The National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study recruited 566,398 subjects, aged 50−71 years at baseline in 1995−96 [4]. All subjects with baseline NCDs were excluded from the analysis. After a median follow-up of 15.5 years, there were 64,464 deaths due to all the causes. There was a significant inverse association between nut consumption and overall mortality [hazard ratio (HR) C4 vs C1 = 0.78, 95% confidence interval (CI) = 0.76, 0.81, $P \leq .001$] [4]. Significant associations were observed between nut intake and reduced risk of mortality due to cancer or to cardiovascular, respiratory, infectious, renal, or liver disease; however, no such association was seen with mortality due to diabetes or Alzheimer's disease. Furthermore, no significant associations were found between peanut butter intake and all-cause (HR C4 vs C1 = 1.00, 95% CI = 0.98, 1.04, $P = .001$) and cause-specific mortality. It is possible that in a middle-class of population, nut consumption may be inversely associated with all-cause mortality and certain types of cause-specific mortality. Unfortunately for the food industry, changing peanuts into peanut butter was not associated with differential mortality [4].

In a metaanalysis, including 31 reports from 18 prospective studies, there were 12,655 cases of type 2 diabetes, 8862 cases of CVD, 6623 cases of CAD, 6487 cases of stroke, and 48,818 mortality cases [5]. The risk ratio (RR) for each incremental serving per day of nut consumption was 0.80 (95% CI: 0.69, 0.94) for type 2 diabetes without adjustment for body mass index; with adjustment the association was attenuated (RR: 1.03; 95% CI: 0.91, 1.16; nonsignificant). For each serving per day of nut consumption the pooled RRs (95% CIs) were 0.83 (0.76, 0.91) for all-cause mortality, 0.72 (0.64, 0.81) for CAD, and 0.71 (0.59, 0.85) for CVDs. For the comparison of extreme quantiles of nut intake, the pooled RRs (95% CIs) were 1.00 (0.84, 1.19; nonsignificant) for type 2 diabetes, 0.66 (0.55, 0.78) for ischemic heart disease, 0.70 (0.60, 0.81) for CVDs, 0.91 (0.81, 1.02; nonsignificant) for stroke, and 0.85 (0.79, 0.91) for all-cause mortality. This metaanalysis indicates that nut intake is inversely associated with CAD, overall CVDs, and all-cause mortality but not significantly associated with diabetes and stroke. The inverse association between the consumption of nuts and diabetes was attenuated after adjustment for body mass index. These findings support the recommendations to include nuts as part of a healthy diet for the prevention of NCDs.

A larger metaanalysis, including 29 publications, assessed the burden of mortality attributable to low nut consumption calculated for selected regions [6] (see Figs. 26.1−26.5). The summary RRs per 28 g/day increase in nut intake were 0.71 (95% CI: 0.63−0.80, $I^2 = 47\%$, $N = 11$) for CAD, 0.93 (95% CI: 0.83−1.05, $I^2 = 14\%$, $N = 11$) for stroke, 0.79 (95% CI: 0.70−0.88, $I^2 = 60\%$, $N = 12$) for CVDs, 0.85 (95% CI: 0.76−0.94, $I^2 = 42\%$, $N = 8$) for total cancer, 0.78 (95% CI: 0.72−0.84, $I^2 = 66\%$, $N = 15$) for all-cause mortality, 0.48 (95% CI: 0.26−0.89, $I^2 = 61\%$, $N = 3$) for mortality from respiratory disease, 0.61 (95% CI: 0.43−0.88, $I^2 = 0\%$, $N = 4$) for diabetes, 0.25 (95% CI: 0.07−0.85, $I^2 = 54\%$, $N = 2$) for infectious diseases, 0.65 (95% CI: 0.40−1.08, $I^2 = 5.9\%$, $N = 3$) for neurodegenerative diseases, and 0.27 (95% CI: 0.04−1.91, $I^2 = 61\%$, $N = 2$) for kidney disease. These results were similar for tree nuts and peanuts, as is shown in Figs. 26.1−26.5 [6]. The findings revealed that increased nut consumption is associated with reduced risk of CVDs, total cancer, and all-cause mortality, and mortality from respiratory disease, diabetes, and infections. If the associations are causal, An estimated 4.4 million premature deaths in the America, Europe, Southeast Asia, and the Western Pacific may be attributable to a nut intake below 20 g/day in 2013 [6]. Metaanalysis of studies are open to bias because assessments are made by different investigators in varied populations having varied cultures and education with little consideration for confounding factors [9]. This metaanalysis included seven studies to assess all-cause mortality, six studies for CVD mortality, and two studies for cancer mortality with a total of 354,933 participants, 44,636 cumulative incident deaths, and 3,746,534 cumulative person-years. Nut consumption was associated with some baseline characteristics, such as lower body mass index and smoking status, as well as increased intakes of fruit, vegetables, and alcohol. One serving of nuts per week and one serving per day resulted in 4% (RR: 0.96; 95% CI: 0.93, 0.98) and 27% (RR: 0.73; 95% CI: 0.60, 0.88) decreased risk of all-cause mortality, respectively, and decreased risk of CVD mortality (RR: 0.93; 95% CI: 0.88, 0.99 and RR: 0.61; 95% CI: 0.42, 0.91, respectively) [9]. The beneficial effects were attributed to decreased deaths due to CAD rather than decreased stroke deaths. Nut consumption was also associated with decreased risk of cancer deaths when the highest and lowest categories of intake were compared (RR: 0.86; 95% CI: 0.75, 0.98), but no dose effect was shown. It is clear that nut intake may be associated with lower risks of all-cause, CVD, and cancer mortality, but the presence of confounding factors should be taken into account in considering such findings [9].

Since metaanalysis have their own weaknesses, large prospective studies are considered more authentic to assess association of risk factors or protective factors with mortality. In a prospective cohort study among 20,742 male physician with a, mean age of 66.6 years, nut intake between 1999 and 2002 via a food frequency questionnaire and

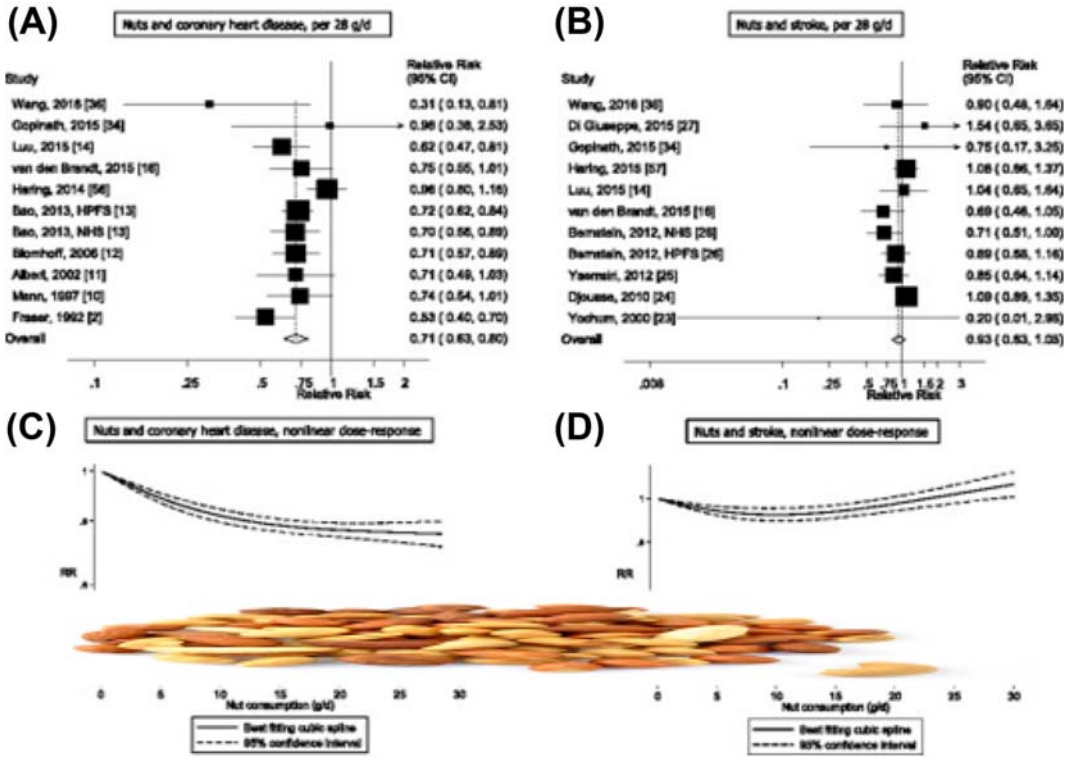


FIGURE 26.1 Nut intake and risk of coronary disease and stroke. *Modified from Aune D, Keum N, Giovannucci E, Fadnes LT, Boffetta P, Greenwood DC, et al. Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: a systematic review and dose−response meta-analysis of prospective studies. BMC Med 2016;14(1):207 [Epub 2016 December 5].*

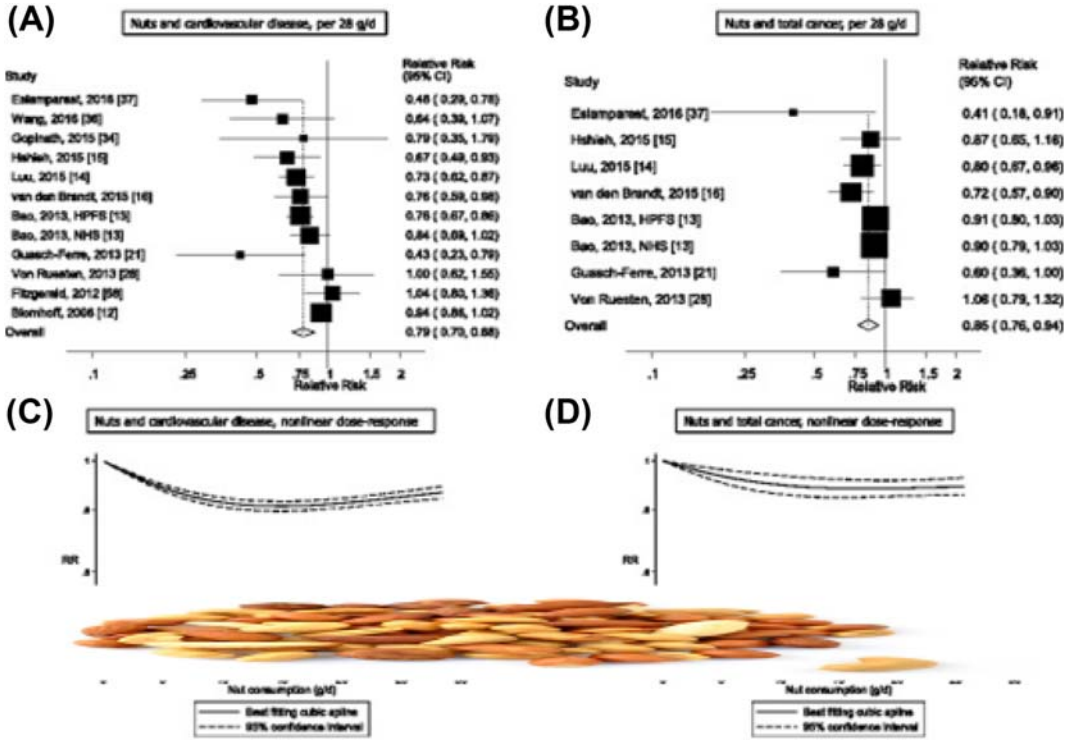


FIGURE 26.2 Nut intake and risk of cardiovascular diseases and total cancer. *Modified from Aune D, Keum N, Giovannucci E, Fadnes LT, Boffetta P, Greenwood DC, et al. Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: a systematic review and dose−response meta-analysis of prospective studies. BMC Med 2016;14(1):207 [Epub 2016 December 5].*

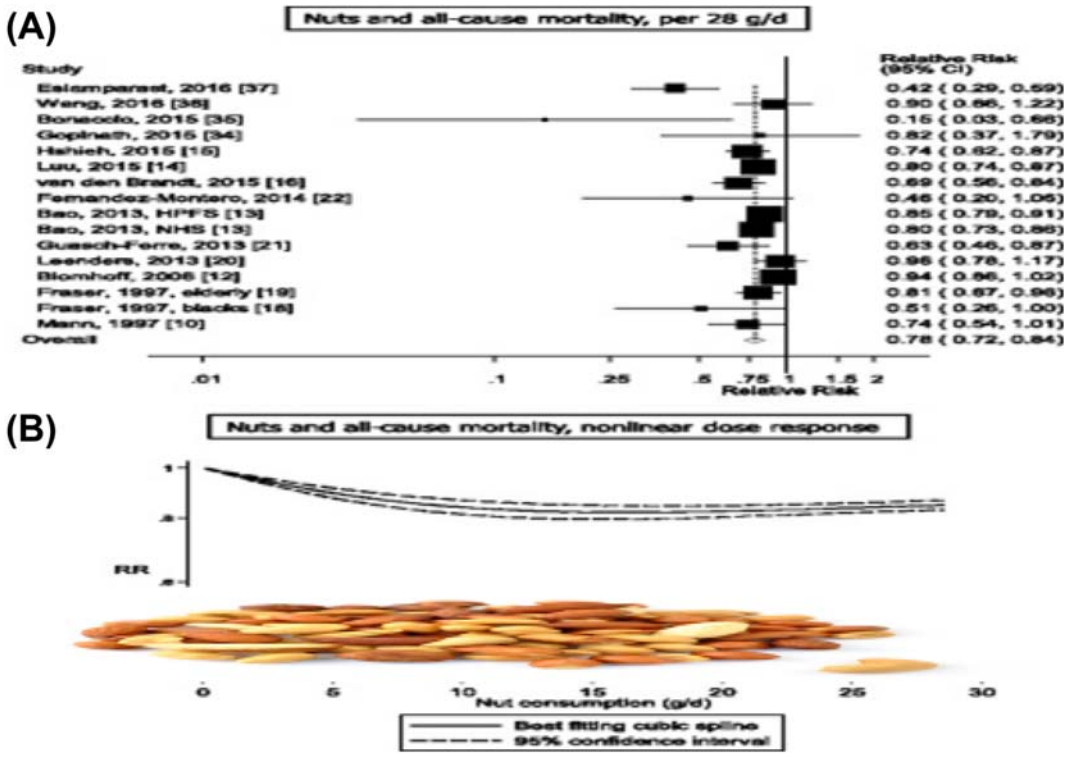


FIGURE 26.3 Nut intake and all-cause mortality.

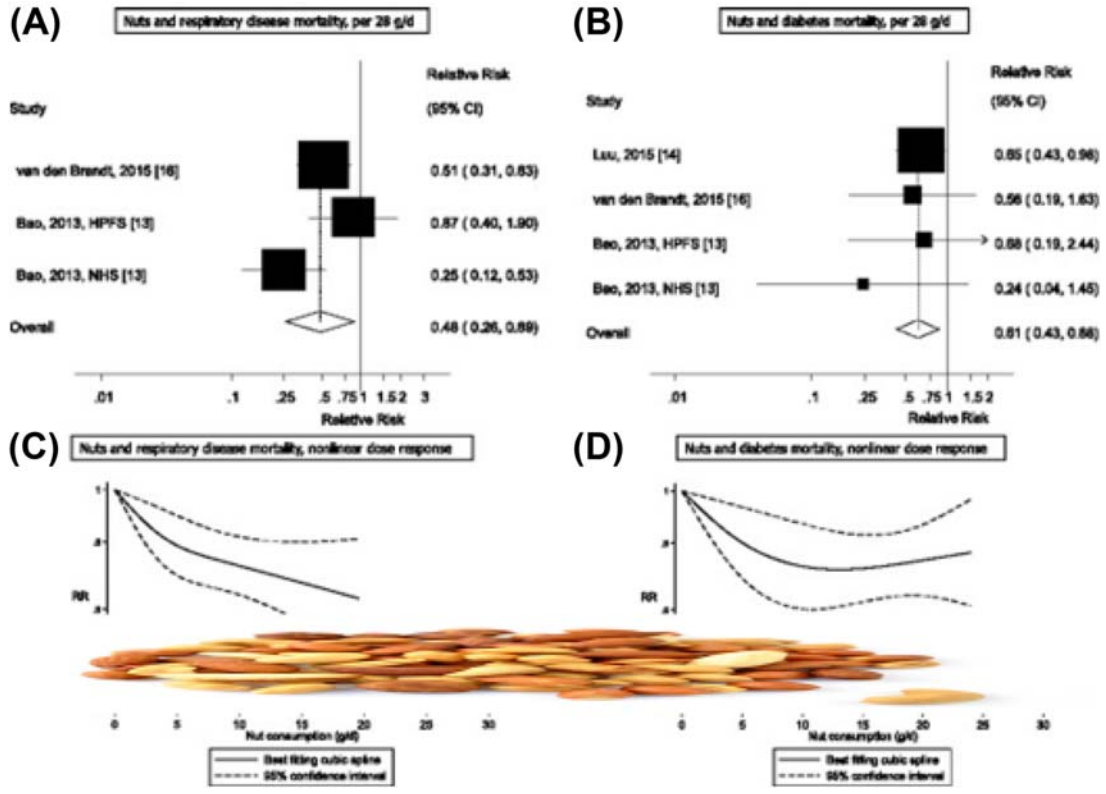


FIGURE 26.4 Nut intake and mortality due to respiratory diseases and diabetes.

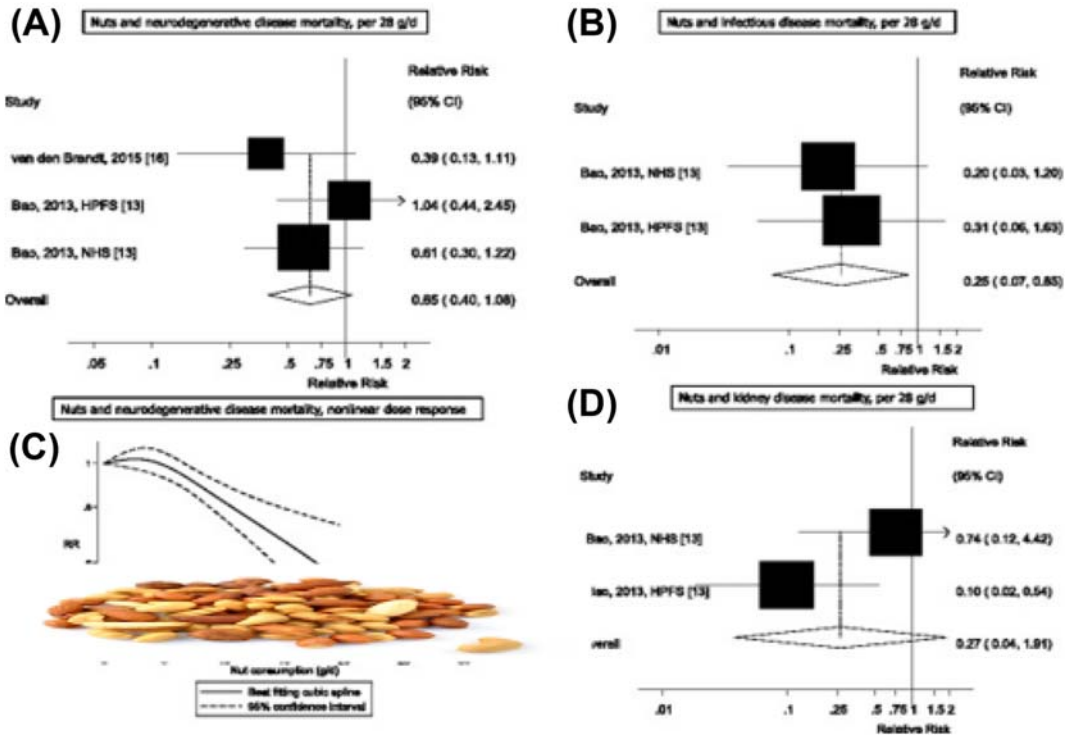


FIGURE 26.5 Nut consumption neurodegenerative disease, infectious disease, and kidney disease mortality.

ascertained deaths through an endpoint committee were examined [7]. During a mean follow-up of 9.6 years, 2732 deaths occurred. The median nut consumption was one serving/week. Multivariable-adjusted HRs (95% CIs) were 1.0 (reference), 0.92 (0.83, 1.01), 0.85 (0.76, 0.96), 0.86 (0.75, 0.98), and 0.74 (0.63, 0.87) for nut consumption of never or less than 1 serving/month, 1−3 servings/month, 1 serving/week, 2−4 servings/week, and 5 or more servings/week, respectively (P-linear trend $<.0001$) after adjustment for age; body mass index; alcohol use; smoking; exercise; prevalent diabetes and hypertension; and intakes of energy, saturated fat, fruit and vegetables, and red meat. In a secondary analysis, results were consistent for CVD mortality but only suggestive and nonstatistically significant for mortality due to CAD and cancer [7]. These data are consistent with an inverse association between nut consumption and the risk of all-cause and CVD mortality in U.S. male physicians. However, cancer and CAD mortality showed only a nonsignificant association, which may be due to inclusion of only a population of physicians who presumably were of high socioeconomic status (SES).

In view of this finding, cause-specific mortality in Americans of African and European descent who were predominantly of low SES and in Chinese individuals in Shanghai, China, were examined in three large cohorts [8]. One included 71,764 U.S. residents of African and European descent, primarily of low SES, who were participants in the Southern Community Cohort Study (SCCS) in the southeastern United States, and the other two cohorts included 134,265 participants in the Shanghai Women's Health Study (SWHS) and the Shanghai Men's Health Study (SMHS) in Shanghai, China. Peanuts were the main nut that were consumed. After a median follow-up of 5.4 years in the SCCS, 6.5 years in the SMHS, and 12.2 years in the SWHS, 14,440 deaths were identified. More than half of the women in the SCCS were ever smokers compared with only 2.8% in the SWHS. The ever-smoking rate for men was 77.1% in the SCCS and 69.6% in the SMHS. Nut intake was inversely associated with risk of total mortality in all three cohorts (all $P < .001$ for trend), with adjusted HRs associated with the highest versus lowest quintiles of intake being 0.79 (95% CI, 0.73−0.86) and 0.83 (95% CI, 0.77−0.88), respectively, for the U.S. and Shanghai cohorts [8]. This inverse association was predominantly driven by CVD mortality ($P < .05$ for trend in the U.S. cohort; $P < .001$ for trend in the Shanghai cohorts). The finding also revealed a significant inverse association for CAD in all ethnic groups (HR: 0.62; 95% CI: 0.45−0.85 in blacks; HR: 0.60; 95% CI: 0.39−0.92 in whites; and HR: and 0.70; 95% CI: 0.54−0.89 in Asians) for the highest versus lowest quintile of nut intake. Only in Asians were the associations for ischemic stroke (HR: 0.77; 95% CI: 0.60−1.00 for the highest vs lowest quintile of nut intake) and hemorrhagic stroke (HR: 0.77; 95% CI: 0.60−0.99 for the highest vs lowest quintile of nut intake) significant. The association between nuts and mortality was similar for

men and women and for blacks, whites, and Asians and was not modified by the presence of metabolic conditions at study enrollment [8]. It is clear from all the cohort studies and metaanalyses that nut consumption was associated with decreased overall and CVD mortality across different ethnic groups and among individuals from low SES groups. The intake of nuts, particularly peanuts (ideally 28 g/day), given their general affordability, may be considered a cost-effective measure for health promotion and for prevention of NCDs and mortality. In a retrospective study, death records of 2222 individuals (1385 men and 837 women) aged 25−64 years were randomly selected from 3034 death records and studied by verbal autopsy questionnaires [10]. All the risk factors and protective factors were assessed by a trained scientist using questionnaires, which were completed with the help of the decedent's spouse and a local treating doctor. The prevalence of optimal prudent foods intake behavior (> 250 g/day of fruits, vegetables, nuts and legumes) was observed among 51.4% ($N = 712$) men and 50.4% ($N = 422$) women. Western-type food (> 255 g/day) intake was observed among 63.2% ($N = 875$) of men and 59.9% ($N = 502$) of women. The prevalence of optimal functional food intake was significantly greater among men compared to women (19.4 vs 14.6%, $P < .01$). Functional food intake, including intake of nuts, was inversely associated with deaths due to NCDs [10].

Effects of nuts on clinical and biochemical risk factors

The findings from more recent studies indicate that inclusion of nuts in the overall diet may be protective against NCDs [3−18]. Hypertension is a risk factor for CAD, stroke, and heart failure, and dietary factors may play an important role in prevention. The consumption of nuts could reduce the risk of hypertension and its complications. However, only a few studies have been published to evaluate this potential association [4,19,20]. A prospective cohort of 15,966 participants from the Physicians' Health Study who were free of hypertension at baseline were examined [19]. During 237,585 person-years of follow-up, 8423 new cases of hypertension occurred. Multivariable-adjusted hazard ratios (95% CI) for hypertension were 0.97 (0.91−1.03), 0.98 (0.92−1.05), 0.96 (0.89−1.03), and 0.82 (0.71−0.94) for nut consumption of 1−2 times per month and 1, 2−6, or more than 7 time per week, respectively, compared to patients who did not eat nuts. In a secondary analysis stratified by body mass index, there was an inverse relation between nut intake and hypertension in lean subjects ($P = .0019$) but not in overweight or obese subjects ($P = .0037$). It is possible that nut consumption is associated with a lower risk of hypertension in U.S. male physicians and that such a relationship may be influenced by adiposity. However, this study did not report on any association with other confounders, such as functional foods and nutrients in the diet and the waist-to-hip ratio.

In another study, of 9919 Spanish university graduates, which examined the association between nut consumption and the incidence of hypertension, the graduates were followed up biennially for a median of 4.3 years [20]. The intake of nuts was classified into four categories: rarely/never, 1−3 times per month, 1 time per week, and 2 or more times per week, and participants were classified according to incident cases of hypertension when, being free of hypertension at baseline, a participant subsequently reported a physician-made diagnosis of hypertension in at least one of the follow-up questionnaires. The incidence of hypertension was 12.4 per 1000 person-years. No association between nut consumption and incidence of hypertension was found after adjusting for sex, age, and other dietary and nondietary potential confounders (HR for those in the highest versus lowest nut consumption category: 0.77, IC 95%: 0.46−1.30; $P = .795$). These data do not provide evidence for an inverse association between nut consumption and incident hypertension in this cohort because consideration of nut quantity was very low (rare intake to two times per week). It is important that nuts should be consumed at least five times a week to have a beneficial effect on health and diseases. Further results from cohorts and trials with a higher baseline risk of hypertension should be obtained to test this relationship.

In the Nurses' Health study [5], the association between nut consumption and risk of CAD was examined among 84,409 nurses during a follow-up of 14 years. Only 5% of nurses consumed five or more servings of nuts a week, whereas one-third hardly ever consumed any nuts, resulting in a 50% reduction in risk of CAD. However, a moderate risk of CAD was observed among subjects who consumed moderate amount of nuts. A decreased risk of CAD from nut consumption was maintained across subgroups stratified to test for major confounding factors, which suggested that the effect may be large and significant. Dietary nut intake has been associated with a reduced risk of CAD mortality; however, the mechanism is unclear. Since components of nuts have antiinflammatory and antiarrhythmic properties, part of the benefit may be due to reduction in sudden cardiac death (SCD) and CAD. In the U.S. Physicians Health study, among 21,464 men, increasing frequency of nut consumption at 12 months follow-up (after a follow-up of 17 years) was associated with a lower risk of SCD and other cardiovascular endpoints after controlling for known cardiac risk factors and other dietary habits ($P = .01$) [13]. Compared with men who rarely or never consumed nuts, those who consumed nuts two or more times per week had reduced risk of SCD (RR: 0.53, 95% CI: 0.50−0.98). In contrast, nut

intake was not associated with a significant reduction in the risk of nonsudden deaths or nonfatal myocardial infarction. It seems that all nuts and the lower quantity of nuts may not have sufficient beneficial effects on blood pressure.

Cohort studies have their own limitations compared to the power of randomized, controlled trials in determining causality, because there is always confounding by other factors. Moreover, frequent nut eaters differ in many respects from people who eat fewer or no nuts. In the Nurses' Health Study, of the four demarcated consumption groups, the high-intake group came out most favorably for 16 of 23 factors, most of which appear to be independent rather than a consequence of nut consumption. The Nurses' Health study and the U.S. Physicians Health study are postal studies whose participants have never been subjected to the clinical routines of other U.S. cohort studies. Self-reported hypertension was marginally least common among the high-consumption group, whereas hypercholesterolemia was marginally most common. The authors indicated eight constituents of nuts that might be beneficial but could not be more specific, which is a problem in demonstrating the independent effects of nuts in beneficial dietary patterns. However, randomized, controlled trials may provide more potential evidence regarding the role of nuts in the prevention of NCDs.

Several previous studies showed consistent benefits of nut and peanut consumption on CAD risk and associated risk factors [15−17,21,22]. These studies have considered various endpoints, including fatal CAD, total CAD death, total CAD, and nonfatal myocardial infarct. A pooled analysis of four U.S. epidemiological studies that were reviewed showed that subjects in the highest-intake group for nut consumption had an approximately 35% reduced risk of CAD incidence, mainly owing to a decline in SCD [18].

Diet, nut intake, and risk of non-communicable diseases

In most studies on dietary patterns, nuts have been considered along with fruits, legumes, and vegetables to demonstrate their influence on various risk factors of CVD [7−18]. In most of these studies, omega-3 fatty acid and arginine content of dietary pattern may have been responsible for an inverse association with ventricular premature contraction, acute myocardial infarction, and inflammation [19,20,23,24]. In other studies, nut consumption was inversely associated with risk of hypertension in one study but showed no association in another [19,20].

Mediterranean-style diets or Western-style diets may have a multidimensional beneficial or adverse effect on NCDs, including atherogenesis, thrombosis, and diabetes, owing to their antioxidants, vitamins, and antiinflammatory and lipid-lowering effects [23−26]. Fruit, vegetable, and nut intake may have an independent role, separate from low fat, calories, and low-density lipoprotein (LDL) cholesterol content. Antioxidants can protect the LDL cholesterol from oxidation in its atherogenic product oxidized LDL, which is more attractive for macrophages during development of atherosclerosis [23,24]. Antioxidants also protect high-density lipoprotein (HDL) cholesterol oxidation, which is protective against atherothrombosis. Dietary dimensions may be provided by hemostatic factors, omega-3 fatty acids, monounsaturated fatty acids (MUFA), amino acids, vitamins, flavonoids, folic acids, plant sterols, alcohol, and wine [21−30]. Other functional foods, such as onions, garlic, spices, green tea, and herbs, could be another dimension that may have a beneficial effects on human health and diseases [25−29].

Controlled trials of nut consumption

Clinical evaluation of the effects of many different nuts and peanuts on lipids, lipoproteins, and various CAD risk factors, including oxidation, inflammation, and vascular reactivity, have been reported in various studies [21,22,26−29,31]. These studies reported a beneficial effect on these risk factors. The LDL cholesterol−lowering response of nut and peanut studies is greater than expected on the basis of blood cholesterol−lowering equations that are derived from changes in the fatty acid profile of the diet. Thus in addition to a favorable fatty acid profile, nuts and peanuts contain other bioactive compounds that explain their multiple clinical benefits. Other macronutrients include plant protein and fiber; micronutrients, including potassium, calcium, magnesium, and tocopherols; and phytochemicals, such as phytosterols, phenolic compounds, resveratrol, and arginine. Nuts and peanuts are food sources that are a composite of numerous cardioprotective nutrients, and if nuts are routinely incorporated into a healthy diet, the population risk of NCDs would be expected to decrease markedly.

Walnuts are a rich source of arginine, antioxidants, and alpha-linolenic acid (ALA), a plant *n*-3 fatty acid. It is possible that walnut intake may reverse endothelial dysfunction. In a randomized, crossover design, 21 hypercholesterolemic men and women were given a cholesterol-lowering Mediterranean diet and a diet of similar energy and fat content in which walnuts replaced approximately 32% of the energy from monounsaturated fat [32]. Participants followed each diet for 4 weeks. After each intervention, fasting blood levels and ultrasound measurements of brachial artery vasomotor function were examined. Eighteen subjects completing the protocol had suitable ultrasound studies. Compared with

the Mediterranean diet, the walnut diet improved endothelium-dependent vasodilation and reduced levels of vascular cell adhesion molecule 1 ($P < .05$ for both). Endothelial dysfunction is associated with CAD and its risk factors and is reversed by antioxidants arginine and marine *n*-3 fatty acids. Endothelium-independent vasodilation and levels of intercellular adhesion molecule 1, C-reactive protein, homocysteine, and oxidation biomarkers were similar after each diet. The walnut diet significantly reduced total cholesterol ($-4.4\% \pm 7.4\%$) and LDL cholesterol ($-6.4\% \pm 10.0\%$) ($P < .05$ for both). Cholesterol reductions correlated with increases in both dietary ALA and LDL gamma-tocopherol content, and changes in endothelium-dependent vasodilation correlated with those of cholesterol-to-HDL ratios ($P < .05$ for all). It is likely that substituting walnuts for monounsaturated fat in a Mediterranean diet improves endothelium-dependent vasodilation in hypercholesterolemic subjects. This finding might explain the cardioprotective effect of nut intake beyond cholesterol lowering. Another study was conducted to investigate whether the addition of walnuts or olive oil to a fatty meal have differential effects on postprandial vasoactivity, lipoproteins, markers of oxidation and endothelial activation, and plasma asymmetric dimethylarginine (ADMA) [33]. Compared with a Mediterranean diet, a walnut diet has been shown to improve endothelial function in hypercholesterolemic patients. In a randomized trial, in a crossover design, 12 healthy subjects and 12 patients with hypercholesterolemia were administered, two high-fat meal sequences to which 25 g of olive oil or 40 g of walnuts had been added [33]. Both test meals contained 80 g fat of and 35% saturated fatty acids, and consumption of each meal was separated by 1 week. Venipunctures and ultrasound measurements of brachial artery endothelial function were performed after fasting and 4 hours after test meals. In both study groups, flow-mediated dilation (FMD) was worse after the olive oil meal than after the walnut meal ($P = .006$, time-period interaction). Fasting, but not postprandial, triglyceride concentrations correlated inversely with FMD ($r = -0.324$; $P = .024$). Flow-independent dilation and plasma ADMA concentrations were unchanged, and the concentration of oxidized LDLs decreased ($P = .051$) after either meal. The plasma concentrations of soluble inflammatory cytokines and adhesion molecules decreased ($P < .01$) independently of meal type, except for E-selectin, which decreased more ($P = .033$) after the walnut meal. It seems that adding walnuts to a high-fat meal acutely improves FMD independently of changes in oxidation, inflammation, or ADMA. Both walnuts and olive oil preserve the protective phenotype of endothelial cells. E-selectin is a proinflammatory factor that is responsible for rupture of the atherosclerotic plaque, resulting into atherothrombosis, indicating that walnuts can prevent rupture of the hot plaque.

An earlier review of recent epidemiological evidence on nut intake and health outcomes focused on studies in which nut consumption was directly assessed or in which nuts were included in a dietary score or pattern [34]. Epidemiological studies have been remarkably consistent in showing an association between nut consumption and a reduced risk of CVDs, as described above. Some evidence has emerged recently to suggest that nuts have health-protective benefits other than those related to CAD. Frequent nut intake probably reduces the risk of diabetes mellitus among women, but its effects in men are unknown. Evidence of the anticarcinogenic effects of nuts is somewhat limited because studies in the past two decades have examined only three tumor sites, and the benefits appear to be manifested only in women. However, the protective benefits of frequent nut consumption against gallstone diseases are observed in both sexes. Long-term nut consumption is linked with lower body weight and a lower risk of obesity and weight gain. A dietary pattern or score that includes nuts is consistently related with beneficial health outcomes, and this provides indirect evidence of the salutary benefits of nut consumption. More longitudinal studies are needed to clarify the possible effects of nuts on diseases other than CAD [13–20].

Nuts are rich in the favorable fatty acid profile containing high total and MUFA and omega-3 fatty acids. which probably contributes to the beneficial effects of nut consumption observed in epidemiological studies related to CAD and diabetes and feeding trials. Besides fat, the complex matrices of nuts contain many bioactive compounds: essential and nonessential amino acids, antioxidants, fiber, minerals, tocopherols, and phenolic compounds. By virtue of their unique composition, nuts are likely to benefit newer cardiovascular risk biomarkers, such as LDL oxidizability, soluble inflammatory molecules, and endothelial dysfunction. Protection against LDL oxidation by nut intake has been documented in some, but not all, clinical studies. Eating one daily serving of mixed nuts may be associated with lower oxidized LDL concentrations. Regarding inflammation, cross-sectional studies have shown that nut consumption is associated with lower concentrations of circulating inflammatory molecules and higher plasma adiponectin, a potent antiinflammatory adipokine. Clinical studies with nuts have documented reduced inflammatory cytokine concentrations but no consistent changes in C-reactive protein. Only walnuts have been formally tested for effects on endothelial function [32,33]. After both walnut diets and single walnut meals, favorable vasoreactivity changes have been observed. Walnut consumption also reduces expression of endothelin 1, a potent endothelial activator, in an animal model of accelerated atherosclerosis. Beneficial effects on vascular reactivity may be ascribed to several constituents of walnuts: L-arginine, the precursor of nitric oxide, ALA, and phenolic antioxidants. Although more studies are warranted, the emerging picture is that nut consumption beneficially influences cardiovascular risk beyond cholesterol lowering.

Nutritional recommendations to prevent CVDs and promote longevity may need to focus on overall dietary patterns rather than individual foods such as nuts or a single nutrient [25,28,29].

In a study of the chronic effects of dietary fat on the postprandial expression of proinflammatory genes in peripheral blood mononuclear cells (PBMCs) in healthy subjects, 20 healthy men followed three different diets for 4 weeks each, according to a randomized crossover design[25]. The Western diet consisted of 15% protein, 47% carbohydrates, and 38% fat [22% saturated fatty acid (SFA)]; the Mediterranean diet consisted of 15% protein, 47% carbohydrates, 38% fat (24% MUFA); the third diet was a carbohydrate-rich and *n*-3 diet, consisting of 15% protein, 55% carbohydrates, and less than 30% fat [8% polyunsaturated fatty acid (PUFA)]. After a 12-hour fast, the volunteers were given a breakfast with a fat composition similar to that consumed in each of the diets: a butter breakfast (35% SFA), an olive oil breakfast (36% MUFA), or a walnut breakfast (16% PUFA, 4% ALA). The butter breakfast induced a higher increase in tumor necrosis factor alpha (TNF-α) messenger RNA (mRNA) expression than did the olive oil and walnut breakfasts ($P = .014$) in PBMCs. Moreover, a higher postprandial response in the mRNA of interleukin 6 (IL-6) with the intake of butter and olive oil breakfasts was found than with the walnut breakfast ($P = .025$) in these cells. However, the effects of the three fatty breakfasts on the plasma concentrations of these proinflammatory parameters showed no significant differences ($P =$ nonsignificant). It seems that consumption of a butter-enriched meal elicits greater postprandial expression of proinflammatory cytokine mRNA in PBMCs, compared to the olive oil and walnut breakfasts. Long-term consumption of walnuts as breakfast may be associated with a significant reduction in the proinflammatory cytokines in the tissues. Esposito et al. administered a Mediterranean diet among patients with metabolic syndrome compared to standard diet [27]. There was a significant increase in endothelial function in the Mediterranean diet group compared to control subjects.

In several clinical trials using Mediterranean-style diets—the Indian Experiment of Infarct Survival, the Lyon Heart Study, the Indo-Mediterranean diet heart study, and the PREDIMED Study—nuts have been used as important food to decrease morbidity and mortality [21,22,26–36]. In the Indian studies, the intervention group was advised to consume 600 g/day of fruits, vegetables, and legumes as well as almonds and walnuts (50–60 g/day) in a soup or semisolid form. Since almonds are hard, they may be soaked with water for few hours or overnight to make them soft, which is a good ancient strategy to protect the gums. Tomato soup or skim milk curd (yogurt) was commonly used to mix crushed almonds and walnuts and other foods, which were grilled with mustard oil. The control group was advised to eat a low-fat diet consistent with the National Cholesterol Education Program (see Tables 26.1 and 26.2). Plasma lipid peroxide

TABLE 26.1 Effect of diets rich in almonds and walnuts in patients with acute myocardial infarction [29] (tubers not included).

Foods	Intervention group ($N = 204$)		Control group ($N = 202$)	
Foods and nutrients	**4–7 days**	**After 1 year**	**4–7 days**	**After 1 year**
Fruits and vegetables (g/day)	508.4 ± 28.66**	575 ± 91.4**	254.4 ± 17.2	220.5 ± 19.6
Legumes and pulses (g/day)	80.5 ± 6.6**	95.0 ± 8.9**	52.5 ± 4.6	45.6 ± 5.6
Almonds and walnuts (g/day)	82.4 ± 5.7**	75.5 ± 5.2**	–	11.6 ± 3.2
Fish (g/day)	52.5 ± 6.5**	22.4 ± 4.1**	20.2 ± 3.1	10.5 ± 3.5
Chicken (g/day)	–	10.2 ± 3.2*	76.2 ± 6.5	66.5 ± 10.5
Mustard or soybean oil	18.4 ± 3.9*	31.5 ± 5.5**	10.5 ± 2.3	6.8 ± 2.8
Butter or clarified butter (g/day)	2.5 ± 0.6**	3.3 ± 0.71*	10.5 ± 2.6	12.6 ± 3.5
Skim milk (mL/day)	161.2 ± 12.0	152 ± 14.5*	150.2 ± 8.0	165.5 ± 16.1
Wheat chapati	5.5 ± 1.6**	30.6 ± 5.5	50.6 ± 6.6	55.6 ± 7.8
Bread, biscuits (g/day)	10.6 ± 2.2*	25.5 ± 6.2**	230.6 ± 20.1	212.2 ± 18.1
Rice and wheat cereals(g/day)	25.6 ± 2.4	30.6 ± 5.5	30.2 ± 3.1	35.6 ± 4.8
Honey or raisins (g/day)	2.6 ± 0.8	5.5 ± 1.2	–	–
Sugar (g/day)	16.4 ± 3.7*	12.6 ± 3.4*	25.5 ± 5.4	30.5 ± 7.6
Alpha-linolenic acid (g/day)	1.0 ± 0.46**	1.8 ± 0.66**	0.5 ± 0.11	0.65 ± 0.14
Ascorbic acid (mg/day)	474 ± 70.5**	440.6 ± 100.6**	150.2 ± 10.6	160 ± 38.0

P values were obtained by comparison of intervention and control groups after 1 week and after 1 year. *$P < .05$; **$P < .01$.

TABLE 26.2 Effect of a diet rich in almonds and walnuts on oxidative stress, vitamins, and cardiac damage in relation to dietary alpha-linolenic acid [28].

	Intervention group ($N = 204$)		Control group ($N = 202$)	
	Baseline, third day	Seventh day	Baseline, third day	Seventh day
Dietary alpha-linolenic acid (g/day)	1.0 ± 0.46	1.8 ± 0.66*	0.5 ± 0.11	0.65 ± 0.4
Plasma ascorbic acids (23.2 ± 3.2, μmol/L)	7.38 ± 1.7	30.6 ± 4.7**	7.9 ± 1.7	15.8 ± 3.8
Plasma lipid peroxides (1.4 ± 0.41, pmol/L)	3.56 ± 0.71	2.9 ± 0.62*	3.48 ± 0.7	3.38 ± 0.62
Lactate dehydrogenase (216.5 ± 36.5, IU/L)	228.8 ± 48.6	656.5 ± 75.6*	224.2 ± 45.4	785.4 ± 81.2

P value was obtained by comparison of intervention and control groups on the seventh day after onset of symptoms of myocardial infarction. Values are mean ± standard deviation. *$P < .05$; **$P < .01$.

TABLE 26.3 Effect of a diet rich in almonds and walnuts diet on cardiac events after 1 year [29].

	Intervention group ($N = 204$)	Control group ($N = 202$)
Nonfatal myocardial infarction	30 (15)**	48 (24)
Fatal myocardial infarction	13 (6)*	19 (9)
Sudden cardiac death (<1 h)	7 (3)*	15 (7)
Suspected cardiac death	–	1 (0.5)
Death due to stroke	1 (0.5)	2 (1.0)
Death due to cancer	–	1 (0.5)
Total cardiac mortality	20 (10)**	34 (17)
Total mortality	21 (10)**	38 (19)
Total cardiac events and deaths	51 (25)**	86 (43)

P value was obtained by comparison of intervention and control group by a *z* test for proportions. *$P < .05$; **$P < .01$.

levels decreased significantly in the intervention group compared with the control group, indicating a decrease in oxidative stress, which is protective against proinflammatory IL-6 and TNF-α as well as endothelial dysfunction, although these data were not measured in the Indian studies. Lactate dehydrogenase (LDH) level increased less in the intervention group than in the control group, indicating that myocardial damage was prevented by the cardioprotective diet rich in almonds and walnuts [28]. The increased intake of *n*-3 fatty acids from mustard oil and walnuts associated with the Mediterranean diet might be responsible for the significant reduction in the cardiac enzyme LDH and lipid peroxides in the intervention group compared with the control group. Total cardiac events, including fatal and nonfatal myocardial infarctions and SCDs, were significantly lower in the intervention group compared with the control group, both after 6 weeks [28] and after 1 year [29] (Table 26.3). The Lyon Diet Heart Study also proposed that the lowest rates of CVDs in the world were observed in populations that followed either a Mediterranean diet or a diet low in omega-6 fatty acids but rich in omega-3 fatty acids. Therefore the best strategy to reduce the rate of complications in patients with established CAD should be to adopt an omega-3 fatty acid–rich Mediterranean diet that is characterized with fruits, vegetables, nuts, poultry, and olive oil [30]. Singh et al. administered 600 g/day of fruits, vegetables, and legumes with walnuts and almonds (50–60 g/day) to 310 patients and a control diet to 315 patients with a high risk of CAD [35]. After a follow-up of 12 weeks there was a significant reduction in systolic and diastolic blood pressures, blood glucose, and blood lipoproteins and an increase in HDL cholesterol.

An umbrella review of all published metaanalyses synthesizing data from both observational studies and randomized controlled trials was performed to determine the impact of nut intake on biomarkers of CVD and cardiovascular events [37]. In total, 14 metaanalyses were included in the umbrella review, showing consistent evidence from intervention

trials reporting significant reductions for total cholesterol. The observational studies reported that higher consumption of nuts was associated with reduced risk of CVDs, including hypertension [37]. The umbrella review showed that nut intake was associated with reduced risk of CVD and hypertension and lower levels of total cholesterol. In a case report and review, the food consumption pattern based on three-day records was fruit, vegetables, and nuts (410 g/day), including almonds and walnuts (42 g/day), legumes and whole grains (350 g/day), refined carbohydrates (250 g/day), visible fat (35 g/day), and milk (100 g/day) [38]. After international travel for 10 days, the subject showed an increase in mean systolic and diastolic blood pressures (142/92 mmHg). He was advised to eat 50−60 g/day of walnuts while continuing to exercise regularly. After about 8 weeks, his blood pressure record showed a decrease in mean systolic and diastolic blood pressures of 130/85 mmHg, and after another 4 weeks, a decline in blood pressures to 128/75 mmHg, without significant decline in body weight. It is clear that a most significant change in the food consumption pattern was that the nut intake was doubled and the increase was mainly in the walnuts. The consumption of ALA, which is found in walnuts, whole grains, leafy vegetables, and mustard oil, increased from 1.2 g/day to 2.6 g/day, as assessed by 3-day food intake records and with the help of the nutrient composition of Indian foods tables [38]. The intake of arginine from walnuts also doubled, and arginine is known to activate nitric oxide and decrease blood pressure.

Blood pressures were measured half-hourly with ambulatory blood pressure monitors (ABPM) for 77 hours. Mean systolic [154(22.47) mmHg] and diastolic [87(14.42) mmHg] blood pressures were higher. Mean pulse pressure was 88 (11.08) BPM. Systolic/diastolic limits during wakefulness were 140/90 mmHg and during sleep were 120/70 mmHg. The highest systolic blood pressure value was 237 mmHg, and the highest diastolic value 119 mmHg. The lowest systolic value was 95 mmHg, and the lowest diastolic value was 55 mmHg. After treatment with walnuts, blood pressures were measured with ABPM for 144 hours. Mean systolic [129(13.95) mmHg] and diastolic [77(11.72) mmHg] blood pressures were substantially lower compared to records taken 2 months before the treatment. The mean pulse pressure was 85(9.4) BPM. The systolic/diastolic limits were 140/90 during wakefulness and 120/70 during sleep. The highest systolic value was 171 mmHg, and the highest diastolic value was 114 mmHg. The lowest systolic value was 89 mmHg, and the lowest diastolic value was 51 mmHg. The decrease in mean blood pressures were 25 mmHg systolic and 10 mmHg diastolic, and pulse pressure was 3 mmHg. There was a marked decrease in the highest systolic value 66 mmHg as well as in the highest diastolic value 5 mmHg. This case report indicates that increased consumption of nuts with increased content of ALA in the diet (2.6 g/day) can decrease blood pressure without any reduction in body weight. There were no changes in alcohol and salt intake. A randomized, controlled trial involving a large number of patients with a long-term follow-up should be conducted to confirm these findings.

In a multicenter trial in Spain, 7447 participants (55−80 years of age, 57% women) who were at high cardiovascular risk were randomized to one of three diets: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet and advice to reduce dietary fat [39]. The results revealed that a primary endpoint event occurred in 288 subjects; there were 96 (3.8%) events in the group assigned to a Mediterranean diet with extra-virgin olive oil, 83 (3.4%) in the group assigned to a Mediterranean diet with nuts, and 109 (4.4%) in the control group. In the intention-to-treat analysis including all the participants and adjusting for baseline characteristics and propensity scores, the hazard ratio was 0.69 (95% CI: 0.53−0.91) for a Mediterranean diet with extra-virgin olive oil and 0.72 (95% CI: 0.54−0.95) for a Mediterranean diet with nuts as compared with the control diet [39].

It is possible that among subjects at high cardiovascular risk, the incidence of major cardiovascular events may be reduced in those assigned to a Mediterranean diet supplemented with extra-virgin olive oil or nuts compared with those assigned to a lower-fat diet. In the PREDIMED Study, 4282 women aged 60−80 years with a high risk of CVDs were recruited [40]. Subjects were randomly allocated to a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet with the advice to reduce dietary fat. After a median follow-up of 4.8 years, 35 confirmed incident cases of breast cancer were recorded. Observed rates (per 1000 person-years) were 1.1 for the Mediterranean diet with extra-virgin olive oil group, 1.8 for the Mediterranean diet with nuts group, and 2.9 for the control group. The multivariable-adjusted HRs versus the control group were 0.32 for the Mediterranean diet with extra-virgin olive oil group and 0.59 for the Mediterranean diet with nuts group [40]. In analyses with yearly cumulative updated dietary exposures, the HR for each additional 5% of calories from extra-virgin olive oil was 0.72. This randomized trial shows for the first time an effect of a long-term dietary intervention on breast cancer incidence. The findings reveal a beneficial effect of a Mediterranean diet supplemented with extra-virgin olive oil in the primary prevention of breast cancer [40]. These results need to be confirmed in longer-term and larger studies. The role of nuts in the prevention of CVDs and other chronic diseases has also been confirmed in other studies [41−44].

In brief, increased consumption of nuts (50−60 g/day) may be protective against CVDs, diabetes, brain degeneration, and cancer. Further studies involving a larger cohort would be necessary to confirm these findings.

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Section 6

Spices as new functional foods

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Chapter 27

Effects of fenugreek seeds on cardiovascular diseases and other chronic diseases

Ram B. Singh[1], Manal M.A. Smail[2], Richa H. Rai[3], Anuj Maheshwari[4], Narsingh Verma[5] and Adrian Isaza[6]

[1]Halberg Hospital and Research Center, Civil Lines, Moradabad, India, [2]Fatima College for Health Sciences, Abu Dhabi, United Arab Emirates, [3]School of Physiotherapy, Delhi Pharmaceutical Sciences and Research University, New Delhi, India, [4]Department of Medicine, BBD CODS, BBD University, Lucknow, India, [5]King George Medical University, Lucknow, India, [6]Alternative Medicine, Everglades University, Tampa, FL, United States

Introduction

Western-type diets and sedentary behavior appear to be important pathways for the development of cardiovascular diseases (CVDs) and diabetes, as well as other chronic diseases, in individuals and populations with an underlying lack of general and health education [1]. Hypercholesterolemia, diabetes, and obesity are risk factors of CVDs, and most health agencies advise a prudent low-fat diet, regular moderate physical activity, and cessation of tobacco and alcohol consumption for prevention of these diseases [1]. Recent studies indicate that certain functional foods, such as fenugreek, may be used for management of cardiometabolic diseases [2–4]. Obesity and central obesity are also important in the pathogenesis of dyslipidemia, metabolic syndrome, and type 2 diabetes mellitus [5–8]. Epidemiological studies and intervention trials indicate that adherence to functional food dietary patterns in conjunction with other healthy lifestyle practices can protect against CVDs [8–11]. Recently, functional food components of Mediterranean-style diets have been demonstrated to be protective against CVDs [8–11]. Hence Mediterranean-style foods and some Asian foods, such as fruits, including grapes and apples (flavonoids, phytosterols, soluble fiber), guavas and star gooseberries (vitamin C), and cranberries (flavonoids); soy products (isoflavones); walnuts (omega-3 fatty acids and essential amino acids); flax seeds (omega-3 fatty acids); fish (omega-3 fatty acids); olive oil (antioxidant flavonoids and monounsaturated fatty acids) and mustard oil (omega-3 fatty acids); bitter gourd (flavonoids); leafy vegetables; tea and cocoa (flavonoids); and spices, including fenugreek, turmeric, cumin, corianderm and peppers (flavonoids and minerals) may be considered to be nutraceutical functional foods to highlight their role in the prevention of NCDs [10–13]. International guidelines advise reducing blood lipoproteins and oxidative stress via nutritional measures before drug therapy [14–16]. This review aims to highlight the role of fenugreek seeds in the management of cardiometabolic diseases.

Fenugreek seeds

The seeds of fenugreek (*Trigonella foenum-graecum* L.) are used as an aromatic plant food spice and also have medicinal uses as a hypoglycemic, hypocholesterolemic, and antiinflammatory agent [2–4,17–20]. Historically, fenugreek has been used as an important multipurpose medicinal herb in the Indian Ayurvedic system. Fenugreek has also been used for several centuries in traditional Chinese and Tibetan medicinal practices. The species name *foenum-graecum* is Latin for "Greek hay," suggesting that fenugreek was well known as a forage crop even in the distant past. The plant is traditionally grown in major parts of South Asia, Middle East, North Africa, and Mediterranean Europe as a spice crop. Fenugreek seeds are also used as an ingredient in East Indian curries and as a part of the traditional curry mix powders of the Indian subcontinent. Fenugreek constitutes an important ingredient of these powders and hence is part of a significant cuisine of traditional Indian faith and practices.

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Composition of fenugreek seeds

Fenugreek contains a number of chemical constituents, including steroidal sapogenins. Diosgenin has been found in the oily embryo of fenugreek. There are two furastanol glycosides, F-ring opened precursors of diosgenin, which have been reported in fenugreek also as hederagin glycosides. Alkaloids such as trigocoumarin, nicotinic acid, trimethyl coumarin, and trigonelline are present in the stem. The mucilage is a major constituent of the seeds. The stem contains about 28% mucilage, a volatile oil, the two alkaloids trigonelline and choline, 5% of a stronger-smelling, bitter fixed oil, 22% proteins, and a yellow coloring substance [2–4]. Fenugreek contains 23%–26% protein, 6%–7% fat, and 58% carbohydrates, of which about 25% is dietary fiber [21–24]. Fenugreek is also a rich source of iron, containing 33 mg/100 g dry weight.

The extracts of endosperm, husk, and fenugreek seed at about 200 μg concentration exhibited 72%, 64%, and 56% antioxidant activity, respectively, by the free-radical scavenging method.

In a 100-g amount, fenugreek seeds provide 1350 kJ (323 kcal) of food energy and contain 9% water, 58% carbohydrates, 23% protein, and 6% fat, with calcium at 40% of the daily value (DV). Fenugreek seeds (per 100 g) are a rich source of protein (46% DV), dietary fiber, B vitamins, and dietary minerals, particularly manganese (59% DV) and iron (262% DV) (Table 27.1).

Figs. 27.1 and 27.2 show the chemical structures of important therapeutic agents present in the fenugreek seeds. The presence of free OH and O groups at double and single bond indicates that these radicals can bind to free radicals and reactive oxygen species while reducing oxidative stress in the cells and the tissues [21].

TABLE 27.1 Nutrient content of fenugreek seeds [23].

Nutritional value per 100 g (3.5 oz)	
Energy	1352 kJ (323 kcal)
Carbohydrates	58 g
Dietary fiber	25 g
Fat	6.4 g
Protein	23 g
Vitamins	**Quantity % (DV†)**
Thiamine (B1)	28% (0.322 mg)
Riboflavin (B2)	31% (0.366 mg)
Niacin (B3)	11% (1.64 mg)
Vitamin B6	46% (0.6 mg)
Folate (B9)	14% (57 μg)
Vitamin C	**4% (3 mg)**
Minerals	Quantity % (DV†)
Calcium	18% (176 mg)
Iron	262% (34 mg)
Magnesium	54% (191 mg)
Manganese	59% (1.23 mg)
Phosphorus	42% (296 mg)
Potassium	16% (770 mg)
Sodium	4% (67 mg)
Zinc	26% (2.5 mg)
Other constituents	**Quantity**
Water	8.8 g

Modified from reference U.S. Department of Agriculture, Agricultural Research Service. https://fdc.nal.usda.gov/index.html [accessed Feb 2021].

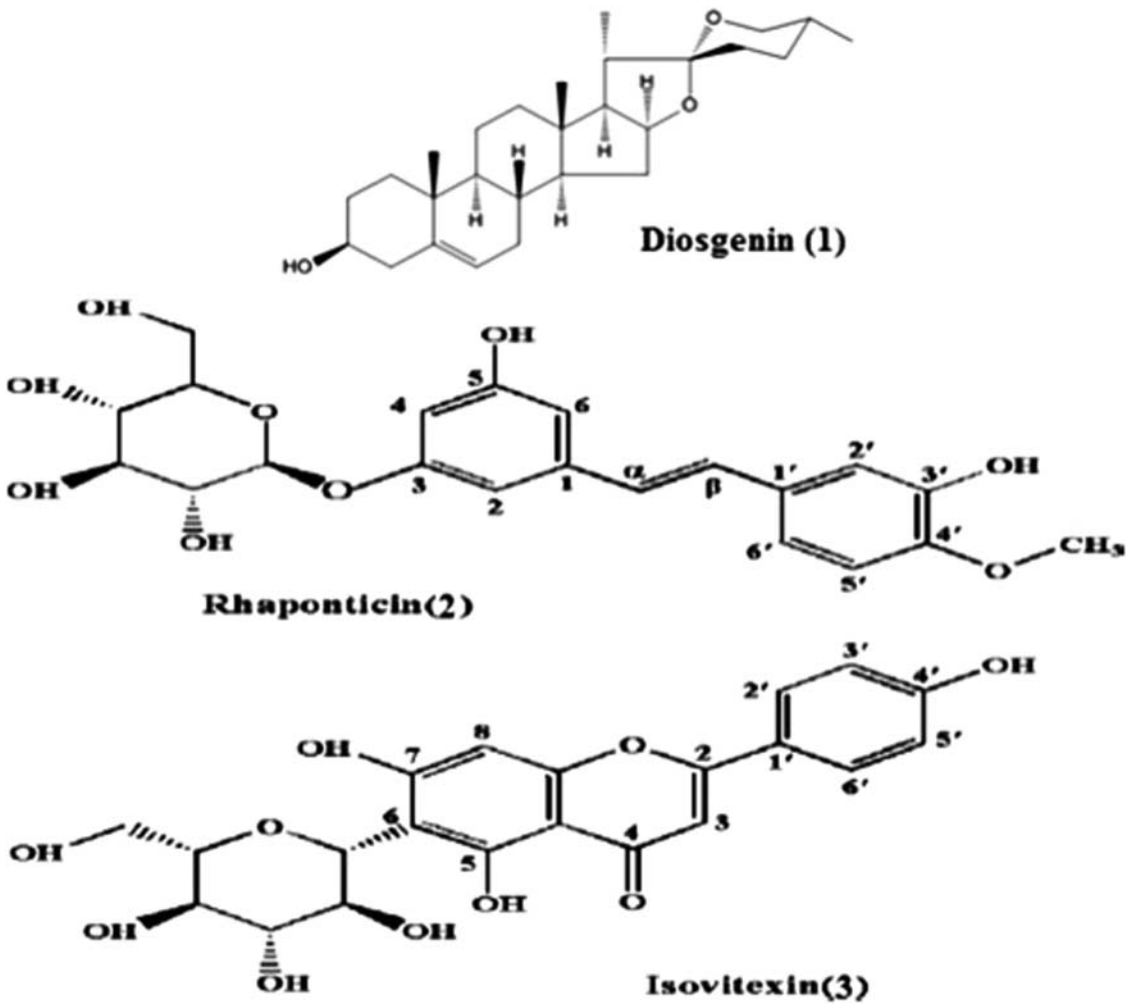


FIGURE 27.1 Chemical structure of flavonoids in the fenugreek seeds [22]. *Modified from reference Wani SA, Kumar P. Fenugreek: a review on its nutraceutical properties and utilization in various food products. J Saudi Soc Agric Sci January 2018;DOI: 10.1016/j.jssas.2016.01.007.*

Mechanisms

Fenugreek is rich in soluble fiber, saponins, trigonelle, diosgenin, and 4-hydroxyisoleucine. Dietary fiber and saponins may be responsible for hypoglycemic actions, but the efficacy for glycemic control in diabetes remains unclear. In humans, fenugreek seeds acutely reduced postprandial glucose and insulin concentrations. Several longer-term clinical trials showed reductions in fasting and postprandial glucose concentrations and glycated hemoglobin (HbA1c). Experimental studies have shown that fenugreek seed extracts have the potential to slow enzymatic digestion of carbohydrates, reduce gastrointestinal absorption of glucose, and thus reduce postprandial glucose concentrations. In addition, fenugreek stimulated glucose uptake in peripheral tissues and had insulinotropic properties in isolated rat pancreatic cells [17,18]. Fenugreek seeds are rich in polyphenolic flavonoids, such as quercetin, trigonelline, saponins (4%−8%), and phytic acid [10,17−20]. Fenugreek seeds also contain lysine and L-tryptophan-rich proteins, mucilaginous fiber, and rare chemical constituents, such as coumarin, fenugreekine, nicotinic acid, folic acid, sapogenins, phytic acid, scopoletin, and trigonelline, which are thought to account for many of the presumed therapeutic effects that may inhibit cholesterol absorption and decrease blood sugar concentrations [2−4,23,24]. This study examined the ethanol extracts from fenugreek seeds, which enhanced glucagon-like peptide 1(GLP-1) signaling. An active compound (N55) with a new N-linoleoyl-2-amino-γ-butyrolactone structure was purified from fenugreek seeds, which was able to promote GLP-1-dependent cAMP production and GLP-1R endocytosis in a dose-dependent and saturable manner [25]. Interestingly, N55 specifically enhanced GLP-1 potency more than 40-fold, but not that of exendin 4, to stimulate cAMP production. However, the current allosteric modulators bind to GLP-1R, whereas N55 binds to GLP-1 peptide and facilitates trypsin-mediated GLP-1 inactivation [25]. The results indicate a new class of modulators of

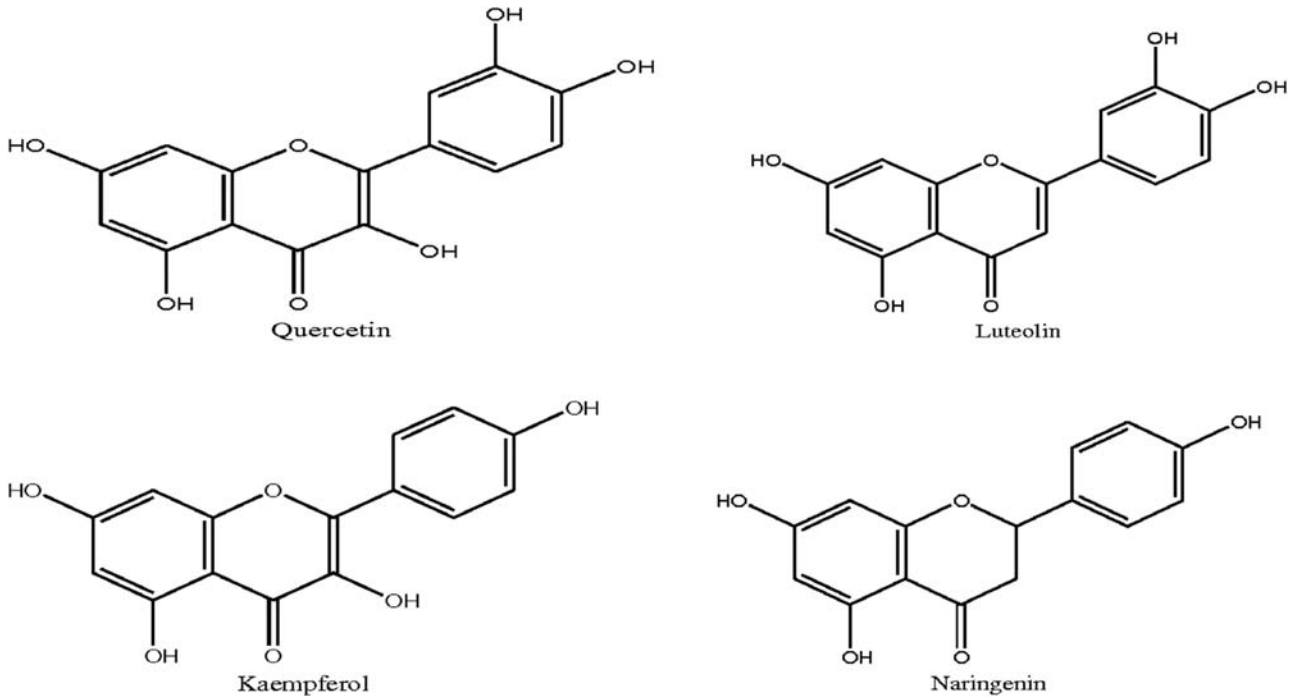


FIGURE 27.2 Chemical structure of chemical contents of fenugreek seeds [21]. *Modified from reference Yadav R, Kaushik R, Gupta D. The health benefits of Trigonella foenum-graecum: a review. Int J Eng Res Appl 2011;1(1):32–35.*

GLP-1R signaling and suggest that GLP-1 be a viable target for drug discovery. It is proposed that the beneficial effects of fenugreek in patients with hyperlipidemia and diabetes may be due to its high content of flavonoids [17]. Five flavonoid compounds were isolated from fenugreek seeds and identified as vitexin, tricin, naringenin, quercetin, and tricin-7-*O*-beta-D-glucopyranoside [26]. Of these the three flavonoids, tricin, naringenin, and tricin-7-*O*-beta-D-glucopyranoside were isolated from fenugreek as well as from the plants of *Trigonella* for the first time in China. The bitterness in fenugreek seeds stems from alkaloids. Fenugreek seeds contain saponin 1 (646.58 mg/100 g dry weight), and the polyphenol content is 103.81 mg/100 g. Recently, fenugreek has been demonstrated to modulate GLP-1 signaling [27]. GLP-1 analogs are approved for treatment of type 2 diabetes and are undergoing clinical trials for other disorders, including neurodegenerative diseases.

Effects of fenugreek seeds on blood lipids and blood glucose

The International College of Cardiology, the U.S. Department of Agriculture International College of Nutrition, the American Heart Association (AHA), and the PREDIMED study provide guidelines for the treatment of hyperlipidemia by restriction of cholesterol and saturated fat with a 30% upper limit for total fat intake. The role of fiber in lowering cholesterol concentration is also acknowledged [1,4,5,11,13]. Hypolipidemic effects have been reported for dietary water-soluble fiber such as guar gum, pectin, oat bran, fenugreek seeds, spirulina, and psyllium [1,2,5]. The PREDIMED study, using a diet rich in functional foods, including natural water-soluble fiber, has been proven as adjunct to the AHA step I diet (prudent low-fat diet) associated with significant reduction in serum total cholesterol and decrease in low-density lipoprotein (LDL) cholesterol without a decrease in high-density lipoprotein (HDL) cholesterol [8–11]. There is scanty evidence, however, regarding the hypolipidemic effect of fenugreek seeds, and there is no scientific study to our knowledge demonstrating their hypocholesterolemic and hypoglycemic effect as an adjunct to National Cholesterol Education Program (NCEP) step I diet in hypercholesterolemia [17–20]. In Asian countries the dietary fat intake is less than 30% kcal/day, within the limits of AHA step I diet, which allows only modest restriction of fat for decreasing a mild to moderate increase in blood lipids [1,14]. For greater safety- and cost-related concerns, there is a need to augment dietary intervention with functional foods that are rich in herbs and fiber supplements as an additional step before prescribing drugs [1,4,5,13]. A clinical study was designed to compare the hypocholesterolemic and hypoglycemic effects of fenugreek seeds in hypercholesterolemia as adjuncts to dietary therapy [4].

Fenugreek is a spice and a functional food, that is one of the foods that contain one or more protective nutrients with the benefit of addressing any biological mechanism in the body. There is little information about adoption of a healthy diet and lifestyle behaviors among individuals with CVDs and type 2 diabetes in communities across a range of

countries worldwide [1]. There is hardly any information about the role of spices (fenugreek, coriander, cumin, turmeric) as adjuncts to the AHA Step I diet in patients with hyperlipidemia. This landmark study showed that administration of an NCEP step I diet for 12 weeks to patients with hyperlipidemia had only marginal beneficial effects on blood lipoproteins and blood glucose concentrations without a decrease in HDL cholesterol (Table 27.2). The lack of benefit from step I diet may be because total dietary fat intake among Asians is lower than that advised in the step I diet [14,15]. Treatment with fenugreek compared to placebo with diet counseling in the two groups of patients for another 12 weeks was associated with significant reductions from reference data in serum concentrations of total and LDL cholesterol, with a nonsignificant decline in the placebo group. The decline in triglycerides from reference was also highly significant in the fenugreek group compared to the placebo group (Table 27.3). We also observed significant declines in total cholesterol, LDL cholesterol, and triglyceride concentrations in the fenugreek group from the values achieved by the step I diet, but such effects were not seen in the placebo group (Table 27.3).

Some other studies have also reported these beneficial effects of fenugreek seeds [18–20]. Bordia et al. reported that fenugreek given in a dose of 2.5 g twice daily for three months to healthy individuals did not affect the blood lipids or fasting and postprandial blood glucose levels [19]. However, administered in the same daily dose for the same duration to patients with coronary disease and non-insulin-dependent diabetes mellitus (NIDDM), fenugreek significantly decreased total cholesterol and triglyceride levels without affecting the HDL cholesterol level. In patients with diabetes without coronary artery disease, the same daily dose of fenugreek was associated with a significant decline in fasting and postprandial blood sugar levels. In a randomized, controlled trial, subjects with prediabetes aged 30–70 years were treated with fenugreek ($N = 66$ patients vs 74 controls) for three years [28]. The dosage of fenugreek powder was 5 g twice a day before meals. After 3 years, the levels of LDL cholesterol decreased significantly, and the cumulative incidence of diabetes was reduced significantly (4.2-fold) in the fenugreek group compared to the control group. The fenugreek group also showed a significant reduction in fasting and postprandial plasma glucose levels, whereas serum insulin levels increased significantly. The outcome of diabetes in fenugreek group was positively associated with serum insulin and negatively associated with insulin resistance [28].

In a recent prospective study, 50 patients aged 40–60 years with type 2 diabetes (Hb1c > 8) and dyslipidemia were divided into two groups: a fenugreek seeds group and a group receiving oral hypoglycemic and hypolipidemic agents [29]. After eight weeks of treatment with fenugreek seeds, patients in group 1 showed a significant improvement in fasting blood glucose concentration (178 $\pm$ 72.4 to 104 $\pm$ 28.2; $P < .0001$), total cholesterol (350 $\pm$ 20.6 to 176 $\pm$ 17.2; $P < .0001$), triglycerides (280 $\pm$ 18.2 to 132 $\pm$ 16.8; $P < .0001$), LDL cholesterol (220 $\pm$ 21.4 to 96 $\pm$ 14.2; $P < .0001$), and HDL cholesterol (27.0 $\pm$ 13.4 to 58 $\pm$ 32.2; $P < .0002$). HbA1C levels showed a nonsignificant decrease. In a clinical trial, 24 patients with type 2 diabetes were given 10 g/day powdered fenugreek seeds mixed with yogurt or soaked in hot water for 8 weeks [30]. After exclusion of six cases for changing in medication or personal problems, the results of 18 patients (11 consumed fenugreek in hot water, and 7 consumed it in yogurt) showed that fasting blood glucose, triglyceride, and very low density lipoprotein (VLDL) cholesterol levels decreased significantly (25%, 30%, and 30.6%, respectively) when fenugreek seeds were soaked in hot water; there were no significantly changes in lab parameters in subjects who consumed fenugreek seeds mixed with yogurt.

TABLE 27.2 Nutrient groups and chemical content of fenugreek seeds [21].

Nutrient group	Chemical constituents of fenugreek seeds
Flavonoids	Quercetin, rutin, vitexin, isovitexin
Alkaloids	Trimethylamine, neurin, trigonelline, choline, gentianine, carpaine, betain
Amino acids	Isoleucine, 4-hydroxyisoleucine, histidine, leucine, lysine, l-tryptophan, arginine
Saponins	Graecunins, fenugrin B, fenugreekine, trigofoenosides A-G
Steroidal sapinogens	Yamogenin, diosgenin, smilagenin, sarsasapogenin, tigogenin, neotigogenin, gitogenin, neogitogenin, yuccagenin, saponaretin
Fibers	Gum, neutral detergent fiber
Lipids	Triacylglycerols, diacylglycerols, monoacylglycerols, phosphatidylcholine phosphatidylethanolamine, phosphatidylinositol, free fatty acids
Other	Coumarin, lipids, vitamins, minerals. 28% mucilage; 22% proteins; 5% of a stronger-selling, bitter fixed oil.

Modified from reference Yadav R, Kaushik R, Gupta D. The health benefits of *Trigonella foenum-graecum*: a review. Int J Eng Res Appl 2011;1(1):32–35.

TABLE 27.3 Blood lipoproteins and glucose concentrations at entry and during follow-up.

Data (mmol/L)	Fenugreek ($N = 29$)	Placebo ($N = 31$)
Total cholesterol		
Entry	6.66 (0.13)	6.71 (0.13)
Reference	6.27 (0.12)	6.22 (0.11)
Final	5.31 (0.08)[b]	6.22 (0.11)
Change from reference (%)	−15.4	−2.0
LDL cholesterol		
Entry	4.31 (0.12)	4.42 (0.14)
Reference	4.22 (0.11)	4.31 (0.12)
Final	3.43 (0.8)[b]	4.15 (0.12)
Change from reference (%)	−18.8	−3.7
HDL cholesterol		
Entry	1.12 (0.06)	1.13 (0.06)
Reference	1.11 (0.06)	1.12 (0.05)
Final	1.17 (0.07)[a]	1.13 (0.06)
Change from reference (%)	+5.4	+1.0
Triglycerides (%)		
Entry	1.75 (0.19)	1.82 (0.21)
Reference	1.63 (0.17)	1.74 (0.19)
Final	1.42 (0.12)[b]	1.68 (0.18)
Change from reference (%)	−12.9	−3.7
LDL/HDL cholesterol ratio		
Entry	3.84 (0.22)	3.91 (0.23)
Reference	3.80 (0.19)	3.84 (0.21)
Final	3.20 (0.16)[b]	3.67 (0.19)
Change from reference (%)	−15.8	−4.4
Fasting blood glucose		
Entry	5.27 (0.12)	5.30 (0.16)
Reference	5.14 (0.11)	5.18 (0.13)
Final	4.61 (0.08)	5.15 (0.12)
Change from reference (%)	−10.4[a]	−0.6
Postprandial blood glucose		
Entry	7.68 (0.22)	7.88 (0.25)
Reference (12 week)	7.68 (0.22)	7.62 (0.22)
Final (24 week)	6.06 (0.18)[b]	7.53 (0.21)
Change from reference (%)	−20.6	−1.2

Results shown as mean (standard deviation).
[a]$P < .05$.
[b]$P < .001$.

The present study also found a significant decline in fasting and postprandial blood glucose concentrations from values achieved by the step I diet. The incremental declines in fasting glucose and postprandial blood glucose levels were 9.8% and 19.8%, respectively, in the fenugreek group. In a recent metaanalysis involving 238 subjects in 10 trials, fenugreek significantly decreased fasting blood glucose levels by −0.96 mmol/L (95% CI: −1.52, −0.40; I^2 = 80%; 10 trials), 2-hour postload glucose levels by −2.19 mmol/L (95% CI: −3.19, −1.19; I^2 = 71%; seven trials), and HbA1c by −0.85% (95% CI: −1.49%, −0.22%; I^2 = 0%; three trials) as compared with control interventions [31]. The findings support beneficial effects of fenugreek seeds on glycemic control in people with diabetes. High-quality trials are needed that use a well-characterized fenugreek preparation of sufficient dose to provide more conclusive evidence. In a clinical study, 12 males with NIDDM experienced four 8-week stages [26]. After eight weeks, a combination of exercise and fenugreek supplementation had better effects than each of them individually, especially with reference to fasting blood glucose, HbA1C, and total cholesterol concentrations.

In a metaanalysis, all the randomized, controlled trials investigating the effects of fenugreek on anthropometric indices and plasma lipids in adults were included [3]. A metaanalysis of 12 controlled trials (14 arms) including 560 participants reported a significant decrease in plasma concentrations of total cholesterol [weighted mean difference (WMD) = −9.371 mg/dL; 95% CI: −15.419, −3.323, P = .002], triglycerides (WMD = −13.776 mg/dL; 95% CI: −26.636, −0.916, P = .036), and LDL cholesterol (WMD = −6.590 mg/dL; 95% CI: −13.042, −0.137, P = .045) as well as an increase in plasma HDL cholesterol (WMD = 3.501 mg/dL; 95% CI: 1.309, 5.692, P = .002), while body weight (WMD = 0.223 kg; 95% CI: −0.509, 0.955, P = .551) and body mass index (WMD = 0.091 kg/m^2; 95% CI: −0.244, 0.426, P = .596) were not altered. It is possible that treatment with fenugreek improved lipid parameters in adults. There are some more interesting studies that have reported that fenugreek seeds have beneficial effects. In a metabolic study involving 15 patients with diabetes, subjects were given randomly, in a crossover design, diets without or with 100 g defatted fenugreek seed powder, each for ten days [32]. Incorporation of fenugreek produced a significant decrease in fasting blood glucose levels and an improvement in glucose tolerance. Insulin responses were significantly reduced. Serum total cholesterol, LDL cholesterol, VLDL cholesterol, and triglyceride levels were significantly decreased without any alteration in HDL cholesterol with the fenugreek diet [32]. Sixty patients with uncontrolled diabetes mellitus (HbA1C > 7.5) were randomized to receive either 30 g of fenugreek seeds three times a day for 8 weeks (group F) or no intervention (Group C) [33]. Patients in both control and fenugreek groups showed a reduction in HbA1c; the reduction was significant in patients treated with fenugreek seeds. Eighteen healthy obese subjects participated in a single-blind, randomized, crossover study of three test breakfasts containing 0 g (control), 4, or 8 g of isolated fenugreek fiber [34]. The 8 g dose of fenugreek fiber significantly increased mean ratings of satiety and fullness and reduced ratings of hunger, palatability, and prospective food consumption and reduction in energy intake at lunch (P < .05).

In another study of 40 subjects, a significant decrease in the insulin/glucose ratio was observed in subjects treated with fenugreek seed extract relative to the placebo group [(0.89 ± 0.09 vs 1.06 ± 0.10 mUI mmol/1); P = .044] [35]. The repeated administration of a fenugreek seed extract slightly but significantly decreased dietary fat consumption in healthy overweight subjects in this short-term study. In another study of 25 patients with type 2 diabetes (fasting glucose < 200 mg/dL), subjects were randomly divided into two groups [36]. Group 1 (N = 12) received 1 g/day hydroalcoholic extract of fenugreek seeds, and Group 2 (N = 13) received the usual care (dietary control, exercise) and placebo capsules for two months [36]. In Group 1 as compared to Group 2 at the end of two months, fasting blood glucose (148.3 ± 44.1 to 119.9 ± 25 vs 137.5 ± 41.1 to 113.0 ± 36.0) and 2 hour post glucose blood glucose (210.6 ± 79.0 to 181.1 ± 69.0 vs 219.9 ± 41.0 to 241.6 ± 43.0) were not different. But the area under the curve of blood glucose (2375 ± 574 vs 27597 ± 274) as well as insulin (2492 ± 2536 vs 5631 ± 2428) was significantly lower (P < .001). HOMA model−derived insulin resistance showed a decrease in percent beta cell secretion in Group 1 as compared to Group 2 (86.3 ± 32.0 vs 70.1 ± 52.0) and an increase in percent insulin sensitivity (112.9 ± 67.0 vs 92.2 ± 57.0) (P < .05). Serum triglyceride levels decreased and HDL cholesterol levels increased significantly in Group 1 as compared to Group 2 (P < .05). In a further study, the efficacy in treating traditional Chinese medicine symptoms was obviously better in the treated group (N = 46) than in the control group (N = 23) (P < .01) [37]. There were statistically remarkable decreases in aspects of fasting and two-hour blood glucose levels, HbA1c, and clinical symptomatic quantity scores in the treated group as compared to the control group (P < .05) [37]. Isolation of a positive modulator of GLP-1 signaling from fenugreek seeds indicate that fenugreek may have independent hypoglycemic effects due to this antidiabetic agent [25]. Fenugreek seeds may also have antiobesity effects by reducing energy intake [34].

Effects of fenugreek seeds on oxidative stress and inflammation

Apart from its known medicinal properties, such as hypolipidemic, carminative, gastric stimulant, antidiabetic, and galactogogue (lactation-inducing) effects, newer research has identified antioxidant, hepatoprotective, antiinflammatory, antibacterial,

antifungal, antiulcer, antilithigenic, and anticarcinogenic of effects of fenugreek. Although most of these studies used whole seed powder or different forms of extracts, some have identified active constituents from seeds and attributed them medicinal values for different indications. The main chemical constituents of fenugreek are proteins rich in lysine and tryptophan; flavonoids, such as saponins, quercetin, trigonelline, and phytic acid: and polyphenols [2,38−40]. Saponin content was 1646.58 mg/100 g fenugreek seeds on a dry weight basis and polyphenol content varied from 103.81 to 150 mg. In China, five flavonoid compounds were isolated from fenugreek seeds and identified as vitexin, tricin, naringenin, quercetin, and tricin-7-*O*-beta-D-glucopyranoside [39]. Three flavonoids—tricin, naringenin and tricin-7-*O*-beta-D-glucopyranoside—were isolated from fenugreek seeds as well as from the plants of *Trigonella* for the first time. The results of phytochemical screening tests confirmed the presence of flavonoids in fenugreek seeds, and the alkaloid and flavonoid content of seeds may be responsible for the antinociception and antiinflammatory effects, respectively [17,41,42]. In a phytochemical screening study, the highest content of total phenolic content (TPC) and antioxidant activity, 1,1-diphenyl-2-picryl hydrazyl radical scavenging (DPPH), and ferric reducing antioxidant power (FRAP) were found in 50% acetone extracts [42]. The TPC for fenugreek seeds was 25.90−15.45 mg gallic acid equivalents/100 g dry weight, antioxidant activity FRAP ranged from 47.49 to 31.85 mg trolox equivalent/100 g dry weight, and DPPH ranged from 67.30% to 43.61%. The largest amount of total phenol content that leads to a more effective radical scavenging effect was shown by 50% acetone extract. Moreover, the amount of phenolic compounds and antioxidant activities increased in acetone extract. Acetone 50% and methanol 50% solvent showed the greatest capability of extracting antioxidants and inhibiting the free radicals produced. It was concluded that extraction solvent has important effects on the phenolics compounds and the antioxidant activity of fenugreek seed extract.

Acrylamide is a hazardous substance that induces oxidative stress,which may be prevented by adding fenugreek seeds as a spice [43]. In an experimental study, 32 male Wistar rats were randomly assigned into four groups. Control group I was given normal saline, group II was given acrylamide (20 mg/kg body weight orally), and groups III and IV were given acrylamide (20 mg/kg body weight) and supplemented with 2.5% and 5% fenugreek seed oil, respectively, in their diets [43]. Administration of acrylamide was associated with significant increase in serum levels of LDH, AST, ALT, APL, γ-GT, cholesterol, uric acid, urea, creatinine, 8-oxo-2′-deoxyguanosine, interleukin 1 beta, interleukin 6, and tumor necrosis factor alpha. It also increased hepatic, renal, and brain lipid peroxidation, while it impaired the activities and concentrations of the antioxidant biomarkers. Supplementation of fenugreek seed oil normalized the altered serum parameters, prevented lipid peroxidation, and enhanced the antioxidant biomarker concentrations and activities in the hepatic, renal, and brain tissues of acrylamide-intoxicated rats in a dose-dependent manner, indicating its protective effects [43].

The antioxidant activity of fenugreek seeds in humans in a randomized trial has not been reported. There is evidence that additional approaches to cholesterol lowering are urgently needed in the management of hyperlipidemia because oxidized LDL cholesterol and oxidation of other lipids are more atherogenic than native LDL and lipids [2]. In developing countries the dietary fat intake is less then 30% kcal/day, which is within the limits of NCEP step I diet. thus allowing only modest restriction of fat for decreasing mild to moderate hypercholesterolemia. For greater safety- and cost-related concerns, there is a need to augment nutritional intervention with herbs and fiber supplements as an additional step before prescribing drugs [2]. A recent study was designed to compare the hypocholesterolemic and antioxidant effects of fenugreek seeds in hypercholesterolemia as adjuncts to dietary therapy. This randomized, double-blind, placebo-controlled trial conducted in a hospital included 61 patients with mild to moderate hyperlipidemia. Subjects were assigned to the NCEP step I diet for a period of 12 weeks and then randomized to two different test agents in identical sachets for another 12 weeks. The test agents were fenugreek seed powder (60.0 g/day) and cellulose placebo (3 g/day). Of 61 subjects with serum cholesterol between 5.17 and 7.76 nmol/L, 59 successfully completed 12 weeks of AHA step I diet and then augmented the diet with one of the fiber or fenugreek supplements for an additional 12 weeks. Incremental differences from placebo for LDL cholesterol were −15.1% for fenugreek; for total cholesterol the differences were −13.4% for fenugreek. The incremental differences in triglyceride levels (significant) for fenugreek were −9.5% with a 4.4% increase in HDL cholesterol. The LDL/HDL cholesterol ratio showed a significant decline from the baseline levels in the fenugreek group without such changes in the control group. Fasting and postprandial blood glucose levels as well as lipid peroxides and diene conjugates (indicators of oxidative stress) and tumor necrosis factor alpha showed a significant decline in fenugreek group, whereas these changes were nonsignificant in the placebo group. The incremental differences in lipid peroxides and diene conjugates were significant for fenugreek. The incremental differences in serum nitrite levels (an indicator of nitric oxide) for fenugreek were significant, causing an increase in nitrite levels. Compliance to treatment varied between 92% and 99%, and only mild gastrointestinal side effects were observed. Treatment with fenugreek seeds revealed significant hypoglycemic, hypocholesterolemic, antioxidant, antiinflammatory, and nitric oxide−activating effects when used as an adjunct to AHA step I diet [2] (Table 27.4).

TABLE 27.4 Effects of fenugreek on blood glucose and oxidative stress during different periods of follow-up. Values are mean (SEM).

Data (mmol/L)	Fenugreek ($N = 29$)	Placebo ($N = 31$)
Fasting blood glucose		
Entry	5.27 (0.12)	5.30(0.16)
Baseline	5.14 (0.11)	5.18 (0.13)
Final	4.61 (0.08)	5.15 (0.12)
Change from baseline (%)	−10.42	−0.6
Postprandial blood glucose		
Entry	7.68 (0.22)	7.88 (0.25)
Baseline (12 week)	7.68 (0.22)	7.62 (0.22)
Final (24 week)	6.06 (0.18)	7.53 (0.21)
Change from baseline (%)	−20.6	−1.2
Lipid peroxides (1.1−2.54 nmol/mL)		
Entry	2.09 (0.18)	1.88 (0.15)
Baseline	2.00 (0.15)	1.82 (0.12)
Final	1.50 (0.12)	1.74 (0.12)
Change from baseline (%)	−25.02	−4.4
Diene conjugates (21.5−25.7 OD unit)		
Entry	28.5 (1.2)	29.5 (1.2)
Baseline (12 week)	27.7 (1.1)	28.0 (1.1)
Final (24 week)	24.0 (1.0)	28.1 (0.9)
Change from baseline (%)	−13.3	+0.3
Nitrite (normal: 0.42−0.61 μmol/L)		0.62 ± 0.15
Entry	0.60 ± 0.16	0.61 ± 0.15
12 week	0.61 ± 0.15	0.61 ± 0.15
24 week	0.61 ± 0.15	0.61 ± 0.15
Change from 12 week (%)	+27.8	-6.4
Tumor necrosis factor alpha (normal: 2.3−7.8 pg/mL)		
Entry	11.8 ± 4.3	10.8 ± 3.3
12 week	10.2 ± 3.8	10.0 ± 3.2
24 week	8.0 ± 3.4	10.0 ± 3.1
Change from 12 week (%)	−24.5	−2.0
Interleukin-6 (normal: 0.0−3.9 pg/mL)		
Entry	6.8 ± 2.8	6.50 ± 2.5
12 week	6.6 ± 2.6	6.3 ± 2.4
24 week	6.6 ± 2.5	6.1 ± 2.4
Change from 12 week (%)	−30.3	−3.2

TABLE 27.5 Adverse effects attributed to different agents. Values are number (%).

Adverse effect	Fenugreek ($N = 31$)	Placebo ($N = 32$)
Nausea	7 (22.5)	1 (3.1)
Fullness	4 (12.9)	2 (6.2)
Heart burn	3(9.7)	2 (6.2)
Intestinal gas	2 (6.4)	2 (6.2)
Flatulence	3 (9.7)	1 (3.2)
Loose stools	2 (6.4)	2 (6.2)
Constipation	2 (6.4)	1 (3.2)
Diarrhea	1 (3.2)	–
Pain in abdomen	2 (6.4)	1 (3.1)
Cramps in legs	1 (3.2)	1 (3.1)
Headache	2 (6.4)	2 (6.2)
Tiredness	–	2 (6.2)
Anal irritation	–	–
Bad taste	4 (12.9)	–
Withdrawal	2 (6.4)	1 (3.1)

Other beneficial effects of fenugreek seeds

Apart from the above benefits, fenugreek is known to have other beneficial effects on the human body. Childbirth becomes easier, and there is a galactogogue effect in mothers after delivery. A study of 66 mothers has shown increases in the volume of pumped breast milk from 34 to 73 mL in those who consumed fenugreek tea [44]. A testosterone booster effect has also been observed in a six-week randomized control study in otherwise healthy males with 600 mg fenugreek extract. Most of the subjects reported increased strength and improved sexual function, while prolactin and testosterone levels remained within the reference range [45]. In another study, 50 male volunteers 25−65 years of age were given protodioscin-enriched extract from fenugreek seeds for 12 weeks in a single−armed, open, nonblind, multicenter study, and improving free testosterone levels up to 46% in 90% were found in the participants; 85.4% of the volunteers showed improvements in sperm count. Sperm morphology improved in 14.6% of subjects. Most of them noticed improvements in mental alertness, mood, and overall sexual performance [46].

High fiber content helps in relieving constipation as well as heartburn. In one study, heartburn diminished in severity after two weeks of intake of a fenugreek fiber product taken 30 minutes before meals twice a day. Fenugreek reduces appetite, which may reduce fat intake [47]. One 14-day study found that participants spontaneously reduced their total fat intake by 17%. Taking 1800−2700 mg of fenugreek seed powder three times daily for the first three days of a menstrual period followed by 900 mg three times daily for the remainder of two menstrual cycles reduced pain in women with painful menstrual periods. The need for painkillers was also reduced. Furthermore, 600 mg of fenugreek seed extract every day seems to increase interest in sex in healthy younger women with a low sex drive [48]. There are no serious side effects, and compliance may be excellent with fenugreek treatment. The response to dietary modification may be nonsignificant in many populations because fat intakes are not very different from the NCEP step I diet, and most subjects who are asymptomatic may be poorly motivated to alter their diets.

There are no serious side effects, and compliance may be excellent with fenugreek treatment (Table 27.5). The response to dietary modification may be nonsignificant in many populations because fat intakes are not very different from those in the NCEP step I diet, and most subjects who are asymptomatic may be poorly motivated to alter their diets.

In brief, the hypolipidemic, hypoglycemic, and antioxidant effects of fenugreek seeds have been documented in humans and animals. Supplementation of fenugreek seeds can decrease obesity, metabolic syndrome, type 2 diabetes, and hyperlipidememia, owing to fenugreek's hypolipidemic and antioxidant activities. This dietary condiment has the potential for widespread use in the food industry because its galactomannan composition has emulsifying and stabilizing properties.

Flour supplemented with 8%–10% fenugreek dietary fiber has been used in the production of baked goods, such as bread, pizza, muffins, and cakes. The antioxidant activity of fenugreek seeds allows it to inhibit food peroxidation, which occurs as a result of storage, refining, and polyunsaturated fatty acids. This application to flour allows for the production of functional foods that may be widely acceptable to consumers consuming Western diets.

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Chapter 28

Functional and therapeutic applications of some general and rare spices

Amit Krishna De[1] and Minakshi De[2]
[1]The Indian Science Congress Association, Kolkata, India, [2]Department of Microbiology, Surendranath College, Calcutta University, Kolkata, India

Introduction

In medieval Asia, besides fine textiles and ivory, spices were considered to be highly important. In this respect, India has been considered the "Kingdom of spices." In ancient economics, spices were ranked with precious inventories of royal possessions. Pepper was regarded as "the black gold of India" and "king of spices," while cardamom was "the queen of spices." Spices were used in perfumes, religious offerings, medicine, preservatives, flavors, cultural marks, cosmetics, insecticides, and condiments. Natural red and yellow colors prepared from red chiles, turmeric, and saffron were used as dyes.

Spices have been used for many centuries in tribal and folk medicines and different traditional forms of ancient medicine, such as the Ayurvedic, Unani, and Sino-Tibetan systems. India grows over 52 spices in different parts of the country and is well known as one of the largest producers, consumers, and exporters of spices products. Most of the available spices have been studied in details, and their active principles have been identified. Some of the important constituents of common spices along with their active principles are listed in Table 28.1.

Spices play a very important role in human health and disease. Apart from serving a crucial role in Indian cuisine, spices are now revealing important properties in preventing or combating ailments, including cancer, arthritis, and metabolic and immunological disorders. Most of the available spices of the 52 native to India have been studied in detail and their active principles have been identified. Daily consumption of disease-targeted functional food prepared with specific spices is slowly becoming popular throughout the world. The functional and therapeutic applications of ten general and rare spices that are a regular part of diet—like anise, asafetida, bishops weed, clove, cumin, fennel, saffron, star anise, sweet flag, and vanilla—are discussed in brief in this chapter.

Anise or aniseed

Anise seeds that date to 1500 BCE have been found in Egypt, where anise was heavily cultivated. It has been often mentioned in the Bible and in the works of many Greek and Roman authors, such as the herbalist Pliny, who recommended chewing anise seed in the morning to rid the mouth of bad odors. Romans enjoyed anise in mustaceus—an aromatic spice cake that was eaten to aid digestion after feasts and rich meals. In the 15th century, King Edward IV of England must have been fond of anise; it was used to perfume his personal linens.

The reported chemical composition of anise (*Pimpinella anisum*), also known as aniseed, is as follows: 9%−12% moisture, 18% protein, 8%−23% fatty oil, 12.25 crude fiber, 3.5% sugar, 5% starch, and 6%−10% ash. Choline is also present [1]. Aniseed has a sweet, strongly aromatic taste and emits a characteristically pleasant odor when bruised or crushed. The distinctive flavor of anise is the result of its high anethole content. Anethole is a white, crystalline substance that makes up 70%−90% of anise's essential oil. The chemical constituents of the plant are volatile oil (1.5%−3.5%), fixed oil (8%−23%), chlorine, starch (5%), sugar, and mucilage. The main constituents of the essential oil are anethole, methyl chavicol (13%−15%), *p*-methoxyphenol acetone, and small amounts of terpenes and sulfur compounds of disagreeable odor. Mannitol and myricanol are present in the seeds and roots. Recently, eight glycosides of 2-C-methyl-D-erythritol have been isolated from the fruit of the anise [2].

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TABLE 28.1 Major constituents of some common spices.

Some common spices	Major constituents
Anise	Anethole, methyl chavicol, *p*-methoxyphenol acetone
Asafetida	Asaresinotannol, glucuronic acid, galactose, arabinose, rhamnose, umbelliferone, ferulic acid, asaresinol ferulate, pinene
Basil	Methyl cinnamate, methyl chavicol, cineole, ocimene linalool
Bishop's weed	Thymol, carvacrol, *p*-cymene, gamma-terpinene, gamma-pinene, dipentene
Chile	Capsaicinoids, caffeic acid, chlorogenic acid, rutin coumaric acid, chlorogenic acid, ferulic acid, quercetin, hesperidin
Cinnamon	Cinnamaldehyde, ethyl cinnamate, eugenol, beta-caryophyllene, linalool, and methyl chavicol
Clove	Eugenol, gallic acid, eugenol acetate, caryophyllene methyl-n-amyl-carbinol, furfural alcohol, vanillin
Coriander	Linalool, caffeic acid, ferulic acid, gallic acid
Cumin	Cuminaldehyde, *p*-cymene, pinenes, cuminyl alcohol, beta-phellandrene
Dill	Phellandrene, carvone, limonene, dill ether, myristicin, coumarins, flavonoids, phenolic acids
Fennel	Anethole, fenchone, feniculin, anisic aldehyde, linalool, r-terphinene, 1,8-cineole, anisic ketone, D-alpha-pinene, camphene, D-alpha-phellandrene, dipentene, D-fenchone, methyl chavicol
Fenugreek	Trigonelline, galactomannan, 4-hydroxy-isoleucine, saponin
Garlic	Diallyl thiosulfonate (allicin), diallyl sulfide, diallyl disulfide, diallyl trisulfide, ajoene, S-allyl-cysteine, S-allyl-cysteine sulfoxide
Ginger	Gingerols, gingerdione, 6-shogaol, galanolactone, paradols
Mustard	Allyl isothiocyanate, 4-hydroxybenzyl isothiocyanate
Nutmeg	Myristic, stearic, palmitic acids, myristicin, eugenol, safrol
Oregano	Thymol, carvacrol
Pepper	Piperine, chavicine, sabinene, pinene, phellandrene, linalool, limonene
Saffron	Safranal, 2,2,4-trimethyl-cyclohexa-1,3-diene carbaldehyde, pinene, cineol, beta-carotene, picocrocin
Sage	1,8-Cineole, camphor, alpha-thujone, beta-thujone, borneol, viridiflorol, rosmarinic acid, carnosic acid, ursolic acid
Star anise	Anethole, protocatechuic acid, alpha-pinene, camphene
Sweet flag	Aserone, azulene, eugenol, calamene, cineole, isoeugenol, linalool, D-pinene, asarone, beta-asarone
Thyme	Carvacrol, flavonoid, *p*-cymene-2,3-diol
Turmeric	Curcumin, demethoxycurcumin, bis-demethoxycurcumin, DL-phellandrene, D-sabinene, cineol, borneol, zingiberene, *p*-tolyl methyl carbinol, sesquiterpene
Vanilla	Vanillin, furfural, hexanoic acid, eugenol, 4-hydroxybenzaldehyde, methyl cinnamate, isobutyric acid

Functional and therapeutic applications

Anise fruit is used as an ingredient in cordial liquors in Europe; in India it is used largely as a flavoring agent in the preparation of sweets, cake, cookies, soups, stews, and breads. Oil of anise is also used in soap making and toiletries. It is also utilized in perfuming satchels or school bags, dental preparations, and mouthwashes. It finds an important application in the preparation of lacquers and varnishes. Recently, it has been shown that anise seeds and root have estrogenic activity in rats. Anise has also been shown to possess antiinflammatory and wound-healing properties [3]. The oil of anise is used as an antiseptic for the treatment of cholera and has fungicidal properties. An alcoholic extract of aniseed kills fungi and is thus useful in treating fungal skin diseases. Anise is carminative and has expectorant properties. Some preparations from semiparched anise seeds are recommended for dysentery. It is employed in flatulent colics, in the preparation of powders for asthma, and in a few veterinary medicines. As an insecticide, aniseed is used against small insects such as mites, lice, and vermin.

Asafetida

Asafetida is a dried gum resin-like substance obtained from rhizomes of several species of *Ferula*, a plant that includes about 60 species found mostly in southwestern Asiatic countries.

The major nutritional constituents of *Ferula foetida* Linn. are 1%−10% moisture, 1.5%−10% ash, 40%−60% resin (asaresinotannol), 25% gum (glucuronic acid, galactose, arabinose, rhamnose, and protein) 10%−17% volatile oil, 6%−10% essential oil, 15%−29% sulfur compounds, umbelliferone, ferulic acid, asaresinol ferulate, and pinene. Recently, phellopterin, isopimpinellin, byakangelicin, luteolin, and leteolin-7-*O*-beta-D-glycopyranoside have been isolated.

Functional and therapeutic applications

In Western and southern India, asafetida is used mainly to impart taste in many preparations, particularly in flavoring pulses and vegetable dishes, pickles, and sauces. In Iran the centers of the stalks and the leaves are also eaten as vegetables. Asafetida is also used as a medicine and a condiment. Even though asafetida resin has various biological activities, its use has been restricted because of its pungent smell and poor water solubility. The gum resin possesses antispasmodic, carminative, expectorant, and stimulant properties. In infants it is used for the treatment of diarrhea, dysentery, atonic dyspepsia, cholera, colic, flatulence, and indigestion. Recent studies have shown several promising activities, particularly relaxant, neuroprotective, memory-enhancing, digestive enzyme, antioxidant, antispasmodic, hypotensive, hepatoprotective, antimicrobial, anticarcinogenic, anticancer, anticytotoxicity, antiobesity, anthelmintic, and antagonistic effects [4]. Estrogen-induced alkaline phosphatase activity in the endometrium of immature rabbits could be inhibited by simultaneous administration of the plant extract. It also has sedative properties and can possibly be used in the treatment of heart diseases [1]. The oil has antibiotic properties and inhibits the growth of microbes. The use of asafetida as a repellent and insecticide against important insect pests and vectors is well established [5,6].

Bishop's weed

Bishop's weed has been used as a carminative medicine in India from the ancient time of *Charaka* and *Sushruta.* Even the ancient Greek physicians Dioscorides and Galen used it in various carminative medicines.

The scientific name of bishop's weed is *Trachyspermum ammi*, and it belongs to Umbelliferae group. Three species are found throughout the world: *T. ammi* (Linn.) sprague syn, *Trachyspermum copticum* (L.) Link, and *Carum copticum* Hiern. The nutritional composition of the bishop's weed fruit is as follows: 8.9% moisture, 15.4% protein, 18.1% fat, 11.9% fiber, 38.6% carbohydrates, and minerals (1.42% calcium, 14.6 mg/100 g iron, 0.30% phosphorus), Its calorific value is 379.4 [1]. Twenty-seven compounds have been identified, of which thymol (61%) is present in the greatest quantity. Among the major components, p-cymene (15.6%) and gamma-terpinene (11.9%) are important. Bishop's weed oil is a colorless or brownish yellow liquid possessing a characteristic odor of thymol and a sharp, burning taste. The principal constituents of the oil are the phenols, mainly thymol (35%−60%), and some carvacrol. The remainder of the oil has the following composition: 50%−55% *p*-cymene (used for germicidal purposes), 30%−35% gamma-terpinene (used as perfume for soap), 4%−5% gamma-pinene, 4%−6% dipentene, and small amounts of camphene and myrcene.

Functional and therapeutic applications

The oil from bishop's weed in both pure and dethymolized forms, is employed as an antiseptic, aromatic, and carminative. It is occasionally used for perfume disinfectant soap and as an insecticide. It is an ingredient of deodorants, mouthwashes, toothpastes, and many pharmaceutical preparations. The oil is reported to act as an expectorant in emphysema, bronchial pneumonia, and other respiration ailments and also seems to possess an antidiuretic effect. The fruit has carminative properties. is a stimulant and an antispasmodic, and is used traditionally as an important remedial agent for treatment of different ailments such as flatulence, dyspepsia, diarrhea, abdominal tumors, abdominal pains, piles, bronchial problems, lack of appetite, galactogogue, asthma, and amenorrhea. Medicinally, it has been proven to possess various pharmacological activities such as antifungal, antioxidant, antimicrobial, antinociceptive, cytotoxic, hypolipidemic, antihypertensive, antispasmodic, and bronchodilating, antilithiasis, diuretic, abortifacient, antitussive, nematicidal, anthelmintic, and antifilaria effects [7]. Alcoholic extract of Bishop's weed also exhibited potent antimicrobial effects, inhibiting the growth of *Bacillus subtilis, Escherichia coli*, and *Saccharomyces cerevesiae* [8−10]. Bishop's weed has potent antioxidant properties. It contains thymol, which is a powerful antiseptic, and has an agreeable odor. It is useful in treating a variety of fungal infections of the skin. Bishop's weed contains methoxsalen, a psoralen, a type of compound that increases the skin's sensitivity to ultraviolet light, which can be used in the treatment of such skin conditions as psoriasis, tinea versicolor, and vitiligo.

Clove

Clove is known to have been in use in China as early as in third century BCE to check tooth decay. It was also familiar in the Roman Empire and had reached Europe in the Middle Ages. Cloves were imported into Alexandra as early as 175 CE. By the 4th century, cloves was well known in the Mediterranean, and by the 8th century they were known throughout Europe. In the 16th century the Portuguese discovered the origin of clove plants in the Molucca Islands.

Cloves are said to have been introduced into India by about 1800 CE by the East India Company. However, the use of cloves in Ayurvedic medicine and homeopathy was well known before that time. In fact, cloves were well established in Ceylon before the arrival of the British in India.

Cloves are the unopened flower buds of *Syzigium aromaticum* and contain a heavy volatile oil (16%−20%), a camphor resin (6%), and eugenin. The main constituents of the essential oils are eugenol (70%−90%), eugenol acetate, and caryophyllene along with methyl-n-amyl carbinol, furfural alcohol, dimethyl furfural, methyl-n-heptyl carbinol, methyl furfural alcohol, alpha-methyl furfural, and vanillin. Among the phenolic acids, gallic acid has been found to be the major constituent [11]. The volatile oil can be extracted by stem distillation from dried clove bud (clove stem oil) or leaves (clove leaf oil) and contains free eugenol, eugenol acetate, and caryophyllene. Besides the above constituents, nutritional analysis of clove shows that it consists of 57.5% carbohydrates, 5.4% moisture, 6.3% protein, 15.5% fat, 13.2% volatile oil, 11.1% crude fiber, 5.0% ash minerals, 0.7% calcium, 0.11% phosphorus, 0.01% iron, 0.25% sodium, 1.2% potassium, 0.0011% vitamin B_1, 0.0004% vitamin B_2, 0.015% niacin, 175 IU vitamin A, and 0.080% vitamin C. Its calorific value is 430 [1].

Functional and therapeutic applications

Cloves have been used in their whole form, or as oleoresin or as oil. Industrial uses of clove include whole or ground cloves for preparing curry powder, sauces, pickles, gravies, spice mixtures, preservatives, and ketchup. The pungency and aroma of clove oil imparts flavor to cakes, puddings, cookies, chocolate desserts, sweet sirups, baked foods, and candies. The custom of chewing a clove alone or with a beetle after a heavy meal or to sweeten the breath is quite usual in India. Cloves are also used for flavoring fermented beverages and as preservatives against oxidative rancidity in oils and fats. Cloves are used in medicine for their carminative, aromatic, and stimulant effects and to treat indigestion and dyspepsia. Cloves promote enzymatic flow and boost digestive functioning. They have traditionally been used in treating various forms of gastric irritability, flatulence colic, chronic diarrhea, and other gastrointestinal disorders. Fried cloves mixed with honey have been recommended for years to control vomiting. It is believed that the anesthetic action of clove controls vomiting. Moreover, chewing a clove with a crystal of common salt halts expectoration, relieves irritation in the throat, and stops coughing in cases of pharyngitis. Clove oil is used extensively in treating rheumatic pains, headache, and toothache. It is used especially for its antiseptic and antibiotic properties in treating toothache. A mixture of clove oil and zinc oxide is used as a temporary filling for tooth cavities. Clove oil is used as an ingredient in many toothpastes and mouthwashes. It is a rubefacient and counterirritant when used externally. Numerous pharmaceutical preparations contain oil of clove for its antiseptic, antiinflammatory, and analgesic properties. Clove oil is also used as a spasmodic and as an aid for digestion. It has bactericidal and mosquito-repellent properties. Recent studies have shown that cloves have antimicrobial properties, that is, both antibacterial and antifungal [12,13].

Cumin

Cumin was highly prized by the ancients throughout the world and was used in cooking and medicine by the Babylonians and Egyptians. The Egyptians used it not only to flavor meat, fish, and stews but also to mummify their dead. Both Hippocrates and Dioscorides described the medicinal attributes of cumin. In the Middle Ages in both Europe and Asia, cumin was commonly used as a natural medicine and was well known for its positive effects upon circulation and digestion. It is grown in some parts of India, especially in the areas of Jalore and Barmer in Rajasthan and Banaskantha and Ahmedabad in Gujarat and on a limited scale in Madhya Pradesh, Karnataka, Andhra Pradesh, Uttar Pradesh, and Tamil Nadu.

The seeds of cumin (*Cuminum cyminum*) are rich in an oil that consists of 35%−62% cuminaldehyde (*p*-isopropylbenzaldehyde) and *p*-cymene, pinenes, cuminyl alcohol, beta-phellandrene, and a terpineol cumene. Moreover, glucosides of luteolin, epigenin, and D-mannitol are also found to be present in the seeds. A pigenin-7-*O*-glucoside and luteolin-7-*O*-glucoside have been isolated from the fruits. Recently, some glycosides were isolated from the fruits of cumin, and their structures were clarified as 1-*O*-beta-D-glucopyranoside, 3-*O*-beta-D-glucopyranoside, and 1-*O*-beta-D-fructofuranoside, respectively. The nutritional composition of cumin seeds is as follows: 62% moisture, 17.7% protein, 23.8% fat, 9.1% crude fiber, 35.5% carbohydrates, 7.7% mineral matter, 0.9% calcium, 0.45% phosphorus, 0.048% iron, 0.16% sodium, 2.1% potassium, 0.0073% vitamin B_1, 0.0038% vitamin B_2, 0.002.5% niacin, 0.172% vitamin C, and 175 IU vitamin A. The calorific value is 460 cal/100 g [1].

Functional and therapeutic applications

Cumin is an indispensable spice in almost all curry preparations, soups, cakes, breads, cheese, pickles, sausages, and mixed spices. It is used as an additive for increasing the flavor of different foods, including fruit pies, cookies, cheese dips, cottage cheese, sandwich spreads, eggs, fish, casseroles, salad dressings, tomato-based sauces, poultry, and meat dishes such as roast pork, sausage, and meat loaf. The oil can also be used in perfumery and for flavoring liquors and cordials Cumin has a variety of medicinal properties. The oil of cumin is used as a carminative, stomachic, and astringent. It is useful against diarrhea and dyspepsia. Cuminaldehyde can be converted into thymol. It has antidiarrheal, antidysenteric, aromatic, astringent, carminative, diuretic, stimulant, and stomachic. The compound is beneficial in treating hoarseness of the voice, irritation due to worms in the abdomen, and eczema. Cumin has multiple medicinal applications in veterinary medicine. Recently, cumin seeds have been found to show antifertility effects in female albino rats [14]. Cumin has antimicrobial activities [8,15]. It inhibits growth of some food spoilage fungi and controls powdery mildewed disease [16]. The oil is helpful for disorders of skin functioning, such as inflammation, acne, eczema, scabies, blunt trauma, skin myelosis, hematoma, neurodermatitis, and psoriasis. The crude oil of *Nigella sativa* and thymoquinone extracted from its seeds and oil are effective against cancer in blood system, lung, kidney, liver, prostate, breast, cervix, and skin with much safety. The molecular mechanisms behind its anticancer role are still not clearly understood. However, some studies have shown that thymoquinone particularly has an antioxidant role and improves the body's defense system, induces apoptosis, and controls Akt pathway [17,18].

Fennel

Fennel dates back to ancient India, when it was used as a condiment and culinary spice. In Greece it was a symbol of success. In Rome the young fennel shoots were used as food. Emperor Charlemagne was known to have encouraged its cultivation in Central Europe. Even today, fennel is indispensable in modern French and Italian cooking. Fennel is one of the most common culinary spices of the world.

Fennel (*Foeniculum vulgare* Miller) contains nutritionally 6.3% moisture, 9.5% protein, 10% fat, 13.4% minerals, 18.5% fiber, 42.3% carbohydrates, 1.3 g calcium, 0.48 g phosphorus, 0.01 g iron, 0.09 g sodium, 1.7 g potassium, 1040 IU vitamin A, 0.41 mg Vitamin B_1, 0.36 mg vitamin B_2, 6.00 mg niacin, and 12.00 mg vitamin C. Its calorific value is 370 [1]. The fruits also contain iodine and traces of aluminum, barium, lithium, copper, manganese, silicon, and titanium [19]. The composition of fennel oil varies widely according to its variety and origin The main constituent of the essential oil is trans-anethole and fenchone, which ranges from 81% to 88% in the oils from the seeds and from 49% to 75% in the oils from whole plants. Fennel has a sweet taste. The fatty acids of the oil are palmitic acid and petroselinic acid. The other constituents are anisic aldehyde, linalool, r-terphinene, 1,8-cineole, anisic ketone, D-alpha-pinene, camphene, D-alpha-phellandrene, dipentene, D-fenchone, methyl chavicol, and feniculin. Water extracts of the seeds shows the presence of thermostable growth-retarding substance. The diuretic properties of fennel are attributed to the presence of glycolic acid.

Functional and therapeutic applications

Fennel is widely used for flavoring soups, sauces, pastries, confectioneries, bread rolls, liquors, meat dishes, and seasoning of pickles. The fruit is commonly used as a masticatory. The seed and the oil have a variety of medicinal properties. The leaves of fennel are digestive, appetizing, and stimulating. They increase the secretion and discharge of urine. The aqueous ethanol extracts of *F. vulgare* var. *dulce* roots were tested for their diuretic activity in rats [20]. Pharmacological evaluation revealed that the extracts increased urine flow and urinary sodium excretion. In rats the extract showed diuretic activity and enhanced bile secretion. In mice the extract exhibited analgesic, antipyretic, and motodepressive activities. The extract inhibited the growth of *Staphylococcus aureus* and *B. subtilis* [21]. They also relieve flatulence and promote the removal of catarrhal matter and phlegm from the bronchial tubes. Oil of fennel, distilled from the dry seeds, is aromatic, carminative, and antispasmodic. It is used in various carminative preparations. The use of fennel is well known as a digestive aid; it is highly beneficial in treating indigestion, biliousness, flatulence, constipation, and atonic dyspepsia. Fennel is one of the safest herbs for colic, helping the baby to release gas and relieve the stomach. Fennel seeds promote menstruation and regulate monthly periods. Traditional use of an infusion of fennel seeds in the treatment of painful menstruation and other menstrual irregularities has been recorded. It is believed that fennel benefits sore or inflamed eyes and is a good medicine for treating cough, bronchitis, and lung abscesses.

The residue left after distillation of essential oil from the fruit is used as a rich cattle feed, as it contains 14%−22% protein and 12%−18.5% fat.

Saffron

Saffron is one of the oldest and most valued aromatic crops known in southern Europe. The saffron plant is native to Greece and Asia Minor, but it is now cultivated in many parts of Europe (especially Italy, France, and Spain), China, and India. The La Mancha region of Spain is the largest producer of saffron in the world. Most experts are of the opinion that saffron came to India from Europe, but interestingly, some indications of its use has been found in ancient Indian literature, such as *Charaka* and *Sanghita*, in which it is referred to as *rudhir*, meaning "red," and is shown to have lot of medicinal properties.

Saffron belongs to the family Iridaceae, and its botanical name is *Crocus sativus* Linn. The nutritional content of saffron is 15.65% moisture, 13.35% starch and sugars, 0.6% essential oil, 5.63% fixed oil, 43.6% total N-free extract, 4.5% crude fiber, 4.25% ash, beta-carotene, lycopene, glycosides, and zeaxanthin. It is also rich in B-complex vitamins such as thiamine and riboflavin. In the essential oil (maximum 1%), several terpene aldehydes are found (e.g., safranal, 2,2,4-trimethyl-cyclohexa-1,3-diene carbaldehyde, 50%), along with terpenes (pinene, cineol). The glycoside crocin is the chief coloring agent together with beta-carotene. The bitter substance is glycoside picocrocin.

Functional and therapeutic applications

Saffron is used principally for its coloring and flavoring properties. It is used for coloring butter, cheese, puddings, pastry, and confectioneries. It is used in Spanish rice specialties and French fish preparations. In Northern India it is used in most types of food, particularly in muglai dishes and milk products. Saffron is famous for its medicinal properties. In India, Ayurvedic and Unani literature indicates that saffron can be used as a stimulant; helps in treating urinary, digestive, and uterine troubles; and is a good remedy for any kind of irregular menstruation problems in women. It is also known to provide strength and improve the sex life of males if taken regularly with milk. It is also used in homeopathic medicine for treatment of hysteria and sudden changes in mood. Pharmacological studies have demonstrated that saffron extracts have antitumor effects, radical scavenger properties, or hypolipemic effects, which are mainly due to crocetin. In addition, recent behavioral and electrophysiological studies have demonstrated that saffron extract affects learning and memory and helps in controlling seizures [22]. Saffron extract improved ethanol-induced impairments of learning behaviors in mice and prevented ethanol-induced inhibition of hippocampal long-term potentiation, a form of activity-dependent synaptic plasticity that may underlie learning and memory. This effect of saffron extract is attributed to crocin (crocetin di-gentiobiose ester), but not to crocetin. Saffron extract and crocetin, crocin, and safranal from saffron have been shown to be useful in treatment of neurodegenerative disorders accompanying memory impairment. Saffron has been shown to have antitumoral, hypolipidemic, and tissue oxygenation enhancement properties [23]. Recently, it has been reported [24] that oral administration of 100 mg/kg of saffron extract in mice significantly inhibited the growth of Dalton's lymphoma ascites and S-180 solid tumor by 87% and 41%, respectively. Crocin probably induced the therapeutic antitumor effect by its provitamin A activity and/or its antioxidant activity or by modulating the functional levels of other antioxidants [25]. Saffron has been shown to exhibit a protective effect against the genotoxicity of cisplatin, mitomycin-C and urethane, some well-known genotoxic agents. Pretreatment of saffron aqueous extract significantly reduced the frequency of urethane-induced micronucleated polychromatic erythrocytes [26].

Star anise

Star anise (*Illicium verum*) is a small genus of evergreen that is indigenous to tropical and subtropical East Asia. It is extensively cultivated in a limited area with particular ecological factors in Kwangsi in Southeast China and Tonkin in Indochina. The commercial sources of star anise are southern China, North Vietnam, and Hainan. In other parts of the world, most imports come from China, but the spice is also grown in Jamaica and the Philippines.

Star anise oil is an almost colorless to pale yellowish liquid. The composition of star anise oil is as follows: anethole, 0.5% (+)-alpha-pinene, traces of camphene, 0.3% (−)-beta-pinene, 0.2% myrcene, 0.5% 3-carene/alpha-phellandrene, 5.0% (−)-limonene, traces of *p*-cymene/gamma-terpinene, 0.5% cineole, 0.15% terpinolene, traces of 1-methyl-4-isopropenylbenzene and cis-anethole, 1% (−)-linalool, 2% terpineol-(4), 12% 8-hydroxy *p*-cymene, 88% trans-anethole (*p*-propenyl anisole), and small quantities of sesquiterpenes. Nutritionally, star anise contains many essential B-complex vitamins, vitamin C, and the minerals calcium, iron, phosphorus, potassium, manganese, zinc, and magnesium. Its calorific value is 0.7.

Functional and therapeutic applications

The eight-pointed star-shaped pods of star anise are a popular spice in China and have been used in Chinese cooking for centuries. Star anise oil is used as a flavoring agent in confectioneries, candies, chewing gums, tobacco, pickles, animal feeds, liquors, and pharmaceutical preparations. Star anise oil is also used in the making of soap and perfume. The fruit is chewed to sweeten the breath and help digestion. In Asian medicine, star anise is used to treat indigestion, facial paralysis, arthritis, and intestinal cramps. It is used as remedy for appetite loss, bronchitis, and cough. The oil is a stimulant, stomachic, carminative, mild expectorant, and diuretic. It is found to be useful in treating flatulence, spasmodic pain, and dysentery. It relieves colic and is a common ingredient in cough lozenges. The oil is employed as an applicant in treating rheumatism and otalgia and as an antiseptic. It is useful against body lice and bedbugs and is used as an ingredient in cattle sprays. It is used in fevers and scabies. It is also highly useful in treating constipation and insomnia. The Chinese use the leaves to prepare a medicinal tea for treatment of stomachache. Recently, three neurotropic sesquiterpenoids—veranisatins A, B, and C—have been isolated from *I. verum*. In brief, star anise has a number of potential uses because of its antioxidant, antimicrobial, antifungal, anthelmintic, insecticidal, secretolytic, antinociceptive, antiinflammatory, gastroprotective, sedative, expectorant. spasmolytic, and estrogenic effects. Star anise has been found to prevent growth of both pathogenic and nonpathogeic bacteria and to inhibit fungal and yeast activity [8,13,27,28]. Extensive studies have indicated that anethole and derivatives of anethole may be responsible for the antimicrobial properties of star anise. It has also been reported to possess antiviral effects [29].

Sweet flag

Sweet flag is native to India, central Asia, southern Russia, Siberia, and perhaps Eastern Europe. It also grows in China and Japan. The root was also used by the ancient Greeks and included in the traditional remedies of many other European cultures. It was also known to many early American settlers and used for a number of folk remedies.

Sweet flag (*Acorus calamus* Linn.) is of the family Araceae. Its chemical constituents include acoric acid, acorin, a bitter glycoside, mucilage, resin, tannins, and sesquiterpenes. The volatile oils include aserone, azulene, eugenol, calamene, camphor, cineole, cis-methyl, isoeugenol, linalool, and pinene. Monoterpene hydrocarbons, sequestrine ketones, trans- or alpha-asarone (2,4,5-trimethoxy-1-propenylbenzene), and beta-asarone (cis-isomer) are contained in the essential oil of the roots. The asarones are MDA-type compounds that are the naturally occurring precursors of TMA-2. The psychoactive constituents break down over time, lessening potency; at a year after harvest, the roots are considered worthless. The nutritional content of sweet flag is as follows: 37.26% carbohydrates, 0.00057% crude lipids, 6.6% crude fiber, and vitamins such as ascorbic acid, beta-carotene, and tocopherol. The total energy value is estimated at 121.65 kcal/100 g, and the total free amino acid content is 25.71 μg/500 mg.

Functional and therapeutic applications

The essential oil from the rhizome of sweet flag is used in the perfume industry and as a flavoring agent for foods, alcoholic beverages, and bitters. Sweet flag has been traditionally used for a number of medicinal reasons, including relief of toothache or headache, for oral hygiene to cleanse and disinfect the teeth, for exhaustion or fatigue, to help cure or prevent a hangover, to treat cough, in a decoction as a carminative, and as an infusion for colic. In traditional Ayurvedic medicine the roots and rhizomes of sweet flag are widely used for improving memory, cognition, intelligence, voice, and other mental abilities. Sweet flag is also used in treating skin diseases (e.g., leprosy, leucoderma) alopecia, keloids, eruptions, cervical adenoids, chronic rheumatism, gastrointestinal diseases, and pain. Recent studies indicate that sweet flag is effective in treating digestive disorder such as, indigestion (dyspepsia), and reduces intestinal gas (flatulence) and bloating after meals, and stimulates the appetite. It is effective against the pain of varicose veins when applied topically. *A. calamus* has antiallergic properties. It inhibits the mast cell−dependent anaphylaxis and allergic reactions [30]. The powdered rhizome also possesses antibacterial, insecticidal, larvicidal, and anthelmintic properties and is useful against bedbugs, moths, and lice [31]. Sweet flag roots are used for the treatment of memory loss, Alzheimer's disease, tremors, anxiety, depression, and pain disorders of neurological origin. The rhizomes and roots of *A. calamus* extract contain asarones, which have sedative/tranquilizing effects on conditioned and unconditioned reflexes, spontaneous and forced motor amphetamine hyperactivity, aggression, toxicity, and drug hypnosis, suggesting that it has brain serotonergic- and catecholaminergic-mediated effects. *A. calamus* extract has potent nonspecific spasmolytic effects on the smooth muscles of the gastrointestinal, respiratory, and genitourinary tracts *A. calamus*

extract has a central skeletal muscle relaxant effect and analgesic and anticonvulsant activity similar to that of tranquilizers such as chlorpromazine [32].

Vanilla

Vanilla is indigenous to southeastern Mexico, Guatemala, and other parts of Central America. It has been reported to have been widely used by the Aztecs not only as a drink but also as tributes to kings and emperors. It is now cultivated in some parts of Madagascar, Uganda, and the Comoros Islands. The United States is the largest importer of vanilla, followed by France and Germany. Vanilla has been thought to have been introduced into India around 1835 CE. It is presumed that the British (East India Company) introduced this spice into India.

Vanilla (*Vanilla fragrans*) extract is a complex mixture of several hundred different compounds, including vanillin (4-hydroxy-3-methoxybenzaldehyde), acetaldehyde, acetic acid, furfural, hexanoic acid, 4-hydroxybenzaldehyde, eugenol, methyl cinnamate, and isobutyric acid. Vanillin is a major contributor to the characteristic flavor and aroma of vanilla. The nutritional composition of vanilla beans is as follows: 25.85%−30.93% moisture, 2.56%−4.87% protein, 4.68%−6.74% fatty oil, 7.1%−9.1% carbohydrates, 15.27%−19.6% fiber, 19.7% calcium, 16.2% potassium, 6.7% sodium, 9.5% phosphorus, and 0.3% iron [1].

Functional and therapeutic applications

Vanilla is widely used in food and beverages for its aroma and flavor; some examples are ice cream, hot chocolate, custard, caramel, coffee, soft drinks, candy, puddings, cookies, and cakes. Natural vanilla is used in commercial preparations in the forms of whole pods, powder, extract, and vanilla sugar. The flavor of vanilla in food is achieved by adding vanilla extract or by cooking with vanilla pods. Vanilla has long been used in cosmetics, particularly in the perfume industry and as a color fixative in deodorants. The liquid extracted from vanilla pods helps in the treatment of various stomach ailments. Studies in mice found that vanillin, ethyl vanillin, and eugenol had appetite-enhancing effects and increased food intake, which could be attributable to the vanillyl group and could occur via stimulation of olfactory receptors [33]. Vanilla is known for its antioxidant properties. Recent studies have shown that ethyl vanillin isolated from vanilla beans can be used as an efficient and novel agent for the prevention of neurodegenerative diseases via inhibition of oxidative stress and cell apoptosis [34]. Vanillin has antiinflammatory, anticancer, and antitumor properties. Vanillin also has antineuroinflammatory properties and may act as a natural therapeutic agent for neuroinflammatory diseases [35].

Discussion

Spices plays an important role in human health and diseases. Food that is enriched with particular spices is prepared in many countries to combat ailments and enhance the body's immune function. The traditional use of spices as medicine in the daily diet is also slowly coming into focus, and disease-targeted functional foods enriched with spices are slowing becoming popular. Spices have antioxidant, antimicrobial, antifungal, anthelmintic, insecticidal, antiinflammatory, gastroprotective, analgesic, hypoglycemic, and cholesterol-lowering properties. Reports indicate that spices have dual types of action showing inflammation, pain, heat, redness, and swelling in acute treatment and antiinflammation, analgesia, antimicrobial, antioxidant, and antimutagenic actions in long-term treatment. Recent studies indicate that spices at low doses are beneficial for human health. In Table 28.2 the functional and therapeutic applications of some important spices are summarized for reference.

TABLE 28.2 Functional and therapeutic applications of some spices.

Applications	Spices
Cholesterol lowering	Garlic, onion, fenugreek, turmeric, chile, pepper
Hypoglycemic	Fenugreek, onion, garlic, cinnamon
Antioxidant	Turmeric, chile, pepper, clove, ginger, sweet flag, vanilla, saffron, cumin, bishop's weed
Antiinflammatory	Chile, turmeric, ginger, mustard, clove, cardamom, vanilla, sweet flag
Antimutagenic	Garlic, mustard, turmeric, saffron, asafetida
Digestive aid	Fennel, chile, bishops weed, mint, onion, fenugreek, turmeric, anise, asafetida, coriander, dill, ginger, lovage, marjoram, sweet flag, cumin
Antimicrobial	Fennel, thyme, chile, turmeric, asafetida, anise, basil, hyssop, sage, cumin, bishops weed, star anise
Analgesic	Chile, pepper, ginger, clove, ginger, sweet flag

Conclusion

As research into the active constituents of herbs continues, increasing numbers of ancient treatments and tonics are being rediscovered, recognized, and brought back into widespread use. Much of the pharmacopeia of academic medicine, including those from spices, have been derived from folk remedies. It is high time more research on the daily consumption of spices as disease-targeted functional foods be encouraged throughout the world.

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Section 7

Probiotics and prebiotics and microbiome

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Chapter 29

Beneficial effects of cinnamon on cardiovascular risk factors and type 2 diabetes

M. Moncada[1], M.A. Bernardo[1], M.L. Silva[1], J. Brito[1], Jaipaul Singh[2] and M.F. Mesquita[1]

[1]CiiEM Research Centre, Egas Moniz Higher Institute of Health Sciences, Caparica, Portugal, [2]School of Forensic and Applied Sciences, University of Central Lancashire, Preston, United Kingdom

Introduction

Cinnamon is obtained from a plant whose products have been used daily by people all over the world. *Cinnamomum verum* belongs to family Lauraceae in the botanical classification of plants [1]. The *C. verum* tree grows to around 10 m high. Its leaves are leathery, usually opposite, and lanceolate to ovate, 11−16 cm long, with sharp tips. The pale yellow flowers, which are tubular with six lobes, grow in panicles that are as long as the leaves. The fruit is tiny, 1−1.5 cm long, and black when ripe.

The word *cinnamon* is derived from the Greek word *kinnamomon*, which means "spice and sweet wood." Approximately 250 species of this genus have been identified, and various parts of the plant (Fig. 29.1), contain the primary constituents cinnamaldehyde and trans-cinnamaldehyde, which are present in the essential oil of the bark, contributing to the fragrance and biological activity of cinnamon [1,2].

Cinnamon has been used for the treatment of coronary risk factors, particularly hypertension diabetes mellitus, and obesity, and for ameliorating dyslipidemia [1,2]. In traditional medicine it was probably used to decrease complications of metabolic syndrome. This chapter aims to highlight the medicinal uses and nutritional aspects of cinnamon used as spices and medicine in treating cardiovascular diseases (CVDs) and diabetes.

The leaf of cinnamon contains eugenol, which is known to inhibit growth of several different multidrug-resistant pathogenic bacteria, and camphor root has similar effects. This genus *Cinnamomum* contains four economically important cinnamon species: *C. verum* (Sri Lankan or Ceylon cinnamon, also known as "true cinnamon"), *Cinnamomum cassia* (Chinese cinnamon), *Cinnamomum burmannii* (Java or Indonesian cinnamon), and *Cinnamomum loureiroi* (Vietnamese or Saigon cinnamon) [1,2]. Camphor is an important chemical compounds derived from *Cinnamomum camphora* that is used in pharmaceuticals, especially liniments, and in insecticides [1,2]. Its bark contains procyanidins



FIGURE 29.1 Cinnamon seeds. *Adapted from https://www.alamy.com/stock-photo/cinnamon-seeds.html.*

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and catechins, which are potential antioxidant flavonoids and may be very useful to treat type 2 diabetes mellitus and insulin resistance. Cinnamon has immense aromatic potential as used in the food and pharmaceutical industries. Its leaf and bark have digestive, blood purifier, astringent, carminative, warming stimulant, antiseptic, antibacterial, antifungal and antiviral properties and can help to reduce cholesterol and blood sugar levels.

Chemical composition

Cinnamon contains a wide range of phytochemical compounds, including aldehydes, acetate, alcohol, terpinenes, flavonoids, alkaloids, anthraquinones, coumarins, phenols, saponins, tannins, carboxylic acid, hydrocarbons, camphene, spathulenol, fatty acids, actinodaphnine, butanolides, lignans, steroids, propenoids, and kaempferol glycosides in various parts of the plant [3]. Further studies are needed on the clinical, medicinal, purification, and identification of the most effective antibacterial activity of cinnamon to cure various infectious diseases. The major chemical contents of the parts of the cinnamon plant are listed in Table 29.1. The chemical structure of the major compounds of cinnamon are presented in Fig. 29.2.

Medicinal uses of cinnamon

Cinnamon has been used as medicine for reducing inflammation and treatment of diabetes in India for several thousand years. In Ayurvedic medicine, cinnamon has been used for its antitussive, antiarthritis, antimicrobial, antifungal, antioxidant, antiinflammatory properties and is used in treatment of pain and dental problems [1,2]. In Asia and Europe, cinnamon is traditionally used for flavoring food and in pharmaceutical preparations against various ailments.

Cinnamon is a popular culinary spice and is used in Indian curries, fried and grilled foods, candy, incense, toothpaste, and perfumes. The oil of cinnamon is used in medicine as a carminative, antiseptic, and astringent. According to the recent studies, cinnamon may prevent or delay diabetes, colon cancer, and bleeding time. A recent investigation by the U.S. National Library of Medicine showed that cinnamon is effective in the treatment of diarrhea, emesis, muscle cramps, infections, molds, flu, and erectile dysfunction [1]. Cinnamon has also been effective against multiple sclerosis, Alzheimer's disease, and human immunodeficiency virus infection

In an extensive review, the plant extracts of cinnamon have been reported to possess warming stimulant, astringent, carminative, blood purifier, digestive, antiseptic, antifungal, antiviral, antibacterial, antioxidant, antiinflammatory, and immunomodulatory properties and also help to reduce cholesterol and blood sugar levels [3].

Cinnamon administration has been claimed to reduce fat mass and raise serum antioxidants [2]. Two species, *C. cassia/aromaticum*, and *Cinnamomum zeylanicum/verum*, are the main species that have been used in various trials [2]. It is possible that about 1−6 g of these cinnamon species, mainly in powder, can be used as an adjunct drug treatment for type 2 diabetes mellitus and other conditions of glycemic impairment, such as myocardial infarction, metabolic syndrome, and sepsis.

In a clinical trial, cinnamon tea was administered for 15 days to subjects with overweight [4]. Data on the subjects' body weight and body mass index (BMI) were collected at baseline and after the 15-day intervention period. Of 30 subjects in the pretest, 70% were overweight and 30% had class I obesity with a BMI mean value of 28.75 kg/m^2. After treatment, 20% of subjects were of normal weight, 66.67% were overweight, and 13.33% had class I obesity [4]. The mean BMI after treatment was 27.45 kg/m^2. The findings revealed that the treatment with cinnamon tea was associated with improvement in the decline of body weight [4]. However, larger studies are needed to investigate the effect of cinnamon in reducing the coronary risk factors among subjects with obesity.

TABLE 29.1 Chemical contents of cinnamon in various parts.

Component	Ingredient
Fruit	Trans-cinnamyl acetate, 41.98%
Leaves	Eugenol, 70%−95%
Bark	Cinnamaldehyde
Root bark	Camphor, 60%
Buds	Terpine hydrocarbons
Flowers	€-cinnamyl acetate, 41.98%; trans-α-bergamotene, 7.9%

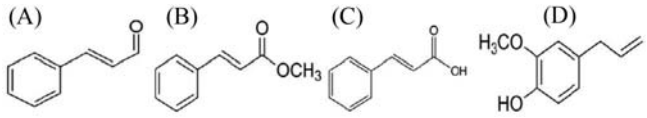


FIGURE 29.2 Chemical structure of the major compounds of cinnamon: (A) cinnamaldehyde, (B) cinnamyl acetate, (C) cinnamic acid, and (D) eugenol.

TABLE 29.2 Mean blood glucose concentrations in healthy subjects obtained prior to the intervention (t_0) and after the ingestion of each meal consisting of custard tart (control group) or a custard tart with cinnamon powder (cinnamon group) at 30 (t_{30}), 60 (t_{60}), 90 (t_{90}), and 120 (t_{120}) minutes after ingestion.

Time	Control group (mmol/L)	Cinnamon group (mmol/L)
t_0	4.76 ± 0.14	4.70 ± 0.14
t_{30}	6.18 ± 0.24	5.71 ± 0.21
t_{60}	5.53 ± 0.24	5.41 ± 0.12
t_{90}	5.06 ± 0.17	4.84 ± 0.15
t_{120}	4.76 ± 0.14	4.72 ± 0.11

All values are expressed as mean ± SEM, $N = 16$ for each group. No interaction between the independent and repeated measures factors was found, $P = .530$ (Repeated Measure ANOVA of mixed type). *Adaptated from*5.

In a clinical trial involving 32 subjects who were randomly allocated into two groups: 16 subjects ingested a Portuguese custard tart (*Pastel de Nata*) with cinnamon powder (cinnamon group) and 16 subjects ingested a custard tart with no cinnamon (control group) [5]. Blood glucose concentrations were measured before the interventions and after 30, 60, 90, and 120 minutes (Table 29.2). Chemical analysis was performed to quantify the total phenolic content and antioxidant activity.

The postprandial blood glucose (PBG) area under the curve (AUC) was significantly lower ($P = .0005$) in the cinnamon group (599.2 ± 9.1) compared to the AUC of the control group (645.7 ± 7.7). The administration of cinnamon powder to the custard tarts slightly decreased PBG mean values compared to custard tart without cinnamon powder, although it did not reach statistical significance ($P = .273$) (Fig. 29.3). The addition of cinnamon to the custard tart improved the total phenolic content (1278.7 ± 0.7 compared to 253.7 ± 22.8 mg/L gallic acid) and antioxidant properties, increasing by 4.4 times the capacity of free radical scavenger compared with custard tart without cinnamon (IC_{50}). The addition of cinnamon powder to custard tart could be beneficial for glycemic control. As reported in other studies with cinnamon [6,7], a new landmark study revealed a beneficial effect of adding cinnamon powder to a high-sugar meal, which could contribute to nutritional and alternative medicine practices [8], in Table 29.2.

Table 29.3 shows the results of the different tests for total phenolic content, FRAP assay, TAS, and TEAC (IC_{50}) of plain custard tart and custard tart with 3 g of *C. burmannii*. The data revealed that custard tart, after addition of cinnamon powder, increased the total phenolic content. Moreover, custard tart with cinnamon addition showed high antioxidant activity and revealed 4.4 times more capacity of free radical scavenging compared with custard tart alone (IC_{50}), in Fig. 29.3.

Comments

Westernized diets containing foods with high amounts of sugar and/or saturated fats and a low fiber content can lead to a number of chronic disorders, including CVDs, obesity, and diabetes [8]. It seems that low glycemic foods have small but clinically useful effects on medium-term glycemic control in diabetic patients, which may be protective against cardiometabolic diseases. Cinnamon has been used for years as a spice but just recently has become increasingly popular for its benefits in glycemic control [9]. In short-term studies, the ingestion of either cinnamon powder or its equivalent in aqueous extract has been shown to significantly improve glycemia in healthy adults [6,10–13]. Moreover, the addition of cinnamon to a high-sugar meal seems to reduce postprandial glucose concentration and gastric emptying rate and to reduce insulin concentrations [14]. Nevertheless, it was also reported that cinnamon powder added to a high-fat meal had little or no effect on postprandial lipidemic and glycemic responses or on the gastric emptying rate [14]. As was revealed by previous investigations involving several medicinal plants, cinnamon is among the most effective

TABLE 29.3 Total phenolic content, Antioxidant Assay Using Ferric Reducing Antioxidant Power (FRAP) assay, Total Antioxidant Status (TAS) and Trolox Equivalent Antioxidant Capacity (TEAC) (IC_{50}) tests of plain custard tart and custard tart containing 3 g of *Cinnamomum burmannii*.

	Custard tart	Custard tart with 3 g cinnamon
Total phenolic (mg/L gallic acid)	253.7 ± 22.8	1278.7 ± 0.7
FRAP assay (μmol Trolox/L)	417.3 ± 12.7	963.0 ± 8.9
TAS test (mmol Trolox/L)	<0.4	417.3 ± 12.7
TEAC (IC_{50}) (mg/L gallic acid)	257.5 ± 42.4	58.9 ± 0.1

All values are expressed as mean ± SEM. *Adaptated from*5.

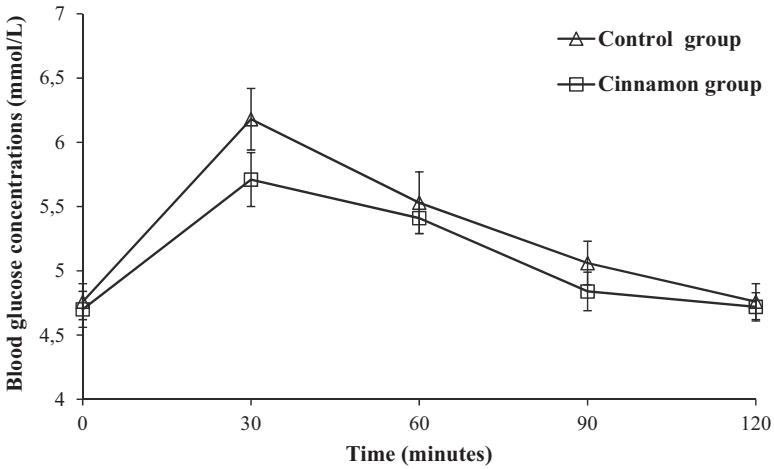


FIGURE 29.3 Time course curves showing mean (± SEM) blood glucose concentrations (mmol/L) in healthy subjects after ingestion of custard tart alone (control group, $N = 16$) and custard tart with cinnamon (cinnamon group, $N = 16$). No interaction between the independent and repeated measures factors ($P = .530$) was found (Repeated Measures ANOVA of mixed type). *Adapted from 5 10.1111/j.1467-789X.2007.00438.x5*

plants in the regulation of blood glucose in vitro [15]. An in vitro study showed that this spice seems to exert a mimetic effect of insulin through increased glucose uptake in adipose tissue and skeletal muscles [16] This effect is believed to be associated with cinnamon's polyphenolic content, which is known to provide protection against cardiometabolic diseases. Specifically, a water-soluble polyphenol type A polymer compound isolated from *C. burmannii* has been shown to enhance insulin action by stimulating the insulin receptor in vitro, and it also shows antioxidant effects, which can protect against CVDs [17].

Several different species of cinnamon have been studied to determine their hypoglycemic effects [18] in both animal [16], and human [7] models. To date, not much work has been done using *C. burmannii*, both investigating its effect in lowering blood glucose concentration and analyzing its antioxidant properties. The results from the present study have shown that the addition of *C. burmannii* powder to a Portuguese custard tart can significantly reduce blood glucose as expressed by the AUC in healthy adults. This result is in agreement with previous studies, which demonstrated that the addition of cinnamon powder (6 g) from *C. cassia* to a high-sugar meal significantly lowered PBG, as expressed as the AUC [7] and blood glucose concentrations [7], compared with the reference meal. This result could be attributed to a delay in gastric emptying as a result of the presence of cinnamon [7]. According to Horowitz et al., the plasma glucose concentration in healthy subjects is inversely related to the rate of gastric emptying at 120 minutes [19]. Moreover, the gastric emptying itself does not seem to be the only mechanism accounting for the effect of cinnamon on glucose homeostasis. Cinnamon can markedly inhibit the enzymes involved in carbohydrate digestion, namely, the intestinal alpha-glycosidase [20] and the pancreatic alpha-amylase [21], which could prevent the absorption of carbohydrates into the small intestine.

In agreement with findings from others studies [6,14], this study found that 3 g of cinnamon powder did not significantly alter C_{max}, ΔC_{max}, or PBG concentrations. This result may be due to the fat content (31%) of custard tart, which seems to affect the glucose absorption, thereby interfering with postprandial glycemia. According to Normand et al., a

carbohydrate-rich meal with medium doses of fat (33%) lowers the postprandial glucose peak [22]. Moreover, in our previous work, ingestion of cinnamon tea in a dose of 6 g significantly lowered postprandial C_{max}, ΔC_{max}, and blood glucose in healthy subjects [23]. These observations suggest that cinnamon may act in a dose-dependent manner to improve glucose utilization through insulin receptor potentiation, as was reported previously in an in vitro study [24].

In addition, chemical analyses performed in this study show that the addition of *C. burmannii* to custard tart increased the total phenolic content. In addition, both the FRAP assay and the TAS test showed a high ability of cinnamon to reduce the ferric complex and to inhibit the free radical $ABTS^{+\bullet}$, respectively. These results are in agreement with previous studies, which demonstrated strong antioxidant activity and high total phenolic content in extracts of different species of cinnamon [25,26]. This high antioxidant property of cinnamon may be attributed to its high content in phenols. In a study by Dudonné et al., a significant relationship between antioxidant capacity and total phenolic content was found, suggesting that these compounds are the major contributors to the properties of this spice [26]. Specifically, polyphenol polymers of cinnamon with double-linked type-A procyanidin may potentiate insulin action by exerting an effect on glucose metabolism in fat cells [17]. Thus the addition of cinnamon powder to custard tart could have a protective effect in patients with diabetes, which is a risk factor of CVD [27], owing to its potential antioxidant activity.

Several mechanisms have been described for the action of polyphenols isolated from cinnamon. These compounds seem to modulate multiple steps of the insulin signal transduction pathway, stimulating the glucose uptake and glycogen synthesis. These include increased tyrosine phosphorylation activity of insulin receptors, [28] increased amount of glucose transporter (GLUT4) protein [28], and increased glycogen synthase activity and decreased glycogen synthase kinase-3 beta activity [29]. These bioactive compounds of cinnamon have also been shown to have insulin-independent effects on the regulation of gene expression in adipocytes by inducing GLUT1 gene expression [30]. According to current evidence, the ingestion of cinnamon, either as whole cinnamon or as cinnamon extract, has been shown to reduce fasting blood glucose [6,13]. However, it is particularly noteworthy that available studies in the literature are heterogeneous, since they have used different species and different compositions, study designs, doses, and formulations [31], which all limit the ability to apply cinnamon to nutritional care.

There are some limitations that should be acknowledged in using cinnamon. In future studies, it would be useful to apply the 24-hour dietary recall method for the dietary record. Moreover, the small number of participants in the various studies compromises the external validation of these results and consequently the nutrition care process. To address these limitations, large randomized, controlled trials on cinnamon powder should be conducted to demonstrate its effects on blood glucose, blood lipids, and obesity.

In brief, this review indicates that cinnamon has potential beneficial effects on blood glucose, body weight, blood lipids, and blood pressures. Its antioxidant activity should be evaluated for inhibition of oxidative stress in various diseases. It is possible that administration of 3 g of *C. burmannii* powder can significantly decrease PBG, blood lipids, and possibly blood pressures. These results could be attributed to a delay in gastric emptying, slowing the glucose absorption as well as antioxidant activity. Another possible mechanism of cinnamon action involves the inhibition of intestinal alpha-glycosidase and pancreatic alpha-amylase, preventing the absorption of carbohydrates in the small intestine.

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Chapter 30

Novel prebiotics and next-generation probiotics: opportunities and challenges

Laila A. Hussein
Department of Nutrition, National Research Center, Giza, Egypt

Introduction

The expansion of industrialization, urbanization, and rising incomes during the last decades has changed many demographic, social, economic, ecological, and biological parameters with increased accumulation of people in cities. The profile of food consumption has accordingly changed and adapted to the new situation. The superfine flours, refined sugars, and semifinished products free from fiber produced by innovations in the food industry represent more than 80% of cereal consumption at present. The fast-food industry is based on foods with more calories than unprocessed natural foods, and the components of fast food are industrially prefabricated, minimizing the time of preparation, and are swallowed faster, and their saturation efficacy is lower, which causes hypercaloric nutrition. It is estimated that 6000 new fat-modified foods were introduced to the retail market within the last decade, and these products target youth and modify the dietary behavior of urban areas with larger residential density than rural populations. The United States provides an example of an obesogenic environment with massive marketing and advocacy of fast foods and soft drinks carried out by multinational restaurants through modern sales promotions [1]. Consumption of fast food and the so-called convenience food products, especially the rapid degradation of starch products to glucose, leads to a short-term elevation of blood sugar and in new feelings of hunger; this stimulates consumption of substantial portions of insulin-activating carbohydrates, which is stressful to the human organism. It is now appreciated that the Western foods weaken the immune system and lead to dysbiosis [2]. Diet-related chronic diseases are cardiovascular diseases, obesity, diabetes, hypertension, stroke, and cancers, which are linked by common preventable factors [3]. Cardiovascular disease is the scientific term used for conditions of the heart—ischemic heart disease and valvular, muscular, and congenital heart disease—and also hypertension and conditions involving the cerebral, carotid, and peripheral circulation [4]. Cardiovascular disease remains the most common single cause of death in old age in both sexes in most countries, and it is predicted that by 2030, cardiovascular diseases will remain the leading causes of death, affecting approximately 23.6 million people around the world. Atherogenic risk factors such as increased blood pressure, blood lipids and glucose intolerance, all of which are significantly affected by dietary factors and play a significant role in the development of coronary heart disease. Hypercholesterolemia is a disorder characterized by high levels of blood cholesterol and elevated low-density lipoprotein (LDL) cholesterol, which represents the first stage of atherosclerosis, a risk factor for congenital heart disease [5]. Because hypercholesterolemia causes no symptoms, preventive measures and regular measurement of cholesterol levels are important for people in high-risk categories. Type 2 diabetes is a chronic condition that develops when the pancreas does not produce enough insulin or when the body cannot use the insulin that is produced. It is estimated that worldwide, type 2 diabetes will rise from 135 million in 1995 to 300 million in 2025 [6]. More than 1900 million adults (over the age of 18) were clinically observed to be obese in 2016 with a body mass index (BMI) greater than 30 [7]. Obese people have a life span that is 7 years shorter than that of nonobese people [8]. Many forms of cancer can be prevented and effectively treated with early detection, and dietary fat seems to be associated with cancer of the colon, pancreas, and prostate [9]. Despite many decades of recommendations for fat reduction, the absolute intake of dietary fat was not reduced among the population as a whole. This review aims to highlight the role of new prebiotics and probiotics in the prevention of diseases.

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Possibilities for altering adverse trends

In the last decade, worldwide health policy agencies have developed different projects and programs targeting populations as a whole with an emphasis on high-risk groups for prolongation of life and improvement of life quality. Increasing healthcare costs and the resulting need for preventive medication resulted in a shift to potential nonmedical route through probiotics and/or prebiotics and functional foods (FF) with no side effects. Knowledge in this field is rapidly extending, and the large development in the production of FF supported by research suggests encouraging new opportunities to improve human health. Dietary fiber (DF) is collectively acknowledged to be the key raw material for prebiotics, but variations in processing technology are enormous. A general overview is given about the bioavailability of new novel bioresources for the production of high-fiber diet from food industrial wastes, mushrooms, and marine seaweeds. This research covers prebiotic production by various techniques, prebiotic supplementation in food, and commercially available prebiotic agents. The consumer's interest in fiber-rich ready-to-eat foods and functional beverages could possibly be modified toward higher doses in the near future. An overview is also provided on the potential newly identified native gut microbiota bacteria candidates grouped to form the next-generation probiotics (NGPs). The detailed physiological and molecular evidence on the isolation, identification, and functional characterization of these beneficial bacteria can potentially be applied for promotion of health or targeted for therapeutic purposes in specific inflammation-related disease. The main clinical trials carried out for the evaluation of FF success or failure are discussed in this chapter. The data presented in this chapter are not intended to cover genetically modified organisms or laboratory-engineered microorganisms. These topics are covered in more detail elsewhere.

The human alimentary tract

In principle, the nutrition of humans is formed by a mixed diet of about 55%−60% carbohydrates, 10%−15% proteins, and 30% fat. The proportion of digestible carbohydrates, however, is essentially determined by its chemistry and its processing. The digestion of glucose containing α-(1→4) and -(1→6) linked polysaccharides (PSs), the so-called starches, is partly performed in the mouth by alpha-amylase contained in the saliva, a kind of predigestion into smaller fragments. After passing through the stomach, these fragments are degraded to glucose by pancreatic and intestinal amylases and maltase in the upper small intestine and transported to the liver by cells of the intestinal mucosa using the portal circuit. The current picture of the gut ecosystem is one of a very diverse, highly individual, yet functionally conserved ecosystem

Prebiotic concept: influence of gut flora and health benefits

A prebiotic is "a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, thereby improving host's health" [10] Prebiotics are nondigestible oligosaccharides with various origins and chemical properties, differing in chain length, monosaccharide composition, linkage type, and branching degree [11]. The prebiotic index is defined as the increase in the absolute number of bifidobacteria expressed divided by the daily dose of prebiotics ingested [12]. Since the introduction of the term *prebiotic* in 1995, its definition has evolved, and the concept has expanded to include noncarbohydrate substances affecting the colonization of beneficial bacterial community within the gastrointestinal environment [13]. The definition is more straightforward and clarifies that the targets extend beyond stimulation of bifidobacteria and lactobacilli while recognizing the health benefits that can be derived from other beneficial taxa that result in specific change, in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefits on the host's health, The prebiotic concept has continued to evolve and tday, a dietary prebiotic is defined as a selectively fermented ingredient, an and the prebiotic concept has been extended to the prebiotic concept has been extended to representing broad categories of eight compounds [14]. Their distribution in nature, chemical structure, and prebiotic activities are described in the following sections.

Modulation of the colon microbiota by dietary prebiotics

The colon microbiota comprises approximately 10^{14} bacteria belonging to more than 1000 species [15]. Most of the gut flora include bacteria that represent 60% of the dry fecal mass, which is estimated to be 1−2 kg. The gut microbiota are important contributors to host health, including nutrition and energy homeostasis, pathogen resistance, the regulation of intestinal epithelial proliferation, and a variety of other factors for the permeability of the gastrointestinal mucosa

and host immune systems [16]. Prebiotic foods are high in special types of fiber that act as growth substrates selectively utilized by human gut bacterial genera with health benefits [13,17]. More than 100 different gut bacteria taxa are affected by prebiotics [18]. According to these investigators the oral administration of prebiotics increased the abundance of *Akkermansia muciniphila* by more than 100-fold to reach 4.5% under a high-fat diet compared with 0.09%–2.5% under a normal diet. These findings were confirmed in different set of experiments. The intake of prebiotics decreases the fecal pH, increases the size of the fecal pool of the short-chain fatty acids (SCFA) acetate, butyrate, and propionate [19]. The liberated butyrate lowers the pH of the colon, promoting the solubility of fatty acid absorption, and the growth of the epithelial cells in the colon stimulated by butyrate [20] might increase their capacity to absorb minerals (see Fig. 30.1) particularly higher absorption of in particular calcium [21]. Some studies have reported a positive stimulating effect of prebiotics on the immune system of the colon. *I*in particular, the production of a number of proinflammatory cytokines (e.g., tumor necrosis factor alpha) and the expression of a number of receptors on T and B lymphocytes and macrophages was reported (see Fig. 30.2).

Total, soluble, and insoluble dietary fiber

DF is the most prominent nutritional-resistant carbohydrate present in nature and is defined as the edible parts of plants carbohydrates that are resistant to digestion and absorption in the human small intestine with complete or partial fermentation in the large intestine [22]. DF consists of nonstarch PSs (cellulose and DFs), resistant oligosaccharides, indigestible dextrins, hemicellulose (glucans, gums, and pectin), lignin, and substances associated with the nonstarch PS and lignin complex in plants (noncarbohydrate component of plant cell walls, i.e., waxes, phytates, tannins, and saponins). More recently, it has been suggested that nondigestible oligosaccharides, such as raffinose, stachyose, oligofructose, and inulin (INU), also function as DF. Soluble fibers (found in fruits, fructan-containing crops, and vegetables) are water-soluble hemicelluloses, pectins, gums, and mucilages that possess a high dispersibility and viscosity and are partially soluble in aqueous systems. Beta-linked nonstarch PSs are completely resistant to amylolytic enzymes, and whole-wheat and most cereal grain products contain relatively high amounts of the insoluble fibers cellulose, high-polymer hemicelluloses and beta-glucans, and the polyphenylpropan lignin. DF is collectively acknowledged to be one of the key factors in a health-promoting diet, and DF intake of at least 25 g/day is recommended. The intake of fibers is low (13–15 g/day) among Americans[23] and marginal (18–22 g/day) among Europeans [24]. Consumption of soluble DF, such as beta-glucan and arabinoxylan (AX), leads to the formation of viscous solutions and increases the viscosity in the intestine, slowing intestinal transit, which in turn delays gastric emptying and slows glucose and sterol absorption by the intestine, and DF that is not fermented in the body is excreted in the feces. Soluble fiber acts as an available substrate for the gut microbiota, and its multiple applications in the host system have been reported [20] (Fig. 30.3). Its

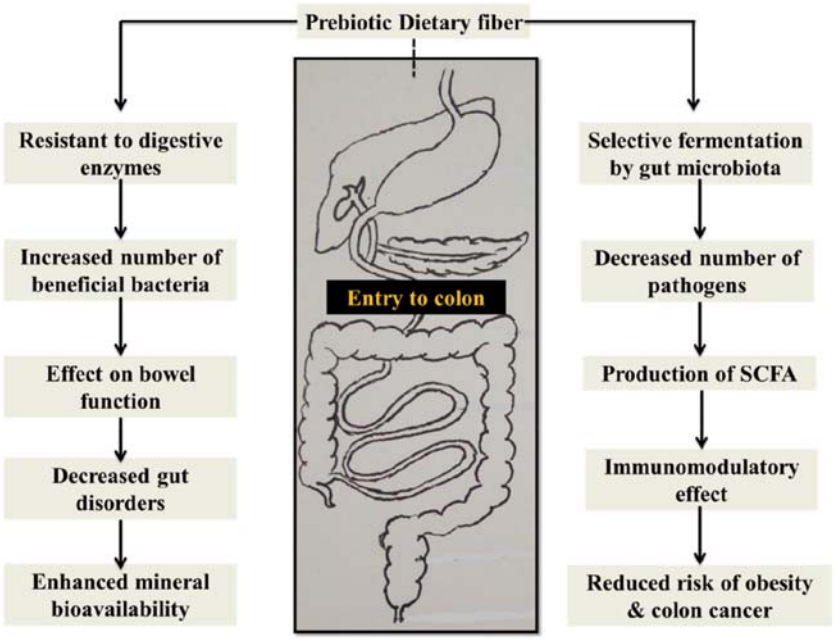


FIGURE 30.1 Benefits of oral administration of prebiotics on diverse functions of the colon.

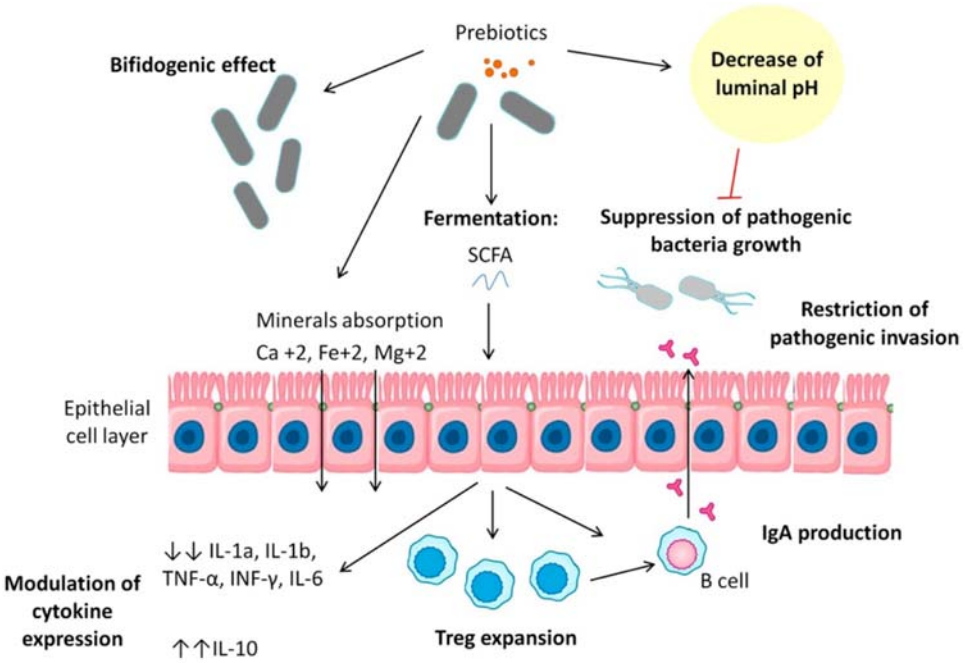


FIGURE 30.2 Mechanism of prebiotic action. These mechanisms include the production of beneficial microbial metabolic products, in particular short-chain fatty acids (SCFAs), the promotion of ion and trace element absorption (such as that of calcium, iron, and magnesium), a decrease in luminal pH, and the regulation of the immune system, increasing IgA production and modulating cytokine production (Cardos).

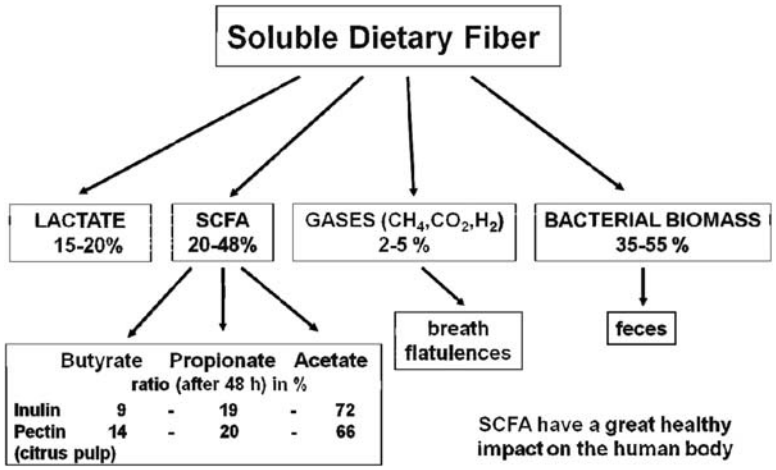


FIGURE 30.3 Physiological functions of dietary fiber in the colon.

beneficial physiological effects include lowering postprandial blood glucose and insulin levels [25] and reducing plasma cholesterol levels. The net energy values of the DF were estimated to be about 30%−40% lower than the calculated values (4.3 kcal/g) in the diet of humans.

Inulin-type fructans

After starch, fructans are the most abundant nonstructural PSs found in nature as a storage carbohydrate. The natural occurrence of fructans-producing plants belong mainly to the composite (25,000 species), such as chicory, dahlia, and Jerusalem artichoke, and to the Liliacea (3500 species), such as onion and garlic, and acts as cryoprotectant. Fructooligosaccharides (FOS) in the plants comprises of 1-kestose, nystose and fructofuranosylnystose in different proportions (Fig and INU have potentially beneficial nutritional effects, which meet the three classification criteria for being considered a prebiotic. The monomers are fructose sugars linked by glycosidic β-(1,2) bonds. These polymers are called fructans, and their fructose chains may contain or not contain glucose molecules in one of its ends.

Chicory INU makes up 65% of the dry weight of chicory roots (Fig. 30.4) and is the best-characterized prebiotic, consisting of galactooligosaccharides (GOS) and fructooligosaccharides (FOS). FOS comprises of 1-kestose, nystose



FIGURE 30.4 Chicory plant with flowers, chicory root, and chicory crude extract.

and fructofuranosylnystose (Fig 30.5). The industrial processing of chicory FOS and INU is successful because of their high solubility in hot water with high-percentage recovery with the technological development of microwave-assisted extraction [26], supercritical carbon dioxide extraction [27,28], and enzyme-assisted hydrolysis. Linear fructan molecules with two to ten moieties are FOS, while INU contains more than ten fructose residues, as in chicory (*Cichorium intybus*). Oligofructose is made from INU by chemical degradation or controlled enzymatic hydrolysis with specific endoglycosidases for the production of FOS with well-defined degrees of polymerization of 2−20. Furthermore, FOS can be produced from sucrose at a commercial scale, using fungal enzymes. Commercial products such as Fructofit are resistant to gastric acidity, to hydrolysis by mammalian enzymes, and to gastrointestinal absorption, and β (2−1) fructans are selectively fermented by most *Bifidobacterium* species, which produce SCFA, the principal product of fermentation in the large intestine of humans and the predominant anion in the colon, lowering its pH. Feeding INU supplements improved metabolic disorders associated with obesity, such as insulin resistance; decreased the fat mass [29]; lowered liver steatosis; and reinforced the gut barrier [30]. The antimicrobial, antioxidant activities of fructan and scavenging of reactive oxygen species have been reported. Fructan is found in the cereal grains (caryopses) along with starch as costorage PSs, and its content is approximately 1.3%−2.5% in wheat grains, which is reduced to 1.0%−1.3% in the wheat flour, with respective content of 3% in the bran. Higher fructan content is found in rye grains, with respective contents of 4%−6%, 2.5%−4%, and 7%. Fructans in grains confer health benefits and physiological effects, including laxative effects, blood cholesterol attenuation, and/or blood glucose attenuation.

Beta-glucan

The bran of barely is a useful natural source of beta-glucan in concentrations ranging between 3% and 11%. Beta-glucan is a nonbranched PS consisting only of β-D-glucopyranosyl units. These units are linked by either (1,3) or (1,4)-β-D linkages; hence its exact name is mixed-linked (1,3),-(1,4)-β-D-glucan. Building blocks of 1,3-linked cellotriosyl

and cellotetraosyl units constitute over 90% of the molecule. The (1,3) linkage prevents close packing of the molecule and makes it partly soluble in water. Soluble beta-glucans deliver viscous and shear-thickening solutions even at quite low concentrations. Barley beta-glucan, for instance, produces a higher viscosity than pectin at a concentration of about 0.5%. The efficacy of beta-glucan in the human intestinal tract depends on its ability to retard the absorption rate of food in the intestine due to increased viscosity, in this way balancing the postprandial glucose and insulin response [25]. Additionally, high viscosity in the small intestine interferes with cholesterol absorption, and beta-glucan has been shown to reduce elevated blood cholesterol levels and balance blood glucose and insulin response after meals; thus it possesses a high prebiotic efficiency.

Cellulose, lignin, and hemicelluloses

Cellulose, lignin, and hemicelluloses are located in the cell wall and are the structure-giving substances of plants. Cellulose is the most abundant organic molecule in nature. It is an insoluble fiber nonbranched polymer of several thousand glucose units connected by beta-linkages in tightly packed aggregates and resists microbial hydrolysis [1,4]. Cellulose microfibrils are linked via hemicellulose links to build up the cellulose-hemicellulose network. Hemicelluloses are heterogeneous polymers of heteropolysaccharides, such as xylan, AX, glucomannan, glucuronoxylan, or xyloglucan. Most of these PSs contain pentose sugars, such as D-xylose and L-arabinose linked with hexose sugars, such as D-mannose, D-galactose, D-glucose, and D-rhamnose, and sometimes include acid sugars, such as glucuronic acid or galacturonic acid. Soluble xylan and AX deliver high prebiotic efficiency. During ripening or because of stress in plant organs, a lignification process to woody material can take place. In vegetables the content of cellulose and lignin accounts for around 30% and 3%, respectively; respective percentages in cereals are 20% and 17% and in cereals 17% and 7% of the total PS fiber content. Lignin, a three-dimensional network built of units of phenylpropane, is the component of the tough or woodlike portions of plants and seeds. Bran and other cereal products are the main sources of dietary insoluble lignin, which is not degraded neither by human enzymes nor by the gut microflora.

Xylooligosaccharides

Xylooligosaccharides (XOS) are extracted and produced from wood and other lignocellulosic materials by enzymatic or chemical processes [31,32]. They are composed of chains of xylose moieties linked by β-(1,4)-linked D-xylopyranosyl residues, some of which are monosubstituted or disubstituted with α-L-arabinofuranosyl residues, and covalent cross-linking of AX chains occurs through dehydrodiferulic acid bridges. AX can be produced at industrial scale from xylan-rich materials (e.g., straw, wood, and some macroalgae, in which they form the hemicellulose portion). XOS are considered soluble DF with prebiotic activity, favoring the improvement of bowel function and immune function and having antimicrobial and other health benefits, such as being able to decrease blood glucose, total cholesterol, and LDL cholesterol levels in patients with type 2 diabetes mellitus. In animal experiments, XOS was more effective than FOS in reducing serum triglycerides and increasing bifidobacteria populations and cecal weight, with marked decreases in the cecal pH and the number of aberrant crypt foci (ACF) in the colon of 1,2-dimethylhydrazine-treated rats. Arabinoxylooligosaccharides with a degree of polymerization of 5 gave the best desirable effects on gut health characteristics in terms of increased number of bifidobacteria, increased concentrations of the cecum acetate and butyrate in the colon, and reduced intestinal protein fermentation, comparable to those fed on FOS [33] in rats [34] and in the feces of elderly people [35] and Korean women [36]. AOS may therefore represent a new prebiotic candidate for reduction of risk in patients with ulcerative colitis in the near future, once in vivo tests have been carried out. Intervention studies performed in humans with AX and arabinoxylooligosaccharides reporting positive physiological effects on metabolic parameters [37–39] had been reviewed recently [40].

Galactomannans

Galactomannans are heteropolysaccharide consisting of β-(1,4)-linked D-mannopyranosyl residues in the main chain with varying degrees of substitution with α-(1,6)-linked D-galactopyranosyl residues in the side chain. Ratios of galactose to mannose determine the physical properties of the galactomannans and their diverse chemical structure. The galactomannan from fenugreek seeds was found to be resistant to gastric acid and pancreatic enzymatic hydrolysis, and upon fermentation (71.4%) by *Bacillus coagulans* MTCC 5856, a significant amount of SCFA was produced, while the growth of *Escherichia coli* ATCC 25922 cocultured with galactomannan was inhibited, suggesting competitive fermentation [41].

Resistant starch

Starch granules of cereals exist in the highly branched amylopectin (70%−80%) and the low and nonbranched amylose with a helical structure (20%−30%). Amylopectin cornstarch is essentially 100% digestible, while the amylose content was inversely related to the amount of rapid digestible starch [42], and it resists digestion by human pancreatic amylase in the small intestine, reaching the large intestine intact, and is fermented by the colon microbiota. Resistant starch (RS) is a linear molecule of α-1,4-D-glucan, essentially derived from the retrograded amylase fraction, and is classified into five general subtypes: RS1−RS5. Retrogradation occurs when starch with preferably high content of amylose is cooked in water beyond its gelatinization temperature followed by cooling and can act as a substrate for microbial fermentation, the end products being hydrogen, carbon dioxide, methane, and SCFA. The designation RS1 is given to starch present in intact cell walls, and it retains its structure and resistance even during processing and preparation of many foods. RS2 are high-amylose starches that are found in corn, peas, and cassava and are nongranular starch-derived materials that resist digestion. Amylose in rice starch granules is resistant to digestion by enzymes [42]. RS3 types are found in cooked and cooled potatoes, processed cornflakes, different kinds of bread, especially after longer storage, and food products produced under specific process conditions with prolonged and/or repeated moist heat treatment. RS4 describes a group of starches that have been chemically modified, for example, by being etherized, esterified, or cross-linked with chemicals in such a manner as to decrease their digestibility. Between 30% and 70% of RS can be absorbed in the large intestine and deliver high prebiotic efficiency similar to that of nonstarch PSs. With the available information on RS, it is very difficult to suggest an amount of RS consumption for general health benefit, although some figures have been proposed for specific health benefits. In 1990 the first commercially available product of RS was prepared as high-quality rich powders by a number of companies using an amylose-rich starch from maize hybrids and cannot be replaced by traditional insoluble fibers [43] RS intake has unique functions on microbiomes, which are associated with the increase of butyrate in the large intestine, a metabolite that contributes to host health by facilitating maintenance of epithelial integrity, regulating inflammation, and influencing gene expression in colonocytes [44]. The intake of RS2 had positive effects on inflammation, glycemic status, endotoxemia, and markers of oxidative stress in patients with type 2 diabetes mellitus [45]. RS preparations reduce the availability of some saccharides in food without affecting the organoleptic properties of the food products. More research will be needed before recommendations on minimum RS consumption can be made for general health benefit.

Pectin

Pectin is found in the primary cell wall of many fruits, particularly citrus and apple fruits. Pectin is a PS consisting of D-galacturonic residues (main chain) with different kinds of sugar such as L-rhamnose, L-arabinose, D-galactose and marginally D-xylose in the side chains of the molecules. It is partly esterified with methanol and possesses nonbranched and highly branched regions. Pectin forms network structures such as gels, where the chains are interconnected to form a three-dimensional network. This network can be solved at higher temperature; however, the gel re-forms after cooling [46]. It is a soluble fiber and effective as prebiotic carbohydrate. Recent studies suggest that it speeds up recovery from infection as a result of its ability to promote antiinflammatory effects.

Gum arabic

The daily administration of 10 g of gum arabic (GA) (EmulGold) in 250 mL of water to healthy adults (31years old) for four weeks was associated with increases in the numbers of *Bifidobacteria*, *Lactobacilli*, and *Bacteroides* that were higher than those obtained for INU. On the basis of these findings, the authors concluded that GA establishes prebiotic efficacy that is at least as good as that of INU, and 10 g is the optimal daily dose [47]. The daily intake of 30 g of powdered GA (Dar Savanna Ltd, Khartoum, Sudan) in 250 mL of water by patients with type 2 diabetes for three months significantly reduced body weight, BMI, and systolic blood pressure, with a significant increase in the plasma high-density lipid cholesterol, indicating the good prebiotic activity of GA [48].

Human milk oligosaccharides as prebiotics

Human milk contains the largest quantities of diverse oligosaccharides, which vary greatly in content and composition for each breast-fed infant and depend on the mother's secretory status. Human milk contains, apart from lactose (70 g/L) and GOS (5 g/L), other complex carbohydrates called human milk oligosaccharides (HMO) (10 g/L). These are important dietary factors with multiple functions during the child's breastfeeding period. HMO composition is very complex; it may consist of more than 200 types of combinations of five monosaccharides: glucose, galactose, fucose,

N-acetylglucosamine, and N-acetylneuraminic acid [49]. Neutral HMO are composed of glucose and galactose but also contain multiple units of N-acetylglucosamine and fucose. Acid HMO contains, besides the above-mentioned carbohydrates, units of N-acetylneuraminic acid (also known as sialic acid). The presence of sialic acid and fucose in terminal positions renders these PSs nondigestible by human digestive enzymes. This facilitates their arrival to colon as unmodified carbohydrates, where they promote growth of diverse beneficial bacterial groups. Large numbers of *Bifidobacterium* are present in breast-fed infants' feces, as they get regular amounts of these prebiotics from their mother's milk. The biological functions of HMO had gained interest because they possess antiadhesive properties through competitive inhibition of pathogens and regulate the immune system [50], contributing to the overall health of the infant's intestine and gut microbiota. When breast milk is ingested by the infant, lactose is digested along with other milk components, while HMO pass through the gastrointestinal tract intact until they reach the colon, where the colonic microbiota ferment the HMO for use as an energy source. The low-molecular-weight HMO, such as 2-fucosyllactose 2-lacto-N-neotetraose and 3-fucosyllactose, have been shown to be absorbed in the bloodstream. Besides their positive effects on the intestinal microbiota, the activities of HMO is evident in cognitive development and allergy alleviation [49]. HMO selectively promote the growth and persistence of certain bifidobacterial strains in the gut by increasing their binding to intestinal cells as well as improving the integrity of intestinal barrier function via regulation of tight junction proteins [51,52]. A growing demand for baby food made especially for infants with nonlactating mothers and the expected rise in the world population by over a billion in the next ten years will drive more demand for baby food. The HMO is also useful for adults, as they help to maintain the health of the digestive system by deriving different microbial challenges in the gut, prevention of diarrhea, and protection from infectious diseases [53]. HMO acts as a microbiota modulator of *A. muciniphila*, *Faecalibacterium prausnitzii*, and *Lactobacilli* and maintains the health of the immune system. HMOs remove the pathogens or toxins from the gut by binding to them and thus protect against enteric infections in infants as well as adults . This dietary manipulation by the use of HMOs finds application in gut disorders among human adults and might also have beneficial effects in reducing food allergies [54]

Enzyme formulations projected toward human milk oligosaccharides manufacturing

Oligosaccharides that mimic HMO have great appeal for potential applications. Today, HMO molecules can be synthesized chemically via fermentation and by enzymatic synthesis for the production of β-l-glucose-1-phosphate, α-d-galactose-1-phosphate, and β-l-xylose-1-phosphate. Several monosaccharides are added to a lactose core by the action of specific glycosyltransferases [55].

Synthetic lactulose

The synthesis of lactulose-derived GOS has attracted the attention of the scientific community because of the prospective prebiotic applications. 4-O-β-D-galactopyranosyl-D-fructofuranose is a synthetic prebiotic disaccharide composed of galactose and fructose linked by a β-(1,4)-glycosidic bond, which can be industrially obtained by chemical isomerization of lactose present in whey permeate. This enzyme-catalyzed synthesis offers new potential for food technology, since it can be carried out with crude lactose materials derived from the dairy industry. Lactulose promotes the growth of *Bifidobacteria* and *Lactobacillus* in rat feeding. It maintains blood glucose and insulin levels and reduces the intestinal absorption of toxic ammonium from lumen, thus preventing hepatic encephalopathy in liver failure.

Isomaltooligosaccharides

Isomaltooligosaccharides (IMO) are a mixture of short-chain carbohydrates obtained enzymatically from starch. They contain α-(1,6)- and α-(1,4) linkages. While human intestinal enzymes can digest α-(1,4)-glycosidic bonds, α-(1,6) linkages are not easily hydrolyzed; therefore they can reach the colon, where they are partially fermented by the microbiota. Different studies have shown that IMO show bifidogenic properties. IMO can also diminish total cholesterol and triacylglycerides levels in patients treated with hemodialysis and can stimulate intestinal and systemic immunity via a shift in the Th1/Th2 balance toward Th1-dominant immunity. In mice, such effects may be due at least in part to the relative increase in *Lactobacillus* numbers in the gut microbiota [56].

Glucooligosaccharides

Are glucose oligomers with α-(1,6) linkages that can also branch via α-(1,2) and α-(1,3). These glycosidic linkages are resistant to hydrolysis by mammals' digestive enzymes. They can be produced from sucrose in the presence of maltose

by enzymatic synthesis or biosynthesized by *Leuconostoc mesenteroides*. In vitro fermentation studies have shown that they favor *Bifidobacterium* growth against harmful bacteria [57].

Galactooligosaccharides

GOS are naturally occurring compounds present in mammals' milk. These prebiotics can be produced industrially from whey lactose by transgalactosylation of lactose, carried out by beta-galactosidases. This fact results in complex mixtures of oligosaccharides with different degrees of polymerization, ranging from two to eight moieties, and different glycosidic linkages: β-(1,1), β-(1,2), β-(1,3), β-(1,4), and β-(1,6) are manufactured from lactose by beta-galactosidases [57] or by direct fermentation of galactose with the bacteria strain *B. bifidum* NCIMB 41171 for the biosynthesis of a novel GOS product, which proved to be bifidogenic in clinical trials [58,59]. A clinical trial compared breast-fed infants (reference group) with infants who were fed formula (control) or the same formula with two HMOs (2'-fucosyllactose and lacto-N-neotetraose) from birth (0−14 days) for a duration of six months. The results demonstrated that at three months, the fecal microbiota types in the group fed the formula with fucosyllactose were closer to that of breast-fed infants than to that of controls, proving that HMOs provide health benefits to infants partly by shaping the development of the intestinal microbiota during early life [60]. The results showed also that infants who were fed formula with fucosyllactose were associated with lower rates of infection-related medication. In a pioneered human study to demonstrate the bifidogenic effects of HMO, eight healthy volunteers ate a controlled diet supplemented with 15 g/day of oligofructose or INU, both of which resulted in almost a tenfold increase in luminal bifidobacteria. The levels then returned to baseline following withdrawal of the prebiotic supplement. Since then, both prebiotics and GOS have been used in many healthy human trials, with a general significant increase in colon bifidobacteria.

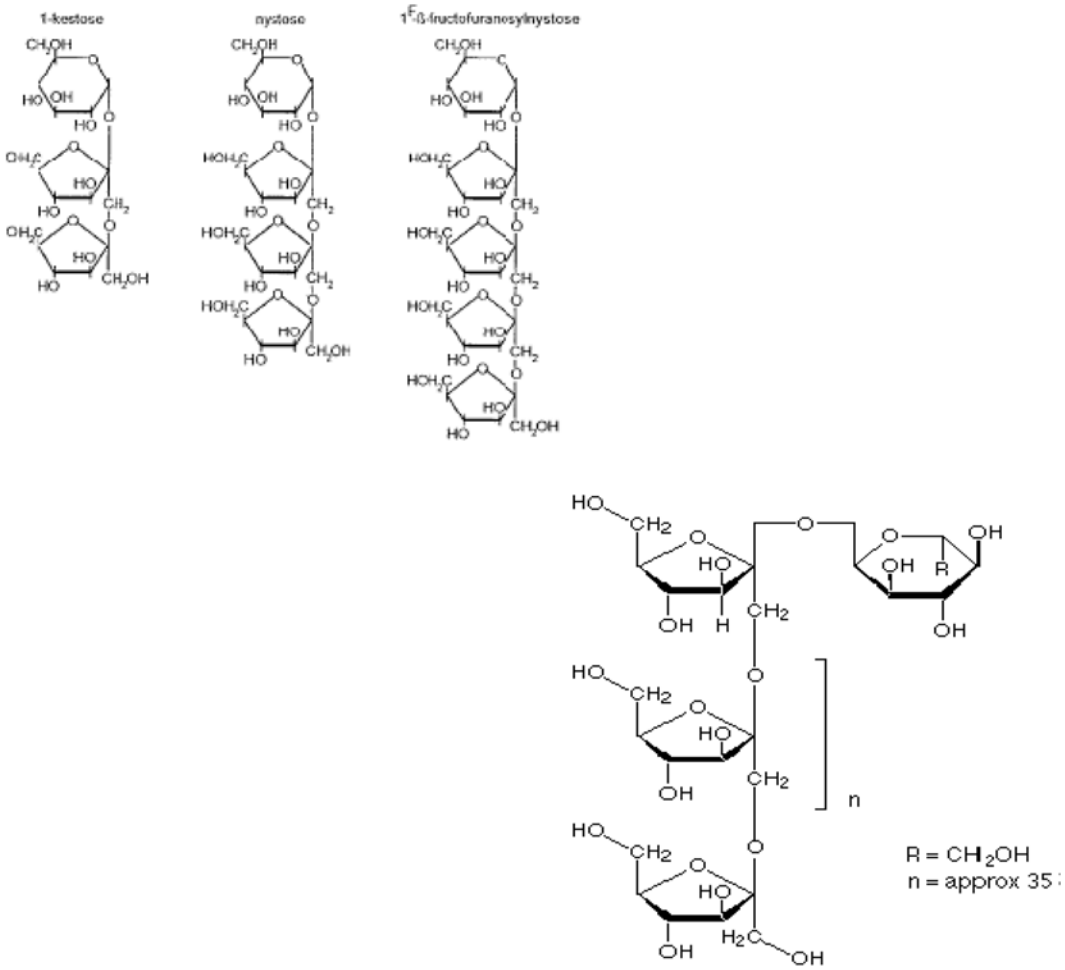


FIGURE 30.5 Chemical structure of kestose (β-D-Fru-(2−1)2-α-D-glucopyranoside, GF2), nystose (β-D-Fru-(2−1)3-α-D-glucopyranoside), and fructofuranosylnystose (β-D-Fru-(2−1)4-α-D-glucopyranoside) (*upper panel*) and inulin (*lower panel*).

Mushroom polysaccharides

Mushrooms have been used for thousands of years, including by the ancient Egyptians and Chinese, as a source of food, and today there are almost 150,000 species all over the world, of which only 5%−10% have been identified. Mushrooms constitute a huge source with extensive medicinal properties and health benefits. Mushrooms carbohydrates, mainly PS, constitute about one-half of mushroom dry matter. These PS are structural components of cell walls and are of two major types: rigid fibrillars of chitin to protect against the external environment and, at the same time, provide flexibility, which enables cell growth, and the more abundant glucans, which shape the fungal cells and form a protective barrier against environmental stress [61]. Beta-glucans include variable proportions of β-1,3 and β-1,6 linkages as well as α-1,3-glucans connected by covalent bonds with chitin chains [62]. This network is under the glycoprotein layer. Key function of alpha-glucans protect beta-glucans and chitin against degrading enzymes (Fig. 30.6).

Prebiotic properties of mushroom polysaccharides

There are about 380 or more species of mushrooms that are potential source of prebiotics, as they contain different PSs, such as chitin, hemicellulose, mannans, alpha-glucans, beta-glucans, galactans, and xylans [63]. Mushroom PS are resistant to gastric juices (more than 90% undigested), and the PS isolated from 53 species of Polish mushrooms were good substrate for growth of the probiotic strains *L. acidophilus* and two strains of *Lactobacillus rhamnosus* more strongly than the popular INU [64]. Similarly, the alkali extracts of *Pleurotus eryngii* mushrooms, containing (1→3)-β-D-glucans, showed the best prebiotic properties in stimulating the growth of nine probiotic strains of *Lactobacillus*, *Bifidobacterium*, and *Enterococcus*. These PS inhibit endogenous pathogen proliferation within the colon by enhancing the growth of probiotic bacteria [65]. *Ganoderma lucidum* is also listed as one of the most important mushrooms in its prebiotic activities, owing to its richness in the specific type β-D-glucan PS, terpenoids, and total phenols. Its potential prebiotic effect was evaluated in batch culture fermentation based on increments in the growth of bacteria used [0.4−1.5 $\log^{10}$ colony-forming units (CFU)/mL] after 18 hours of fermentation. The daily administration of 0.1−0.4 g Chaga mushroom per kilogram of rat body weight increased the Bacteroidetes at the phylum level and induced changes toward a healthy bacterial profile. *Coriolus versicolor* is rich in polysaccharopeptides with β-1,3-glucan and β-1,6 branches. In a clinical trial on healthy volunteers, a daily intake of 1200 mg of the dry extract of *C. versicolor* for 14 days was associated with fecal modification of *Bifidobacterium* spp. and *Lactobacillus* spp. and regulated the microbiome composition. In mice that were fed a high-fat diet, *G. lucidum* (GL) reversed and prevented gut dysbiosis, as indicated by modulating the composition of gut microbiota, reducing the Firmicutes/Bacteroidetes ratios and endotoxin-bearing Proteobacteria levels and altered the intestinal barrier. GL reduced obesity in mice and controlled obesity-related metabolic disorders, such inflammation and insulin resistance. The antiobesogenic properties of GL that were reported in experimental mice were mediated by shifts in the gut microbial composition and suggest that GL is a potential prebiotic agent to prevent gut dysbiosis and obesity-related metabolic disorders in obese individuals. The mechanism by which mushrooms regulate the gut microbiota and the exact role of the active constituents of some mushrooms have not been studied sufficiently, and future research needs to be study the role of mushrooms in gut microbiota regulation.

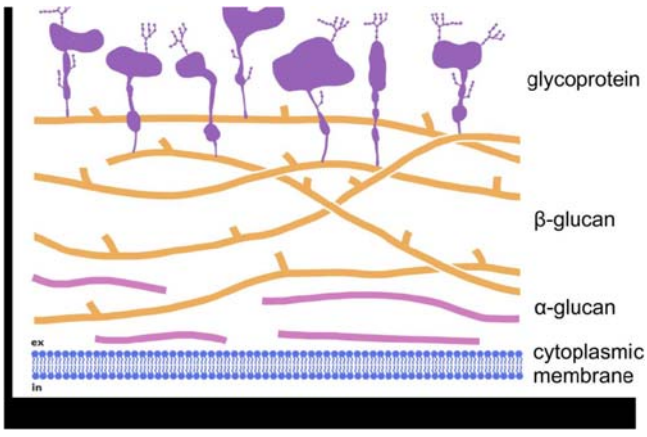


FIGURE 30.6 Structure of fungal cell wall structure and biosynthesis of fungal beta-glucans. *Source: Grün C.H., Structure and Biosynthesis of Fungal -Glucans. Ph.D. Thesis, Univ Utrecht, Utrecht, The Netherlands, 2003. The source of figure 30.6 is Grun CH (2003).*

Mushrooms polysaccharides and immunological activities

The medicinal properties of mushroom glucans along with other PS allow increased competency of the immune system. The most active mushroom PS include (1,4)-, (1,6)-, and (1,3)-β-D-glucans, which are known to induce activity and differentiation of immune cells, such as macrophages, leukocytes, or natural killer cells. These compounds contribute to both innate immunity (mainly macrophage-dependent immune system responses) and adaptive immunity (including B and T cell activity). Among them, monocyte activation is considered to be an initiating stage of immune responses after glucan impact. Chemical modification of α-D-glucans, such as sulfation, aminopropylation, hydroxyethylation, or methylation, is an important procedure, leading to an increase in the solubility of glucans in water and causing these agents to become much more biologically active than the native, underivatized components with simultaneous enhancement of their immunomodulatory activity [61]. Glucan-based preparations that stimulate the immune system are commercially available.

Antitumor properties

GL contains water-soluble PS with antitumor proapoptotic activities in colorectal cancer cells [66]. The biological activity of the Chaga mushroom (*Inonotus obliquus*) is mainly due to the presence of several PS, which constitute the sugars Man, Rha, Glu, Gal, Xyl, and Ara in a ratio of 9.8:13.6:29.1:20.5:21.6:5.4 as monosaccharides. Its ethanolic extract induced G1 cell cycle arrest in HT-29 human colon cancer cells; therefore it is a promising medicine to treat colon cancer. *C. versicolor* PSP showed in vitro and in vivo antitumor [67] and antimetastatic effects on mouse mammary 4T1 carcinoma [68] and the spleen lymphocytes of tumor-bearing mice. The mushroom maitake (*Grifola frondosa*) is unique in its richness in the proteoglucan PS, with immune-stimulatory capacity. This proteoglucan had the capacity to decrease cell viability, increase cell adhesion, and reduce the migration and invasion of mammary tumor cells in a murine model of breast cancer, leading to less aggressive cell behavior [69]. The proliferation of hepatocellular carcinoma was also inhibited by its water extract, which arrested the induction of the cell cycle and apoptosis in Hep3B hepatoma cells [70]. *Phellinus linteus* has been proved to have antitumor effects on skin, lung, and prostate cancer cells.

Marine seaweed polysaccharide biofunctionality for a healthy gut

Seaweeds contain 2.97%−71.4% complex PS [71], equivalent to 25%−70% by dry weight. These PSs are mostly undigested in the gastrointestinal tract and act as DF [72], dominated by 50%−80% soluble DF [73] (Fig. 30.7). Other complex PS include alginate, fucoidan, and laminarin in brown seaweeds; xylan and sulfated galactans such as agar, carrageenan, and porphyran in red seaweeds; and xylan in green seaweeds [71]. Soluble and insoluble DF are found in seaweeds [20]. Seaweed PS are found with a wide variety of chemical structures, but the following general characteristics have been identified [43]. They are rich in hydroxyl (-OH) groups, making them hydrophilic and often water soluble, and are known to establish intrachain hydrogen-bond networks, making them stiff and rigid and suitable as thickeners. The regularity of their structures also promotes interaction with external ions and interchain hydrogen bonding (e.g., gelation). The extracted PS from *Ulva* spp. (12% of the algal dry weight) have been reported to contain 16% sulfate and 15%−19% uronic acids, and each molecule of these heteropolysaccharides is made up of several different residues, the major sugars being glucuronic acid, rhamnose, arabinose, and galactose in a variety of combinations.

The extraction of seaweed PS is conventionally completed with water or diluted acid. The cell wall of macroalgae is complex, consisting of PS embedded with proteoglycans to form an extracellular matrix and bounded ions, such as calcium and potassium, making the extraction process hard and time-consuming. For FF development with high yield and favorable biological properties, carbohydrase cell wall−degrading enzymes, such as endo-β-glucanase cellulases, viscozymes, and Ultraflo, at optimal temperature and pH break down the heterogeneous algal cell wall or release of the PS in high yield with minimal damage [74−76] and desirable bioactivities [74]. The PS extracts are crude mixtures with monosaccharide composition, sulfate groups, and variable molecular weight followed by purification procedures such as chromatography and filtration techniques [77].

Laminarin

Laminarin constitutes up to 35% of the dry weight of the brown algae and is a storage PS. The purified preparation is a group of low-molecular-weight (about 5 kDa) water-soluble PS and is a member of the 1−3-β-D-glucan family, consisting of a linear structure of (1,3)-β-D-glucopyranose residues (about 20−25 glucose moieties) with a small degree of branching (Fig. 30.8) [79].

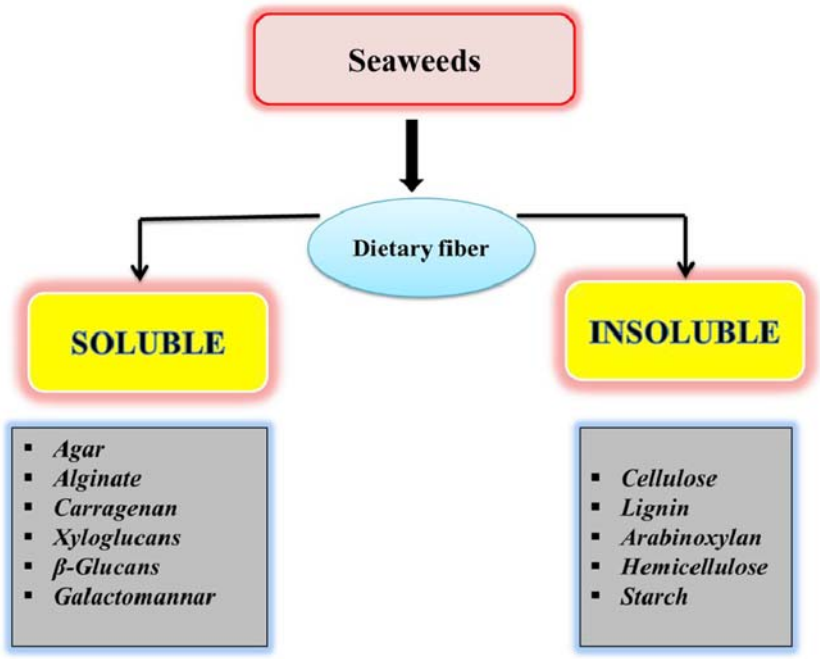


FIGURE 30.7 Classification of soluble and insoluble dietary fibers among seaweeds (Praveena et al., 2019).

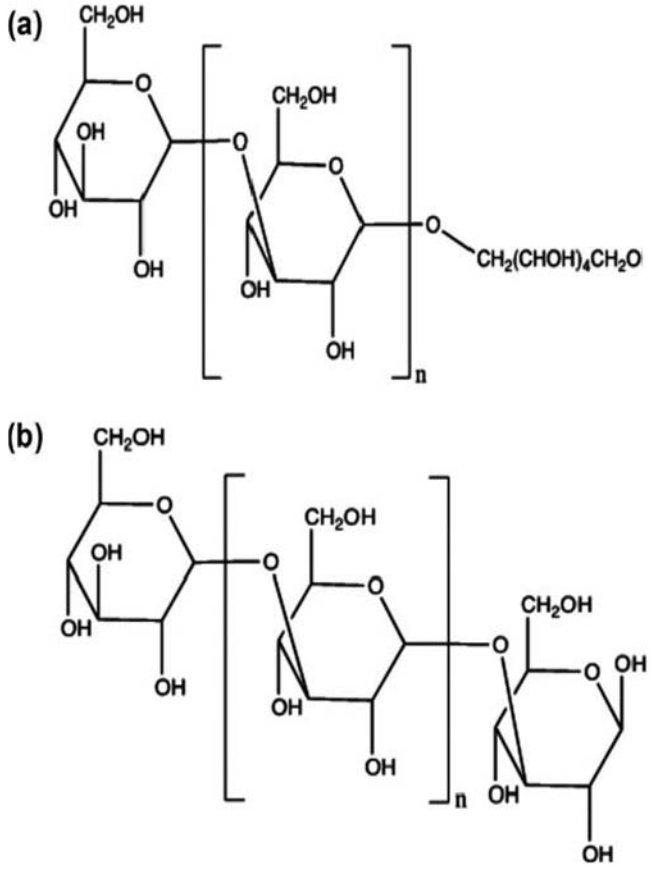


FIGURE 30.8 (A) Chain structure of laminarin. (B) G chain structure of laminarin [78].

The hydrogen bonds are resistant to hydrolysis in the small intestine and are considered to be DF. Laminarin had been identified as a modulator of intestinal metabolism through its effect on mucus composition, intestinal pH, and short-chain fatty acid production, especially butyrate [80].

Laminarin has antibacterial, immunomodulating, antioxidative, and anticoagulant properties [81].

Alginate

Alginate is a water-soluble fiber with prebiotic activities. It is purified by extraction from the dry macerated seaweed with sodium carbonate. The filtrate is treated with sodium and calcium chloride to form the Na/Ca salts of alginate, which are precipitated as fibrous precipitate. Alginic acid was obtained by treatment with hydrochloric acid. Purified preparations were dried and powdered. Alginic acid is a linear PS containing 1,4-linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues, arranged in a nonregular blockwise order along the chain. The residues typically occur as (-M-)n, (-G-)n, and (-MG-)n sequences or blocks. Mannuronic and guluronic acids are classed as uronic acids. The uronic acids are simple monosaccharides in which the primary hydroxyl group at C6 has been oxidized to the corresponding carboxylic acid. Galacturonic acid has the same configuration as galactose, and the structure of glucuronic acid corresponds to that of glucose [82].

Fucans/fucoidans

Brown algae contains 5%−20% fucoidan in the fibrillar cell walls and intercellular spaces, and they play a role in cell organization and may be involved in the cross-linkage of alginate and cellulose. Fucoidans are a complex series of sulfated PSs that are composed mainly of α-(1,2)- and/or (1,3)-linked fucose [83], 40% of which is sulfate esters [84] and with molecular weights that are typically of the order of 1,000,000 (Fig. 30.9).

Fucoidans display multiple physiological and biological activities, and their therapeutic potential increases with the degree of sulfation. These include antibacterial, anticancer, anticoagulant, antiinflammatory, antithrombotic, antioxidative, antitumor, antiviral, and immunomodulatory activities. The binding of fucoidans to the membrane toll-like receptors -2 and -4, but not with TLR-5 in human dendritic cells and macrophages led to the activation of the Nuclear Factor Kappa B (NF-κB) and the stimulation of the immune defences for the release of the pro-inflammatory factors, cytokines and chemokines. Fucoidans induce the up-regulation of CD40, expression and production of interleukin-6(IL-6), IL-12 and tumor necrosis factor-α(TNF-α) in spleen. Development of fucoidan as a new generation of polysaccharide immune

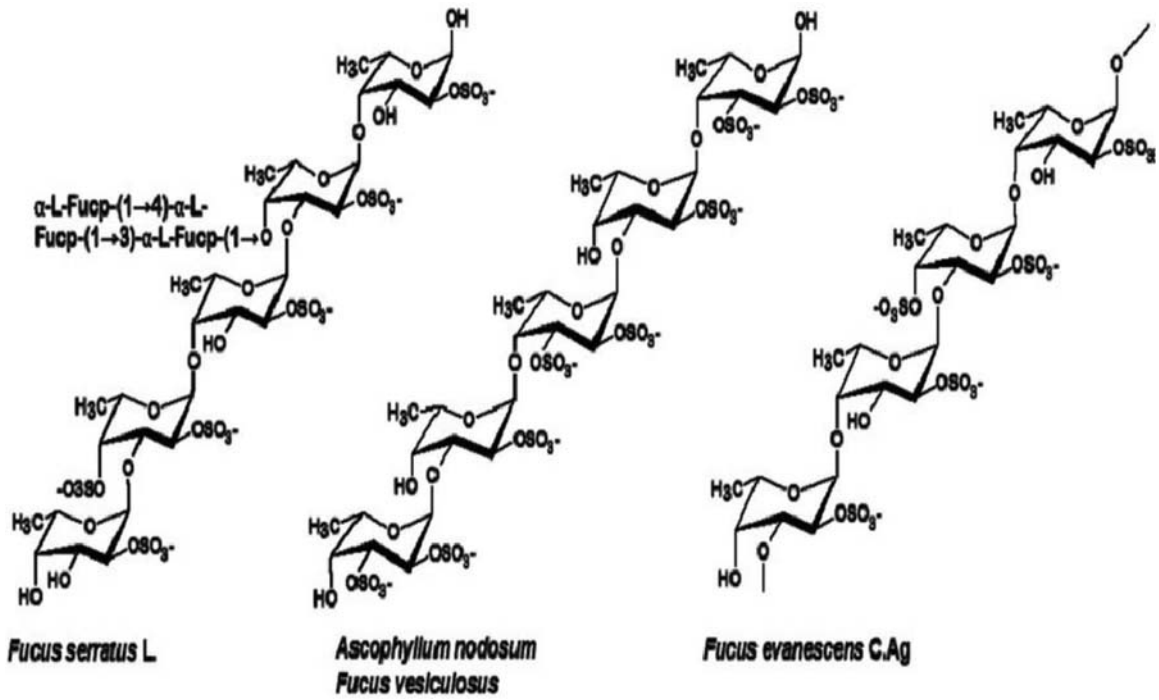


FIGURE 30.9 Fucoidan structure from three different sources. *From Ale MT, Mikkelsen JD, Anne S. Meyer AS (2011). Important determinants for fucoidan bioactivity: A critical review of structure-function relations and extraction methods for fucose-containing sulfated polysaccharides from brown seaweeds. Mar. Drugs 9:2106-2130 in the credit line of Figs. 30.9 and 30.10.*

modulator [83,85]. Fucoidans specifically contribute resistance to disorders associated with Alzheimer's disease, the cardiovascular system, the cerebral system, ischemia, the kidney, the liver, and the urinary system [83,85]. The immune-enhancing activities of brown seaweed fucoidan is via macrophage activation mediated by three membrane receptors: Toll-like receptor 4, with cluster of differentiation CD14 as a coreceptor, competent receptor 3, and scavenging receptor [83,85]. The immune-enhancing activities lead to the production of cytokines, which control and regulate activation of natural killer cells and T lymphocytes (Fig. 30.10). Fucoidans protect gastric mucosa against the proteolytic activity of gastric juice. Furthermore, studies have demonstrated that fucoidan may prevent *Helicobacter pylori* infection in the stomach, thereby reducing the risk of associated gastric cancers. Biomarkers of food intake specific to seaweed intake were included: hydroxytrifuhalol A, 7-hydroxyeckol, C-O-C dimer of phloroglucinol, diphloroethol, fucophloroethol, dioxinodehydroeckol, and/or their glucuronides or sulfate esters, all of which belong to the phlorotannins. These biomarkers could serve as objective measurements in observational studies and dietary intervention studies linking the intake of seaweeds with their health effects [86].

The beneficial effect of prebiotics on health

Prebiotic impact on the gut microbiota

Physical, biochemical, and immunological barriers comprise the gut barrier function, which is required to block the entry of exterior antigens and toxins [87]. Current understanding of development of chronic inflammation-related diseases is mainly due to gut microbiota dysbiosis, which is characterized to have altered composition, reduced diversity and stability, and increased levels of lipopolysaccharide. Dietary supplementation with prebiotic fibers (as FOS and INU) and dietary animal reduction are capable of modulating composition and metabolic function of gut microbiota, promoting the growth of specific groups of bacteria, including *Bifidobacteria* and *Bacteroides*, reducing simultaneously the relative amount of Firmicutes, thereby preventing diverse infectious, inflammatory, and neoplastic intestinal diseases [11]. Numerous studies have reported an association between consumption of nondigestible fiber ingredients (e.g., prebiotics) and increased levels of reputedly beneficial bacteria in the gut, such as Ruminococcaceae, *Bifidobacterium*, *Lactobacillus*, *Faecalibacterium*, and *Roseburia* [88]. A major prerequisite to the success of a particular prebiotic is that the target bacteria must be present at a specific threshold. If levels are below that threshold, owing to factors such as aging or antibiotic use, the prebiotic may not be effective in increasing the numbers of desirable bacteria to the necessary level to confer the anticipated health benefits [44]. A metaanalysis based on 64 studies with a total of 2099 participants revealed a significant increase in the abundance of bacteria from the genera *Bifidobacterium* and *Lactobacillus* as well as higher levels of fecal butyrate concentration following DF intervention, particularly involving fructans and GOS, compared with placebo low-fiber comparators [89]. Similarly, the consumption of RS has been shown to enrich *Ruminococcus bromii* and *Eubacterium rectale*. Prebiotic-based nutritional approaches seem very attractive in targeting extremely oxygen-sensitive commensals *F. prausnitzii* (an NGP), which is an abundant antiinflammatory gut species

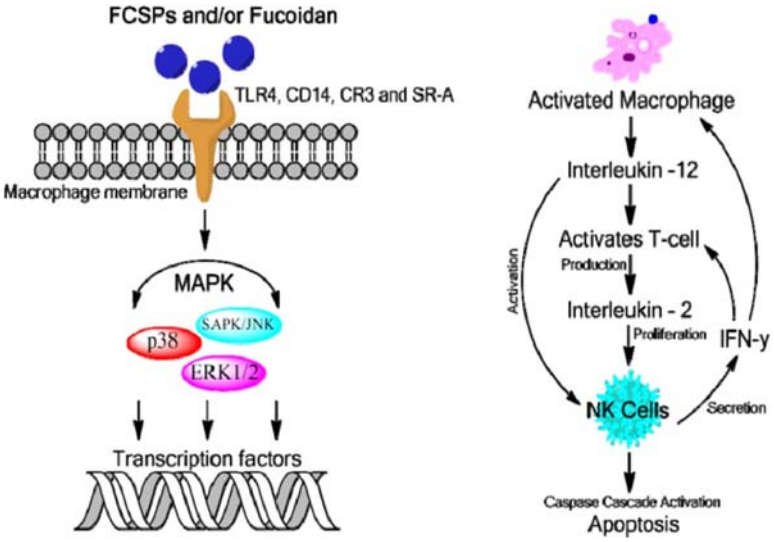


FIGURE 30.10 Fucoidan interaction with macrophage. *From Ale et al. (2011).*

and is depleted in individuals with inflammatory bowel disease (IBD). The true challenge today is, to relate a prebiotic to specific ecosystem shifts and/or metabolite production and finally to the health benefits for the host.

Prebiotics and obesity

The increased availability of food in Western countries and increases in the proportion of dietary fat share markedly led to variations of microbiome composition in association with obesity pathogenesis [90]. Obese women consuming daily 16 g of INU/oligofructose mix [50:50] showed at the end of the three months of prebiotic supplementation increases in the gut microbiota *Bifidobacterium* and *F. prausnitzii*, with reduction in the serum metabolic endotoxic lipopolysaccharide levels. The prebiotic supplementation decreased the counts of the fecal *Bacteroides intestinalis*, *B. vulgatus*, and *Propionibacterium*, associated with a slight decrease in fat mass and with phosphatidylcholine levels. On the basis of the study, the authors concluded that prebiotic supplementation affects several key metabolites that are implicated in obesity and/or diabetes. [91]

Prebiotics as dietary modulators in diabetes and cardiovascular diseases

Prediabetes is linked with increased concentration of the blood inflammatory toxic lipopolysaccharides [92]. Prediabetes is linked with gut microbiota alterations of the natural microbiota and dysbiosis that is involved in the development of type 2 diabetes and cardiovascular diseases. Prebiotics such as INU are involved in the selective functioning of natural microbiota and decrease the concentration of endotoxin, reduce permeability of the intestines, and limit metabolic dysfunction in rodents. The impact of prebiotics on the cardiovascular functions of patients who are at risk of type 2 diabetes is still unknown. Prebiotic supplementation along with INU could be used as a preventive strategy for limiting the risk of cardiovascular diseases in patients who are at risk of type 2 diabetes.

Prebiotics modulation of immune function

The role of the defensive machinery of the immune system in disease prevention and health promotion is of great significance. Immune-related diseases include rheumatological disease, allergy, asthma, ulcerative colitis, and IBD. Conventional treatments for immune-related diseases face the challenges of impaired immune responsiveness, hypersensitivity, immunogenicity, and drug resistance. Owing to their potential to strengthen the immune system and prevent degenerative diseases [93,94], there is increasing focus on nutritional strategies to counter the rising global burden of allergic disease [95]. There has been a particular focus on nondigestible oligosaccharides, which undergo microbial fermentation by commensal gut bacteria to produce SCFA. The health benefits of SCFA in early life immune development protects against the risk of early childhood allergic diseases [96]. The biological effects of HMO is the typical ideal prebiotic with influence on infant immune development. The effects of prebiotics in enhancing the immunity of the host was reviewed recently, and there is sufficient proof indicating that prebiotics such as INU help in the modulation of immunological parameters in gut-associated lymphoid tissues, secondary lymphoid tissues, and peripheral circulation. The intake of prebiotics consisting of XOS, FOS, resistant dextrin, and polydextrose had a positive impact on the structure of gut microbiota in perioperative colorectal cancer patients.

Prebiotics in controlling cancer

Aberrant crypt foci (**ACF**) are the first detectable abnormal growth of cells, appearing as lesions in the colonic mucosa [97]. The development of the ACF into polyp, adenoma, and adenocarcinoma occur as the result of the buildup of numerous genetic and biochemical modifications. Some fibers that stimulate the formation of a stable butyrate-producing colonic ecosystem diminished the rate of ACF, and it became clear that the colonic ecosystem that produces stable butyrate decreases the risks of developing colon cancer [99]. A double-blind, randomized clinical trial was conducted on 140 perioperative colorectal cancer patients between the ages of 40 and 75 years. The patients were divided randomly into two groups an intervention group that received 30 g/day of prebiotic supplementation for seven days and a control group that did not receive supplementation. The immunological and nutritional indices of both groups were evaluated before and after the operation and were compared with their baseline levels. Also the fecal samples of 40 patients chosen at random from the both groups were taken to examine the gut microbiota. There was a significant reduction in the abundance of intestinal microbiota from pre to post operation in the control group. Intake of prebiotics is recommended to improve immunological indices in patients having colorectal cancer for seven days before surgery. Prebiotics enhanced the concentration of four commensal microorganism-containing opportunistic pathogens in patients having colorectal cancer. Surgical stress decreased the population of intestinal microbiota. A study was conducted to

check the impact of prebiotics intake consisting of XOS, FOS, resistant dextrin, and polydextroseon immunity and the structure of gut microbiota in perioperative colorectal cancer patients [98].

Prebiotics and anxiety

Administration of prebiotics resulted in increased levels of acetate and propionate and reduction in the concentration of isobutyrate, which have significant correlation with the positive effects on behavior [100]. Long-term treatment of the prebiotic combination of FOS and GOS has antidepressant effects and is involved in reducing the level of corticosterone in the body, mainly by limiting its release [101]. Prebiotics are involved in modifying the expression of specific genes related to the concentration of SCFA in the hypothalamus and hippocampus. An animal diet supplemented with FOS and GOS reduced the level of proinflammatory cytokines resulting from the chronic stress, normalized the anxiety and depression-like behavior, and mitigated the impact of stress on the microbiota [102].

Probiotics

Traditional probiotics

The perception of traditional probiotics was originally derived from the wisdom of the ancestors that regular consumption of lactic acid bacteria−fermented dairy products was associated with enhanced health and longevity in the elders of the Bulgarian people. Since then, the term *probiotics* has been linked to beneficial bacteria for health promotion, although its precise definition has evolved over time [103].

The characteristics of traditional probiotics are as follows:

1. They are generally regarded as safe at the strain level (U.S. Food and Drug Administration) or as qualified presumption of safety at the species level (European Food Safety Authority).
2. They target subhealthy people in the general population.
3. They are isolated from gut, breast milk, and fermented foods.
4. They have a long history of use.
5. They belong to limited genera. mainly *Lactobacillus* spp. (Firmicutes), *Bifidobacterium* spp. (Actinobacteria), *Streptococcus* spp. (Firmicutes), *Bacillus* spp. (Firmicutes), and *Saccharomyces cerevisiae* (yeast). Specific bacterial strains from the genera *Bifidobacterium* and *Lactobacillus* have the potential to strengthen the immune system and prevent degenerative diseases.

Probiotic bacteria act on the intestinal tract at three levels: (1) in the gastrointestinal tract, including the interaction of the probiotics with the pathogen and resulting in phagocytosis or endocytosis; (2) improving the barrier function of the mucosal layer [104], and (3) enhancing the systemic immune system [105], which includes the Toll-like receptors mediating the interaction of probiotics and pathogen with host cells. There is currently no doubt about the fact that the system of intestinal microorganisms and its desirable modification with probiotic formulas and products may protect people against enteral problems and influence the overall improvement of health. Probiotics may be helpful in the treatment of inflammatory enteral conditions, including ulcerative colitis, Crohn's disease (CD), and nonspecific ileitis. The current understanding of the development of chronic inflammation-related diseases is mainly due to gut microbiota dysbiosis, which is associated with altered composition, reduced diversity and stability, increased levels of lipopolysaccharides, and chronic and recurrent infections or inflammations of the intestine. Clinical studies have demonstrated that probiotics lead to the remission of ulcerative colitis and are helpful in cases of lactose intolerance [106], irritable bowel syndrome, and peptic ulcer [107], and the prevention of colorectal cancer [108]. In addition, probiotics have demonstrated efficacy in reducing blood urea levels in chronic renal failure [109], treating and preventing atopic dermatitis [110], reducing transaminases and measures of fibrosis in nonalcoholic steatohepatitis [111], improving depression, and preventing antibiotic-associated diarrhea [112]. In recent years the action of probiotics has been dramatically broadened to include virtually every organ system in the body [113]. Unfortunately, most of the currently available commercial probiotics do not include dominant commensal human isolates; this is a reason why these probiotic strains do not colonize the human gut. Negative evidence regarding administration of traditional probiotics was reported by few investigators [114]. *Lactobacillus reuteri* DSM 17938 is considered in the management of infantile colic [115], but this bacterial strain has a lack of efficacy in treatment of acute gastroenteritis [116]. Children with diarrhea who were given combined *L. rhamnosus* and *L. helveticus* probiotics twice daily developed moderate to severe gastroenteritis within 14 days after enrollment [117]. Preschool children with acute gastroenteritis who received a five-day course of *L. rhamnosus* GG also did not have better outcomes than those who received placebo. So far, clinical use of traditional probiotics for prophylaxis vary, owing to inconsistent efficacy, the general effects being either minor, statistically marginal, or even

not significant. This is due to the situation that current research results obtained reflected an incomplete understanding of the relationship between development of the intestinal microbiome, the microbiome dysbiosis, diseases development, and use of traditional probiotics. A recent study indicated that traditional probiotics might not be able to colonize some individuals' gut, and this personalized colonization resistance to traditional probiotics was demonstrated to be associated with unique host and microbiome features [118]. Moreover, a markedly delayed postantibiotic reconstitution of the human microbiome induced by traditional probiotics was reported [119]. These reported findings underscore the need for rational selection of disease-specific probiotics and NGPs to prevent diseases

Next-generation probiotics (NGP)

The advent of various genomic tools accompanied by improvements in culture-based approaches (culture-omics) led to growing knowledge of the importance of the human microbiota suggests that commensal species can be isolated and used for therapeutic purposes as so-called NGPs. NGPs are potential novel health-promoting commensal strains that have not yet been used for nutritional and therapeutic purposes and could possibly be exploited in dietary and pharmaceutical applications. Emerging evidence shows that a large number of commensal species across all major intestinal phyla have the ability to strengthen the epithelial barrier and alleviate inflammation [120]. The research in many of these areas is in its infancy, and there is a requirement to better understand the underlying mechanisms of action in conjunction with high-quality phase III studies if probiotics are to be integrated into widespread mainstream clinical practice.

Characteristics of NGPs are as follows [121]:

1. They are mostly derived from commensals.
2. They are identified from comparison results between healthy and disease animals/people.
3. Next-generation sequencing technique is used for the identification of the microbiota.
4. They belong to diverse genera.
5. Strict safety and regulations required.
6. They Including genetically modified bacteria.
7. Multifaced information (mechanisms) is required.
8. The functions of individual strains may vary.
9. They range from food additives to live biotherapeutic products (drugs).

A more universally validated and accepted favorable bacterial consortium or personalized and precise probiotic is necessary to complement patients' dysbiotic microbiota composition [114]. In contrast to the traditional probiotics that target the general target population, which focus on gut health, development of NGPs for other disease areas is growing strongly and is closely associated with targeting specific diseases. At the same time, as more and more scientific evidence is being gathering, there will be a big growth in probiotics positioned for different life stages [122]. It is worth emphasizing that the ameliorative effects of NGPs depend on specific bacterial strains and on the dosage used [123]. One cannot judge the functions of NGPs only by the nomenclature of bacterial species identified. Adherence to the intestinal epithelium and immunomodulation have been considered as desired probiotic properties [124], and screening for such properties may prove useful for the strain selection of NGPs. With the introduction of NGPs, we are entering a new era of probiotic research, and in the future, we are likely to see probiotics that have been developed to target specific health issues and needs.

Akkermansia muciniphila

A. muciniphila is a gram-negative non-spore-forming bacterium that belongs to the phylum Verrucomicrobia. It has been identified in early life and is one of the most abundant single species in the human intestinal microbiota of healthy subjects (0.5%−5% up to 8%) of the total bacteria [124]. It has been detected in mothers' milk [125,126]. Healthy human subjects who had high levels of *A. muciniphila*−like bacteria were sensitive to penicillin and tetracycline derivatives but resistant to vancomycin [127]. The genome sequence of *A. muciniphila* did not reveal antibiotic resistance genes that are linked to known genetically transferrable elements [128]. *A. muciniphila* colonizes the mucus lining; mucus is the abundant glycoprotein that is specifically produced and degraded in the colon, acting as a prebiotic, or microbial substrate for *A. muciniphila* [125]. *A. muciniphila* is highly abundant in lean and nondiabetic subjects, while its abundance was decreased in several pathological situations, such as high-fat diet [18,129], obesity, type 2 diabetes, cardiometabolic diseases, low-grade IBD, hypertension, and liver diseases [129,130]. *Akkermansia* colonization improved the state of obesity and its associated liver disorder changes in the host; the gut barrier is restored either

physically (at the mucous layer or the level of tight junctions) or at the level of the gut ecosystem, and reduced inflammatory responses are often induced by endotoxemia or LPS via TLRs and downstream cytokines, which improve intestinal permeability [131]. *A. muciniphila* improved metabolic health during a dietary intervention in obesity [132]. A large body of evidence suggested that *A. muciniphila* may contribute to protection from specific metabolic disorders and cardiometabolic risk factors associated with a low-grade inflammation. Antidiabetic treatments, such as metformin administration and bariatric surgery, were both found to be associated with a marked increase in the abundance of *A. muciniphila*. The daily administration of 2×10^8 *A. muciniphila* cells to mice protected them against diet-induced obesity and reduced the levels of visceral and subcutaneous fat mass by half, while markers of fatty acid oxidation in the adipose tissue increased, with no signature of insulin resistance and infiltration of inflammatory cells (CD11c) in the adipose tissue [133]. The administration of 10^9 and 10^{10} pasteurized live *A. muciniphila* bacteria cells per day for 0.5−3 months to individuals with metabolic syndrome was well tolerated and showed beneficial effects on clinical parameters related to liver function, muscles, and renal functions as well as markers of immunity and inflammation. These findings have subsequently been confirmed and extended to other specific disorders. *A. muciniphila* potentially activated and restored the expression of the specific antimicrobial nucleotide oligomerization domain−like receptors and Toll-like receptors, which specifically modulate intestinal homeostasis and host metabolism [134]. The live *A. muciniphila* restored the mucus layer thickness and the endogenous production of antimicrobial peptides and increased the endogenous production of specific lipids having antiinflammatory activity that belong to the endocannabinoid family, which involves the control of glucose and energy metabolism [135]. Preliminary study reported that *A. muciniphila* may also be used as part of anticancer immune-therapy, such as anti-PD-1 treatment [136]. Its use as prognostic tool for the success of diet interventions is proposed [130]. *A. muciniphila* was reported to have various advantages as compared to other beneficial microbes and specific probiotics, at least in the context of the metabolic syndrome, particularly after the success achieved for growing the bacterium in a synthetic medium with high yield. The positive effect of pasteurization (70°C for 30 minutes) on increasing the efficacy, stability, and potential shelf life of *A. muciniphila*; the identification of the Amuc_1100 outer membrane protein as the key mechanisms of interaction; and its safety in the human targeted population strongly position this bacterium as a novel future NGP candidate. Its use in a dietary supplement or nutraceutical preparations that target pathologies in which the intestinal barrier function is compromised. This unique character does not preclude the fact the human investigations and safety assessment must be done. The goal is the successful growth of *A. muciniphila* on a synthetic medium with high yield and devoid of compounds incompatible with administration in humans [137].

A. muciniphila is widely considered to be a novel future NGP candidate and novel food by the European Food Safety Authority in Europe. The use of live or pasteurized *A. muciniphila* in a dietary supplement may be subject to regulatory requirements relating to safety properties

Bifidobacterium Breve *M-16V [M-16V]*

Bifidobacterial species have been isolated from the gastrointestinal tract of humans and could be categorized as human-residential bifidobacteria (HRB); other species that are natural inhabitants of the outer environment are categorized as non-HRB [138]. Colonization by commensal bifidobacteria during early life is indispensable for the normal development and growth of the gastrointestinal tract, particularly for epithelial barrier function and mucosal immunity. Infant-type HRB include *B. longum* subsp. *infantis* (*B. infantis*), *B. longum* subsp. *longum* (*B. longum*), *B. bifidum*, and *B. breve*, and they are all capable of utilizing HMOs with different metabolic pathways and degrees of degradation, demonstrating that they are well adapted to the transmission routes and growth conditions in the infant gut with a large repertoire of genes for the utilization of HMO [138]. *B. breve* M-16V is a nonmotile, non-spore-forming, rod-shaped anaerobic gram-positive bacterium that is highly accessible to human gastrointestinal tract with strong adherence activity [138]. *B. breve* M-16V produces L-lactic acid and possess conjugated bile salt hydrolytic activity hydrolyzing the conjugated bile acids taurocholic and glycocholic acid to the primary bile acid (cholic acid). M-16V was first commercially available in Japan in 1976. It was added to several powdered formulas called *Yochien-Jidai* in Japan and has since been incorporated into several products, including term and preterm infant formula [139]. The lyophilized powder of M-16V has excellent stability during storage and high survivability in finished products, such as powdered formula, until consumption. M-16V is nonpathogenic, nontoxigenic, nonhemolytic, and non-antibiotic-resistant probiotic bacterium and has been included in the list of authorized probiotic strains for safe baby food. To date, M-16V is widely used in feeding low-birth-weight infants to reduce the risk of preterm birth complications in more than 120 neonatal intensive care units in many hospitals distributed around the world [140]. Premature infants are born with an immature gut and exhibit delayed gut colonization with beneficial commensal bacteria such as *Bifidobacterium*, where instead they

are more susceptible to colonization by Enterobacteriaceae and *Enterococcus*, and they are also at elevated risk to develop multiple health comorbidities, one of which is the devastating necrotizing enterocolitis. Moreover, the use of antibiotics in premature and low-birth-weight infants disturbs the colonization patterns of *Bifidobacterium* and shifts the gut microbial composition toward a high abundance of Proteobacteria, with a decrease in the overall diversity of the infant's gut microbiota [141]. This is a challenging way for preterm infants to begin life. Preventive intervention with HRB in the neonatal period, including M-16V probiotic, is an excellent and timely opportunity to promote bifidobacterial colonization, facilitate the development of the gut mucosal immune system, reduces the risk of infectious atopic disease, improve infant health in the first stage of life, and prevent stage II necrotizing enterocolitis or all-cause mortality in neonates younger than 34 weeks of age [140]. The supplementation of 159 preterm neonates (gestation $<$ 33 weeks) and low-birth-weight infants ($<$2250 g) with M-16V (3×10^9 CFU/day) for three weeks significantly increased the levels of fecal *B. breve* compared to placebo control; the *B. breve* counts were below detection level [142]. The M-16V supplement was well tolerated by all enrolled preterm neonates. The findings suggest that M-16V is a suitable probiotic strain for routine use in preterm neonates to promote the acquisition of beneficial commensal bacteria. The intragastric administration of M-16V(1.6×10^8 CFU in 0.5 mL of 5% glucose sterile distilled water twice daily) to preterm low-birth-weight infants, with mean gestation 32.8 weeks and birth weight 1486 g within 7.2 hours or 36.5 hours after birth until the infants were discharged from the hospital showed the best bifidobacterial colonization compared to the respective result with the controls, who received no supplementation. The authors stressed that the timing of administration of M-16V was highly important for better promoting the colonization of bifidobacteria and reducing the susceptibility to colonization by potentially harmful bacteria. Other clinical studies have also shown the potential capability of M-16V (at a dose of 5×10^8 CFU/day for eight weeks) in feeding very low-birth-weight premature infants ($<$1250 g) in colonizing of *Bifidobacteria* and may assist in the development of mucosal immunity and attenuate inflammatory reactions in preterm infants through upregulation of transforming growth factor beta 1 signaling. The prevalence of allergic diseases in infants has increased strikingly worldwide in the past few decades [143]. While the pathogenesis of allergic diseases is likely to be multifactorial, deviations in gut colonization during early life are possible major factors promoting abnormal postnatal immune maturation [144], as was demonstrated in Italian children with a mean age of 9 ± 2.2 years, who were treated with a probiotics mixture containing M-16V (1×10^9 CFU), *B. longum* BB536 (3×10^9 CFU), and *B. infantis* M-63 (1×10^9 CFU) for four weeks [145]. This probiotic treatment protected the children against pollen-induced IgE-mediated allergic rhinitis and intermittent asthma, while the placebo showed worsening in the respective parameters. This study implies that the effectiveness of a mixture of probiotic microorganisms is superior to that of a single organism. When pregnant women were given a probiotics powder formulation (two sachets daily, 1 g/sachet) containing M-16V and *B. longum* BB536 (5×10^9 CFU/g of each strain) one month before the expected date of delivery and postnatally to their infants (one sachet daily) for six months, their infants had a decreased risk of developing eczema and atopic dermatitis during the first 18 months of life as compared to the control group [146]. The relative abundance of Proteobacteria was also significantly lower in mothers who received the bifidobacteria mixture at the time of delivery than in those in the control group and was positively correlated with that of infants at four months of age. The supplementation with a bifidobacteria mixture of *B. breve* M-16V and *B. longum* BB536 during pregnancy modulated both the maternal and neonatal gut microbiota for prevention of allergies in infants later in life. The administration of *B. breve* M-16V (5×10^9 CFU/day for three months) to infants with cow's milk hypersensitivity with atopic dermatitis (aged 3.1−18.5 months) ameliorated the allergic symptoms and improved the gut microbiota composition [147].

Faecalibacterium prausnitzii

F. prausnitzii belongs to the *Clostridium* cluster IV, and several strains of *F. prausnitzii* were characterized that survive passage through the acidic, enzymatic, and bile environments of gastrointestinal tract [148]. *F. prausnitzii* is one of the most abundant species to be found in the large intestine of healthy adults and may comprise more than 5% (3%−5%) of the total fecal bacteria [149]. *F. prausnitzii* is considered the sensor and an actor of human intestinal health. Its depletion in the fecal and mucosa-associated microbiome has been reported in several intestinal disorders, most consistently in patients suffering from intestinal and metabolic disorders such as IBD, CD, irritable bowel syndrome, colorectal cancer, obesity, and celiac disease, as well as in frail elderly. Moreover, this species may be a biomarker of choice to assist in ulcerative colitis and CD discrimination [150]. These properties and protective effects of *F. prausnitzii* were identified in different animal models [149]. All *F. prausnitzii* strains and their supernatants secrete peptides of microbial anti-inflammatory molecules, which inhibit the nuclear factor kappa-B cells pathway in vitro and in vivo [149], confirming the antiinflammatory and therapeutic properties of *F. prausnitzii*. *F. praunitzii* upregulates the production of CD4

CFoxp3C regulatory T cells (Tregs). Additionally, it induces the *Clostridium*-specific interleukin 10-secreting regulatory T cell subset, present in human colonic cells, which lowers IL-12 and interferon gamma and maintains the gut barrier immune function. The levels of antiinflammatory cytokines and immunoglobulins, immune cell proliferation, and production of proinflammatory cytokines produced by the T cells may be modulated following probiotic supplementation. On the basis of their antiinflammatory properties, *F. prausnitzii* probiotics are considered an alternative strategy for treatment of chronic gut inflammation pathologies, such as CD. The development of specific formulation to keep this extreme oxygen-sensitive bacterium alive at ambient air has been described for patients with intestinal dysbiosis−associated illness [151]. So far, only two strains have been tested in vivo: *F. prausnitzii* A2−165 [152] and the biofilm-forming strain HTF-F [153]. The antiinflammatory properties of other *F. prausnitzii* isolates await further investigation, as the probiotic properties are usually strain-specific ones. Therefore it seems reasonable that if there is a causal link between disease status and the absence of this organism, then by simply feeding it to the individual, its health-promoting features should be restored; thus *F. prausnitzii*. may be considered a novel potential NGP candidate for its efficacy as a probiotic to reverse the symptoms of IBD when fed to humans.

Cocktails of Clostridium *clusters IV and XIVa*

Clusters IV and XIVa (also known as *Clostridium leptum* and the coccoides group, respectively), which are members of *Clostridium* spp. are exceptional inducers of regulatory T cells (Tregs) in the colon and can be considered as therapeutic options for IBD and allergies. Tregs can regulate immune homeostasis and serve as a therapeutic target for different gut inflammatory disorders. Induction of the colonic Tregs is dependent on special properties of the commensal bacteria. Seventeen strains belonging to *Clostridium* clusters XIVa, IV, and XVIII were isolated from a human fecal sample, which were effective in Treg cell differentiation and accumulation in the mouse colon [154]. The SCFAs produced by this community influenced the expression of Foxp3, a key gene controlling Treg cell development [154]. Incidentally, *Clostridium* clusters XIVa and IV are decreased in fecal samples from patients with IBD, and the cocktail of the 17 strains could potentially reverse this dysbiosis and enhance the homeostasis of the host-gut microbiota. The administration of *Eubacterium hallii* in obese and diabetic db/db mice increased energy metabolism and improved insulin sensitivity. However, increasing the dosage of *E. hallii* did not affect body weight or food intake, indicating that this strain can be a safe and effective alternative for insulin sensitivity [155].

Prebiotics and probiotics in the management of obesity

Obesity is a global pandemic that is complicated to treat, owing to its multifactorial pathogenesis [156]. The interaction of numerous factors are involved in the etiology of obesity, such as neuronal, hormones, genetic, epigenetic, and lifestyle factors [157]. Scientific evidence supports the idea that obesity and metabolic consequences are strongly related to changes in both the function and composition of the gut microbiota, and modifications of gut microbiota composition have been associate with variations in body weight and BMI [158−160]. New therapeutic strategies to treat and prevent obesity are based on gut microbiota as a modifiable trait for translational intervention to improve the metabolic profiles of obese patients by prebiotics or/and probiotics [161]. *Lactobacillus gasseri* BNR17, an isolate of human breast milk, is typical example with antiobesity activity in animal experiments. The intake of *L. gasseri* BNR17 reduced postprandial and fasting serum nonesterified fatty acid levels in Japanese hypertriacylglycerolemic adults [162]. Obese subjects were given daily capsules with a total of 60 billion CFU divided equally by the three main meals for 12 weeks in the subjects in the intervention group showed slight reductions in body weight and waist and hip circumferences in comparison to subjects in the placebo group, but there were no significant differences between the two groups [162]. A recent study using the same bacterium at a daily dose of ten billion cells per day for 12 weeks resulted in significant decreases in waist circumference and visceral adipose tissue compared with the respective placebo group [163]. Other lactic acid bacteria, such as *L. plantarum* FH185 [164], *L. plantarum* HAC01 [165], *L. plantarum* FH185 [164], *L. plantarum* HAC01 [165], *L. plantarum* K21 [166], and *L. plantarum* LG42 [164], have been explored with varying degrees of success.

Christensenella minuta is a member of the Christensenellaceae family in the phylum Firmicutes phylum of bacteria. It colonizes different parts of the colon in low abundances of 0.01%. One interesting feature of *C. minuta* is its greater abundance among lean subjects compared to the obese and among centenarians compared to the younger population group. Its characteristics were reviewed recently [167], and it is one of five taxa that are considered a signature of a healthy gut [168]. Yet its exact function in the gut is unclear. Research on whether some probiotics, such as some *Lactobacillus* strains, may help people to lose weight or body fat is still relatively new and growing. Probiotics could

be one part of a comprehensive weight loss program, but there is no guaranteed weight loss strategy, and probiotic administration will certainly not replace diet and exercise efforts. The best way to use probiotics for overall health and weight loss may be to include them in a nutritious, varied diet that is rich in fiber.

Conclusion and future research

Today, there are more than 10,000 results representing research publications on prebiotics and probiotics including new products, biological efficiency in animal models and in clinical trials and metaanalyses focusing on clinical presentations. Many studies demonstrate the importance of prebiotics and probiotics in health maintenance and prevention of intestinal diseases and cancer, yet their intake is not common in diets of most of the world population and this extensive body of research with already success stories, has not translated into clearly defined health or medicinal claims for prebiotics and probiotics. In this case, health and nutrition professionals should be responsible for keeping people informed and encourage the use of functional ingredients containing probiotics and prebiotics, making them part of the daily diet. The increase in the FF market, specifically in regard to foods that contain prebiotics, has been tremendous over the last two decades. Aiming to satisfy this new market, some prebiotics, especially INU and FOS, have been incorporated into a wide variety of foods and beverages that are part of a natural diet, including dairy products, breads, cereals, and dietary supplements. As a result of this growth, consumers can appreciate tasty meals while promoting beneficial effects to their own health. The interaction of gut microbes and prebiotics leads to several metabolic mechanisms that affect human health. The oral administration of prebiotics, such as the INU-type fructans, increases the abundance of *A. muciniphila* by more than 100-fold, and this finding is confirmed in different set of experiments. Globally, the prebiotics market is expected to continue to grow, exceeding $7.5 billion by 2023. Much activity can be expected in the area of phytonutrient enrichment of foodstuffs that will demand a more sophisticated approach to the nutritional safety of foods and to nutritional epidemiology. Among the key markets for HMO, the United States accounted for around 25.0% of global market share in 2015. This chapter acknowledges the availability of several potential nonconventional novel cost-effective sources of plant, fungal, and marine origin that have been studied extensively. Active research using such bioresources provides opportunities to explore their biotherapeutic and prebiotic PS properties in more depth. Technical cooperation programs are warranted to standardize the PS extraction and purification techniques to find the most effective strategy for mass production of well-defined purified preparations, particularly in the less developed countries, where the uses of prebiotics are most needed. Deadly and chronic diseases, such as diabetes, cancer, and obesity, can be well controlled or treated by these less economically and extensively available preparations. Combinations of different bioactive carbohydrates for particular groups, such as infants, older adults, and athletes, have high potential for the future. The concrete findings that are emerging will enhance the commercialization prospects of such bioresources and possible incorporation into FFs. Greater investment should be dedicated to food health risk analysis and risk minimization strategies for FFs. Furthermore, proper design and well-planned human trials are necessary to confirm the optimum dosages, duration, and target populations to put forward optimal conditions for maximizing the biofunctionalities of these preparations and thus aid in realization of the potential impacts in the healthcare world. With regard to the global market of probiotics, most of the health success has come with food-based approaches using traditional food commodities that have been subject to fortification technologies, such as fermentation with *Lactobacilli*, *Bifidobacteria*, or *Saccharomyces*. The translation of gut microbiota research over recent years has shifted from simple, depending on changes in bacterial populations, to research that aims to understand the functional features of the microbiota that are relevant to host physiology, such as the functions that SCFAs play in human physiology and the manipulation of metabolite profiles in the gut. Species belonging to the community of lactate producers (e.g., *L. rhamnosus*) may also belong to other communities being described by a metabolic function (e.g., lactate production) or by any other functional attribute, such as regulatory T cell induction or p40, the bioactive soluble protein expressed by *L. rhamnosus*, which mediates intestinal epithelial homeostasis. The difficulty of growing new NGPs on conventional media is another challenge, since NGPs grow exclusively on selective synthetic media, whose safety should be checked for compatibility with administration to humans. The safety status of the new probiotic products containing strains from humans needs to be closely aligned to the products' evolutionary history, and their potential beneficial effects should be proven. Improved knowledge of several commensal bacterial strains is now essential for careful analysis and demonstration of causality before making functional conclusions of some bacterial species and thus encouraging new opportunities to improve human health. It is highly recommended to take into account all relevant science and technology and to embrace all available techniques when investigating the gut microbiome to achieve complementary integrated information. Some authors believe that the term *NGP* will disappear, and the members of this group of probiotics will either merge with

current probiotics or will take a pharmaceutical route to market, in which case they would be live biotherapeutic products.

The health benefits of promising NGP candidates, such as *A. muciniphila*, which has been claimed to treat specific metabolic disorders and cardiometabolic risk factors associated with low-grade inflammation, should be confirmed in large-scale randomized human trials. The optimal bacterial count, the form of delivery (e.g., capsule, food supplement), and the duration of treatment for therapeutic applications or food supplements need to be well defined and characterized. The use of probiotics appears to be cost-effective. owing to their preventive and therapeutic role in the management of diseases [169].

There is evidence of a direct or indirect interrelationship between prebiotics and some probiotic bacteria strains in stimulating an immune response with beneficial commensals. Clinical trials on human beings are limited, and well-designed large-scale randomized, controlled trials are highly warranted to provide science-based evidence of the efficiency and safety of prebiotics and probiotics and symbiotic supplementation. This strategy can affect the clinical practices by setting and accepting dietary recommendation by the medical and scientific community. Profitability and potential problematic outcomes following the introduction of certain FFs with consumer engagement and consideration of individual and public health issues need to be well characterized. To the best of my knowledge, there has been no economic analysis of the cost-effectiveness of using prebiotics or probiotics except for a single study. This study is based on the cost-effectiveness of probiotic used to prevent *Clostridium difficile* infection [1,169]. According to the data collected from a published metaanalysis, the use of probiotic is cost-effective only if the *C. difficile* infection exceeds 1.6% in the adults receiving antibiotics after taking into consideration probiotic efficacy, the risk of probiotic sepsis, probiotic cost, and age [169]. Cost-effectiveness analyses are highly warranted, especially when medical insurance companies do not cover the expenses of treatment with prebiotic or probiotic supplements.

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Chapter 31

Effect of lysed *Enterococcus faecalis* FK-23 as a tyndallized probiotic in allergic diseases

T. Kiyoi[1], S. Liu[2] and M. Mogi[1,2]

[1]*Division of Analytical Bio-medicine, Advanced Research Support Center, Ehime University, Toon, Japan,* [2]*Department of Pharmacology, Ehime University Graduate School of Medicine, Toon, Japan*

Introduction

Allergic diseases, including allergic rhinitis and asthma, reduce the quality of life depending on the severity of presentation. The frequency of sensitization to inhalant allergens is increasing in the developed world. Allergic diseases are conventionally characterized by immunoglobulin E (IgE)-mediated reactions against inhaled allergens and involve mucosal inflammation driven by type 2 helper T (Th2) cells [1]. There are several kinds of disease-modifying treatments, such as administration of steroids, histamine antagonists, and leukotriene antagonists. Allergen immunotherapy has also been shown to be effective for allergic diseases, with a high level of evidence [2]. These medications have been proven to be effective for symptomatic relief, but there remain some problems of incomplete symptom resolution [3] and undesirable side effects [4].

Recently, it has been suggested that probiotic therapies using lactobacilli, including *Enterococcus faecalis*, have a significant effect on allergic diseases through regulation of the systemic immune response with low adverse effect profiles. Probiotics are living microorganisms that can be found in foods such as yogurt, sauerkraut, and pickles [5,6]. The role of tyndallized probiotics for health promotion has also been investigated because some of the lactobacilli, such as *E. faecalis* are gram-positive, facultative anaerobic organisms, and cause a variety of infections, including endocarditis, urinary tract infections, prostatitis, intra-abdominal infection, cellulitis, and wound infection as well as concurrent bacteremia [7]. In addition, there are reported cases in which tyndallized treatment with *E. faecalis* such as FK-23 (LFK) augmented the health-promoting effect [8]. Several lines of evidence suggest that *E. faecalis* as a tyndallized probiotic also has effects on allergic diseases experimentally and clinically. A LFK preparation as a tyndallized probiotic has been shown to provide therapeutic benefit in allergic diseases. Many of the studies were conducted by a group at Nichinichi Pharmaceutical Co., Ltd. We have also reported that oral administration of LFK provides therapeutic benefit in an ovalbumin (OVA)-induced asthma model mice through regulation of Treg/Th17 balance [9]. The effects of LFK preparations on allergic diseases are introduced in this chapter.

Animal experiments

It has been reported that oral administration of LFK brought significant relief of symptoms in a pollen antigen−sensitized allergy model in mice. In cedar antigen−sensitized mice, oral administration of LFK reduced the ratio of total eosinophils to total peritoneal accumulated cells, and there was a tendency for decreased total IgE, although without significance. This responsiveness differed between inbred mice with different genetic backgrounds. It was also suggested that LFK may have an effect on the allergic response through Toll-like receptors (TLRs), especially TLR-2 or TLR-6 [10]. LFK treatment also exhibited a decrease in peritoneal accumulated eosinophils in ragweed antigen−sensitized mice as well as cedar antigen−sensitized mice [11].

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Lactobacillus preparations may change the balance between Th1 and Th2 responses through downregulation of T cell activation and interleukin 4 (IL-4)-induced IgE synthesis by indirect mechanisms [12,13]. In cedar pollen−sensitized mice the specific IgE/IgG2a ratio was reduced by LFK treatment. However, there were no significant differences in the production of Th2 cytokines (IL-4, IL5) and Th1 cytokines (interferon gamma, IFN-γ) in allergen-stimulated cultured splenocytes of LFK-treated (three weeks) mice compared with control. In OVA-sensitized mice, BALB/c mice that were fed LFK for four weeks showed an effective reduction in the active cutaneous anaphylaxis reaction through IgE-mediated mast cell degranulation. Therefore it was suggested that LFK may have partial antiinflammatory effects on IgE-mediated allergy [14]. In an OVA-sensitized allergic rhinitis model in mice, LFK alleviated nasal symptoms and reduced nasal eosinophils. There were no significant effects of LFK on levels of IL-4 and IFN-γ in serum and splenocyte culture supernatant as well as OVA-specific IgE titer in serum. On the other hand, LFK induced an increase in percentage of splenic CD4 + CD25 + Tregs. These results suggest that LFK may be effective for improvement of allergic rhinitis through an increase in Tregs rather than regulation of Th1/Th2 balance [15]. In addition, in OVA-sensitized allergic asthma model mice, oral administration of LFK improved airway hyperresponsiveness, one of the most important characteristics of allergic asthma, and reduced accumulation of inflammatory cells in the lung. In the LFK-administered group, there was a decrease in Th17 cells, which produce IL-17A in splenocytes, lung cells and intestinal lamina propria lymphocytes, and the expression levels of transforming growth factor beta (TGF-β) and IL-6 were decreased in splenocytes and lung cells. LFK acts to restore the Treg/Th17 balance through TGF-β and IL-6 cytokine-dependent signaling pathways. As a consequence, it was clarified that LFK is able to suppress asthma by suppression of Th17 cell activity [9]. Recently, Molina et al. suggested that *E. faecalis* CECT7121 induces strong dose-dependent activation of dendritic cells and secretion of high levels of IL-12, IL-6, tumor necrosis factor alpha, and IL-10 via TLR signaling. This results in skewing the activation of T cells toward the production of IFN-γ [16].

In addition, oral administration of LFK may provide therapeutic benefits in patients who are given the drugs. Antibiotics disturb the microbiota of the gastrointestinal tract and may have an inhibitory influence on the immune system [17]. It has been suggested that LFK supplementation can modulate the response of the intestinal flora to the effects of antibiotic therapy [18]. In cedar antigen−sensitized mice the ratio of serum total IgE to IgG2a levels was significantly increased in erythromycin-treated mice relative to that in either LFK-treated mice or erythromycin-treated mice with LFK supplementation. This suggests that administration of LFK might be beneficial in preventing the subsequent development of allergy after receipt of antibiotics in early life [19]. Shoseiryuto (TJ-19), which has antiallergic and antiinflammatory properties, is a traditional Japanese drug originating from ancient Chinese medicine. It was suggested that combined administration of a low dose of Shoseiryuto and a low dose of LFK efficiently inhibits the allergic responses in cedar antigen−sensitized BALB/c mice through a decrease in peritoneal accumulated eosinophils [20].

Clinical evidence

It is well recognized that cedar and ragweed pollen can induce allergic diseases, and many patients suffer from pollen allergy. There is some evidence that LFK as tyndallized probiotic treatment improves the clinical symptoms of allergic rhinitis in Japan. Enomoto et al. conducted a double-blind, placebo-controlled trial to evaluate the effect of LFK on seasonal allergic rhinitis induced by cedar pollen. A total of 22 patients with hay fever were assigned to LFK and placebo groups, and LFK was administered to patients in the LFK group before the cedar pollen−scattering season. Clinical symptoms such as sneezing and nasal congestion were improved in the LFK group [21]. The effects of probiotics on allergic rhinitis are not clear and are often inconsistent. Schaefer et al. have investigated the effects of *E. faecalis* DSM 16440 as a probiotic in a total of 120 patients with allergic rhinitis who were randomly assigned to four different groups: double-blind probiotic, double-blind placebo, open-label placebo, and no-treatment group, to control for spontaneous variation in symptoms to evaluate the trial design [5]. Clinical evidence based on a more detailed study design is needed to clarify the role of LFK in allergic diseases.

Conclusion

Oral administration of LFK has been shown to have the potential to have an effect on allergic diseases such as asthma and allergic rhinitis in animal experiments and clinical studies by influencing the systemic immune response. The mechanism of the role of LFK in health promotion has been gradually elucidated. In animal experiments, it was suggested that LFK acts to activate Treg cells but not to regulate the Th1/Th2 balance. Especially in asthma models, LFK acts to restore the Treg/Th17 balance through TGF-β- and IL-6 cytokine-dependent signaling pathways. These responses may be induced by participation of dendritic cells via TLR signaling. Although the mechanisms of the effects of LFK on

allergic diseases have been elucidated incrementally in animal experiments, it is also necessary to further investigate the clinical benefit of LFK and to consider the method to evaluate the clinical trial protocol.

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Section 8

Bee products

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Chapter 32

The bee propolis for preventing and healing non-communicable diseases

Ahmad Sulaeman[1], Al Mukhlas Fikri[1,2] and Ade Heri Mulyati[1,3]

[1]Department of Community Nutrition, Faculty of Human Ecology, IPB University, Bogor, Indonesia, [2]Department of Nutrition, Faculty of Health Sciences, University of Singaperbangsa Karawang, Karawang, Indonesia, [3]Department of Chemistry, Faculty of Mathematics and Natural Sciences, IPB University, Bogor, Indonesia

Introduction

Propolis is a dark-colored bee product derived from plant resins and has many health benefits [1,2]. Bees produce several products such as honey, royal jelly, pollen, and propolis. Propolis, referred to as bee glue, is a resinous substance with a gummy texture, a distinctive odor, and a blackish-brown color. To make propolis bees collect resin from trees and then mix it with nectar, forming a waxy substance. Bees use propolis to defend the hive, lighten the inside of the hive, protect the colony, maintain the environmental temperature, and make the bees stronger and more resistant to external threats, including the threat of larger insects [3]. Huang et al. [4] stated that the plant species that is the main source of resin in temperate regions is *Populus*. In subtropical regions the source of resin is more diverse and usually comes from flowers [4]. For resin sources in tropical regions such as Indonesia the source of the resin comes mostly from mango, durian, banana, sengon, mahogany, acacia, and other types of tropical trees [5].

Propolis is a herbal product with a diverse variety of active compounds. There are at least 300 types of compounds contained in propolis, which can be categorized as flavonoids, terpenes, phenolics, sugars, minerals, and hydrocarbons [4]. However, each propolis has different chemical composition characteristics that affect its biological activity [6,7]. The chemical composition of propolis depends on the location and species of the plant source of the resin, and the extraction methods [4].

Propolis can protect bees because it has antibacterial activity, mummifies parasites, and increases the immunity of bee colonies [8]. Humans have used propolis as folk medication for thousands of years. Propolis was an important substance in the field of medicine, chemistry, and preservation of Egyptian mummies [1]. Propolis has become increasingly known after many studies conducted to prove its health benefits. Propolis has proven to have antibacterial, antiviral, antiprotozoan, antiinflammatory, antitumor, antifungal, and antioxidant properties and to be an apoptotic trigger and immunomodulator [1,9,10]. Propolis is also indicated to have antidiabetic and antiplatelet [11,12] and antiemetic [13,14] properties. The various kinds of biological activity of propolis give it great potential as a drug of the future [15].

What is propolis?

Propolis is a substance produced by honeybees. It is a sticky type of resin that is sometimes called bee glue. Propolis plays a role in nest building; if it is lacking, the nest will not be perfect. According to Bankova [6], propolis in hives is used by worker bees to close cracks and to minimize and close holes. Bee propolis is produced by collecting resins from various plants. Resins are collected from buds, skins, or other parts of plants, and then the resin is mixed with saliva and enzymes in bees to form a new resin that is different from the original resin [16]. It is then mixed with wax and flower pollen, which makes it elastic. This elastic mixture is propolis.

The nature of the biological activity of propolis is related to plant origin [17]. This is because although propolis is an animal product, its constituent components are mostly derived from plants. Kumazawa et al. [18,19] suggested that the flavonoids in propolis originate as flavonoids in plants. Chemically, the chemical composition of propolis is very

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complex; it is rich in terpenes, benzoic acid, caffeic acid, cinnamic acid, and phenolic acid. Propolis also contains many phenol compounds, especially flavonoids, so propolis is a good source of flavonoid compounds [20]. Król et al. [10] state that flavonoids are a group of chemical compounds that are known to have antioxidant activity, especially their ability to bind free radical scavenging and metal chelating. Phenol compounds are commonly found in plants that are reported to have various bioactivity abilities, including antioxidant activity [21]. One of the phenol that bonds in propolis, caffeic acid phenethyl ester (CAPE), reaches 50% of all components. CAPE is the active side of flavonoids that work to maximize the activity of scavenger against free radicals by reducing the activity of hydroxyl radicals (● OH) so that they are not as reactive [22]

Toreti et al. [23] have reviewed the compounds contained in propolis that have antibacterial and antibiotic activity, namely, flavanones, flavones, phenolic acids, and their esters, prenylated p-coumaric, labdane diterpenes, prenylated flavanones, and prenylated benzophenones. A review by Cantrell et al. [24] mentioned that the compounds of diterpene, triterpenes, and sesquiterpenes have antimycobacterial activity. The results of research by Katerere et al. [25] revealed that pinocembrin has antimycobacterial activity and that this compound increased its activity in the presence of other phytochemicals. This shows that multiphytochemical preparations are more effective than monophytochemical preparations. Yadav et al. [26] tested a number of pure preparations of flavonoids and found that luteolin, baicalein, quercetin, myricetin, and hispidulin had antituberculin activity. Some studies have found that flavonoids or flavonoid propolis are antimutagenic and antioxidant. For example, Tiwari and Mishra [27] found that flavonoids from natural sources (myricetin and apigenin) were able to prevent DNA damage, and Oršolić et al. [28] found that epigallocatechin gallate and propolis reduce DNA damage in peripheral lymphocytes in diabetic model mice. Montoro et al. [29] tested the cytotoxic and genotoxic activity of ethanolic extract propolis (EEP) at concentrations of 0−2000 μg/mL in human peripheral lymphocytes. EEP at concentrations of 2000 μg/mL were cytotoxic and genotoxic, whereas at lower concentrations the indication did not appear. Propolis is a material that contains complex phytochemicals, with the main content of flavonoids. The active components of propolis that act as antibacterial agents are flavanones, flavones, phenolic acids, and their esters, prenylated p-coumaric acid, labdane diterpenes, and prenylated benzophenones. The active components of propolis that act as hepatoprotective compounds are caffeic acid, ferulic acids, CAPEs, prenylated p-coumaric acid, flavonoids, lignans, and caffeoylquinic acids.

Research on the safety of propolis has been widely carried out, especially in experimental animals. In general, propolis is relatively safe for consumption. Burdock [30] conducted a study related to the upper limit of propolis consumption without side effects and found a value of 1400 mg/kg body weight as a no observed adverse effect level in experimental animals. Studies with higher doses have shown that propolis is still relatively safe for consumption. Doses of up to 5 g/kg body weight in mice showed no acute toxic symptoms, while doses of 500 mg/kg body weight subchronic (eight weeks) showed no toxic symptoms [31]. The results of the study by Mohammadzadeh et al. [3] showed that the administration of propolis at a dose of 2 g/kg body weight five times per week for nine weeks was considered safe. Security studies of propolis in humans have been carried out by Menniti-Ippolito et al. [2] through a surveillance study of the side effects of propolis consumption in Italy for five years. The study found that 18 cases were thought to be related to propolis, involving allergies, asthma, and gastrointestinal disorders. The allergic effect is thought to be caused by pollen, which is extracted so that in normal physiology, propolis is safe for consumption.

Chemical and nutrient composition of propolis

As a resinous compound produced by honeybees that has diverse biological activities with low toxicity, propolis has attracted the attention of modern scientists for more than 50 years [6]. Propolis is a complex bioactive mixture produced by bees that is known to have different biological activities, especially in countries with high biodiversity [32]. Propolis is a natural substance collected by honeybees from various plants such as poplar, palm, pine, conifer secretion, gum, resin, mucus, and leaf buds, which are collected and carried by honey bees to seal cracks and gaps in the hive, as an antiseptic to protect the hive bees from microbial infections, and to prevent the decomposition of hive components. Propolis has been used for centuries in traditional medicine. The biological characteristics of propolis depend on its chemical composition, plant source, geographical zone, and season [33,34]. Propolis contains many chemical compounds because bees collect chemical compounds from plants in their ecological environment. Propolis is prepared and used by honeybees to protect and defend themselves, to seal cracks, to smooth the walls, and to maintain the temperature and humidity stability of the hive [4]. The composition of propolis depends on the time, vegetation, and collection area [35−39]. Research into propolis has attracted the attention of scientists because of the ability of honeybees to collect secondary metabolites of plants in their environment, sources of substances in plants that protect their hives from infections and weather [6].

Raw propolis usually contains plant resins, waxes, essential oils, aromatic compounds, pollen, and other organic substances. Propolis also contains vitamins and minerals. Propolis contains vitamins B_1, B_2, B_6, C, and E as well as minerals such as magnesium, calcium, potassium, sodium, copper, zinc, manganese, and iron. Iron and zinc are the main minerals in propolis. Propolis contains essential amino acids needed for cell regeneration, such as arginine and proline, with levels around 45.8%. However, its mineral content is strongly influenced by the environment in which the originating plants grow [6]. Some enzymes, such as glucose-6-phosphatase, succinate dehydrogenase, acid phosphatase, and adenosine triphosphatase, are also present in propolis [1]. Our study showed that raw Indonesian propolis contained protein (2.02 ± 0.41 to 3.05 ± 0.01%), ash (1.31 ± 0.01 to 3.42 ± 0.02%), crude fat (38.67 ± 0.34 to 61.64 ± 0.05%), dietary fiber (45.02 ± 0.65 to 58.72 ± 0.47%), and carbohydrate (25.80 ± 0.04 to 64.91 ± 0.49%). Moreover, Indonesian propolis may be the source of micronutrients, including sodium, potassium, copper, zinc, iron, calcium, niacin, pyridoxine, and folic acid [40].

Indian propolis were collected from six different regions: Karnal from Haryana State, Hamirpur from Himachal Pradesh, Sarangpur from Uttaranchal, Palladam from Tamil Nadu, Hubli from Karnataka, and Sultanbatteri from Kerala. It consists of carboxylic acids (20.4%), terpenoids (15.0%), steroids (11.5%), hydrocarbons (9.6%), sugar (6.4%), alkaloids (6.4%), flavonoids (4.3%), phenols (3.2%), ketones (2.1%), amino acids (2.1%), vitamins (2.1%), and other compounds (15.0%) [41]. Propolis is a honeybee hive product, has a wide range of pharmacological potentials, including antioxidant, antiseptic, antiinflammatory, antibacterial, antimycotic, antifungal, antiprotozoan, antiviral, anticancer, antitumor, antiulcer, and hepatoprotective properties [33]. Propolis has been reported to have various health benefits related to allergies, gastrointestinal disorders, and gynecological, oral, and dermatological problems [42,43].

Extensive research on the bioactive compounds of propolis has been carried out. Phenolic compounds, terpenes, and tocopherols were identified as the main compounds of propolis [32]. More than 300 compounds, such as polyphenols, phenolic aldehydes, coumarins, sesquiterpene quinines, steroids, amino acids, and inorganic compounds, have been identified in propolis [1]. From 2000 to 2012, a total of 241 compounds were identified in propolis from the flavonoid, phenylpropanoid, terpene, stilbene, lignans, coumarin, and prenylated groups. The composition depends on the species of bees, plant sources, and the geographical location [4]. Flavonoids in propolis come from plant resins [18]. In 2004, Volpi used capillary zone electrophoresis to determine 12 different flavonoids (chrysin, rutin, pinocembrin, acacetin, myricetin, quercetin, kaempferol, catechin, naringenin, galangin, luteolin, and apigenin), two phenolic acids (caffeic acid and cinnamic acid), and one stilbene derivative (resveratrol) in propolis extracts used in medicine [44]. Twenty-one compounds were identified in ethanol extract of Canadian propolis, of which 18 were polyphenols [34]. Flavonoids are the major components of propolis, with flavones (i.e., chrysin and apigenin), flavonols (quercetin, galangin, pinobanksin, and their derivatives), and flavanones (pinocembrin) being the most common [45]. More than 300 compounds have been identified in propolis, such as phenolic compounds, aromatic acids, essential oils, waxes, and amino acids [33].

Some studies have been carried out continuously to inventory the bioactive compounds contained in propolis by using various separation techniques and identification methods with high specifications, including high-performance liquid chromatography, ultraperformance liquid chromatography, gas chromatography, and thin-layer chromatography, and identification techniques, such as mass spectroscopy, and nuclear magnetic resonance, have been widely used to identify bioactive compounds in propolis, including flavonoids, terpenes, phenolics, esters, sugars, hydrocarbons, and mineral elements. Flavonoids are the main component of bioactive compounds in propolis that provide the largest contribution to the pharmacological activity of propolis. The quality and quantity of flavonoids in propolis are often used as criteria for evaluating the quality of propolis. Flavonoids have a broad spectrum of biological activity, such as antibacterial, antioxidant, antiviral, and antiinflammatory effects. According to their chemical structure, flavonoids in propolis are classified into flavones, flavonoids, flavanones, flavanonols, chalcones, dihydrochalcones, isoflavones, isodihydro flavones, flavans, isoflavones, and neoflavonoids.

The raw propolis that is used for various preparations generally contains flavonoids as the main species, with flavones (chrysin and apigenin), flavanones (pinocembrin), and flavonols (quercetin, pinobanksin, galangin, and their derivatives) [45]. The type of solvent, temperature, time of extraction, composition, and physical characteristics of the propolis sample greatly affect the quality and quantity of extraction results and the quality of the final product.

The solvent is very important for extraction because the solvent determines the extracted compound. Selectivity, solubility, cost, and safety are the main considerations in the selection of solvents. Based on the polarity theory that solvents with the same polarity properties as the polarity of solutes interact more strongly with the principle of like dissolve like. Mello and Hubinger [46] stated that important factors affecting the content of phenolic compounds in propolis extracts were pH and the type of solvent used. Siripatrawan et al. [47] stated that the extraction efficiency of phenolic compounds increases with increasing ethanol concentration in solution. Ethanol and methanol are universal solvents in extraction for phytochemical investigations [48]. Ethanol propolis extract did not provide significant toxic effects in mice, so it can be used for nutritional products [49].

Propolis as an antioxidant and immunomodulator

Propolis is a promising natural source of antioxidants [50]. Mărghitaş et al. [51] found that propolis had an IC_{50} between 0.3 and 5.6 mg/mL. The flavonoid and phenolic contents of propolis play a major role in antioxidant activity. Both of these compounds muffle the free electrons resulting from oxidation. According to da Silva et al. [52], measuring the antioxidant activity of propolis with DPPH has been studied in depth. Other methods that can be used are ferric reducing ability power, TBARS assay, xanthine oxidase activity inhibition, and ABTS radical-scavenging activity.

Propolis is active to counter superoxide radicals [50]. Flavonoids and phenolics are the main constituents of propolis functioning as an antioxidant. According to Nagai et al. [53], flavonoids act as scavengers in the initial phase of lipid peroxidation through reactions with peroxy radicals from polyunsaturated fatty acids, thus stopping the chain reaction. Catechol groups of phenolic compounds are free radical recipients of free radicals [54]. Caffeic acid, flavonol, quercetin, and gallic acid, which commonly found in propolis, possess high antioxidant activity as measured by the DPPH method [55,56] found that CAPE in propolis has higher antioxidant activity than galangin. Banskota et al. [57] evaluated the antioxidant activity of propolis from Brazil, the Netherlands, China, and Peru; the results of this study found that, using the DPPH method, propolis from Brazil and China had higher antioxidant activity than the others.

Researchers have proven that propolis is a strong antioxidant agent. Both in vitro and in vivo research has been conducted. Ichikawa et al. [58] evaluated the antioxidant activity of propolis in mice in vivo. The study found that administration of propolis (2% diet) for ten weeks could increase the antioxidant capacity in the liver and brain of rats. Kwon et al. [59] also tested the antioxidant activity of propolis in the skeletal muscle and liver of rats. The subjects were divided into four groups; the propolis group, exercise group, propolis + exercise group, and control group. A total of 50 mg/kg of propolis was administered for six weeks. The results showed that the propolis + exercise group had higher levels of superoxide dismutase (SOD) and glutathione peroxidase (GPX) in skeletal muscle than the other groups. Meanwhile, all treatment groups had higher levels of SOD and GPX in the liver than the control group. Malondialdehyde (MDA), a marker of tissue damage due to free radicals, in the muscle was significantly lower in the propolis + exercise group than in the others, while MDA in the liver indicated no differences.

The propolis constituents are very diverse. The botanical source, species of bee, and extraction method are the main factors affecting propolis constituents [17]. Surendra et al. [60] revealed that the flavonoid content of propolis produced by *Trigona* spp. was higher than that of *Apis mellifera* propolis. Tropical countries including Indonesia have abundant biodiversity, leading to the produced propolis also being diverse. Thus we have done research to analyze the antioxidant activity of *Trigona* propolis with two methods of extraction. According to Fikri et al. [14], Indonesian *Trigona* propolis had IC_{50} ranging from 452.52 ± 29.27 up to 1027.288 ± 25.47 mg/L. The mean of phenolics and flavonoids ranged from 10.30 ± 0.16 up to 28.65 ± 10.67 mg/g GAE and 0.76 ± 0.26 up to 3.39 ± 1.08 mg/g QE, respectively. Ethanol extracts had relatively higher total phenols, flavonoids, and antioxidant activity than water extracts. According to Pietta et al. [61], 70% ethanol is the most often used solvent in propolis extraction. Extraction using ethanol is effective to produce fewer waxes and more polyphenol components. Extraction with ethanol effectively extracts lipophilic compounds, such as benzoic acid, flavonoids, and cinnamic acid [62]. Our recent study showed that Indonesian propolis probably had more bioactive compounds than our last findings. Mulyati et al. [63] found that total phenol, flavonoid, and IC_{50} of Indonesian propolis ranged from 152.46 ± 55.61 up to 158.81 ± 78.06 mg/g GAE, 6.16 ± 1.24 up to 17.08 ± 0.53 mg/g QE, and 150.20 ± 16.02 up to 207.63 ± 7.66 mg/L, respectively. Total phenol, felvonoid, and IC_{50} of Indonesian propolis can be seen in Table 32.1. We speculated that our previous findings had relatively higher temperature than our recent study. Thus more wax was extracted, and this led to a lower concentration of bioactive compounds.

We have identified the chemical composition of Indonesian propolis from South Sulawesi, South Kalimantan, and Banten (unpublished data). There were 47 compounds from all three samples identified by using gas chromatography and mass spectroscopy. The compounds were then classified on the basis of their group and consisted of triterpenes, alkenyl resorcinols, alkenyl phenols, anacardic acids, fatty acids, and chromanone derivates. The latter was found in propolis for the first time. The botanical sources of the tested propolis were mainly *Mangifera indica*. The *Calophyllum* plant was indicated to be another botanical source of propolis from South Sulawesi.

Propolis and diabetes

Diabetes is a non-communicable disease that has increasing prevalence. The results of the study of Jain et al. [64] showed that around 366 million people in the world suffer from diabetes. That number is responsible for one death per seven seconds in the world, or around 4.6 million deaths every year. According to the American Diabetes Association,

TABLE 32.1 Antioxidant activity, total phenol, and flavonoid of Indonesian stingless bee propolis.

Origin	Solvent	Total phenol (mg/g GAE)	Total flavonoid (mg/g QE)	IC_{50} (mg/L)
Banten[a]	Ethanol	15.25 ± 1.55	0.76 ± 0.26	568.99 ± 20.30
Banten[a]	Water	15.64 ± 0.09	1.80 ± 0.55	503.93 ± 2.06
South Sulawesi[a]	Ethanol	22.30 ± 0.50	3.39 ± 1.08	543.09 ± 20.51
South Sulawesi[b]	Ethanol	152.46 ± 55.61	10.64 ± 1.49	150.20 ± 16.02
South Sulawesi[a]	Water	15.32 ± 0.11	1.50 ± 0.26	810.75 ± 2.43
South Kalimantan[a]	Ethanol	28.65 ± 10.67	2.61 ± 4.10	452.52 ± 4.88
South Kalimantan[a]	Water	10.3 0 ± 0.16	1.42 ± 0.31	1027.29 ± 6.37
Riau Archipelago[b]	Ethanol	158.81 ± 78.06	6.16 ± 1.24	204.09 ± 20.89
Lampung[b]	Ethanol	327.86 ± 38.15	17.08 ± 0.53	207.63 ± 7.66

[a]*Fikri et al. [14].*
[b]*Mulyati et al. [63].*

about 10.5% of the U.S. population over 20 years of age had diabetes in 2018. Type 1 diabetes is generally caused by autoimmune disease, while type 2 diabetes is a multifactorial disease. Although obesity is believed to be a major factor, according to Bagchi et al. [65], diabetes is also caused by dietary factors and genetic susceptibility.

Several studies have shown propolis to have antidiabetic effects. Rivera-Yañez et al. [66] found that Mexican propolis was able to improve the symptoms of diabetes in STZ-diabetic mice. The study found that Mexican propolis inhibited increased blood glucose and weight loss in diabetic mice. These results are supported by the research conducted by El-Sayed et al. [67], who found that Brazilian green propolis was able to ameliorate the serum glucose, lipids, lipoproteins, nitric oxide, and antioxidant enzymes of diabetic rats. Moroccan propolis was also reported to improve the symptoms of diabetes in STZ-induced rats. Moroccan propolis increased body weight, inhibited lactic acid dehydrogenase, improved dyslipidemia, and improved liver and kidney function in diabetic rats [68]. The antidiabetic activity of propolis has also been reported in several clinical studies. By using a randomized double-blind design, Zakerkish et al. [69] reported that after administration for 90 days, Iranian propolis was able to reduce glycosylated hemoglobin (HbA1c), insulin, HOMA-IR, tumor necrosis factor alpha (TNF-α), and high sensitive C-reactive protein (CRP) in patients with type 2 diabetes. Another randomized clinical trial conducted by Fukuda et al. [70] found that intake of Brazilian green propolis for eight weeks was able to protect type 2 diabetic patients from developing worse blood uric acid and estimated glomerular filtration rate. Propolis may increase the antioxidant capacity of type 2 diabetes patients [12].

Propolis has an antidiabetic effect due to increasing either the production or the sensitivity of insulin. This effect may be primarily associated with its antioxidant activity [66,67]. Oxidative stress affected by several factors, including obesity, aging, pollution, and psychological stress, is commonly found among diabetic patients. Oxidative stress can cause inflammation and lead to insulin resistance. The antioxidant activity of propolis may help diabetic patients by reducing oxidative stress. Also, propolis may increase the expression of peroxisome proliferator-activated receptor gamma (PPAR-γ), which has an important function in energy regulation. Increased expression of PPAR-γ helps the body to increase adiponectin, which functions to improve the sensitivity of insulin [71]. Another mechanism has been proposed by Kitamura [72], which is that propolis improves the insulin response in muscle and liver by the IR/Akt/mTOR pathway. Chrysin and pinocembrin would be the responsible chemical compound for this action. Propolis also increases the secretion of insulin by inhibiting beta cell death. Glucose-6-phosphatase is an enzyme that has a function in gluconeogenesis and glycogenolysis. This enzyme is much higher in patients with type 2 diabetes, and inhibition of this enzyme may have a beneficial effect on these patients. Propolis can reduce the expression of glucose-6-phosphatase caused by the inhibition of the autophosphorylation of Y279 and Y216 of GSK3-α and -β, respectively [73].

Propolis and renal diseases

Chronic kidney disease (CKD) is a major cause of death and disability throughout the world. In recent years, CKD has reached epidemic proportions, at least in part because of aging, obesity, and the increasing prevalence of diabetes and hypertension in the world. According to the National Kidney Foundation, CKD has fulfilled all the basic criteria to be considered a major public health problem, which can explain the mechanisms involved in the development of chronic nephropathy disease as well as the basis for the development of new therapies to reduce its development. CKD is a public health problem throughout the world, and proteinuria is a marker of disease progression in CKD patients. Propolis, a

natural resin produced by bees from plant material, has antioxidant and antiinflammatory properties, acts as an immunomodulator, and has been shown to have antiproteinuric effects in experimental CKD studies [74,75].

Research on diabetic Wistar rats induced by intraperitoneal streptozotocin injection (60 mg/kg) showed that the thickness of the glomerular base membrane and glomerular area of the kidney of diabetic rats increased significantly. Treatment of diabetes mellitus in rats with propolis extract significantly reduced the thickness of the glomerular base membrane and glomerular area. The results of this study indicate that Iranian propolis extract can increase levels of antioxidants and histopathological changes in rat kidneys [76]. Research on mice that have paracetamol-induced kidney, liver toxicity, and hematology shows that propolis has an essential function for the treatment of liver and kidney diseases, especially proteinuria [77].

Research on animal models of renal damage that have been induced by gentamicin shows that propolis can protect against the effects of gentamicin [78]; results showed normal glomeruli on cellular examination, reduction of tubular injury, reduction of collagen, reduction of reticular fiber deposition, apoptosis reduction, reduced kidney injury, and reduced oxidative stress [79]. Propolis shows antihyperglycemic, antihyperlipidemic, and hepatorenal effects in diabetes and increases of carboxymethyl lysine, interleukin-6, and immunoglobulins in diabetes. Renal function increased, while potassium and sodium levels decreased [80], and significantly reduced elevated lactic acid dehydrogenase [68]. Brazilian green propolis extract was safe and tolerated, significantly reducing proteinuria in patients with diabetic and nondiabetic CKD Abdelsalam et al. [74,75]. Propolis can be combined with other substances to increase biological activity. The effect of propolis combined with marjoram could cause a significant improvement in the renal function of rats with chronic renal failure, and renal histology recovered after treatment with the combination of propolis and marjoram [75]. Research on rats shows that Indonesian propolis extract prevents kidney damage by reducing oxidative stress (MDA) and systolic blood pressure (SBP) [81]. Malaysian propolis extract on aorta rats induced with phenylephrine showed a relaxation response [82].

Propolis and hypertension and cardiovascular diseases

Hypertension is a major health problem in the world, and the prevalence continues to increase every year [83]. Hypertension has become a silent killer and the main risk factor for death worldwide. The epidemiology has been shifting from infectious disease to non-communicable diseases [84]. Hypertension is a major risk factor for many non-communicable diseases. Hypertension is closely related to the incidence of cardiovascular disease. According to Kokubo and Matsumoto [85], hypertension is the main risk factor for coronary vascular disease, heart failure, atrial fibrillation, cardiomyopathy, kidney disease, diabetes [86], renal failure, and preeclampsia. Other studies on the effects of hypertension show that hypertension can reduce cognitive performance. Furthermore, according to Alcocer and Cueto [87], hypertension is associated with macroeconomic and microeconomic losses.

The American Heart Association and the American College of Cardiology issued the latest hypertension treatment guidelines on November 13, 2017. The new hypertension guidelines change the definition of hypertension to a condition of having SBP higher than 130 mmHg or diastolic blood pressure higher than 80 mmHg [88]. Hypertension is a condition in which the blood pressure in blood vessels increases chronically and can trigger progressive cardiovascular syndrome arising from complex and interrelated etiologies [89]. This condition occurs because the heart pumps blood harder to meet the body's oxygen and nutritional needs. Hypertension can interfere with the function of organs, especially the heart and kidneys. Hypertension is a polygenic and multifactorial disease that has attracted attention because of the high prevalence not only in the West but also in developing countries. Hypertension in humans is a heterogeneous disease because of the result of complex interactions between genetic and environmental factors.

Currently, society uses pharmacological therapy in hypertension. Captopril is a pharmaceutical therapy that inhibits angiotensin-converting enzyme (ACE), an enzyme that is involved in increasing blood pressure. However, pharmacological treatment has several side effects and is relatively expensive, which may cause noncompliance by a hypertension patient. Moreover, Caligiuri and Pierce [90] state that pharmacological therapy has not been effective in reducing the prevalence of hypertension. The result shows that pharmacological therapy must be accompanied by other therapies, such as natural product consumption.

Previous studies indicate that propolis can decrease blood pressure. Kubota et al. [91] succeeded in showing that Brazilian propolis has antihypertensive activity through the vasorelaxation effect. Maruyama et al. [92] succeeded in isolating dihydrokaempferol, isosakuranetin, and betuletol from propolis and succeeded in using the compounds in decreasing blood pressure in spontaneous hypertensive rats. Other studies conducted by Xuan et al. [93] showed the antihypertensive activity of Chinese propolis through inhibiting the activity of specific phosphatidylcholine phospholipase C and decreasing levels of reactive oxygen species (ROS). The vasorelaxation mechanism occurs as a result of the

activity of catecholamine-producing enzymes and tyrosine hydroxylase [92,94,95], which inhibit angiogenesis [96,97] and protect the body against the atherosclerotic lesions.

Our study also revealed that Indonesian propolis has potential as an antihypertensive agent. Propolis samples from three regions in Indonesia—Riau Archipelago, Lampung, and South Sulawesi (200 mg/kg)—significantly decreased systolic and diastolic blood pressure of NaCl-induced hypertension in rats after 1 week of administration [40,98]. Fig. 32.1 shows the antihypertensive activity of Indonesian propolis. The study proposed that the antihypertensive activity of Indonesian propolis is the result of a diuretic effect and blood lipid improvement. Our study showed that 24-hour urine volume was significantly high in rats that were fed two propolis samples, including propolis from Riau Archipelago and Lampung. Moreover, high-density lipoproteins (HDL) and low-density lipoproteins (LDL) levels were improved in rats that were fed propolis from Lampung and South Sulawesi, respectively.

The antihypertensive activity of propolis is associated with the ability of propolis to prevent dyslipidemia. Some research results show that propolis is a potential antihyperlipidemia agent in experimental animals [68,99]. Moreover, the results of Purohit et al. [11] showed that propolis has an activity equivalent to that of statins (drugs for hypercholesterol therapy). This ability is suspected because propolis can affect the expression of PPAR-α and PPAR-β [100].

Antihypertensive activity of propolis has also been reported by several previous studies [92,93]. Four flavonoid compounds from the ethanol extract of Brazil's green propolis—dihydrokaempferol, isosakuranetin, betuletol, and kaempferide—have vasodilator activity in antihypertensive mechanisms [92]. Vestitol, an isoflavonoid from Brazilian red propolis, can trigger smooth muscle relaxation through the cAMP and cGMP pathways [101].

Flavonoids from bee products have been reported to have antihypertensive activity. Flavonoids could increase coronary vasodilation, decrease the formation of plaque by platelets, prevent oxidation of LDL levels, increase HDL levels, and increase endothelial function [102]. Propolis has vasorelaxation activity [92,94] because it can inhibit the activity of the catecholamine-producing enzyme tyrosine hydroxylase [95]. The propolis effect on human hypertension is unknown. However, in the blood vessels of animal models, propolis could modulate blood vessel function by stimulating vasorelaxation [92,94] and inhibiting angiogenesis [96,97], preventing atherosclerotic lesions [103].

The intervention of propolis in rats induced by L-NW-nitro-arginine methyl ester (L-NAME) can reduce blood pressure. Propolis decreases tyrosine hydroxylase activity in hypertensive rats that are inhibited by nitric oxide synthetase (NOS) and therefore can modulate catecholamine synthesis, thereby decreasing blood pressure [95]. Research on the effect of CAPE in propolis on hypertensive rats induced by isoproterenol shows that CAPE is a beneficial agent to protect the heart from injury caused by isoproterenol through the induction of antioxidant enzymes and the inhibition of lipid peroxidation [104]. CAPE increases cGMP phosphorylation and then inhibits protein kinase C activity, thereby inhibiting P47 phosphorylation, which finally inhibits platelet aggregation. This suggests that CAPE could be a new and powerful antiplatelet agent for the treatment of arterial thromboembolism [105]. Research on the antihypertensive effect of Brazilian propolis on hypertensive rats shows that the antihypertensive effect of propolis is mediated by acetylcholine-induced vasodilation [91]. The intervention of Brazilian red propolis can reduce blood pressure and structural kidney damage through a reduction in inflammation and oxidative stress [106]. CAPE increases the cyclic GMP/VASP Ser157 phosphorylation and inhibits protein kinase C activity, resulting in inhibition of P47 phosphorylation, and inhibits platelet aggregation [105].

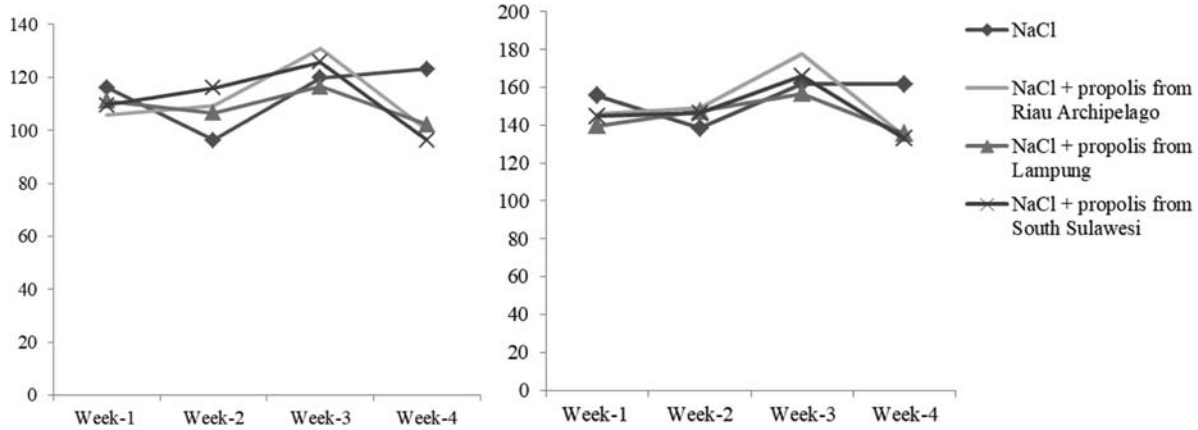


FIGURE 32.1 Systolic (*left*) and diastolic blood (*right*) pressure of hypertensive rats. The hypertension was induced by a high-sodium diet (8%) for three weeks (week 1−3), and propolis was administered 1 week later [98].

Active compounds of natural products that have long been known could reduce blood pressure. Natural bioactive compounds can prevent the formation of angiotensin II vasoconstrictors such as ACE inhibitors and chymase activity in the renin-angiotensin system. Bioactive compounds keep the vasodilation effect by blocking the bradykinin B1 receptor, regulating intracellular calcium concentration through blocking Ca^{2+} channels to induce vasorelaxation; releasing vasodilation substances such as prostaglandin I2, nitric oxide (NO), and carbon monoxide; reducing oxidative stress; and increasing opioid activity [107].

Propolis of Australian stingless bees (*T. carbonaria*) could relax pig coronary arteries by inhibition of Ca^{2+} channels [103]. At low concentrations, methanol extract from propolis shows high antioxidant activity. The inhibitory effect of propolis on lipid peroxidation in vitro results from hypoxanthine-xanthine oxidation reactions and NO radicals [108]. Increasing endothelial NO induces smooth muscle cell relaxation, vasodilation, and decreased blood pressure [109]. SOD activity and oxidative stress in the brain and plasma of rat given 2% propolis decreased significantly compared to controls. This result shows that propolis has high antioxidant activity in vitro and in vivo [108]. Propolis 1% was declared safe and sufficient to induce hypolipidemic and hypocholesterolemic effects in the serum of rats fed a high-cholesterol diet [110].

The role of propolis in hypertension and cardiovascular disease is associated with the role of antihyperlipidemic propolis in hyperlipidemia. Hyperlipidemia is a condition of the body that involves high levels of fat in the blood. Hyperlipidemia generally occurs in people with obese nutritional status [111]. Overweight is a risk for hypertension. Sukhonthachit et al. [112] showed that obese people have a tenfold higher risk of hypertension compared with people who have a normal nutritional status. According to Must et al. [113], 60%−70% of hypertension is related to obesity. The close relationship between obesity and hypertension is caused by overeating and a high-salt diet. According to Cocores and Gold [114], foods with high-salt content are addictive. Salt not only gives a sensation of taste but also stimulates opiate and dopamine receptors in the brain's center sense of comfort. The stimulation triggers hunger and overeating.

Increased levels of fat in obese people can trigger vasoconstriction in the blood vessels. The influence of obesity on blood pressure occurs through several pathways, namely, endothelial dysfunction, stimulation of the sympathetic nervous system, and induction of the renin-angiotensin aldosterone system. Endothelial dysfunction can be caused by an increase in inflammation that is characterized by an increase in several groups of interleukin, TNF-α, and CRP. This condition is associated with an increase in oxidative stress due to obesity. Endothelial dysfunction is also caused by increased production of plasminogen activator inhibitor-1 (PAI-1) and thromboxane A2. These proteins function to increase platelet buildup. The fat accumulation also causes increased angiotensinogen synthesis so that RAA increases, causing sodium retention and an increase in blood volume, which triggers hypertension. Increased levels of leptin could trigger increases in the sympathetic nervous system through melanocortin receptors [115].

Propolis is reported to have antihyperlipidemic activity. Abdulbasit et al. [99] showed that Nigerian propolis (200 mg/kg) can reduce LDL and total cholesterol levels and increase HDL levels of alloxan-induced diabetic rats. Similar research results were found by El-Sayed et al. [67], who showed that Brazilian propolis (200 mg/kg) could reduce triglyceride, total cholesterol, and LDL levels and increase HDL levels in streptozotocin-induced diabetic rats. The propolis activity to prevent hyperlipidemia has been studied at the cellular level. Ichi et al. [100] showed that propolis increased lipid metabolism in rats that were given a high-fat diet. An intervention of 0.5% of propolis in the diet can reduce triglyceride, LDL, total cholesterol levels and increase HDL levels. Propolis can increase PPAR-α expression, increasing fat oxidation. Propolis also decreases PPAR-β expression, which affects fat accumulation. Furthermore, SREBP-1 and HMG-CoA reductase decreased after the administration of propolis. Both of these proteins play a role in the biosynthesis of fatty acids and cholesterol.

Flavonoids are strong antioxidants, free radical scavengers, and metal chelators. Propolis inhibits lipid peroxidation and has other physiological activities, such as antihypertensive and antiarthritis effects [116]. Antihypertensive effects occur through ACE inhibition, vasodilation by parasympathetic stimulation, or inhibiting the release of noradrenaline from the sympathetic nerve [92]. Some flavonoids have been reported to have vasodilation and hypotensive effects [117]. CAPE is the main constituent of propolis, with extensive biological activity, including inhibition of NFκ-B, inhibition of cell proliferation, induction of cell cycle capture, and apoptosis [4]. Propolis has activity in cardiovascular protection through antiinflammatory pathways [118].

Hypertension is divided into essential hypertension and secondary hypertension. Essential hypertension, also known as primary hypertension or idiopathic hypertension, is hypertension without clear pathology. More than 90% of hypertension cases are essential hypertension. The causes of hypertension include genetic factors (sensitivity to sodium, stress, etc.) and environmental factors (lifestyle, emotional stress, etc.). Secondary hypertension accounts for 5%−10% of hypertension cases, such as cardiovascular hypertension (increased peripheral resistance due to atherosclerosis), renal hypertension (renal artery occlusion or kidney tissue disease), endocrine hypertension, and neurogenic hypertension [119].

Hypertension is caused by endothelial dysfunction that occurs through several pathways, including decreasing the production of endogenous NO, regulating angiotensin I receptors in vascular smooth muscle, and vasoconstrictive and proatherogenic effects of angiotensin II. Angiotensin II increases vascular inflammation by stimulating inflammatory cytokines and monocyte uptake and inducing oxidative stress [120]. Serum uric acid levels are a marker of inflammation and oxidative stress in hypertension. Wang et al. [121] evaluated about 3500 subjects with hypertension to identify biomarkers that related to risk of hypertension with a multimarker approach such as CRP, fibrinogen, and PAI-1, brain natriuretic peptide, homocysteine, serum aldosterone, plasma renin, and the urinary albumin/creatinine ratio (UACR). The results showed that three biomarkers—CRP, PAI-I, and UACR—became the main biomarkers of hypertension. However, cohort data show that urinary albumin excretion predicts the incidence of hypertension better than CRP and PAI-1 do [121]. Several studies have shown a positive relationship between hypertension and the ratio of neutrophils to lymphocytes (neutrophil-lymphocyte ratio, or NLR). NLR is a biomarker that arises in cardiac and noncardiac disorders with cases of systemic inflammation. Cohort studies in China show that an increase in NLR is significantly correlated with an increased risk of developing hypertension [122,123].

The inhibition of NO synthesis or bioavailability has a very important role in hypertension development. NO has an important role in the physiological control of blood pressure. NOS inhibitors such as L-NAME are commonly used as inducers in hypertension models [95]. Blocking NOS activity can cause vasoconstriction through ROS production [124]. NO is a key regulator of paracrine for the vascular system. Physiologically, NO inhibits leukocyte-endothelial cell adhesion, proliferation and migration of vascular smooth muscle cells, and platelet aggregation to maintain the health of vascular endothelium. Decreased NO bioavailability in blood vessels reduces the vasodilation effects and contributes to hypertension. The enzyme that catalyzes NO synthesis is NOS. NO counters the effects of angiotensin II, endothelin, and ROS. NO diffuses into adjacent smooth muscle and interacts with the other receptor molecules, such as guanylyl cyclase [125].

Propolis and cancer

Many studies have investigated propolis as an anticancer agent [126–129]. However, those studies investigated stinging bee propolis; research evaluating the anticancer effect of stingless bee propolis and the underlying mechanism is still limited. Choudhari et al. [130] proved the anticancer effect of Indian stingless bee propolis on several cancer cells (breast, colon, colorectal, and skin cancer cells) through induction of the apoptosis pathway. Cinegaglia et al. [131] found an anticancer effect of Brazilian stingless bee propolis on osteosarcoma cells. The most recent and comprehensive research conducted by Kustiawan et al. [132] showed a cytotoxic effect of Indonesian stingless bee propolis on lung, stomach, liver, colon, and breast cancer cells. The content of triterpenes and phenolic lipids, which are the main constituents of Indonesian stingless bee propolis, has also been reported by many studies to have anticancer effects [133–135]

Several researchers have proposed various anticancer mechanisms of propolis. Flavonoids, triterpenes, and CAPE, which are the main constituents of propolis, have been shown to reveal anticancer effects [136]. Immunomodulatory activity is thought to underlie the anticancer effect of propolis. Propolis is believed to induce TNF-related apoptosis-inducing ligands (TRAIL), which mediate the cell apoptosis programming [137]. Sawicka et al. [138] explained that propolis may induce apoptosis in two ways: extrinsic and intrinsic induction. Extrinsic induction via TRAIL may activate caspase cascades and induce apoptosis. Meanwhile, intrinsic induction is through the inhibition of bcl-2 and the stimulation of cytochrome c production by mitochondria. Bcl-2 is a protein that plays a critical role in inhibiting cell apoptosis, while cytochrome c plays a role in triggering cell apoptosis. Cytochrome c may also activate apoptotic protease activating factor 1 and caspase cascade. Propolis may also directly induce caspase cascades through caspase 3.

The solvent is one of the important factors that determines the anticancer activity of propolis. Although there has been no research comparing the anticancer effects of propolis between the solvents, 70% ethanol has been accepted as the best solution to produce high biological activities. However, several studies have reported the anticancer effects of water extract of propolis. Najafi et al. [139] first performed propolis extraction with water, and the extract was applied to several cancer cells (Sp20, HeLa, Hep-2, McCoy, BHK21). The results showed that water extract of propolis inhibited the growth of cancer cells. Inoue et al. [140] stated that the water extract of propolis was able to reduce the number of cells and the weight of tumors in mice. Erhan Eroğlu et al. [141] also succeeded in determining that water extract of propolis has the potential to be an agent of anticancer because it reduced the growth of bladder cancer cells. Drigla et al. [142] recently found that a combination of water extract of propolis and bee venom reduced breast cancer cell proliferation. Kustiawan et al. [132] found a tendency for the cytotoxic effect of methanol extract of stingless bee propolis from East Kalimantan to be stronger than ethyl acetate and hexane extracts, although the tendency was weak. However,

this can be explained by Mouse et al. [143], who stated that the anticancer effect of propolis depends not only on the chemical composition of propolis, but also on the type of cancer cells. Also, the biological activities of propolis are not because of a single compound but rather the result of the interaction of several compounds contained in propolis [136].

Conclusion

Propolis has been recognized since long time to have many beneficial health effects. Even the Quran mentioned its benefits more than 16 centuries ago as a bee product along with honey, pollen, and royal jelly. However, only in the last 50 years has the scientific reason for its benefits been disclosed. Besides having benefits in treating communicable diseases, such as tuberculosis and HIV, propolis has shown its potency in preventing and curing communicable diseases such as cancer, renal disease, hypertension, and cardiovascular disease.

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Chapter 33

Nutraceutical and medicinal properties of native stingless bees honey and their contribution to human health

Jesús F. Martínez-Puc[1,2], William Cetzal-Ix[2], Saikat Kumar Basu[3], Justo R. Enríquez-Nolasco[2] and Miguel A. Magaña-Magaña[1]

[1]*Division of Graduate Studies and Research, National Technological Institute of Mexico, Technological Institute of Conkal, Yucatán, Mexico,* [2]*National Technological Institute of Mexico, Technological Institute of Chiná, Campeche, Mexico,* [3]*Performance Seed, University of Lethbridge, Lethbridge, AB, Canada*

Introduction

Beekeeping refers to the breeding and use of honeybees (*Apis mellifera* L.), and meliponiculture refers to the breeding and management of native stingless bees (NSBs) (family Apidae, tribe Meliponini) [1,2]. NSBs are mainly characterized by the lack of a functional stinger, a less pronounced wing venation, and a brushlike hairy structure in the widest part of the tibia, which is known as the penicillium [1]. The term meliponiculture was coined by Paulo Nogueira Neto to define people who are dedicated to the breeding and care of NSBs, activities that are practiced in various tropical and subtropical regions of the Americas, Africa, Asia, and Australia [3].

The greatest diversity of stingless bees (Meliponini) is found on the American continent, with more than 400 described species, followed by the Indo-Australian region with about 90 species and the African continent with about 30 species [1]. In Mexico a total of 46 species of NSBs have been identified in 11 genera; of these, 17 species are found in the Yucatan peninsula (YP) [1,4].

Native stingless bee honey

Honey is defined as a sweet substance produced by bees of the species *A. mellifera* from the nectar of flowers or exudations from other living parts of plants, which these bees collect and combine with specific substances, which they then store in their honeycombs [5–7]. However, in the case of honey produced by NSBs, there is still no official recognition of it as honey, owing to the great variation in its physicochemical characteristics [6,8]. These physicochemical variations have been observed at the species level within the same genus of bees and are the result of the differences in the floral resource available in each geographical area and other intrinsic factors [6]. But NSB honey is considered a natural product with high nutritional value that has been used in traditional medicine worldwide because of its antibacterial and antiinflammatory properties [9,10].

The honeys obtained from some NSB species [*Melipona beecheii* Bennett (Fig. 33.1), *M. trinitatis* Cockerell, and *Melipona favosa* Fabricius] show marked differences in their physicochemical characteristics compared to the honeys produced by *A. mellifera*, mainly owing to the high moisture content of NSB honey [11]. Currently, NSB honey is valued because it is used in the treatment of various respiratory, dermatological, and gastrointestinal conditions [11,12]. According to Zamora and Arias [6], NSB and *A. mellifera* honeys have a similar inhibitory effect against *Escherichia coli, Pseudomonas aeruginosa*, and *Salmonella* sp.; NSB honeys have a greater inhibitory capacity against other bacteria, such as *Staphylococcus aureus* and *Staphylococcus epidermidis* (Winslow and Winslow). Most of these microorganisms are considered as the main foodborne pathogens. Honey from *M. beecheii* has been proposed as an alternative for

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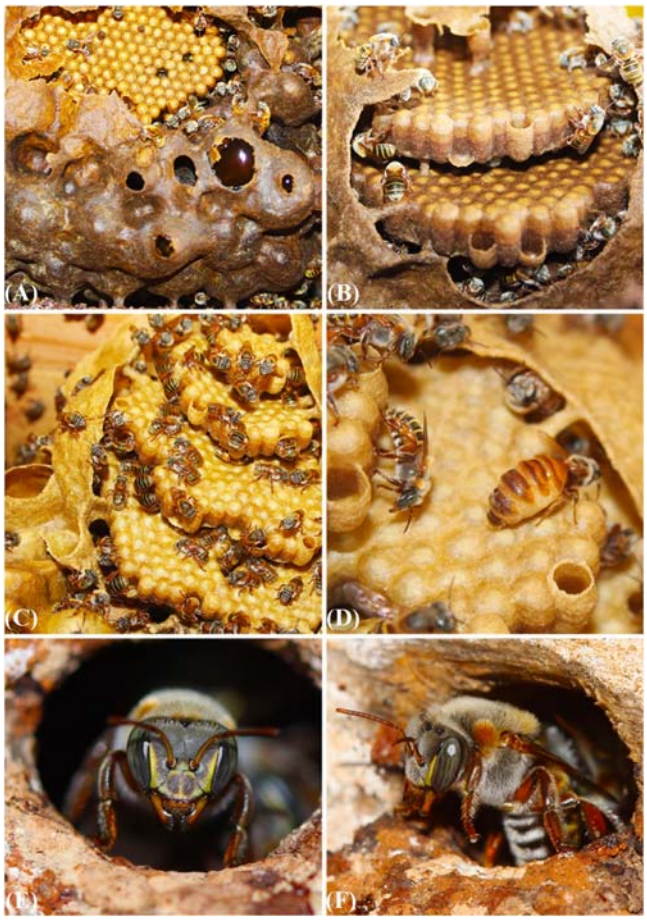


FIGURE 33.1 *Melipona beecheii*. (A–D) Bee on honeycomb. (E–F) Morphology.

obtaining bioactive compounds with antioxidant activity and as a natural food to reduce the danger of some types of cancer associated with the oxidative stress of the physiological cells of the human being [10].

Physicochemical characteristics of native stingless bee honey

A physicochemical characterization is carried out to determine the qualities of honey and for the purpose of its commercialization, but the physical and chemical composition of NSB honey is based on the parameters established to evaluate *A. mellifera* honey [12]. Several studies of the physicochemical characteristics of NSB honeys have been carried out in countries such as Brazil [13–18], Peru [19], Guatemala [12], and Mexico [20,21]. One of the main characteristics of NSB honeys is that they have a higher moisture content compared to *A. mellifera* honey [21,22]. However, despite studies of the physicochemical composition in honeys of some species of NSB, sensory characterization has been limited only to honeys of *A. mellifera* [23].

Physical characteristics of native stingless bee honey in Yucatan

In Yucatan state, Mexico, it has been observed that there are no differences between the main physical parameters such as pH and electrical conductivity (EC) of the honeys of *M. beecheii* (Fig. 33.1) and *S*captotrigona *pectoralis* (Fig. 33.2) compared to honey from *A. mellifera*. The pH values of the honeys were 4.5 ± 0.4 for *A. mellifera*, 4.3 ± 1.1 for *M. beecheii*, and 4.0 ± 0.5 for *S. pectoralis*. The EC of the honeys was 0.4 ± 0.1 mS/cm for *A. mellifera*, 0.3 ± 0.2 mS/cm for *M. beecheii*, and 0.3 ± 0.1 mS/cm for *S. pectoralis* [24].

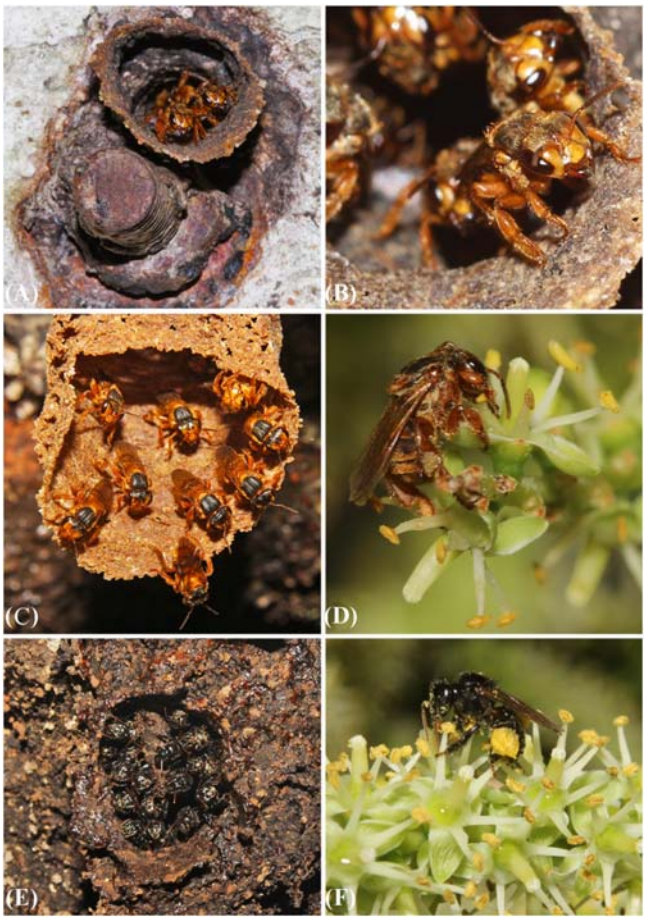


FIGURE 33.2 *Scaptotrigona pectoralis*. (A–C and E) Nests. (D and F) Foraging native flora.

Chemical characteristics of native stingless bee honey in Yucatan

Humidity

The honeys from *M. beecheii* and *S. pectoralis* obtained from samples in Yucatan had higher moisture content in comparison to honey from *A. mellifera*, 24.1% versus 17.3%, respectively [24]. The moisture content of the nectar that is transported by the worker bees of *A. mellifera* and *M. beecheii* from the flowers to their entrance to the colony is similar; but there are differences in the percentage of humidity of honey in both bee species, before and after being capped, which indicates that the most important losses of humidity occur inside the nest and are more pronounced in *A. mellifera*, revealing a greater efficiency in the moisture loss process compared to NSBs [25].

Acidity

In *A. mellifera* honey, at least 18 organic acids have been registered, which are important for the flavor, gluconic acid being the one in greatest quantity; other acids such as formic, acetic, butyric, lactic, oxalic, succinic, tartaric, maleic, pyroglutanic, pyruvic, alpha-ketoglutaric, and glycolic, have also been found [26]. In Yucatan it has been observed that the acidity of the honeys of *M. beecheii* (40.3 mg/kg) and *S. pectoralis* (44.7 mg/kg) is slightly higher than that of honeys of *A. mellifera* (38.1 mg/kg) [24] (Table 33.1).

Total reducing sugars

The content of total reducing sugars (TRS) influences the viscosity, hygroscopicity, granulation, and energy value of honeys [24]. Reducing sugars (glucose and fructose) are dominant fractions with 85% and 95% of carbohydrates present

TABLE 33.1 Physicochemical parameters of honeys from *Apis mellifera, Melipona beecheii,* and *Scaptotrigona pectoralis* in Yucatan, Mexico.

Characteristics	Parameters	*Apis mellifera*	*Melipona beecheii*	*Scaptotrigona pectoralis*
Physical	pH	$4.5^{a} \pm 0.4$	$4.3^{a} \pm 1.1$	$4.1^{a} \pm 0.5$
	Electrical conductivity (mS/cm)	$0.4^{a} \pm 0.1$	$0.3^{a} \pm 0.2$	$0.3^{a} \pm 0.1$
Chemical	Humidity (%)	$17.3^{a} \pm 1.6$	$24.1^{b} \pm 1.2$	$24.1^{b} \pm 1.3$
	Acidity (mg/kg)	$38.1^{a} \pm 4.0$	$40.3^{a} \pm 10.5$	$44.7^{a} \pm 15.5$
	Total reducing sugars (%)	$74.2^{a} \pm 9.4$	$68.8^{a} \pm 11.3$	$56.2^{b} \pm 10.9$
	Glucose (%)	$36.7^{a} \pm 8.3$	$10.0^{b} \pm 1.8$	$13.4^{c} \pm 2.5$
	Sucrose (%)	$0.4^{a} \pm 0.1$	$0.1^{b} \pm 0.1$	$0.01^{c} \pm 0.0$
	Hydroxymethylfurfural (mg/kg)	$8.6^{a} \pm 2.9$	$5.7^{a} \pm 8.3$	$1.2^{b} \pm 0.9$

^{a,b,c} in the table entries denotes different statistical values for the estimated mean of each parameter.
Based on Catzin-Ventura GA. Caracterización fisicoquímica, actividad antibacteriana y origen botánico de mieles de *Apis mellifera, Melipona beecheii* y *Scaptotrigona pectoralis*, en Yucatán [M.Sc. Thesis]. Mérida: Universidad Autónoma de Yucatán; 2011.

in honey; in Yucatan it has been observed that the percentage of TRS is higher in honeys from *A. mellifera* (74.2%) and *M. beecheii* (68.8%) in comparison to honey from *S. pectoralis* (56.2%) [24].

Glucose and sucrose

The majority of sugars in honey correspond in 40% to fructose (which has little solubility and determines the tendency of the crystallization of honey) and 34% to glucose (which is highly hygroscopic, making its sweetness possible and highlighting the natural smells) [24]. But when there is a greater amount of glucose, crystallization of honey occurs rapidly, and when the amount of fructose is greater, the tendency toward crystallization is less [24]. In Yucatan, significant differences in glucose and sucrose content have been found between honeys from *A. mellifera, M. beecheii*, and *S. pectoralis* (see Table 33.1) [24]. Table 33.2 shows some parameters of honey quality in Guatemala from some NSB genera [23].

Medicinal properties

NSB honey has been used for its medicinal properties since ancient times in Mexico by various indigenous groups, mainly the Zapotecos, Mixes, and Zoques of the Isthmus of Tehuantepec [27]. NSB honey has been used in traditional medicine to treat diseases such as pharyngitis, respiratory tract infections, and eye infections [2,23,28]. Recently, an interest has emerged in verifying the various therapeutic qualities of NSB honey for their antiinflammatory, antibacterial, healing, and antioxidant properties [10,29]. The most interesting quality is antimicrobial activity, since that could give NSB honey clinical application [29]. Furthermore, the NSB honeys are used to feed women in the postpartum recovery period [23]. Currently, there has been no study that indicates all the benefits that NSB honeys provide in the area of health (Table 33.3) [23,30]. The healing and medicinal effects of these honeys have been applied to a wide range of diseases or conditions; in this sense, it is important to mention that the healing properties of honeys are rooted in people's beliefs and traditional knowledge [31].

Chemoprevention

Chemoprevention can be described as the use of natural or synthetic compounds to decrease the risk of cancer development [10,32,33]. In this sense, NSB honey can be considered to be a chemopreventive agent, since it has antioxidant and antiinflammatory activities [10,29,34], as well as apoptotic, antiproliferative, estrogenic, and immunomodulatory activities, which could be considered as the possible mechanisms of honey for cancer prevention [34]. Also, it has been suggested that the consumption of honey can exert several beneficial effects on the immune response of people, promoting the multiplication of B and T lymphocytes in the blood and the activation of neutrophils under cell culture conditions [35]. Furthermore, honey is used to protect against gastrointestinal infections, gastritis, and gastric ulcers [36].

TABLE 33.2 Values established for some quality parameters for honeys of some genera of native stingless bees.

Quality parameters	*Melipona*	*Scaptotrigona*	*Trigona*
Humidity (%)	Max 30.0	Max 30.0	Max 30.0
Acidity (mg/kg)	Max 70.0	Max 85.0	Max 75.0
Ashes (%)	Max 0.50	Max 0.50	Max 0.50
Total reducing sugars (%)	Min 50.0	Min 50.0	Min 50.0
Sucrose (%)	Max 6.0	Max 2.0	Max 6.0
Hydroxymethylfurfural (mg/kg)	Max 40.0	Max 40.0	Max 40.0

Based on Vit P, Medina M, Enríquez E. Quality standards for medicinal uses of Meliponinae honey in Guatemala, México and Venezuela. Bee World 2004;85:2–5.

TABLE 33.3 Main medicinal uses of native stingless bee honey.

Species	Medicinal uses
Melipona beecheii	Digestive disorders, eye diseases, respiratory infections, postpartum recovery, fatigue, ulcers
Melipona favosa	Labor enhancer
Melipona paraensis	Postpartum recovery
Melipona trinitatis	Gastritis
Scaptotrigona mexicana	Respiratory infections
Nannotrigona perilampoides	Cataracts, stomachaches, bruises
Plebeia jatiformis	Cataracts, stomach pains, external head injuries
Trigona angustula	Stomach disorders, cataracts, respiratory infections, wound healing

Based on Vit P, Medina M, Enríquez E. Quality standards for medicinal uses of Meliponinae honey in Guatemala, México and Venezuela. Bee World 2004;85:2–5.

Antiinflammatory properties

Inflammation is a complex process that is frequently associated with pain and involves situations such as increased vascular permeability, increased protein denaturation, and altered membranes. When tissue cells are injured, they release kinins, prostaglandins, and histamines, which act as chemical messengers that attract some of the body's defense cells [37]. The antiinflammatory capacity of honey is associated with the prevention of the formation of serous exudates capable of being colonized by bacteria and with the stimulation of tissue growth and repair [6].

According to Ruiz-Ruiz et al. [38], honey contains different phytochemical compounds and therefore exhibits multiple biological activities, affirming that the phenolic acids and flavonoids present in *M. beecheii* honey are related to its antioxidant and antiinflammatory properties. Moreover, phenolic compounds present in honey may also be involved in the antiinflammatory activity, as they have been shown to inhibit production of the inflammatory cytokine of tumor necrosis factor alpha [33].

In vitro tests have shown that the chemical properties of phenolic acids and flavonoids play an important role in promoting bioactivities, for which the therapeutic use of honeys produced by NSB has been recommended for the treatment of aging and inflammation [38]. The antiinflammatory properties of honey have been proven in various animal clinical studies, but its antibacterial effect should not be confused with the antiinflammatory properties [39].

Antibacterial and antifungal properties

Antibiotics are synthetic products, and microorganisms can develop resistance to them due to their improper use. Likewise, the use of antibiotics can cause secondary effects such as liver lesions, toxic action on hematopoietic organs, and allergic reactions such as dermatitis [40]. In this situation, NSB honey becomes a natural antibacterial treatment alternative [41]. The antimicrobial action is due to the high osmolarity that honey presents, mainly due to the effect of the hydrogen peroxide that is produced slowly and sustained by the enzyme glucose oxidase, maintaining an

antimicrobial effect with a concentration 1000 times higher than that of a common antiseptic [42]. Antimicrobial actions also include an increase in the production of lymphocytes, antibodies, and cytokines and the strengthening of the immune system [42].

Honeys of NSBs have an inhibitory effect on approximately 60 species of bacteria (gram-positive and gram-negative) [6]. NSB and *A. mellifera* honeys have a similar inhibitory effect against *E. coli, Salmonella* sp. and *P. aeruginosa*, although the NSB honeys have a greater inhibitory capacity against *S. aureus* and *S. epidermidis* [6]. On the other hand, honeys of *Geotrigona acapulconis, M. beecheii, Melipona solani, Melipona yucatanica, Nannotrigona perilampoides, Plebeia* sp., *Scaptotrigona mexicana, Scaptotrigona pectoralis*, and *Tetragonisca angustula* show antibacterial activity at concentrations of 2.5%−10% (v/v), against eight pathogenic microorganisms, six bacteria, and two yeasts (*Bacillus subtilis, Candida albicans, Cryptococcus neoformans, E. coli, Mycobacterium smegmatis, P. aeruginosa, Salmonella typhi*, and *S. aureus*) [6]. Additionally, in vitro studies with NSB honeys have shown that they have a higher antimicrobial activity than *A. mellifera* honeys [43,44], even at lower concentrations [45].

Healing

Physiological processes of wound repair can be divided into three stages: inflammatory, proliferative, and remodeling [33,46]. In the inflammatory stage, honey stimulates monocytes to release inflammatory cytokines and nitric oxide, which can induce collagen synthesis by fibroblasts [33]. In the proliferative or granulation stage, the stimulation of angiogenesis by honey supplies the necessary oxygen in the wound-healing process. Finally, in the remodeling stage, collagen is remodeled and realigned along tension lines, and cells that are no longer needed are removed by apoptosis; at this stage, it has been observed that the use of honey in wound treatment reduces scabs and produces thin scar formations [46].

It has been observed in diabetic patients that the formation of infectious ulcers in the lower limbs is increasingly frequent. Therefore hospitals in developed countries use cheaper alternatives for professional wound care [47]. In Mexico the efficacy of *M. beecheii* and *M. solani* honey has been evaluated and compared to a conventional treatment (collagen and chloramphenicol). The researchers concluded that honey contributes better to the healing of ulcers in the feet of diabetic patients without the need to combine the honey treatment with other medications, helping to reduce the cost of treatment to 150 Mexican pesos compared to 2000 Mexican pesos for conventional treatment [48]. Meanwhile, Nufio-Oliva [49] evaluated wound healing in rabbits with honeys from *A. mellifera* and *M. beecheii* compared to conventional treatment (neomycin and clostebol); they observed that honey from *M. beecheii* showed the best average (1.4 mm daily) reduction in wound size per day.

Dietary supplement

Honey is a nutritional supplement and considered an important energy food. However, it cannot be considered a complete food by the nutritional standards of human beings; rather, it constitutes a potential dietary supplement. A serving of 100 g of honey provides 300 kilocalories as well as facilitating the absorption of calcium and magnesium [50]. Honey contains approximately 0.5% protein, mainly enzymes and free amino acids. It contains all the vitamins necessary for health (thiamine, niacin, riboflavin, pantothenic acid, pyridoxine, and biotin in addition to vitamin C). Furthermore, unlike fruits and vegetables, which lose part of their vitamin content during harvest, storage, and preparation, honey loses these properties only when heated [51]. Table 33.4 shows the values of the mineral content of honey from the NSBs [52]. However, in the YP, Mexico, the nutrient content of NSB honeys has not yet been determined.

Conclusion

Currently, the human population uses antibiotics improperly, and microorganisms develop resistance to them. In addition, the use of antibiotics can sometimes produce various side effects, such as liver lesions, toxic action on hematopoietic organs, and allergic reactions such as dermatitis. In this sense, NSB honey contains different phytochemical compounds (phenolic acids and flavonoids) and with multiple biological activities (hydrogen peroxide) related to antioxidant, antiinflammatory, and antibacterial properties. For this reason the search for new natural treatments with antibacterial properties becomes necessary to reduce the use of antibiotics.

The knowledge of the nutraceutical and medicinal benefits of honey from NSBs is ancient in the Americas; in Mexico, indigenous groups such as the Mayans, Zapotecos, Mixes, and Zoques have used honey for its medicinal properties, mainly to treat diseases such as pharyngitis and eye infections. The antimicrobial action of honey from NSBs is

TABLE 33.4 Mineral content of honey of some native stingless bees.

Taxa	Ash (g/100 g)	Sodium (mg/kg)	Potassium (mg/kg)	Calcium (mg/kg)	Magnesium (mg/kg)	Iron (mg/kg)	Copper (mg/kg)	Zinc (mg/kg)
Melipona compressipes	0.09	63.6	299.8	55.0	20.0	4.8	1.2	10.8
Melipona favosa	0.01 ± 0.01	–	–	–	–	–	–	–
Melipona sp.	0.20 ± 0.01	67.7 ± 33.6	545.7 ± 138	150.3 ± 0.9	32.5 ± 1.8	3.3 ± 0.3	0.8 ± 0.4	6.7 ± 2.5
Nannotrigona sp.	0.33	154.5	961.2	117.0	4.7	49.6	1.9	14.9
Scaptotrigona limae	0.04	–	–	–	–	–	–	–
Tetragona sp.	0.06	–	188.3	51.5	37.4	15.1	0.6	19
Tetragonisca angustula	0.21 ± 0.70	155.0 ± 65.1	576.6 ± 177.6	199.6 ± 63.4	56.0 ± 27.5	5.8 ± 2.3	0.9 ± 0.3	19.6 ± 8.3

Based on Fuenmayor C, Díaz-Moreno C, Zuluaga-Domínguez C, Quicazán MC. Honey of Colombian stingless bees: nutritional characteristics and physicochemical quality indicators. In: Vit P, Pedro S, Roubik D, editors, Pot-honey. New York: Springer; 2013. p. 383–94.

to the result of the high osmolarity due to the effect of hydrogen peroxide, which is produced slowly and sustainably by the enzyme glucose oxidase.

Furthermore, in vitro assays with NSB honeys have shown that the chemical properties of phenolic acids and flavonoids play an important role in promoting bioactivities, being recommended for therapeutic use for the treatment of various diseases such as cancer and neurological disorders, to counteract aging, and to treat inflammation. Most studies still focus on evaluating *A. mellifera* honey, although it has been shown that NSB honey is highly effective for therapeutic uses.

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Section 9

New approaches in food development

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Chapter 34

Genetically modified organisms and foods: perspectives and challenges

Ram B. Singh[1], Sanjay Mishra[2], Prashant Saxena[3], Madhvi Saxena[4], Priya[5], Manal M.A. Smail[6] and Sudha R Velluri[7]

[1]Halberg Hospital and Research Center, Civil Lines, Moradabad, India, [2]School of Biotechnology, IFTM University, Moradabad, India, [3]Department of Biotechnology, KS Vira College of Engineering & Management, Bijnor, India, [4]University College of Engineering, Vinoba Bhave University, Hazaribhag, India, [5]All India Institute of Medical Sciences (AIIMS), New Delhi, India, [6]University of Central Lancashire, Preston, United Kingdom, [7]National University SanDiego, California, United States

Introduction

People have, over the centuries, custom-fitted the genomes of the two plants or animals to impart favorable properties. For most of our history this was done through simple experimentation with life forms that had desired characteristics. Cultivation was performed with the aim of developing and delivering novel plants and animals that would be advantageous to people, offering better value food, enabling individuals to move and transport items, allowing for more efficient agricultural work, providing protection from maladies, and so forth. However long its history, the creation of genetically modified life forms, also known as genetically modified organisms (GMO), is not without strife. From one viewpoint, complaints made by debaters of genetically modified animals concern the control of life itself. From another viewpoint, individuals contend that such alterations are on a very basic level an expansion of accepted plant development and animal-rearing procedures. There are also clashes with respect to the hazards to the welfare of the members of the plant and animal world, including humans, from utilizing genetically modified living beings, which have caused much discussion that has prompted progress on administrative regulation for the evaluation of genetically modified yields. Be that as it may, the lack of an all-around acknowledged stage has had the effect of hindering mechanical advancement, with negative outcomes for specific parts of the world that could profit from novel advances. Therefore while genetically modified yields can give most extreme preferences in sanitation and in adjusting harvests to open atmosphere variety, the lack of changes, like the insufficient harmonization of the structures and sets of laws regulating the genetic changes, brings about each one of those foreseen points of interest with regard to utilizing genetically modified harvests being suspended. In any case, it is clear that the development of genetically modified plants and animals will continue. Therefore it is important to discuss the impact of genetic modification on clinical advancements, horticultural creation, product costs, land use, and the environment. These hazards and perils are discussed in this chapter.

Probable risks of making use of genetically modified products

Basically, a gene is a section of DNA (an unmistakable arrangement of nucleotides framing some portion of a chromosome) that gives guidelines to amalgamation of a particular protein or a specific sort of RNA. These are required, for example, for creation of compounds for digestion in cells or for articulation of a specific attribute in the X chromosome. The use of genetic editing allows a genetic substance to be transferred from any species into plants or different living organisms. The expression of a trait into various cells can have varying results, and despite infections that need a host cell for their support and multiplication, the example of gene articulation can be changed by the presentation of a solitary gene. The arrangement of the gene and its function in the contributing organism may have a specific capacity in the living being from which it is disengaged. However, this "accuracy" in the understanding of a gene does not imply that the outcomes of the exchange are known or can be anticipated [1]. Duplicates of a gene might be incorporated,

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extra sections embedded, and gene groupings revised and erased, which may bring about the absence of the desired activity, or interaction with other genetic capacities perhaps causing some potential dangers [1]. In this way, there could be various unsurprising and capricious dangers identified with the arrival of GMOs beyond all detectable inhibition conditions. The report by the Law Center of the International Union for the Conservation of Nature (2004) lists various natural dangers that are prone to happen in the utilization of GMOs in the field. These significant dangers are discussed in the following sections.

Environmental risks

There is evidence that genetically modified plants appear to interconnect with their state [1,2]. During the last 40 years, investigations have attempted to establish a correlation between the natural tendency of evolving humans and its impact on individuals' welfare. To look at whether there is a connection requires investigation of its degree and any hidden components, integrating knowledge and methods from different disciplines. This overview begins by looking into discussions pertaining to humans' natural tendency associations, ultimately evaluating and reclassifying them from an integrating approach point of view. The concept as well as sequential background of well-being is then investigated in view of the World Health Organization's definition. Consolidating these ideas, the human instinct relationship and its effect on human well-being are then investigated through creation of a reasonable model. It is contended that utilizing an interdisciplinary point of view can encourage a more profound comprehension of the complexities required for achieving ideal well-being at the human-nature interface. This pertains to the question of how qualities brought into genetically modified plants might be moved to different plants or even to different organisms [3−5]. The capability of genetically modified plants to meet the necessities of developing populations is not as a rule adequately perceived at present. This is an outcome of concern raised by the general population and pundits about their applications and discharge into the earth. These include impact on human welfare and biosafety, world exchange imposing business models, dependability of open foundations, honesty of administrative offices, loss of individual decision-making ability, morality, and wariness about the genuine capability of the genetically modified plants. Such concerns are tremendous and predominant even today. Nonetheless, it ought to be recognized that most of them are not specific to genetically modified plants, and general society should not overlook that the conventionally raised plants that they eat may also pose comparable dangers. In addition, many of the worries are theoretical and need logical foundation. Genetic exchange between plants, explicitly among interconnected plants, can bring about genetic contamination through the spreading of pollen to associated plant species [6,7]. This possibility is a source of natural apprehension. Until there has been more research relating to the ecological effect of new genes on native yields, such apprehension along with administrative concerns suggest the need for quality control in future perspectives for GM crops. Certain other control systems may likewise be valuable in confining quality streams, together with vegetative and agamic seed arrangement, self-treatment without opening of the blossom, genome contrariness, compound acceptance and/or cancellation of transgenes, natural product explicit extraction of transgenes, and transgenic moderation. Hitherto, however, no system has been demonstrated to be extensively relevant to all harvest species, and a blend of approaches may be best for designing the up and coming varieties of GM crops [7]. Since conventional wild plant assortments presumably have much lower yields in comparison genetically modified plants, the conventional plants will be unable to endure, causing a decrease or vanishing of wild assortments [8,9]. Interestingly, biotechnology is providing us an ample scope of options for exploiting farming and business interests for the development of genetically modified crops on enormous tracts of land, and their coordination with the evolved pattern of human life appears to be a tremendous global genetic test covering all organisms, including humans. Thinking about the rapidness of novel advancements that are underway in regard to genetically modified harvests, buyers, farmers, and policymakers overall should work together to arrive at a concurrence that will enable the ultimate provision of food to all who need it around the globe. The current food technology debate outlines the authentic conflict between two scientific points of view: (1) that of agribiotechnology speculators and relevant subsidiary researchers thinking about agrarian biotechnology as a solution for food deficits, scarcity of natural resources, and weeds and pests that decrease crop and livestock yields and (2) independent researchers, environmental campaigners, farmers, and consumers who warn that genetically engineered food presents new hazards for food security, risks to environmental and human welfare (e.g., diminution of biodiversity, growth of super weeds and super pests, and development of food hypersensitivities), and further unintentional effects. This overview presents noteworthy perspectives that are currently being discussed, providing a platform for thoughtful debate on the merits and demerits of biotech harvests for human welfare, biosystems, and biodiversity. In this particular circumstance, although certain guidelines exist, it is mandatory that each country that is engaged in developing genetically modified food (GMF) carefully follow specific universal rational biosafety monitoring guidelines, accommodating trustworthy predischarge investigations and

postdischarge trail of GM plants to guarantee the welfare of humans and the environment and to maintain a tactical space to prevent ecological harm [9]. Changing biodiversity worldwide will prompt expansion of a few types of weeds, while others will diminish or vanish, hence producing total and common disorders in environments [10,11]. Farmland biodiversity is a significant concern in surveying the supportability of rural practices and is of significant universal concern. Logical information demonstrate that agrarian strengthening and pesticide application are among the principal pilots of natural heterogeneity disaster. It is preferably shown that the proper and safe application of herbicides leads to safe and healthy footprints on agronomical and horticultural practices [11]. It is an article of faith in logical circles that examination should be drawn out to survey the dangers and advantages of harvests more decisively as well as effectively.

Hazards to human well-being

Genetic modifications may have allergenic impacts—generally in people who are prone to allergies—or other undesirable effects on individuals' health [12]. Biotechnology offers a wide range of prospective advantages as well as hazards. It has improved food production by making plants less susceptible to drought, cold, insects, and viruses and by enabling plants to compete more efficiently against weeds for soil nutrients. In a small number of cases, it has also enhanced the quality as well as nutrition of foods by changing their composition. Nevertheless, the utilization of biotechnology has also led to concerns about probable hazards to the environment and to human beings. For example, some people fear that general plant pests could build up resistance to the introduced pesticides in GM crops, which were thought to fight against them. Genetic engineering provides a way to introduce genes into plants through mechanisms that are different in some respects from classical breeding. A variety of commercialized, genetically engineered varieties, most remarkably cotton, canola, soybeans, and maize, were produced by means of this technology, and currently the traits introduced are herbicide and/or pest tolerance. Gene technology enables increased production in plants as well as the rise of resistance to pests, viruses, and frost. Gene transfer is used to modify the physical and chemical composition and nutritional value of food [12].

Genetic exchange in animals will have an influence in the prospects of improving subjective and quantitative attributes. Crop yields, meat qualities, nutritional content, and protection from ailments in animals can be improved. On the other hand, possible negative impacts of quality innovation on animals, human, and conditions ought to be considered. A diagram showing different examinations that present both positive and negative effects of GMF on human well-being is given in Mishna and Singh [12]. Trial concentrates in animals have demonstrated weight gain, changes in the pancreas and kidneys, poisonous impacts on the immune system, and changes in blood chemistry among different impacts [13,14]. The absence of large-scale, long-term epidemiological studies, which lead to safe decisions about the allergenic impacts of genetically modified plants, means that analysts can only speculate about the effects of utilization of genetically modified items. For example, genetic modification might involve a gene that communicates a nonallergenic protein even though the intention was not to deliver an item without allergenic activity. Also, sensitivities from genetically modified items might be increasingly extraordinary and risky, as the allergenic capability of these nourishments is more grounded than that of customary plants [15,16].

Resistance to antibiotics

It ought to be noted from the earliest starting point that the utilization of antitoxin safe qualities has halted in most transformed items. The primary issue currently lies in the across-the-board utilization of antibiotics in feed, which inevitably end up in the human body through ingestion of dairy items and meat and eventually make safe germs in the human digestive system [17,18]. Because of the expanded interest in animal protein in developing nations, cultivation is increased, which brings about the buildup of antibiotics in animal products and subsequent antimicrobial resistance. Antimicrobial resistance is of vital concern in light of the fact that the resistant microorganisms that develop in animals might be pathogenic to people and can easily be transmitted to people by means of natural ways of life and broadly dispersed in the earth through animal wastes [17,18]. These may cause muddled, untreatable, and delayed contaminations in people, prompting higher social insurance costs and decreased well-being. In some nations, antimicrobial resistance is so extensive and troublesome because of unreasonable use of antibiotics in both clinical and agribusiness settings, low financial status, and poor sanitation and sterile status. In addition, zoonotic bacterial pathogens are not routinely refined, and their protection from regularly utilized antiinfection agents have barely been examined [18]. The difficulties that follow are of local, national, regional, and global concern, as there are no geographic limits to obstruct the spread of antimicrobial resistance. Furthermore, the data amassed in this investigation through an intensive organized

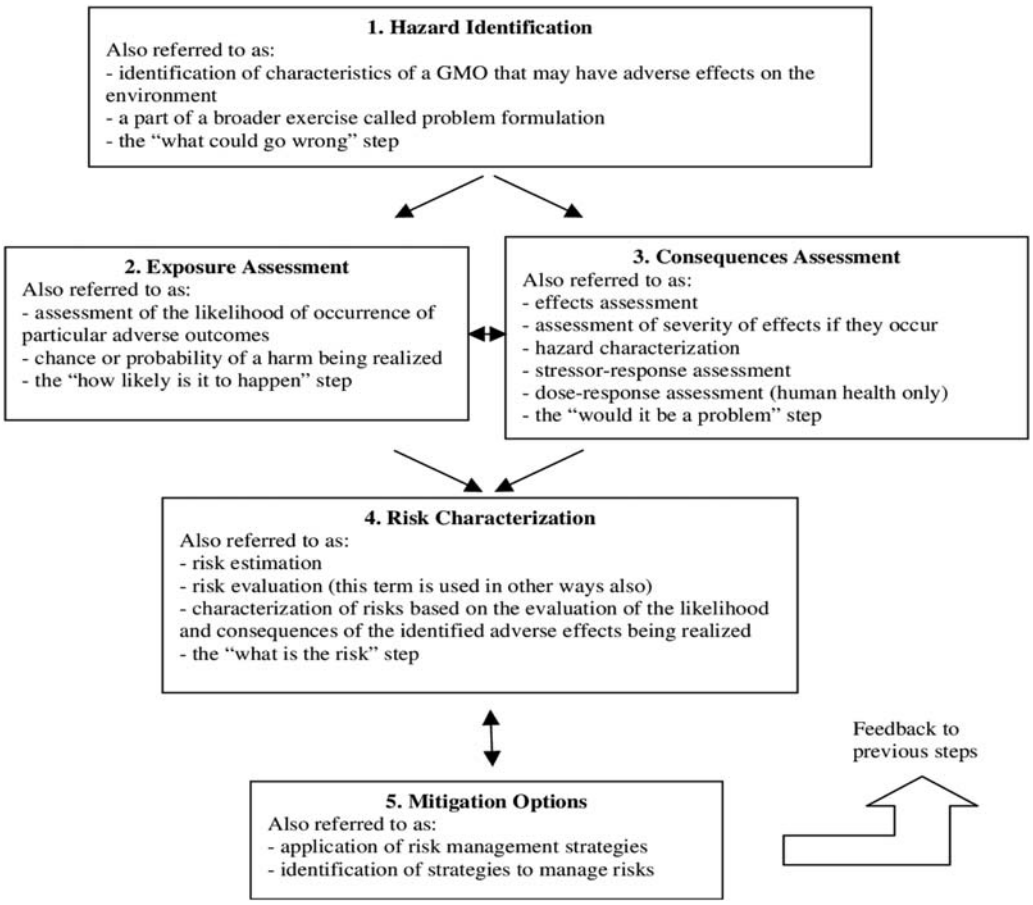


FIGURE 34.1 The top-down approach for designing the risk assessment process in genetically modified organisms. *https://www.semanticscholar.org/paper/Conceptualizing-risk-assessment-methodology-for-Hill/82f8005c3f6787b669ab3ba9efe7998ced4365aa/figure/0*.

survey of distributed discoveries underlined the prevalence of antibiotics in animal products and the amount of multi-drug resistance in natural examples. This underlines the need to reinforce the guidelines for antimicrobial production, dispersion, administration, and solution and encourage antimicrobial stewardship. A joint coordinated effort around the world led by global organizations is expected to help the developing nations to actualize great observation of antibiotics use and drug resistance [18]. All things considered, more research and studies are required to determine the qualifications between transgenic plants from customary plants and whether genetically modified plants present extra dangers to the consumer [19,20] (Fig. 34.1).

Benefits of using genetically modified products

Appetite elimination

One of the arguments set out by supporters of genetically modified products is that they can solve the problem of hunger in the world, a statement that has elicited different responses [21–23]. The business capability of biotechnology is huge, since the extent of its action covers the whole range of human life. The most powerful biotechnological approach is the exchange of explicitly developed genetic material through different procedures [23]. Nonetheless, this intentional modification of genetic material and the resulting substances have become a bone of contention everywhere throughout the world. Advantages aside, GMOs have consistently been viewed as a danger to human and environmental well-being. Taking this into account, biosafety controllers in various nations have seen it as vital to test the attainability of GMOs in contained and controlled conditions for any potential dangers they may present. Genetically improved micro-organisms are able to reproduce and establish themselves as persistent populations and may have subtle and long-term effects on biological communities and natural ecosystems. Results of DNA modification may not be limited only to the

particular characteristics of the replaced gene. It is therefore important to ensure that when these organisms are released into nature they do not harm the environment or human health. Such concerns have led to broader interests in the theme of risk assessment in the release of GMOs. A cautious approach is necessary to assess environmental risks which may occur due to introduction of recombinant organisms in the natural environment. Prakash et al. depict the different types of hazard, their appraisal, and the board, which are basic in dynamic with respect to the protected utilization of GMOs [23]. Proficient endeavors are fundamental for usage of guidelines. The significance of the hazard appraisal, the executives, and preparatory methodology in ecological understanding and activism are likewise discussed [23]. A progression of broad and long-term research has demonstrated that the advantages of developing genetically modified yields in the battle against worldwide food deficiencies and appetite are paramount. The consistent growth in the worldwide population has driven analysts to concentrate on the upsides of growing genetically modified plants and animals, in contrast to the potential dangers they present [24,25]. Furthermore, biofortification through plant cultivation is a feasible way to improve nutritive value of food crops. The majority of people rely on staple food crops, most of which are low in key micronutrients. Biofortification to improve the nutritional profile of basic crops has expanded significance in many agricultural programs in the previous decade [25]. The key micronutrients of focus have been iron, zinc, selenium, iodine, carotenoids, and folates. Lately, a few biofortified bean crops, including regular beans and lentils, have been discharged by HarvestPlus with worldwide accomplices in developing nations, which has helped in defeating micronutrient insufficiency in the populations of these countries. As of late, a diagram has concentrated on recent research advances and future systems for the biofortification of basic crops [25].

The data shown in Table 34.1 represent the contributions of engineered agriculture. The contribution in these field is increasing every year. The United States accounts for approximately 68% of total GM crops, followed by other countries. The amounts of the crops are continuously increasing, and it was found that pest resistance is the main benefit of the GMO.

Economic benefits

Genetic modification of plants was first recorded 10,000 years ago in Southwest Asia, where people originally reproduced plants through artificial selection and selective breeding. From that point forward, progressions in farming science and innovation have led to the present GM crop insurgency. GM crops are promising to moderate current and future issues in business farming, with demonstrated contextual analyses in Indian cotton and Australian canola. However, dubious examinations of current issues connected to antimicrobial resistance and potential dangers well-being to well have imperiled acceptance of GMO by the general population and policymakers, prompting full and partial bans in some nations. By the by, the ebb and flow in development pace of the GM seed, currently at 9.83%−10% compound annual growth rate, alongside promising exploration roads in biofortification, exact DNA coordination, and stress resilience show that GM yields can lead to efficiency and success to business farming [26−28]. Various investigations have shown the monetary advantages of utilizing genetically modified products. From 1996 to 2011, farmers' overall income increased by $92 million as a result of the utilization of genetically modified harvests. Some portion of the income is because of the more effective treatment of weeds and bugs, while another explanation is a direct result of lower development costs. The most extreme monetary advantages have been accomplished in the United States, Argentina, China and India. Meanwhile, development costs have fallen sharply [26]. However, there are also opposing reports [27,28].

Insect resistance

Bacillus thuringiensis (BT) is a gram-positive, soil-dwelling bacterium that is used as a biological pesticide. During sporulation, many BT strains give rise to crystal proteins (proteinaceous inclusions), called delta-endotoxins, which have insecticidal action. This has led to their application as insecticides and, more recently, to genetically modified crops employing BT genes, such as BT corn. The principal use of these plants is to fight against the European corn borer, an insect that is responsible for the destruction of maize crops, with a loss of up to one billion dollars a year [27].

Nematode resistance

Parasitic nematodes are responsible for a great part of the crop yield failures. Root-tie nematodes are infinitesimal roundworms that assault various plants by pulverizing the root framework. Nematodes, which are basically a worm animal group, can live in soil in exceptionally troublesome conditions for a long time. Their assaults influence the

TABLE 34.1 The impact of genetic modified crops as a tool for matching with the required demand of food for hunger removal and their impacts on the crop.

Nation	1996	1997	%	1998	%	1999	%	2000	%	2001	%	2002	%
By nation													
United States	1.5	8.1	+440.0	20.5	+153.0	28.7	+40.0	30.3	+5.6	35.7	+17.8	39.0	+9.2
Argentina	0.1	1.4	+1300.0	4.3	+207.0	6.7	+56.0	10.0	+49.0	11.8	+18.0	13.5	+14.4
Canada	0.1	1.3	+1200.0	2.8	+115.0	4.0	+43.0	3.0	−25.0	3.2	+6.7	3.5	+9.4
China	0	<0.1		<0.1		03	+200.0	0.5	+67.0	1.5	+200.0	2.1	+I40.0
South Africa	0	<0.1		<0.1		0.1		0.2	+100.	0.2	0	0.3	+50.0
Australia	0	<0.1		0.1		0.1	0	0.2	+100.0	0.2	0	0.3	+50.0
World	1.7	11.0	+547.0	27.8	+153.0	39.9	+43.0	44.2	+10.7	52.6	+19.0	58.7	+11.6
By crop													
Soybean	0.9	5.1	+467.0	14.5	+184.0	21.6	+49.0	25.8	+19.4	33.3	+29.0	36.5	+9.6
Maize	0.6	3.2	+433.0	8.3	+159.0	11.1	+34.0	10.3	−7.2	9.8	−4.8	12.4	+26.6
Cotton	0.1	1.4	+1300.0	2.5	+79.0	3.7	+48.0	5.3	+43.0	6.8	+28.0	6.8	0
Canola	0.1	1.2	+1100.0	2.4	+100.0	3.4	+42.0	2.8	−17.6	2.7	−3.6	3.0	+11.0
World	1.7	11.0	+547.0	27.8	+153.0	39.9	+43.0	44.2	+10.7	52.6	+19.0	58.7	+11.6

Data presented in million hectares with the annual percent increase by nation and crop (Instituto Nazionale di Ricerca per gli Alimenti e la Nutrizion elaboration from Integrated Science Assessment Model statistics).
https://www.researchgate.net/publication/8645151_Transgenic_Foods_as_a_Tool_for_Malnutrition_Elimination_and_Their_Impact_on_Agricultural_Systems.

efficiency of crop cultivation by diminishing the sum and the bore of the organic products. Compound control is generally utilized against nematodes, but it is restricted in light of the fact that there is a high ecological hazard [29]. Organic control seems, by all accounts, to be a superior arrangement, chiefly utilizing microorganisms to diminish the amount of pests contaminating yields. Organic control methods are growing step by step, and with time, more items are being promoted around the world. They can involve microscopic organisms, infections, or filamentous growths, which can crush and feed on phytoparasitic nematodes. To be utilized by farmers, biopesticides must be legitimized by national and local authorities, which has prompted the foundation of a lawful structure for their utilization, contrived by different legislative associations [30]. The main normal approach to manage this is through yield revolution (the act of growing a progression of disparate or various sorts of harvests in a similar region in sequenced seasons), yet this is often impractical because of the high monetary expense [29,30]. Therefore modification with genes from nematode-safe plants is by all accounts the best way to manage the issue [31].

Resistance to herbicides

The use of herbicides and pesticides has been shown to cause major problems for the environment and therefore for human well-being. In zones where wheat is developed, that is, the places where the utilization of herbicides has expanded, crop productivity is diminishing, and children are born with serious medical issues, mainly identified with mental hindrance and chemical imbalances [32]. A review incorporates the physiological and yield limitations of herbicide applications with unique reference to wheat profitability. The 20th century inability of Indian agribusiness to feed all of the country's population prompted the random utilization of concoction pesticides, which decayed the profitability payoff explicitly of wheat and rice. The previous scarcely any decades have seen the potential use of specific phytohormones in enlarging abiotic worry to dispose of yield hole and efficiency limitations [33]. Genetically modified products empower farmers to utilize smaller amounts of herbicides. For example, the herbicide Roundup contains glyphosate, which demolishes the activity of a plant catalyst, thus destroying the plant. Plants can be genetically modified to produce a glyphosate-resistant variant of this catalyst, empowering the plant to be safe and not influenced by the activity of the herbicide [34–36]. Cases have recently been made that glyphosate-safe (GR) crops sometimes have mineral inadequacies and increased plant diseases [37]. The results of a survey assessing these cases determined that (1) despite the fact that there are conflicting reports on the impacts of glyphosate on mineral contents in GR crops, most of the report shows that mineral contents in GR crops are not influenced by either the GR quality or the use of glyphosate; (2) a large portion of the accessible information bolsters the view that neither the GR transgenes nor glyphosate use in GR crops increase plant diseases; and (3) yield information on GR crops do not bolster the speculations that there are considerable mineral content or plant disease issues that are explicit to GR crops [37]. Scientists conflict in their estimation of the effects on human and animal well-being [38].

Cold resistance

A huge benefit of genetically modified plants is the development of varieties that are impervious to cold temperatures that would ordinarily cause the plants to freeze, ruining the plant and causing crop losses. Since the mid-2010s, because of rapid worldwide climate change, plants cannot adjust to new temperature varieties, and researchers have changed their attitude toward transgenic plants to address this issue [39].

Heat resistance

Sooner rather than later, according to climate researchers, worldwide temperature alterations are likely to lead to hotter temperatures. This will have lead to problems in agriculture, particularly in territories where water shortages are already happening. Alterations in certain genes (Sh2 and Bt2) can help plants to withstand high temperatures [40,41] (Fig. 34.2).

Basic concepts related to genetically modified products

The notion of substantial equivalence

The idea of substantial equivalence has been presented in discussions of genetically modified products to guarantee that their nutritional contents are protected [37]. Genetic modification is an innovative arrangement of genes that adjusts the genetic sequences of animals, plants, or microorganisms. Combining genes from various life forms is known as



FIGURE 34.2 Genetic modification in crops. (A) The genetic modifications in the rice crop make it more resistant to insects and other pests. (B) The genetic modification in the plant tissue culture shows the stable growth and ability to fight against the pests. *https://gillingsproject.files.wordpress.com/2012/05/golden-rice.jpg*.

recombinant DNA technology, and the subsequent organism is said to be "genetically modified," "genetically designed," or "transgenic" [37]. The main transgenic crops in terms of economics are herbicide- and pesticide-resistant soybeans, corn, cotton, and canola. Additional crops that have been developed field-tested are yams that are impervious to an infection that could devastate the vast majority of the African crop, rice with expanded iron and nutrients that may reduce chronic disease in Asian nations, and an assortment of plants that can endure more extreme climates [37]. There are also bananas that produce human antibodies against irresistible infections such as hepatitis B, fish that develop especially rapidly, foods grown from ground trees that yield produce years sooner than their conventional ancestors, and plants that produce new plastics with unique properties. Advances in genetically modifying nutrient levels in plants offer hope for solving of most prominent problems facing populations in the 21st century. Like every new innovation, genetically modified crops pose some dangers, both known and unknown. Debates and questions about the nutrient contents and yields of genetically modified plants ordinarily center on human and environmental well-being, labeling and customer choice, protected innovation rights, morals, food security, decreased poverty, and ecological preservation. With these new technological innovations, what are the dangers of "altering Mother Nature?" What impacts will this have on the earth? What are the concerns about well-being that consumers ought to know about? Is recombinant DNA innovation sufficiently helpful? A substantial equivalence audit addresses some significant worries about the safety, natural and environmental dangers, and well-being risks involved in GM nutrients and recombinant innovation [42]. The rule of substantial equivalence holds that if the toxicology and nutrition contents of a genetically modified item are generally comparable to those of its conventional counterpart, no further well-being rules are necessary. Along these lines, the standard of genetic identicalness is a device for assessing whether genetically modified products have negative elements, such as allergens because of the nearness of new proteins [37,41,43]

The precautionary principle

As indicated by the precautionary principle, any novel genetically modified item ought not be made accessible to consumers unless there is direct proof that the item is safe or there are no conflicting assessments among analysts of the safety of the item in question [44,45]. One of the requirements for delivering food security is to build the acceptance of biotechnology by farmers through the utilization of logical advances, for example, GMOs and GMF. Be that as it may, the spread of information and misinformation about their safety reinforces the demands for obligatory GMF labeling [45]. An important review of food-naming strategies has considered the standards recommended by the Codex Alimentarius Commission and investigated the ramifications for the world food security of the Brazilian labeling arrangements contrasted with those of developed nations [45]. It likewise discusses the unfair use of obligatory labeling of GMF without any logical proof that the food can cause social damage and interferes with research, creation, and appropriation of food and consumers' entitlement to data [45]. Certain specialists nonetheless have contended that the precautionary principle can act as a disincentive to the development of science and society, as it might stop or defer any novel innovation that could be useful for tackling natural or financial issues [46]. It is clear, in any case, that questions have been raised about the usefulness of the precautionary principle and the way in which it works [47].

The safeguard clause

The safeguard clause licenses member states of the European Union to refuse to import genetically modified products that are liable to be unsafe to its residents [48,49]. GMOs have been available since the 1990s, permitting developers to increase crop yields through bioengineering that makes herbicide-resistant and pest-resistant plant varieties. However,

consumer information about GMOs has not expanded at a similar rate [49]. Shoppers overall are showing misunderstanding, confusion, and even resistance to GMO food items. Numerous consumers report that they get data about GMO food items from the media, the Internet, and different news sources. These sources might provide less solid information than specialists who can provide more trustworthy and science-based data [48]. Although there is pressure in the United States for obligatory GMO labeling (like current European norms), customer attention to current GMO labeling is low. Differentiation should likewise be made between GMO nature and logical comprehension, on the grounds that the individuals who are increasingly acquainted with it will in general be progressively impervious to bioengineering, though those with higher logical information scores will in general have more positive perspectives toward GMOs [49]. It is important to scrutinize the connection between logical education, sources of data, and general customer information on GMO food products.

The Cartagena Protocol

The aim of the Cartagena Protocol on Biosafety to the Convention on Biological Diversity is to monitor the world's biodiversity by providing thorough guidelines on the safe handling and transport of genetically modified products between nations [23,50].

Marking of genetically modified products

The presence of genetically modified products has prompted the prerequisite for labeling these items [49,51]. GMF products ought to have a particular mark to indicate that they contain genetically modified components. However, as straightforward as it sounds, the issue of naming genetically modified products is especially unpredictable and troublesome, as there are huge questions about how the labeling should be done [9,52]. For instance, it has been contended that items containing either modified protein or transgenic DNA should bear a special mark. However, there are genetically modified products that do not contain modified protein or transgenic DNA. There is the discussion as to whether these products need special labeling or not. [5,9,37] (Table 34.2).

Moral concerns

The focal moral issue raised by the development of genetically modified plants is that the age of these yields is on a very basic level an obstruction to the regular progression of life [23,53]. GM plants have attracted a lot of media attention [54]. In spite of this, the overall population remains to a great extent ignorant of what a GM plant really is or what

TABLE 34.2 Procedure of labeling the product and their description manufactured using the GMO concept, currently conceptualized in Brazil.

Legislation	Requirements
Decree no. 4.680/2003	Both industrialized and natural foodstuffs that contain more than 1% of GMOs should be labeled. The label must include the name of the gene donor species. If a food is animal material and the animal was fed GMO feed, it must also be labeled.
Ordinance no. 2,658/2003	Prescribes the use of the letter "T" in the center of a yellow triangle with a black outline as a GM symbol in the label.
Interministerial Normative Instruction no. 1/2004	Establishes the Technical Regulation on Food Labeling and Food Ingredients that contain or are produced from GMOs.
Law no. 11,105/2005 (also known as Biosafety Law)	States that information about the GM nature must be included on the label of foods and food ingredients intended for human or animal consumption but does not specify how this should be done.
Decree no. 5.591/2005	Regulates the Biosafety Law, does not specify GMO labeling procedures. and merely reproduces the text of the law (Article 91).
Decree no. 6.041/2007	Establishes a Biotechnology Development Policy and creates the National Biotechnology Committee. One of the guidelines of the policy is the creation of regulation of conformity assessment, including labeling.

https://www.frontiersin.org/articles/10.3389/fbioe.2018.00181/full.

favorable circumstances and burdens the innovation brings to the table, especially as to the scope of uses for which these plants can be utilized. As the development of GM crops has progressed, two principle regions of concern have risen: hazard to nature and hazard to human well-being. As GM plants are steadily being brought into the European Union, there is probably going to be expanding concern with respect to potential medical problems. In spite of the fact that it is common for the media to embrace "well-being efforts," the data they distribute are regularly sensational and unrepresentative of the accessible logical information on these matters. It is important for physicians to have up-to-date information, as they are frequently the first source a concerned patient will consult and they are in a situation to give educated advice [54]. The moral difficulty shows up in terms of how to locate the center ground in the utilization of genetically modified products, given that various nations have various impression of the extent of hazard, with numerous nations prohibiting the utilization of genetically modified products, while organizations delivering these items focus on benefits and do not consider the issues that might emerge. The issue here spotlights the high level of confusion about the effects of utilizing GMOs, which often involve financial and political interests [37,55]. Shoppers' disposition is of particular significance, as they are buying and paying for their vote of endorsement simultaneously. Shoppers may be divided into two classes: those who favor GMOs and those who want to restrict them. Purchasers' perspectives are affected by the data they are offered, the current guidelines, the confidence they have in the government to manage the issues that emerge, and what they are willing and able to pay [37,55].

Morals and the environment

Natural morals have a vital place in conversations about biotechnology and genetic engineering. Many of the proposals that have been introduced against genetic modification have to do with whether it is ethically acceptable to genetically modify living beings and the earth, as this may have genuine ecological effects. This concern is clear even in commercials for products, in which organizations state that natural insurance is a need for them [56,57].

Ethics and intellectual property rights

Particularly regarding animals, present-day moral thinkers tend to hold that animals, like people, have rights and that these rights ought not be abused [9,58]. Animals should be treated as living life forms and not as objects. Genetic modification and testing of animals can prompt intense changes in the physiology and conduct of the animal. The outcomes may not be attractive, and at times, they may even be deplorable [59].

Patenting genetically modified organisms

The production of new life forms definitely prompts the need to patent them and designate their possession. Yet even in patenting a novel item, the proprietor of the new animal must guarantee that the genetic modification does not have unfortunate effects on the earth and people, as the proprietor will be liable for any issues that may emerge [60,61]. Further, it is a key purpose of issue that people have consistently changed the genome of the two plants and animals [62]. This obtrusive procedure, which has existed for a great many years, ordinarily through missteps and disappointments, was initially helped out through the intersection of life forms with attractive qualities [63]. This was done with the goal of making and delivering new plants and animals that would profit people, that is, they would offer better-quality food, more opportunities for individuals to move and transport items, better return on investment, protection from infections, and so forth. However, making GMOs does not come without conflict. One such clash concerns protests made by disputants of GMOs to the control of life, whereas proponents contend that genetic modification is basically an augmentation of customary plant development and animal-rearing procedures. There are additionally conflicts with respect to the dangers to the earth and human well-being from utilizing GMOs [28]. Worries about the dangers to nature and human well-being from genetically modified products have been the subject of much discussion, which has prompted the advancement of administrative systems for the assessment of genetically modified yields. In any case, the lack of an all-inclusive acknowledged structure has the impact of hindering mechanical advancement with negative ramifications for parts of the world that could profit by new innovations [28,64]. Along these lines, while genetically modified harvests can give provide benefits in sanitation and in adjusting yields to existing environmental change, the absence of information and the lack of modification of the structure and guidelines about the advantages of utilizing genetically modified yields in these situations, have led to suspension of GM crops in some case. However, it is clearly that the development of genetically modified products will not stop [28,64]. For that reason, examine because of genetic

TABLE 34.3 Comparative analysis of agriculture biotechnology inventions and their patent protection.

Inventions	Brazil legislation	U.S. legislation	European Union legislation
Process to obtain a transgenic plant	Industrial Property Law (Law no. 9.279/96)	Title 35 U.S. Code (Utility Patent)	Directive 98 44 hC[a]
Transgenic plants	Plant Variety Protection Law (Law no. 9.456/97)	Title 35 U.S. Code (Utility Patent)	Directive 98/44/fcC[b]
Plant variety sexually reproduced	Plant Variety Protection Law (Law no. 9.456/97)	Title 7 U.S. Code (Plant Variety Protection Act)	Community Plant Variety Right—CVPR
Plant variety asexually reproduced	Plant Variety Protection Law (Law no. 9.456/97)	Title 35 U.S. Code (Chapter 15, Plant Protection Act)	Community Plant Variety Right—CVPR

[a]*Besides the Directive 98/44/EC, the European Union has the European Patent Convention and Implementing Regulation to enforce patent protection.*
[b]*"2 Inventions that concern plants or animals shall be patentable if the technical feasibility of the invention is not confined to a particular plant or animal variety." [Article 4(2) of Directive 98/44/EC].*
https://www.scielo.br/img/revistas/aabc/v83n2/a29tab02.jpg.

adjustment on clinical advancements, agrarian creation, item costs, land use and on the earth when all is said and done, ought to subsequently carry on in future also [65] (Table 34.3).

Conclusion

As of late, there has been broad innovative progress in the production of GMOs. There is no uncertainty that later on there will be a continuum that will be affected by both logical turns of events and open perspectives toward GMOs. Making GMOs, in any case, does not continue without controversy. There are the disputants of GMOs who consider them to be a control of life, and there are clashes in regards to the dangers to nature and human well-being. All things being equal, clearly the advancement of genetically modified harvests will not stop. Research on the effect of genetically modified harvests on agrarian development, ware costs, land use, and the earth by and large ought to proceed along these lines. Also, it is important to provide buyers with information that will enable them to comprehend the purpose of present-day innovation in crops and rural creation and particularly to comprehend the noteworthiness of genetic changes. There should also be unyielding and enforceable standards for the utilization of GMOs, an assessment of the potential dangers of genetically modified harvests, and justifiable references explaining the effects and consequences of genetic alterations on the earth and on human well-being.

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Section 10

Nutrition, NCDS and brain dysfunction

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Chapter 35

Circadian disruption and metabolic disease risk

Germaine Cornélissen
Halberg Chronobiology Center, University of Minnesota, Minneapolis, MN, United States

Introduction

As was recently reviewed elsewhere [1], the widespread manifestation of circadian rhythms and the critical difference they can make in terms of screening, diagnosis, and treatment [2] can no longer be ignored. Time-restricted feeding in the singly-housed mouse model results in life or death depending on whether food was accessible during the usual active span or the usual rest span [3]. In humans a single daily meal is associated with weight loss when it is consumed as breakfast but not when it is consumed as dinner, whether the meal contains a fixed 2000 Kcal or is free-choice [4]. These results published over 40 years ago indicate that meal timing matters [5]. Many studies by different investigators have largely confirmed the critical importance of meal timing in relation to the metabolic syndrome [6–9]. Reports that earlier meal timing is associated with improved effectiveness of weight loss therapy in overweight and obese patients [10,11] support Halberg's first documentation that meal timing may serve as an effective clinical intervention.

Circadian rhythms are orchestrated by the suprachiasmatic nuclei (SCN), which are synchronized by light [12]. Clock genes are present in almost every cell [13]. Peripheral organs, notably those related to metabolism, can also be synchronized by the feeding schedule [14]. Food intake can thus become an important aspect of circadian rhythms and the role they play in relation to metabolism. Time-restricted feeding was shown by Halberg to override the otherwise dominant lighting schedule in relation to the adrenocortical cycle [15]. The finding that under conditions of relative starvation the gut can override the hypothalamus was later extended to circadian aspects of the liver, lung, and pancreas [16,17].

While focus herein lies on the consequences of circadian disruption, the independent effect of caloric restriction per se should be noted. Not only do laboratory rats live longer, they also have fewer age-associated diseases when food intake is restricted, an observation dating back to the 1930s [18]. Caloric restriction has consistently been shown to prolong life in several animal models [19]. Another important observation is the persistence of circadian rhythms during starvation, the extreme form of caloric restriction. Already in 1843, Chossat reported a day-night difference in the cloacal temperature of pigeons [20]. The difference, which persisted in the absence of food and water for well over a week, increased until death from starvation and dehydration [5]. Forsgren [21,22] and Ågren et al. [23] later extended to mammalian liver glycogen the finding that circadian variation persists under conditions of food and water deprivation.

Internal circadian desynchronization resulting from competing synchronizers

In addition to spontaneous circadian rhythms characterizing most physiological variables in most organisms, the response of these organisms to a given intervention also changes predictably in a circadian-rhythmic fashion. The response to time-restricted feeding depends on when during the circadian cycle food is made available. The large difference in outcome seen in the singly-housed mouse model [3] stems from the fact that the two major synchronizers of circadian rhythms, the lighting regimen and the feeding schedule, compete with each other, thereby bringing about internal circadian desynchronization when the two synchronizers are not aligned.

Halberg showed that the timing of daily meals affects the timing of circadian hormonal and other rhythms. The circadian variation in both liver glycogen and plasma free fatty acids is almost completely reversed between rats fed ad

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libitum and rats fed a single daily meal (during the first 4 hours of the light span) [24]. In mice, manipulating the time when access to food is available can change the phase of certain circadian rhythms, as has been demonstrated for blood eosinophil counts [25–27]. The phase of circadian rhythms in murine core temperature, liver glycogen, serum corticosterone, and corneal mitoses differs when animals are fed only in early dark or only in early light [28]. The extent of phase shift brought about by time-restricted feeding depends on both the timing of food availability and the physiological variable being examined. While the circadian phase of the mitotic index of corneal epithelium, which is primarily synchronized by the lighting regimen, is only slightly affected by time-restricted feeding [29], much larger phase shifts affect variables such as liver enzymes [30–33], murine body temperature [34], murine corticosteroid and liver glycogen [35,36], eosinophil counts [37,38], and CO_2 emission in rats [39]. In nonhuman primates the circadian rhythm in plasma triglycerides is shifted by about 7 hours when a single meal is offered either in early light or 9.5 hours later, while the shift in skin temperature was less than 4 hours [40–42]. In humans, some circadian rhythms, such as cortisol, change their phase only slightly, while others, such as insulin, glucagon, and growth hormone, undergo larger phase shifts in response to a change from breakfast-only to dinner-only [43].

This body of evidence suggests that the internal constellation of phase relations among the various physiological functions matters and that meal timing can be used to optimize health. This conclusion is supported by more recent studies that have associated disruptions of the circadian system to a host of undesired conditions, including obesity, type 2 diabetes, hyperlipidemia, and high blood pressure [44–48].

Circadian rhythm amplification by caloric restriction and time-restricted feeding

Halberg's experiments documented that food restriction amplified the circadian rhythm of blood eosinophil counts in addition to lowering them in mice [15]. The circadian amplitude of rectal temperature, corticosterone, and liver glycogen was larger when food intake was restricted to a single daily "meal," compared to ad libitum feeding [49,50]. Life span was prolonged and the incidence of mammary tumors was decreased in mice that were kept on a caloric-restricted diet all their lives [50]. Factors that are thought to contribute to these beneficial effects of food restriction are a lower body temperature, a reduced overall metabolic rate, and an increased circadian amplitude [50].

The amplification of the circadian rhythm of variables such as body temperature, corticosterone, and liver glycogen brought about by caloric restriction and time-restricted feeding, which are associated with a healthier life and longer survival, illustrates the critical importance of a robust circadian system. The feeding schedule may more readily synchronize organs such as the liver, muscles, fat tissue, beta cells, and gut, all of which are involved in glucose metabolism [1]. Appropriately resetting peripheral rhythms could constitute an important mediator of longevity in calorie-restricted animals [51]. It has also been reported that caloric restriction may synchronize the circadian system in the SCN [52].

The circadian stage at which food is offered in studies of time-restricted feeding is important. This is illustrated in a rat model of shift work examining the after-effects of 4 weeks of time-restricted feeding either during the light (rest) or dark (active) span [53]. These feeding patterns are respectively misaligned or aligned with the light-synchronized circadian system and have been associated with poor versus good health outcomes, respectively. While dark-fed animals showed enhanced circadian variation in food intake, activity, and respiratory exchange ratio, light-fed animals displayed smaller circadian excursions in these variables and in body temperature. Effects on gene expression were both tissue- and gene-dependent [53].

Eating late at night is recognized as one of the factors contributing to circadian disruption, which is associated with a damping of the circadian system. For instance, in women with night eating syndrome, amplitudes of the circadian rhythms of food intake, cortisol, ghrelin, and insulin were reduced [54]. The circadian amplitude of leptin in obese women was smaller when they were on the same weight-maintaining diet proportioned into eight day and night equal portions as compared to three equal portions [55]. Retrospective analyses of human nutrition data and studies in animal models have shown that increased late-night eating or reduced length of overnight fasting increases the risk for metabolic diseases, including obesity and diabetes [56]. Inappropriate eating habits, such as skipping breakfast and/or eating late at night, are associated with a higher risk for abnormal weight gain and adiposity [57]. Eating behavior and circadian rhythm thus prove to be important factors in the etiology of metabolic diseases. It should be noted, however, that the global concern with the rising prevalence of metabolic dysfunction also identifies other risk factors, such as insomnia, a depressed mood, and distress, in addition to late-night eating and that the circadian system also plays an important role in relation to sleep and a depressed mood.

At the molecular level, late-night eating was found to bring about an overall 4-hour delay in the phases of key clock genes in addition to an increase in body weight (associated with decreased physical activity), hepatic

lipid accumulation, and systemic inflammation in peripheral tissues [58]. A significant alteration in the compositions and functions of gut microbiota was also noted in this study, contributing further to the development of metabolic disorder. Mice that were fed during the light (rest) span showed physiological changes, such as muscle loss, concomitant with changes in the gut microbiota structure and composition [59]. By contrast, mice that were fed during the dark (active) span displayed lasting changes in fat accumulation, glucose metabolism, intestinal barrier function, and systemic inflammatory markers as well as potentially beneficial structural shifts in the gut microbiota [59]. Time-restricted feeding is thought to confer protection against nutritional challenges that predispose individuals to obesity and metabolic risks through involvement of circadian locomotor output cycles protein kaput genes and gut microbiome [60]. A study comparing healthy men who practiced or did not practice time-restricted eating found that time-restricted eating ameliorated the serum lipid and liver profiles of the individuals and enhanced gut microbial richness [60]. Activation of sirtuin-1, which was positively associated with gut microbiome richness, may have been responsible for enhanced circadian gene expression related to time-restricted eating [60].

A word of caution is warranted. Caloric restriction, intermittent fasting, and time-restricted eating may be attractive lifestyle modifications that are conducive to health promotion, but their implementation is best undertaken for preventive purposes or undertaken under medical supervision. There are cases in which time-restricted eating may not be recommended. For instance, it has been noted that omitting late-night eating may cause hypoglycemia in basal-insulin-treated patients with type 2 diabetes [61]. In patients with type 1 diabetes treated with insulin pumps, short sleep duration rather than late-night snacking seems to be associated with poorer glycemic control [62]. It has also been reported that time-restricted eating early in life may cause pleiotropic adverse effects, including severe irreversible metabolic disorders, depressed immune function, and retarded puberty [63].

Circadian rhythm alterations associated with metabolic dysfunction

Circadian rhythms are strongly affected by obesity, type 2 diabetes, and other dietary-induced metabolic diseases. With increasing age, the circadian system also undergoes significant changes, which contribute to the dysregulation of metabolic rhythms [9]. It is now well accepted that cardiovascular and metabolic processes not only are affected by the behavioral sleep/wake cycle but also are partly coordinated by the circadian pacemaker located in the SCN [44] and that circadian disruption leads to insulin resistance and obesity [45,48,64]. There is also evidence for altered circadian characteristics in the presence of conditions such as type 2 diabetes and obesity, suggesting a bidirectional relationship between circadian rhythms and metabolism.

In our studies, we found that obesity is associated with higher serum leptin concentrations and attenuated relative circadian amplitude [65]. The circadian amplitude of systolic (S) and diastolic (D) blood pressure (BP) of 30 clinically healthy Southeast Asian immigrant Indians who underwent 7-day/24-hour ambulatory BP monitoring (ABPM) decreased as a function of body mass index (SBP: $r = -0.440$, $P = .010$; DBP: $r = -0.355$, $P = .053$) [66]. Circadian rhythm characteristics estimated from ABPM records provided by 26 clinically healthy glycemic controls, 17 patients with glucose intolerance, and 117 patients with type 2 diabetes were interpreted in the light of chronobiological reference standards [67]. A dampened circadian rhythm of BP was associated with a higher value of fasting glucose (SBP: $P = .047$ in women, $P = .016$ in men; DBP: $P = .033$ in women, $P > .05$ in men) and a higher value of glycosylated hemoglobin (SBP: $P = .043$ in women, $P = .018$ in men). Fasting glucose was also elevated in patients with an odd timing in their circadian BP rhythm ($F = 13.938$, $P < .001$) [67].

However, glucose intolerance, reflecting a prediabetes state, was associated with a larger circadian amplitude of SBP ($F = 3.938$, $P = .021$). Patients with an abnormally large circadian amplitude of SBP or DBP were also found to have a higher glucose 2 hours after loading (SBP: $F = 4.651$, $P = .017$; DBP: $F = 11.277$, $P < .001$) [67]. Abnormal BP variability was also detected in patients with prediabetes in another study [68].

Overweight middle-aged people with metabolic dysfunction, prediabetes, or type 2 diabetes have progressively disrupted circadian rhythms of fasting blood glucose, body temperature, and heart rate [69]. Adverse changes in metabolic state were accompanied by dampened circadian amplitudes of body temperature and heart rate. Circadian disruption in these variables provided early signs of the prediabetes metabolic state [69].

Similar findings have been reported by others. Diabetic patients were found to exhibit a reduced circadian amplitude of glucose tolerance and insulin secretion [70]. Conversely, metabolic diseases and cardiovascular events were more prevalent among shift workers [71]. Genomic variations in clock genes have been linked to obesity and metabolic syndrome in humans [72]. These results support a bidirectional relationship between circadian disruption and metabolic pathologies in humans.

Clock genes and nutrient-sensing pathways

A growing body of evidence suggests that meal timing is an important factor for metabolic coordination and that the circadian clock interacts tightly with metabolic functions. The proper functioning of the circadian clock is critical for maintaining metabolic health. Therefore chrononutrition, which investigates the relationship between circadian rhythms, nutrition, and metabolism, has attracted increasing attention in recent years [9].

CLOCK and BMAL1 are transcriptional activators that bind the enhancer sequences of PER and CRY (cryptochrome proteins) [73]. PER and CRY proteins accumulate in the cytoplasm and translocate to the nucleus to inhibit CLOCK: BMAL1 [73]. SIRT1, a nicotinamide adenine dinucleotide−dependent deacetylase, interacts directly with CLOCK and deacetylates BMAL1 and PER [74]. The nutrient sensor AMPK directly phosphorylates and destabilizes CRY1 [75], acting upstream of PER. AMPK can coordinate SIRT1 activity [76] and participate with the core circadian clock machinery in an intricate nutrient-sensing signaling loop [77]. AMPK can be viewed as an energy sensor, since it binds to and is coordinated by AMP and ATP. AMPK is implicated in a multitude of metabolic processes. One of its downstream targets is the mammalian target of rapamycin (mTOR), a positive effector of cell growth and division [78]. In murine SCN, TOR is coordinated by circadian function [79]. Conserved nutrient-sensing pathways are integrated into the circadian clock network, which is likely to ensure organism-wide time function and survival [77]. Circadian clocks are thus tightly coupled to cellular metabolism, as they share a number of nutrient-sensing pathways [80].

Molecular pathways that are thought to be involved in obesity, diabetes, and the metabolic syndrome include AMPK and mTOR, since they are implicated in metabolism and impinge on the circadian system [78,81]. Coordinating a variety of metabolic processes, AMPK maintains cellular energy functioning through repression of several energy-consuming processes with simultaneous enhancement of energy-producing processes. By identifying essential pathways, aging interventions may delay and prevent disease onset for a number of chronic conditions [82]. Metformin, an oral antidiabetic drug that activates AMPK in the liver, was found to decrease cardiovascular disease risk, cancer incidence, and overall mortality compared to other antidiabetic drugs [82,83].

Time-restricted feeding affects the circadian pattern of clock gene expression in the liver and the activity of nutrient-sensing pathways such as TOR, AMPK, and SIRT1 [84−86]. Food-restricted mice have desynchronized peripheral circadian rhythms but an intact SCN pacemaker [81,84,87], thus leading to a misalignment of circadian rhythms at the molecular level. *Bmal1*$^{-/-}$ and *Per2*$^{-/-}$ mice are models of diabetes and obesity [77]. Mutation of the circadian clock gene *Per1* leads mice to consume more food during the rest span and predisposes them to metabolic diseases [88]. By restricting access to a high-fat diet only during the night (active span), however, obesity can be prevented in *Per1* mutant mice [84]. Functional clock genes are present throughout the murine gastrointestinal tract [89]. While daytime feeding in nocturnal rodents is a strong synchronizer of gastrointestinal clock genes, it is associated with circadian misalignment at the molecular level in the same way that late-night eating brings about circadian disruption at the organismic level, as reviewed earlier in the chapter. Indeed, clock gene expression is shifted at the RNA and protein levels but not in the SCN [89]. In a mouse model of diabetes, clock gene expression is altered to a larger extent in organs that are intimately associated with food processing and metabolism, such as the stomach, colon, and liver, as compared to the lungs or kidneys [90].

Concluding remarks

The interaction between meal timing and light determines the internal phase relationships among circadian rhythms in mammals. A recent systematic review and metaanalysis summarized the most recent evidence on the effect of time-restricted eating on weight loss and cardiometabolic variables in comparison with unrestricted-time regimens [91]. Time-restricted eating regimens achieved a superior effect in promoting weight loss and reducing fasting glucose compared to approaches with unrestricted time in meal consumption [91]. Further long-term and well-designed trials are needed, however, to draw definitive conclusions.

In animal models, time-restricted feeding can prevent and reverse aspects of metabolic diseases. Time-restricted feeding even prevents obesity and metabolic syndrome in mice lacking a circadian clock (whole-body *Cry1* and *Cry2* and liver-specific *Bmal1* and *Rev-erbα/β* knockout mice), perhaps through reduced accumulation of hepatic lipids and enhanced cellular defenses against metabolic stress [92]. Human pilot studies show that time-restricted eating reduces the risks of metabolic diseases in otherwise healthy individuals. New evidence suggests that time-restricted eating improves cardiometabolic health for patients with metabolic syndrome receiving standard medical care, including statins and antihypertensive medications [93]. Postprandial plasma lipid profiles emerge as being strongly affected by meal timing and associated with insulin sensitivity [94].

Time-restricted feeding during the active daily span has beneficial effects beyond metabolism. It was shown to improve metabolic profile of Lewis lung carcinoma-bearing mice [95]. Research carried out during the last two decades has documented the link between feeding behavior and cognitive processes and highlighted the impact of circadian disorders on cognitive decline [96]. In the absence of any calorie restriction, intermittent fasting from dawn to sunset for 30 consecutive days was reportedly associated with an anticancer proteomic signature and upregulated key regulatory proteins of glucose and lipid metabolism, circadian clock, DNA repair, cytoskeleton remodeling, immune system, and cognitive function in healthy humans [97]. The mechanistic target of mTOR and circadian clock gene pathways that include AMPK, Wnt1-inducible signaling pathway protein 1, erythropoietin, and SIRT1 provide novel strategies to treat cognitive loss that has its basis in metabolic cellular dysfunction [98]. Time-restricted feeding, which imposes daily cycles of feeding and fasting without caloric reduction, sustains robust circadian rhythms and can alleviate metabolic diseases. These findings highlight an integrative role of circadian rhythms in physiology and offer a new perspective for treating chronic diseases of which metabolic disruption is a hallmark [99].

Health promotion goes hand in hand with addressing issues related to aging. As in the case of metabolic disorders, reduced circadian amplitude is a feature of aging [100]. In an attempt to offset social and economic consequences of the current shift in the aging segment of the population, geroprotectors (substances that slow aging, repair age-associated damage, and extend healthy life span) are being developed to prevent and treat age-related pathologies [83]. Among nonpharmacological interventions affecting life span and aging biomarkers are physical exercise and caloric restriction. Caloric restriction delays aging in both rodents and primates and improves aging biomarkers in humans, including body mass index, blood pressure, glucose, insulin, and lipids. Moreover, caloric restriction decreases the risks of aging-associated diseases, such as diabetes and cardiovascular disease [83].

Aging, metabolic disorders, and other disease conditions are associated with circadian disruption, characterized by a weakened circadian system. By contrast, large-amplitude circadian rhythms are hallmarks of health and longevity. A lowered metabolism being implicated in obesity, meal timing (if not overall caloric restriction) presents itself as an appealing and available lifestyle option to increase metabolism and reduce body weight [100]. Physiological monitoring of variables such as temperature, heart rate, blood pressure, and blood glucose is becoming increasingly easy to perform noninvasively and may represent one way to assess the effectiveness of interventions aimed at improving health.

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Chapter 36

Anticancerous compounds in fruits, their extraction, and relevance to food

Ekta Jain[1], Abhishek Dutt Tripathi[1], Aparna Agarwal[2], Kamlesh Kumar Mauraya[1], Dinesh Chandra Rai[1], Richa Mishra[3], Ram B. Singh[4] and Al Mukhlas Fikri[5]

[1]Department of Dairy Technology and Food Technology, Institute of Agricultural Sciences, Banaras Hindu University, India, [2]Department of Food Technology, Lady Irwin College, University of Delhi, India, [3]Department of Home Science, Arya Mahila Degree College, Banaras Hindu University, India, [4]Halberg Hospital and Research Center, Civil Lines, India, [5]Department of Nutrition, Faculty of Health Sciences, University of Singaperbangsa Karawang, Indonesia

Introduction

An estimated 9.6 million people die of cancer annually, making it the second leading cause of death worldwide. According to evidence, lifestyle and nutrition play key roles in the development of diseases. Regular consumption of a diet that is rich in saturated fats and red meats and low in fresh fruits and vegetables has been shown to increase the risk of cancer. As has been stated by the U.S. National Institutes of Health, one to two servings of fruits and vegetables a day can prevent common diseases including cancer [1]. Cancer is a disease in which abnormal cells divide without control and invade nearby tissues, converting normal cells to malignant cells. Cancer is a complex disease and normally associated with both increasing effects at molecular as well as cellular level. It is caused by genetic instabilities such as mutations in DNA repair genes, tumor suppressor genes and oncogenes. There are several factors that can cause cancer, such as tobacco, radiation, and pollutants. Among the different cancers, lung cancer is the most reported in males and breast cancer in females. Strategies that limit DNA damage and increase the probability of DNA repair will decrease the incidence of cancer.

In the year 2014−15, India placed second in the world in fruit production after China, with a total production of fruits reaching 6.00907 tons/hectare. India ranks first in production of bananas (22.94%), papayas (44.03%), and mangoes (including mangosteens and guavas, together accounting for 37.57%) in exports [2]. The diverse climatic conditions found in India ensure the availability of a variety of fruits. In the parts of India where the majority of tribal populations dwell, with severe malnourishment and multiple nutrient deficiency disorders, intersection of health and nutrients, replenished by natural vegetation, that is, underutilized crops, assumes importance. Underutilized crops are defined as crops that are neither grown commercially on a large scale nor traded widely. Such crops are easier to grow, are hardy in nature, growing even in adverse soil and climatic conditions, and are rich sources of carbohydrates, fats, proteins, energy, vitamins (A, B_1, B_2, B_3, B_6, B_9, B_{12}, C, and folic acid), minerals (calcium, phosphorus, and iron), and dietary fiber, thereby having the nutritional capacity to prevent and cure diseases such as kwashiorkor, marasmus, night blindness, anemia, diabetes, cancer, hypertension, and hidden hunger [3].

Fruits and phytochemicals

Plants are considered to have immune-modulatory and antioxidant properties, which gives them anticancer properties. Fruits are one of the important plant products that are rich in bioactive compounds and other important components, such as calcium, fiber, folate, iron, magnesium, potassium, sodium, Vitamin A, and C, antioxidants, and phenols, which have been shown by metaanalyses and case control studies to have cancer-preventive effects. These act by stimulating specific and nonspecific immunity and by inhibiting the progression of cancer. Phytochemicals are present in many parts of the plant, such as fruit, seed, bark, leaves, root, and stem. Fruit is an important part of the plant, as it is edible [4].

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The main phytochemicals that show anticancer properties are vitamins (A, C, E, K), carotenoids, terpenoids, flavonoids, polyphenols, native enzymes, minerals (selenium, copper, zinc, chromium), alkaloids, lignans, and biomolecules. These compounds and their metabolites play a significant role in inhibiting the cancer cell—activating proteins, enzymes, and pathways. (Fig. 36.1) **[5]**. Anticancer properties have been demonstrated through extraction of natural compounds, that is, the desired bioactive compound from natural products. Bioactive compounds are naturally occurring compounds in fruits possessing a variety of physiological functions for general body development and disease prevention. Being nonessential biomolecules, they are extranutritional constituents that occur in small quantities in plant products and lipid-rich foods in the form of glycosylated, esterified, thiolyated, and hydroxylated derivatives. They have several beneficial metabolic activities in the treatment of diseases and on target tissues, such as cancer. Bioactive compounds of natural origin exert antiinflammatory activity by modulating proinflammatory gene expressions [6]. Overall, the health benefit of fruits is due to the synergy or interactions of bioactive compounds and other nutrients in whole foods [7].

Rich in phytochemicals that have numerous bioactive properties, fruits are considered to be endowed with anticancer and antioxidant properties. Phytochemicals are nonnutrient plant chemicals in fruits, vegetables, and other plant foods that may provide desirable health benefits that reduce the risk of major chronic diseases. Examples are phenolics, alkaloids, nitrogen-containing compounds, organosulfur, phytosterols, and carotenoids. Chemopreventers are phytochemicals that occur naturally and possess anticarcinogenic and other beneficial properties. Antioxidant activity is mainly

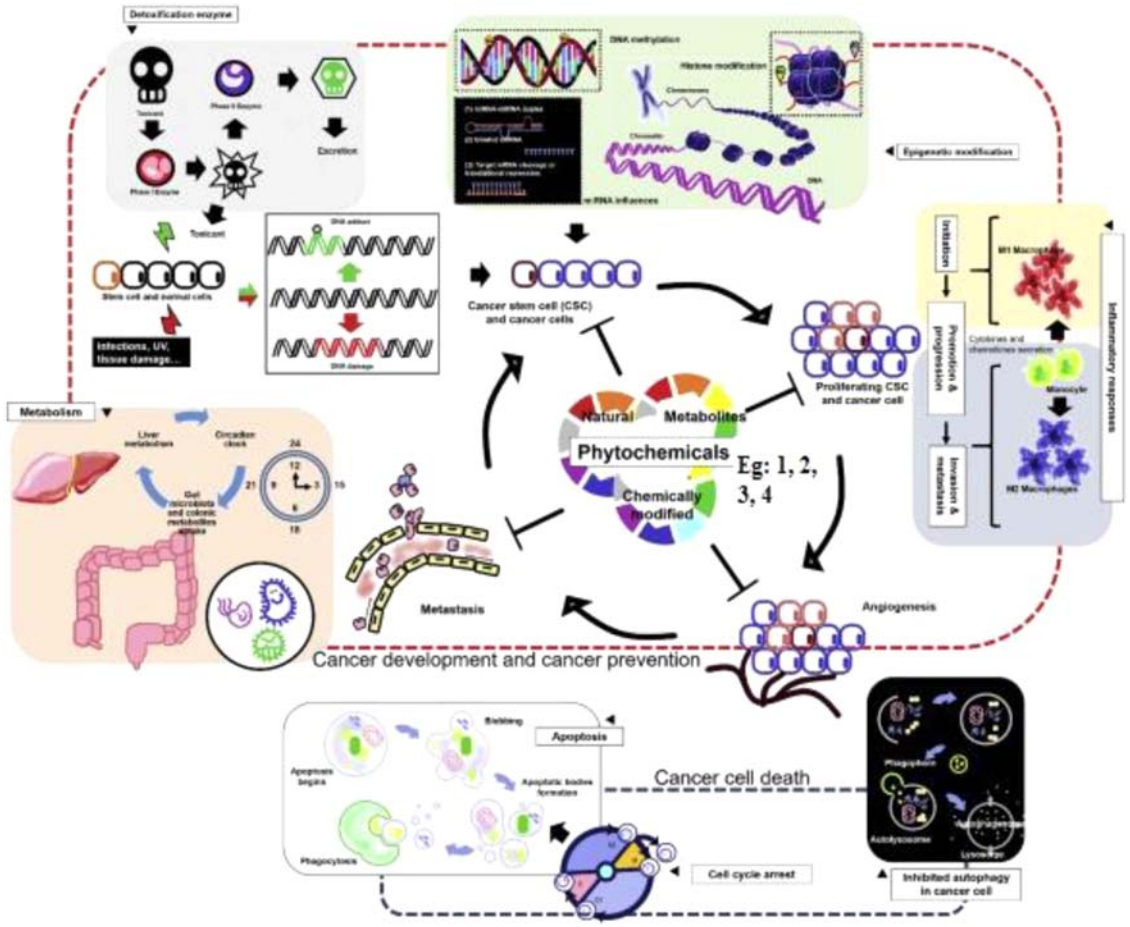


FIGURE 36.1 Schematic representation of carcinogenesis model and effect of phytochemicals on prevention/ inhibition of cancer progression. Phytochemical examples: (1) triterpenoids such as lupane, present in apples, with a molecular weight of 412.7 g/mol and molecular formula of $C_{30}H_{52}$, (2) Polyphenols such as ellagic acid, present in berries, with a molecular weight of 302.19 g/mol and molecular formula of $C_{14}H_6O_8$, (3) Flavonoids such as quercetin, present in apples, grapes, and berries, with a molecular weight of 302.23 g/mol and molecular formula of $C_{15}H_{10}O_7$, (4) Resveratrol, present in grapes and berries, with a molecular weight of 228.2433 g/mol and molecular formula of $C_{14}H_{12}O_3$. *Adapted from Koh YC, Ho CT, Pan MH. Recent advances in cancer chemoprevention with phytochemicals. J Food Drug Anal 2020;28(1):14—37.*

due to the capacity to scavenge free radicals. Among the most investigated chemopreventers are vitamins, plant phenols, pigments such as carotenoids, chlorophylls, flavonoids, and betalains [6].

The first isolated plant compounds that were used as anticancer agents are vinca alkaloids, vinblastine, and vincristine from the Madagascar periwinkle, *Catharanthusroseus* (Apo-cynaceae). They are the first agents used in the treatment of cancer along with chemopreventive drugs [8].

Table 36.1 lists the different anticancerous compounds that are present in fruits.

Table 36.2 lists the molecular and structural formulas of the polyphenolic and flavonol-based anticancer compounds along with their effects on the human body to prevent cancer.

Table 36.3 lists the molecular and structural formulas of the other polyphenolic, polyketide, and enzyme-based anticancer compounds along with their effects on the human body to prevent cancer.

Table 36.4 lists the molecular and structural formulas of the polyester, enzyme, terpenoid, and pycenoid-based anticancer compounds along with their effects on the human body to prevent cancer.

Mechanism of phytochemicals in reducing the risk of cancer

Carcinogenesis occurs in three phases: initiation, promotion, and progression. Cancer induction is triggered at the initiation stage, when interactions occur between carcinogens and the DNA of normal cells, which lead to changes in heritable mutations. Promotion and progression are the later stages of carcinogenesis. They can be explained as clonal expansion of genetically altered cells and their eventual extrusion and metastatic spread to other organs.

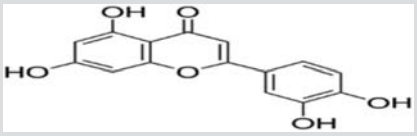
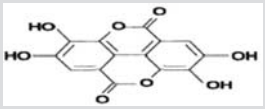
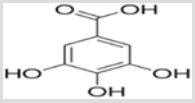
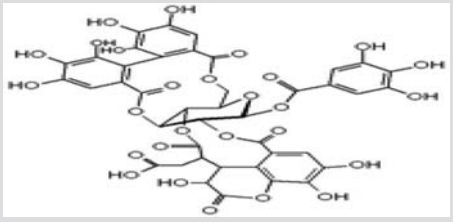
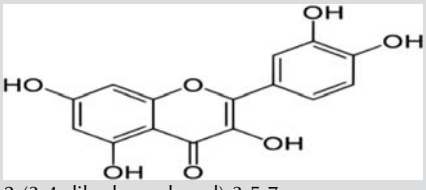
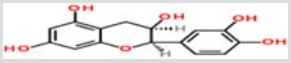
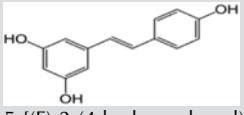
Bioactive compounds showing high antioxidant activity are efficient interceptors for DNA reactive elements. Chemical carcinogens are electrophilic in nature, and these mutagens or carcinogens are attracted to electron-rich sources in the cell. Electron-rich sources are DNA, RNA, and proteins, and carcinogens are attracted to them because of electrophilicity and high nucleophilic potential. Stable bonds form between the mutagenic agent and nucleoproteins and lead to formation of a single molecule adduct. Adduction of DNA is considered to be the start of the carcinogenic process.

Fruits contain several compounds, among which antioxidants play an important role in anticancer activity, as they can prevent DNA adduction, presumably by presenting alternative targets for attack by carcinogens.

TABLE 36.1 Anticancer compounds in fruits.

Fruit	Anticancer compound	Reference
Phyllanthusemblica Linn. (Indian gooseberry)	Luteolin, 3-*O*-glucoside derivatives	[9]
	Gallic acid, ellagic acid, mucic acid, 1,4-lactone 3-*O*-gallate, chebulagic acid	[9]
Aeglemarmelos (L.) Corr. (bael)	Skimmianine	[10]
Lycopersiconesculentum (tomato)	Alpha-tomatine	[11]
	Tomatidine	[11]
Achrassapota (sapodilla)	Methyl 4-*O*-galloylchlorogenate,4-*O*-galloylchlorogenic acid	[12]
Ziziphus jujube (Ber)	Quercetin, epicatechin	[13]
Anonasquamosa (custard apple)	Bullatacin	[14]
Vitisvinifera (grape skin)	Resveratrol	[15]
Ananascomosus (pineapple)	Bromelain enzyme	[16]
Maluspumila (apple peel)	Triterpenoids	[17]
Maluspumila (apple pomace)	Procyanidins	[18]
Rubus (berries)	Ellagic acid	[19]
Citrus sp. (citrus peel)	Nobiletin	[20]
	Tangeretin	[20]

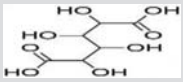
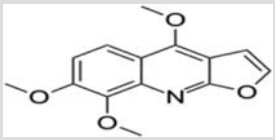
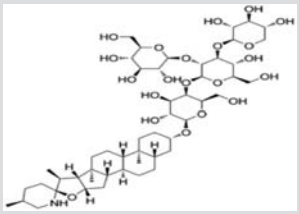
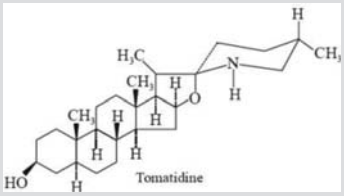
TABLE 36.2 Molecular and structural formula of the polyphenolic and flavonol-based anticancer compounds along with their effects on the human body to prevent cancer.

Anticancerous compound	Structural formula of anticancerous compound	Effect
Luteolin	 491−70−3; 3′,4′,5,7-Tetrahydroxyflavone	• Induces apoptosis • Inhibits cell proliferation, metastasis, and angiogenesis • Sensitizes cancer cells to therapeutic-induced cytotoxicity
Ellagic acid	 2,3,7,8-Tetrahydroxy-chromeno[5,4,3-cde] chromene-5,10-dione	• Inhibits the activity of human DNA topoisomerase (topo) I and II, prevents topo I and topo II poisons from stabilizing the cleavable complex
Gallic acid		• Antiproliferative through selective toxicity • Induces apoptosis
Chebulagic acid		• Free radical scavenging activity • Radioprotective properties • Antianaphylactic action • Antiinflammatory • Analgesic activity
Quercetin	 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one	• Scavenging highly reactive hydrogen peroxide, superoxide anion and hydroxyl radicals • Inhibition of enzymes responsible for activation of carcinogens
Epicatechin	 (2 R,3 R)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol	• Neutralizes reactive oxygen species in the cell • Antiproliferative
Resveratrol	 5-[(E)-2-(4-hydroxyphenyl)ethenyl]benzene-1,3-diol	• Cell-apoptosis • Antiproliferation • Antiinflammation

Isothiocyanates are also chemopreventive agents and are efficient modulators of carcinogen activation and detoxification.

Organosulfur compounds are also powerful and highly reactive biological molecules that influence both carcinogen activation (phase 1) and detoxification (phase 2). These water-soluble sulfur compounds are potent chemopreventers in animal models against colon and esophageal cancer.

TABLE 36.3 Molecular and structural formula of the other polyphenolic, alkaloid, polyketide, and enzyme-based anticancer compounds along with their effects on the human body to prevent cancer.

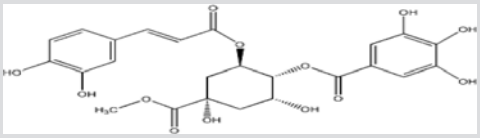
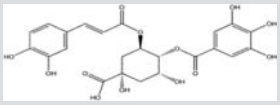
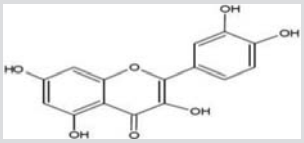
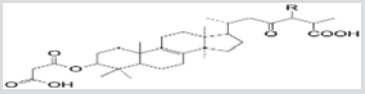
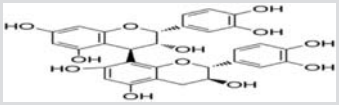
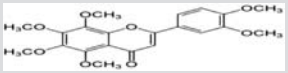
Anticancerous compound	Structural formula of anticancerous compound	Effect
Mucic acid	 (2 S,3 R,4 S,5 R)-2,3,4,5-Tetrahydroxyhexanedioic acid	• Cytotoxic activity
Skimmianine	 4,7,8-trimethoxyfuro[2,3-b]quinolone	• Antiinflammatory • Antineoplastic effect • Radioprotective effect
Alpha-tomatine	 (22 S,25 S)-5α-spirosolan-3β-yl β-D-glucopyranosyl-(1→2)-[β-D-xylopyranosyl-(1→3)]-β-D-glucopyranosyl-(1→4)-β-D-galactopyranoside	• Induces apoptosis • Inhibits growth of cells • Cytotoxic effect • Inhibited tumor growth • Exposure causes loss of mitochondrial membrane potential
Tomatidine		• Inhibits cell growth by blocking the cell cycle in G0 and G1 phase
Bullatacin	 4-[(13 R)-2,13-dihydroxy-13-[(2 R,5 S)-5-[(2 R)-5-[(1 S)-1-hydroxyundecyl]oxolan-2-yl]oxolan-2-yl]tridecyl]-2-methyl-2H-furan-5-one	• Cytotoxic effect • Induces apoptosis

Another possible mechanism by which phytochemicals affect the cancer process is by suppressing the mutated *ras* oncogene. Cancer cells grow rapidly as a result of activation of the oncogenes; that is, these genes are "turned on" and allowed to escape factors that regulate cell growth. The *ras* oncogene is one of the most mutated genes found in human cancers. As many as 50% of the cancers harbor the *ras* oncogene. Monoterpenes are a class of phytochemicals, and limonene compound suppresses the growth of mammary cancer cells when fed to rats. Limonene is involved in the repression of the mutated *ras* oncogene, thereby altering the course of the tumors in the later stages of development [21].

Extraction techniques for anticancer compounds from fruits

To obtain valuable natural anticancerous compounds from plants for commercialization numerous extraction techniques have been investigated. Extraction methods should provide high rates of extraction, should be nondestructive, and should save time. Earlier methods, such as the Soxhlet method of extraction, although simple and cheap, are time

TABLE 36.4 Molecular and structural formula of the polyester, enzyme, terpenoid, and procyanidin-based anticancer compounds along with their effects on the human body to prevent cancer.

Anticancerous compound	Structural formula of anticancerous compound	Effect
Methyl 4-O-galloylchlorogenate (methyl ester)	 [(1 R,2 R,4 S,6 R)-2-[(E)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxy-4,6-dihydroxy-4-methoxycarbonylcyclohexyl] 3,4,5-trihydroxybenzoate	• Cytotoxic effect
4-*O*-galloylchlorogenic acid(methyl ester)	 (1 S,3 R,4 R,5 R)-3-[(E)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxy-1,5-dihydroxy-4-(3,4,5-trihydroxybenzoyl)oxycyclohexane-1-carboxylic acid	• Antiangiogenesis • Antiproliferative • Induction of apoptosis • Antiinflammation • Antioxidation
Bromelain(enzyme)		• Cytotoxic effect • Antiproliferative
Triterpenoids	 (4aS,6aR,6aS,6bR,8aR,9 R,10 S,12aR,14bS)-10-hydroxy- 2,2,6a,6b,9,12a-hexamethyl-9-(sulfooxymethyl)-1,3,4,5,6,6a,7,8,8a,10,11,12,13,14b-tetradecahydropicene-4a-carboxylic acid	• Induce apoptosis • Inhibit signal transducer • Activate transcription and angiogenesis
Procyanidins	 2-(3,4-dihydroxyphenyl)-2-[[2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3,4-dihydro-2H-chromen-3-yl]oxy]-3,4-dihydrochromene-3,4,5,7-tetrol	• Antiproliferative • Antiinflammatory • Inhibition of intracellular signal transduction
Nobiletin	 2-(3,4-dimethoxyphenyl)-5,6,7,8-tetramethoxychromen-4-one	• Induces apoptosis, cell-cycle arrest

consuming, employ a large quantity of solvent, and produce inconsistent results. They may even lead to thermal decomposition of labile compounds and may cause environmental pollution.

Faster extraction techniques with higher efficiency have been introduced to overcome such problems. Some of the assisted extraction techniques are ultrasound, enzyme, microwave, pulsed electric field (PEF), supercritical fluid, pressurized liquid, high hydrostatic pressure, solid-phase, and ionic liquid methods. Some of these listed above are considered to be green techniques, as they comply with the standards set by the U.S. Environmental Protection Agency [22] to ensure safe and high-quality extracts for the food and nutraceuticals industries. The challenge to protect both consumers and the environment while simultaneously enhancing competition in industries to be more ecologically and economically productive and innovative has been perhaps addressed by green extraction of natural products.

Ultrasound-assisted extraction

Ultrasound-assisted extraction creates expansion and compression cycles in the medium, utilizing sound waves higher than 20 kHz, inducing a phenomenon called cavitation [6]. It causes high shear forces in the media. Implosion of

cavitation bubbles on a product's surface results in microjetting, which generates several effects, such as surface peeling, erosion, and particle breakdown. In addition, microturbulences and micromixing are caused by implosion of cavitation bubbles in liquid media. Here, temperature assumes importance, leading to increased extraction yield. According to reports, beneficial effects have been observed as the temperature rises from 20°C to 70°C, owing to an increase in the number of cavitation bubbles, larger solid solvent contact area, and enhancement of solvent diffusivity with consequent enhancement of desorption and solubility of the desired compound. But when the temperature is the near the solvent's boiling point, the beneficial effect decreases. A beneficial effect at low temperature (below 30°C) has been reported in the case of ultrasound-assisted extraction [23]. To prevent the degradation of thermolabile compounds, it is important to choose the extraction temperature according to the target compound. Thus optimization of the temperature parameter should be performed to obtain the highest yield of target compounds without degradation, since this parameter varies depending upon the type of product.

Enzyme-assisted extraction

Enzymes are defined as ideal catalysts that do not take part in the reaction but alter the rate of reaction by assisting in the extraction of anticancer compounds of natural origin. Efficiency of extraction depends on the inherent ability of enzymes to catalyze reactions with exquisite specificity and region selectivity and an ability to function under mild processing conditions in aqueous solution. Through disruption of the structural integrity of the plant cell wall, various enzymes such as cellulases, pectinases, and hemicellulases thereby enhance the extraction of compounds from plants. To use enzymes effectively, it is imperative to understand the catalytic property, mode of action, and optimal operational conditions of enzymes and which enzyme or enzyme combination is appropriate for the plant material selected. For example, the extraction of an antioxidant may be enhanced by processing of pectic polysaccharide in the presence of an enzyme system wherein the enzyme at 1%w/w increased extraction from 1.7 to 7.4 g/kg of raw material dry weight [24]. According to recent observations, enzymes can be used to disrupt the pectin cellulose complex in citrus peel and increase flavonoid (naringin) production. The extraction rate was enhanced from 32.33% to 61.9%. Extraction of polyphenols from grape pomace was recently carried out on a pilot plant scale wherein a 120-minute enzymatic step during treatment of the pomace resulted in a 65.8% increase in the anthocyanin yield [24]. This is well illustrated by Table 36.5.

Microwave-assisted extraction

Microwaves are electromagnetic waves with a frequency range of 0.3−300 GHz [6]. The principle is based on the direct effect of microwaves on molecules by ionic conduction and dipole rotation. The solvent absorbs microwave energy and passes it on in the form of heat to the other molecules depending upon the dissipation factor. A closed extraction vessel under controlled pressure and focused microwave ovens are the preferred equipment for extraction purpose [25]. The procedure includes the following steps:

1. Separation of solutes from the active site of the sample matrix under increased temperature and pressure
2. Diffusion of the solvent across the sample matrix
3. Release of solutes from the sample matrix to the solvent

In comparison to conventional heating, wherein a finite period of time is needed to heat the vessel before heat is transferred to the solution, in microwave-assisted extraction there is a reduction of extraction time as microwaves heat the solution directly. This procedure also allows for significant reduction in organic solvent consumption and the possibility of running multiple samples.

TABLE 36.5 Enzyme-assisted extraction of anticancer compounds from citrus source.

Anticancer compound	Source	Enzyme used	Maximum yield (%)
Phenolics	Citrus peel	Celluzyme MX	65.5
Polyphenols	Grape pomace	Pectinolytic	98.1

Pulsed electric field–assisted extraction

PEF has gained immense importance for improving mass transfer operations in the food industry. Short pulses of electricity (10–20 kV/cm) are used to destroy cell membranes of plants for increased extraction [6]. For PEF treatment of plant materials, a simple circuit with exponential decay of pulses is generally used. It consists of a treatment chamber with two electrodes where plant materials are placed. The advantage of PEF is that it minimizes degradation of heat-sensitive compounds [26]. It can also be applied to plant material as a pretreatment process prior to conventional extraction in order to lower the extraction effort.

Supercritical fluid extraction

In comparison to conventional extraction methods, supercritical fluid extraction brings greater benefit, as it uses supercritical solvents, with different physicochemical properties, such as diffusivity, density, viscosity, and dielectric constant. Owing to the low viscosity and higher diffusivity, supercritical fluids have better transport properties than liquids, can diffuse easily through solid materials, and can therefore give faster extraction rates [6]. An alternative possibility of modifying the density of fluid by changing its pressure and/or temperature also exists, as density is related to solubility; thus by altering the extraction pressure, the solvent strength of the fluid can also be modified. The most commonly used supercritical fluid is CO_2. It is a gas at room temperature, so as the extraction process completes, the system is decompressed, eliminating CO_2, yielding a solvent-free extract. The major advantage of CO_2 is its low critical temperature, thus playing a key role in the preservation of bioactive compounds in the extract [27].

Pressurized liquid extraction

In the pressurized liquid method of extraction, liquid solvents at high temperature and pressure are used. Enhanced solubility and mass transfer properties are the major advantages of using solvent at a temperature above their boiling point. Temperatures range from room temperature to 200°C and pressures range from 35 to 200 bar. The following steps are included in the extraction and recovery of analyte from the sample matrix: (1) To remove the analyte from the extraction vessel, the compound is first desorbed from its site in the sample matrix. It is then diffused through the organic part of the matrix to be able to reach the matrix-fluid interface. (2) Now the analyte is distributed into the extraction phase. It then diffuses through the extraction phase that is present within the pore, after which it reaches the part of extraction phase most affected by convection. (3) Finally the extracted analyte is collected [28]. Owing to the presence of moisture in the sample matrix, the efficiency of extraction is lowered; therefore an inert diatomaceous earth is used both as a dispersion and dehydrating agent called hydromatrix. It is used mainly to adsorb water from the matrix, thereby enhancing the extraction process. Temperature, time, and solvent type are the factors affecting extraction. The process is depicted in Fig. 36.2.

High hydrostatic pressure extraction

Compared to the other methods, high hydrostatic pressure reduces the processing time and provides higher extraction yields without having any adverse effects on the activity and structure of bioactive compounds. High pressure ranging from 100–1000 MPa is used. Enhanced cell permeability and secondary metabolite diffusion is achieved through enhanced mass transfer rates. This also causes deprotonation of charged groups and disruption of salt bridges and

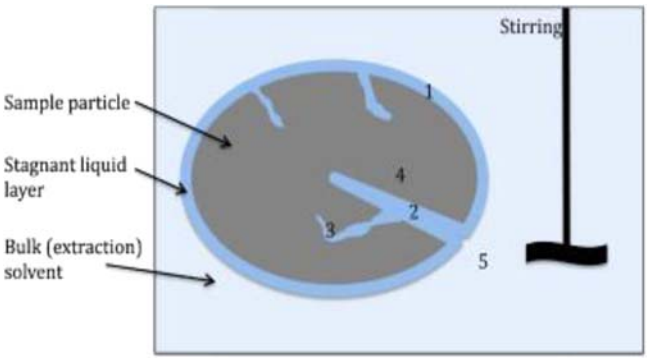


FIGURE 36.2 Schematic diagram showing bioactive compound encapsulation phenomenon.

hydrophobic bonds, resulting in conformational changes and protein denaturation, causing cellular membranes to be less selective. Extraction is easy up to equilibrium following high hydrostatic pressure extraction [29]. The higher the hydrostatic pressure, the more solvent enters the cell; consequently, more compounds permeate the cell membrane, resulting in a higher extraction yield. Owing to large differential pressure between the interior and exterior of cell membrane, rapid permeation is observed.

Solid-phase extraction

Solid-phase extraction involves adsorption of analytes or unwanted impurities on a solid phase, thus purifying the extracts is the major characteristic of the solid-phase extraction method. A wide range of stationary phases with diverse chemistry, such as silica gel, reverse phase material, ion exchange resins, or mixed mode material and hydrophilic interaction chromatography stationary phases in a prepacked glass or plastic column, are used in this method. Using this method, either the unwanted impurities (e.g., chlorophyll) are removed by adsorption on the stationary phase or the analytes of interest are adsorbed on the stationary phase, whereas impurities are eluted. Next, the concentrated analytes are removed from the column. The compound of interest is eluted stepwise by applying a gradient with increasing eluting power similar to the process in vacuum liquid chromatography [30]. For example, development includes the design of molecular-imprinted polymers to be used in solid-phase extraction applications for selective enrichment of various compounds. Either ionic liquid−imprinted silica particles or copolymers of acrylamide and ethylene glycol dimethacrylate with respective template compounds are used to create material that will have high affinity to the template structures. The unwanted materials are removed from the solid-phase extraction column. Alternatively, target compounds bound to the solid phase are obtained in concentrated solution upon elution with organic solvents such as methanol, followed by additional purification using chromatographic methods and are further lyophilized.

Ionic liquid−assisted extraction

Designated "designer solvents," ionic liquids are organic salts in a liquid state consisting of an organic cation and an organic or inorganic anion. The main characteristics of ionic liquids are the ability to dissolve a wide range of polar to nonpolar compounds, low vapor pressure, and high thermal stability and low combustibility, with few being biodegradable. Utilization of ionic liquid as a new solid-phase microextraction stationary phase causes problems due to contamination of the gas chromatography injector when directly inserted into the system. N,N-dimethylcarbamate proved to be a distillable ionic liquid and is more easily removed from the extract compared to a majority of ionic liquids, which are minimally volatile.

Table 36.6 compares traditional and recent extraction techniques [31].

Methods of application of anticancer compounds in food

Microencapsulation

To ensure the protection and delivery of anticancer compounds in food, microencapsulation has been considered as an emerging technique. Microencapsulation has been defined as the technology of entrapping or coating small particles of solid, liquid, and gaseous materials with protective material or in small capsules that release their contents at controlled rates. Encapsulated material consists of a component, the core or active material, packaged within secondary material, that is, wall material and delivered in small particles. Microcapsules generally range from 2 to 5000 μm. Initially, the method was used for flavor encapsulation, in which flavors are stabilized and their release is controlled. Since then, it has been used for incorporation of sensitive bioactive components in fortified food without compromising the taste, aroma, and texture of the food. The main advantages are reduction in off-flavors due to certain vitamins and minerals, time-dependent release of nutrients, increased stability in extremes of temperature and moisture, and minimization of undesirable chemical interactions between ingredients [32].

Application of the microencapuslation process in the food and pharmaceutical industries is generally done to protect the core material from degradation, to release the active material from the core at a controlled rate, or to prevent unwanted flavoring of the active core material.

For the development of successful encapsulation, knowledge of the stability of the chosen bioactive (the core), properties of the secondary wall materials (encapsulant), and suitability of the delivery system (microcapsule) and microencapsulation technology is essentially required. Some of the properties of the core, such as bioactivity of the material,

TABLE 36.6 Comparison of traditional and recent extraction techniques of anticancer compounds.

Method	Description	Extraction time	Sample size	Solvent usage	Advantages	Drawbacks
Microwave-assisted extraction	Sample is immersed in a microwave-absorbing solvent in a closed vessel and irradiated with microwave energy.	3–30 min	1–10 g	10–40 mL	1. Fast, multiple extractions 2. Low solvent volumes 3. Elevated temperature	1. Extraction solvent must be able to absorb microwaves 2. Cleanup step needed 3. Lag time for the vessels to cool down
Pressurized liquid extraction	Sample and solvent are heated and pressurized in an extraction vessel. When the extraction is finished, the extract is automatically transferred into a vial.	5–30 min	1–30 g	10–100 mL	1. Fast extractions 2. Low solvent volume 3. Elevated temperature 4. No filtration required	1. Cleanup step needed
Supercritical fluid extraction	Sample is loaded in a high-pressure vessel and extracted with supercritical fluid (most commonly CO_2 at pressure of 150–450 bar and temperature of 40°C–150°C). The analytes are collected in a small volume of solvent or onto a solid-phase trap, which is rinsed with solvent in the subsequent steps.	10–60 min	1–5 g	2–5 mL (solid trap) 5–20 mL (liquid trap)	1. Fast extraction 2. Minimal solvent volume 3. Elevated temperatures 4. Relatively selective toward matrix interferences 5. No cleanup or filtration required 6. Concentrated extracts 7. Automated systems	1. Many parameters to optimize, especially the analyte collection
Soxhlet	Sample is placed in a glass fiber thimble, and by using a Soxhlet extractor, the sample is repeated percolated with condensed vapors of the solvent	3–48 h	1–30 g	100–500 mL	1. No filtration required	1. Long extraction times. 2. Large solvent volume 3. Cleanup step needed
Sonication	Sample is immersed in solvent in a vessel and placed in an ultrasonication bath	10–60 min	1–30 g	30–200 mL	1. Multiple extractions	1. Large solvent volumes 2. Repeated extractions may be required 3. Cleanup step needed

TABLE 36.7 Commonly used wall materials for encapsulation of anticancer compounds.

Material class	Type of materials
Protein	Casein, whey, soy, wheat, egg protein, zein, hydrolyzed proteins
Carbohydrate	Sugars: Fructose, galactose, glucose, maltose, sucrose, oligosaccharide, corn syrup solids, dried glucose syrup. Starch: maltodextrins, dextrins, starches, resistant starch, modified starch. Gums: agar, alginates, carrageenan, gum acacia, gum arabic, pectin, carboxymethyl cellulose, chitosan, cyclodextrins
Lipid	Natural fats and oils, fractionated fats, monodiglycerides and diglycerides, phospholipids, glycolipids, beeswax, carnauba wax

solubility, stability to environmental conditions, taste, and activity of the wall material, are important. The activity of the wall material is dependent on various factors, such as propensity to interact with other food components, solubility, viscosity, and stability to environmental conditions such as pH, salts, temperature, shear, enzyme degradation, film-forming and emulsification properties, and regulatory status for food application. The activity of core active material of the microcapsule depends on the format for delivery (liquid or powder), storage, stability, release, properties, particle, size, and cost of production, etc.

Wall materials that are commonly used for encapsulation are listed in Table 36.7.

Some of the methods commonly used for microencapsulation are as follows:

1. Physical processes: Spray drying, spray chilling, fluidized bed coating, centrifugal extrusion, spinning disk coating, pressure extrusion, hot-melt extrusion, and use of supercritical fluids
2. Chemical processes: Solvent evaporation, liposomes, chemical adsorbents, inclusion complexation, in situ polymerization
3. Physicochemical methods: Single-core or multicore coacervation, sol-gel encapsulation, and liposome encapsulation

Spray drying

Spray-drying methods are frequently used. These are categorized as spray drying, electrospray, spray coagulation, and spray freeze-drying methods. Spray drying involves three stages: suspension or emulsion preparation (conversion of liquid in the form of emulsion into dry powders using protein or carbohydrate as the matrix material), homogenization (of core material with the wall materials), and atomization and dehydration of the atomized particles. The liquid, as a solution, emulsion, or dispersion, is atomized to form microdrops, which come into contact with hot air, causing rapid evaporation and formation of microcapsules. Particle size is 10−400 μm. Spray-drying technology is relatively simple, fast, well established, and 30−40 times cheaper than other encapsulation methods with a low process cost. Fewer shell materials are available for this method, which makes its use limited. Another limitation is that the high temperatures during the process will lead to the loss of activity and denaturation of the bioactive compounds. Since almost all spray-drying processes in the food industry are carried out with water-soluble feed formulations, the shell material must be soluble in water. Typical shell materials include gum acacia, maltodextrins, hydrophobically modified starch, and mixtures thereof [33]. Other polysaccharides, such as alginate, carboxymethylcellulose, guar gum, and proteins, can also be used as the wall material in spray drying, but their use becomes very tedious and expensive because of their low solubility in water.

Spray cooling or spray chilling

The spray-cooling or spray-chilling method is the same as that of the spray drying except that the air desiccants are cold. The bioactive compounds are dispersed in a heated lipid solution, which is then homogenized, atomized, and cooled. This is one of least expensive methods. Moreover, temperature-sensitive compounds can be encapsulated, and active compounds will be released within a few minutes after being incorporated in the foodstuff [4,34].

Fluidized bed coating

Fluidized bed coating is commonly used for coating solid particles. The mechanism of formation of microcapsules has three stages: nucleation, transition, and ball growth. First, a coating solution is prepared (e.g., starch, cellulose, plant

exudates), and particles are suspended in the coating chamber. Fluidization of the core particles is done in the chamber. At the end of this process, droplets are evaporated and formed into microcapsules. The greatest advantage of this method is that particles will be uniformly coated with the shell material. This method of microencapsulation is highly versatile, has a relatively high batch size, and is simple [35]. The benefits of microcapsules include ease of handling, controlled release, and improved aesthetics, taste, and color in the product. This technique is used to encapsulate vitamins such as C and B, ferrous sulfate, ferrous fumarate, sodium ascorbate, potassium chloride, and multinutrient premixes that can be used as nutritional supplements.

Lyophilization

Lyophilization, also known as freeze drying, is a process that is used for the dehydration of heat-sensitive materials. The principle behind the method is freezing the material and then reducing the pressure and allowing the frozen water in the material to sublimate directly from the solid phase to the gas phase. Except for the long dehydration time, freezing drying is a simple technique that is most commonly used for aromatic materials.

Coacervation

Coacervation is a process in which aqueous colloidal solutions were separated into two liquid phases, one rich in colloid (coacervate) and the other poor in colloid. According to the International Union of Pure and Applied Chemistry, 1997, coacervation is defined as the separation of colloidal systems into two liquid phases.

Coacervation involves the formation of three immiscible chemical phases: separation of a liquid phase of coating material from a polymeric solution followed by the coating of that phase as a uniform layer around suspended core particles. The coating is then solidified.

There are two types of coacervation in aqueous phase: simple and complex based on the involved phase separation mechanism. Simple coacervation is based on the principle of salting out by the action of electrolytes or by desolvation by the addition of a water-nonmiscible solvent, such as ethanol. Complex coacervation involves a reaction that is due to the attraction forces of oppositely charged polymers (protein and polysaccharide), also called the polymer-polymer interaction method. Some hydrocolloids that are used to produce complex coacervates include different proteins and polysaccharides such as gelatin, whey proteins, pea protein, lactoglobulin, alginate, carrageenan, pectin, and gum arabic. This process is complex and expensive, and it uses glutaraldehyde, which must be carefully used as per the country's laws [36,37].

Supercritical fluid technology

Supercritical fluid technology creates a dispersion of an active agent in supercritical fluid and releases the fluid to precipitate the shell. The advantage of this method is that it yields a solvent- free product; also it does not include toxic organic solvents [36,38].

Liposome entrapment

Liposomes are produced by sonication, extrusion, and a number of related techniques. Active ingredients can be entrapped within the aqueous phase of the vesicle (i.e., the liposome interior) or incorporated within the lipid structure. Liposomes have been effectively used for delivery of enzymes and vitamins into the body. They consist of one or more layers of lipids, making them nontoxic and acceptable. Liposomes can range from a few nanometers to a micron. They were initially developed for medical purposes and cosmetics. This method is a highly valuable resource, owing to their high encapsulation efficiency, stability, and easy production in food applications. For example, one food application of liposomes is in cheese-making.

Emulsion-based processes

Emulsion-based processes are one of the most widely used methods for food encapsulation because they allow the encapsulation of both water-soluble and oil-soluble food ingredients.

Emulsion-based techniques have been successfully used to encapsulate bioactive compounds including fatty acids, vitamins, phenolic compounds, anthocyanins, oils, and bioactive extracts.

Dried emulsions may be in the form of encapsulates or an instant formulation, which can be used for numerous food products.

Molecular inclusion

Molecular inclusion is a method of encapsulation that is not commonly used. In this method, the bonding between the encapsulated compound and the shell material occurs by hydrogen bonds, van der Waals forces, or hydrophobic effects. Cyclodextrins or their derivatives are the most widely used shell material for molecular inclusion.

Molecular inclusion protects active compounds against oxidation and heat degradation and can be used for masking undesired smell or taste and increasing solubility in food applications [36–38].

Nanoencapsulation

Nanoencapsulation is defined as the technology of packaging nanoparticles of solid, liquid, or gas, also known as the core or active matrix, within a secondary material, referred to as the matrix or shell, to form nanocapsules. The core contains the bioactive compound or active ingredient, while the shell coats and protects the active ingredient from the surrounding shell material. The shell is temporary which allows the release of core active ingredient by diffusion or by trigger of shear, pH or enzyme action. The particles have dimensions less than 100 nm for the desired structural and functional characteristics. The main application of nanoencapsulation is in the design and development of novel delivery systems for bioactive compounds with improved water solubility, stability, functionality, and bioavailability [39,40].

Application of fruit extracts as anticancer agents

Fruit extracts have been proven to be associated with the treatment of various diseases. Natural compounds or extracts from fruits are important leads in the development of anticancer drugs that will not have the side effects of chemotherapy and cytotoxic drugs currently used for treatment of cancer.

Numerous studies have proved that fruit extracts and their active components have anticancer and cytotoxic activities. Polyphenols, flavonoids, terpenes, and alkaloids are the important active components that possess the biological activity of the fruits. Triterpenoids such as saponin, squalene, oleanolic acid, betulinic acid, lupeol, lanosterol, and lanostane have been reported to exert cytotoxic effects. Other flavonoids, such as kaempherol, myricetin, quercetin, and rutin, have also been reported to display anticancer properties. Additionally, several alkaloids, such asmatrine and sanguinarine, have been reported to possess anticancer activities.

One of the important mechanisms of action of cytotoxic effect is that these compounds act as antioxidants and scavenge the free radicals in the body.

The current trend in the application of the natural extracts is the use of encapsulation technology or nanoencapsulation. This technology generates several formulations with advantages such as encapsulation of different compounds in one formulation, targeted delivery to the organs, protection and conservation of the biological activity, and controlled release of the active components.

Campomanesia xanthocarpa O. Berg (guabiroba) fruit extract, which is rich in carotenoids, was encapsulated by using PLGA, and it reduced reactive oxygen species (oxidation) in human colon adenocarcinoma HT-29.

Another fruit extract with potential anticancer activity in cell line A549 was obtained from *Phytolacca decandra*. PLGA nanoparticles of *P. decandra* proved to be more effective in releasing the extract and showed higher antitumor efficacy.

Encapsulated mangosteen fruit (*Garcinia mangostana*) extract has been shown to have anticancer activity. *G. cambogia* encapsulated in nanoparticles was incorporated in the formulations and tested for cytotoxic activity on the HeLa cell line. The methylcellulose particles showed higher cytotoxic activity (almost double) in comparison to ethyl cellulose particles. The in vitro studies done for the nanoparticles established that particles were internalized by an endocytosis mechanism mediated by clathrin and were mobilized internally through the endolisosomal pathway [41].

Kiwi and pomegranate plant extracts have been proved to show cytotoxic effects on two tumor cell lines. Mixtures of two plant extracts are good sources for human leukemia cell inhibition. It was also proved that there was a correlation between the anticancer activity and the antioxidant activity of the natural plant extracts [42].

Berries are another class of fruits that are rich in flavonoids and anthocyanin. Extracts of blackberry cultivars treated with methyl jasmonate showed enhanced inhibition of leukemia and lung cell proliferation and induced the apoptosis of leukemia cancer cells.

Chinese bayberry fruit extract inhibited tumor development by scavenging the free radicals and decreasing the oxidative stress. An animal study that involved berry fruit extract proved that the extract reduced *N*-nitrosomethylbenzylamine tumorigenesis in the rat esophagus.

Apple extracts have shown high antiproliferative activities in several cancer cell lines, particularly in colon and stomach cancer cells. This was attributed to the high content of flavanoids and chalcones. they also showed high antiproliferative activity in several cancer cells. Cherry extracts inhibited colon cancer cell proliferation [41,43,44].

Grapes contain high amounts of flavonoids and cinnamic acid, to which chemopreventive activity has been attributed. Resveratrol, a phytochemical that is found abundantly in the skin of grapes shows chemopreventive potential. There are numerous studies of grapes and grape-based products for cytotoxic activity.

In a study with purple grape juice extract, inhibition of carcinogen DMBA-induced mammary tumorigenesis was observed in rats [15,45].

Annona sqamosa (sweetsop) fruit pericarp showed cytotoxic effect against Dalton's lymphoma cells and HeLa cell lines. Silver nanoparticles synthesized from *A. squamosa* leaf extracts showed potential cytotoxic effects against breast cancer cells. The cytotoxic effect is mediated by different mechanisms, such as necrosis, stimulation of signaling pathways, lysosomal damage, caspase-mediated signal transduction, and apoptosis [46].

Gold nanoparticles made using the fruit extracts of *Aegle marmelos* (bael), *Eugenia jambolana* (Malabar plum), and *Annona muricata* (soursop) showed curative properties against various diseases. This is attributed to a number of bioactive compounds present in the extracts, such as alkaloids, flavonoids, phenols, alkaloids, tannins, and proteins. MTT cytotoxicity assay revealed that the particles are able to act on the cancer cells and destroy them by various chemical reactions. However, the destruction rate depends on the concentration of the fruit extract as well as the gold nanoparticles. Among the three fruit extract nanoparticles, soursop showed the highest cytotoxicity against human breast cancer cell lines (MCF-7). The possible mechanism involved is photothermal therapy [47].

Vaccinium macrocarpon (cranberry) is rich in phytochemicals such as flavonols, anthocyanins, proanthocyanidins, catechins, hydroxycinnamic and other phenolic acids, and triterpenoids. The polyphenolic extracts showed inhibition of the growth of the cancer cells in breast, colon, prostate, lung, and other tumors. This is due to the synergistic effect of the various phytochemicals. The chemopreventive mechanism of action include induction of apoptosis of the tumor cells, reduced ornithine decarboxylase activity, and decreased expression of metalloproteinase, which are associated with tumor metastasis [48].

Pomegranate extracts showed therapeutic effects against human breast cancer cells (MCF-7). the extracts showed drastic growth inhibition of the cells by induced apoptosis in the cancer cells. Growth inhibition was higher when pomegranate extracts were used along with genistein. The main mechanism of cell death has been identified as the induction of the apoptosis [49].

Mechanism of action of nanoparticles

Several mechanisms are involved in the cytotoxic activity by the fruit extracts illustrated by various researchers. Possible mechanisms include phytothermal ablation, mechanical damage, and delivery of anticancer agents (tumor necrosis factor or doxorubicin), with minimal injury to healthy cells. Necrosis results as a result of disruption of cellular and nuclear membranes under extreme physiological conditions. Necrosis and apoptosis induce cell death in tumor cells. The nuclear contents of the cytoplasm leach out of the cell in case of necrosis, and the nuclei of the apoptotic cells shrank with condensed chromatin. Several other factors, such as reduced membrane integrity, ion exchange, DNA damage, and hampered phagocytosis, could lead to cell death.

Fruit extracts and their nanocapsules have proven to be effective way of delivering the phytochemicals in formulations that possess cytotoxic activity along with other benefits, such as antimicrobial, antioxidant, and antiinflammatory activities. This has led to a decrease in the use of synthetic compounds, which are being replaced by natural sources, such as plant extracts products.

However, the use of the plant products involves concerns such as poor chemical stability during processing, effective delivery of nutrients, bioavailability, biocompatibility, and nanotoxicology.

Conclusion

Cancer is a chronic diseases that is prevalent all over the world, affecting millions of people annually. Although, medical science has made tremendous advances in curing cancer, its prevalence has increased significantly in the last few decades. There is an urgent need to adopt preventive measures to overcome the lethal effects of cancer. Previous investigations have determined that plant products, specifically fruits, have tremendous potential in cancer treatment. The antioxidants that are present in fruits in the form of polyphenols and flavonoids exhibit anticancerous activities. These anticancerous compounds can be incorporated into a variety of food products via different infusion techniques to inhibit

the carcinogens that exist in the food products. Although there have been advances in the infusion techniques for increasing the stability of the anticancerous compounds incorporated in the different food products, it is still not effective. There is a need to develop novel processing tools and encapsulating techniques for increasing the efficiency and stability of anticancerous compounds with enhanced efficiency once they have been incorporated in food.

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Chapter 37

Antioxidant diets and functional foods attenuate dementia and cognition in elderly subjects

Sanit Wichansawakun[1], Kanokkarn Chupisanyarote[1], Wannisa Wongpipathpong[1], Ginpreet Kaur[2] and Harpal S. Buttar[3]

[1]Department of Internal Medicine, Faculty of Medicine, Thammasat University, Bangkok, Thailand, [2]Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM's NMIMS, Mumbai, India, [3]Department of Pathology & Laboratory Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada

List of abbreviations

AD	Alzheimer's disease
ADAS-J	Alzheimer's disease assessment scale-cognitive subscale
apoE4	Apolipoprotein E4
APP	Amyloid protein precursor
C3G	Cyanindin-3-O-ß-D-glucopyranoside
CNS	Central nervous system
CVDs	Cardiovascular diseases
DASH	Dietary Approaches to Stop Hypertension
DHA	Docosahexaenoic acid
EPA	Eicosapentaenoic acid
ESPEN	European Society for Clinical Nutrition and Metabolism
GABA-A	Gamma-aminobutyric acid A
GB	*Ginkgo biloba*
G6PDH	Glucose-6-phosphate dehydrogenase
MED diet	Mediterranean diet
MIND	Mediterranean-Dietary Approaches to Stop Hypertension Intervention for Neurodegenerative Delay diet
MMSE	Mini-Mental state examination
MUFAs	Monounsaturated fatty acids
NADPH	Nicotinamide adenine dinucleotide phosphate
NCDs	Non-communicable diseases
NO	Nitric oxide
PUFAs	Polyunsaturated fatty acids
PSEN1	Presenilin-1
PSEN2	Presenilin-2
QOL	Quality of life
RCT	Randomized controlled trial
ROS	Reactive oxygen species
SOD	Superoxide dismutase
SPM	Specialized pro-resolving mediators
TrkB	Tropomyosin receptor kinase B
WHO	World Health Organization

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Introduction

The incidences of non-communicable diseases (NCDs), such as neurodegenerative disorders, cardiovascular diseases (CVDs), diabetes mellitus, obesity, musculoskeletal abnormalities, osteoarthritis, and cancer, are currently surpassing those of communicable diseases and are imposing a major healthcare burden globally. The most common acute neurological abnormalities in adult and adolescent groups are epilepsy, autism-spectrum disorder, bipolar disorder, depressive episodes, anxiety, learning problems, hyperactivity, and attention deficit disorder in children, whereas the elderly population is generally afflicted with chronic neurological disorders such as dementia, impairment of cognition, mood swings, insomnia, depression, Alzheimer's disease (AD), and Parkinson's disease. Myocardial infarction and stroke due to brain hemorrhage or intraarterial brain thrombosis often requires long-term hospitalization and rehabilitation, irrespective of the age group. The chronic neurodegenerative diseases are characterized by the progressive degeneration of neurons, leading to central nervous system (CNS) dysfunction and enhanced neuronal death due to hypoxia and oxidative stress. One of the biggest health concerns in the aging population is declining mental functions and higher incidences of AD, dementia, and cognition deficit as well as depression and insomnia experienced by millions of elderly humans worldwide. These ailments not only cause memory loss, interfere with cognition and executive function, and cause motor impairments, but also adversely affect daily life activities and quality of life (QOL) in the geriatric population. Unfortunately, the social and economic burden of neurodegenerative diseases is largely underestimated and does not receive appropriate healthcare attentions. In September 2019 the World Health Organization (WHO) updated its estimates of these important issues and announced that the total number of people with dementia and cognition impairment is around 50 million worldwide. Approximately 60% live in low- and middle-income countries, and nearly 10 million new cases occur every year. These numbers are expected to reach 82 million in 2030 and 152 million by 2050. The total healthcare cost for treating dementia, particularly related to AD, is $818 billion per year and this number is likely to increase as the estimates of prevalence advance in the future [1]. In view of these implications, AD and dementia are considered a major public health priority worldwide. New alternative treatment modalities and strategies for the prevention and care of dementia will be the key factors to reverse the increasing trend of this disease. Consumption of wholesome healthy foods, modification of lifestyle factors, low alcohol consumption, cessation of tobacco smoking (including e-cigarettes and marijuana smoking), and physical activity would be the most cost-effective strategies in delaying the onset and prevention of dementia and cognitive decline in the elderly population. The other potential risk factors for dementia are medical conditions: diabetes mellitus, CVDs, obesity, respiratory disorders, air pollutants, and exposure to environmental toxicants. To date, a large body of literature has addressed protective roles of dietary interventions, functional foods, lifestyle modifications, reduction of sedentary habits, and exercise in slowing the incidence of dementia and improve cognitive function.

The hypothesis of this review is that aging humans who consume antioxidant and antiinflammatory diets, functional foods, do not smoke, drink moderate amounts of red wine, and have a physically active lifestyle will have a reduced risk of memory loss and impaired cognition caused by chronic neurodegenerative diseases. We have attempted to examine the impact of modifiable and nonmodifiable risk factors causing memory loss due to AD, stroke, diabetes, and obesity. We have also addressed the potential roles of functional foods, nutraceuticals, and micronutrients (vitamins, trace elements) and memory-enhancing phytomedicines in mitigating or preventing dementia and improving cognition in the elderly population.

Overview of the pathophysiology of neurodegenerative diseases

Among the most important neurodegenerative diseases that causing dementia are AD, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis [2]. Many theories have been propounded and modified over the years about neuroinflammation and neurodegeneration caused by AD, and several therapeutic strategies have been proposed. The widely recognized histopathological and biomolecular mechanisms consist of the deposition of microglia-mediated inflammation products and protein aggregates in different cerebral areas of the brain, leading to neuronal dysfunction [3]. Several studies have found that neuronal cells undergo progressive degradation due to neuroinflammation and oxidative stress–induced cascades of proteases and brain phospholipids, to name just a few. There seem to be two types of neuronal cells associated with this cascade: microglial cells and astrocytes. Microglia cells mediate astrocytes by activation of cytokines, such as interleukin 6, tumor necrosis factor alpha, caspase 1, and promote the end stage of neuron damage, which leads to cellular dysfunction and programmed cell death termed apoptosis [4]. Apoptosis causes reduction of the activity of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and glutathione biosynthesis [5].

It has been well documented that men are at higher risk of Parkinson's disease, autism-spectrum disorders, and schizophrenia, whereas women have increased risk of AD, depression, and stress-related illnesses. The incidences of chronic neurodegenerative diseases such as stroke, AD, Parkinson's disease, depression, schizophrenia, and anxiety-associated disorders are greater in postmenopausal women. The sex differences are attributed to sex hormone effects (testosterone, estrogens) on the CNS. Androgens and estrogens have neuroprotective actions on neuronal and glial cell viability. Neuroprotection is decreased in hormone-deficient men and women. Oxidative stress is also enhanced in aged men and women, and sex hormones (testosterone, estrogen) protect against oxidative stress in both genders [6].

Postmortem examinations have revealed that the cerebral cortex shrinks dramatically or atrophies in the AD brain, and the gross appearance of the AD brain is very different from that of the normal brain. Among all the neurological diseases, AD is the most prevalent cause of dementia. In AD, abnormal brain tissue is accompanied by the presence of beta-amyloid plaques and neurofibrillary tangles and the deposition of hyperphosphorylated tau. Animal models have also shown similar pathological features. Genetic susceptibility is an important factor in causing familial AD. Apolipoprotein E4 (apoE4) is the major genetic risk factor, with strong evidence of mutations in amyloid protein precursor (*APP*), presenilin-1 (*PSEN1*), and presenilin-2 (*PSEN2*). APP is the precursor of beta-amyloid plaques, and APP mutations affect beta-amyloid cleavage and aggregation, causing toxic conformation of beta-amyloid plaques and tau or both. These events result in the degeneration of brain blood vessels, causing leakage in the blood-brain barrier and age-related neurodegeneration independent from beta-amyloid plaques. These histopathological and biochemical characteristics of the brain are probably the core features of AD [7–10]. The quest to find the underlying pathological mechanisms and causes of AD has been ongoing for several decades, but the exact underlying causes and mechanism involved in producing this age-related neurodegenerative disease remains unknown. Evidence from multidisciplinary research points toward a link between cardiovascular risk factors and the importance of brain and cognitive reserve. Both diabetes and hypertension can cause cerebrovascular lesions. It appears that cerebral atherosclerosis and neurodegeneration might have shared mechanisms, such as oxidative stress and inflammation-induced pathological changes in the neurons. Some neuropathological studies have shown that psychosocial factors can modify the association of neurodegenerative abnormalities with cognitive function involving the reserve memory hypothesis. For example, people with high levels of education or rich neuronal networks generally have less cognitive impairment and depression than people with low educational attainments [9].

About one-third of AD cases worldwide have revealed prevention opportunities from several modifiable and nonmodifiable risk factors: midlife hypertension, midlife obesity, diabetes, physical inactivity, smoking, low educational attainment, and depression [11]. Nonetheless, the mainstay of AD treatment is supportive care from family members and other caregivers and maintenance of care for loved ones to preserve personal well-being of the patient. The well-known modifiable and nonmodifiable (genetic) risk factors and protective factors of neurodegenerative diseases are shown in Table 37.1 [9].

AD and related dementias are associated with escalating personal, societal, and healthcare economic burdens. Therefore the race for preventing and treating AD with synthetic pharmaceuticals, including acetyl choline inhibitors, and alternative therapies is continuing rigorously all over the world. Unfortunately, no new drug moieties or alternative remedies have been discovered or shown effectiveness over the last 20 years. As the disease progresses, new symptoms emerge caused by unknown factors not targeted by the medication. The new approaches of drug discovery and development for AD have focused on disease-modifying agents such as antiamyloid approaches, including active and passive immunization strategies, gamma-secretase and beta-secretase inhibitors, tau-targeted therapies, neurotransmitter-based therapies, neurotropic and hematopoietic growth factors, and antioxidant or antiinflammatory therapies [12]. To date, clinical trials of anti-AD drugs have not met expectations. In the future, anti-AD therapies may be combined with lifestyle modifications, dietary interventions, and smoking cessation for improving general brain health and jointly targeting factors to combat this debilitating disease [8].

Role of nutrition in the attenuation of dementia and cognition

One strategy to address the modifiable risk factors of dementia is a combination of a wholesome diet that is rich in fresh fruits and vegetables, less red meat, dairy products, and omega-3 fatty acids; moderate consumption of red wine; lifestyle changes; and physical activity. Several epidemiological studies have reported that diets containing antioxidants and micronutrients may prevent or attenuate cognitive impairment in elderly folks. The data of most of these studies were obtained from patients with mild cognitive impairment or normal populations [13,14]. Therefore the findings of such studies might not be applicable to patients with moderate or severe cognitive impairment. Evidence-based practice has shown that some specific nutrients can prevent neurodegenerative diseases through multiple mechanisms. However,

TABLE 37.1 Nonmodifiable genetic factors and modifiable risk factors involved in causing neurodegenerative diseases.

Risk factors	Protective factors
Genetic risk factors	**Certain protective factors**
• Old age • Genetic history • Familial aggregation of genes (two or more family members with disease) • *APOE* ε-4 allele • Other susceptibility genes (*CR1*, *PICALM*, *CLU*, *TREM2*, *TOMM40*) • Hyperhomocysteinemia • Brain trauma or infectious diseases that cause brain tissue injury	• Some proposed genes: 1 APP, APOE ε-2 allele
Modifiable risk factors	Proposed protective factors
• Vascular and metabolic risk factors: ◦ Cardiovascular diseases caused by atherosclerosis ◦ Diabetic mellitus and prediabetes ◦ Midlife hypertension, overweight and obesity, high serum low-density lipoprotein cholesterol level • Lifestyle: sedentary habits, tobacco smoking, heavy alcohol consumption • Dietary nutrients: ◦ High intake of saturated fats, deficiency of vitamin B_6, vitamin B_{12}, and folate	• Higher education and socioeconomic status • Rich social network and social engagement • Lifestyle: physical exercise, low to moderate alcohol consumption, especially red wine • Dietary patterns and some nutrients ◦ Mediterranean diet ◦ Polyunsaturated fatty acids, especially omega-3 fatty acid ◦ Vitamins A, B_6, B_{12}, C, D, and E and folate

Source: Modified from Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. Lancet Neurol 2016;15(5):455–532.

these studies did not reveal strong evidence of clinical outcomes in the elderly population [14]. Nevertheless, nutritional interventions focusing on specific dietary patterns rather than specific nutrients, such as the Mediterranean (MED) diet, the Dietary Approaches to Stop Hypertension (DASH) diet, and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet, have shown positive effects on neuroprotection in humans who follow these dietary patterns on a regular basis [13,15]. Epidemiological studies have reported that consumption of diets that are rich in flavonoids is associated with reduced risk of coronary heart disease and stroke [16]. However, evidence on the relationship between dietary flavonoids intake and the improvement of dementia and cognition is lacking.

Influence of specific nutrients to protect against neurodegenerative diseases

Many biologically active phytochemicals and polyphenolic substances that are present in dietary supplements have suggested their preventive role in neurodegenerative diseases [17]. For example, *Ginkgo biloba* (GB) is one of the most popular phytomedicine used as a memory enhancer and preventive treatment for cognitive decline in the aging population. In addition, dietary phytochemicals, such as curcumin, resveratrol, catechins, and anthocyanin, have been proposed to prevent neurodegenerative diseases [17]. Vitamins (A, B_1, B_2, B_3, B_6, B_{12}, C, E) and trace elements (zinc, magnesium, manganese, and selenium) have shown some positive influence in the prevention of AD [18]. It has been argued that dietary supplements containing vitamin D, omega-3 polyunsaturated fatty acids (PUFAs), including eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), may slow the progression of AD [18]. Epidemiological, clinical, and animal studies support the role of polyphenols at nutritional doses in the prevention of NCDs, such as neurodegenerative diseases, cardiovascular disorders, and some types of cancer. Emerging evidence suggests that dietary supplements containing flavonoids, carotenoids, and antioxidants modulate gene and protein expression and thereby modify endogenous metabolic pathways and homeostasis and consequently reduce the risk of chronic diseases that are multifactorial in origin. It appears that phytochemicals, botanicals, nutraceuticals, and functional foods are promising candidates for delaying the onset and progression of age-related neurodegenerative diseases, including AD and cognitive impairment. The impact of plant-derived polyphenols, phytomedicines, probiotics, vitamins, and trace elements for neuroprotection is described below.

Ginkgo biloba

Numerous experimental and clinical studies have been published regarding the neuroprotective actions of GB. The major bioactive ingredients of GB (ginkgolides, sesquiterpene, bilobalide, isoginkgetin, flavonoids, and proanthocyanindins) possess strong antioxidant antiinflammation properties and inhibit oxidative stress and inflammation in the brain. GB extracts are used as an alternative therapy for treating anxiety, dementia, and psychiatric disorders [19]. According to Cicero et al., one of the mechanisms involved in the prevention of neurodegeneration by GB is due to the increased cerebral blood flow via inhibition of platelet-activating factor and enhanced production of nitric oxide (NO) [20]. Furthermore, GB's antioxidant bioactive ingredients may also act as free radical scavengers and produce modifications in the serotonergic and monoamine neurotransmitter systems [21]. On the basis of human studies, there seem to be no impact of GB on age-related cognitive decline in people with normal cognitive function [22]. A metaanalysis of two randomized controlled trials on supplemented GB above 200 mg/day for 24 weeks has revealed some improvement in cognitive function in patients suffering from mild to moderate cognitive impairment [23]. The usual recommended doses of GB extracts range from 120 to 240 mg/day [13]. However, some investigators suggest a 200-mg/day dose for at least five months to maximize the benefit of GB extract on neurodegenerative decline [20]. Some side effects include headache, gastrointestinal (GI) disturbance, and bleeding problems due to interactions with anticoagulants such as aspirin, warfarin, ticlopidine, clopidogrel, and dipyridamole, resulting in an increased risk for internal bleeding [19]. In view of these adverse reactions, administration of GB extracts should be avoided in patients who may be using antiplatelet or anticoagulant drugs.

Curcumin

Curcumin (diferuloylmethane) is the polyphenolic bioactive ingredient of the turmeric rhizomes of *Curcuma longa* (ginger family: Zingiberaceae). Turmeric is commonly used as a curry spice in India and many South Asian countries. Turmeric has also been used in the Ayurveda system of medicine for wound healing, skin care, GI disorders, ulcerative colitis, and rheumatic disease. Currently, many turmeric products are marketed for health benefits in Europe, the United States, and Canada. Turmeric's bioactive compounds (curcumin and curcuminoids) have shown strong antiinflammatory and antioxidant properties and have displayed high affinity toward perhydroxyl radicals and scavenger of free radicals produced by oxidative stress. Lately, curcumin has been linked to improved brain function and reduced depressive symptoms. However, the clinical trial outcomes with curcumin have shown conflicting results due to the lesser absorption and low bioavailability in humans [20]. The results of a population-based cohort study ($N = 1010$) provided tentative evidence that regular curry consumption improved cognitive performance in 60- to 93-year-old nondemented subjects [24]. In an AD animal model, curcumin showed reduction in amyloid deposition and improved overall cognitive function [25]. A 24-week randomized, double-blind, placebo-controlled study was done in 36 subjects with mild to moderate AD. Patients received either placebo-filled capsules or 2 and 4 g/day of oral Curcumin C3 Complex in two divided doses for 24 weeks. Curcumin was generally well tolerated, but three subjects withdrew because of GI side effects. Curcumin treatment was associated with lowered hematocrit and slightly increased glucose levels. The concentration of curcumin in plasma was found to be very low (7.32 ng/mL), suggesting the limited bioavailability of curcumin, presumably owing to its extensive metabolism in the GI tract. The results of this study demonstrated neither clinically nor biochemically significant evidence of curcumin efficacy in AD patients [26]. So far, clinical trials and animal studies have yielded conflicting results regarding the effectiveness of curcumin in preventing or ameliorating age-related memory loss, cognitive decline, mood disorders, and schizophrenia in AD patients. Some investigators have suggested that curcumin may be more effective in improving cognitive function in the elderly than treating AD related symptoms [27,28]. Nanoformulations of curcumin or curcuminoids may enhance their bioavailability and delivery in the CNS and improve their therapeutic efficacy in elderly patients.

Polyphenolic compounds

One of the best-known polyphenols with neuroprotective effects is resveratrol. Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a metabolized polyphenol compound released from grapes and berry plants in response to environmental attack or injury. The compound is present in red wine and dark chocolate. The neuroprotective effects of resveratrol are due to its potent antiinflammatory and antioxidant properties [29]. A clinical study showed that individuals who took resveratrol had stable levels of amyloid-beta 40 protein, whereas the level declined in the control groups [30]. Resveratrol may also help to prevent blood-brain barrier leakage via increased sirtuin 1 levels [30]. Sirtuin 1 may reduce matrix

metalloproteinase 9, which causes blood-brain barrier breakdown [29]. Administration of 250−500 mg/day doses of resveratrol showed an increase in cerebral blood flow in healthy adults [29]. The overall current data from human studies do not provide definitive evidence about the neuroprotective effects of resveratrol in the therapeutic management of cognitive impairment [30].

Another famous polyphenolic compound is epigallocatechin-3-gallate, which is found in tea plants and green tea [20]. It has also been proposed as a potent antioxidant to prevent neurodegenerative diseases [20], and it seems to help by scavenging highly reactive oxygen species, which are harmful to neuronal cells. Consumption of green tea may improve cognitive function and reduce memory decline [31]. However, most studies have been conducted in animals, and there is no strong evidence of clinical outcomes in humans. Another polyphenolic compound (flavonol) is found in *Theobroma cacao*. This flavonol has been asserted to have a protective effect on neuronal cells. There are several flavonoid-binding sites present on neurons, such as adenosine, gamma-aminobutyric acid A, delta-opioid, nicotinic, tropomyosin receptor kinase B, estrogen, and testosterone [20]. Flavonoid attachment with these receptors may activate signaling pathways resulting in increased neuronal activity [20]. Additionally, cocoa flavonols may trigger the secretion of NO, which can increase cerebral blood flow [20]. Desideri et al. showed that the regular daily consumption of a dairy-based cocoa drink containing moderate to high doses of flavanols (520−990 mg/day) may improve the cognitive function of elderly people with mild cognitive impairment [32]. However, there is a difference between processed cocoa and cacao powder extracted from *T. cacao*, because heating processes can destroy antioxidant potential and other nutrients such as fatty acids and soluble vitamins in the processed cocoa.

Nobiletin is a bioactive polyphenol that has been used in patients with AD and Parkinson's disease. It is a component of polymethoxylated flavone extracted from the dried peelings of citrus fruits, *Citrus depressa* and *Citrus reticulata*. Many studies have been conducted in animal models using nobiletin to improve cognitive function. The results revealed that nobiletin could improve short-term memory and working memory by protecting cholinergic innervation of the hippocampus, thereby increasing the activity of intracellular antioxidant enzymes and reducing oxidative stress with hyperphosphorylation of tau and decreasing beta-amyloid deposits and, at the same time, increasing the formation of beta-amyloid plaque in the hippocampus [33]. A small clinical study was conducted by Seki et al in 11 patients with mild to moderate AD. Six patients received nobiletin extracts (13.0 g/day + donepezil 5.0 mg/day), while five patients received donepezil 5.0 mg/day alone for one year. The cognition scores showed better results in the Mini-Mental state examination and Alzheimer's disease assessment scale-cognitive subscale, and no adverse events were observed, but the results were not statistically significant [34]. Further well-designed, randomized, placebo-controlled, multicenter clinical trials are needed to establish the safety and efficacy of nobiletin for the prevention and treatment of AD.

Mulberry (*Morus alba* L.) is a famous fruit in traditional Eastern medicine. Mulberries contain alkaloids and flavonoid, antioxidants, anthocyanins, and flavonoid pigment polyphenol [35]. Cyanindin-3-O-β-D-glucopyranoside (C3G) is a bioactive phytochemical that is present in the extract of mulberry fruit. C3G has inflammation-suppressing and free radical−scavenging activity that protects against endothelial dysfunction [36]. The neuroprotective effects of anthocyanin have been reported in animal models. For example, a study was done in adult Wistar rats treated orally with mulberry extract at doses of 2, 10, and 50 mg/kg for 7 days before and 21 days after the occlusion of the right middle cerebral artery. The results showed that administration of mulberry extract increased the densities of neurons, decreased oxidative stress in the hippocampus, and improved memory impairment in rats with vascular dementia [37]. So far, no studies have been done in humans to evaluate the beneficial effects of mulberry fruit in improving memory function or cognitive deficit.

Another fruit that is rich in polyphenolic compounds and ellagic acid is the pomegranate. Owing to the strong antioxidant and antiinflammatory effects of pomegranate components, many animal studies have been carried out to determine the neuroprotective actions of pomegranate juice. The results of animal models showed that pomegranate juice could decrease beta-amyloid deposition in the hippocampus, protect against oxidative stress, and improve memory in rats. On the basis of these studies, it was hypothesized that antioxidant polyphenols present in pomegranate juice may prevent neural damage by scavenging free radicals produced by oxidative stress, and consequently improve hemodynamics and neuroplasticity. However, the exact neuroprotective actions of pomegranate ingredients remain to be ascertained. To evaluate the benefits of pomegranate juice on cognitive health, 28 middle-aged and older men and women volunteers were randomly assigned to 8 ounces/day of either pomegranate juice ($N = 15$) or a flavor-matched placebo drink ($N = 13$) for 4 weeks. Subjects who drank pomegranate juice showed a significant improvement in standardized verbal and visual tasks, suggesting that polyphenols present in pomegranate juice augmented memory functions in older adults [38]. Another randomized, double-blind, placebo-controlled trial with pomegranate juice was performed for 12 months in 261 middle-aged and older adults (50−75 years). The subjects were given 8 ounces of either pomegranate juice or a matched placebo drink without pomegranate polyphenols. The mental functions of 98 pomegranate juice

subjects and 102 placebo subjects who completed the study did not differ significantly. However, daily consumption of pomegranate juice over a 12-month period improved visual skills and stabilized the learning ability in elderly subjects [39]. Additional well-designed, randomized, placebo-controlled, multicenter studies are needed to evaluate the neuroprotective potential of pomegranate juice and its bioactive ingredients on different memory functions in older adults.

Omega-3 polyunsaturated fatty acids

Long-chain omega-3 PUFAs, such as EPA, DHA, and arachidonic acid are mainly found in cod liver oil and oily fish. PUFAs are beneficial both nutritionally and pharmacologically and play an important role as antiinflammatory agents. Nicotinamide adenine dinucleotide phosphate (NADPH) is an essential reducing agent for anabolism and is one of the cofactors for the synthesis of PUFAs and other fatty acids. Glucose-6-phosphate dehydrogenase (G6PDH) is the key enzyme for the NADPH generation. PUFA production can be enhanced by stimulating G6PDH. Many animal and human studies have reported that PUFAs can prevent atherosclerosis and can modulate glucose metabolism, leading to the reduction of cardiovascular and cerebrovascular diseases. The PUFAs can reduce the production of proinflammatory cytokines, increase specialized pro-resolving mediators [40], and modulate innate immunity by enhancing beta-amyloid phagocytosis [41].

PUFAs are essential components of the neuronal cell membranes that preserve membrane fluidity for the neurotransmitter communication and synaptic-signaling processes. Lower levels of DHA in the brain can alter neuronal membrane properties and change enzyme activity and electrophysiological transmission in the brain, consequently decreasing spatial memory performance [42]. A metaanalysis showed that EPA and DHA were reduced in patients with dementia, while EPA was significantly lower in patients with predementia [43].

Based on the antiinflammatory effects of PUFAs, many clinical trials have been conducted to investigate the effects of PUFAs on cognitive function. However, the current evidence provides conflicting results. Some randomized controlled trials have reported that PUFAs have beneficial effects in the improvement of cognitive function in elderly subjects with mild cognitive impairment [44–47]. On the other hand, some trials have yielded altogether negative results [48–51]. The discordant findings might have resulted from different study designs and settings, such as dose differences, study duration, and sources of PUFA supplements. Hence further well-designed, randomized, and placebo-controlled clinical trials are needed to determine the beneficial role of PUFA on memory function and resolving psychiatric problems in the elderly population.

Tryptophan

Tryptophan is an essential amino acid which is not synthesized in the human body and is only available in the diet. Tryptophan occurs in L- and D-isomeric forms with an indole ring and aromatic side chain. The L-form occurs most commonly in the biological systems particularly in the higher organisms, including humans. The D-form is confined to some bacterial cell wall proteins and certain peptide antibiotics. The principal role of tryptophan in the human body is synthesis of proteins and muscle tissues. Tryptophan is the precursor of key molecules such as serotonin, melatonin, tryptamine, niacin, quinolinic acid, and kynurenic acid, and nicotinamide adenine dinucleotide, which are critically important for neuronal development and synaptogenesis, neuroimmune activity, and mitochondrial function [52].

Dietary sources of tryptophan are dairy products, meats, fish, eggs, bananas, oats, pumpkin and sesame seeds, chocolate, dried dates, soy, tofu, tree nuts, peanuts, and peanut butter. Breast milk is the primary source of tryptophan for nursing infants. Adequate intake of this amino acid is crucial for growth and development of children and adults. Excessive dietary restriction and malnutrition decrease brain serotonin stores and lead to behavioral changes, such as hyperactivity, depression, anxiety, suppression of appetite, anorexia nervosa, and behavioral impulsivity. Dietary supplementation of tryptophan improves these disorders [52].

Elderly subjects usually have sleep problems and mood disorders resulting from a natural decline in circulating serotonin and melatonin and from reductions in the neuronal synthesis of these molecules. Sleep deprivation impairs cognitive function and causes memory and learning problems. As was mentioned earlier, L-tryptophan is the precursor for the biosynthesis of serotonin, melatonin, and kynurenine [52]. These neuroactive molecules are important for maintaining neurological function and neuroprotection [53]. Serotonin helps to stabilize mood and enhance cognitive function [52,54]. Melatonin is widely known for regulating sleep-wakefulness timing and has also the ability to maintain memory and cognitive functions in healthy humans [55]. Melatonin supplements may help to improve mental functions in patients with dementia and Parkinson's disease. Another important metabolite of tryptophan is kynurenine, which is involved in the pathogenesis of inflammation-induced neurodegenerative diseases [52]. The 3-hydroxy anthranilic acid

that is produced from activated 3-hydroxy kynurenine in the kynurenine pathway plays an important role in neuroprotection during inflammation or infection [52]. In view of the neurotransmitter and neuroprotective actions of tryptophan and its metabolites, the intake of tryptophan dietary supplements could be useful in elderly patients with dementia and cognition problems. The estimated daily requirement of tryptophan for adult humans is 4−5 mg/kg/day [55]. However, megadoses of tryptophan (225−425 mg/day) have been used in some clinical studies [52]. The amounts of tryptophan found in dome dietary products are listed in Table 37.2. Chia seeds, soybeans, cocoa, whey protein concentrate and isolate, chicken meat, and eggs are good dietary sources of tryptophan, which is needed for muscle protein synthesis and to provide neuroprotective or neuroenhancement benefits in the elderly subjects.

Role of probiotics and prebiotics in the improvement of memory and cognition

Trillions of diverse microbes live in a symbiotic relationship in the human tract. Their beneficial functions are depicted through the gut-brain axis, which is a bidirectional communication system between the CNS and the GI tract. Accumulating evidence suggests that the hormones secreted by the GI tract and the neurotransmitters produced by the gut microbiota play a critical role in regulating normal functioning of the gut-brain axis. It is well recognized that tryptophan metabolism in the GI tract produces serotonin, which acts as a key neurotransmitter at both terminals of the gut-brain network [56]. A limited number of clinical studies, with small numbers of patients, have shown an association between dysbiosis of gut microbiota and neuropsychiatric disorders such as autism and schizophrenia compared to the healthy controls [57]. Whether any relationship exists between pathological alterations in gut microbiota and the occurrence of memory loss, cognition deficiency, behavioral problems, and chronic neurological diseases among the elderly population needs to be explored with well-designed studies.

Cognitive frailty is a geriatric syndrome combining physical frailty and cognitive impairment without any clinical symptoms of AD. Several factors can cause cognitive frailty, such as specific personality, depression, CVDs, diabetes and insulin resistance, age-related sarcopenia, and malnutrition. On the basis of studies done in animal disease models and clinical observations in humans, it has been suggested that modulation of gut microbiota may predispose frail and elderly individuals to the development of dementia and cognitive impairment by promoting chronic inflammation and anabolic resistance as well as reduced synthesis of neuroactive substances by the gut microbes. In view of these observations, administration of probiotics and prebiotics may prove beneficial to attenuate dementia and preserve cognition in aging humans [58,59]. A number of neurotransmitters (e.g., serotonin, norepinephrine, acetyl choline, and gamma-aminobutyric acid) are needed for learning ability and memory function. Some investigators have proposed an association between dysbiosis and decreased secretion of neurotransmitters in the GI tract of older adults. The hypothetical explanation is based on the distortion of the microbiota-gut-brain axis [60]. Consumption of probiotics containing nonpathogenic live bacteria (present in foods such as yogurt and cheese) promotes healthy microbiota in the gut and confers health benefits on the host. Someone who cannot consume probiotics because of lactose intolerance should look for *Lactobacillus* and *Bifidobacterium* in the food ingredients list.

Prebiotics consist of nondigestible oligosaccharides that promote growth of beneficial bacteria in the gut. Short-chain fatty acids such as butyrate produced by carbohydrate fermentation by gut microbiomes have been asserted to reduce neural inflammation while promoting neurotransmitters and hormone secretions from the gut [61,62]. It must be

TABLE 37.2 Tryptophan-rich foods.

Food	Amount of tryptophan (mg/100 g)
Chicken boneless meat	400
Cheese	325
Cocoa	290
Beef	230
Chicken egg	165
Soybeans	160
Oat bread or bran	140
Chia seeds, dried	440

Source: Adapted from Nayak BN, Singh RB, Buttar HS. Role of tryptophan in health and disease: systematic review of the anti-oxidant, anti-inflammation, and nutritional aspects of tryptophan and its metabolites. World Heart J 2019;11(2):161−178.

emphasized that most of the above-mentioned observations are extrapolated from animal models of neurological diseases and the analysis of gut or fecal microbiota. Considering the ability of probiotics and prebiotics to confer benefits on the host by promoting a healthy microbial population in the gut, the potential effects of probiotics and prebiotics should be investigated in elderly humans to prevent and/or reduce neurological diseases associated with dysbiosis in this population.

There are some negative aspects to the role of gut bacteria. For example, cyanobacteria can secrete neurotoxins such as β-*N*-methylamino-alanine, which contributes to beta-amyloid accumulation in AD [63]. Interestingly, overproduction of tryptophan metabolites by the gut microbiota may increase oxidative stress, resulting in cell death, tau phosphorylation, and tangle formation in AD [60]. Therefore dietary amino acid balance remains an important concern to balance human health and neurological functions.

Multivitamins and trace elements

Many metaanalyses evaluated the relationship between multivitamins and trace element supplementation and the occurrence of neurodegenerative diseases [14]. It has been suggested that deficiencies in folic acid, vitamins B_{12} and B_6, and high blood levels of homocysteine may play some role in causing dementia, whereas dietary supplements containing vitamins B_{12} and B_6, folic acid, and trace elements may help in the prevention of CVDs and neurological abnormalities [64]. However, according to the Cochrane Database Reviews, intake of vitamins and mineral supplements showed little or no impact on long-term cognitive function [65]. Also, single doses or combination supplements of antioxidant vitamins C and E, beta-carotene, and trace elements (zinc, copper, selenium) have shown mixed results [66]. Thus clinical evidence for the long-term benefits of micronutrients is lacking. In other words, there are currently no micronutrient supplements that can help to treat or delay cognitive impairment in the elderly population [66,67]. The European Society for Clinical Nutrition and Metabolism has recommended that a single micronutrient supplementation should not be used in the prevention or treatment of dementia unless there is clinical evidence of deficiency [14].

Vitamin D deficiency commonly occurs in children and adults as a result of lack of ultraviolet exposure at northern latitudes, dark skin pigmentation at southern latitude, covering of skin by clothes, and vegetarian diets. The impacts of vitamin D on the absorption of calcium from the gut, bone development, osteoporosis, and immunomodulation are well documented in the biomedical literature. Epidemiological and experimental studies have shown an association between vitamin D deficiency and psychiatric disorders and neurodegenerative diseases, including depression, autism-spectrum disorder, and AD. It has been suggested that vitamin D supplementation could have neurotrophic and neuroprotective actions as well as decreasing neuroinflammation and help to improve cognitive functions [68,69].

Dietary pattern for improving dementia and cognition

Mediterranean diet

The MED diet is characterized by high consumption of olive oil, fresh fruits and vegetables, nuts, seeds, and whole grains; moderate consumption of fish, seafood, poultry, dairy products, and red wine; and low consumption of red meat and processed foods [67]. This dietary pattern provides many essential nutrients that exert neuroprotection through their antiinflammatory and antioxidant properties, resulting in delayed cognitive impairment. Monounsaturated fatty acids from olive oil, PUFAs from fish and seafood, and antioxidants from fruits and vegetables have yielded benefits for people with neurodegenerative diseases [70]. Several studies have shown that continued adherence to the MED diet decreases the risk for dementia and cognition [71–74]. In 2019 the results of Maine Syracuse longitudinal study showed that adherence to the MED diet was associated with improvements in global cognitive function, visual-spatial organization, memory, scanning and tracking in the aging participants (older than 70 years). However, there was no correlation in the population aged less than 70 years [75]. A large-scale, randomized, controlled trial study (PREDIMED) showed preventive effects on cognition function with MED diet supplements such as extra-virgin olive oil and nuts [76,77]. Furthermore, other dietary patterns that are similar to the MED diet, such as the MIND diet, prudent diet, and Baltic Sea Diet, showed results similar to those obtained with MED diet. One recent study was conducted as a multicenter trial with a whole-diet intervention, known as the NU-AGE diet, which is similar to the MED diet, in healthy elderly subjects from five different European countries. The findings revealed results similar to those obtained with the MED diet. The highest adherence to the NU-AGE diet showed a significant improvement in episodic memory [78]. In addition, several systematic reviews have shown that higher adherence to MED diet is associated with a reduced risk for cognitive impairment [79–84]. The 2019 WHO guidelines recommend that MED-type diets should be advocated for

older adults with normal cognition or mild cognitive impairment to reduce the risk for cognition decline and/or dementia [1].

Dietary approaches to stop hypertension diet

The DASH dietary pattern is recommended for treating hypertension. It includes high amounts of fruits, vegetables, low-fat dairy products, whole grains, fish, poultry, and nuts; small amounts of red meat, sweets, and sugar-sweetened beverages; and low amounts of sodium, total cholesterol, and saturated fat [85]. The components of the DASH diet are similar to those of the MED diet, except that the DASH diet emphasizes low-fat dairy products, low-sodium foods, and no alcohol.

Many studies have reported a positive correlation between the DASH diet and cognitive function. A prospective cohort study was done in postmenopausal women (aged 65−79 years), including 499 cases of mild cognitive impairment and 390 cases of Parkinson's disease. The results showed a statistically significant inverse relationship between adherence to the DASH diet and risk for mild cognitive impairment but not for Parkinson's disease. A few improvements also occurred in global cognition, episodic memory, and semantic memory with the DASH diet [86,87]. DASH diet scores from another study indicated better global cognitive function and verbal memory but were not associated with long-term changes in cognitive function [88]. The ENCORE study enrolled 124 subjects with high blood pressure, body mass index over 25 kg/m^2, and a sedentary lifestyle. The subjects were randomized to the DASH diet, the DASH diet with a weight reduction program, and their usual diet. The result showed that intake of the DASH diet significantly improved psychomotor functions. Also, the subjects who consumed the DASH diet for weight reduction indicated significant improvement in executive function, memory, and learning ability [89].

Mediterranean + dietary approaches to stop hypertension intervention for neurodegenerative delay diet

The MIND diet is a combination of the modified MED and DASH diets. The differences in the MIND diet are that it emphasizes the consumption of green leafy vegetables and berries, but it does not include high consumption of fruits, fish, and dairy products [90]. It consists of 10 brain-healthy foods, such as green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, seafood, poultry, olive oil, and red wine, with avoidance of five unhealthy foods: red meats, butter and stick margarine, cheese, pastries, sweets, and fried/fast foods. The 10 brain-healthy foods provide strong evidence of neuroprotection. Leafy green vegetables are rich in lutein, folate, vitamin E, beta-carotene, and polyphenols, all of which are known for having a strong preventive effect against cognitive impairment [91,92]. Berries containing high levels of polyphenols have been shown to improve memory in animal models [93] and to slow cognitive decline in humans [94].

A cross-sectional study reported that higher MIND scores were significantly associated with better cognitive performance and lower risk for poor cognitive performance [95]. The findings from longitudinal studies were concordant with previous investigations [96,97]. Persistent adherence to the MED diet or the MIND diet was associated with better cognitive function and lower risk of cognitive impairment. Some studies found that compared with the MED and DASH diets, greater adherence to the MIND diet was superior in slowing the decline of global cognition and in lowering the risk of dementia [90,98]. Currently, there is an ongoing intervention study (phase III randomized, controlled trial) to evaluate the effects of the MIND diet on cognitive decline and neuroprotection. The results will be available in 2021 [NCT02817074] [99].

Physical activity

Age-related sarcopenia is commonly observed in elderly subjects, particularly in malnourished elderly patients. The prevalence of cognitive decline is also significantly higher in elderly patients with sarcopenia [100,101]. One strategy for prevention of sarcopenia is increased physical activity. Therefore regular exercise may be an effective way to prevent sarcopenia and cognitive decline. Lifestyle modification, particularly physical exercise and smoking cessation, is a reasonable and cost-effective method to reduce the risk of NCDs and osteoporosis, improve insulin resistance, and reduce mental stress, which are potential risk factors for dementia and AD [102,103]. It is well known that regular physical activity induces vasodilation, reduces blood pressure, improves triglycerides, and attenuates oxidative stress in healthy subjects by improving the capacity of antioxidant enzymes and increasing antiinflammation molecules. Physical exercise can prevent NO^- degradation through decreased oxidative stress. Also, regular physical activity reduces

oxidative stress and inflammation in atherosclerotic patients and improves endothelial function, consequently lowering the incidence of coronary heart disease, dementia, and depression.

Innumerable studies have shown the overall health benefits of physical activity. It helps to protect against obesity, diabetes, heart disease, stroke, the progression of cognitive impairment, depression, psychiatric disorders, and some cancer types (prostate, breast, colon). Results of metaanalysis studies have revealed that physical activity can be an effective modality to prevent cognitive decline and dementia [104,105]. Hamer and Chida analyzed the data of 16 prospective studies to determine the association between physical activity and neurodegenerative diseases in 163,797 nondemented participants and found that physical exercise was associated with a 26% reduction in all types of dementia and a 45% reduction in AD and Parkinson's disease [106]. Since the pathophysiology of either early-onset or late onset AD involves the accumulation of beta-amyloid, and this accumulation can occur over a period of 20 years prior to diagnosis of AD [107], regular physical activity for preventing cognitive decline should be started no later than middle age in order to see the benefits of exercise. It has been observed that people who perform strenuous or higher levels of physical activity have lower levels of brain amyloid deposition load than are seen in people who perform low levels of exercise [107].

Overwhelming evidence from observational and epidemiological studies provides evidence that regular physical activity can mitigate potential risk factors of dementia and chronic neurological diseases such as AD and Parkinson's disease. Exercising can also induce neuroplastic changes in the human brain. However, the duration, quality, and quantity of exercise may differ among individuals. Because of this heterogeneity the impact of physical activity may vary in different individuals. Since the benefits of exercise on cognitive function can vary in different individuals, such heterogeneity differences may originate from a single-nucleotide polymorphism. Some subjects were found to be responders and some were nonresponders in terms of improved cardiorespiratory and metabolic parameters in adaptation to exercise, resulting in different health benefits on neuroplasticity and cognitive functionnulla In view of these observations, for the management of dementia and cognitive function, exercise programs should be designed according to individual needs to improve QOL, and overall health and well-being. Current recommendations for physical activity in the prevention of dementia and cognitive decline remain the same as general recommendation for the prevention of other NCDs, that is, regular physical exercise for 150 minutes per week or 30 minutes each day for five days per week with moderate intensity. Depending upon the individual's needs, the exercise sessions can be broken up into 10−15 minutes throughout the day.

While regular physical exercise has many health benefits, it has also been found, paradoxically, that intense and prolonged exercise can cause oxidative damage to contracting myocytes as a result of the production of free radicals, resulting in muscle weakness and fatigue [108]. There is strong evidence that people who perform moderate physical activity and play recreational sports have a strong immune function system and reduced risk of upper respiratory tract pathogenic infections. On the other hand, prolonged intensive physical activity or training of endurance athletes (mainly triathletes, swimmers, and cyclists) suppresses the immune system and make them more susceptible to upper respiratory tract infections, such as common cold [109]. The overall beneficial effects of physical activity appear to arise from the improved vascularity and oxygenation of body organs as well as immune function system. Therefore to maximize the benefits of physical exercise, the duration, quality, and quantity of exercising should be individualized, as in personalized medicine.

Discussion and conclusion

People are living longer as a result of advances in medical and surgical technologies, improved sanitary and living conditions, and availability of wholesome foods. At the same time, the prevalence of NCDs, such as diabetes, obesity, cancer, heart disease, stroke, neurodegenerative abnormalities, depression, dementia, and cognitive decline have also increased with prolonged aging. In some older patients, cognitive decline and mood impairment may be related to poorly controlled hypertension and thyroid function. Although the genetic risk factors involved in the brain's aging process cannot be changed, nongenetic risk factors, such as smoking, excessive alcohol consumption and substances of abuse, sedentary habits, and intake of unhealthy foods, can be modified and consequently help to prevent the NCDs and progression of mental ailments. It has been observed that tobacco smoking accelerates the aging process. Nicotine from cigarettes causes vasoconstriction and hypertension and promotes atherosclerosis and arterial thrombogenesis. Carbon monoxide from cigarettes decreases the O_2-carrying capacity of the blood and O_2 transport to the brain and other organs and tissues. In addition, carcinogens produced by cigarette pyrolysis cause lung cancer. Hookah and cigarette smoking also produces oxidative stress in the body. The free radicals that are produced by oxidative stress trigger the production of inflammatory cytokines in the body, and this phenomenon is considered one of the causes of neurodegenerative

abnormalities and other chronic diseases. Free radical−scavenging polyphenolic antioxidant compounds that are present in fresh fruits, vegetables, and herbal remedies decrease the risk of chronic conditions.

The popularity of fresh fruits, vegetables, nuts, and probiotics is increasing because of their antioxidant and antiinflammatory properties, dietary fiber, bioactive phytochemicals, and promotion of healthy microbiota that collectively provide several health benefits. There is overwhelming evidence that the Mediterranean-style and DASH-type diets, functional foods, probiotics, and regular physical exercise have the strongest positive impact in the prevention of NCDs, including neurodegenerative disorders. Several antioxidant and antiinflammatory nutrients, such as polyphenolic compounds and carotenoids, have been well studied and have shown beneficial effects in attenuating dementia and cognitive decline. Overall, consumption of healthful foods that are rich in antioxidant and antiinflammatory nutrients appear to be the key factors in reducing oxidative stress and to prevent or delay the onset of cognitive decline and neurodegenerative diseases in elderly humans. In brief, dietary interventions and exercise may be highly useful strategies for preventing dementia and maintaining cognitive function, improving sleep patterns, and decreasing depressive symptoms in older adults. Nevertheless, determination of optimal nutritional components is needed for the prevention of these disorders. Further well-designed and placebo-controlled clinical studies, including postmarketing surveillance, are needed to ascertain the long-term safety and efficacy of memory-enhancing dietary supplements or natural health products sold in health food stores and on the Internet to evaluate their benefits for the prevention of neurodegenerative diseases. It appears that smokers and hypertensive, obese, and diabetic patients are at high risk for stroke and mental disorders. Stroke induced by hypertension, obesity, and diabetes mellitus is a serious problem all over the world. Consumption of saturated fatty acids, especially trans-fatty acids, and tobacco smoking, including e-cigarettes, increase the risk of stroke, which can result in physical disability, mental disability, and death. Stroke-inflicted patients spend considerable amounts of time in hospitals and rehabilitation centers, resulting in economic loss and enhanced healthcare burden. Intake of MED- and DASH-type healthful foods such as fresh fruits and vegetables, whole grains, foods containing omega-3 fatty acids, poultry, nuts and seeds, olive oil, dairy products, less red meat, and moderate consumption of red wine is linked with the reduction of mortality and morbidity associated with cardiovascular and cardiometabolic diseases and neurodegenerative disorders. Ingestion of functional foods, vitamins (A, B_1, B_2, B_3, C, E, etc.) and minerals (zinc, copper, manganese, magnesium, selenium, etc.), and amino acids (e.g., tryptophan) assist in improving overall health beyond basic nutritional functions. Emerging evidence suggests that dietary supplements containing flavonoids, carotenoids, and antioxidants modulate gene and protein expression and thereby modify endogenous metabolic pathways and homeostasis and consequently reduce the risk of chronic diseases multifactorial in origin. Moderate exercise (30 minutes/day), smoking cessation, intake of dairy products that promote healthy gut microbiota, antioxidant diets, and functional foods not only reduce the risk of stroke, CVD, and neurodegenerative disease, but also promote overall health and well-being. Several studies have demonstrated that people who are sedentary or less physically active have a nearly 50% higher risk of stroke compared to those who perform regular exercise three times a week for 20−30 minutes [109]. It is well recognized that regular physical activity helps to reduce body weight and blood pressure, improves blood triglycerides, lowers blood sugar and low-density lipoprotein cholesterol levels and increases the high-density lipoprotein cholesterol level. Exercise also lowers the incidences of colon, prostate, and breast cancer. Since movement can be said to be a nonpharmacological medicine, an active lifestyle improves physical, mental, sexual, and emotional health. It therefore appears that a holistic approach to health promotion is the most cost-effective antidote for the prevention of chronic diseases such as cancer, diabetes, obesity, heart disease, stroke, and neurodegenerative abnormalities.

The incidence of chronic renal failure is relatively higher in elderly people and cancer patients. Accumulation of toxic catabolic products, blood urea nitrogen, and hyperuricemia due to chronic kidney disease or renal failure may also increase the risk of dementia, cognitive decline, and behavioral abnormalities. The relationship of neurological complications such as dementia, cognition impairment, and psychosocial aspects should be assessed in patients with chronic renal failure and dialysis patients at early stages for treatment interventions [110−113]. Chronic renal failure may also increase the risk of stroke, and stroke-related obstruction of blood to the brain can cause nerve paralysis, neuronal dysfunction, and memory loss.

It may be worth mentioning that the majority of diet-related mental health problems in children emerge during the preadolescent years (ages 7−11 years) as a result of indulgence in excessively caffeinated and sugar-loaded drinks, frequent snacking, eating excessively fatty food, and eating processed foods containing high amounts of salt and carbohydrates. Consumption of large amounts of unhealthy diets by children triggers the development of obesity and obesity-related problems as well as common mental disorders such as poor-quality sleep, anxiety, increased risk of depression, and low academic achievement. In view of these observations, engaging parents and children is an important strategy for the prevention of childhood obesity and the promotion of good mental health in children. Children should be

encouraged to consume good-quality diets consisting of fresh fruits, vegetables, whole grains, nuts and seeds, low-fat dairy products, poultry, and fish [114]. As has been emphasized in this review, one of the biggest challenges with aging is declining mental functions. The major way to keep brain function healthy is to keep the brain stimulated. Several researchers have reported that brain-stimulating activities can create new neuronal connections or synapses between nerve cells and may even help the brain to generate new cells. To keep the brain young and healthy, older adults should be encouraged to exercise at a gym or at home, eat healthful foods and antioxidant diets, learn a new language, take a continuing education course, read books, play Scrabble, or crossword puzzles, Sudoku, or other puzzle games. If an elderly person is relatively healthy and does not suffer from any comorbid conditions and follows these strategies, his or her brain will remain younger and healthy, and he or she should be able to enjoy a good QOL and reduce dementia and cognitive dysfunction as well as depression and insomnia.

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Chapter 38

The role of modified Mediterranean neuroprotective diet on emotion, cognition, and depression

Ram B. Singh[1], Rie Horiuchi[2], Agnieszka Wilczynska[3,4], Sonia Suchday[5], Garima Tyagi[6], Aminat Magomedova[7], Ghizal Fatima[8], Manal M.A. Smail[9], Adrian Isaza[10], Monica Jain[3,4], Fabien De Meester[3,4], Toru Takahashi[7,11], Shaw Watanabe[12], Teiji Nakamura[13] and Lekh Raj Juneja[14]

[1]Halberg Hospital and Research Center, Civil Lines, Moradabad, India, [2]Department of Food Sciences and Nutrition, School of Food Science and Nutrition, Mukogawa Women's University, Nishinomiya, Japan, [3]The American University in Dubai, UAE, [4]WSB University in Torun, Poland, [5]Department of Psychology, Pace University, New York, NY, United States, [6]Alternative medicine, Everglades University, Tampa, FL, United States, [7]Department of Population, Faculty of Economics, Moscow State University by Lomonosov, Moscow, Russia, [8]Department of Biotechnology, Era's Medical College and Hospitals, Lucknow, India, [9]Fatima College for Health Sciences, Abu Dhabi, United Arab Emirates, [10]Alternative Medicine, Everglades University, Tampa, FL, United States, [11]Department of Food and Nutrition, Faculty of Human Sciences, Kanazawagakuin University, Kanazawa, Japan, [12]Clinical & Functional Nutriology, Life Science, Tokyo, Japan, [13]Kanagawa University of Human Services, Yokohama, Japan, [14]Halberg Hospital and Research Institute, Moradabad, India

Introduction

Katvamlalavanatyusnteekshanaruksha vidahinah

Ahar rjassyestah, dukhahshokmaypradah. (in Sanskrit)

The foods that are bitter, acid, fried, burnt, pungent and dry, give rise to grief, mental stress and diseases.

As is clear from above verse of the ancient scripture known as the *Bhagavad Gita*, dating from 5000 BCE, wise people knew even in ancient times that food may increase the risk for depression and other mental health disorders. The incidences of these disorders are increasing rapidly around the world, and they are a threat to public health [1,2]. Over 300 million people suffer from depression, which is the leading cause of nonfatal disease burden [2,3]. Mental illness has a pervasive effect including its comorbidity with non-communicable diseases (NCDs) such as cardiovascular diseases (CVDs) and its contribution to difficulties coping with daily life, including family and work [1,4]. Diet, lifestyle, and habits contribute to mental health [5]. Data from the Organization for Economic Co-operation and Development suggest that the cost of poor mental health in the European Union may be more than 4% of gross domestic product, which corresponds to over 600 billion euros [2]. The high global prevalence and cost of depression in 2015 led to the World Health Organization (WHO) plan titled "The European Mental Health Action Plan" [1]. This action plan covers mental health and mental disorders across the life course and is fully aligned with the values and priorities of the new European policy framework for health and well-being, Health 2020. This emphasis on depression is also consistent with the emphasis on prevention and treatment of NCDs in sustainable development goals established in 2015 by the U.N. General Assembly [4]

Recently, several experts have emphasized that it is important to understand emotional determinants of health apart from social, political and commercial determinants, because these factors may be additive to the development of psychological disorders as well as cardiometabolic diseases (CMDs), such as CVDs and diabetes [1–5]. Further studies indicate that emotional determinants of health such as psychological factors and well-being are tightly linked to CVDs [2–6]. It is possible that the link is bidirectional; in other words, emotion, depression, and cognition interact and

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determine the risk of CMDs and portend worse outcomes, or psychosocial conditions may preexist and precede CMDs [4–6]. Diet and physical activity together may be neuroprotective and cardio protective, whereas a Western diet and sedentary behavior may have adverse effects on both the systems. Mental ill health, manifesting itself in a wide range of conditions such as depression, anxiety, and stress, represents one of the leading causes of the burden of disease worldwide, also substantially increasing the risk for NCDs [1–5]. Mental disorders also adversely affect quality of life, relationships, and the ability to work as well as adverse effects on healthy lifestyles [5]. There is an unmet need to establish the role of inexpensive and effective methods to reduce the burden of mental health problems and to improve the psychological well-being of the population [1–6]. Further research is necessary on the role of genetic and biological factors, as well as on role of lifestyle factors, including dietary intake and other lifestyle factors, in the promotion of psychological well-being and the prevention of mental illness [7–9].

Morris and colleagues observed that a modified Mediterranean diet, called MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay), may be useful in the management of cognitive decline [7–9]. In a landmark experimental study by Ramirez et al., activation of positive memory engrams suppressed depression-like behavior, which may be associated with happiness [10,11]. It seems that neurons are also highly susceptible to damage due to magnetic forces from space and weather as well as planets and pollution, which are known to predispose circadian clock dysfunction in energy metabolism with increased risk of CMDs as well as neurodegenerative diseases [8,12]. Mediterranean-style diets have been demonstrated to have beneficial effects in patients with cognitive deficit and dementia as well as beneficial effects on emotions [13–17]. Mood disorders and dementia can predispose circadian dysfunction. which may be associated with greater morbidity and mortality [18–22]. It is proposed that a modified Indo-Mediterranean neuroprotective diet consisting of combining whole grains, spices, and mustard oil with a Mediterranean-style diet, may have protective effects on emotion, cognition, and depression, apart from its effects on CMDs [23–27]. This review aims to highlight the role of nutritional factors on disorders of emotion, cognition, and depression.

Burden of psychological disorders

It is possible that social determinants of health contribute mood disorders and depression as well as cognitive deficits due to conditions in which people are born, grow, live, work, and age. These circumstances are shaped by the distribution of money, power, and resources at global, national, and local levels, which are under the strong influence of commercial and political determinants of health [1]. However, social determinants of health may also be responsible for the increased risk of CMDs and mental disorders, via unfair and avoidable differences in health status seen within and between countries as well as within two populations and in the same population [1,5,6]. Psychological disorders, including mental stress and mood disorders, may predispose some people to higher morbidity and mortality compared with a general population [3,18,21]. A metaanalysis of 203 studies reported a relative risk for mortality of 2.22 for those with psychological disorders compared with matching populations and estimated that approximately eight million deaths worldwide (14.3%) can be associated with these disorders [18]. The prevalence of dementia is lower among other Asian countries with lower life expectancy compared to Japan and Western countries with greater life expectancy, such as the United Kingdom [8]. The prevalence of psychological disorders, including Alzheimer's disease (AD) and dementia, has increased rapidly in recent years, owing to rapid increases in industrialization and urbanization with accompanying changes in diet and lifestyle (Fig. 38.1).

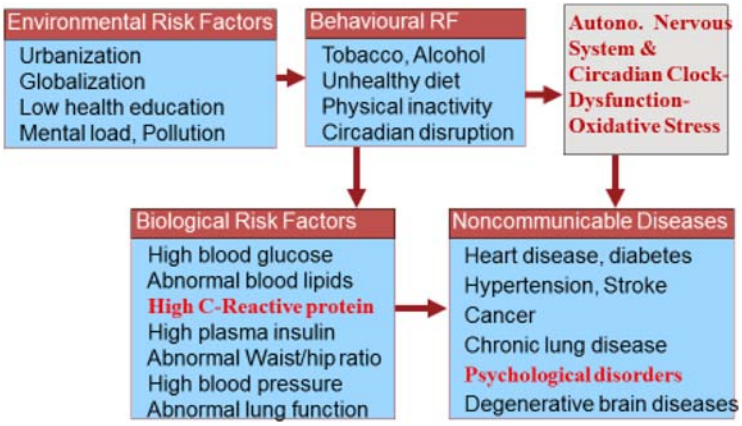


FIGURE 38.1 Pathways for development of psychological disorders and dementia.

Risk factors and protective factors in mental disorders

There is limited epidemiological evidence that interventions targeting built environmental factors encourage elderly subjects to engage in favorable behaviors to decrease the risk for dementia and improve cognition [8]. The increase in risk for dementia and AD in these countries may be due to multiple associated factors such as the Western diet, sedentary behavior, obesity, alcohol and tobacco consumption, and aging of populations in conjunction with a lack of protective factors (Table 38.1).

In a study from India, low cognitive activity, sedentary behavior, tobacco intake, Western diet, diabetes, and CVD were independent risk factors for dementia [28]. Low education was not associated with risk. Of 59 (2.95%) subjects having cognitive deficit or dementia, only 2 (0.10%) had AD (as shown by MRI), 21 (1.05%) had dementia, and 36 (1.80%) had memory dysfunction. It seems that the lower prevalence of dementia and cognitive decline among Indians compared to developed countries, may be due to lower survival rate after the age of 55 years ($N = 196$, 9.8%) and lower prevalence of subjects eating a Western-type diet and sedentary behavior, most likely due to physically demanding occupations. There was an increased prevalence of risk factors: Western-type foods (refined, fried, rapidly absorbed fast foods rich in trans and saturated fat, red and preserved meat, and sugar), tobacco intake, and sedentary behavior among patients with cognitive deficit [28]. Yoga therapy, including meditation, yoga postures, and yoga breathing ($N = 221$, 10.26%); prayer ($N = 1215$, 56.4%); physical activity ($N = 232$, 10.8%); an Indo-Mediterranean-style diet ($N = 501$, 23.3%); and time-restricted eating at evening ($N = 55$, 2.55%) were protective factors. Along with obesity, and diabetes, CVD were also quite common risk factors among these subjects [8,28]. Multivariate logistic regression analysis revealed that yoga therapy, active prayer, physical activity, restricted eating at evening, and Indo-Mediterranean diet were significantly inversely associated with dementia. It is possible that decreased intake of Western-type foods, prevention of sedentary behavior, and cessation of tobacco use can protect against dementia among Indians.

Nutrition in psychological disorders

There is consistent evidence that nutritional factors may have a role in the pathogenesis of psychological disorders [7,9]. Clinical studies that have explored potential associations between nutrient intake (carbohydrates, B vitamins, antioxidants such as vitamins C and E, and polyphenols or foods rich in these nutrients, fruits, vegetables, legumes, coffee, and chocolate) and psychological well-being have produced conflicting results [7,13–17]. Hence Morris and colleagues proposed MIND for prevention of dementia and delay in neurodegeneration [7]. It seems that a modified Indo-Mediterranean neuroprotective diet, because of the addition of whole grains, spices, and mustard oil to Mediterranean-style foods, may have better protective effects on emotion, cognition and depression, compared to the MIND diet proposed earlier [7]. The modified Indo-Mediterranean-style diet contains more whole grains, wheat porridge, millets, dry pulses, peas, grams, spices, and mustard oil, along with Mediterranean-type foods such as fish and olive oil, but without red meat and poultry [23–27] (Table 38.2).

Previous studies have demonstrated that Western diets characterized by sugar and salt, red meat and preserved meat, and highly refined foods have adverse effects on neuronal function, whereas Mediterranean-style diets may be protective [7–9,13–17]. The Japan Gerontological Evaluation Study, a population-based cohort study of subjects aged 65 years and older, examined the association of neighborhood food environment with incidence of dementia [29]. After a

TABLE 38.1 Risk factors and protective factors of dementia.

Risk factors	Risky behaviors	Protective factors
Obesity and central obesity	Short sleep	Physical activity
Hypertension	Tobacco	Mediterranean-type diet
Diabetes mellitus	Alcoholism	Meditation and prayer
Hyperlipidemia	Depression and stress	Yoga postures
Stroke	Sedentary behavior	Intermittent fasting
Coronary artery disease	Low cognitive work	Circadian restricted energy intake
Low education	Late-night eating	Low-caloric diet
Pollution	Western-type diets	Music
Age	Negative thoughts	Intellectual work
	Light at night	No pollution with light, noise

TABLE 38.2 Modified Indo-Mediterranean-style neuroprotective diet.

Food category	Type of foods
Whole grains (400 g/day)	Wheat porridge, millets, beans or pulses; red beans, green beans, black beans, kidney beans, grams, peas
Spices, (20–50 g/day)	Turmeric, cumin, coriander seeds, fenugreek, cinnamon, cloves, cardamom
Vegetables (200–300 g/day)	Leafy greens, fenugreek, radish, mustard, gram, spinach, gourds, cauliflower, okra, radish root, carrots
Fruits (200–300 g/day)	Apples, guavas, papayas, grapes, berries, tomatoes
Dry fruits (30–60 g/day)	Peanuts, almonds, walnuts, pistachios, hazelnuts
Fats and olive oils (30–80 g/day)	Mustard, rape seed olive oil or a blend of these oils
Animal foods (100–300 g/day)	Curd, buttermilk, yogurt, milk, fish, seafoods

Indo-Mediterranean foods (Modified from references Singh RB, Rastogi SS, Verma R, Laxmi B, Singh R. Randomized, controlled trial of cardio protective diet in patients with acute myocardial infarction: results of one year follow up. BMJ 1992;304(6833):1015–1019; Singh RB, Dubnov G, Niaz MA, Ghosh S, Singh R, et al. Effect of an Indo-Mediterranean diet on progression of coronary disease in high risk patients: a randomized single blind trial. Lancet 2002;360 (9344):1455–1461 [23,24]).

follow-up of 3 years, the dementia incidence for 49,511 participants was assessed through the public long-term care insurance system. During a follow-up of 3 years, a total of 3162 cases of dementia occurred. Compared with the highest quartile for objective availability of food stores, the hazard ratio adjusting for age and sex was 1.60 [95% confidence interval (CI): 1.43, 1.78] for the second-lowest quartile. Compared with the highest subjective availability of food stores, the hazard ratio was 1.74 (95% CI: 1.49, 2.04) for the lowest category. After successive adjustment for sociodemographic characteristics, health status, and other geographic neighborhood factors (availability of restaurants, convenience stores, and community centers), the hazard ratio remained statistically significant. It is possible that a lower availability of healthy food stores was associated with greater incidence of dementia [29,30].

Diets for cognition and dementia

The WHO estimate that the number of people living with dementia including cognitive deficits, worldwide, may be approximately 50 million which is projected to increase to 75 million by 2030. Epidemiological studies indicate a consistent relationship between the development of cognitive impairment and dementia with lifestyle-related risk factors, such as physical inactivity, unhealthy diets, short sleep, night shift work, tobacco use, and harmful use of alcohol [1–9]. Apart from behavioral risk factors, CMDs; obesity, hypertension, diabetes, stroke and hypercholesterolemia, as well as depression are also associated with decline in cognition and with an increased risk of dementia [7–9]. In a few studies, social isolation and cognitive inactivity have been reported to be associated with dementia. The risk of dementia can also increase as a result of lack of protective health behaviors such as optimal sleep, moderate physical activity, Mediterranean-style diets, caloric restriction or intermittent fasting, circadian restricted eating, supplementation of cocoa and probiotics, yoga therapy, and moderation in alcohol intake [8]. These health behaviors may also prevent biological risk factors of dementia, such as obesity, hypertension, hypercholesterolemia, stroke, diabetes, and depression [9]. Morris et al. have demonstrated that improvement in cognition is possible through modification of diet via implementation of key interventions that delay or slow cognitive decline or dementia [7–9,13–17].

Cognitive deficit or dementia is not a normal part of aging. It appears to be a syndrome characterized by a chronic or progressive nature, and it is estimated that the prevalence will almost triple by 2050. In the Asia Pacific region the number of people with dementia will increase from 23 million in 2015 to almost 71 million by 2050. Epidemiological studies have shown a relationship between the development of cognitive impairment and dementia with lifestyle-related risk factors, such as physical inactivity, tobacco use, unhealthy diets, and harmful use of alcohol [7–9,13–17]. The exact prevalence of memory dysfunction or dementia in Asia, including Japan, as well as the changes in prevalence are not well known. In a systemic review, 21 studies were selected from 782 references [31]. The criteria for the clinical diagnosis of dementia were made on the basis of the guidelines of the Diagnostic and Statistical Manual of Mental Disorders in a majority of the studies. The prevalence of all types of dementia, including memory dysfunction, ranged from 2.9% to 12.5%, which has been gradually progressive over the past few years. The risk factors of dementia were not duly studied in most of the surveys, because the authors found that advancing age and low education were the only consistently reported risk factors.

Epidemiological studies indicate that a Western-type diet is a risk factor for cognitive deficit, whereas Mediterranean-style diets may improve cognition [7–9,13–17]. Accumulating evidence suggests that higher adherence to a Mediterranean diet is associated with higher overall cognitive performance and brain structural integrity as well as decreased risk of AD and vascular dementia. It is possible that dietary transition might explain the rising trend in the prevalence of dementia in Japan and in developing countries [29]. This study used two approaches to determine whether dietary or other changes could explain AD trends in Japan and developing countries. One approach involved comparing trends of AD in Japan with changes in national dietary supply factors, alcohol consumption, and lung cancer mortality rates from zero to 25 years before the prevalence data. In the second approach, the prevalence of AD for eight developing countries was compared with dietary supply factors from zero to 25 years before the prevalence data [30]. The findings revealed that for Japan, alcohol consumption; animal product, meat, and rice supply; and lung cancer rates correlated highly with prevalence of AD, the strongest correlation being for a lag of 15–25 years. The findings in the eight-country study showed that total energy and animal fat correlated highly with the prevalence of AD, with a lag of 15–20 years. The possible mechanisms to explain the findings include increased obesity for the eight countries and increases in cholesterol, saturated fat, and iron levels due to higher intake of animal products and meat for Japan. It is possible that the prevalence of AD will continue rising in nonWestern countries unless we address major risk factors as well as behavioral risk factors, including diet, obesity, alcoholism, and smoking. The effects of diets on the brain in a study using magnetic resonance imaging are shown in Fig. 38.2.

The role of dietary patterns and their potential association with risk of incident dementia was examined in a Japanese population comprising 1006 community-dwelling subjects without dementia, aged 60–79 years [27]. All the subjects were followed up for a median of 15 years. In the results, seven dietary patterns were identified; of these, dietary pattern 1 was correlated with high intakes of soybeans and soybean products, vegetables, algae, and milk and dairy products and a low intake of rice. During the follow-up period of 15 years, 271 subjects developed all-cause dementia. Of these 271 subjects, 144 subjects had AD, and 88 subjects had vascular dementia [27]. After adjustment for potential confounders, risks of development of all-cause dementia, AD, and vascular dementia were reduced by 0.66 (95% CI: 0.46, 0.95), 0.65 (95% CI: 0.40, 1.06), and 0.45 (95% CI: 0.22, 0.91), respectively, in subjects in the highest quartile of scores for dietary pattern 1 compared with subjects in the lowest quartile. It is possible that a higher adherence to a

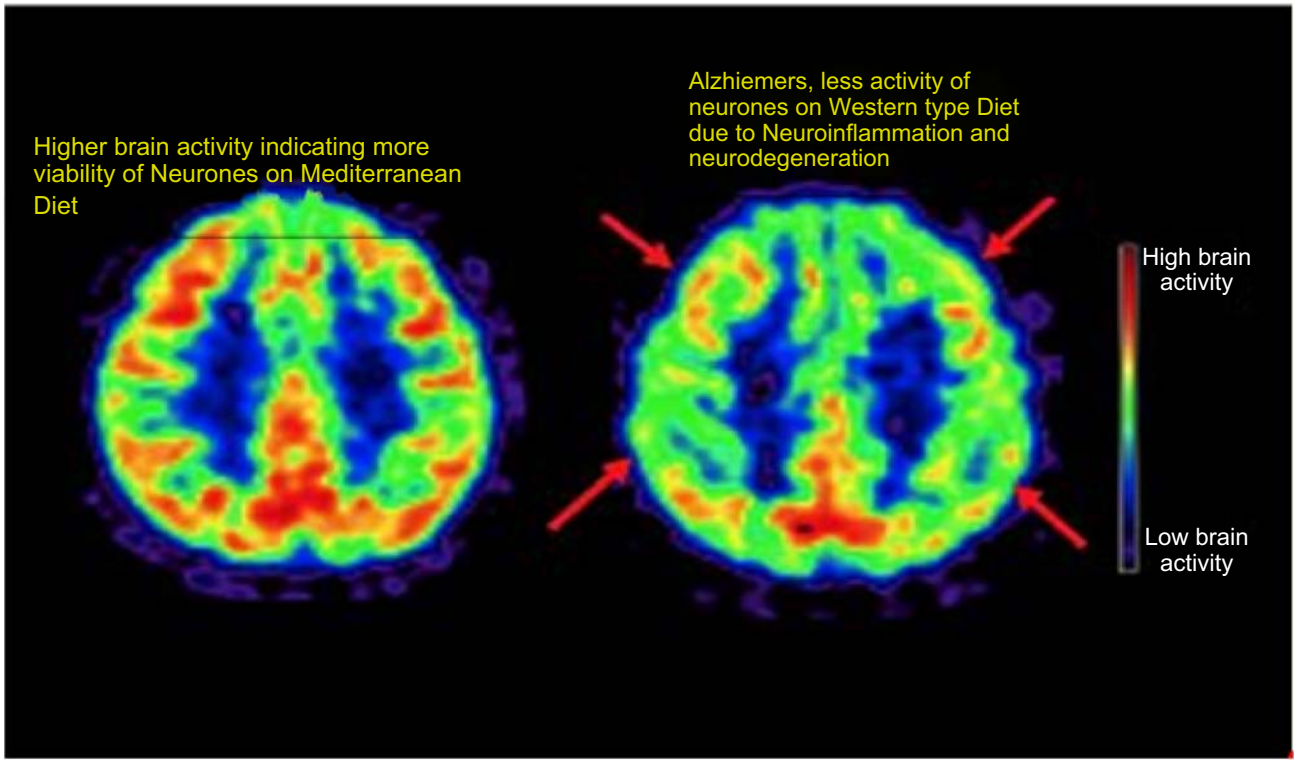


FIGURE 38.2 Effects of a Mediterranean-style diet and a Western-style diet on brain structure via magnetic resonance imaging, indicating higher activity in red.

dietary pattern characterized by a high intake of soybeans and soybean products, vegetables, algae, and milk and dairy products and a low intake of rice is associated with a reduced risk for dementia [27]. In another study, a cohort of nondemented, nondepressed older adults, including community-dwelling subjects ($N = 82$; aged ~68.8 years; 50% female, 50% minority) underwent food frequency assessment and neuropsychological assessments along with neuroimaging [19,32]. The scores for Mediterranean-style diets were quantified with the use of published criteria, and participants were divided into high and low (median split) adherence groups. The results revealed that compared with the low Mediterranean diet group, the high Mediterranean diet group was associated with better learning and memory performance and larger dentate gyri via neuroimaging. Mediterranean diet adherence was not associated with information processing or executive functioning. It is possible that there is an association between increasing adherence to Mediterranean-style diets and specific cognitive and neuroimaging phenotypes and that altered diets may be associated with AD [32].

Although it has been observed that the Japanese dietary pattern has a preventive effect against incident dementia, there is little evidence investigating this issue [27,32,33]. One prospective cohort study investigated the association between dietary patterns and incident dementia among 14,402 elderly Japanese subjects (≥65 years) participating in a community-based, prospective cohort study [33]. Three dietary patterns (Japanese pattern, animal food pattern, and high-dairy pattern) were derived by using principal component analysis of the consumption of 39 food and beverage items assessed by using a food frequency questionnaire.

The incidence of dementia was 9.0% with 71,043 person-years of follow-up. The score for the Japanese dietary pattern was associated with a lower risk of incident dementia (hazard ratio of the highest quartile versus the lowest: 0.80; 95% CI: 0.66−0.97; P-trend = .016). The animal food pattern and the high-dairy pattern showed no significant association with incident dementia. This study confirmed that the Japanese dietary pattern was associated with a decreased risk of incident dementia [33]. It is clear from these studies that increased intake of alcohol, animal products, meat, and white rice as well as Western-type foods (salt, sugar, and saturated fat) may be underlying dietary factors responsible for the rising prevalence of dementia in Japan and other Asian countries [8]. Modification of these diets by substituting medical rice and other whole grains for white rice in conjunction with Mediterranean foods (vegetables, fruits, fish, olive oil, and/or mustard oil) may be protective against dementia [8]. These diets and moderate physical activity are also protective against CMDs, cancers, and osteoporosis, which are major causes of deaths and disability among elderly populations [8].

Mediterranean-style diets and cognition

Mediterranean-style diets are rich in fruits, vegetables, whole grains, nuts, olive oil, and fish with lower amounts of refined foods, red meat, and preserved meats [8,13−17]. These diets can lower the risk of cognitive decline by reducing the risk of developing CMDs, a known risk factor for dementia, as well as by their direct effect [13−17]. The mechanism of action of this diet is that it also has an antioxidant and antiinflammatory effects that are major mechanisms underlying dementia [13]. There is strong evidence for protective effects of vitamin E, B vitamins, magnesium, vitamin D, flavonoids, amino acids, and n-3 fatty acids and deleterious effects of sugary and rapidly absorbed refined fast foods, saturated and trans-fat, and red and preserved meats on dementia [26,27,32−34]. Intake of food pellets containing pregerminated brown rice has been found to alleviate cognitive deficits caused by beta-amyloid peptide 25−35 in mice [34]. Among specific foods with evidence of neuroprotection are leafy and other vegetables, berries, whole grains (beans and pulses, porridge, grams, flax seeds, other seeds, soybeans, and millets) and seafood [13−17,35]. The PREDIMED study assessed 522 participants at high vascular risk (44.6% men, age 74.6 ± 5.7 years at cognitive evaluation) enrolled in a multicenter, randomized, primary prevention trial [15]. After adjustment for sex, age, education, apolipoprotein E genotype, family history of cognitive impairment or dementia, smoking, physical activity, body mass index, hypertension, dyslipidemia, diabetes, alcohol, and total energy intake, participants allocated to the Mediterranean diet + extra-virgin olive oil (EVOO) showed higher mean Mini-Mental State Examination (MMSE) and clock-drawing test (CDT) scores with significant differences versus control (adjusted differences: +0.62, 95% CI: +0.18 to +1.05; $P = .005$ for MMSE, and +0.51 95% CI +0.20 to +0.82, $P = .001$ for CDT). The adjusted means of MMSE and CDT scores were also higher for participants allocated to the Mediterranean diet + nuts versus control (adjusted differences: +0.57, 95% CI: +0.11 to +1.03; $P = .015$ for MMSE and +0.33, 95% CI: +0.003 to +0.67; $P = .048$ for CDT). An intervention with Mediterranean diets enhanced with either EVOO or nuts appears to improve cognition compared with a low-fat diet [15].

In a metaanalysis, 32 studies from 25 unique cohorts, including 5 randomized, controlled trials and 27 observational studies, met the inclusion criteria [13]. The majority of studies showed that a Mediterranean-style diet was associated with improved cognitive function, a decreased risk of cognitive impairment, and decreased risk of dementia or AD.

Of the total, three studies reported no correlation between the diet and AD, another three studies reported no association between the diet and cognitive impairment, and five studies found no association between the diet and cognitive function. In view of the large heterogeneity, differences in quality, and the limitations in study design, it is possible that adherence to a Mediterranean-style diet was associated with better cognitive performance [14]. A more recent review, following PRISMA guidelines and conducted by using four databases, resulted in 31 articles of interest [16]. Cross-sectional studies and cohort studies in non-Mediterranean regions showed mixed results. However, cohort studies in the Mediterranean region and randomized controlled trials showed more cohesive outcomes of the beneficial effect of Mediterranean-style diets on cognitive function [16]. Although more standardized and in-depth studies are needed to strengthen the existing body of evidence, results from this review indicate that a Mediterranean diet may have a major role in cognitive health and risk for AD and dementia. According to another review, several studies have examined dietary patterns, particularly the Mediterranean and DASH (Dietary Approaches to Stop Hypertension) diets. However, neither of these diets is tailored to the specific foods and nutrients that have been identified as neuroprotective [17].

A recently developed diet, called MIND, incorporates many elements of the Mediterranean and DASH diets but with modifications that reflect the best evidence for neuronal protection [7]. The problems of the association of Mediterranean-style diets with dementia may be explained by inadequate attention to nutrient or food intake in the interpretation of results of the study. In a further study, the German Study on Aging, Cognition and Dementia in Primary Care Patients, dietary intake of red wine, white wine, coffee, green tea, olive oil, fresh fish, fruits and vegetables, red meat, and sausages was assessed by a single-food questionnaire [36]. Participants aged 75 + ($N = 2622$) were regularly followed over 10 years for incidence of AD ($N = 418$). The results showed that only higher red wine intake was associated with a lower incidence of AD (HR = 0.92; $P = .045$). However, this was true only for men (HR = 0.82; $P < .001$), while in women, higher red wine intake was associated with a higher incidence of AD (HR = 1.15; $P = .044$), and higher white wine intake with a more pronounced memory decline over time (HR = −0.13; $P = .052$) [35]. The majority of studies showed that the Mediterranean-style diet was associated with improved cognition, with a decreased risk for dementia. Three studies found no correlation between the diet and cognitive impairment, and five studies found no association between diet and cognitive function [37]. There are numerous studies to support that certain foods such as fish, olive oil, nuts, coffee, tea, and wine can improve cognition with a decline in dementia. The major benefit is achieved as a result of the flavonoid, peptide, amino acid, and omega-3 fatty acid content of these foods [38−52]. No evidence was observed that single foods are protective against cognitive decline, with the exception of red wine, which reduced the risk for AD only in men.

Medical rice, as a whole-grain component of Mediterranean-style diets, is rich in functional ingredients [dietary fibers, gamma-aminobutyric acid (GABA), selenium, magnesium, phenolic acids, flavonoids, anthocyanins, proanthocyanidins, tocopherols, tocotrienols, gamma-oryzanol, and phytic acid] that provide a good balance in the bacterial flora and the immune system if consumed as whole grains [36,53−55]. An experimental study by Mamiya et al. [34] suggested that continuous feeding of food pellets containing pregerminated brown rice attenuates the Aβ25−35-induced impairments of cognitive function and inhibited increases in lipid peroxidation in the hippocampus related to cognition [54]. Whole grain is also an important ingredient of the MIND diet, which incorporates many elements of the above-mentioned diets for neuroprotection [55]. A previous review included 32 studies from 25 unique cohorts, including 5 randomized, controlled trials and 27 observational studies, also showed that eating Mediterranean-type diets causes improvement in cognition [52]. Apart from the diet quality, restriction of calories can also improve cognition, depression, and emotion as will be discussed in more detail later in this chapter [56−63].

Association of diets with depression

It is possible that dietary behavior and depression may have a bidirectional influence. There is evidence that increased intake of processed meat, red meat, white chocolate, sweet desserts, fried food, refined cereals, and high-fat dairy products may predispose people to depression, whereas patients with depression may alter their diet to eat more of sweetened refined food products that are consistent with Western-type diets. Previous studies have reported that a Mediterranean-type of diet that is rich in fruits, vegetables, nuts, seeds, and fish in conjunction with olive oil but low red meat and dairy products, can prevent mood disorders and depression as well as other NCDs [13−17]. There is an unmet need to conduct more research to determine the connection between neuropsychiatric disorders, including dementia, depression, and emotional dysfunction, with reference to Mediterranean-style and Western-type diets [5,13−17,64−66].

In 2000, Borovikova et al. reported that vagus nerve stimulation attenuates the systemic inflammatory response to endotoxins, indicating that any agent that can activate the vagus nerve may have antiinflammatory effects due to increased release of acetylcholine, which is a precursor of nitric oxide [67]. An activation of afferent vagus nerve fibers

by endotoxins or cytokines stimulates hypothalamic-pituitary-adrenal antiinflammatory responses. It has been reported that the parasympathetic antiinflammatory pathway involving acetylcholine, the principle vagal neurotransmitter, significantly attenuated the release of cytokines, including tumor necrosis factor, interleukin (IL) 1beta, IL-6, and IL-18, but not the antiinflammatory cytokine IL-10, in lipopolysaccharide-stimulated human macrophage cultures [67]. Since Mediterranean-style diets are known to reduce systemic inflammation, including neuroinflammation, the same may contribute to the modulation of the neurotransmitter systems and vagus activity, which could underlie its antistress and antidepressant effects [26]. Dietary supplementation with omega-3 fatty acids and flavonoids, which are found in abundance in Mediterranean-style diets, can increase dopamine levels and D_2 receptor binding, with reduced monoamine oxidase B activity in the prefrontal cortex and D_2 receptor binding in the striatum leading to beneficial effects on cognition, anxiety and mood disorders [68–70].

Apart from a decline in cognition, dementia is characterized by noncognitive features, which are the behavioral and psychological manifestations of dementia. Of all the clinical manifestations, the prevalence of depression is 40% among patients with dementia, so it may be considered to be a risk factor for AD. Imaging of the brain may show atrophy of the hippocampus due to the neurotoxic effects of depression, linked to oversecretion of cortisol or abnormally low concentration of brain-derived neurotrophic factor (BDNF) [68,69]. It seems that depression could be induced by metabolic disorders of monoamine neurotransmitters that are involved in noradrenaline, serotonin, and dopamine signaling. Thus anxiety and depression have been found to increase the severity of cognitive dysfunction in patients with AD, which may be due to greater oxidative stress and proinflammatory effects of these problems [68–71]. There is evidence regarding an emerging class of signaling molecules, present in the Mediterranean diet and MIND, such as omega-3 endocannabinoids and flavonoids, which may regulate the physiological and pathophysiological processes in the body, including neurons, concerned with the hypothalamus-pituitary axis and release of anandamides, serotonin, and dopamine, which are responsible for satiety and well-being [68]. Flavonoids and omega-3 fatty acids in the diet may also have beneficial effects via cell signaling in the endothelial cells, smooth muscle cells, and cardiomyocytes as well as adipocytes and beta cells of the pancreas in the prevention of NCDs [23–27].

Epidemiological studies on diet and depression indicate that Mediterranean-style diets rich in nutrients have a beneficial effects of mental diseases [5,64–66]. In a cohort study comprising 3014 studies, only 20 were high-quality studies that were included in the analysis, consisting of 110,857 subjects [64]. There were 51,834 males and 49,588 females. The results revealed that overall there was support for an association between healthy dietary patterns or consumption of a high-quality diet and lower levels of depression or better mental health. Similarly, there was a relationship between Western-type diets and consumption of low-quality foods and depression or poor mental health. However, the sizes of the effects were small where significant relationships were reported. It seems that high adherence to dietary recommendations (avoiding processed foods, intake of an antiinflammatory diet, magnesium and folic acid, various fatty acids, and fish consumption) had a protective effect against depression [5]. Public health professionals who work to support and motivate healthy eating habits may help to prevent and treat depression on the basis of the evidence presented in the results of this study. Further research is needed to strengthen evidence of a causal relationship and define evidence-based strategies to implement in prevention and treatment.

The evidence of a positive impact on depression or depressive symptoms via alteration in diets indicates that people should be motivated to prevent and promote healthy lifestyle habits. With reference to the costs that mental illness entails, it should be of interest for public health prevention that can lead to a reduced cost burden for the society [5,64–66]. It seems that lifestyle factors such as unhealthy eating, sedentary behavior, tobacco intake, and substance use contributed to an increased risk of depression, and several of the factors simultaneously strengthen the relationship with diet and lifestyle. The second clinical guideline was based on the evidence that physical exercise is effective as a treatment for depression. The third guideline was based on only a few studies but still demonstrated the effect of providing support for smoking cessation and dietary recommendations as a depression treatment. In the view of the studies showing a relationship between diet and lifestyle factors with depression and other mental disorders, future research on the relationship between diet and mental health in young people should use more clearly defined constructs to define diet and include or control for important confounders.

High adherence to dietary advice, using various methods of dietary intakes, was associated with a significantly reduced risk of developing depressive symptoms [5,64–68,72–93]. These methods were modified French Program National Nutrition Santé guideline score, Probability of Adequate Nutrient Intake dietary score [74], Diet Quality Index-International, and Alternative Healthy Eating Index-2010 (AHEI-2010). The decline in risk of depression was estimated to be 21%, 20%, and 12%, respectively, in the first three; no significant difference was detected in the AHEI-2010 group. High adherence to the French recommendations on diet and physical activity showed a highly

significant association with reduced risk of depression. Adherence to dietary recommendations of all the methods has been found to be effective in achieving improved mental health. The relationship was significant among men, for whom poorer adherence to a Mediterranean diet and AHEI were associated with a significantly higher risk of depression. In a few studies, adherence to the DASH diet showed no significant association with depression. AHEI has shown a significant association with protective effects against depression in women. High intake of vegetables, fruits, and fiber and low intake of trans fats were associated with a lower risk of recurrence in depression in the same study. An analysis of dietary points based on AHEI revealed a dose-response relationship that was significant for women. The women who improved their AHEI scores over 10 years had a 65% lower risk of recurrent depressive symptoms compared to the women who continued to have low AHEI scores. In Finland, among the middle-aged Finnish men who were studied, a significant protective effect was found with a higher degree of adherence to a healthy dietary pattern. The protective effect was measured at a 25% reduced risk of suffering from depressive symptoms. The risk for depressive symptoms with a Western diet was measured at a 41% increase in the same study [64]. Recommendations of a healthy diet and intake of fruits and vegetables have shown significant protective effects for mental illness among immigrants in Canada, and a higher intake of fruit and vegetables was associated with 19%–23% improved mental health.

Several studies showed an association between dietary intake with inflammatory potential and risk of depression in different populations [5,64–66,72–77]. Foods such as vegetables, whole grains, olive oil, and fish have less impact on inflammation. However, food products such as sweets, refined flour, high-fat products, and red and processed meat were associated with a greater impact on systemic inflammation [73]. The results showed that a proinflammatory diet was associated with a significantly increased risk of depression in the subgroups of women, middle-aged adults, and people with overweight and obesity, with an inference that the relationship was strongest in people with comorbid overweight, obesity, and metabolic syndrome [77]. The risk of depression increased in association with a high proportion of processed foods in the diet, and for each 10% increase of the proportion of processed foods, the risk was greater. Higher consumption of proinflammatory food was associated with significantly increased risk of depressive symptoms. In subgroups of male smokers with low physical activity, a diet consisting of a higher proportion of proinflammatory foods significantly increased the risk of depressive symptoms [73]. A high intake of proinflammatory foods and nutrients may be significantly associated with the occurrence of frequent anxiety in the same study, whereas antiinflammatory nutrients and fish may have beneficial effects [5,72–86]. Interestingly, the dietary glycemic index was associated with a significantly increased risk of depression in postmenopausal women in the United States [82]. In the same study, a higher intake of added sugar was associated with a significantly increased risk of depression, and high consumption of fruits, vegetables, and fiber was associated with a significantly reduced risk of depression [82].

Fish consumption was included as a variable in one study in which proinflammatory diet and risk of depression symptoms were studied in men and women [72]. Increased intake of proinflammatory food was associated with a significantly increased risk of depression symptoms [72]. However, subjects with the highest risk had a significantly lower intake of meat, fish, and eggs compared to those who ate a more unprocessed diet; this relationship applied to both men and women. A previous study showed that regardless of diet, the risk of depression increased significantly with the number of foods excluded from the diet [88]. The prevalence of depressive symptoms was highest for vegans (28.4%) and lowest among omnivores (16.2%). A dose-response relationship emerged in young women regarding fish consumption and the risk of depression; the trend was a 6% reduction per serving of fish [89]. Women who ate fish twice a week or more had a 25% lower risk of depression during the follow-up period compared to women who ate fish less often than twice a week. Women who developed depression during the follow-up period were 15% less likely to eat fish twice a week compared to women who did not develop depression. Fish intake was not significantly associated with depression in men [89].

In randomized, controlled trials, increased adherence to a healthy diet was associated with a significantly better therapeutic outcome compared to conventional treatment [90,91]. The duration of counseling conversations and social support were similar in both groups. Those who received dietary modification showed a significantly reduced risk of depression, and the strength of the result was calculated to the number needed to treat [90]. Increased adherence to Mediterranean-style diets led to significantly improved mental health in adults with depression [91]. The intervention group that received group training in consuming the Mediterranean-type foods had significantly higher intake of vegetables, fruits, whole grains, and nuts and a significantly lower intake of sweets than the control group who received group meetings with social activity. In the dietary intervention group, a 1.68-fold reduction in depression symptoms was calculated, which remained during the 6-month follow-up period [91]. The improvement in mental health on increased intake of Mediterranean foods may be due to the antiinflammatory effects of these foods [92,93].

Association of micronutrients intake with depression

Most experts agree that the neuroprotective effects of modified Mediterranean-style diets are due to increased contents of flavonoids, B vitamins, omega-3 fatty acids, minerals, and essential and nonessential amino acids [23–26]. The consumption of micronutrients, omega-3 fatty acids, flavonoids, and magnesium has been associated with a decreased risk of mental illness [68–71,78,83,84,86]. Association between intake of folic acid, vitamin B_{12}, and magnesium was also observed in the result where the main purpose was to investigate adherence to healthy dietary advice [74]. Those with the highest adherence to healthy dietary advice in the same study had a lower risk of depressive symptoms and a significantly higher intake of magnesium, folic acid, and vitamin B_{12} in the diet. Interestingly, another study showed that high intake of processed food increased the risk of depression, and those with high intake of processed food had significantly lower intake of vitamin B_{12}, magnesium, and folic acid in their diet compared to the group that had the lowest intake of processed foods [73]. Significant associations in both genders have been calculated regarding vitamin B intake and the risk for depression [84]. In women, those with the highest intake of vitamin B_6 had a reduced risk and among men, and those with the highest intake of vitamin B_{12} had a reduced risk. Low levels of vitamins B_6 and B_{12} were associated with an increased risk of depression in the same study. In one study, dietary intake of flavonoid subclasses had a significant protective effect against risk for depression among women [78]. Furthermore, the highest intakes of flavanols, flavones, and flavanones were significantly associated with a 7%–10% lower risk for depression compared with the lowest intakes in a study from the United States [78]. In a study by Godos et al., dietary intakes of total polyphenols and their classes, subclasses, and compounds were assessed in relation to depressive symptoms [83]. In their result, no significant association with depressive symptoms was found with the total polyphenol intake. In subclasses, this study assessed significance, indicating that higher flavonoid intake may be inversely associated with depressive symptoms. The intake of fatty acids in the diet was investigated as mediators of risk of inflammation and associations with depression in older people [87]. The proinflammation markers in the study were measured with C-reactive protein (CRP) and IL-6, which showed that omega-3 and polyunsaturated fatty acids (PUFAs) had protective effects against depression in men [87]. Furthermore, the total intake of fat, saturated fatty acids, and monounsaturated fatty acids had a significantly increased impact on both CRP and IL-6 in women. In middle-aged men, magnesium intake through diet was significantly associated with the risk for developing depression [86]. Calculations were made between three statistical models regarding the content of magnesium in the diet, and the lowest intake of magnesium was associated with a significantly increased risk for depression. When all three models in the study were compared, it was found that those with the highest magnesium intake experienced a protective effect against depression [86].

A metaanalysis was conducted to determine the role of omega-3 fatty acids, with 17 cohort studies examining the associations between blood n-3 levels and risk for all-cause mortality [94]. Over a median follow-up of 15 years, 15,720 deaths occurred among 42,466 individuals. After adjustment for relevant risk factors, risk for death from all causes was significantly lower (15%–18%) in the highest versus the lowest quintile for circulating long chain omega-3 fatty acids but not for the 18-carbon omega-3 fatty acids. These novel findings suggest that higher circulating levels of marine omega-3 PUFA may be associated with a lower risk of premature death. Previous studies also suggested that inadequate levels of omega-3 PUFA in the brain may represent a risk factor for these disorders [69]. These fatty acids are derived from the diet to form a major component of neuronal membranes and are of particular importance in the development of neuronal function. Omega-3 PUFA deficiency in the neurons influences the brain's dopamine systems and, when combined with appropriate genetic and other factors, increase the risk of developing these disorders and/or the severity of the disease. As elements of the cell membrane, long-chain PUFAs contribute to the cell membrane's physicochemical properties and thus influence the function of lipid rafts and membrane-bound proteins, such as receptors, transporters, and ion channels [69,95]. It seems that alteration in the membrane PUFA composition may alter the function and/or signaling of a variety of receptors, including dopaminergic, cholinergic, and GABAergic receptors as well as the Na^+/K^+ ATPase [69,95–98]

Along with omega-3 fatty acids, arachidonic acid is another potential fatty acids distributed evenly among cell types within the brain and is an important signaling molecule in inflammatory cascades [99]. It is preferentially cleaved from phospholipids in the brain by both cytosolic phospholipase A_2 and secretory phospholipase A_2. A portion of the released arachidonic acid can by metabolized by cyclooxygenases (COX) and lipoxygenases (LOX) to form a class of compounds known as the eicosanoids, which include a variety of mediators of cellular activity, including prostaglandins, leukotrienes, and lipoxins. Most of the metabolites derived from arachidonic acid have proinflammatory functions, although it contributes to mediators with a broad range of functions in the modulation of signaling, memory, and learning [100].

Docosahexaenoic acid (DHA) is highly enriched in neuronal and synaptic membranes, suggesting an important role in neural cell signaling. DHA is incorporated preferentially into phosphatidylethanolamine and phosphatidylserine on

the inner membrane layer of synapses, and its steric incompatibility with cholesterol drives the formation of either DHA- or cholesterol-rich lipid rafts [101]. These rafts serve as protected microdomains and function in compartmentalization of various cell-signaling molecules. DHA also affects membrane fatty acid chain fluidity, ion permeability, elasticity, protein function, phase behavior, and fusion [95,101]. DHA acts as a ligand for a variety of receptors, such as the peroxisome-proliferator-activated receptor (PPAR), the retinoid X receptor (RXR), and the toll-like receptors (TLR). DHA is metabolized by COX and LOX to form docosanoids, such as the resolvins, protectins, maresins, neuroprotectin D1, and the recently discovered electrophile oxo-derivatives (EFOXs) [100,102–106]. The resolvins are a class of anti-inflammatory compounds produced by the COX- athway in the presence of aspirin. Like DHA, neuroprotectin D1 affects membrane structure and stability and alters the balance of n-3 to n-6 PUFAs in the membrane, which in turn influences the cascade of arachidonic acid by suppression of COX-2. Maresins, DHA-derived metabolic products with antiinflammatory properties similar to those of the resolvins and NDP1, are produced by macrophages under inflammatory conditions [106]. COX-2 EFOX metabolites act as antiapoptotic Nrf-2 activators, PPAR-γ agonists, and inhibitors of cytokine and nitric oxide production [104]. DHA also has the ability to inhibit TLR4, an important proinflammatory factor, and various nuclear receptor initiators of the nuclear factor kappa light-chain enhancer of activated B cells (NF-κB) -mediated antiinflammatory response [102].

In clinical studies, omega-3 fatty acids have been found to decrease cytokine production and COX-2 activity [102]. Increased oxidative stress can cause oxidation of DHA into neuroprostanes, a class of prostaglandin-like compounds formed without COX. These compounds trigger formation of reactive oxygen species at both sides of the phospholipid membrane. However, as a result of increased availability of antioxidants, such as flavonoids and CoQ10 as well as catalase, superoxide-dismutase, and ceruloplasmin, in the cell membranes, DHA activates syntaxin 3, a crucial factor in neuronal growth and regeneration, which may contribute to DHA's role in optimal brain growth and development [65]. Like DHA, eicosapentaenoic acid (EPA) forms eicosanoids, most of which are less inflammatory than their arachidonic acid–derived counterparts, as well as antiinflammatory mediators such at the E-series resolvins. EPA competes with arachidonic acid for the same enzymes, so the n-6:n-3 ratio influences EPA metabolite production. Under conditions of cell membrane damage (such as oxidative stress), abundant intracellular calcium, and inflammatory stimuli, phospholipase LA_2, and COX-2 transcription are upregulated, leading to increased production of arachidonic acid metabolites [100]. DHA is one of a number of ligands for the nuclear receptor RXR; therefore dietary DHA intake may play a role in RXR regulation [103]. The RXR family consists of three main isotypes: RXR-α, RXR-β, and RXR-γ. RXR-α is expressed in the liver, kidney, spleen, placenta, epidermis, and visceral tissue; RXR-β is expressed in nearly every body tissue; and RXR-γ is expressed mostly in muscle and brain tissue. The physiological roles of RXR are complex and not completely understood, but RXR isoforms are known to be involved in muscle metabolism, insulin resistance, atherosclerosis, cholesterol metabolism, apoptosis, and a variety of differentiation processes, including neuronal development.

Polyphenols in psychological disorders and dementia

Epidemiological studies indicate that psychological disorders and dementia are among the leading causes of increased burden of mental diseases worldwide [1–5,7,34,35,107]. A growing body of data has emerged supporting the role of Mediterranean-style diets, especially polyphenols, in affecting behavior and mood as well as cognition and emotion, through anxiolytic and antidepressant-like properties [7,34,35,65,90,108–111]. Moreover, given that recent studies have demonstrated the pathophysiological role of oxidative stress and inflammation in the onset and progression of depression, polyphenols have been examined both in vitro and in vivo as a potential antidepressant treatment, although randomized controlled trials are still scarce in the field [111]. The richest sources of polyphenols in the human diet include fruits (e.g., berries, grapes, apples, and plums); vegetables (e.g., cabbage, eggplant, onions, and peppers); plant-derived beverages, including tea, coffee, red wine and fruit juices (e.g., apple juice); seeds; nuts; and chocolate (particularly dark chocolate) [66,111–115].

It is possible that the most effective dietary ingredient responsible for beneficial effects of foods on dementia may be flavonoids, which are found in whole grains such as medical rice, legumes, millets, flax seeds, and corn [7,34,35]. Flavonoids constitute a large group of polyphenolic compounds with numerous beneficial effects on behavior and cognition, which vary from learning and memory enhancement to improvement in general cognition. Flavonoids have also been implicated in neuronal proliferation and survival by acting on a variety of cellular signaling cascades, including the ERK/CREB/BDNF and PI3K/Akt pathways, reduction of oxidative stress, and relief from clinical manifestations of AD [7,35]. The electrophysiological aspect in the brain indicates that flavonoids can promote long-term potentiation in the hippocampus, supporting the hypothesis of synaptic plasticity mediation, indicating a neuroprotective effect of

flavonoid compounds in the brain. It is possible that the flavonoid content of Mediterranean foods could be a clinical direction for prevention and/or attenuation of cognitive decline deterioration that accompanies various brain disorders [7,35,37−44].

Catechin flavonoids that are found in tea and cocoa as well as resveratrol (grapes, apples, red wine, and peanuts) can reduce cognitive decline and the levels of beta-amyloid in AD. Improvement in cognitive function is not always accompanied by a change in pathological features, so it is not known whether flavonoids have a direct impact on beta-amyloid [37,50,51]. There is evidence that components of the germ layer and bran of brown rice help to maintain good health and prevent dementia [36,53−55]. Since the germ layer and bran absorb much less water and are very hard and difficult to cook, they are often removed during processing. To solve these problems, in this study, we tried to use a high-pressure technique to solubilize the rice. High-pressure treatment increased the water absorbency of brown rice without nutrient loss. It also ameliorated cognitive dysfunction and reduced the levels of beta-amyloid, which is a major protein responsible for AD, in the brain. In this experiment, the authors analyzed the benefits of brown rice (*Oryza sativa* L.) (Table 38.2) for the prevention of dementia and other dementias because it is widely cultivated and consumed in Asia and other regions. Brown rice is often processed to remove the germ layer and bran because they are very hard, difficult to cook, and poorly digested. Interestingly, these parts of the rice grain contain many ingredients that can be used to prevent dementia.

Ferulic acid has antioxidant potential, and it is neuroprotective effects and inhibits beta-amyloid production and aggregation [35]. They also include vitamin B_6, vitamin B_{12}, and folic acid, which are essential for methionine metabolism; deficiencies in these nutrients leads to an increase in blood homocysteine levels, increasing the risk of vascular diseases and dementia. The levels of GABA, which acts as an excitatory neurotransmitter in the brain and plays a crucial role in regulating nerve excitation, are reduced in the brains of patients with AD in comparison to the brains of healthy adults [35]. The Indian Lifestyle and Heart Study reported that the prevalence of cognitive decline and dementia was 2.95% ($N = 59$) associated with a diet score below 6 on a scale of 1−10, indicating increased intake of a Western dietary pattern and a lower Mediterranean diet pattern. There is potential epidemiological evidence of a strong correlation among diet, lifestyle factors, and the onset and consolidation of dementia and AD [27].

It has been demonstrated that cognition and dementia are linked to diabetes, obesity, insulin resistance, and CVD pathologies. Preventive strategies and nutritional interventions seem to be promising approaches to delay neurocognitive decline and reduce the risk of dementia and other nonpsychiatric comorbidities. In this regard, healthy dietary patterns, characterized by high intake of plant-based foods, probiotics, antioxidants, soybeans, nuts, and omega-3 PUFAs and a low intake of saturated fats, animal-derived proteins, and refined sugars, have been shown to decrease the risk of neurocognitive impairments and eventually the onset of dementia. In brief, the aging population is accompanied by increased rates of cognitive decline and dementia, which have profound impact on an individual's health and quality of life and that of their caregivers. The beneficial effects of the Mediterranean diet for the prevention or the delay of AD and dementia are associated with overall diet composition rather than with single-nutrient supplementations. The Mediterranean diet has been known to aid in reducing the risks for CVDs, cancer, and diabetes. The most important beneficial components of Mediterranean-style diets are vegetables and whole grains because they are rich in polyphenolics and flavonoids. Medical rice is a whole grain that is rich in GABA, selenium and magnesium phenolic acids, and the flavonoids anthocyanins, proanthocyanidins, tocopherols, tocotrienols, and gamma-oryzanol, which have potential antioxidant effects [32]. Flavonoids have recently been linked to better cognitive function in the elderly population. However, the majority of findings come from epidemiological studies that provide evidence for a correlation between Mediterranean diets and cognition but not for a cause-and-effect relation. More controlled trials are required to establish whether there is a causational relationship.

In a randomized, controlled trial involving 99 patients aged 40−65 years with mild hypertension, the effect of a high-polyphenol diet was compared to that of a low-polyphenol diet on aspects of psychological well-being in the Polyphenol Intervention Trial for 8 weeks [65]. After a follow-up of 8 weeks, no differences in anxiety, stress, self-esteem, or body image perception were observed. The findings suggest that the adoption of a polyphenol-rich diet could potentially lead to beneficial effects, including a reduction in depressive symptoms and improvements in general mental health status and physical health in hypertensive participants [65]. Cocoa is rich in flavanols, which are the major content with neuroprotective effects [108]. Biochemical effects of cocoa include antioxidant, antiinflammatory, vasodilatory, and anticoagulant properties that may serve to counteract depressive brain disorders [108]. Clinical studies have described links between intake of flavanol-rich cocoa-derived products such as dark chocolate and improved mood, while behavioral studies in laboratory animals have reported antidepressant effects of flavanols [108]. Epidemiological studies support a role for polyphenols in the prevention of chronic NCDs, such as CVDs and neurodegenerative diseases [90,109,110]

The modified Indo-mediterranean neuroprotective diet and emotions

Chanchalam heh manah Krishna, pramathi balved draham,

Tasyam nigraham voyoruih sudushkaram.

The mind is very unsteady, tenacious, turbulent, and difficult to curve, but it can be controlled by feeling of dispassion and Meditation.

The two lines in the above verse from the *Bhagavad Gita*, in Sanskrit followed by an English translation, emphasize the state of mind and emotions. The mind consists of mental states: emotions, thoughts, fear, pleasure, beliefs, attitudes, cravings, and images [116]. There is evidence that physiological responses within the body inculcate emotions, whereas brain activity in the hippocampus and hypothalamus cause emotional responses, leading to formation of emotions via thoughts or behavior [1,11,31,116]. Each mental state is associated with either a positive or a negative effect on the physiology and metabolism of neurons and other body systems. The mental states of anger and anxiety are associated with increased stress hormones: cortisol and glucocorticoids [8–10]. Emotions appear to comprise anger, sorrow, depressive thoughts, and happiness and are also affected by neuropsychological disorders such as depression and dementia, which may lead to the occurrence of other NCDs [6,8–10]. Thus emotions are known to exert an incredibly powerful force on human behavior that may predispose the individual to adverse effects on health, including psychological disorders and even suicide [8–10,116–119]. Strong emotions can initiate actions that the person might not normally perform or may cause the person to avoid situations. However, it is not known exactly why humans have emotions or what the physiology and biology of emotions are. Many experts, including researchers and philosophers, have proposed various theories to explain how and why human emotions occur. Emotions appear to be influenced by depression, anxiety, and mood, which may be associated with anger or happiness as their crucial components. Since taste and qualities of foods and mating can create happiness or anger, it is possible that the emotions may have environmental origins [6,11,31,116–119].

Clinical and experimental studies indicate that the impact of nutrition on cognition, emotion, and depression can occur throughout the lifespan, through its influence on neuronal and inflammatory responses [11,31,117–121]. Early-life stresses among children, as well as factors related to overnutrition and undernutrition, may interfere with neuronal development and proinflammatory responses, leading to cognitive and emotional disorders and depression, which may act as risk factors for cardiometabolic disorders [117,118]. However, appropriate diet and lifestyle changes, including increased intake of foods related to MIND, high in omega-3 fatty acids and polyphenolics, can lower oxidative stress and inflammation with improved neuronal function. There may be an increased activation of endocannabinoid receptors, which may cause greater release of anandamides, which are natural antioxidants, responsible for satiety and pleasure [119]. Chronic depression and dementia may show atrophy of hippocampus on brain imaging studies, due to the neurotoxic effects, linked to oversecretion of cortisol or abnormally low concentration of BDNF and serotonin [68,69]. It is possible that depression could be induced by metabolic disorders of monoamine neurotransmitters that are involved in noradrenaline, serotonin, and dopamine signaling. Thus anxiety and depression have been found to increase the severity of cognitive dysfunction in patients with AD, which may be due to greater oxidative stress and proinflammatory effects caused by these disorders [68–71]. It is proposed that these mental disorders may also influence emotions, leading to anger and suicides.

Caloric intake and diet composition have large and lasting effects on cognition and emotion, especially during critical periods in development, but the neural mechanisms for these effects are not well understood [117]. An understanding of the cognitional and emotional processes that underlie desires to consume excess of foods can assist in finding more effective prevention and treatment strategies for overweight and obesity. It seems that apart from preconception factors and perinatal factors, early-life diet and exposure to stress can lead to cognitive dysfunction throughout life, and there is potential for early nutritional interventions to prevent these deficits. Acute consumption of a high-fat diet primes the hippocampus to produce a potentiated neuroinflammatory response to a mild immune challenge, causing memory deficits and depressive symptoms [117]. Low dietary intake of omega-3 fatty acids and/or flavonoids can also contribute to depression and dementia, as well as increased susceptibility to stress, through its effects on endocannabinoid and inflammatory pathways in the hippocampus and hypothalamus, leading to synaptic phagocytosis by microglia, contributing to memory loss and depressive symptoms with reduced processing of thoughts [11,117–119]. Understanding the relationships between diet, cognition, emotion, and depression is necessary to uncover the mechanisms involved in and strategies to prevent or attenuate comorbid neuropsychological disorders in the population [15,117–122]. The psychology of exclusion and the body-mind index are other expressions that have been proposed by Wilczynska and De Meester to explain the role of mind on body functions [123–125].

The Singh and Wilczynska hypothesis on emotions

The moody mice experiment indicated that certain areas in the brain can regulate happiness, depression and emotion, and also possibly cognition [11,31]. This landmark study by Ramirej and coworkers used light to stimulate clusters of neurons in the hippocampus having stored memories of a positive experience, which started glowing red in this mouse hippocampus which was fired [11,31]. As shown in Fig. 38.3, the neurons where a happy memory was encoded fired when stimulated by light.

Interestingly, Tonegawa and coworkers identified neurons that fired when male mice enjoyed a rewarding experience: spending time with a female [11,120]. After the movements of the male mice were restricted for 10 days, the animals lost their natural preference for sugar water (tasty food) over plain water, indicating a loss of interest in pleasurable experiences. There was a significant decline in struggle by the stressed-out animals when they were lifted by their tails. However, directly stimulating a happy memory encoded in the neurons, before depression began, may have helped the mice to bypass some depression-induced dysfunction in the brain [11]. It seems that this work explores the circuit dysfunctions underlying mental disorders. It is possible that these studies of mapping neuronal circuits, in which boosting activity has a positive effect, can provide the potential for developing future therapies by diets or drugs. Tonegawa and colleagues have used optogenetics to demonstrate that a particular targeted memory (engram) or group of cells that was active during fear-learning is sufficient to drive freezing behavior in mice during subsequent reactivations [120]

Since stimulation of a happy memory circuit encoded in the neurons of hippocampus may reverse some depression-induced dysfunction, resulting in happiness, Singh and Wilczynska proposed that neurons in the hippocampus may have an influence on the release of anandamides as well as the hormones dopamine, endorphins, serotonin, oxytocin, and melatonin, which are associated with happiness [11,31]. These neuronal circuits of happiness may suppress amygdala flutter via neurotransmitters, which occurs during depression, resulting in systemic inflammation. It is also possible that an emerging class of signaling molecules, the omega-3 endocannabinoids, may regulate the

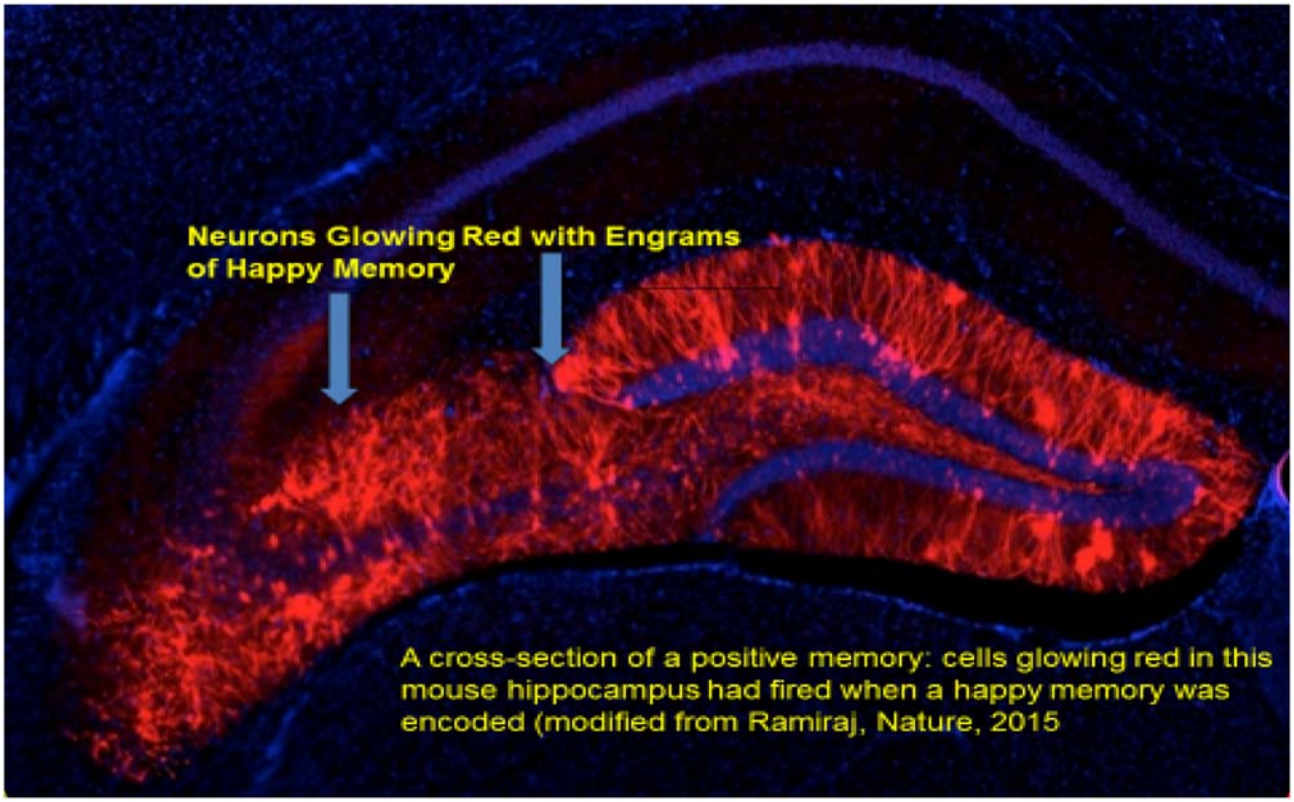


FIGURE 38.3 Cross section of mouse hippocampus showing positive memory neurons glowing red when a happy memory was encoded. *Adapted from references Ramirez S, Liu X, MacDonald CJ, Moffa A, Zhou J, Redondo RL, et al. Activating positive memory engrams suppresses depression-like behaviour. Nature 2015;522(7556):335–339. doi: 10.1038/nature14514, Shen H. Activating happy memories cheers moody mice, Nat N Nat 2015;doi:10.1038/nature.2015.17782.*

pathophysiological processes in the neurons of the hippocampus and hypothalamus that are concerned with the hypothalamus-pituitary axis and release of anandamide, serotonin, and dopamine, which are responsible for satiety, well-being, and pleasure [68,116–121]. Omega-3 fatty acids, arachidonic acids, and polyphenols are known to have beneficial effects via cell signaling in the neuronal cells, endothelial cells, smooth muscle cells, and cardiomyocytes as well as adipocytes and beta cells of the pancreas concerned with the pathogenesis of NCDs [23–27,107,122]. Electrophysiological studies indicate that flavonoids and fatty acids may promote long-term potentiation in the hippocampus and suppress amygdala flutter, supporting the hypothesis of synaptic plasticity mediation, indicating a neuroprotective effect of flavonoid and fatty acid compounds in the brain [7,35]. The nutrient contents in diets related to MIND, in particular flavonoids, omega-3 fatty acids, and amino acids contents, could be a potential clinical direction for prevention and/or attenuation of the cognitive decline that accompanies various brain disorders [7,35,37–44]. The amino acids L-theanine, tryptophan, tyrosine, histidine, and arginine are used by the brain for the synthesis of various neurotransmitters and neuromodulators [126–128]. Choline is a potential nutrient that may induce sleep, muscle movement, learning, and memory by maintaining the structure of cellular membranes and aids in the transmission of nerve impulses. It also assists in the absorption of fatty acids. All these nutrients are found in abundance in the food content related to MIND nutrition.

Emotions generated due to stress, pleasure, and thought processes may alter the individual's behavioral strategies in a way that will increase the likelihood of achieving certain goals, with underlying alterations in neurotransmitters [126–128]. It is possible that attraction, lust, and love or attachment as well as agony (distress) and ecstasy (immense happiness) may be distinct but intertwined processes in the brain, each mediated by its own neurotransmitters and neuronal circuit [119,120,126–128]. While sexual craving and ecstasy are mediated by testosterone and estrogen with the amygdala as an important center, attraction is mediated by hormones of stress and reward, including dopamine, norepinephrine, cortisol, and the serotonergic system (serotonin) and has the nucleus accumbens and the ventral tegmental area as key mediators [126–128]. The circuits in the brain may feed on and reinforce each other via emotional pleasures and the relevant neurotransmitters [11,120,126–128]. It seems that love could be defined as an emergent characteristic of a cocktail of neurotransmitters: oxytocin and dopamine and neuropeptides that act on hippocampus neurons and amygdala. Fig. 38.4.

There is evidence that dopamine is a hormone associated with happiness and serotonin with depression [127]. Previous studies indicated that an activation of dopamine and serotonin increased the production of oxytocin, a hormone that reduces pain perception and increases the emotional connection [126,127]. The amygdala is concerned with fear behavior and regulates all the components of brain. However, after the amygdala has been disconnected, the parts of the brain that are active against negative emotions are activated, resulting in an increase in the proinflammatory neurotransmitters cortisol and glucocorticoids [126–128]. It seems that the way we understand ourselves and the environment around us may determine the status of our mind and emotion. The human mind has learned from evolution that the best defense is attack, so the amygdala evolved to be ready to respond with fear, which leads to negative emotions as well as oxidative stress and inflammation [126,127]. Acetylcholine is the primary neurotransmitter released from nerve endings in both central and peripheral nerves as an antiinflammatory agent, responsible for muscle movement, alertness, concentration, and memory [128]. The optimal levels of acetylcholine maintain an elevated mood, with focused mind and intelligence in decision making. However, lower levels of

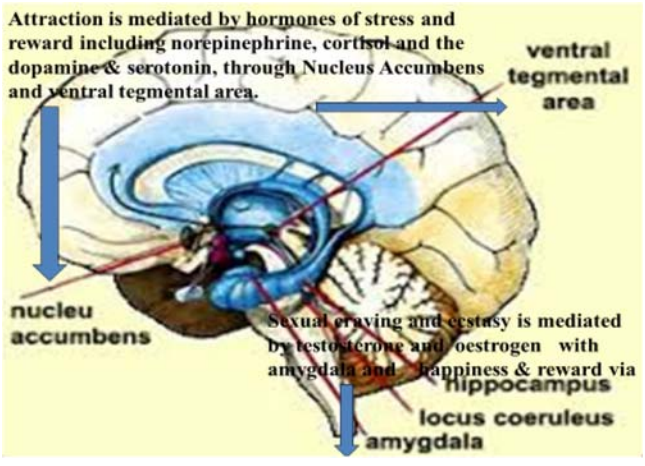


FIGURE 38.4 The hippocampus, amygdala, and nucleus accumbens as mediators of agony and ecstasy, love, sex, and happiness.

acetylcholine may predispose the person to poor learning, recall, and ability to think with a decline in thought processing. Acetylcholine also regulates emotions, primitive drives as well as anger, fear, rage, and aggression, which may deviate according to the environment around us. Therefore an imbalance in these neurotransmitters inculcate emotions that may affect both the individual and people around them [128]. There appears to be an inverse relationship between acetylcholine and serotonin, which means that if the quantity of one increases, the quantity of the other decreases. A lower level of acetylcholine may act as a stimulant for the brain because it activates the release of dopamine and serotonin. However, too much acetylcholine can inhibit the brain, predisposing the person to depression [128]. It seems that certain foods that are rich in arachidonic acid, omega-3 fatty acids, and amino acids, such as fish, eggs, dairy, soy products, poultry, and foods containing lecithin, significantly increase acetylcholine. The nutraceuticals choline, lecithin, fish oil, and flax seed oil as well as physical activity also increases acetylcholine concentration. These foods can also activate the endocannabinoid system [119]. However, eggs and meat are also known to produce triamino-methyl-N-oxide, which is an oxidant and thrombotic that may increase the risk of CVDs, although arachidonic acid provided by these foods is healthful.

The endocannabinoid system consists of receptors, endogenous ligands, and ligand metabolic enzymes [119,121]. These are cannabinoid receptors CB_1 and CB_2, the eCB ligands anandamide (AEA) and 2-arachidonoylglycerol (2-AG), and their metabolic enzymes [119]. In the brain, cannabinoid receptor 1 (CB_1) is the most abundant G protein−coupled receptor expressed, with particularly dense expression in the substantia nigra, globus pallidus, hippocampus, cerebral cortex, putamen, caudate, cerebellum, and amygdala [119]. CB_1 is also expressed in nonneuronal cells, such as adipocytes and hepatocytes, and in musculoskeletal tissues. Cannabinoid receptor 2 (CB_2) is principally associated with cells governing immune function, although it may also be expressed in the central nervous system [119]. It seems that metaphorically the endocannabinoid system represents a microcosm of psychoneuroimmunology, or the brain-body connection [119,121]. The endocannabinoid ligands are *N*-arachidonoylethanolamide (AEA, released on demand) and 2-AG, which have related enzymes. In several chronic diseases, such as psychological disorders, irritable bowel syndrome, migraine, fibromyalgia, and other conditions, there may be a chronic deficiency of endocannabinoids activity. It is proposed that increased supplementation of MIND foods may provide adequate amount of fatty acids and flavonoids to activate the endocannabinoid system, which in turn may activate neuronal circuits in the hippocampus and hypothalamus, leading to improved cognition, lower depression, and pleasurable emotions. The essential agents with therapeutic effects in the endocannabinoid systems are AEA and ethanolamine. The chemical structures of both the agents have free OH in a single bond, indicating potential antioxidant activity (Fig. 38.5).

Several classes of pharmaceuticals, including antidepressants, antipsychotics, anxiolytics, and anticonvulsants, have been shown to upregulate the endocannabinoid system [119,121]. Other such pharmaceuticals include analgesics: acetaminophen, nonsteroidal antiinflammatory drugs, opioids, and glucocorticoids. Physical and complementary interventions such as massage and manipulation, acupuncture, and herbal medicines also can upregulate the endocannabinoid system [119]. Lifestyle modifications, such as diet, weight control, exercise, and the use of psychoactive substances (alcohol, tobacco, coffee, and cannabis), also modulate the endocannabinoid system. Endocannabinoids often act as retrograde messengers, emanating from morphologically undifferentiated regions of postsynaptic principal cells and traveling backwards across synapses [121]. These molecules may transiently inhibit the release of either the inhibitory neurotransmitter GABA or the excitatory transmitter glutamate on the interactions of CB_1 and CB_2 with the central neurotransmitters, such as dopamine, serotonin, noradrenaline, GABA, glutamate, and endorphins [121]. The endocannabinoids AEA and 2-AG are

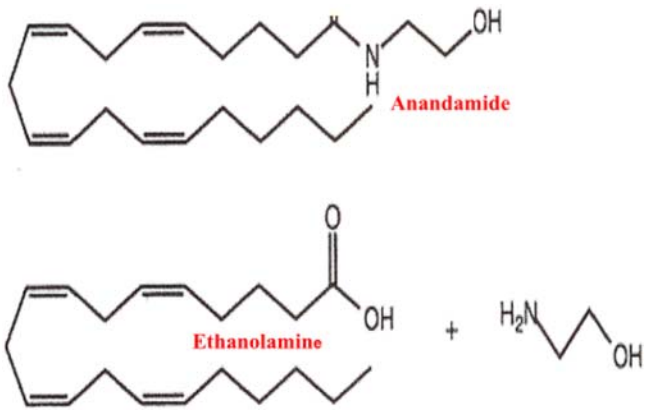


FIGURE 38.5 Chemical structures of anandamide and ethanolamine. *Modified from reference McPartland JM, Guy GW, Di M. Care and feeding of the endocannabinoid system: a systematic review of potential clinical interventions that upregulate the endocannabinoid system. PLoS One 2014;9(3):e89566. https://doi.org/10.1371/journal.pone.0089566 [119].*

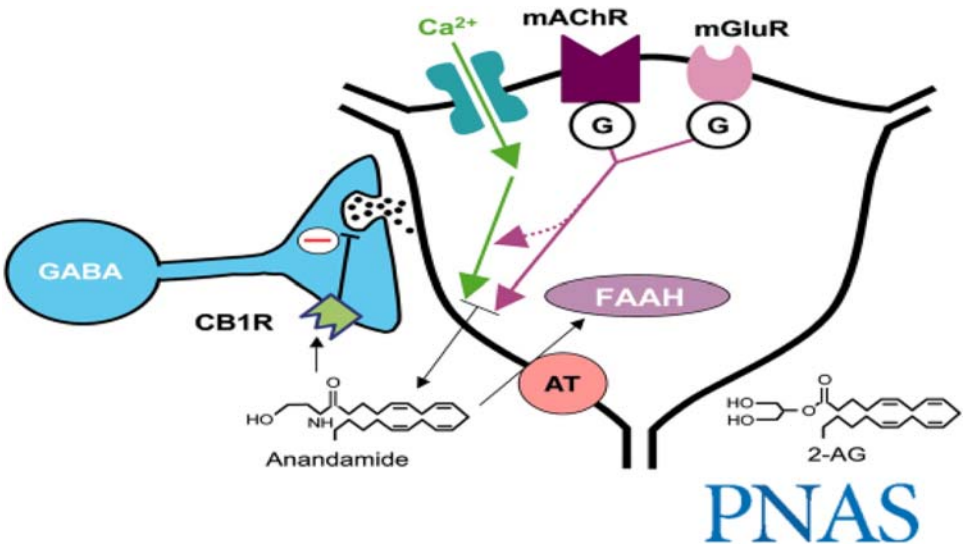


FIGURE 38.6 Synthesis of anandamides is initiated by calcium influx through voltage-gated calcium channels or by the activation of G protein–coupled neurotransmitter receptors, including type I metabotropic glutamate receptors or muscarinic acetylcholine receptors. *Adapted from reference Cohen K, Weizman A, Weinstein A. Modulatory effects of cannabinoids on brain neurotransmission. Euro J Neurosci 2019;50:2322–2345 [121].*

synthesized in postsynaptic target cells, such as hippocampal pyramidal cells, with inhibition of GABA or glutamate release by inhibiting calcium channels and activating potassium channels [121]. The endocannabinoids are taken up into postsynaptic or presynaptic cells by the anandamide transporter. The endocannabinoids gain access to the extracellular space and activate CB_1 found concentrated on certain nerve terminals, for example, those of cholecystokinin-containing GABAergic interneurons in hippocampus (Fig. 38.6).

The theories of emotions

Emotion is defined as a complex state of feeling that results in physical and psychological changes that may influence thoughts and behavior [116]. Emotionality is associated with a range of psychological phenomena, including personality, mood, temperament, and motivation. Emotions in human beings may also involve physiological arousal, expressive behaviors, and conscious experience. Neurological theories propose that activity within the brain leads to emotional responses. Cognitive theories argue that thoughts and other mental activity play an essential role in forming emotions [116]. The evolutionary theory of emotion indicates that our emotions exist because they serve an adaptive role, motivating people to respond quickly to stimuli in the environment, that may be helpful in improving the chances of success and survival. Charles Darwin proposed that emotions evolved because they were adaptive and allowed humans and animals to survive and reproduce. Feelings of love and affection lead people to seek mates and reproduce. Feelings of fear compel people to either fight or flee the source of danger. It seems that understanding the emotions of other people and animals also plays a crucial role in safety and survival. It has been observed that a hissing, spitting, and clawing animal is frightened or defensive, which appears to confirm that behavior is a manifestation of emotion. The human capability to interpret correctly the emotional displays of other people and animals allows us to respond correctly and avoid danger.

Another theory suggests that seeing an external stimulus leads to a physiological reaction, and the emotion involved is dependent upon how we interpret those physical reactions. According to the Cannon-Bard theory of emotion, emotions and experience are physiological reactions such as sweating, trembling, and muscle tension that may occur simultaneously. The physical symptoms associated with fear include shaking hands, rapid breathing, and a rapid heart rate. This theory proposes that emotions result when the thalamus sends a message to the brain in response to a stimulus, resulting in a physiological reaction. At the same time, the brain also receives signals triggering the emotional experience. Cannon and Bard's theory suggests that the physical and psychological experience of emotion happen at the same time and that one does not cause the other. According to another theory, the physiological arousal occurs first, and then the individual must identify the reason for this arousal to experience and label it as an emotion. A stimulus leads to a physiological response that is then cognitively interpreted and labeled, resulting in an emotion [116]. This theory also emphasizes that similar physiological responses can produce varying emotions. It seems that an increased heart rate and sweating palms while talking with others or during an interview indicate anxiety. If such physiological responses occur on a date, they may be interpreted as love, affection, or arousal [116]. In the appraisal theories of emotion, thinking must occur first before experiencing emotion. Richard Lazarus was a pioneer in this area of emotion, and this theory is

often referred to as the Lazarus theory of emotion. The sequence of events first involves a stimulus, followed by thought, which then leads to the simultaneous experience of a physiological response and the emotion. There may be facial expressions that are connected to experiencing emotions. Charles Darwin and William James both noted early on that physiological responses often had a direct impact on emotion rather than simply being a consequence of the emotion. It seems that emotions are directly tied to changes in facial muscles, because people are forced to smile pleasantly at a social function or while viewing comedy on television.

Regenerative therapies for emotion, depression, and cognition

The association of night eating habits with metabolic syndrome and its components has been reported in longitudinal studies [56,57]. This is important because obesity and CVDs are risk factors for decline in cognition and dementia. It has been shown that caloric restriction improves cognition, delays aging, and possibly delays the development of AD [58−62]. The mechanism may involve interoceptive cues as well as reduced energy intake per se, which act by influencing central circadian clock and peripheral clocks regulating metabolism. The study showed that hunger alone, induced by a ghrelin agonist, reduced AD pathogenesis and improved cognition in the APP-SwDI mouse model of AD. Both treatments also reduced levels of beta-amyloid beta and inflammation (microglial activation) at 6 months of age compared to the control group, similar to the effect of caloric restriction [58]. It seems that a hunger-inducing drug attenuates pathogenesis of AD in the absence of caloric restriction, and the neuroendocrine aspects of hunger also prevent age-related cognitive decline [59,60].

The vulnerability of neuronal health to aging is all too often manifested in neurodegenerative disorders such as AD and Parkinson's disease. In this review of literature we describe evidence indicating that two dietary interventions—caloric restriction and intermittent fasting—can prolong the health span of the nervous system by impinging upon fundamental metabolic and cellular signaling pathways that regulate the lifespan. Restriction of calories and intermittent fasting influence energy and oxygen radical metabolism and cellular stress response systems in ways that protect neurons against genetic and environmental factors to which they would otherwise succumb during aging [58−60]. There are multiple interactive pathways and molecular mechanisms by which these two methods benefit neurons, including those involving insulin-like signaling: FoxO transcription factors, sirtuins, and peroxisome proliferator-activated receptors. It is possible that these pathways stimulate the production of protein chaperones, neurotrophic factors, and antioxidant enzymes, which are protective to neurons to inhibit the stress and resist disease. A better understanding of the impact of these agents on the aging of neurons will likely lead to novel approaches for preventing and treating neurodegenerative disorders.

Intermittent fasting appears to be an effective dietary intervention to counteract the associated metabolic abnormalities with CMD [61,62]. It has been proposed that browning of white adipose tissue is the main underlying mechanism for the occurrence of fasting -mediated metabolic benefits. It remains unclear whether fasting can retain its efficacy in different models, such as genetically obese or diabetic animals. In one experiment, leptin-deficient *ob/ob* mice were subjected to 16 weeks of isocaloric intermittent fasting, and comprehensive metabolic phenotyping was conducted to assess the metabolic effects of fasting intermittently. Interestingly, isocaloric intermittent fasting-subjected *ob/ob* animals failed to exhibit reduced body weight gain, lower fat mass, or decreased liver lipid accumulation. Intermittent fasting with isocaloric diet showed no effects on thermogenesis and did not induce browning of white adipose tissue in *ob/ob* mice. Despite the lack of improvement in insulin sensitivity, isocaloric diet on intermittent fasting in *ob/ob* animals resulted in improvement in glucose tolerance as well as higher postprandial insulin levels, with elevated incretin expression, indicating that intermittent fasting with an isocaloric diet is effective in improving nutrient-stimulated release of insulin, which is relevant for all the CMDs [61−63].

Prayer, meditation, and yoga

The role of prayer, meditation, and yoga has been examined for utility in the treatment of psychological disorders [129−133]. In an epidemiological study involving 209 subjects, blood pressure and heart rate were recorded every 30 minutes by ambulatory blood pressure monitoring for 3−7 days. The results showed that a larger circadian amplitude of heart rate was associated with active prayer in Indians of the Hindu religion [129]. In a prospective Nurses' Health Study, a cohort of 74,534 women who were free of CVDs and cancer at the start were recruited; their religious service attendance was assessed by a self-reported questionnaire, which was collected initially in 1992 and subsequently every 4 years [130]. The investigators identified 13,537 deaths, including 2721 due to CVDs and 4479 due to cancer, during follow-up from 1996 until 2012. The results showed that attending religious service more than once per week was

associated with a 33% reduction in mortality compared with women who never attended religious services (HR = 0.67, 95% CI: 0.62−0.71; *P*-value for trend < .0001). In a comparison of women who attended religious services more than once per week with those who never attended, the HR for cardiovascular mortality was 0.73 (95% CI: 0.62−0.85; *P*-value for trend < .0001), and cancer mortality was 0.79 (95% CI: 0.70−0.89; *P*-value for trend < .0001). This study provided strong evidence that social support, depressive symptoms, smoking cessation, and optimism mediated the relationship between religious service attendance and reduced mortality. Interestingly, the findings of this study indicated that frequent religious service attendance may be associated with significantly lower risk of all causes of CVDs and cancer mortality [130]. Fig. 38.7 illustrates the relationship between greater prayer intervention and lower mortality, whereas increased mortality occurred in the group with fewer prayer days.

In a previous study, the effects of direct contact in person-to-person prayer on depression, anxiety, and positive emotions were examined during a follow-up of 1 year [131]. The study included 44 subjects who had undergone prayer intervention consisting of 6 weekly 1 hour prayer sessions conducted in an office setting. The postprayer assessments done after 1 month and 1 year showed significantly less depression and anxiety, more optimism, and greater levels of spiritual experience than did the preprayer measures ($P < .01$ in all cases). All patients with anxiety and depression maintained significant improvements for the duration of at least 1 year after the final prayer session [131]. It appears that direct contact in person-to-person prayer may be a useful adjunct therapy with to standard drug treatment for patients with disorders of emotion, depression, and anxiety [129−131].

Meditation is the hallmark of concentration, which appears to be the most important component of yoga therapy. Yoga therapy also includes yoga postures, yoga prayer, and yoga breathing as its major components, which can influence health and behavior by their effects on the autonomic nervous system [134−139]. In a randomized, controlled trial of transcendental meditation, the components of metabolic syndrome in subjects with coronary artery disease were examined [138]. The results showed that practice of regular meditation can cause a significant decline in systolic blood pressure. Chronic hypertension is an important risk factor for heart failure and metabolic syndrome, which are risk factors of dementia and which can be controlled by yoga therapy [138]. In all the regenerative therapies related to yoga, there is increased autonomic function with an increase in parasympathetic activity and a decline in sympathetic activity, leading to high vagal nerve activity [133−139]. Borovikova et al. have demonstrated that vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin, indicating that increased vagal activity acts by increased production of nitric oxide, a precursor of acetylcholine [67].

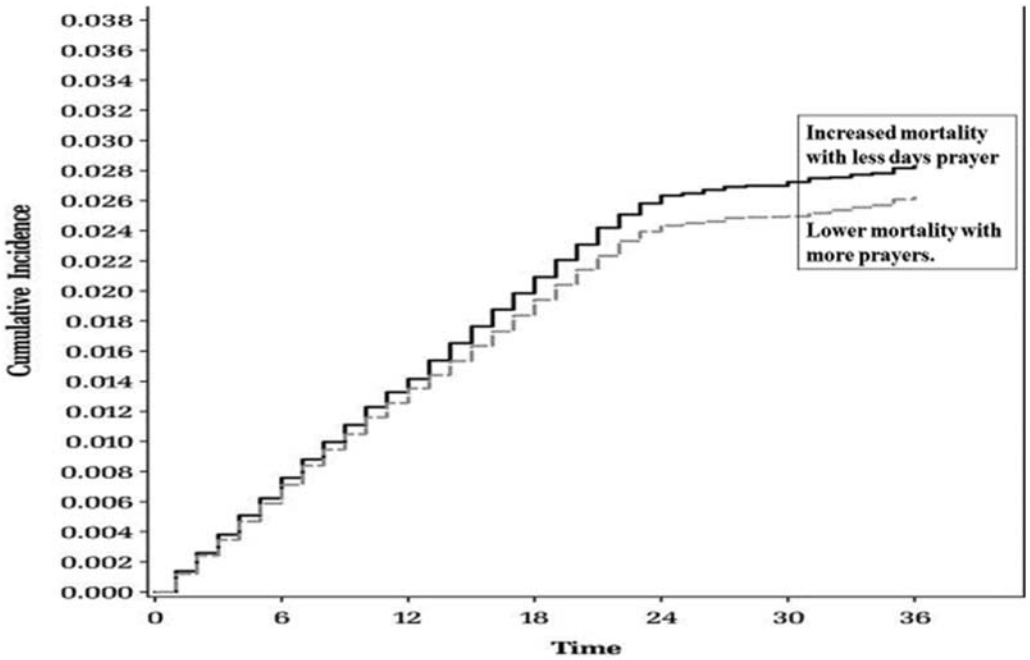


FIGURE 38.7 Time course graphs showing an association of increased mortality with fewer days of prayer compared to lower mortality associated with more days of prayer. *Adapted from reference Li S, Stampfer MJ, Williams DR, Tyler J, VanderWeele TJ. Association of religious service attendance with mortality among women. JAMA Intern Med 2016;176(6):777−85. doi: 10.1001/jamainternmed.2016.1615 [130].*

Meditation is known to improve sleep, decrease depression, reduce anxiety, downregulate inflammatory genes, upregulate immune system genes, improve insulin and glucose regulatory genes, and increase telomerase by 43%; the largest increase ever recorded [140]. Meditation also improves psychospiritual well-being or spiritual fitness, important for maintenance of cognitive function and prevention of AD [140]. In a clinical trial involving 81 subjects, treatment with kundalini yoga was associated with significant improvement in memory and depressive symptoms along with short- and long-term improvements in executive functioning and broader effects on depressed mood and resilience [141]. In another clinical trial among 100 subjects, 27 subjects practiced Raja Yoga meditation for 6 months to 5 years (short term), and 73 subjects practiced Raja Yoga meditation for more than 5 years (long-term) [142]. A comparison between short-term and long-term meditation showed that the changes from baseline values (from premeditation to postmeditation at 15 and 30 minutes) in the short-term group were not statistically significant ($P > .05$). However, within-group differences in the long-term group revealed that changes in the physiological variables, heart rate, and blood pressure, were statistically significant in a comparison between premeditation and postmeditation at both 15 and 30 minutes. The study suggests that the long-term practice of Raja Yoga meditation improves basic cardiorespiratory functions, owing to shifting of the autonomic balance in favor of the parasympathetic nervous system instead of the sympathetic nervous system. Another study of middle latency auditory-evoked potentials during Brahmakumaris Raja Yoga meditation revealed that there was a decrease in the peak latency of the Na wave (a negative wave between 14 and 19 ms) during meditation [143]. Since the neural generator of this wave lies at the midbrain-thalamic level, one can infer from the results that the meditation reduces conduction time at this level. The regular practice of mental repetition of the syllable "OM" can cause significant changes in the middle latency auditory-evoked potentials, indicating that it facilitates neural activity at the mesencephalic or diencephalic level [144]. The study comprised 30 subjects aged 20−55 years, who had a minimum of 6 months experience in meditating using "OM." Each subject was assessed in four sessions: two meditation sessions and two control sessions. The two control sessions were *ekagrata*, that is, a single-topic lecture on meditation, and *cancalata*, that is, nontargeted thinking. The two meditation sessions were *dharana*, that is, focusing on the symbol "OM," and *dhyana*, that is, effortless single-thought state using "OM." All four sessions were recorded on four different days and consisted of three states: that is, premeditation, during meditation, and postmeditation. The findings revealed that the wave V peak latency significantly increased in *cancalata*, *ekagrata*, and *dharana*, but no change occurred during the *dhyana* session [144]. It is possible that information transmission along the auditory pathway is delayed during *cancalata*, *ekagrata*, and *dharana* but there is no change during *dhyana*. It may be said that auditory information transmission was delayed at the inferior collicular level as the wave V corresponds to the tectum.

Previous studies published on the effects of mindfulness-oriented interventions on psychological health and laboratory-based experimental research on the immediate effects of mindfulness inductions on emotional and behavioral functioning have been published [145,146]. The present model of health has been considered the worst, because it puts only minor emphasis on spiritual behavior and psychological behaviors and is pushing the world toward slow-motion disaster in terms of total health and care for patients [147]. Therefore newer studies and others indicate a surge of interest in the research on mindfulness as a psychological construct and as a modality of treatment [140,148−151]. Currently, it is not clear how the teachings of Buddha and Western psychological aspects of mindfulness differ and, furthermore, how mindfulness can be integrated into modern medicine. There are cross-sectional studies and clinical trials on the associations between mindfulness and various indicators of psychological health. Mindfulness may bring about various positive psychological effects, including reduced emotional reactivity, greater subjective well-being, reduced psychological symptoms, and improvement in regulation of behavior. Another review obtained a greater insight into the effects of mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT) on mental health. The review involved 23 studies: 22 on the effects of MBSR and 1 on the effects of MBSR in combination with some aspects of MBCT. The results showed that the strongest outcomes were reduced levels of emotional exhaustion (a dimension of burnout), stress, psychological distress, depression, anxiety, and occupational stress. There were significant improvements in terms of mindfulness, personal accomplishment (a dimension of burnout), sleep quality (occupational) self-compassion, and relaxation, indicating that MBSR may help to improve psychological functioning [145,146].

Many protective therapies to treat patients with depression and dementia are still not in practice because of an unmet need in research on these models of treatment, and caregivers often focus on one or the other group rather than the dyad. New strategies such as meditation, singing and music, and behavior with mindfulness are needed to train caregivers to support the well-being of both caregivers and people suffering from depression, dementia, and other emotional states [140,148−150]. In several studies, intervention with mindfulness training has been shown to improve psychological well-being in both healthy subjects and patients with dementia [151]. There is evidence that Kirtan Kriya meditation

(singing religious songs) is an easy, cost-effective meditation technique requiring only 12 minutes a day. It has been successfully employed to improve memory in studies of people with subjective cognitive decline, people with mild cognitive impairment, and highly stressed caregivers, all of whom are at increased risk for subsequent development of AD [150]. It also improves sleep, decreases depression, reduces anxiety, downregulates inflammatory genes, upregulates immune system genes, improves insulin and glucose regulatory genes, and increases telomerase by 43%, the largest increase ever recorded [150]. Singing of religious songs also improves psychospiritual well-being or spiritual fitness, which is important for maintenance of cognitive function and prevention of dementia and depression. Kirtan Kriya is easy for aging individuals to learn and practice, along with other modalities, such as dietary modification, physical exercise, mental stimulation, and socialization, which may be beneficial as part of a prevention program for all psychological disorders.

Mechanisms

There is evidence that during the process of aging, f dysfunctional and damaged cellular proteins and organelles accumulate, resulting in a disruption of cellular homeostasis and progressive degeneration, which increases the risk of cell death [60,61,152–156]. The association of APOE Îµ4 with cognitive function over the adult life course and incidence of dementia has also been observed [156]. Interestingly, physical activity and caloric restriction are known to promote healthy aging and mitigate age-related pathologies that can modulate the proteome, possibly by influencing intracellular protein quality [74]. Moreover, exercise-induced target of rapamycin complex 1 (TORC1) and autophagy signaling share common pathways with that of restriction of calories. It is possible that the longevity effects of exercise and restriction of calories may stem from the maintenance of the proteome by balancing the synthesis and recycling of intracellular proteins and thus may represent practical means to promote longevity [61,62]. It is known that autophagy is an evolutionarily conserved recycling pathway that is responsible for the degradation and turnover of cellular proteins and organelles, which may be linked to the aging process. TORC1, a central kinase involved in protein translation, is a negative regulator of autophagy, and inhibition of TORC1 enhances the lifespan, which can decrease the production of cellular proteins that may otherwise enhance the deleterious accumulation that is observed in aging. TORC1 may also exert its effects in an autophagy-dependent manner. Caloric restriction and exercise may cause a concomitant downregulation of TORC1 activity and upregulation of autophagy in a number of tissues [62,157]. Freeman et al. have proposed foundational advances in eicosanoid signaling involving the free radical biology of oxygen and nitric oxide and mass spectrometry to enable the discovery of nitrated unsaturated fatty acids [153]. Fatty acid nitroalkenes species undergo rapid and reversible alterations due to unique biochemical actions and mechanisms of biological nucleophiles such as cysteine, leading to the posttranslational modification of low-molecular-weight and protein thiols. According to present knowledge about fatty acids, the nitro-fatty acid reaction with the alkylation-sensitive cysteine proteome leads to physiologically beneficial alterations in transcriptional regulatory protein function and gene expression [153]. It has been demonstrated clearly in in vivo rodent model responses to metabolic and inflammatory stress. Clinical development of nitro-fatty acids as new drug candidates for treating acute and chronic metabolic and inflammatory disorders is in process and needs clinical trials in patients with psychological disorders as well as those with other NCDs.

Fatty acids, which regulate functions of the mind, are contained in all human cells, similarly to nucleic acids (genes), which determine people's bodily functions [158–162]. As De Meester reported, fatty acids are synchronized with brain waves, express them, and affect them. One characteristic of fatty acids is that they are capable of carrying chemical and physical information. The body (heart and brain), which is unchangeable in its structure at a given moment, resonates with the physical emission of the Schumann frequency [152,163]. The heart's electric field is very strong, about 60 times as strong as that generated by the brain, which cooperates with the heart. This resonance is observed as waves in electrocardiographic and electroencephalographic recordings. The mind issues instructions for the body, as a result of which the physical information (mind/electron spins) can interact with the chemical information (body/genes). As a result, this influences the transcription of genes and, ultimately, people's behavior [152,163].

Some still unexplained phenomena can be explained by referring to the biochemical and psychophysically conductive mixture of phospholipids, xanthophylls, and microelements contained in the red blood cells, which circulate in the human body. The red blood cells transport and disseminate oxygen alongside spatiotemporal and socioenvironmental information across the body, thereby determining the mode of behavior, that is, the phenotype. This is nothing else than the mind that science has been looking for and that, while not found in the protein particles of genes, is being found today in the lipids of red cell membranes. It is indeed high time to seriously consider De Meester's suggestion that scientists focus on the evolutionally selected substrate of the mind, that is, on the lipids of red blood cell membranes and their components, paying particular attention to the evolutionarily selected allylic double bond [107,152,153].

Guidelines for prevention of mental disorders

There is an unmet need to determine the effects of diet and lifestyle guidelines on cognition, depression, and emotion as well as other related disorders such as insomnia, anxiety, type A behavior, and mood disorders. Living in a green environment, time restriction on eating, exercise training, prayer, meditation, and yoga may have protective effects on all the psychological disorders by their influence on biological mechanisms to emphasize their role in prevention [158−162,164−168]. Of the several guidelines that are proposed for prevention of dementia, a few of them appear to be interesting because they target inflammation, nutrient deficiency, and accumulation of toxic substances [152,163,169−172]. Since these markers have adverse effects on body systems, we need to include protective health behaviors and related markers that can inhibit these markers and activate other markers, such as increase in immunoglobulins (immunity), IL-10 (inflammation), HDL cholesterol (lipids), oxidative stress (superoxide dismutase, catalase, coenzyme Q10), lipoxins (protectins, marasins, resolvins, hepoxins, and nitrolipids), and prostaglandins (inflammation) [153]. Thus there is need to consider the power and the effects of behaviors, qualities of diets, and biomarkers in light of magnetic resonance imaging and positron emission tomography for assessment of these markers, while developing guidelines for prevention of psychological disorders [154].

Diabetes is an additional condition that is associated with microinflammation and leaky body systems and can rapidly promote neuropsychological disorders, including AD. These guidelines provide only a broad framework for assessment, management, and follow-up of older people with dementia. While most of the recommendations are evidence-based, these guidelines should not be considered to be a substitute for professional knowledge and clinical judgment. The recommendations made as part of these guidelines should be tailored to address the clinical needs of the individual patient and the treatment setting. American Academy of Family Physicians guidelines and others give greater emphasis to neuropsychological evaluation to identify the onset and type of mild cognitive impairment and dementia so that early intervention can occur [154,172]. Such evaluation can be useful in predicting the degree of driving risk and in determining decision-making capacity in individuals with dementia. Evaluation can enable identification of cognitive deficits, predict ion of functional outcomes, and monitoring of patient recovery after traumatic brain injury. Psychological disorders are a highly prevalent acquired disorders of cognition, depression, and emotion that interfere with activities of daily living, relationships, and quality of life [169]. Recognition and effective management strategies are necessary to provide comprehensive care for these patients and their families. High-quality clinical practice guidelines can improve the quality and consistency of care in all aspects of dementia diagnosis and management by clarifying interventions supported by sound evidence and by alerting clinicians to interventions that lack proven benefit. Indian experts have proposed clinical practice guidelines for the diagnosis of mild cognitive impairment compared to dementia [170]. These guidelines need modification by adding functional magnetic imaging or PET screening of brain. Moreover, no attempt has been made to exclude the presence of depression and emotional behaviors in the existing guidelines, indicating that the guidelines are incomplete [172].

Future research

Since the threat of infection with SARS-CoV-2, the virus that causes the illness known as COVID-19, appeared and a state of pandemic was proclaimed, the scientific community has been concerned about the presence of chronic low-grade inflammation after an acute episode of inflammation due to the epidemic of COVID-19 (R.B. Singh, personal communication). This pandemic has been associated with mental disorders in all societies. According to a 2020 survey carried out by the University of Southern California, about 40% of the population were afraid of contracting COVID-19, and more than half of them avoided some or all other people. In 2020, in comparison to the 2018 NHIS sample, US adults in April 2020 were eight times more likely to fit criteria for serious mental illness (27.7% vs 3.4%) and three times more likely to fit criteria for moderate or serious mental illness (70.4% vs 22.0%). Basically, almost all people around the world have been pressed to practice social distancing and self-isolate. This drastically changes the WHO statistics, with the new official data unavailable at the time of writing [123].

1. Psychologists warn that the coronavirus pandemic declared in 2020 may cause a worldwide depression and anxiety epidemic. This particularly concerns certain types of disorders, including obsessive-compulsive disorder, generalized anxiety disorder, social anxiety disorder, agoraphobia, acute stress disorder, and separation-related anxiety disorder.
2. Similarly, the pandemic may take a grim toll on the health of patients with depression and paranoia. Undoubtedly, it will have a deep impact on the elderly, lonely people, the residents of nursing homes and other care facilities, and all people who cannot be visited on a regular basis.

3. In the years to come, the consequences of pandemic self-exclusion may basically be experienced by everybody, including people who do not report mental problems but fear for their future and the future of their families and the world. This will certainly be more challenging for people with limited adaptive skills, those who feel helpless in the face of the loss of their previous stability, and those who do not experience a sense of community with others.
4. The pandemic period has increased the feeling of loneliness in young children and adolescents. Lack of contact with other young people, which is necessary for optimal psychosocial development, will change the functioning of this entire generation in the future.
5. Russia is one of the countries with the highest depression rates, as reported by Professor Stanislav Poltorak of the St. Petersburg V.M. Bekhterev Psychoneurological Research Institute, and it has the highest rate of suicide by males in the world. The average suicide rate stood at 26.5 deaths per 100,000 people in 2016 (48.3 males and 7.5 females) in Russia. By comparison, the equivalent figure in the corresponding period for the United Arab Emirates was 2.7, and that for Poland was 13.7. How the pandemic will affect rates of suicide around the world has yet to be seen.

Besides depression diagnoses, a new disorder will soon be officially recognized, diagnosing difficulties in job performance. Starting on January, 1, 2022, a new WHO classification of diseases will come into force. This classification includes professional burnout, that is, a syndrome composed of depleted energy or exhaustion, decreased professional effectiveness, and negative work-related emotions. Chronic psychosocial stress, which is characteristic of burnout, cripples people's individual and social functioning, interferes with cognitive capacities, and affects the neuroendocrinal systems, eventually leading to evident changes in the anatomy and functions of the brain. The construct of professional burnout was first proposed by Christina Maslach. Currently Professor Emeritus of the University of California in Berkeley and the world's leading burnout researcher, Maslach began to study this new phenomenon in the 1970s. Published in *Human Behaviour* in 1976, her article "Burned-Out" revealed the scope of this phenomenon and its severe consequences for people in the field of work life. The American National Mental Health Institute reports that almost 25% of adult Americans grapple with mental health problems, such as anxieties and depression. According to the analyses of Mind Share Partners (a US nongovernmental organization), as many as 75% of American Generation Z (i.e., people born between 1997 and 2012) have quit work because of mental disorders. In comparison, in the generation of their grandparents (Baby Boomers), the problem was almost unknown, as only about 10% of them quit their jobs for the same reason. Loneliness is described as an epidemic of today's world. A report of a British governmental committee states that at least 9 million adult U.K. residents consider themselves to be "often or always lonely" (this accounts for about 15% of Britons). With a view to combating social isolation haunting the UK citizens, the world's first Minister of Loneliness was appointed. Although turnover in the post has been high, programs and grants have been established to tackle loneliness in the United Kingdom.

In brief, all the psychological disorders appear to be biological disorders similar to chronic neurodegenerative diseases, which are associated with oxidative stress and inflammation that may predispose individuals to NCDs. Anxiety disorders and mood disorders such as depression are highly prevalent in developed countries such as in the United States as well as in developing countries, where, with increases in industrialization and urbanization, these are rapidly emerging as the most frequent mental disorders, which may result in exclusion from social and family life. Western diet, sedentary behavior, occupational and family stress, and sleep problems are major risk factors for the rapid emergence of disorders of cognition, depression, and emotion. Mediterranean-style diets, in particular the modified Indo-Mediterranean neuroprotective diet, have been found to be protective against NCDs, including neurodegenerated diseases. Effects of diets may be better if the diet is combined with caloric restriction, time-restricted feeding, and physical training. Further cohort studies and randomized, controlled trials would be necessary to confirm our suggestions.

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Section 11

Antioxidants in functional foods

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Chapter 39

Role of nutraceuticals, functional foods, and spices in the management of metabolic syndrome and related disorders

Avinash Shenoy[1], Harpal S. Buttar[2], ParnikaDilip Dicholkar[1], Ginpreet Kaur[1] and Meena Chintamaneni[1]
[1]*Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM's NMIMS, Mumbai, India,* [2]*Department of Pathology & Laboratory Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada*

Introduction

Metabolic syndrome (MS) represents a cluster of events associated with distortion of carbohydrate and fat metabolism as well as macrovascular and microvascular complications. This malady is characterized by the presence of multiple risk factors of metabolic origin and is linked to an increased risk for cardiovascular and cerebrovascular disorders. There is growing evidence that the incidences of MS, including non-communicable diseases, are higher in urban centers than in rural areas. Unhealthy food habits, high intake of sugar and sugar-loaded drinks, fast foods rich in saturated fat and sodium, and a sedentary lifestyle are primarily responsible in causing diabetes and obesity. MS affects nearly one-fourth of the adult population worldwide. Because of the increased risk of morbidity and mortality as well as the prolonged hospitalization and recovery period of patients with coronary heart disease and stroke, MS is posing serious clinical and economic challenges to global healthcare systems [1,2]. The main components of MS are visceral obesity, insulin resistance, type 2 diabetes mellitus, atherosclerosis, dyslipidemia, decreased glucose tolerance, and high blood pressure. The probability of MS in patients with type 2 diabetes is nearly fivefold greater, and the risk of developing cardiometabolic diseases (CMDs) is twofold to fourfold higher in MS subjects [2]. Furthermore, patients with MS have an increased risk of coronary heart disease and stroke. This is because the majority of the MS elements are interconnected with each other. For example, insulin resistance is generally associated with diabetes, obesity, hyperglycemia, and hyperlipidemia, which in turn cause an increase in low-density lipoprotein (LDL) cholesterol and decreases in the high-density lipoprotein (HDL) cholesterol and triglyceride levels, resulting in atherosclerotic cardiovascular events and the formation of atherosclerotic plaques. These patients are at a higher risk for developing hypertension due to the excessive renal retention of sodium and water in the body. The MS-induced pathophysiological changes in the endothelium cause endothelial dysfunction and promote atherosclerosis as a result of the secretion of inflammatory cytokines and invoke increased expression of endothelial transcription factors and impairment of nitric oxide synthesis [3].

Generally, the management of MS patients requires multiple pharmacotherapies. However, owing to the adverse effects of drugs experienced by some patients with comorbidities, some restrictions and extra precautions are needed for the use of drugs in patients with hyperglycemia, dyslipidemia, prehypertension, and kidney and liver problems, thereby limiting the use of synthetic drugs for treating MS patients. In view of such circumstances, alternative therapies such as nutraceuticals and functional foods are being sought for the management of MS. It is expected that antioxidant and antiinflammation diets, lifestyle modifications, and physical exercise (30 minutes/day) would be beneficial for MS patients. Currently, studies are being done with nutraceuticals and functional foods to determine the long-term safety and efficacy and optimal dose levels of these products. Fewer side effects and better efficacy are expected from functional foods, nutraceuticals, and alternative therapies for MS patients when pharmaceuticals cannot be used [4].

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The term *nutraceutical* was coined from the combination of two words: *nutrient* and *pharmaceutical*. According to the definition, nutraceuticals are considered to be drugs as well as dietary products, and such dual action assists in the prevention and treatment of non-communicable diseases (NCDs) at a lower cost when compared with that of synthetic drugs. Nutraceuticals include bioactive plant-derived products, vitamins and minerals, amino acids, and fatty acids, which not only promote health and well-being but also prevent cardiovascular and neurodegenerative diseases as well as inhibiting the development of cancers through their multidimensional therapeutic activities. Intake of functional foods, such as vitamins, minerals, and amino acids aid, enhance overall health beyond their basic functions. Modern data suggest that dietary supplements containing flavonoids, carotenoids, and antioxidants regulate genes and protein expression. Thus they modify endogenous metabolic pathways and homeostasis and consequently reduce the risk of chronic NCDs multifactorial in origin. The combination of antioxidant and antiinflammation actions provides significant effects of plant-derived bioactive compounds and/or their metabolites. Probiotics, prebiotics, and synbiotics confer health benefits on the host through the promotion of healthy microbiota in the gastrointestinal tract, improvement of gut endothelium integrity, and boosting the immune function in the body. Nutraceuticals and functional foods are considered to have an important role in the future development of natural health products for promoting good health, as has been demonstrated through studies in lowering the risk of diabetes, obesity, and atherosclerotic cardiovascular diseases (CVD). This situation has prompted the search for new phytotherapies to reduce the overall risks of NCDs. Clinical trials with several nutraceuticals have shown beneficial effects in treating MS and associated complications [5].

Complications associated with metabolic syndrome

Insulin resistance

Insulin resistance is a pathophysiological state in which a normal insulin concentration does not produce an adequate response in the peripheral target tissue such as liver, muscle, and adipose. In these patients there is disabled glucose metabolism due to an unconventional response to glucose, which causes an elevation in fasting glucose level or hyperglycemia. To counteract the hyperglycemic state, the patient's pancreatic beta cells secrete more insulin, thus leading to hyperinsulinemia. This, in turn, leads to an overexpression of insulin activity in various delicate tissues. The prominence of a few insulin actions combined with a resistance to other actions of insulin leads to the clinical manifestation of MS [6]. The continual inability of pancreatic beta cells to produce insulin and rectify the worsening tissue insulin resistance leads to hyperglycemia, which eventually results in type 2 diabetes [7]. In insulin resistance the phosphoinositide-3-kinase (PI3K) pathway is altered, while the mitogen-activated protein (MAP) kinase pathway is unaltered. The inhibition of the PI3K pathway promotes a reduced levels of endothelial nitric oxide and glucose transporter 4 (GLUT-4) translocation which results in endothelial dysfunction, decreased skeletal muscles and fat glucose uptake. Since the MAP kinase pathway remains unchanged, there is a continues production of endothelin 1 (ET-1). This is an expression of vascular cell adhesion molecules and a mitogenic stimulus for the vascular smooth muscle cells. Therefore insulin resistance results in vascular irregularities that incline toward the manifestation of atherosclerosis [2,8].

Abdominal obesity

The rise in the incidence of obesity globally has been steady since the 1980s and has affected more than 73 countries with more than two billion people suffering from health conditions resulting from obesity or being overweight [9,10]. Increased consumption of high-calorie food and decreased physical activity lead to severe effects on adipose tissue (a heterogeneous mixture of adipocytes, stromal preadipocytes, immune cells, and endothelium). The combination of obesity and progressive adipocyte enlargement diminishes the supply of blood to dipocytes, causing hypoxia [11]. Investigations says that hypoxia gives rise to the root cause of necrosis and macrophage infiltration into the adipose tissue. Ultimately, there is excess production of biologically active metabolites known as adipocytokines, which include free fatty acid, glycerol, C-reactive protein, proinflammatory mediators (tumor necrosis factor alpha, interleukin 6), and plasminogen activator inhibitor 1 [12]. This result in localized inflammation in adipose tissue that escalates into whole systemic inflammation, which is linked to growth of comorbidities. The increasing prevalence of obesity is associated with significant metabolic complications, such as type 2 diabetes, hypertension, hyperlipidemia, and CVD [2,13].

Dyslipidemia

Dyslipidemia is a characterization of a variety of qualitative lipid abnormalities that indicate a disturbance in metabolism, biological activity, and structure of both antiatherogenic HDL cholesterol and lipoproteins. They include an

escalated levels of minor particles of LDL cholesterol, low levels of HDL cholesterol, increased triglycerides, and high levels of lipoproteins that contain apolipoprotein B. Insulin resistance in multiple ways results in atherogenic dyslipidemia. (1) Insulin generally suppresses lipolysis in adipocytes; therefore impaired insulin promotes lipolysis, which increases free fatty acid levels. Free fatty acids are one of the constituents aiding synthesis of triglycerides in the liver and maintaining balance in production of apolipoprotein B, resulting in higher production of very low-density lipoprotein (VLDL) cholesterol. (2) Insulin generally degrades apolipoprotein B via PI3K-dependent pathways; therefore insulin resistance increases VLDL cholesterol production. (3) Regulation of insulin is sustained by the activity of lipoprotein (rate-limiting and a major mediator of VLDL clearance). Therefore hypertriglyceridemia in insulin resistance is due to the increase in VLDL production and reduction in VLDL elimination. Studies have proved that dyslipidemia is associated with insulin resistance because of increased VLDL secretion by the liver [2,14].

Cardiovascular disease

CVDs are disorders of the heart and blood, including heart failure and peripheral vascular disease, leading to cerebrovascular disorder and other disorders. CVDs are common in the elderly population. CVD is also an important factor in diabetes, which can aggravate disorders such as atherogenesis, coronary heart disease, and other such vascular complications. CVD has two categories of risk factors: modifiable and nonmodifiable. Modifiable risk factors include obesity, hypertension, diabetes, dyslipidemia, MS, and lifestyle style risk factors, including smoking, lack of physical activity, and unhealthy diets. Dietary factors have a significant role in contributing to cardiovascular risk, including effects on other risk factors. This denotes a major impact on mortality due to CVDs, particularly blood pressure and lipid levels [15].

Hypertension

Hypertension is often linked with various customary metabolic irregularities such as glucose intolerance, dyslipidemia, and obesity. Research proposes that both hyperinsulinemia and hyperglycemia activate the renin-angiotensin system by elevating the expression of angiotensin II. Angiotensin II receptor type 1 and angiotensin promote hypertension in individuals with insulin resistance. The documented proof indicates that hyperinsulinemia and insulin resistance result in sympathetic nervous system activation. This increases reabsorption of sodium by the kidneys, leading to an increase in cardiac output vasoconstriction in the arteries and eventually causing hypertension [2,16] (Fig. 39.1).

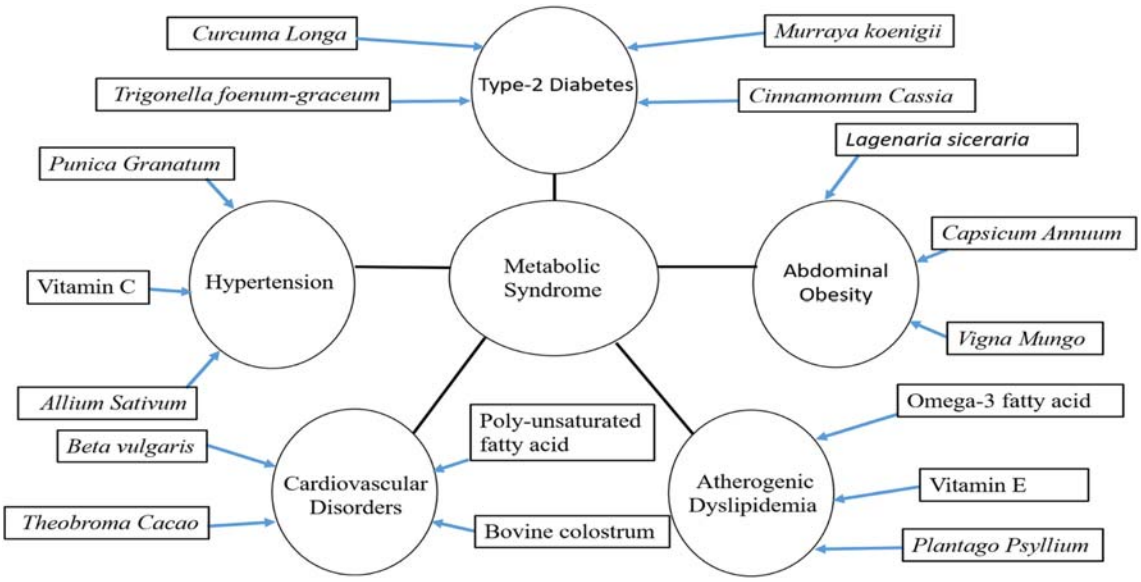


FIGURE 39.1 Diagrammatic representation of complications associated with metabolic syndrome and the preventive role of nutraceuticals and phytotherapies.

Categories of nutraceuticals and their marketed products

A nutraceutical can be classified in various ways depending on its structure or its applications. The different categories of nutraceuticals from research and marketing points of view are summarized in Fig. 39.2 and Table 39.1.

Probiotics, prebiotics, and synbiotics

Prebiotics are a type of dietary fiber that readily ferment and act as a fertilizer for the good bacteria in the gut. They are commonly found in bananas, asparagus, soybeans, polyunsaturated fatty acids (PUFAs), and so on [38]. Probiotics are live bacteria that can be found in yogurt and other fermented foods. The best example of a marketed probiotic is Yakult, a fermented milk beverage. Some prebiotics are inulin, lactulose. and lactobionic acid [39].

Dietary fibers

Dietary fiber is a type of nutrient that cannot be broken down by enzymatic reaction into basic units as other nutrients can. It consists of resistant starch and soluble and insoluble fibers, which are typically found in fruits, beans, barley, oats, and so on.

Herbs and spices

Herbs and spices are generally obtained from plants as raw material or their extracts. They are the plant's secondary products, which are further segmented into phytoconstituents according to their chemical structures. They include terpenes, alkaloids, polyphenolics, nitrogen (N)-containing compounds, and organosulfur-containing compounds. Further details are given in Table 39.1 [40].

Macronutrients

Macronutrients are generally present in plant raw materials in large amounts and can be easily broken down into basic units. For example, protein can be enzymatically broken down into amino acids or fats into fatty acids. Further examples include milk (protein), wheat (carbohydrate), and insulin, the first marketed protein and FDA-approved drug, used for the treatment of diabetes.

Vitamins and minerals

Vitamins are a distinct group of organic nutrients that are chemically or metabolically unrelated. They nutritionally form a small consistent group of compounds that are essential in small amounts in a diet of an individual to maintain normal health and metabolic integrity. They are different from essential minerals, trace elements, amino acids as the latter are required in larger amounts. Some of the vitamins such as vitamin D and vitamin K are produced by the body while the remaining such as vitamin C, vitamin A, vitamin E are supplemented through diet. Since the body cannot synthesize minerals, they must be acquired through diet. The major minerals that are used and stored in large quantities by the body to maintain homeostasis and perform functions are calcium, chloride, magnesium, phosphorus, potassium, sodium, and sulfur.

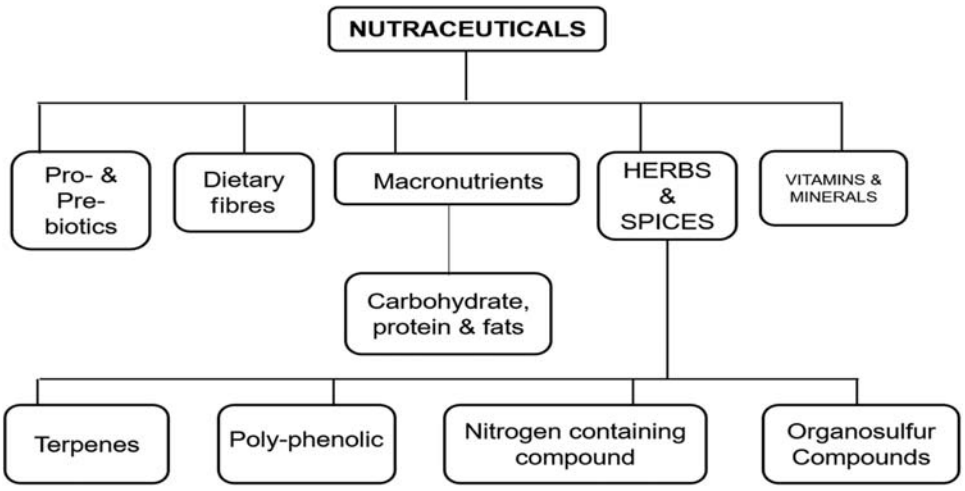


FIGURE 39.2 Basic components and categories of nutraceuticals.

TABLE 39.1 Antioxidant and antiinflammatory effects of nutraceuticals and their constituents.

Phytoconstituents	Name	Description	References
Terpenes			
Monoterpenes, sesquiterpenes, diterpenes	Eugenol and ester euginin (clove, clove oil in injection or solution)	*Source:* clove flower, buds, whole plant *Properties:* antimicrobial, antifungal, antiinflammatory, analgesic, antiseptic, anesthetic.	[17]
Triterpenes, tetraterpenes, sterols	Azadirachtin, nimbin, nimbidinin, nimbidic acid, nimbolide, *Azadirachta indica* leaf (over-the-counter products)	*Source:* neem plant (mostly in leaves and seed extract) *Properties:* antiinflammatory and antiarthritis activities, antipyretic, analgesic, antiulcerogenic activities, against leishmanias, antidiabetic	[18]
Polyphenolics			
Flavonoids: flavones, isoflavones, flavonones, flavonols	Ascorbic acid (present in many multivitamin tablets in many dosage forms)	*Source:* green tea, lemon, apple, wine, cocoa *Properties:* antioxidant, antidiabetic, treatment of scurvy, treatment of delayed wound and bone healing, urine acidification	[19,20]
Phenolic acid	Curcumin	*Source: Curcuma* rhizomes *Properties:* anticarcinogenic, antiinflammatory, antioxidant, anticancer, antimicrobial	[21,22]
Stilbenes, coumarins	Resveratrol	*Source:* grapes, cocoa, peanuts, pine trees, strawberries, bilberries, cranberries, tomatoes, red and white wines *Properties:* cardioprotective, antiinflammatory, antioxidant, antiatherogenic, improvement in glucose metabolism and endothelial function	[23–25]
Lignan, lignin	Secoisolariciresinol	*Source:* high in flax seed, kiwi fruit, blackberries, lingonberries, sea buckthorn, black current, cranberries; low in avocado, pineapple *Properties:* anticarcinogenic (possibly breast cancer)	[26,27]
Carotenoids	Beta-cryptoxanthin	*Source:* tangerines, papayas, oranges *Properties*: antioxidant, anticancer, enhances immune system and bone health	[28,29]
Anthraquinones	Aloe juice (local marketed) contains aloe-emodin, aloe-emodin-9-anthrone, aloin A and B chrysophanol	*Source:* aloe vera *Properties:* soothe skin condition and eczema, secondary burns, radiation dermatitis, sunburn, acne urticaria, antineuroectodermal, anticarcinogenic (colon), laxative	[30]
Nitrogenous compounds			
Alkaloids	Caffeine (injection and oral solution with 20 mg/mL; tablet/alert tab 100 mg)	*Source:* tea, cocoa products, coffee *Properties:* psychostimulator, manage fatigue and migraine, cardiac/muscle stimulant with mild diuretic effect against orthostatic hypotension, apnea of prematurity in infants (respiratory stimulant)	[31]
Nonprotein amino acid	Ornithine (precursor of glutamate)	*Source:* widely distributed (nonenteric bacteria, fungi, green algae, legumes, transgenic plants such as tomatoes, etc.) *Properties:* synthesis of protein, enzymes, and muscle tissue, releases growth hormone, regulation of glutamate neurotransmitter	[32,33]

(*Continued*)

TABLE 39.1 (Continued)

Phytoconstituents	Name	Description	References
Cyanogen glycoside	Amygdalin	*Source:* seeds and kernels of fruits such as apricot, almond, apple, cherry, plum, peach, and nectarine *Properties:* Antitumor, antitussive, antiasthmatic, improves immune function, analgesic effect, treats gastritis, stops angiogenesis in diabetic condition	[34,35]
Organosulfur compounds			
Allinin and thionins	L-cysteine	*Source:* papain and legumain plant families. *Properties:* regulate insulin secretion, wound healing, immunomodulation, digestive conditions, neoplastic alterations, antihelminthic, antiinflammatory	[36,37]

Impact of nutraceuticals in the prevention and management of metabolic syndrome and related disorders

Antioxidant nutraceuticals

Multiple studies done in animal models have shown that administration of dietary antioxidants may prevent or impede diabetic complications, including renal dysfunction, central nervous system disorders, and CVDs caused by oxidative stress. However, only a limited number of studies have been reported in humans on this subject [5,41,42]. Well-designed human interventions and clinical trials are needed to decipher the potential role of nutraceuticals and dietary supplements in the prevention and management of MS—related disorders.

Vitamin C

Vitamin C, also known as ascorbic acid, is a chain-breaking antioxidant that plays a significant role in protecting free radical—induced injuries by directly scavenging reactive oxygen species (ROS), which otherwise would result in reduced protein glycation [20]. In animals, vitamin C displayed the ability to decrease diabetes-induced sorbitol buildup and lipid peroxides in erythrocytes. When 800 mg/day of vitamin C was administered, it partially replenished the levels of vitamin C in patients with type 2 diabetes but did not exhibit any signs of enhancing insulin resistance or endothelial dysfunction [43]. In another study, observation showed that when vitamin C was given in combination with metformin, there was a significant decrease in postprandial blood glucose, fasting blood glucose, and HBAC1 levels [44]. A combination of vitamin C with dental maneuvers has shown improvements in chronic periodontitis, which is common in type 2 diabetes patients [45,46].

Vitamin E

Vitamin E, biologically known as alpha-tocopherol, is an essential fat-soluble vitamin and an element of the total peroxyl radical with an antioxidant system that reacts to the superoxide and peroxyl radicals and singlet oxygen. This assists in protecting the membrane from lipid peroxidation. Individuals with low levels of vitamin E show increased peroxide and aldehydes levels, which lead to higher incidences of diabetes [19]. Observations show reduced blood glucose levels and hypertension and high glutathione and superoxide dismutase levels in individuals who have consumed vitamins C and E [47]. Another study observed that vitamin E slowed the progression of diabetes by decreasing levels of postprandial blood sugar, total cholesterol, and diastolic blood pressure [48].

Alpha-lipoic acid

Alpha-lipoic acid is a natural antioxidant component that has strong ROS-scavenging activity and in it oxidative state reduces several radicals [19]. Alpha-lipoic acid plus dihydrolipoic acid function as a redox couple that has other antioxidant properties, such as chelation of transition metals and regeneration of other antioxidants such as Vitamin C, glutathione and vitamin E [49]. In vitro and in vivo studies demonstrated to protect the retina against ischemia-reperfusion injuries. In diabetic

TABLE 39.2 Results of preclinical and clinical studies done with nutraceuticals.

Nutraceutical	Preclinical studies	Clinical studies	References
Vitamins			
Vitamin C	Diabetic male Wistar rats and concurrent controls were given a combination of vitamin C (50 mg/kg) and vitamin E (100 mg/kg) for 30 days. The results showed improved memory and learning in diabetic rats.	In a double-blind study, diabetic patients were given 800 mg/day of vitamin C for 4 weeks. Treatment resulted in partial replenishment of vitamin C levels in diabetic patients.	[43,98]
Vitamin E	Obese mice were given alpha-tocopherol (150 mg/kg) twice per week. The treatment improved insulin sensitivity and hypertriglyceridemia.	Vitamin E caused glucose control in diabetic patients at a dose of 100–1600 mg/day for 2–4 months.	[99]
Plant extracts			
L-carnitine	Streptozocin-induced diabetic rats were given L-carnitine (100 mg/kg). L-carnitine improved fasting glucose levels and reduced body weight.	In two randomized placebo-controlled trials, patients were given two doses of acetyl-L-carnitine (ALC), 500 mg and 1000 mg/day t.i.d. ALC alleviated pain and improved nerve regeneration in diabetic neuropathy.	[96,100]
Trigonella foenum-graceum	Alloxan-induced diabetic rats were orally given ethanol extract of fenugreek (200 and 400 mg/kg). The 200 mg/kg ethanol extract showed the highest hypoglycemic effect.	Type 2 diabetic patients were given 25 g of fenugreek as part of a diet for 24 weeks. Fenugreek diet reduced the levels of triglycerides, LDL cholesterol, and total cholesterol.	[101,102]
Camellia sinensis	Male Swiss mice received green tea extract (50 mg/kg) daily for 8 weeks. The extract decreased both body weight and white adipose tissue weight.	Female MS patients consumed 200 mL of green tea t.i.d. for 8 weeks. The results showed a decrease in blood pressure, blood sugar, and lipid profile.	[103]
Cinnamomum cassia	Rats fed a high-fat and high-fructose diet were given cinnamon (20 gm/kg) along with the diet. Cinnamon caused alteration in body weight composition and improved insulin sensitivity.	Prediabetic and MS patients were supplemented with cinnamon extract 500 mg/day for 12 weeks. The results showed reduction in fasting blood glucose level and systolic blood pressure.	[104,105]
Murraya koenigii	Alloxan-induced diabetic rats were orally administered 200 mg/kg of an aqueous solution of *M. koenigii*. The extract of *M. koenigii* caused hypoglycemic activity.	No clinical study reported	[106]
Emblica officinalis	Streptozocin-induced diabetic albino Wistar male rats were administered 100, 200, 300, and 400 mg/kg standardized doses of aqueous *E. officinalis* extract. It was observed that the dose at 300 mg/kg had the greatest hypoglycemic and antidiabetic effect.	Diabetic patients were administered 2 to 3 g/day of *E. officinalis*. Results indicated improvement in HDL and cholesterol levels.	[107,108]
Momordica charantia	Mice were fed a 45% high-fat diet for 7 weeks and were given two doses of *M. charantia* aqueous extract (0.5 or 1 g/kg/day) and ethanol extract (0.5 or 1 g/kg/day). Both extracts reduced body and visceral tissue weight. It was concluded that *M. charantia* possesses an antiobesity effect.	Eight randomly selected diabetic patients were given 50 mg/kg of *M. charantia* for 7 days. The results showed greatly improved glucose tolerance as well as decreased glucose excretion in the urine.	[109,110]
Phytochemicals			
Curcumin	Streptozocin-induced diabetic male rats with a high-fat diet were administered 200 mg/day of curcumin. Treatment improved insulin sensitivity and decreased fasting glucose levels in both type 1 and type 2 diabetes.	In a randomized double-blind trial, patients received curcumin filled capsules for 9 months. Curcumin improved beta cell function without any adverse effects.	[74,111]

(*Continued*)

TABLE 39.2 (Continued)

Nutraceutical	Preclinical studies	Clinical studies	References
Capsaicin	Obese mice on a high-fat diet for 10 weeks were supplemented with 0.0015% of capsaicin for another 10 weeks. Capsaicin produced obesity-induced glucose intolerance as well as reduced body weight and fat mass.	In a randomized, double-blind study, 44 pregnant women with gestational diabetes mellitus were given 5 mg/dL of capsaicin. There was an improvement in fasting lipid metabolism and a reduction in postprandial hyperglycemia and hyperinsulinemia.	[112,113]

retinopathy, visual loss are mainly due to ischemic injury of retina [41]. Thus alpha-lipoic acid boosts insulin sensitivity in type 2 diabetes by 18%−20% [49]. According to the reports, a positive effect on severe symptoms and disease progression was seen when clinical trials were conducted for the treatment of diabetic neuropathy.

Plant extracts used in the management of metabolic syndrome and related disorders

Trigonella foenum-graceum

Trigonella foenum-graecum, commonly known as fenugreek, is used as a spice and also has multiple medicinal and chemical properties, especially in its leaves and seeds. These properties arises from three main chemical constituents: steroidal sapogenins, isoleucine, and galactomannans. Steroidal sapogenins applicable in hypercholesterolemia or in diabetes. The precursor of isoleucine(amino acid) modulate the secretion of insulin. The seed contains amino acids like 4-hydroxy isoleucine that gives majority of antihyperglycemic and hypoglycemic systemic effects. Galactomannans are found in fenugreek seeds. The major part of it is polysaccharide component with unique 1:1 or 1:2 galactose to mannose ratio. This high ratio of galactose allows it to absorb water leading to forming highly viscous solutions in small concentrations and resulting in decreased glucose absorption in the digestive tract. This property helps in controlling type 2 diabetes [50]. A study conducted in a fructose-fed rat model by Kannapann and Anuradha determined that polyphenols derived from fenugreek seeds had an insulin-sensitizing and tyrosine phosphorylation status that was comparable to that of metformin, as it improved insulin signaling and sensitivity which promoted cellular action of insulin [51]. Another study conducted by Morani et al. showed the ameliorating effects of fenugreek seeds on agonizing peripheral neuropathy in a diabetic rat model [52].

Camellia sinensis

Camellia sinensis, commonly known as green tea, is a popular beverage that has been studied extensively for its protective effects in humans. It has polyphenolic compounds, such as catechin and epigallocatechin-3-gallate (EGCG), that are abundant and extensively studied. The leaves of green tea contain three main components—the xanthine bases caffeine and theophylline, polyphenolic compounds, and essential oils—that have beneficial effects on human health. A study conducted in Japan observed that subjects who drank more than six cups of green tea daily had a decrease in the rate of diabetes as compared to the subjects who drank less than one cup a week. In another study, 20 patients with type 2 diabetes who that consumed oolong tea containing 386 mg of EGCG had reduced levels of plasma glucose and fructosamine. Similar effects were seen in healthy patients who consumed green tea extract (300 mg of EGCG) for 12 weeks. They showed low levels of plasma glucose and insulin along with slight weight loss, which could be the cause of decreased insulin sensitivity [50,53].

Although the data available to support the beneficial effects of green tea in regard to the risk of CVDs are limited, many epidemiology studies have linked the consumption of green tea to the reduction of CVDs. Various investigations have determined that the compounds in green tea act on LDL cholesterol oxidation. Since oxidation of LDL cholesterol increases the risk of atherosclerosis and other CVDs. Owing to availability of EGCG in green tea, it has function of antioxidant hence, inhibits the oxidation of LDL cholesterol. In a study of overweight but healthy patients, the intervention group consumed a diet that contained oolong tea enriched with tea catechin. Twelve weeks later, a substantial reduction in body weight was observed in this group as compared to the control group. The results of this study connected the effects of green tea with improvements in cardiovascular risk factors such as systolic blood pressure and LDL cholesterol levels in a large population [50,54].

Cinnamomum cassia

Of the major *Cinnamomum* species, *Cinnamomum zeylanicum* and *C. cassia* are the most extensively studied. The in vivo and in vitro studies of cinnamon indicate several health benefits, which are mainly concerning glucose and lipid-lowering action [55]. In vivo investigations reported that streptozocin-induced diabetic rats display oral consumption of cinnamon. This results into competitively and reversibly inhibition of alpha-glucosidase and improves postprandial hyperglycemia [56]. In another study, diabetic rats that were administered active components cinnamaldehyde significantly improves muscle and hepatic glycogen content, which in turn increased glucose uptake through GLUT-4 translocation in peripheral tissues [4,57].

Murraya koenigii

Murraya koenigii belongs to the family of Rutaceae and is widely used as a spice for flavoring foods. It has been used in traditional medicine for treating hepatitis, cough, and hypertension. In addition, the plant has antihyperglycemic, hypolipidemic, and antiinflammatory effects. Studies suggest that the leaves, known as curry leaves, can be used as a supplement in dietary therapy, and its only chief constituent is carbazole amine [58]. The antidiabetic effect of curry leaves is mainly due to the increase in the concentration of hepatic glycogen and a decrease in the concentration of gluconeogenic enzyme and glycogen phosphorylase. It has the potential property of scavenging free radicals [50]. A study conducted on streptozocin-induced diabetes rats observed that when they were administered *M. koenigii*, elevated HDL cholesterol levels and diminished triglyceride, LDL cholesterol, and fasting glucose levels were observed. Thus it was concluded that *M. koenigii*, which contains carbazole amine, possesses antidiabetic and antilipidemic properties and that it can be used for management of diabetes linked with abnormal lipid profile and related CVDs [59].

Punicagranatum

Pomegranate (*Punicagranatum*) has been extensively used in traditional medicine in various countries. It is a rich source of polyphenols with a high antioxidant capacity that could be beneficial in preventing or treating several cardiovascular risk factors, including hypertension, hypercholesterolemia, oxidative stress, hyperglycemia, and inflammation. Pomegranate contains approximately 0.8−1.2 mg/100 g of flavanol per fresh fruit weight. It was hypothesized that pomegranate counteracts the downregulation of endothelial nitric oxide that is induced by oxidized LDL cholesterol and that it has beneficial effects in the atherosclerotic process. In hypertensive patients, it was further deduced that *Punicagranatum* lowers blood pressure by angiotensin-converting enzyme (ACE) activity. This activity can be seen during the attenuation of angiotensin II−induced hypertension in diabetic rats. It was determined that pomegranate juice blocked the effects of different catecholamines on arterial blood pressure and vasoreactivity by responding to the increased ACE activity in diabetic hypertensive rats after chronic administration. A study conducted by Aviram et al. observed that pomegranate juice decreased serum ACE levels by 36% and decreased systolic blood pressure by 5% [60,61].

Lagenaria siceraria

Lagenaria siceraria, often known as bottle gourd, is grown in India and other subtropical regions. It is from the family of Curcurbitaceae. It is used in folk medicine and is known to have cardiotonic, antihyperglycemic, heptatonic, and antihyperlipidemic properties. The fruit has been found to contain ascorbic acid, pectin, quinic acid, beta-carotene, campesterol, and linoleic acid. It has fibrinolytic, antiatherosclerotic, and antithrombotic properties. A study on *L. siceraria* showed that it induced low triglyceride, total cholesterol, and LDL cholesterol levels when the participating subjects, aged 40−60 years, were asked to consume bottle gourd juice for 90 days on an empty stomach [50]. The results of the study showed that *L. siceraria* promoted HDL levels while decreasing fasting glucose and LDL cholesterol levels [62]. Another study observed that administration of *L. siceraria* inhibited pancreatic lipase, thus potentially helping in the control of obesity and its related symptoms [63].

Emblica officinalis

Emblica officinalis is usually known in India as amla, and it is the most important Indian medicinal plant of the family Euphorbiaceae. It contains components of dietary nutrition such as minerals, amino acids, and vitamin C. The whole plant and its fruit have medicinal uses. It contains antiinflammatory, liver tonic, and digestive properties. A study observed that the administration of amla extract led to increased levels of lipids such as cholesterol and triglycerides in the serum as well as the liver being subdued. The oral administration of *E. officinalis* substantially increased the levels of hepatic peroxisome proliferator−activated receptor alpha (PPARα), which is responsible for the regulation of

transcription of genes that are involved in lipid and cholesterol metabolism [64]. This indicates that *E. officinalis* can prevent age-related hyperlipidemia by reducing the oxidative stress in the aging process. It also has a crucial effect on decreasing levels of LDL cholesterol, triglycerides, and total cholesterol [50].

Vigna mungo

Vigna mungo (black gram) is the richest source of protein for human and animal nutrition [65]. Multiple studies hypothesize that proteins are more satiating than carbohydrates or fats, thus limiting overall food intake and helps in maintaining regular body weight. Therefore a high intake of gram protein can have a beneficial weight loss effect. In addition, plant proteins lead to a lower kidney workload as compared to animal proteins [66]. It has been hypothesized that the specific action of black grams on alpha-amylase protein inhibitors could potentially be used for the prevention of obesity. To find evidence for this hypothesis, studies were done involving normal, diabetic, and obese patients who were orally administered wheat alpha-amylase, which has shown delayed carbohydrate absorption and a decrease in peak postprandial plasma concentration of with no malabsorption or any other symptoms. More recently, the association between porcine pancreas, alpha-amylase, and wheat alpha-amylase inhibitors along with the thermal stability of proteins has confirmed the potential use of *V. mungo* [50].

Momordica charantia

Momordica charantia (bitter gourd) is a common vegetable that is found mostly in Southeast Asia and subtropical areas of South and Central America. It is used as a conventional treatment for diabetes. It works by decreasing islet cell necrosis and repairing damaged cells while also protecting functional islets. It also reduces adiposity and the resultant release of inflammatory factors that are released by adipocytokines such as tumor necrosis factor alpha (TNF-α). Treatment with *M. charantia* regulates hepatic enzymes which are responsible for the breakdown of lipids such as gluthionine S-transferase. A recent study involved MS patients who were treated with 4.8 g/day of lyophilized bitter gourd. After seven weeks, the subjects showed improved fasting glucose levels and waist circumference [4,67]. Another investigation on bitter gourd showed average hypoglycemic effect and considerably decreased fructosamine levels in patients newly diagnosed with type 2 diabetes. The hypoglycemic effect of bitter gourd is lower than that of metformin, but a significantly higher efficacy was observed in comparison to rosiglitazone in worldwide management of type 2 diabetes [68,69].

Lagerstroemia speciosa

Commonly known as banaba in the Philippines, *Lagerstroemia speciosa* is used in traditional medicine for its antidiabetic and antiobesity effects. Although the mechanism is unclear, it is assumed that increased cellular uptake of glucose, inhibition of hydrolysis of starch and sucrose, reduced gluconeogenesis, and regulation of lipid metabolism mediated by PPAR, mitogen-activated protein kinase (MAPK), nuclear factor kappa B, and additional signal transduction factors may be responsible for its action. The chief active components of banaba extract are ellagitannins, corosolic acid, Penta-*O*-galloyl-glucopyranose, and tannic acid. In a study conducted on mice, it was observed that banaba decreased hepatic lipid content and body weight and inhibited glucose elevation and plasma total cholesterol. Banaba extract also inhibited adipocyte differentiation in preadipocytes. In human studies, extracts of banaba that were standardized to 1% corosolic acid were administered, and after two weeks it was observed that there was a 30% reduction in blood glucose level, thus confirming its antidiabetic activity [4,70].

Phytochemical compounds used in the management of metabolic syndrome and related disorders

Betanin

Betanin is obtained from beetroot (*Beta vulgaris rubra*) and has been used as a medicine since ancient Roman times. In the past few decades there has been increased scientific interest in betanin for application as medicine primarily because of the discovery that beetroot is the source of dietary nitrate, which can help in the management of CVDs [71]. Beetroot supplement contains a high inorganic nitrate content, and the main constituent betalain (betanin) significantly lowered blood pressure. Betanin reduces oxidative damage and the hemolysis of red blood cells, and in atherosclerosis it binds with LDL cholesterol, which leads to the inhibition of oxidation of LDL. Both betanidin and betanin appear to be more effective and potent than vitamin E. Thus its hypolipidemic and antiatherosclerosis properties aid in cardioprotective activities [72].

Curcumin

Curcumin, which is chirally called 1,7-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5dione, is obtained from *Curcuma longa*. It is the active component and is responsible for its yellow color. It possesses various pharmacological actions [50,73], including antidiabetic and antiinflammatory properties, and can be effectively used to delay the development of type 2 diabetes, improve the functions and prevent the death of beta cells, and reduce insulin resistance and blood glucose levels in animals. A recent study conducted on prediabetic patients concluded that curcumin delayed the onset of type 2 diabetes by enhancing beta cell function, which was manifested by increase in HOMA-β and decreased C-peptide [74]. A study conducted on diabetic rats found out that when curcumin was given in combination with piperine and quercetin, it had a significant effect on blood glucose levels as compared to curcumin alone [75].

Obesity presents itself with a major component: inflammation. The occurrence of chronic and subclinical inflammation has major impact in the development of obesity-related atherosclerosis and diabetes [50]. Curcumin is used in the treatment of various types of inflammation ailments, including obesity and other metabolic disorders. It does so by downregulating the expression of multiple nuclear factors of beta-regulated proinflammatory adipokines, including chemokines such as monocyte chemoattractant protein 1 (MCP-1) and MCP-4 and interleukins such as IL-6 and IL-1. It also subdues oxidative stress−induced loss of function of endothelial reticulum protein−folding enzyme, thus reducing the accumulation of misfolded proteins in the cells [73]. A study conducted by Jain et al. reported that curcumin supplementation in a diabetic rat model decreased the production of high glucose-mediated monocytes by inflammatory cytokines, which included TNF-α, IL-6, IL-8, and MCP-1. Observation reported that the curcumin diet reduced the glycosylated hemoglobin and blood levels of glucose [76].

Capsaicin

Capsaicin is a biologically active ingredient that is found in red chile peppers, which are consumed as vegetables and flavorings [77]. Capsaicin and various related compounds together are called capsaicinoids, which are produced as a secondary metabolite and act as deterrents from being consumed by certain fungi and herbivores. There are many preclinical and clinical studies on the antiobesity effects of capsaicin, which activates the TRPV1 cation channel and increases catecholamine secretion. This ultimately leads to change in lipid metabolism−related proteins and thermogenesis available in the skeletal muscles and white adipose tissues. It has been shown that obese adipose tissue and isolated adipocytes have antiinflammatory effects in diminishing the effects TNF-α and other inflammatory adipocytokines (IL-6 and MCP-1). This is done by regulating PPARγ and proinflammatory transcription factors [78]. An investigation conducted on mice that were fed a high-fat diet observed that treatment upgraded glucose homeostasis by modulation of the gut microbiome and significantly lowered body weight [79]. A study conducted by Zhu et al. displayed capsaicin action in prevention of adipogenesis by activation of TRPV1 [80,81].

Conjugated linoleic acid

Conjugated linoleic acid (CLA) is a geometric isomer of linoleic acid (cis-9, cis-12-octadecadienoic acid) and is a naturally occurring fatty acid that has many health benefits. It is primarily found in flax seeds, nut oil, fish, and poultry eggs. CLA lowers body fat and raises cholesterol levels in the blood, which is accomplished by decreasing plasma triacylglycerol by decreasing the VLDL/apolipoprotein B production. It also manipulates the genetic expression of certain adipocytokines, modifying their proliferation. CLA also has an insulin-sensitizing ability, which it defines by the activation of hepatic PPARα, thereby increasing fatty acid oxidation. A study conducted by Ryder et al. on Zucker diabetic fatty rats demonstrated that supplementing their diets with 1.5% CLA not only reduced adiposity but also improved glucose tolerance when compared to controls [82]. Lee et al. established CLA's hypocholesterolemic and antiatherogenic properties in a study in which rabbits were fed high-cholesterol diets along with a controlled amount of CLA per day. It was observed that rabbits that were fed CLA had reduced triacylglycerol and total cholesterol levels, which resulted into decreased atherosclerosis as compared to rats that were fed a high-cholesterol diet without CLA [83]. Another study observed that when rodents were fed a high-cholesterol diet with addition of CLA, it prevented the onset of obesity-induced muscle insulin resistance [84].

Polyunsaturated fatty acids

PUFAs contain omega-3 fatty acids, which work as endogenous ligands to maintain inflammatory responses. Saturated fatty acids activate toll-like receptor 4 on fat cells and macrophages, thereby promoting inflammation. But PUFAs such as eicosapentaenoic acid and docosahexaenoic acid (DHA), which are present in fish oil and fish meal, are comprehended as

antiinflammatory factors that stop activation of inflammation in obesity conditions [84]. The omega-3 fatty acids sense G protein−coupled receptor 120 (GPR120), which is highly expressed in adipose tissue macrophages and fat cells. DHA activates this receptor, thus attenuating the proinflammatory effects of TNF-α, IL-6, and lipopolysaccharide present on macrophages. Omega-3 fatty acids activate GPR120, which suppresses macrophage-induced inflammation and gives rise to potent insulin sensitization and other antidiabetic effects. Besides this, PUFA also activates PPARγ, which has been associated with the prevention of high-fat diet−induced adipose tissue inflammation and remodeling [85]. A study conducted by Sekiya et al. demonstrated that PUFA significantly decreased the mature form of sterol regulatory element−binding protein 1 (SREBP-1). This in turn limits the expression of lipogenic genes such as stearoyl-CoA desaturase and fatty acid synthase in the liver of ob/ob mice. Eventually, low liver function tests such as alanine transaminase levels and triglycerides are observed. The administration of PUFA also improved both hyperglycemia and hyperinsulinemia in ob/ob mice. Downregulation of SREBP-1 and activation of PPARα improved obesity-related symptoms such as insulin resistance and hepatic steatosis by PUFA [86]. A study by Robinson et al. established that dietary n-3 PUFAs modulated individual aspects in the trio of obesity—fatty acid metabolism, adiposity, and inflammation—with specific attention to the role of the postprandial period as a factor in the pathophysiology of MS [87].

Berberine

Berberine is a quaternary ammonium salt extract that has hypoglycemic, antihypertensive, and lipid-decreasing properties [88]. Through the actions of AMP-activated protein kinase activation, MAPK inhibition, and modulatory effects on PPARα and PPARγ, it stabilizes liver LDL receptor mRNA [89,90]. Studies have found that it has insulin-sensitizing effects that are comparable to that of metformin via a mechanism that involves retinol-binding protein 4 and GLUT-1, along with an insulinotropic effect which is different from sulfonylureas through an increase of both mRNA expression of hepatic nuclear factor 4α and glucokinase activity [91,92]. Furthermore, it increases glucagon-like peptide, which acts directly on the pancreas [4]. In a study conducted on a group of patients diagnosed with MS, the patients were given berberine for three months before meals, and the results showed that they had significant decreases in systolic blood pressure and triglycerides. Therefore it was concluded that the administration of berberine results in remission of MS and increases insulin sensitivity [93].

Psyllium fibers

Soluble dietary fibers have the most substantial metabolic effect. Though real psyllium comes from *Plantago psyllium*, the husks and seeds of *Plantago ovata* (family Plantaginaceae) are also referred to as psyllium. Psyllium has multiple actions, such as antidiabetic, antihypertensive, and lipid-decreasing actions. Psyllium works on the body by delaying the gastric emptying and depressing the appetite. It has a lower glycemic index, which has been observed to decrease postprandial insulin and glycemic fiber. It also decreases the rate of glucose absorption by trapping glucose and hence slowing its absorption [85]. It lowers LDL cholesterol levels in the human body by reducing bowel absorption and enhancing the fractional turnover of both cholic acid and chenodeoxycholic acid. Studies conducted on animals propose that psyllium inhibits the activity of cholesterol-7α-hydroxylase, which is the rate-limiting enzyme for bile acid synthesis [4]. Randomized clinical studies conducted on psyllium displayed crucial results in blood pressure and also that it ameliorates vascular function when measured through an augmentation index [85,94].

Nutraceuticals of animal origin used for the management of metabolic syndrome and related disorders

L-carnitine

L-carnitine (β-hydroxy-γ-trimethylaminobutyrate) is a constituent in mammalian plasma and tissue and is largely distributed among skeletal and cardiac muscles. External dietetic sources are obtained by biosynthesis of lysine and methionine [95]. Investigations on L-carnitine show that it stimulates insulin sensitivity and controls lipid levels. This is achieved by performing several essential intracellular and metabolic functions, such as fatty acid transport across the inner mitochondrial membrane into the matrix for beta-oxidation, detoxification of possibly harmful metabolites, regulation of the mitochondrial acyl-CoA/CoA ratio, and stabilization of the cell membrane. L-carnitine enables the elimination of short- and medium-chain fatty acids that can accumulate in the mitochondria. This occurs in abnormal glucose metabolic conditions, influencing the oxidative metabolism of glucose in tissues. In fructose-fed rat models, L-carnitine could accelerate insulin action in skeletal muscle, which is vulnerable to oxidative damage and an insulin-sensitive tissue, showing insulin site resistance in the rat model. The results of this study suggest that supplementation with

L-carnitine may have beneficial effects on patients suffering from insulin resistance [5]. In another study, a combination of L-carnitine, alpha-lipoic acid, and *N*igella *sativa* in diabetic rats led to a significant enhancement in carbohydrate metabolism and to some extent lipid metabolism, indicating a higher rate of success in the management of diabetes mellitus [96].

Bovine colostrum

Colostrum, also known as beestings or "first milk," is the mammary secretion that mammals provide to their offspring during the initial 24−48 hours after parturition. All mammalian species produce colostrum, and its intake during the initial few hours after birth lays the foundation for lifelong immunity. Bovine colostrum contains a substance called proline-rich peptide, which regulates the function of the thymus gland and inhibits pain, swelling, and inflammation; this can prove beneficial in the prevention of non-communicable diseases. It also contains growth hormones and growth factors such as insulin-like growth factor 1, which lowers LDL cholesterol levels and elevates HDL cholesterol levels. This has a major role in restoring deteriorated heart muscle by rejuvenating the growth of blood vessels in the coronary circulation. In vitro and ex vivo studies have revealed significant free radical−scavenging ability, inhibition of lipid peroxidation, and concentration-related antioxidant activity. It was observed that when colostrum was administered with enalapril to rats, the combination manifested notable cardioprotective effects in comparison to the actions of enalapril or colostrum alone [97] (Tables 39.2 and 40.3).

Discussion

Several nonclinical and clinical studies have provided robust evidence that nutraceuticals and functional foods derived from plants and animals (e.g., bovine colostrum) not only have physiological benefits in promoting health and well-being, but also provide protection against non-communicable diseases. Since nutraceuticals, functional foods, and spices are readily available in nature, they appear to be the most cost-effective and affordable alternative therapies for the prevention of diabetes mellitus, obesity, CVDs, and certain cancers. A number of functional foods and nutraceuticals have been extensively studied to evaluate their therapeutic effects and their various components in the prevention and management of MS in humans. However, there still remain many gaps in our knowledge about the long-term safety and effectiveness, dosage schedules, and mechanisms of action of nutraceuticals. Overall, the underlying mechanism of action of different nutraceuticals is not fully understood at the cellular, genetic, and molecular levels. They appear to be involved in cell-signaling pathways, antiinflammation and antioxidant defenses, gene expression, cell differentiation and proliferation, and in the preservation of mitochondrial integrity.

TABLE 39.3 Marketed nutraceutical formulations and their purported mechanisms of action.

Nutraceutical	Marketed formulation	Company	Dose	Mechanism of action
L-carnitine	Carnipure	Lonza	2 g	Improves insulin signaling and decreases lipid levels by regulation of acyl-CoA/CoA. Causes stabilization of cell membrane along with transportation of fatty acid across the inner mitochondrial membrane into the matrix for beta-oxidation.
Curcumin	Cursol	Bioextract	500 g	Lowers levels of blood glucose and glycosylated hemoglobin through the regulation of the polyol pathway. Also suppresses increased bone resorption by inhibiting osteoclastogenesis and expression of AP-1 transcription factors C-fos and C-jun.
Cinnamomum cassia	Cinsulin	Vita-Tech	250 mg	Improves glycemia by modulating hepatic glucose metabolism through the altered expression of PPARγ and inhibition of intestinal glucosidases. Also changes the pyruvate kinase and phosphenol pyruvate carboxykinase.
Emblica officinalis	Saberry	Sabinsa	200 mg	Decreases plasma cholesterol by increasing PPARα expression along with increased lipid oxidation via carnitine palmitoyltransferase and reduced activity of hepatic lipogenic enzymes, such as glucose-6-phosphate dehydrogenase, fatty acid synthase, and malic enzyme. It also restores glucose homeostasis

In this review, we have described the usefulness of marketed nutraceutical formulations (e.g., L-carnitine, curcumin, *Cinnamomum cassia*, *Emblica officinalis*), besides several other nutraceuticals (e.g., *Camellia sinensis*, *Trigonella foenum-graceum*) intended for human use and prevention of non-communicable diseases, including the management of MS. Many nutraceuticals that are marketed on the Internet lack data about their bioavailability, pharmacokinetics, pharmacodynamics, and long-term safety and effectiveness. The nutraceuticals and functional foods that are sold on the Internet and not approved by the food and drug regulatory authorities should be used only with great caution. Some flavonoid-type nutraceuticals have demonstrated lesser protection against chronic diseases as well as low bioavailability after oral administration. There could be multiple reasons for the low bioavailability, and these products suffer from lack of metabolamic investigations, short duration of studies, and lack of analytical methodology to analyze and quantitate the biodegradation products of flavonoids excreted into bile and urine [114]. Healthcare providers and patients should be made aware of the benefits of nutraceuticals and the possibility of adulteration of nutraceuticals with synthetic drugs [4]. Some nutraceuticals and dietary supplements have been found to be laced with synthetic drugs. Furthermore, the beneficial health claims made on the labels of marketed nutraceuticals, functional foods, and bioactive spices and their constituents should be verified by rigorous testing on large populations under well-controlled clinical settings to evaluate their long-term safety. Such well-designed and placebo-controlled clinical studies will provide authentic scientific evidence regarding safety, efficacy, toxicity, and drug-food interactions [4]. Efforts should also be made to create better formulations to enhance the bioavailability of nutraceuticals and to increase patient compliance. Good manufacturing practices should be used in the manufacture of nutraceuticals and functional foods. Novel approaches, such as nanoencapsulation and complexation with cyclodextrin, should be used to enhance the bioavailability of flavonoid-type nutraceuticals.

Hippocrates, known as the Father of Medicine (c. 460−370 BCE), advocated the healing effects of foods. He said, "Leave your drugs in the chemist's pot if you can heal the patient with food." It is now well recognized that regular intake of foods that are rich in flavonoids, polyphenols, and carotenoids—namely, fresh fruits and vegetables—and probiotics and prebiotics as well as lower consumption of salt and sugar-loaded drinks, less saturated fat, smoking cessation, and moderate exercise (30 minutes/day), collectively help in the prevention of CVDs and CMDs. This holistic approach may be the most cost-effective method for health promotion and prevention of chronic diseases such as cancer, diabetes, obesity, CVDs, CMDs, and neurodegenerative disorders. Consumption of healthful foods such as whole grains, foods containing omega-3 fatty acids, poultry, nuts and seeds, olive oil, and dairy products; eating less red meat; and moderate consumption of red wine are linked to the reduction of mortality and morbidity associated with CVDs and CMDs. Ingestion of functional foods vitamins, minerals, and amino acids assist in improving overall health beyond their basic nutritional functions.

Conclusions and future directions

In this chapter we have tried to provide information about the health benefits of nutraceuticals, functional foods, and spices. Regular intake of these dietary products and lifestyle modifications help to reduce oxidative stress and inflammation as well as a wide array of non-communicable diseases, including cardiovascular and neurodegenerative diseases, diabetes, obesity, MS, cancer, and immune disorders.

Nutraceuticals are defined as substances that provide physiological benefits and assist in improve overall health beyond their basic nutritional functions and protect against non-communicable diseases. Generally, nutraceuticals consist of products that have been isolated or purified from vegetables and fruits, colostrum supplements, and dairy products, and they are sold in medicinal forms in health food stores or on the Internet. Some examples of nutraceuticals are vitamins, minerals, bovine colostrum, amino acids, trace elements, and omega-3 and omega-6 fatty acids. Reports indicate that intake of nutraceuticals and functional foods can regulate gene and protein expression. This modifies endogenous metabolic pathways and homeostasis, lowering the risk of chronic diseases. Also, an adequate daily intake of nutraceuticals maintains overall health and well-being as well as health-related quality of life in humans. It seems that the antioxidant and antiinflammatory properties of nutraceuticals, functional foods, and spices has an important role in decreasing risk factors associated with arterial atherosclerosis and occurrence of heart disease and stroke.

With the rise in urbanization and change in lifestyle, city dwellers have become more prone to risk for diabetes, abdominal obesity, dyslipidemia, hypertension, heart attack, and stroke as well as MS. While most of the treatment involves a change in lifestyle and diet, pharmacological intervention should be considered for factors that cannot be treated by modifications in lifestyle. There is an upsurge in the development of nutraceuticals and functional foods for the management of CMDs associated with obesity and diabetes. Nonpharmacological cost-effective and affordable alternative therapies are being developed for the management of MS. More basic research is needed to understand the

mechanism of action of nutraceuticals and functional foods. Furthermore, well-designed, randomized, placebo-controlled clinical trials should to done to evaluate the long-term safety and efficacy and dose levels of functional foods and nutraceuticals for the prevention and treatment of MS.

The influence of nutraceuticals, functional foods, natural health products, dietary supplements, and probiotics, prebiotics, synbiotics is often neglected by healthcare professionals and leading experts in medicine. However, dietary interventions may be one of the biggest drivers for curing the global epidemic of chronic non-communicable diseases, including obesity, diabetes, CVDs, and certain cancers. However, the evidence-based dietary advice is hampered by poor-quality science; a limited number of randomized, placebo-controlled studies; and unresolved controversy about the role of clinical nutrition in curing lifestyle diseases. Data analysis from a limited number of preclinical and clinical studies showed improved the triglyceride and lipid profiles in animals and humans treated with some nutraceuticals and plant products.

On the basis of the current knowledge, studies should also be done with nutraceuticals to explore their antiobesity, antidiabetic, and anticancer potential for the prevention of non-communicable diseases when conventional therapies have proved less effective. Although nutraceuticals possess enormous health benefits, large-scale randomized, placebo-controlled, double-blind clinical trials with adequate end-points and biomarkers will confirm the therapeutic claims and enable evaluation of the safety of nutraceuticals and plant products described in this review. Good manufacturing practices and high-quality control standards should be used for the manufacture of nutraceuticals and plant products. Farmers should be encouraged to cultivate nutraceutical-containing plants organically for sustainable availability and to build bridges between agriculture, clinical nutrition, and medical practice.

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Chapter 40

Nutraceuticals as a natural alternative for preventive and proactive health care

Aastha Visen[1], Srishti Visen[1], Asha Sharma[2] and Pradeep K.S. Visen[1,3]

[1]Nutra-V Inc., Toronto, ON, Canada, [2]Nutra-V Natural Care Private Limited, Lucknow, India, [3]Formerly, University of Toronto, Toronto, ON, Canada

Introduction

Nutraceuticals have seen a meteoric rise in popularity over the last few years, especially for preventive and proactive health care and disease management. The evolution of the health-focused ecosystem has given rise to the emergence of nutraceuticals. Although nutrition is a relatively new healthcare segment, it is attracting considerable interest from both consumers and the medical community. This is because of the growing awareness of the impact of our lifestyle and diet on our health.

The growing health consciousness among consumers marks a paradigm shift in the way we approach to food. *Nutraceutical* is a term used for any product of food origin with added health benefits in addition to the basic nutritional value of the food. It can be considered as a nonspecific biological therapy for promoting general health, controlling symptoms, and preventing malignant processes. The modern lifestyle of consumers has undergone phenomenal changes. The faster pace of life, with the accompanying pressure on the work and life balance, affects health and wellness. At the same time, emergence and access to media and information allows for better understanding of the latest developments across all arenas. Many people, young and old, are interested in consuming more healthful foods and beverages, enhancing their energy in a holistic manner, and balancing their diet.

The term *nutraceutical* was coined by the nutritionist and pharmacist Stephen DeFelice, President of the Foundation of Innovation Medicine, in 1989 from the terms *nutrition* and *pharmaceutical*. He defined *nutraceutical* as "a food, or part of a food, that provides medical or health benefits, including prevention and/or treatment of a disease." The nomenclature and regulatory classification of nutraceuticals may vary from country to country, although they are typically treated as being a class of foods. According to the ancient Greek doctor Hippocrates (known as the Father of Medicine), the philosophy behind nutrition and health care is to focus on prevention. The role of nutraceuticals in human nutrition is one of the most important areas of investigation and has a broad impact on consumers, healthcare providers, regulatory agencies, and food producers and distributors.

Health Canada defines *nutraceutical* as "a product prepared from food, but sold in the form of pills or other medicinal forms, which are generally not associated with food and made from plants, minerals and vitamins" [1]. Specifically, a nutraceutical is a formulation of active compounds taken from foods of plant origin or animal origin that have a physiological and/or pharmacological benefit and nutritional value. After the evidence of their safety, bioavailability and health effects has been established, these formulations can then be used to effectively prevent or treat diseases [2,3].

Categories and subcategories of nutraceuticals

Broadly, nutraceuticals are foods or part of foods that play a significant role in modifying and enhancing the normal physiological functioning that maintains good health in human beings. The food products that are used as nutraceuticals, on the basis of their natural source, chemical grouping, and categories, can be categorized as nutrients, herbals, dietary supplements, dietary fiber, prebiotics, probiotics, polyunsaturated fatty acids, antioxidants, and other different types of herb or /natural foods [4].

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Nutraceuticals can be classified according to the chemical nature, food availability, and mechanism of action of their bioactive compounds. The category of food availability can be subcategorized into traditional and nontraditional nutraceuticals. Compounds that have been acquired directly from nature without changing their form are considered traditional nutraceuticals, such as probiotic bacteria, chemical compounds, enzymes, nutrients, herbal extracts and compounds, and phytochemicals. Fortified and recombinant nutraceuticals fall into the category of nontraditional nutraceuticals.

Additionally, nutraceuticals that are based on mechanism of action include subcategories such as anticancer properties, positive impact on lipid profile, antioxidant activity, antiinflammatory effects, and osteogenic or bone-protective functions.

The category into which the greatest number of nutraceutical products are placed is that of the chemical nature of the bioactive compounds being used. Subcategories include carotenoids, collagen hydrosylates, dietary fiber, polyunsaturated fatty acids, flavonoids, glucosinolates and isothiocyanates, phenols, plant sterols, prebiotics and probiotics, spices, saponins, soy proteins, phytoestrogens, sulfides/thiols, and tannins.

Nutraceuticals have many ingredients, including vitamins and minerals that directly contribute to health. Macrominerals are required in large quantities; examples are sodium, potassium, calcium, magnesium, and phosphorus. Microminerals are required in small quantities; examples are zinc, iodine, copper, selenium, manganese, and chromium.

Nutraceuticals are often confused with dietary supplements and functional foods. But there is a clear distinction among these three groups in their meaning and uses. Nutraceuticals can be in the form of isolated compounds, whole foods, or dietary supplements that not only supplement the diet but also help in the prevention and treatment of disease. A nutraceutical is a collection of natural bioactive ingredients of plant or animal origin. A food is made functional by the addition of nutraceutical ingredients. Dietary supplements are concentrated source of nutrients extracted from food sources or made synthetically, either alone or in combination, that have physiological effects that complements the diet. Nutrient compounds include vitamins, minerals, fiber, fatty acids, and amino acids. A functional food, a category that was originally introduced in Japan in the mid-1980s, can be any fresh or processed food that has been fortified with nutrients to ensure a physiological effect on health or to prevent disease. Some instances of functional foods are omega-3-enriched eggs, oats, fatty fish, fortified margarines, iodized salts, soy products, tomatoes and tomato products, probiotics, yogurt, nuts (e.g., walnuts, cashews, pistachios), and leafy greens [2].

Future prospects for nutraceuticals

Nutraceuticals provide several benefits to consumers. They improve the nutrition and health value of an individual's diet; they help to prevent medical deficiencies; and they are an advantageous alternative for consumers who have specific deficiencies and needs [5–7].

The nutraceutical market is a fairly new section of the food industry that is growing rapidly. This growth is parallel to the growing concerns of consumers about their overall health and life expectancy and how these can be balanced well through eating food that is increasingly supported by evidence connecting diet and health. The importance and role of basic nutrients in the growth, maintenance, and wellness of the body are well established. Food supplies energy, nutrients (fats, carbohydrates, proteins, vitamins, and minerals), and nonnutrients (fiber, antioxidants, inducers of beneficial enzyme activities, prebiotics, and probiotics), and the human body is well capable of utilizing all these molecules from the food.

Nutraceuticals are expected to play a central role in preventive health care. The logic seems simple: An aging population gives rise to lifestyle-related diseases, whose impact can be lessened by making healthier choices earlier in life. This leads to a sharper focus on measures, such as a health-promoting diet, to prevent people from ever getting ill. Both publicly and privately funded healthcare research will need to consider the implications not just of new so-called superfoods, to take one example, but also in terms of ways to persuade people to make better choices about their diet. Future superfoods could tackle the underlying causes of conditions such as diabetes, obesity, and cardiovascular disease (CVD) by linking diet to health. Competitive advantage will be gained by companies that have a superior product strategy, juggling ingredients, technology and labeling to optimize the product portfolio in each country [5,8].

Nutraceuticals cover a wide range of products, from sports drinks, which are available on supermarket shelves, to prescription drugs for patients with serious medical conditions. These offer opportunities for pharmaceuticals companies to make their products more consumer-oriented and to create brands with a medical image [2,3].

Global nutraceutical market

Over half of the adult population in many Western countries consume nutraceuticals because of their purported therapeutic benefits, accessibility and convenience. Several studies have demonstrated that they may also serve as a useful adjunct to pharmaceuticals to better manage chronic conditions or offset negative side effects. Individuals are advised to consult their physician before using nutraceuticals, but this advice is often overlooked. Thus the community pharmacist plays an increasingly important role in assisting consumers with selecting a nutraceutical that is safe and for which there is evidence of therapeutic efficacy.

The global nutraceutical industry, valued at U.S. $182.6 billion in 2015, is one of the fastest-growing industries today and was expected to expand at a compound annual growth rate (CAGR) of 7.3% from 2015 to 2021 (Fig. 40.1) [2,9,10].

Currently, the United States, Europe, and Japan account for almost 93% of the total global nutraceutical market. The market, however, seems to have attained maturity in all three regions. Therefore the nutraceutical industries around the world are now turning their attention to emerging markets [2].

Nutraceutical market in India

The nutraceuticals industry in India is one of the rapidly growing markets in the Asia-Pacific region. According to a recent report, the nutraceutical industry in India is worth about U.S. $2.2 billion and is projected to grow at 20% to U.S. $6.1 billion by 2019–20 (Fig. 40.2). The popularity and growth of this industry can be attributed to consumers' increased inclination toward good health and nutrition. Over the past decade there has been a radical change in the lifestyles of Indians. Adoption of fast foods and packaged foods and a sedentary lifestyle has led to an increase in the incidences of lifestyle diseases such as diabetes, CVDs, and obesity. As a result, Indian consumers, predominantly those in the higher socioeconomic and upper middle class, are perceiving nutraceuticals as an alternative to prescription drugs. Furthermore, they have been showing a keen interest in products for boosting energy and improving their physical endurance and mental alertness [2].

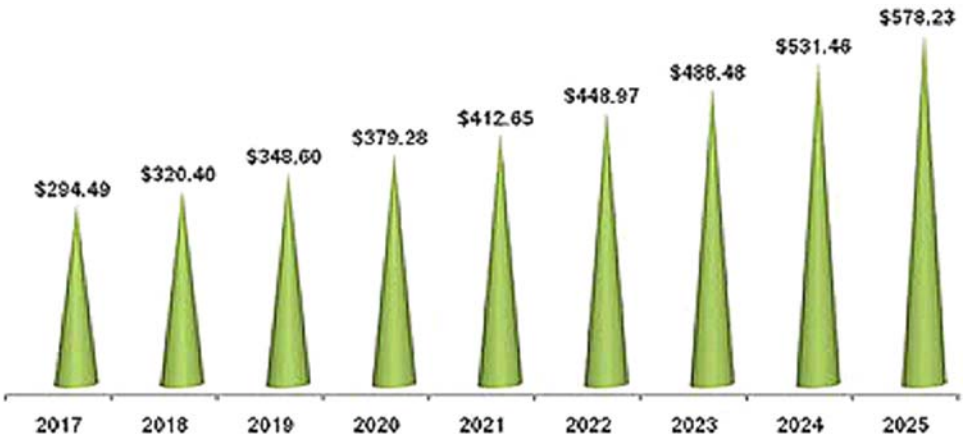


FIGURE 40.1 Global nutraceutical market size (in billions of U.S. dollars).

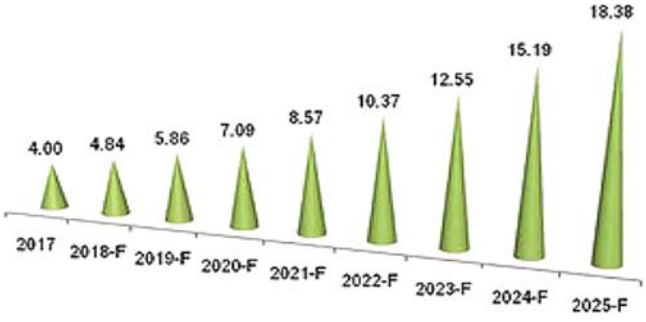


FIGURE 40.2 Nutraceutical market in India (in billions of U.S. dollars). *F*, fiscal year that runs from April to March.

Nowadays, the demand for nutraceuticals and natural health products (NHPs) is increasing in both developing and developed countries. The reason behind the resurgence of the use of NHPs is their long history of clinical use, better patient tolerance and acceptance, no or fewer side effects, and safe combinations of chemical ingredients acting on multiple targets that may be more effective than single-target modern medicines. Also pharmaceutical drugs are very expensive and may have problematic side effects. As nutraceuticals blur the line between food and drugs, it is often difficult—by legal definition—to distinguish between nutrients, food additives, drugs, and nutraceuticals. But it is a fact that nutraceuticals will play an important role in future therapeutic developments.

Nutraceuticals from medicinal herbs

Medicinal plant research should be focused on producing useful nutraceuticals from medicinal and food plants for human welfare. Globally, NHPs have been considered an important alternative to modern allopathic medicine. Currently, there is growing public interest in the self-usage of complementary and alternative medicines (CAM) as well as nutraceuticals, functional foods, and NHPs because of their wellness benefits, lesser or no side effects, and relatively lower cost [11].

Botanicals or medicinal herbs are major components of traditional healing systems in developing countries. According to the World Health Organization (WHO), 80% of people in developing countries depend on traditional medicines for primary health care. Furthermore, the consumption of traditional and alternative medicines in the primary healthcare system has increased manyfold in the West. The percentages of population in each developed country that have used medicinal plants at least once are: 90% in Germany, 70% in Canada, 49% in France, 48% in Australia, 42% in the United States, and 31% in Belgium [12].

In the 21st century, with the increased efficacy of the pharmacological effects of medicinal plants, nutraceuticals are considered to be promising future medicines for the management of health care. Recently, there has been a universal trend from synthetic to nutraceutical and NHP, which is claimed as a "return to nature." Medicinal plants have been exploited since ancient times and are highly esteemed all over the world as a rich source of therapeutic agents for the prevention and management of diseases and ailments. As per the estimate of the WHO, herbal medicines are one of the most commonly used types of primary health care for around 3.5−4 billion people around the world, and a major portion of traditional medicine involves plant extract−derived medicines and decoction, which may also be termed "modern herbal medicine" or nutraceuticals [13].

Scientific validation of medicinal herbs for nutraceuticals

Our planet is home to approximately 420,000 species of plants; however, there is a lack of appropriate knowledge about them and their varied uses. There are three major areas, namely, food (foodstuffs), medicine (folk and traditional medicines), and research (phytochemical analysis), that predominantly find an immense use for herbal preparations and products and hence can be explored further. Over the last decade there has been an enormous increase in products derived from medicinal plants in terms of interest and use. What used to be the exclusive domain of health food and specialty stores has now gained considerable popularity in the mainstream market, as is evident from their impressive sales at major retail outlets, their publicity and advertising in the media, and the entry of various pharmaceutical giants into the area of phytomedicines. Although they have become very popular, only certain herbs have been scientifically evaluated for their potential in medical treatment.

Unfortunately, the vast majority of herbs that are offered for sale lack quality control, standardization, and clinical scrutiny for disease treatment [4,9,14]. Thus individuals continue consuming herb products with no evidence of their efficacy. To prevent this, we must identify through scientific evidence what herbs are efficacious for what diseases, what components within herbs are responsible for the beneficial effects, and how the components act mechanistically [4].

For both the developing and developed countries, WHO study groups strongly emphasize optimal and rational uses of nutraceuticals, dietary supplements, traditional medicines, and CAM therapies. The Australian Food Trade Commission, U.S. Food and Drug Administration, and Health Canada are deeply concerned about their efficacy and safety. The increasingly high demand for nutraceuticals, dietary supplements, functional foods, CAM, and NHPs; lack of evidence for their safety and efficacy; inadequate regulatory standards; and lack of patient disclosure to physicians and physician education have prompted unified calls from the medical and scientific community for conducting well-designed, randomized, placebo-controlled clinical trials in order to understand healing potential of these products for various disorders and to provide a valid scientific basis for the legitimate health benefits and therapeutic claims.

While some nutraceuticals are safe, others have the potential to be toxic. For a large number of nutraceuticals, no toxicity or safety data are available, owing to a lack of pharmacological and toxicological studies. The safety of some nutraceuticals can be compromised by contamination with toxic plants, metals, mycotoxins, pesticides, fertilizers, drugs of abuse, and so on. Knowledge of pharmacokinetic and toxicokinetic studies appears to play a pivotal role in safety and toxicity assessment of nutraceuticals. Interaction studies are essential to determine efficacy, safety, and toxicity when nutraceuticals and therapeutic drugs are used concomitantly [15–17].

Scientific validation model

The scientific validation of medicinal herbs to prepare safe and effective nutraceuticals with reproducible results is essential for the following reasons [9,14,18]:

- Lack of scientific and clinical scrutiny for the majority of medicinal herbs
- Consumption of herbs with no efficacy and safety
- Lack of proper techniques and use of improper methodologies to make herbal extracts
- Lack of isolation and standardization of active chemical ingredients
- No quality assurance regarding identification of medicinal herbs, adulteration, and herb-drug interaction
- No standardization of commercial herbal products and variance in their active ingredients
- Not all plants are safe; careful scientific research is therefore needed to determine their true efficacy and safety

The following steps are essential in developing ideal nutraceutical/plant-based alternative medicine (Fig. 40.3):

1. Selection of plants
2. Collection and validation of data
3. Preparation of plant extracts
4. Toxicity studies: acute and long-term toxicity studies in animals
5. Efficacy evaluation:

a. In vivo study (humans): unequivocally establish the presence of biological activity and to provide a rationale for clinical use of the preparation

b. In vitro study: cell culture to determine the preventive and curative activity of the preparation and the mechanism of action

6. General pharmacology: effects on the central nervous system, cardiovascular system, etc. It is necessary to predict possible side effects and precautions during clinical use and ways of counteracting the side effects

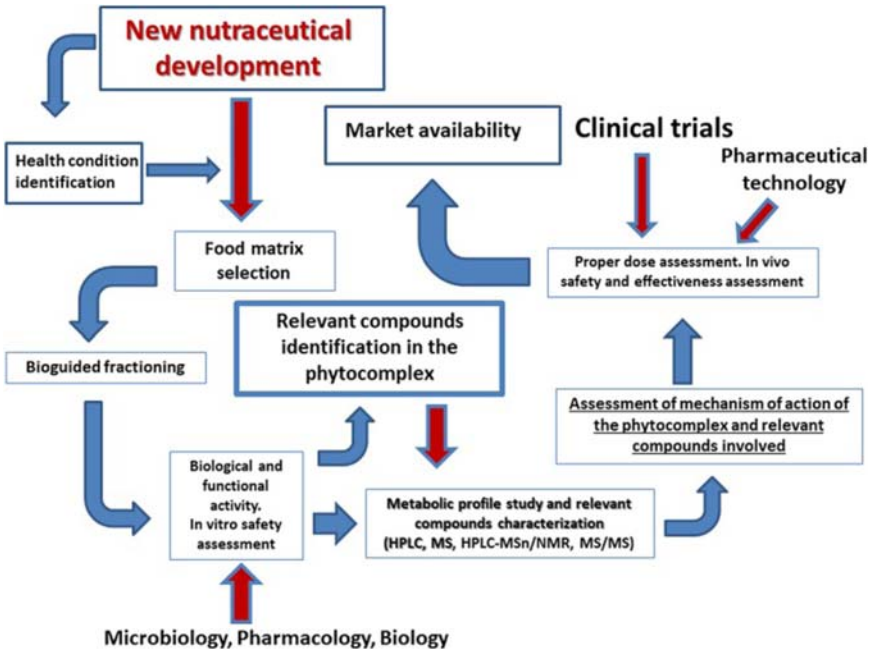


FIGURE 40.3 Development of evidence-based nutraceuticals.

7. Pharmaceutical analysis: stability studies
8. Quality control: using modern techniques, for example, High Performance Thin Layer Chromatography (HPLC), Thin Layer Chromatography (TLC), Tandem Mass Spectrometry (MS/MS)
9. Acute and long-term (60−90 days) clinical trials
10. Product development
11. Commercialization

Nutraceuticals in the management of key diseases

As countries worldwide become more developed, the incidence of diet-related diseases is also increasing as a result of the increased availability of high-calorie foods and a sedentary lifestyle. Most common health conditions, such as obesity, diabetes, atherosclerosis, various types of cancers, arthritis, and neurodegenerative diseases, share a common pathogenic pathway of low-grade inflammation. Therefore nutraceuticals may provide a novel therapeutic approach to prevent or reduce the instances of diet-related diseases by exerting beneficial antiinflammatory responses.

Cardiovascular diseases and heart health

The impact of CVD is significant. It is the number one cause of death globally [2,19]. The risk of contracting CVD is associated with lifestyle choices, including a poor diet. There are three main opportunities for nutraceuticals in heart health. The first is to reduce cholesterol, the second is to reduce the circulation of free radicals (which contribute to plaque formation in arteries), and the third is through fibrinolytic activity (plaque breakdown). Any food and drink that can demonstrate progress in these areas will have wide-reaching impacts on the disease.

There is already an abundance of products that focus on cholesterol reduction, with most evidence supporting the role of vitamin E and omega-3 fatty acids [20,21]. Preliminary research is being conducted to evaluate products that have combinations of "natural enzymes" to help promote fibrinolysis. Products that can demonstrate even a small health benefit in this area will be successful [22].

Polyphenols prevent and control arterial disease. Flavonoids strengthen the capillaries that carry oxygen and essential nutrients to cells. Dietary fiber, such as rice bran and cereal grains, lowers the level of low-density lipoprotein (LDL) cholesterol and increases high-density lipoprotein (HDL) cholesterol for optimum cardiovascular health [23]. The essential fatty acids, such as omega-3, omega-6, and omega-9 fatty acids, also promote heart health by reducing cholesterol levels. Corn contributes to heart health because of its rich fiber content and high concentration of folate. It reduces the damage to blood vessels that leads to heart attack, stroke, or peripheral vascular disease [24−29].

Diabetes

According to *International Diabetes Federation Atlas 2019*, the incidence of diabetes is increasing worldwide, and the estimated number of adults with diabetes is currently 463 million; this is expected to rise to 578 million by 2030 and to 700 million by 2045 [30]. Sustained exposure to high blood glucose is linked to the consumption of foods that are high in fat and sugar. Foods that release sugars slowly enable better glucose control, which can reduce the impact of diabetes on people who have the disease and can also help to prevent the onset of type 2 diabetes.

The European Food Standards Authority (EFSA) has recently approved a low glycemic−index sugar substitute for diabetics. There are also a number of studies looking at food products that resensitize the body to insulin. One product that is developing traction is a soluble fiber gum that has registered for approval of its claim that it can increase insulin sensitivity following successful trial results [3].

Fatty acids have been proven to have benefits in diabetic patients. Docosahexaenoic acid is responsible for modulating insulin resistance and plays a vital role in neurovisual development [31]. Lipoic acid, a strong antioxidant, may be helpful in the treatment of diabetic neuropathy. Dietary fibers help in managing glucose levels in diabetic patients and reduce lipid levels in hyperlipidemia. Presently, a lot of attention is being given to nutraceuticals and certain phytochemicals that are integral parts of the human diet. It is believed that a clearer understanding of their roles may be crucial to noninvasive or minimally intrusive management with regard to the daily lives of patients [32].

Metabolic syndrome represents a clustering of risk factors related to an elevated risk of CVD and type 2 diabetes. Metabolic syndrome and diabetes and their vascular complications share several pathogenic features, including subclinical low-grade inflammation, altered oxidative/antioxidant status, and persistent platelet activation. Several

nutraceuticals used in clinical practice have been shown to target the pathogenesis of diabetes mellitus, metabolic syndrome, and their complications and to favorably modulate a number of biochemical and clinical endpoints. These compounds include antioxidant vitamins such as vitamins C and E, flavonoids, vitamin D, conjugated linoleic acid, omega-3 fatty acids, minerals such as chromium and magnesium, alpha-lipoic acid, phytoestrogens, and dietary fiber [33–40].

Brain health and aging

Dementia is defined as acquired objective cognitive impairment. It is a social problem in the aging society of advanced countries. Presently, 46.8 million people affected with dementia worldwide, and it may increase to 130 million by 2050. Alzheimer's disease (AD) is the most common form of dementia [41]. Scientists are increasingly looking to food products to help slow disease progression and treat symptoms.

There are a range of products in the pipeline that attempt to improve cognitive function. Enhancing brain glucose metabolism to delay cognitive decline has been the target of some products. There is also an increasing number of products that claim to enhance normal brain function. As adults become more aware of cognitive diseases, there will be a greater market for preventative treatments [42,43]. With large investments happening in this area, innovative products are likely to hit the market within five years.

Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia. There is a dramatic epidemic of AD, due to the growth of the aging population worldwide [41]. Target options to reduce the incidence of AD include natural nutrition, nutritional supplement, cognitive activity, and physical exercise. Flavonoids modulate neurological processes by increasing cerebral blood flow, antioxidant enzymes, and neuronal repair. Anthocyanidins present in berries exhibit antioxidant effects and antidepressant properties. Curcumin from turmeric exerts antiinflammatory effects in neurons that slow neuronal degeneration. Current evidence clearly shows that the synergistic action of combined supplementation and complex dietary patterns provides stronger benefits than any single component considered separately. Recent studies reveal the growing importance of novel factors, such as dietary advanced glycation end products (d-AGE), gut microbiota, butyrate, and vitamin D_3, on inflammatory processes in AD [44–47].

Parkinson's disease

Parkinson's disease is the second most common aging-related disorder leading to motor and cognitive impairment and dementia. Extensive research has indicated two major risk factors: oxidative stress and mitochondrial dysfunction. Many nutraceuticals aim to diminish these risk factors to prevent or delay the progression and severity of Parkinson's disease. Examples include vitamins C, D, and E; coenzyme Q10; polyunsaturated fatty acids; and polyphenols. Vitamins C and E are strong antioxidants that reduce the oxidative stress in neurons. Vitamin D, fatty acids, and polyphenols possess neuroprotective properties that reduce inflammation and CoQ10 primarily attenuates mitochondrial dysfunction [48–50].

Obesity

Caloric restriction and increased physical activity have been shown to be moderately successful in managing obesity. Nutraceuticals that help to increase energy expenditure while decreasing calorie intake may play a synergistic role in preventing and treating obesity when combined with daily exercise and calorie restriction [7]. For example, green tea contains polysaccharides, flavonoids, B vitamins, and catechin compounds that possess antiobese properties. Additionally, dietary phytochemicals and prebiotics and probiotics can potentially suppress the growth of fat tissue and stimulate the breakdown of fat [51–55].

Cancer

Phytochemicals derived from dietary plants such as soybeans, ginger, garlic, and honey may possess chemopreventive activities by inducing cell death. Flavonoids, tea polyphenols, and quercetin have been widely studied for their chemopreventive applications. Similarly, a correlation has been established between dietary consumption of carotenoids and reduced risk of cancers and CVD. Tomatoes, for example, are rich in lycopene and carotenoids that may induce cell

death in cancer cells present in the skin, testes, prostate, and adrenal glands. Curcumin from turmeric and sulfide compounds from garlic also exert chemopreventive effects on colon, lung and breast cancer cells. In recent years, calorie-restricted dietary regimens and compounds such as vitamins, curcumin, green tea extracts, and omega-3 fatty acids have attracted attention for their potential anticancer effects [8,55–60].

Osteoarthritis

Osteoarthritis (OA) is the most common form of debilitating joint disorder that reduces physical activity, leading to weight gain. This increased weight, in turn, exacerbates existing problems by exerting additional pressure and stress on joints. Glucosamine, chondroitin sulfate, and hyaluronic acid are examples of widely used nutraceuticals that alleviate symptoms of OA by regulating antiinflammatory activities. Flavonoids with free radical–scavenging antioxidant properties and plant-based immunomodulators such as curcumin also play a role in attenuating immune response to joint degeneration, thus minimizing arthritic joint damage.

OA is a chronic disease of the joints. It is highly prevalent, particularly in elderly people, and is commonly associated with pain that interferes with quality of life. Because of its chronic nature, pharmacological approaches to pain relief and joint repair must be safe for long-term use depending on their quality. Nutraceuticals are dietary compounds that have a role in the balance of anabolic and catabolic signals in joints. Their regulatory function in homeostasis of cartilage metabolism nutraceuticals is increasingly considered for the management and, above all, prevention of OA.

Nutraceuticals are compounds or materials that can function as nutrition and exert a potential therapeutic effect, including the relief of pain, such as pain related to arthritis, of which OA is the most common form. In human trials, nutraceuticals have recently been shown to have potential in relieving OA pain. Emerging evidence indicates that nutraceuticals may represent promising alternatives for the relief of OA pain [61–65].

Eye disorders

A healthy lifestyle and a diet that is rich in antioxidants, such as fatty acids, lutein, and zeaxanthin, have beneficial effects on age-related macular degeneration. High concentrations of polyphenols and flavonoids, such as in green tea, vitamins C and E, CoQ10, and other carotenoids possess strong antioxidant properties that may slow down or reverse macular degeneration. Astaxanthin is a carotenoid that is abundant in seafood, such as salmon, trout and shrimp, and protects against oxidative damage. Lutein is a plant-based carotenoid that is present mostly in leafy green vegetables, tomatoes, carrots, mangoes, corn, and squash [66–71].

Immunity disorders

The immune system is the body's chief defense mechanism. It evolved to fight against viruses, bacteria, and germs. A weakened immune system leaves us vulnerable to various illness. A wide variety of nutraceuticals play a crucial role in immunity status and susceptibility to some diseases. Nutraceuticals in the category of immune boosters help to increase immune function. They include extracts of the herbs of the genus *Echinacea*. Phytoestrogens are another subcategory that are recommended for conditions linked with hormonal imbalances. Other examples include garlic, which stimulates the immune system, and morphine, which suppresses immunity. The relationship between intestinal health and the immune system has given credence to the use of nutraceuticals for infectious diarrhea and other inflammatory bowel conditions. Probiotic nutraceuticals may help to improve the balance between proinflammatory and antiinflammatory molecules and manipulate gut flora to increase nonpathogenic bacteria and reduce pathogenic bacteria. In this case, nutraceuticals as an alternative therapy provide a high index of safety and can reduce the use and harmful effects of antibiotics. On the basis of a large body of research, the top ten vitamins, minerals, and supplements that help to strengthen our immunity are vitamin C, vitamin E, vitamin D, B-complex vitamins, zinc, selenium, curcumin, garlic, elderberry, and *Andrographis paniculata* [72].

Immunity-related disorders are one of the leading causes of mortality in the world. Bovine colostrum is rich in immunity, growth, and antimicrobial factors, which promote tissue growth and the maturation of digestive tract and immune function in neonatal animals and humans. The immunoglobulins and lactoferrin that are present in colostrum are known to build natural immunity in newborns, which helps to reduce the mortality rate in this population. Also, the side-effect profile of colostrum proteins and possible lactose intolerance are relatively less in comparison with cow's milk. In general, bovine colostrum is considered safe and well tolerated [73].

Gastrointestinal health

Gut health issues, from indigestion to more serious conditions such as celiac disease, motivate consumers to look to over-the-counter products for symptom relief. It is estimated that over 100 million people globally are effected by "gut health" problems, and the prevalence is rising [74,75]. Household products such as Yakult help to provide some symptom relief. They have a positive effect on the millions of organisms that live in the human intestine (known as gut flora). Many consumers purchase some form of product labeled "probiotic," and the market is growing [76].

For the last few decades, bacteria known as probiotics have been added to various foods because of their beneficial effects on human health. The mechanism of action of probiotics is related to their ability to compete with pathogenic microorganisms for adhesion sites to antagonize these pathogens or to modulate the host's immune response. The potential application of probiotics includes prevention and treatment of various health conditions and diseases, such as gastrointestinal infections; inflammatory bowel disease; lactose intolerance; allergies; urogenital infections; cystic fibrosis; various cancers; reduction of antibiotic side effects; prevention of dental caries, periodontal diseases, and oral malodor; and many other effects that are under investigation. The results of many of these clinical investigations suggest that probiotics may be useful in preventing and treating various health conditions and diseases [77−80].

The gastrointestinal microbiota has an important role in human health, and there is increasing interest in utilizing dietary approaches to modulate the composition and metabolic function of the microbial communities that colonize the gastrointestinal tract to improve health and prevent or treat diseases. One dietary strategy for modulating the microbiota is consumption of dietary fiber and prebiotics that can be metabolized by microbes in the gastrointestinal tract. Human alimentary enzymes are not able to digest most complex carbohydrates and plant polysaccharides. Instead, these polysaccharides are metabolized by microbes that generate short-chain fatty acids, including acetate, propionate, and butyrate [81,82].

Gang-deviant behavior in adolescents and psychosocial health

Nutritional psychiatry is a term that encompasses a new frontier of psychiatry and psychosocial health that explores this brain-gut axis further, focusing on how diet affects each individual's mental health. Dietary supplements can be an important factor, filling any nutritional gaps as well as providing additional support for the body [83].

Youth gang-deviant involvement is a serious public health challenge. Adolescents who are involved in gangs are more likely than others to engage in violence, aggression, antisocial activities, and bullying. They are involved in the activity of repeated physical or verbal aggression that is continued over a period and intended to hurt one or more other individuals physically, mentally, or emotionally.

To better understand gang involvement, a study was carried out to assess the role of protective factors (empathy and parental support) and risk factors (peer deviance and lack of safety at school) as well as their interactions in predicting adolescent gang affiliation. The study involved a sample of 300 students (males aged 12−15 years) at different schools in Meerut city (U.P., India), who were surveyed to investigate a wide range of youth health and risk behaviors. The findings indicated that poor empathy and parental support in childhood, excessive stress and trauma, association with deviant peers and antisocial elements, and perception of school as unsafe were positively correlated with gang membership. At the school level, lack of safety and type of school (special education, vocational, or alternative school vs comprehensive school) were associated with a greater probability of gang membership [84].

Gang-deviant behavior thus affects emotional, mental, physical, and social health. It adversely affects the interconnection between mind, body, and spirit. These adolescents thus suffer from severe anxiety, depression, negativity, and other psychological and mental and physical disorders. According to American Psychological Association, nutraceuticals effectively help in the treatment of psychosocial disorders and gang-deviant behavior. Vital nutrients, such as omega-3 and omega-6 fatty acids; vitamins B6, B9 (folate), and B12; vitamin C; vitamin D; the minerals magnesium, zinc, and selenium; probiotics; and amino acids play a very important role in the management of these disorders [85−87]. The amino acids reduce symptoms as they are converted into neurotransmitters that control depression, anxiety, and common mental disorders and aggressiveness. The antioxidants that are present in plants such as ashwagandha, brahmi, tulsi, chamomile, kava kava, lavender, lemon balm, passion flower, rhodiola, St. John's wort, and valeria are valuable long-term nutraceutical antidotes to clinical anxiety and depression [85−87]. They soothe and calm anxious thoughts and panic attacks. Medicinal herbs combined with vital nutrients are thus reported to reduce physical, emotional, and environmental stress, which then work synergistically to normalize and balance the body. Additionally, they effectively help in the improvement of symptoms of stress and anxiety: emotional instability, phobias, loss of focus, loss of motivation, and feelings of impending doom.

Evidence-based nutraceuticals with researched dose from Nutra-V Inc. as examples of natural alternatives

1. Nutra-V Livgard Forte Rx
   a. Hepatoprotective activity

      Liver-Protective Plant Extracts with Standardized Evidence-Based Active Ingredients: *Phyllanthus amarus* (phyllanthus), *Silybum marianum* (milk thistle), *A. paniculata* (kalmegh), and *Emblica officinalis* (amla)

      Vitamins and Minerals (strong antioxidants): vitamin E, vitamin C, selenium, zinc, and copper

      These evidence-based standardized medicinal ingredients—in appropriate quantity, dosage, and combination—have shown liver-protective activity against cell damage induced by a variety of hepatotoxins. They also promote cleansing of the liver by the process of detoxification. The product helps in restoring healthy liver function by acting as a natural regenerator that additionally may help in the management of cholesterol and glucose levels in blood. It may protect the liver against alcohol-induced toxicity and prevent fat infiltration (fatty liver), thus protecting against cell damage and restoring normal liver enzyme levels. Scientific evidence suggests that the product may further help in the restoration of normal liver function in infective hepatitis and may prevent, in addition, the onset of cirrhosis and associated liver damage [88].

      Vitamins and minerals act as strong antioxidants by increasing the level of glutathione, an amino acid that neutralizes the harmful effects of free radicals. The strong antioxidants further boost immunity and promote appetite and digestion. The product also helps to rejuvenate general body health, and provides physiological benefits, and maintains the body's ability to metabolize fat, protein, and carbohydrate [88].

   b. Immunomodulatory effect

      The liver plays an important role in detoxifying body; therefore a weak liver function means a weak immune system. The liver is directly involved in the functioning of the immune system by eliminating microorganisms, including bacteria and viruses.

      The product Nutra-V Livgard Forte Rx, with its above evidence-based plant ingredients, vitamins, and minerals, supports healthy liver function through its effect on regeneration of liver cells, preventing free radicals from damaging liver cells via its antioxidant effects and maintaining healthy immune function via its immunomodulatory effects.

      With these specifications the product also qualifies under the international norms of the WHO and U.S. Centers for Disease Control and Prevention in regard to preventing or/and managing viruses by modulating immunity according to severity of infection, thus helping in preventing autoimmune disorders, kidney failure, and liver fatality, which are major causes of mortality. By its strong immune-stimulant activity, the product helps to protecting the healthy population from infection by maintaining healthy liver function and strong immune function.

      Known Adverse Reaction: Hypersensitivity, such as allergy to milk thistle, has been known to occur. A laxative effect may also occur.

2. Nutra-V LoChol Forte Rx

Heart-Protective Plant Extracts With Standardized Evidence-Based Active Ingredients: *Commiphora wightii* (guguli-pid), *Terminalia arjuna* (arjuna), *Saccharum officinarum* (policosanol), and *Allium sativum* (garlic).

Strong Antioxidants: *Vitis vinifera* (grape seed extract), coenzyme Q10, and niacin (inositol hexanicotinate).

These plant ingredients have long been used in traditional medicine and well documented in Ayurveda medicine as heart-protective. The product has a combination of standardized evidence-based plant extracts with minerals in appropriate quantity, dosage and combination, which helps in maintaining healthy blood cholesterol levels. In the formulation the available flavonoids have been reported to exert antioxidant, antiinflammatory, and lipid-lowering effects while glycosides are supposed to be a heart tonic. The product helps in optimizing the ratio of good cholesterol (HDL) to bad cholesterol (LDL), thus maintaining a healthy lipid profile by increasing HDL cholesterol levels and lowering LDL cholesterol levels. Evidences show that these ingredients decrease cholesterol production in the liver and increase the breakdown of LDL cholesterol to maintain a healthy lipid profile. The product also reduces the side effects of statin medication and helps to prevent unexpected increases in glucose and cholesterol levels [88].

The strong antioxidants in the product promote free radical−scavenging activity and maintain healthy heart, blood vessels, and arteries by removing toxins from the blood.

The product helps to rejuvenate general body health, provides physiological benefits, and maintains the body's ability to metabolize fat, protein, and carbohydrate [88].

Known Adverse Reaction: No adverse reactions have been reported with any of the ingredients used.

Safety: All the ingredients in both Nutra-V Livgard Forte Rx and Nutra-V LoChol Forte Rx have been found to be safe in in vitro, animal, and clinical studies. They contain no dairy products, egg, gluten, yeast, artificial colors, artificial flavors, sweeteners, or preservatives. They are non-GMO and vegetarian.

Regulatory guidelines

India

The manufacture, storage, distribution, sale, and import of nutraceuticals in India are regulated under the Food Safety and Standards Act (FSSA), which was legally implemented in January 2018. The required manufacturing oversight is less strong than that for pharmaceuticals, which may affect Indian producers' ability to produce nutraceuticals for export.

For the first time, this law recognizes the terms *nutraceuticals* and *functional foods*, which are defined as foods that are specially processed or formulated to satisfy particular dietary requirements that exist because of particular physical or physiological conditions or specific diseases and disorders. The law also states that such categories contain the following:

- Plants or botanicals or their parts in form of powder or extracts
- Minerals, vitamins, proteins, metals, their compounds, amino acids, or enzymes
- Substance of animal origin
- Dietary substances for use by human beings to supplement the diet by increasing the total dietary intake

The law is very similar to the Dietary Supplement Health and Education Act (DSHEA) of 1994, which regulates dietary supplements and health claims in the United States. Indian law states that nutraceuticals, food for special dietary uses, functional foods, and health supplements cannot claim to cure or mitigate any specific disease, disorder, or condition except for certain health benefits or such promotion claims as may be permitted by regulations under the FSSA.

Currently, the FSSA does not allow health claims for functional foods, supplements, or nutraceuticals. However, it will be important to see whether the Indian regulatory body will allow health claims based on scientific data for nutraceuticals as the market grows. This could follow the same lines as Japan's Food for Specified Health Uses (FOSHU), which is composed of functional ingredients that affect the structure or function of the body and are used to maintain specific health conditions.

By recognizing the term *nutraceutical* for functional foods and dietary supplements, the FSSA opens a new chapter in the Indian supplements market [2,3].

United States

In the United States, nutraceuticals are mainly found in the category of vitamins and dietary supplements. A range of regulations apply, notably the DSHEA from 1994, which covers dietary supplements, the Federal Food Drug and Cosmetic Act, which covers all foods and food additives, and Good Manufacturing Practice regulations from 2007. Under these the manufacturer:

- is responsible for ensuring the safety of supplements that it makes or distributes;
- must make no false or misleading claims;
- cannot claim that the product will diagnose, cure, mitigate, treat, or prevent a disease;
- must notify the FDA if wishing to use any ingredient not sold before October 15, 1994, with the notification containing information the manufacturer/distributor has used to certify the product's safety;
- must guarantee the identity, purity, strength, and composition of the manufacturer's supplements (deadline for compliance by all manufacturers was June 2010).

In 1988 the FDA awarded orphan drug status to medical foods to encourage their development, and some U.S. healthcare plans reimburse for medical foods [3].

European Union

A complex range of regulations applies to nutraceuticals in the European Union, depending on the product type. These are mainly overseen by the EFSA, which also evaluates claims and has a public Register of Nutrition and Health

Claims. If a product is not on this certified list, it cannot be used until it is approved for inclusion following detailed scientific testing by the company and subsequent review by the EFSA. The EFSA also sets maximum and minimum levels of ingredients to be added to supplements. Labels cannot contain claims that their product will diagnose, cure, mitigate, treat, or prevent a disease. Nutrition and health claims must be authorized at an EU level.

Between 2008 and 2011 the EFSA evaluated 2758 food-related general health claims to assess whether they were supported by scientific evidence. Only around 10% of the claims could be substantiated [3,89,90].

China

China has a lengthy and costly registration process with three main entities involved in policing the industry. The State Food and Drug Administration (SFDA) is in charge of dietary supplements and registration. The Ministry of Health oversees the SFDA and the approval of novel food ingredients. Finally, the Administration of Quality Supervision Inspection and Quarantine controls all the imports and exports [3].

Japan

Foods with nutrient function claims are not heavily regulated in Japan and simply must satisfy the standards for the minimum and maximum daily levels of twelve vitamins and five minerals. FOSHU requires premarketing approval and refers to products containing dietary ingredients that have reported beneficial physiological effects and promote health. Disease risk reduction claims are not allowed [3].

Many studies have led to an understanding of the potential mechanisms of action of pharmaceutically active components contained in food that may improve health and reduce the risk of pathological conditions while enhancing overall well-being. Nevertheless, there is a lack of clear information, and the claimed health benefits of nutraceuticals are often not properly substantiated by safety and efficacy information or in vitro and in vivo data. This can induce false expectations and miss the target for a product to be effective as claimed. A growing demand exists for nutraceuticals, which seem to reside in the gray area between pharmaceuticals and food. It also seems wise to validate the safety, mechanism of action, and efficacy of nutraceuticals with clinical data [91].

Discussion and conclusion

Zeisel [92] defined a nutraceutical as "a diet supplement that delivers a concentrated form of a biologically active component of food in a nonfood matrix in order to enhance health" [91]. Considering this important role of nutraceuticals, the viewpoint has shifted drastically in recent times from one of treating diseases to one of maintaining good health and well-being. Nutraceuticals are a promising alternative approach that is expanding globally for promoting optimal health, reducing chronic diseases and related healthcare costs, increasing life expectancy, and maintaining the balanced functioning of the human body. The comprehensive list of nutraceuticals is evolving continually on the basis of current market development, research, and consumer interests. Many studies have established that nutraceuticals may be involved in a wide array of biological processes, such as modulating cell-signaling pathways, antioxidant defenses, and regulating gene expression and differentiation [6–8,13].

Owing to the growing popularity of nutraceuticals in natural ingredients, the e plant dietary supplements market is expected to increase considerably during the forecast period. These supplements come in a variety of forms, including dried, solid, or liquid extracts; tablets; capsules; powders; and tea bags. The low cost and easy availability, compared to prescription drugs, are factors that are expected to increase demand over the next eight years. The North American nutraceuticals market is a mature market that may grow at a CAGR of more than 7.8% from 2018 to 2024. The utilization of functional foods and beverages by the baby boomers in North America is expected to increase market growth during the forecast period. Owing to the growth in demand for nutritional and nutraceuticals products in Brazil, the CAGR from 2017 to 2025 is expected to reach 9.0%. Owing to the rapid growth of China, Japan, and India, the Asia-Pacific region is expected to rise at the fastest CAGR of 9.9% during the forecast period. Global participants rely on an extensive distribution network to ensure sales across regions [2,3].

Manufacturers participate in extensive research and development to develop innovative products and maintain market competition. However, there remain numerous barriers to successful implementation of cost-effective manufacturing processes. These challenges must be addressed with particular focus on stability, bioavailability, and consumer acceptance. Future demand for nutraceutical depends on consumers' perception of the relationship between diet and disease. Although nutraceuticals have significant promise in the promotion of human health and disease prevention, health

professional, nutritionists and regulatory toxicologists should work together strategically to plan appropriate regulation to provide the ultimate health and therapeutic benefit to humankind. Long-term clinical studies are required to scientifically validate the use of nutraceuticals for various medical conditions. The interaction of nutraceuticals with food and drugs is another area that should be addressed. The effect of different processing methods on the biological availability and effectiveness of nutraceuticals remains to be determined. As for drugs, there should be strict regulatory controls for nutraceuticals [2−4,12,13].

Regulation presents significant challenges to the globalization of nutraceuticals. The major challenge is that regulatory variations between countries hinder global trade and marketing. For instance, most of the countries discussed take a relaxed approach to regulation, but China's process for dietary supplement approval involves a strict testing protocol, in line with the U.S. process for pharmaceutical approval. Unlike DSHEA, the regulations of some nations do not seem to provide adequate distinction between food, drugs, and nutraceuticals [3].

The shift in health care from treatment to prevention is encouraging clinicians and patients to think differently about health and disease and creating momentum for nutraceuticals with opportunities for pharmaceutical and food companies to get involved in the disease/care pathway. The potential market for nutraceuticals may be large, but a global blockbuster product will require top-class compliance with a patchwork of regulations in each country plus tenacious marketing to navigate the vagaries of national tastes. As the industry expands, the main players have to ensure a steady supply of such ingredients as plant extracts, dairy products, whey proteins, and omega-3 fish oils. The nutraceuticals industry is likely to see food and pharmaceutical companies collaborating for an advantageous position. Success in the nutraceuticals market will depend on an ability to take the long view while adeptly seizing short-term opportunities as they arise [93].

The discovery, development, and marketing of food supplements, nutraceuticals, and related products are currently the fastest-growing segments of the food industry. This trend is driven by several factors, mainly resulting from current consumer perceptions. The first and dominant of these is that "natural" is good. The second is the increasing cost of many pharmaceuticals and their negative effects. However, the central point is that nutraceuticals, botanicals, and other herbal remedies, including the entry of new functional foods, are important because of their acceptance as the novel and modern forms to benefit from natural substances. Owing to the rapid expansion in this area, the development of several aspects is considered, as it could negatively influence the future of the market of these products: an imbalance between the increasing number of claims and products on the one hand and the development of policies to regulate their application and safety on the other, along with rapid and valuable controls to check the composition of the plant extracts and adulteration to improve efficacy, such as the presence of synthetic drugs [3,13,15,94].

Although the availability of scientific data is rapidly improving, the central aspect concerns the validation of these products. The first step of this crucial aspect is the security of the composition, obtained by the useful and adapted analytical approach. On the other hand, in the first instance, security is ensured by the long history of the use as food of the great majority of these plants. The importance and novelty of functional food are inherent in the possibility of renewing the secure use of plants to maintain healthiness of humans in novel forms of use adapted to modern times.

According to available research data, only 20% of the total of nutraceuticals undergo phytochemical analysis, while 10% reach the biological screening stage [1,2]. The rest still need some amount of exploration, making use of modern technologies. The future of medicinal plant−derived drugs and evidence-based nutraceuticals therefore seems to have tremendous scope for discovering new and exciting therapeutic strategies and products [93].

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Chapter 41

International food security directed toward older adults: an overview

Douglas W. Wilson[1,2], Paul Nash[2], Ram B. Singh[3], Fabien De Meester[4], Toru Takahashi[5] and Harpal Buttar[6]

[1]Formerly, School of Medicine, Pharmacy, Health and Wellbeing, Durham University, Durham, United Kingdom, [2]Centre for Ageing & Dementia Research, Swansea University, Swansea, United Kingdom, [3]Halberg Hospital and Research Center, Civil Lines, Moradabad, India, [4]TsimTsoum Institute, Kraków, Poland, [5]Graduate School of Human Environment Science, Fukuoka Women's University, Fukuoka, Japan, [6]Department of Pathology & Laboratory Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada

Introduction

Definitions

This section outlines definitions relating to food security and older adults, providing a detailed overview of participant material. Whereas it is impossible for many reasons to discuss food security for older adults in all 196 or so countries, themes have been identified in developed and developing countries that are summarized in the Discussion section and are intended to have general utility. There are countries in transition, so a broad brush definition is used for them, and not all examples concern older adults per se, owing to lack of specific data, but they are adjudged to contain relevant information, for example, food security in households with families including one or more older adults. A complementary paper by these authors on antioxidants, functional foods, and health promotion for older adults provides useful information on food and health [1].

International

The term *international* is intended to be subsumed by two difficult-to-define categories: developed and developing countries. For structural convenience in presenting this overview and in keeping with United Nations use but not by formal definition, we categorize North America, all of Europe, Japan, Australia, and New Zealand as developed and 159 other countries as developing. The U.N. Development Programme groups countries into low-, medium-, high-, and very high-income countries, states that could be attributed to families in any country. The United Nations uses other categorizations, such as those used by the World Economics Situation and Prospects: developed economies, economies in transition, and developing economies [2].

Food security

Food security and its converse, food insecurity, can be reasonably defined as follows: "Food security exists when all people, at all times, have physical, social and economic access to sufficient, safe and nutritious food which meets their dietary needs and food preferences for an active and healthy life. Household food security is the application of this concept to the family level, with individuals within households as the focus of concern. Food insecurity, exists when people do not have adequate physical, social, or economic access to food as defined above"[3]. Food insecurity is a manifestation of vulnerability, which is a high probability for people to "be exposed to risk without having the resources to cope with the situation without damaging economic, social, physical, cultural or political losses" [4]. Hunger is "[t]he uneasy or painful sensation caused by a lack of food... The recurrent and involuntary lack of access to food ... Hunger may produce malnutrition over time ... Hunger ... is a potential, although not necessary, consequence of food insecurity" [5] and obviously afflicts some of the homeless even in developed countries [6]. Food insecurity and corruption

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restricting access in developed and developing countries using the Corruption Perception Index are not discussed in this chapter [7].

Older adults

The term *older* is used here in the context of the English meaning, but scientifically speaking, biological, social, chronological, and cosmic aging exist as does the space in which it takes place [8]. Here, we consider aging as part of the process of senescence (natural aging) or senility (predisease or during disease) [9], though the difference between the two states is often difficult to establish because of the experimental designs and associated methodologies that often focus on the duration of study and required outcomes and confounding factors. In the older adult, food insecurity may affect sleep quality and therefore is a health risk [10] as a result of psychological stress and desynchronization of body rhythms, which may be especially important in older patients with neurodegenerative diseases. Food insecurity, as would be expected, is associated with worse medical outcomes for hypertension, diabetes, human immunodeficiency virus (HIV), and depression in low-income veterans who participated in the Veterans Aging Cohort Study [11]. Even suicidal ideation appears to be associated with food insecurity [12]. It is interesting to note that middle-aged and older people in Puerto Rico have a faster cognitive decline in cases of food insecurity than in a food-secure group [13].

Feeding/food

This term *food* refers to what is eaten. It also embodies actions associated with the timing and frequency of meals, the role of caregivers [14], their perception of a healthy diet [15], and the patient's dietary or nutrient intake [14], such as knowing when to "give in" or "step in" with the patient at mealtime [16], especially in hospitals and nursing institutions [16], with restricted dietary intake and potential beneficial changes to longevity [17,18]. Such actions are conducted to optimally add "years to life" and "life to years." They may give way to perhaps to perceptions of dietary composition and health, with benefits to physical and mental health outcomes, which are the underlying topic of this chapter. Before leaving this section, it is important to consider flavor-nutrient learning and whether we can be trained to increase our satiety based on the energy content of food alone, using orosensory matched food, and to assess whether there are cultural differences, for example, Samburu (Kenya) versus U.K. participants [19]. Childhood patterns of food may reveal feeding characteristics of the older adult. In HIV/AIDS communities food security may befall the grandparents providing for grandchildren [20]. In certain areas of the world, food insecurity is influenced by water availability for agriculture. Agropastoral or pastoral livelihoods are found in well-known areas of the world but also in unexpected areas, such as the port of Turbo, the capital of the Urabá region of the Antioquia Department, Colombia, which is located on the coast of the Gulf of Urabá [21].

Overview

This overview is based on searches of Medline Ovid, PubMed (over 700 selected reference limited mainly to the years 2000−17) at Durham University, and related databases, such as Web of Science, using Boolean operators with terms in the title and keywords to narrow the search and Google search engines based on the keywords in the abstract and to retrieve the full reference papers.

Background

The subthemes are intended to provide a general sense of food security in the older person for the main body of the overview nested in examples of developing, developed, and transition countries of the world.

Scope

The food security needs of older adults, (not including those of refugees, such as Palestinians [22], or displaced persons [23], which are not substantially covered in this overview) are different depending on country. For example, contrast Ethiopia [24,25] with South Africa [26] or Iran [27] with Taiwan [28]. Also contrast people living in long-term care homes [29] in rural or urban communities, those in developed or developing countries, and those with cognitive impairment or other health problems. Indeed, older adults are heterogeneous in their functional food requirements, which should be borne in mind throughout this overview [30]. Those with sufficient mental capacity have a common feature, which is a fear of living with hunger and perhaps is associated with cognitive decline [13] and other premature health problems, which are discussed in the context of health promotion.

Food access

In a global context, insufficient data exist to accurately estimate food nutrient supplies [31], for example, in Southeast Asia [32], but traditional foods have largely been maintained in preference to Western-style snacks in Philippines, Malaysia, and Indonesia (among people aged 18−77 years) [33], and consumption of healthy foods is so critical in many countries that issues of food labeling pale into insignificance [34]. This is also the case for food placements and price reductions in retail outlets [35], although food and environmental policies should be considered by all countries [36]. Much research has been carried out on accessibility of food retail outlets in developed countries such as the United States, where shopping frequency and perceptions of healthy food availability may be relevant [37] beyond the distance to the supermarket [38]. Also important is how households cope with impending crises, particularly in sub-Saharan Africa [39]. Poverty is very important and has been discussed by this group elsewhere [40] and is complemented herein for the United Kingdom [41].

Cause and effect of food insecurity

Furthermore, attempts to define cause-and-effect relationships concerning nutrition and behavior are difficult but offer guidance [42] using strong, medium, and weak models of nutritional behavior. However, there is not a practical usable universal model for all, as this presentation demonstrates, owing to the diversity of socioeconomic factors and nutritional environment and the difficulties associated with categorization and standardization, for example, in Latin America (counties where Spanish and Portuguese are the predominant languages) [43].

Sociodemography

Globally, food and housing security [44] and insufficient sleep generating psychological stressors and poorer mental health [45] need to be understood in sociodemographic and socioeconomic contexts [46] such as ethnicity (Aboriginal and Torres Strait Islander peoples [47], Inuit people [48], Native American reservation dwellers [49−51]) and disability [52], and the ability to measure determinants [53] such as food, stress, and social gradient (see the Republic of Ireland [54]), social support [55], transport [56], and residents of care homes with dementia [29] with validated tools (see, e.g., Thailand [57]) or indicators of food insecurity (see, e.g., South Africa [58] or New Zealand [59]).

Food intervention and health

In South Africa, as in New Zealand, with a possible link between psychological stress in both sexes and food insecurity [60], food intervention could be used to treat mental health, as there is a strong association between DSM-IV (*Diagnostic and Statistical Manual*, 4th Edition) psychiatric diagnosis and food insecurity, and age (see Tables 1 and 2 of Sorsdahl et al. [61]). For example, in the United States, living in a household with food insecurity has been associated with poorer self-reported health outcomes and mental health than those with food security. Also, healthcare utilization is higher in food-secure households compared with food-insecure households [62]. From a body mass index (BMI) perspective, in Northern California [63], little is known exactly about how the distribution of retail outlets affects BMI [64] of the older adult; the same applies to a study from Melbourne [64]. BMI is just one component of healthy living, particularly for people with type 2 diabetes [63]. Food insecurity may be related to glucose control, but the relationship is difficult to define except that people who participated in the Supplemental Nutrition Assistance Program (SNAP) in the United States had better glucose control [65].

Good access to retail locations and healthy food may slow the development of atherosclerosis in middle-aged and older men [66]. So the concept and consequences of urban food deserts have been raised, and solutions have been sought [67]. Predictors of food insecurity have been investigated (e.g., Medicaid, lack of money, food prices, renting one's home rather than owning) as adjudged by the La Crosse study in Wisconsin [68] and high levels of food insecurity are associated with cost-related medication nonadherence in older adults of mean age 74.6 years [69]. Notably, a good food junction cooperative grocery store was implemented in Saskatoon [70], but implementation of grocery stores in food deserts, such as Philadelphia, even given food awareness, might not improve healthy eating [71] unless food prices for high--quality items approach those of junk food items [72]. As an aside, food insecurity is more common in those with migraine in Canada [73]. Food security may also be important in antiretroviral programs [74]. Using kernel density methods [75], those living in a higher-density area or one of high density healthful food venues may have a lower BMI when stable cohorts are followed up, but the underlying cause may be increased physical activity but also social inequalities [76] or associated factors, such as amount of time since retirement age [77].

Use of satellite technology in production and consumption

Global positioning systems and mapping of fertilizer position for maximum yield and minimum fertilizer usage [78] and forecasting weather conditions using synoptic satellite systems [79] help production. Mapping food outlets in a domiciliary environment is a useful tool [80] in obtaining valid and sufficient objective data to help understand consumption patterns.

Traditional plants and diets

In developing or transitional countries, food security is generally based on modern agriculture, but it is important also to investigate the nutritional value of other plants used in traditional or past times, such as *Senna occidentalis* Linn. (see, e.g., Tables 1−3 of Nnamani [81]). Similarly, the use of edible traditional weeds in Zimbabwe [82] particularly supports income for women [83]. This overview now focuses on international examples of factors affecting food insecurity in developed and developing countries but not on nutrition in general, for example, the leveling off of nutritional composition between Northern Europe and the advantageous Mediterranean diet [84] or all of the tribal populations, such as the older Yoruba of southwest Nigeria, where women may be more vulnerable than men [85].

Near-horizon advances for the 21st century

Cellular meat production, urban horticulture (e.g., the Siyakhana Project in Johannesburg [86]), and the dislike in Western cultures of eating insects are not discussed further [87]. As the earth becomes hotter and drier and CO_2 production increases, we may see a reversal of the evolutionary C-3 to C-4 photosynthetic pathway and the need to bioengineer plants such that C-4 and crassulacean acid metabolic traits of tolerance to high temperatures, higher yields, and resistance to drought and salinity can be encoded into C-3 plants [88]; this is part of climate change and is not discussed further in this chapter.

Results

Food security in developing countries

Brazil

Though not explicitly for older adults, the Bolsa Família Programme (BFP) Household Budget Survey [89] was conducted in 2008−09 by the Brazilian Institute of Geography and Statistics among low-income households (monthly per capita income less than R$210.00, $N = 11{,}282$), of which 48.5% were beneficiaries of the BFP; the rest were nonbeneficiaries. The beneficiary group received, on average, R$20.20 (i.e., 20.20 reals) per capita per month, and food consumption was categorized into groups using the ANOVA method [90] as follows:

- Group 1: *In natura* or minimally processed foods, such as rice, beans, cassava flour, wheat flour, pasta, meat, milk, eggs, fish, fruits, vegetables, roots, and tubers
- Group 2: Processed culinary ingredients such as substances obtained directly from Group 1 or from nature by processes such as pressing, refining, and/or milling and usually used in home or restaurant kitchens to prepare, season, and cook Group 1 foods
- Group 3: Canned or bottled vegetables, fruits, and legumes; salted, cured or smoked meat; canned fish; fruits in sirup
- Group 4: Ultraprocessed food and drink products, such as carbonated drinks, pizzas, and margarine

Twelve months after the start of the study, the beneficiaries had 115.5 kcal higher total food availability. The major part of this food purchase was *in natura* or minimally processed foods. The take-home message was that with a little assistance, low-income households were able to spend more on food and consume better-quality and more diverse foods such as vegetables, particularly in the *in natura* group. In Campinas, São Paulo, food-insecure families had older members with low income and low levels of education, whereas in food-secure families the older members contributed to family income [91].

Chile

In the Greater Santiago area of Chile, medium-low-income and low-income residents ($N = 344$; aged 65−74 years) took part in a socioeconomic, demographic, nutritional, and food insecurity cross-sectional observational survey. The

perceived food insecurity was highest in the low-income families, especially in relation to the number of people in the home [92] (full article in Spanish).

China

The Baidi village of the Naxi is at 27°30′ to 27°28′N and 100°01′ to 100 05′E, in the northwest of Yunnan Province, China, in the foothills of the Himalayas. The Naxi are a traditional people whose diet includes wild plants. The main plant family is Rosaceae; however, the authors of the Baidi study documented 173 wild edible plant species from 76 plant families. Species that were consumed as food supplements included *Cardamine macrophylla*, *Cardamine tangutorum*, and *Eutrema yunnanense*, of good nutritional value. Opportunities exist for product marketing similar to that done for wild plants from Takht-e-Sulaiman in Pakistan, including reversing the knowledge decline in the younger generation at Baidi [93].

Costa Rica

Another problem in assessing the impact of food insecurity on health outcome is the ethnobiological, nutritional and socioeconomic transitions that occur while adapting to modern societies in food consumption patterns. For example, among the Ngabe people of Southern Conte-Burica, Costa Rica, the preference for store-bought food rather than culturally grown food is high, probably reflecting state global activity as assessed by interviews and workshops ($N = 72$ from 35 distinct households) [94]. No discussion of older adults and health and food insecurity was apparently undertaken except that 10 older participants provided information on changes in agroculinary practice.

Ecuador

In 2011 the World Food Program implemented a six-month study of Colombian refugees and Ecuadorean low-income families in seven urban areas in the provinces of Carchi and Sucumbios, Ecuador, in the form of food transfers equivalent to U.S.$40 per month. The food transfers consisted of lentils, rice, canned sardines, and vegetable oil distributed from local warehouses. Food vouchers could be exchanged in supermarkets. The study of intimate partner violence, predominantly aimed at women, were assessed 21 months later using a mixed methods approach; the schema is illustrated in Figure 2 of Buller et al. [95] and the conclusions were that women's well-being was improved through a reduction in violence and the household was happier.

Ghana

Older women ($N = 59$; 60−92 years) with poor eyesight and teeth in rural villages in the Ashanti region of Ghana are at risk of the paradox of undernutrition (41%) and overweight/obesity (17%), illustrating the need for health promotion using anthropometric techniques [96].

India

Wilson et al. have published a detailed account [40] of therapy in India that embraces agriculture (food and water) at the government, community, and individual levels, though they do not specifically discuss food insecurity of older adults. Older adults in India receive substantial improvements in social security through old-age programs because traditional support is waning and state-based systems are providing a measure of support in retirement benefits, but more needs to be done, especially in rural areas [97]. Data on food security and estimates of health prevalence in urban areas and elsewhere in India can be obtained even when the participant is deceased [98] and used in conjunction with dietary guidelines [99].

Iran

In a systematic review and metaanalysis of 31 studies on food insecurity, a household prevalence of 65% in the older population (95% confidence interval: 44%−86%) was estimated, which is high, illustrating the need for priority programs in low- and middle-socioeconomic-level households [27]. In women in the age range 25−65 years who participated in the Teheran Lipid Glucose study, cultural aspects, food access, and food preferences were barriers to a healthy diet [100].

Mexico

In Mexico a study of 6790 participants, aged 60 years and older, from 6591 households demonstrated that household food insecurity was associated with low weight. The prevalence of food insecurity was greater in native-speaking households, rural households, and those who were receiving food aid benefit [101]. Therefore policies should recognize these areas for possible intervention, particularly for older adults.

The Middle East

Elsewhere in the world, such as the Middle East, food insecurity may stem from inadequate micronutrients such as iron, vitamin D, and folate as well as the generally better-known dietary components in the developed world, which tend to be less known elsewhere. This can be remedied through public and private initiatives [102]. In a Lebanese rural settlement of Bedouins, food security is governed by agricultural practices, which should be supported [103].

Mozambique

Mozambique is a country with high food insecurity and epidemic proportions of HIV infection. Food insecurity is a risk factor for nonadherence to antiretroviral therapy as part of the government's Positive Prevention Programme [74]. The situation is similar in Honduras [104] and Peru [105]. Food insecurity is also a factor among the urban poor in relation to risky sex practices and HIV in developed countries, for example, in San Francisco, California, in the United States [106] and in British Columbia in Canada [107].

Nepal

Information on wild edible plants, which can improve food security, was collected from focus groups in Nepal and found to be 81 species, of which 74 were angiosperms. Traditional knowledge is waning, and habitat is threatened by erosion; unexpectedly perhaps, it is the younger herdsmen who are most knowledgeable [108]. This is contrary to the typical situation with traditional knowledge elsewhere in developing or transition countries, as in Mundimitar [109], in the Molise region of southeastern Italy, and is discussed elsewhere in this overview, such as in the discussions of Nigeria, Costa Rica, Pakistan, and China.

Pakistan

Another type of agroculinary practice that promotes food security is the use of traditional wild food plants for survival and transitional generational change due to declining knowledge as a result of exposure to other ecological zones, surrounding vegetation, and population age. An example comes from the indigenous inhabitants of the Thakht-e-Sulamian hills in North-West tribal belt of Pakistan, situated between the east of the Iranian plateau and the Asian subcontinent (at approximately 31°N and 70°E) at high altitude and with little agricultural land. There is definitely potential for domesticating, harvesting, and marketing of these wild plants which are often highly nutritious in terms of fiber, minerals, and fat, and this pattern is not uncommon elsewhere around the globe in mountainous regions. In Thakht-e-Sulamian, 51 wild plant species belonging to 28 families were reported. Rosaceae was the dominant plant family, July was the peak month for availability of wild plants, and fruit was the was the most commonly consumed part of the plants. The most cited species were *Amaranthus spinosus* and *Olea ferruginea* with the largest number of species and highest frequency of citation. Food security can be supported on the basis of knowledge of wild plants [110].

Rwanda

The Partners in Health Food Security and Livelihood Program was launched in Rwanda, and 600 households in three rural districts (Kayonza, Kirehe, and Burera) took part to assess whether a food security program executed in areas of severe food poverty in 2013 could improve food security. The outcome was positive. Household Food Insecurity Access Scale scores and Household Food Consumption Scores were measured at baseline, and after one year of program implementation these outcomes were improved, providing an example to other places in the world where government or nongovernment organization initiatives could be successful [111].

Tanzania

In 2012 in the Rufiji District of the Pwani Region of Tanzania, the Health and Demographic Surveillance System (established in 1998) monitored over 100,000 people (approximately 20,000 households) [112]. However the emphasis

appears to be placed on maternal and child health rather than food insecurity in older adults, although food insecurity was linked to the number of days that household members were ill. This is not discussed further; neither is hunting success in relation to food security in households of younger Hadza men [113].

Uganda

A cross-sectional survey of Ugandans [114] in the Gulu Health and Demographic Surveillance System from September 2011 to June 2013 assessed their sociodemographic characteristics, food security, smoking, and alcohol intake. Part of these findings was that older men (>55 years) were significantly underweight, were divorced or separated, and smoked. Findings for women were similar for underweight only. The hunger gap was in the rainy period from May to July. Food security needs to be strengthened in the rainy season and for men, possibly for loneliness. The hunger gap period is one in which food from last year's harvest runs out before food from the current year's production can be accessed. Refugees can exacerbate this delicate balance, such as refugee settlement in the Diffa region in southeastern Niger [115]. Of relevance also is the "coping with crisis" strategy for example, in households in pastoral or agropastoral communities. The latter have less diet diversity and, with households headed by persons over 65 years of age, are more vulnerable to food insecurity [116].

Food security in developed countries

Australia

Older adults (age ≥65 years) are the fastest-growing group in Australia; the prevalence is expected to be 24% by 2036 [117,118]. In a cross-sectional cohort of the Blue Mountain Eye study of Australians ($N = \sim 3500$, age >49 years) the results showed that the prevalence of food insecurity was greater in women (15.7%) compared with men (9.4%) and in younger men (age <70 years) (15.7%) compared to older men (age ≥70 years) (8.4%) [119]. The main reasons for food insecurity were living in rented accommodation and living on a pension. Therefore it is anticipated that there will be an increased demand of government resources to cover older adults' increase in social and medical needs. Furthermore, where the proportion of healthier grocery stores is higher in comparison to unhealthy ones, consumption of fruit and vegetables is higher [120]. A study based in Melbourne demonstrated that cost, inability to lift, and access to a car for food shopping governed food access in households with a low socioeconomic position [121]. A cross-cultural study of Macedonians, Anglo-Celts, Serbians, Maltese, and so on, aged between 58 and 85 years and living in the Shire of Melton, within metropolitan Melbourne, Victoria (total $N = 37$), provided data designed to elicit themes and subthemes from focus groups on food security barriers and found that cost, transport issues, health and physical factors, and availability of preferred food were barriers to food security [122]. In a study of community-dwelling older Australian adults ($N = 8881$, age ≥65 years), 1 in 50 reported food insecurity over a one-month period in New South Wales due to insufficient finances, poorer health, gender, and age [123].

Canada

In Canada there was a very wide spread of food insecurity across the country from ~10.6% (Saskatchewan) to 46.8% (Nunavut) depending on location and ignoring Ontario, Labrador, Newfoundland, and Yukon, which did not provide data [124]; this may be influenced not only by accessibility to food outlets but also by the time spent in the home, for example, in the city of Toronto [125]. In a Canadian Community Health survey of a younger age range population (19−70 years), 6.9% of those who were food-insecure had a significant mental health problem, and intervention may alleviate this poor mental health [126]. Indeed, changing food security may well improve health outcomes [52], including mental health.

A recent large ($N = 12{,}377$) Canadian study, based on data from the Canadian Community Health Survey Cycle 2.2, generally was inconclusive about the BMI and overweight associated with people who ate breakfast compared with non-breakfast eaters, but the cohort had a large age range (≥18 years), and it was a cross-sectional study. When older men or women (≥71 years) were examined, lower odds ratios were found for ready-to-eat cereal consumption (females: 0.58, males: 0.84; reference: no breakfast = 1), but the 95% confidence intervals were large, substantially straddling unity [127]. Among the Inuit in Ulukhaktok, Northwest Territories, settlement single women were at greater risk of food insecurity than single men, and families were better placed than single people [48]. However in large communities such as Iqaluit (which had a population of 7082 in 2016), the territorial capital of Nunavut, the findings of food insecurity may not apply [128].

In a cross-sectional self-reporting survey, data from the 2009−10 Canadian Community Health Survey ($N = 100,401$) showed that the prevalence of mental illness was higher in both men and women, exacerbated in situations of high stress and social isolation, and in cases of severe food insecurity compared with food security [55]. Canadian community food interventions comprise traditional and alternative forms; traditional interventions are akin to food banks to alleviate hunger, whereas alternative interventions include collective kitchens and community gardens and are described in more detail elsewhere [129,130]. Traditional interventions seem to focus on people who have less access to resources than alternative interventions; alternative interventions are more focused on nurturing solidarity and creativity along the lines of social justice, but the age range is wide, and those over 65 years of age were excluded, and this study is discussed no further [131]. The Dene nation, who are Athapaskan speaking, live in the subarctic region in the West of Canada and depend on location to feed on caribou; they live in small family groups, are often hungry, and have infectious diseases and so are vulnerable to seasonal food insecurity, especially lack of vitamin D [132]. Concern is also expressed about reduced food intake in Calgary's main adult diabetes clinic, where, perhaps because of financial constraints, people are unable to manage their diabetes effectively [133]. Despite programs designed to support older Canadian adults in moving out of food insecurity, changing the age of public pension from 65 years to 67 years of age may do the reverse [134].

Canada and France joint study: older population

A dietary study compared two populations that have a common ancestral background and whose diets were similar except that the North American arm was influenced by its dietary patterns. The first population was in France (three cities: Bordeaux, Dijon, and Montpellier), comprising 9294 community dwellers aged 65 years or older selected from the electoral rolls. The baseline year was 1999−2000; the follow-up year was 2001−02 (wave 1),) which was a 12-year longitudinal study designed for investigating vascular risk factors for dementia: the Bordeaux cohort was only used in wave 1 ($N = 1712$). The second population was randomly selected from Quebec's Medicare database and stratified by age and sex as part of the NuAge study, which was a four-year longitudinal study (age = 67−84 years, $N = 1973$, in this study 1596) in 2003−05 designed to assess the role of nutrition in physical and cognitive status, functional autonomy, and social participation [135]. The diet quality was assessed by the Canadian Eating Index [136] (see also [137]). The higher the index, the better the quality. Higher education and nonphysical occupations over a lifetime were associated with healthy patterns in the France and Quebec arms. Living alone, BMI < 25, and being an ex-smoker were associated with the healthy category in the NuAge study. The two healthy patterns showed important similarities, with adequate food variety, consumption of healthy foods, and associations with common sociodemographic factors [138].

The former Soviet Union

A cross-sectional study of fruit and vegetable consumption, as part of the "Health in Times of Transition" project, of nearly 18,000 participants in 2010, some 19 years post Soviet Union, (aged 18−95 years) from Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Russia, and the Ukraine [139], was undertaken using WHO/FAO guidelines [140]. As might be expected, older males of low education and lack of financial resources had lower fruit and vegetable security; food security for these commodities was positively associated with the availability of shops for women. In the Suntar region of western Sakha, northeastern Siberia, the older person's elders from Kutana [141] interact and share their agropastoral knowledge with younger people. Focus groups from four villages framed this knowledge into planning a sustainable future.

Japan

Mayoral support from prefectures in Japan, for example, Hokkaido, Aomori, Saitama, Niigata, and Yamaguchi, and the use of geographic information system tools and socioeconomic and accessibility indicators comprising a self-reporting questionnaire enabled the study of the single older (65−90 years) person's food insecurity in terms of how far they lived from a supermarket (0−500 m, 500−1000 m, >1 km). As would be expected, food insecurity is governed by risk factors associated with inaccessibility of food outlets, for example, poor walking ability (~ 1 km), no car ownership, poor eyesight, and no one to help, as adjudged from a seven-city/town study of some 2028 people (725 men and 1303 women) who completed a questionnaire [142]. A limiting factor was the very approximate 50% response rate due to the postal service and poor eyesight.

Korea

In older Koreans the relationship between cognitive function, anthropometric data, and dietary intake was assessed in randomly selected free-living individuals (210 men, 239 women, age ≥ 60 years) [143]. The outcome variables were Kwon's Mini-Mental State Examination for Koreans (MMSE-K) with modification [144] for cognitive function test, 24-hour dietary recall method, food behavior, anthropometric indices, and health variables [143], and the results showed that the prevalence rate of the poor cognitive function group (PCFG) (MMSE-K score: ≤ 19, normal cognitive function: ≥ 24) was higher in women (31%) compared with men (12.3%), and cognitive capacity was negatively associated with age and higher education. When compared to the normal cognitive function group men in the PCFG had a significantly ($P < .05$) lower consumption of intakes of fruits, fiber, and vitamin C, whereas corresponding data for women were lower intakes of total amount of foods, cereals, vegetables, fruits, milk, spices, and energy, protein, fat, carbohydrate, calcium, phosphorus, iron, vitamin A, thiamine, riboflavin, and niacin. The MMSE-K score for females exhibited a positive correlation with total amount of foods, cereals, beans, fruits, milk, oil, spices, and energy, protein, fat, carbohydrate, calcium, iron, phosphorus, riboflavin, and niacin intakes [143]. However, good Korean health promotion should recognize people with chewing difficulties [145].

Data from the Fifth Korea National Health and Nutrition Examination Survey, covering 2010–12 ($N = 15{,}603$, 8898 households, age >19 years), showed that less protein and more carbohydrates were consumed by people with severely insufficient food intake. Consumption of meat, fish, eggs, beans, vegetables, and fruits was significantly lower as the food insufficiency level decreased. Food group consumption also differed by sex. Overall eating and health behaviors were poorer in the mildly and severely food-insufficient groups, who received more food assistance but less nutritional education [146]. Perhaps an obvious conclusion is that food insecurity for a representative Korean sample is associated with reduced dietary intake of healthy foods and nutrients [147].

Portugal

Solitary older adults (age ≥ 65 years) from the Portuguese Household Budget Survey from 1989/1990 ($N = 1967$), 1994/1995 ($N = 2219$), 2000/2001 ($N = 2533$), and 2005/2000 ($N = 2441$), though not stratified for categories of food security, demonstrated that "cereals, fats/oils, potatoes and sugar/sugar products decreased.". The highest food value was for couples, and the lowest was for solitary men; solitary women consumed more fruit and vegetables, and solitary men consumed over time more sugar and alcoholic beverages. There were, of course, exceptions. However, over time there may be a decrease in diet quality [148].

Singapore

Data on Singaporeans ($N = 465$, aged ≥ 55 years) who received public assistance showed that those older than 75 years were at risk of malnutrition, were unmarried, had impaired basic attributes of active living (similarly those in nursing homes), and should be part of a nutrition and food services and education program [149].

Switzerland

In the high-income country of Switzerland, adherence to healthy eating guidelines has been low, and of the six barriers to self-reported healthy eating (taste, price, daily habits, time, lack of willpower, and limited options), only the prevalence of taste, price, and time have been over 30%. The data were reasonably stable over 15 years follow-up but largely independent of age, sex, income, and education [150].

The United Kingdom

In the United Kingdom, residents appear to interact with the food environment of supermarkets in four different ways, that is, chaotic, working around the store, item by item, and restricted and budgeted [151], as adjudged from a qualitative study of 26 residents (18–70 years of age) at Sandwell, West Midlands, of whom 20 were Caucasian and over 30 years of age. However, the sample was small, bearing in mind paid employment, ethnicity, sex, the source of recruitment, and visits to multiple stores. Little information is available on the proximity of healthy food outlets to place of work, as in the Socioeconomic Status and Activity in Women survey of women in Australia [152].

Identification of areas of poor food retail provision, known as food deserts, is important. Major advances to reach this goal were described by Donkin et al. [153,154], using a geographic mapping technique to generate availability and price indices of "healthy" food items. Wrigely [155] used the concept of food deserts to illustrate the social exclusion and health inequalities of low-income households in poor neighborhoods and the research policies that needed to be addressed by the U.K. government. Clarke et al. [156] extended this work to identify areas of shopping flows and food

access to two centers—Leeds/Bradford (joint) and Cardiff—using a local mapping approach and a citywide modeling approach [156] to assess the impact of the opening of new retail outlets, which is important in planning and interpreting health promotion issues. The development of urban model-based accessibility performance indicators has been reviewed by Bertuglia et al. [157]. Clarke et al. [156] used customer interactions with grocery outlets to identify food deserts, which involve poor access not only to retailing but also to high-quality food. More research is needed, especially mapping epidemiological layers relating to oxidative stress and associated diseases, such as cardiovascular disease, diabetes, and mental health, onto food access and implicating time both within a growing dynamic framework of food provision and the life-course characteristics of the individual, for example, the older adult.

The United States

Food insecurity is more complicated that purely a matter of access. It also depends on the mix of retail stores and racial-ethnic group choices. For example, in another longitudinal study based on food package purchases recorded in a U.S. National Consumer Panel database from 2007−12 and cluster analysis [158], non-Hispanic African American households purchased foods with higher energy, total sugar, and sodium densities than did non-Hispanic White and Hispanic households. In a Salt Lake City, Utah, study program [159], low-income participants aged 18 years and older ($N = 96$) receiving SNAP benefits and participating in the Double-Up Food Bucks program at the Salt Lake City Downtown Farmers' Market for fruit and vegetables only were assessed by using a pretest/posttest based on a 28-item survey, which had 16 questions on demographics, fruit and vegetable consumption, food security, food assistance use, and shopping habits. The results indicated improved food security; similar results were found for a scheme in San Diego [160]. Food environment is related to severe food insecurity [161].

In the United States, in certain states, the older low-income person is often beset by high medical costs, but those requiring food assistance and who are on Standard Medical Expense deduction can benefit [162]. In Oregon the Housing Choice Voucher Program helps very low-income families and single older adults to rent or buy safe housing, and it has been found that food insecurity (and homelessness) is lower and income higher than those of comparable persons who have applied and live in public housing, which is a health promotion issue [163]. It would appear that there is a race difference in homebound older adults (see Tables 1−4 of Sharkey and Schoenberg [164]), with Blacks worse off than Whites in North Carolina.

Food insecurity is a nutrition-related factor that paradoxically coexists with obesity among low-income individuals, but data from a cohort of older adults in New Jersey (aged 50−70 years; $n = 5688$) found that obesity appeared to be related to the density of fast food and storefront outlets, as in a study of low-income individuals in Belo Horizonte in Brazil [165], rather than supermarkets [166]. Lack of supermarket patterns of food insecurity by income and low income with fewer fast-food outlets was found for Copenhagen [167] and the United Kingdom [156].

From 21,000 participants in the National Health Interview Survey (2011−12) in the United States, researchers extracted those who were 60 years of age or older, had a federal poverty level of 1.99 or less, and a BMI of 18.5 or more, and those who provided information on a list of covariates were stratified according to sex, such as ethnicity ($N = 5506$; 3519 females, 1987 males). Food insecurity was defined as lack of availability or access to healthy food through ill health and lack of resources. It was found in women but not in men that there is a paradox: that food insecurity is positively associated with BMI (see Table 2 in Hernandez et al. [168], confirming findings of a previous study in Texas [169]); although poor health status was a covariate, a cognitive assessment was not apparently one of these variables. In central Texas in an older age group (50−59 years) and those 60 years and older (seniors), being a woman, being Black, being perceived as being worse off than others, having lower social capital, and having a low income were associated with greater food insecurity in a largely rural community [170]. However, in a national study, food insecurity ($N = 1851$; 60−85 years of age; excluding cardiovascular-related diseases) was positively associated with cognitive decline as measured by the Digital Substitution Symbol Test [171].

Other aspects of poor health may be related to disease progression and food insecurity, such as those with chronic kidney disease having end-stage renal disease, as assessed by a longitudinal study outcome [172], (e.g., very high food insecurity and increased 10-year cardiovascular risk in those age 30−59 years [173]), albeit in a younger age range ≥ 20 years. Those with chronic kidney disease ($N = 2320$) and food insecurity were likely to have more diabetes, hypertension and albuminuria, or peripheral arterial disease [174] and had a higher risk of end-stage renal disease compared to a control group ($N = 10{,}448$) when these participants in the Third National Health and Nutrition Examination Survey (NHANS III) were followed up for a median duration of 12 years. In Louisiana, participants older than 59 years (SD = 14 years; $N = 98$) undergoing hemodialysis had food insecurity (16%); 64% were mildly to moderately malnourished, and 13% were badly malnourished [175].

Household-rented abodes are likely to be an indicator of food insecurity in comparison to home ownership, and the high cost of heating and cooling homes may also make a contribution [176]. However, groups of vulnerable house owners may experience precarity in terms of economic instability, such as recession, for example, in Canada [177] and in the United Kingdom pending Brexit [178]. Home ownership policies may be important in food security, particularly in the United Kingdom with Brexit.

In the United States, malnutrition is a problem affecting three million people who are rarely identified by healthcare providers, owing to lack of screening [179], so emergency departments are a valuable source of older participant material. Cross-sectional observational data on noncritically ill older adults (≥65 years) from three such departments in the South, Midwest, and Northeast ($N = 252$) included risk factor assessment for depression, restricted mobility, loneliness, lack of transport, and side effects of medicines, qualified by whether the patient reported that the risk factor affected their diet. A population-attributable risk proportion for malnutrition was estimated for each risk factor, and food insecurity was 12%, adjudged to be an identifiable modifiable dietary component as a potential intervention in older adults [180]. Patients attending emergency departments in Boston from food-insecure households reported more chronic and mental health problems and had difficulty paying for food or medicine [181].

Childhood food insecurity and hunger may lead to impulsive behavior problems, such as violence and crime [182]. It has been reported that food transfer programs in northern Ecuador reduced intimate partner violence [95]. It has been reported that household psychological stress has been reduced in beneficiaries of the SNAP [183] and that increasing depression is associated with increasing household food insecurity [184]. Similar results were reported in North Carolina in older adults aged 60−74 years [185]. This relationship was also found in other U.S. cohorts (aged 30−70 years), for example, in a randomized control trial in King County, Washington [186]. Furthermore participants in SNAP may not receive health benefits in the short term [187]. Food insecurity is also linked to obesity and poorer control of type 2 diabetes (mean: 9.8 years; mean age: 54 years) in low-income Latino agricultural communities, for example, in the San Joaquin Valley in California [188].

The Older Americans Act Program serves the community by supporting older adults at home. These people, who get community-delivered and home-delivered support in the form of meals (from public and private sources) are poorer, more sick, and more at risk of being institutionalized than other older Americans [189] (e.g., Georgians [190]). Meal delivery programs provide benefits [191] and, for the older adult being discharged from the hospital (≥60 years), reduce their anxiety [192]. Older adults are more likely to spend more on products that are labeled as having healthy eating benefits when they receive grocery vouchers than are younger men, with similar results for older women and older men [193]. This could possibly be aided by a "Choices" nutrition logo in supermarkets, as in the Netherlands [194].

In older adults in NHANS III ($N = 4731$; age ≥ 60 years), frailty was evaluated on the basis of four criteria: slow walking, muscular weakness, exhaustion, and low physical activity; have two or more of these criteria constitutes frailty, and prefrailty is any one of these. Frailty, which is often associated with aging, is a state of decreased physical functioning and is a significant complication of aging. Smit et al. examined frailty with regard to energy and macronutrient intake, biomarkers of nutritional status and food insufficiency in U.S. older adult (age ≥ 60 years) participants in NHANS III ($N = 4731$). Food intake was assessed by dietary recall of frail or prefrail people who were likely to be food insufficient, a pointer to where heath programs should be targeted [195]. Walkability as a factor related to food security has been identified elsewhere (e.g., New York City [196]), as have disability and obesity-related problems in older Georgians [197]. Using qualitative interviews of older people (60−88 years of age; Black, White, Latino men and women) in Brooklyn, New York, part of a multilayered system of acquiring food via public transport was food batch size [198], an obvious point observed in post−World War II Britain, when women predominantly used bicycle panniers to transport food.

Clearly, human survival age has increased over time, and the role of food insecurity or malnutrition in intrinsic causes of death, antagonistic pleiotrophy, or programmed death is not yet fully understood. Adequate calorific intake is essential, but restricted calorific consumption may increase longevity through weight loss by timing of dietary intake, as shown by isocalorific breakfast, lunch, and dinner, from the Natick studies of Halberg's group [199]; in this case the circadian cycle is important, just as in Hippocrates' observations on timing of disease and the discipline of chronopharmacology [200,201]. In neighborhoods along the Mexico-Texan border, Mexico-born older women 50 years of age and older have greater food insecurity than non-Mexico-born women [202].

Food insecurity and homelessness

General

Homelessness is defined as the condition of not having an abode, rented or otherwise, and usually being unable to afford one. Stereotypically, with exceptions, homeless people usually live in a hostile or unsafe environment and choose

to dispose of whatever income they acquire on drugs, alcohol, and other commodities in preference to appropriate clothing, shelter, clean water, and good-quality food. Some homeless people work in the sex industry, practice unsafe sex, and are involved in criminal activities. Many have mental health problems, HIV/AIDS, and other medical problems. There is a huge variance in why people become homeless, and the media tends to focus on children and young adults rather than older adults. However, the Joseph Rowntree Foundation in the United Kingdom focuses on "inspiring social change," of which, homelessness, dementia, and aging are just part [203]. Most of the information on food insecurity and homeless people are based on research carried out in the United Kingdom, Canada, and the United States. In the United States there is a food insecurity-obesity paradox or poverty-obesity relationship [204] particularly in adult women [204]. This is also observed in Minnesotan women. In the case of the former there was a Hispanic factor and in the latter an ethnic difference in the food quality purchasing system [205]. Furthermore, coping with homelessness and hunger or food needs appear not to be exactly aligned, and Lee and Greif make four important contributions to our body of knowledge [206].

Homelessness in the United Kingdom

The BBC quoted "Shelter" [207] by saying conservatively that 268,000 people are homeless in England, which is 1 in 25 in the worst-affected areas, where homelessness was defined as "rough sleepers (4100: 1 in 206 people)," single people in hostels (21,000, including those housed by social services), and those in temporary accommodation (242,000). Homelessness is rising, allegedly in part as a result of so-called welfare reforms, by which homeless people are given one-way train tickets and forced to move away. Three in ten cases of homelessness are caused by loss of private tenancy. The government is committed to tackling all forms of homelessness. Since food security is linked to adequate housing, it is reasonable to assume that food insecurity is a problem. In the year 2016−17 the Trussell Trust, a charitable organization [208], provided over a million three-day food supplies from its 425 food banks, and it has concerns over the rise in the number of people on universal credits to 16.85% requiring emergency food compared to the national average of 6.64, and the potential difficulties that volunteer staff may have in serving future needs.

Homelessness and mental health in Canada

Studies of homeless people with mental health problems in Vancouver [for extensive details of sample size, see Table 1 (stratified by food security/insecurity, sociodemographics, healthcare utilization, mental health, substance use, physical health, other behaviors) and Table 2 (logistic regression analysis of covariates) of food insecurity in Parpouchi et al. [209]] found that they had a food insecurity prevalence of 64%, which is approximately eight times higher than that in general households in Canada [210]. There is a clear need for a health promotion policy. Food insecurity was negatively associated with age; perhaps the younger homeless were less adaptable than older people.

Homelessness and depression in families in Paris

As an aside, because of a younger population, a survey in 2013 found that 10,280 families in Paris [211] of low income (828 euros/month), 94% of whom were born outside of France, had a high prevalence of food insecurity (77% of parents, 69% of children); 30% of mothers had mental health issues, and 20% of children showed signs that mental health problems were likely to develop in the future. This is clearly a target group for intervention.

Homelessness in the United States

HIV

In the United States, in the San Francisco area, 34 structured in-depth interviews were undertaken of low-income individuals living with HIV who were received food assistance in 2014 [212]. Participants experienced food intermittency and therefore hunger and perceived poor health because of their reliance on family, friends, and charity food sources and giving sex for food, stealing, and selling controlled drugs. They had limited disability income and faced high costs of gentrification and require structured policy assistance beyond just food security. In another larger study of 346 participants living with HIV in the same area [213], food insecurity tended to be associated with depression or poorer HIV outcomes or adherence to antiretroviral therapy [214]. Food insecurity was also associated with risky sexual practices, and attention to this may reduce secondary HIV transmission [215]. Antiretroviral adherence was also impaired by poor housing and food insecurity in a study in Florida [216].

Food security and homelessness: the worst medical control

Of the 6709 participants registered in the Veterans Aging Cohort Study who have accessed health care in the time span 2000−08, 24% reported food insecurity ($N = 1624$; age = 48 years; recent homelessness <30 days = 447; by comparison with the food-secure $N = 5085$; age = 50 years; recent homelessness = 403; see Table 1 of Wang et al. [11]). Those who were food insecure were more likely to be Black, to be homeless, to have a low income (<$25,000/year), to use drugs, to have higher alcohol consumption, to have HIV, to be depressed, and to have a lower BMI than food-secure individuals. However, participants who were food secure were more likely to have hypertension and had approximately the same prevalence of diabetes as the food-insecure group. From a policy point of view, the food-insecure group is a worse control of medical conditions than the food-secure group and should be addressed. There is also evidence that homelessness and food insecurity culminate in an increased use of hospital services and need for emergency departments [217].

Food risk and health insecurity in Rhode Island

Homeless adults [6] ($N = 319$; 64% male, 36% female; aged 18 to >65 years; mixed ethnic groups; for anthropometric measures, see Table 1 of Martins et al. [6]), of whom 197 provided information on 24-hour dietary recall and food security, were measured on a six-item subset of the USDA Food Security Core module. As might be expected, 94% were food insecure, and 64% had hunger.

Discussion

This overview began with definitions of keywords used in the title, which focused on studies of food security in selected developing, developed, and transition countries that were evidence-based and illustrated key issues, which were largely not repetitive save for reinforcement. It concluded with a brief account of homelessness and food security in the United Kingdom, Canada, and the United States. It began with a structured introduction on scope, food access, cause and effect of food insecurity, sociodemography, food intervention and health, satellite technology production and consumption, traditional plants and diets, and near-horizon advances for the 21st century. According to the WHO, the number of older adults (>60−70 years) has increased continuously during the past 60 years, and the projected global increase in the older population will be 56%, from 901 million to 1.4 billion people, between 2015 and 2030. It is estimated that in 2030, the number of 80-year-old persons will become three times greater than in 2015 [218]. Although there is a worldwide increase in life expectancy resulting from the advancement of healthcare systems, improved nutrition, better sanitation, and higher socioeconomic status, older people are also facing increased incidences of non-communicable diseases (NCDs), such as diabetes mellitus, obesity, cardiovascular diseases, neurodegenerative disorders, and cancers. The NCDs not only increase healthcare costs and pose economic burdens in developed and developing countries, but also result in poor quality of life among older adults, especially in poor countries [219−221]. There is an overwhelming evidence that both genetic and epigenetic factors contribute to the occurrence of NCDs, including a number of lifestyle factors (e.g., cigarette smoking, sedentary habits), unhealthy dietary habits, heavily salted foods, sugar-loaded beverages, malnutrition, and lack of micronutrients (vitamins and trace elements). Many epidemiological studies and metaanalyses have focused on the specific food nutrients (e.g., Mediterranean-type diet), nutritional supplements, intake of functional foods and probiotics, and lifestyle modifications that slow the onset of aging and reduce age-related illnesses, consequently promoting healthy aging, longevity, and improvement in quality of life among the older population.

By 2050 there will be two billion people over the age of 60 years in the world, with increasing need for nutrition support from agencies, international institutions, and public and private organizations. Emphasis should be placed at multiple levels—individual, household/family, and community—and involve developments in the food and supplements industry, public policy, and the notion of "All-together-better," for example, linking government and local aid to food insecure older persons in the state of Georgia in the United States [222]. However, much of the available information is from the United States, so there is a need to conduct research in other areas of the world [223,224].

In the United States, about one in seven people experience food insecurity because of their low or intermittent income. A review of 19 of 65 studies found that food insecurity and obesity are positively associated in women [225]. Despite discussion of food deserts, not all studies are in accord. For example, a study in Boston showed that preferences in food deserts and in food oases were similar [226].

Food insecurity, even in rich nations, is becoming a problem that should be addressed for people of all ages [227] and in the older adult population [228], especially in the economic context to aid policymakers. Gradually, the older

adult is becoming more information technology (IT) literate, and the mass media could be a vehicle for organizations to implement policies. But 30 million Americans are functionally illiterate, that is, unable to read and write, and therefore there are constraints for those who cannot read food labels. In many countries the situation is worse, except rural communities have practical knowledge to sustain themselves, given available natural resources.

A study in Melbourne, Australia, compared objective and perceived food security, and the agreement was poor, which underlies the importance of good experiment design [229]. The spatial modeling of food outlets in urban areas must take into consideration the temporal changes in planning new retail activities. This is important in considering cause and effect of food insecurity and health issues.

Food redistribution centers are being set up in many countries of the world, especially in developed countries, but it is difficult to evaluate food insecurity in generally vulnerable groups such as those who have retired and single-parent families. Some participants "top-up" their food stocks and are heavy smokers and consumers of alcohol (e.g., in Berlin [230]). Older women in urban Thailand view food insecurity as a consequence of the global economic downturn and adapt their circumstances around food, health, money, and family, but this was a very small interview-based study ($N = 30$) [231].

The use of telemedicine education [232] to manage type 2 diabetes in rural older adults ($N = 74$; aged ≥ 55 years) living in central and northern upstate New York through the purchase and consumption of appropriate meals as part of the IDEATel project [233] found that in response to food insecurity or otherwise, both groups followed the dietician's advice and had a similar outcome based on glycemic control. The use of such technology could reach all parts of the globe, suitably adapted to organizational and political infrastructure. Use of IT and solar power is likely to benefit medical education, including food security.

In New Zealand, data from the longitudinal survey of families, income, and employment ($N = 18{,}950$) [234] conducted in 2004−05, albeit in a very wide age range (≥15 years), demonstrated that of this sample, over 15% were food insecure, and the prevalence was greater in women (19%) than in men (12%). The main predictors of food insecurity were low income, single marital status, single parenthood, lower socioeconomic group, renting accommodation, low self-reporting health status, being of Maori or Pacific ethnicity, and unemployment. The higher food insecurity may be due to women feeding husbands and children in preference to themselves, a common practice, for example, in the mining communities of South Wales in the 20th century and earlier (D.W.W. personal communication with inhabitants). Many national support programs give preference to the young rather than older people. For example, older African adults who are in urgent need of support may have to give way to children and pregnant or lactating women. Availability of resources is also affected by war, corruption, and HIV/AIDS [235].

Studies on homelessness and associated factors have generally indicated that food insecurity has had a detrimental effect on HIV treatment adherence and mental disorders and has given rise to an obesity paradox in women

Conclusion

Notwithstanding natural disasters, diaspora due to war, and climate change, each country has its own priorities, as indicated in this overview. The solutions for the problems of food security for older adults must involve multilevel organizations, institutions, and private input, which can be dovetailed to maximum effect, given available resources over a stable time span for a set of conditions. More evidence-based data on food security are needed for the developing and transitional countries and subsequent evaluation with appropriate methodologies.

Author contributions

D.W., R.S., F.D.M., T.T., and H.B. conceived the topic; D.W., R.S., and H.B. contributed to the literature; P.N. (world health) provided support on the social science of the older person; D.W. wrote the paper; substantial proofing contributions have come from P.N., H.B., and D.W., and all have received and read the final submitted manuscript.

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Section 12

Eating disorders

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Chapter 42

New choices of functional foods for modification of eating habits of children for prevention of non-communicable diseases in later life

Rie Horiuchi[1] and Toru Takahashi[2]

[1]*Department of Food Sciences and Nutrition, School of Food Science and Nutrition, Mukogawa Women's University, Nishinomiya, Japan,*

[2]*Department of Food and Nutrition, Faculty of Human Sciences, Kanazawagakuin University, Kanazawa, Japan*

Introduction

Poor diets are major risk factors for non-communicable diseases [1]. Accordingly, controlling adults' diets would decrease the development of non-communicable diseases. Diets are controllable, at least in theory [2]. However, it is difficult to control diet because food palatability does not change radically [3]. In animal experiments, favorite diets in adult rats were similar to dominant diets in their juvenile stages [4]. Hence favorite diets in adult rats seem to be controlled by what they ate in their juvenile stages. The association between food palatability in adults and eating history during childhood is still unclear in humans. Generally, food palatability develops in childhood; perception of tastes and diet preferences are learned [5]. Accordingly, food palatability in adults might be affected by their eating history during childhood [6]. This chapter showed the transition of eating history and favorite diets in the life stages, which suggest modulators of the dominant diet and food palatability in adulthood. This chapter also suggested strategies to change frequencies of ingredients of children's diets in kindergarten to control food palatability and eating habits in adulthood.

Transition of eating history and food palatability

A previous study using rats showed an association between food palatability and eating history [4]; the addition of fat to the diets of juvenile rats increased their choice to eat fat even in the adult stages. Dominant diets and favorite diets in adulthood might be connected with those of the childhood even in humans. Accordingly, the transitions of dominant diets and favorite diets in the life stages were investigated in female healthy volunteers with ages in their 20s using a correspondence analysis [7]. The distance between dominant diets or favorite diets and the life stage symbols on the correspondence analysis graph indicates the degree of association between a diet and the life stage of the subject [8]. If the distance between a diet symbol and a life stage symbol is short, then the dish was eaten frequently during that particular life stage [8]. Transitions of the dominant diets showed similar U-shaped curves, with ends observed at the kindergarten and university stages (Fig. 42.1). The first dimension on the graph in Fig. 42.1 could be attributed to the amount of fat in the dishes. The amount of lipids in the dominant diet increased from the kindergarten years through the younger grades of the elementary school stage; after the junior high school stage, the amount of lipids decreased as the life stage progressed (see Fig. 42.1). Similarities in the dominant diets between the kindergarten and university stages emphasize that habituation to a prudent diet in the junior high and high school years may not provide the basis needed to control the diet as an adult. Previous studies have shown that junior high and high school students enjoy Western-type diets with high fat content [9,10], consistent with our results (see Fig. 42.1). It is difficult to control the diets of students in the junior high and high school years because their preference for foods that are high in fat and

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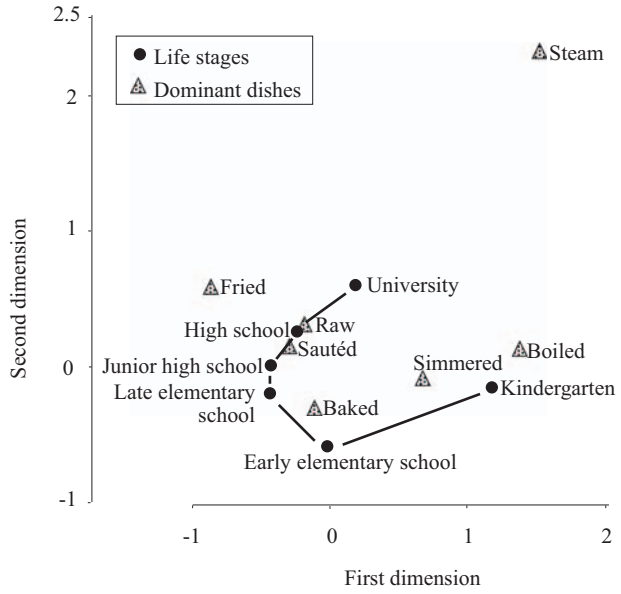


FIGURE 42.1 Associations between dominant recipes and life stages. The contributing ratio of the first dimension on the abscissa was 0.744, indicating that the first dimension can explain 74.4% of the variations (correspondence analysis). The contributing ratio of the second dimension on the vertical axis was 0.170; thus the second dimension can explain 17.0% of the variations ($P < .001$). $n = 174$. The first dimension on the panels could be attributed to the amount of fat in the dishes.

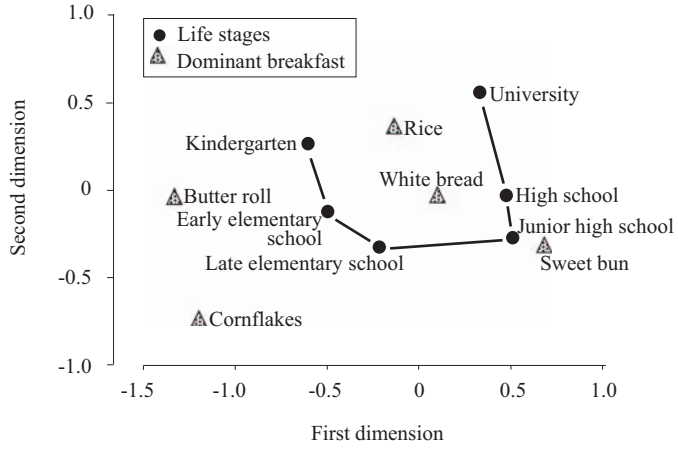


FIGURE 42.2 Associations between favorite recipes and life stages. The contributing ratio of the first dimension on the abscissa was 0.725 (72.5% of the variation was explained by the first dimension). The contributing ratio of the second dimension on the vertical axis was 0.229 (22.9% of the variation was explained by the second dimension; $P < .001$). $N = 174$. The first dimension on the panels could be attributed to the amount of fat in the dishes.

protein favors Western-type foods [11]. It may be easier to control the dominant diet in the kindergarten stage. The dominant diets were indices of eating history. The eating history in the kindergarten stage might be a modulator of the eating history in adulthood. Parents or caregivers determine the diets of children at the kindergarten stage [12]. Accordingly, parents or caregivers are typically responsible for diets of children at the kindergarten stage. Thus parents or caregivers in a sense determine their children's risk for non-communicable diseases in adulthood.

Food palatability preferences develop in childhood [5]. Food palatability preferences in adults might be affected by their eating history during childhood [6]. The transitions of the favorite diets showed similar U-shaped curves, with ends observed at the kindergarten and university stages (Fig. 42.2). The first dimension on the graph in Fig. 42.2 could be attributed to the amount of fat in the dishes. The amount of lipids in the favorite diets increased from the kindergarten years through the younger grades of the elementary school stage; after the junior high school stage, the amount of lipids decreased as the life stage progressed (see Fig. 42.2). Dominant favorite diets in adulthood were affected by those of childhood even in humans.

Food palatability preferences (favorite diets) might be affected by eating history (dominant diets) [6]. Both the eating history and food preferences in the university stage appear to be associated with those of the kindergarten stage (Figs. 42.1 and 42.2). Similar U-shaped curves in the transitions of eating history (dominant diets) and food palatability (favorite diets); this similar transition pattern was attributed to basic learning and memory phenomena [5]. Learning and memory for dominant diets would increase the palatability of the dominant food in childhood [3]. The effect of the

eating history on food palatability suggests a method of controlling food palatability in adults. Food palatability in the university or older life stages could be controlled by the dominant diet in the kindergarten stage. The dominant risk factor for death due to non-communicable diseases was diet [13]. Thus careful control and monitoring of the diet in the kindergarten stage may help to control food palatability in adults and may decrease the likelihood of developing a non-communicable disease. In this case, public health officials should emphasize and provide supplementary education on the importance of a proper diet in the kindergarten years.

Unfavorable diet in lunch in kindergartens

In Japan, almost all kindergarteners have lunch boxes, which are made by mothers or caregivers. The ingredients of the lunch boxes are a part of the children's dominant diets at the kindergarten stage. Ingredients of lunch boxes also can be associated with food palatability in adulthood. We found a severe problem in the ingredients of kindergarteners' lunch boxes using a questionnaire assessment of the ingredients [14].

Table 42.1 shows common ingredients in children's lunch boxes. The options of frequencies were "Never use" = 1, "Hardly ever use" = 2, "Sometimes use" = 3, "Usually use" = 4 and "Always use" = 5. The value of 4.5 for meat showed that mothers usually use meat, and the value of 2.7 for fish showed that mothers sometimes use fish (Table 42.1). Generally, higher frequencies of items show higher amounts of items of diets [15]. Favorable consumption of fish was same as that of meat [16]. We found much less fish consumption in lunch boxes in kindergarteners (Table 42.1), which points to one of the problems in diets in children in Japan. Very low fish consumption in kindergarteners' lunch boxes would reduce food palatability of fish and decrease fish consumption in their adulthood. Fish consumption reduced the omega-6/omega-3 fatty acid ratio in the diet [17]. Fish consumption in kindergarteners' lunch boxes would reduce the omega-6/omega-3 fatty acid ratio in their adult diet, which contribute to the prevention of cardiovascular disease [18].

Strategies to change frequencies of the ingredients for young children

As was mentioned earlier in the chapter, low fish consumption in kindergarteners' lunch boxes is likely to decrease fish consumption in their adulthood. We need strategies to increase fish consumption in kindergarteners' lunch boxes. Then we investigated factors to control or affect fish consumption in kindergarteners. We assumed causal relationships of items to affect fish consumption. We performed a path analysis to prove the causal relationship.

Fig. 42.3 shows factors to control or affect fish consumption. Use of fish in lunch boxes increased duration time of cooking lunch boxes (Fig. 42.3). Mothers and caregivers avoided using fish in lunch boxes because of the long time it took to cook fish [17]. Actually, mothers and caregivers wanted to know recipes for quick cooking of fish to be used in lunch boxes [19]. Good recipes for quick cooking of fish would increase fish consumptions in kindergarteners' lunch boxes. On the other hand, emphasizing the importance of balanced nutrition increased the frequency of fish in children's lunch boxes (Fig. 42.3). Promoting the importance of balanced nutrition to mothers and caregivers could increase the frequency of fish in lunch boxes. Good recipes for quick cooking of fish in lunch boxes and promoting the importance of balanced nutrition to mothers and caregivers would increase fish consumption in kindergarteners and thus might increase fish consumption in their adulthood, which would contribute to the prevention of the cardiovascular disease.

TABLE 42.1 Frequencies of ingredients of kindergarteners' lunch boxes.

Ingredient	Mean	Standard deviation	$P^{\$}$
Vegetables	4.6[a]	0.7	.001
Meat	4.5[a]	0.6	
Eggs	4.1[b]	1.1	
Frozen food	2.9[c]	1.1	
Fish	2.7[c,d]	0.7	
Beans	2.6[d]	0.8	

Notes: The number of mothers who responded to the food consumption questionnaire was 488. There were no nonresponders. Never use = 1; Hardly ever use = 2; Sometimes use = 3; Usually use = 4; Always use = 5.
[$] *Effects of type of food was analyzed in the food consumption using a one-way ANOVA.*
[a,b,c,d] *There were significant differences between the different signs (*$P < .05$*, Tukey's multiple comparisons).*

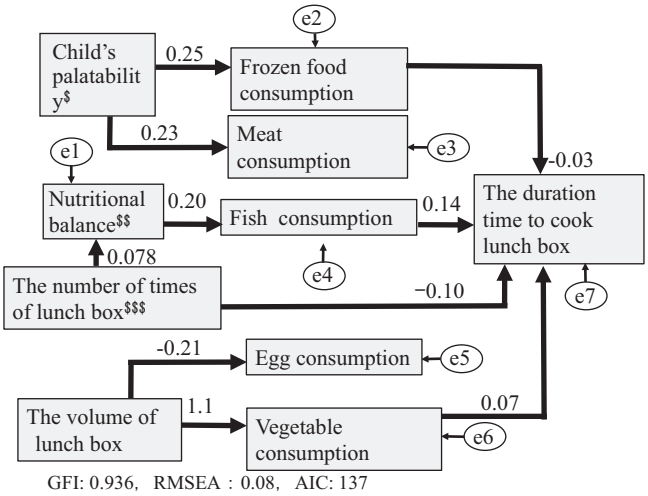


Figure showed significant path (p<0.05) .
The number belong arrow showed partial regression coefficient.
$: Child's palatability defined as cooking lunch box emphasizing child's palatability.
$$: Nutritional balance defined as cooking lunch box emphasizing nutritional balance .
$$$: The number of times of lunch box defined that kindergartens of lunch box system once a week wass one, kindergartens of lunch box system three times a week was three.

FIGURE 42.3 Path analysis of the factor to control or affect vegetable consumption, meat consumption, fish consumption, egg consumption, and frozen food consumption. A path analysis was performed with regard to food consumption by using a questionnaire, the duration time to cook lunch box, the volume of lunch box, and the number of times of lunch box using AMOS. The numbers with the arrows showed a partial regression coefficient.

Conclusion

Food palatability in adults was controlled by the dominant diet in the kindergarten stage of childhood. Controlling food palatability in adults by serving a dominant diet in the kindergarten years would facilitate a more prudent diet selection as an adult. However, there were problems in dominant diets in kindergarteners. For lunch, kindergarteners take lunch boxes, which seldom included fish dishes. Such low fish consumption in children is likely to decrease palatability and consumption of fish in adulthood, which induce a high omega-6/omega-3 fatty acid ratio. However, our study showed that promoting the importance of balanced nutrition and recipes for quick cooking of fish increased the frequency of fish in children's lunch boxes, which might lead them to eat more fish in their adulthood, which in turn would promote a healthier diet as an adult and possibly minimize the risk of developing a non-communicable disease. Controlling food palatability in adults by promoting the importance of balanced nutrition and learning of recipes of quick cooking of fish among children's caregivers would facilitate more prudent diet selection when the children become adults.

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Section 13

Nutraceuticals

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Chapter 43

Vitamins and minerals as nutraceuticals in cardiovascular diseases and other chronic diseases

Richa H. Rai[1], Ramesh K. Goyal[1], Ram B. Singh[2], Svetslav Handjiev[3], Jaipaul Singh[4], Teodora Handjiev Darlenska[3] and Manal M.A. Smail[5]

[1]*Delhi Pharmaceutical University and Technical Sciences, New Delhi, India,* [2]*Halberg Hospital and Research Center, Civil Lines, Moradabad, India,* [3]*Department of Pharmacology, Sofia University, Sofia, Bulgaria,* [4]*National Heart Hospital, Al Ain, United Arab Emirates,* [5]*Fatima College for Health Sciences, Abu Dhabi, United Arab Emirates*

Introduction

Environmental risk factors in conjunction with a modern lifestyle may be associated with increased intake of Western-type diets, pollution, alcoholism, tobacco intake, physical inactivity, and increased intake of ready-prepared processed foods with lower intake of Mediterranean-style foods, which may predispose individuals to deficiencies in antioxidants, vitamins, and minerals, leading to oxidative stress [1−3]. A deficiency in antioxidants and an increase in free radical stress may cause inflammation in various tissues of the body, leading to an increased risk of non-communicable diseases (NCDs) [4−7]. Oxidative stress is known to play an essential role in the pathogenesis of NCDs, such as cardiovascular diseases (CVDs), diabetes, neurodegenerative diseases, and cancer [1−3]. The risk of oxidative stress−induced tissue damage increases if there is dietary deficiency of antioxidant vitamins and minerals in the body [4−7]. Long-term exposure to increased concentrations of prooxidant factors may cause structural damage in the tissues at a mitochondrial DNA level and functional alteration of several enzymes and cellular structures, leading to aberrations in gene expression [2]. However, increased intake of Mediterranean-type foods, antioxidant-rich plants, and vitamins and minerals may prevent oxidative stress−induced tissue damage and thus may be protective against NCDs [3−6]. All the physiological functions of the body, such as breathing, digestion of food, metabolism of alcohol and drugs, and turning fats into energy, produce harmful compounds called free radicals [2]. Increased production of free radicals is usually inhibited by the body's natural antioxidant system, consisting of superoxide dismutase, catalase, glutathione peroxidase, ceruloplasmin, coenzyme Q10 (CoQ10), and antioxidants present in the cells [2−6]. If the antioxidant system is deficient, it might not be able to cope properly, which could allow free radicals to trigger a negative chain reaction in the body that can destroy the cell membrane, block the action of major enzymes, prevent cellular processes necessary for proper functioning of the body, prevent normal cell division, destroy deoxyribonucleic acid (DNA), and block energy generation [2−6]. Epidemiological studies indicate that antioxidants in the blood and in the diets may be inversely associated with risk of NCDs [2−9]. This review examines the role of oxidative stress and antioxidant deficiency in the pathogenesis of NCDs as well as role of antioxidant vitamins and minerals in the prevention of NCDs.

Antioxidant defenses and oxidative stress

Oxidative stress appears to be the most important determinant of cellular damage in the pathogenesis of NCDs [2,8,9]. However, the hypothesis of free radical production due to break down of oxygen has been known for over 50 years as a physiological mechanism for protection of the cells [9]. Only in the last three decades has their role been established in the development of diseases and the role of antioxidant nutrients in the prevention from these diseases [2,8,9]. Free radicals play an essential role in several biological processes and are necessary for cell survival, such as the intracellular

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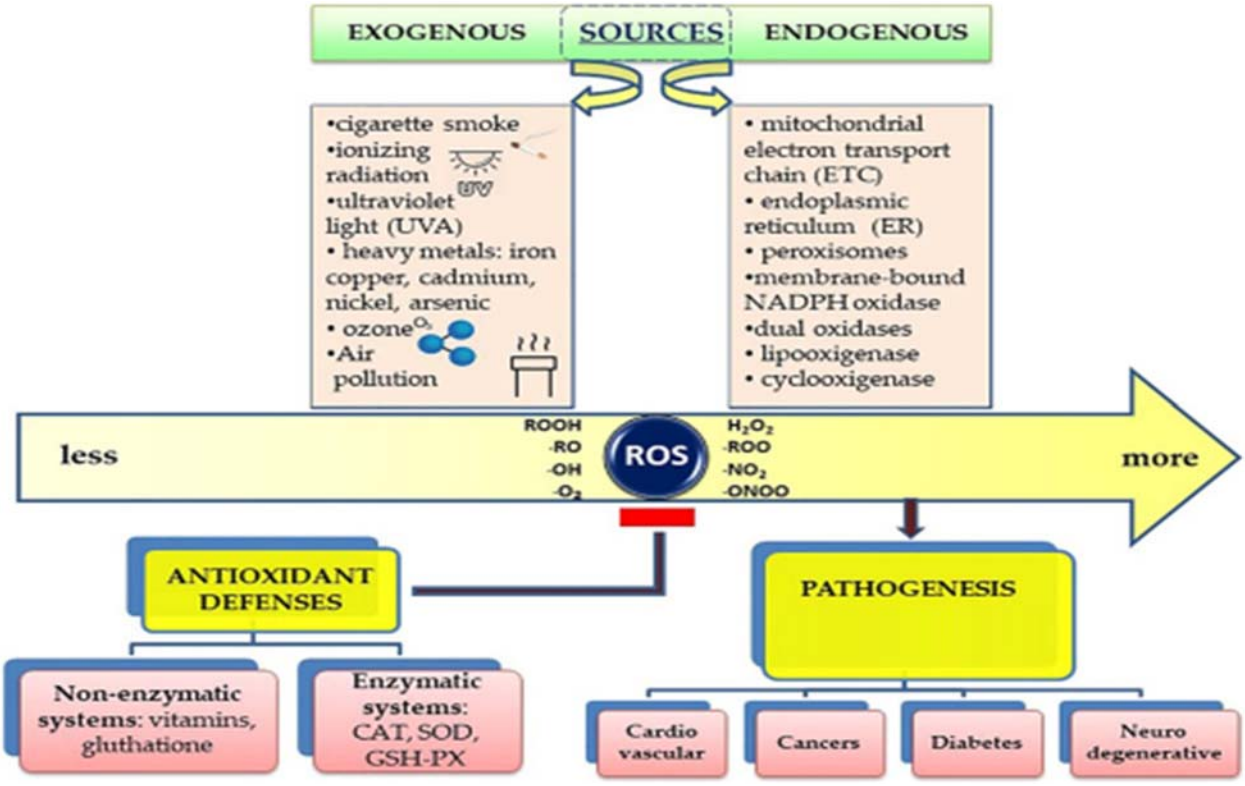


FIGURE 43.1 Schematic presentation of effects of antioxidant defenses on free radicals causing non-communicable diseases. *Modified from reference Sharifi-Rad M, Anil Kumar NV, Zucca P. Lifestyle, oxidative stress, and antioxidants: back and forth in the pathophysiology of chronic diseases. Front Physiol 2020. https://doi.org/10.3389/fphys.2020.00694.*

destruction of bacteria or virus by phagocytes, especially by granulocytes and macrophages [9]. It is possible that free radicals are also involved in some cellular-signaling processes, such as redox signaling [8,9]. Thus it may be highly protective to produce moderate amounts of reactive oxygen species (ROS), which may be beneficial both in regulating processes related to maintenance of homeostasis as well as a wide variety of cellular functions [2,8–10]. There are several endogenous and exogenous processes, that are known to generate ROS, which may cause oxidative damage to DNA, proteins, and lipids, leading to cellular dysfunctions [8–10]. It is possible that the imbalance between ROS production and antioxidant defenses may predispose the individual to free radical stress–induced cell damage, causing molecular dysfunction of various organs and leading to increased risk of NCDs [8]. The role of environmental factors in producing free radical–induced damage to body systems leading to NCDs is shown in Fig. 43.1.

Increased production of ROS is an important determinant of structural modification of cellular proteins and the alteration of their functions, leading to cellular dysfunction and disruption of vital cellular processes [8–10]. The ROS are known to break the lipid membrane and increase membrane fluidity and permeability. Protein damage involves site-specific amino acid modification, peptide chain fragmentation, cross-linked reaction products aggregation, electric charge alteration, enzymatic inactivation, and proteolysis susceptibility [10]. ROS can also cause damage to DNA through oxidizing deoxyribose, breaking strands, removing nucleotides, modifying bases, and cross-linking DNA protein [10]. Increased availability of antioxidant vitamins and minerals as well as endogenous antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and ceruloplasmin may be protective against cell damage [8–10] (Fig. 43.2).

Role of nutraceuticals in the prevention of cell damage

All body systems are susceptible to damage via oxidative stress and inflammation, which may become worse in the presence of deficiencies in vitamins and minerals [5–8]. Beta cells of the pancreas, endothelial cells, smooth muscle cells, adipocytes, and hepatocytes are open to damage, but availability of vitamins and minerals in small amounts may be protective for cell function. Vitamins, A, E C, and D; beta-carotene; vitamins B_1 and B_2; pyridoxine; and vitamin

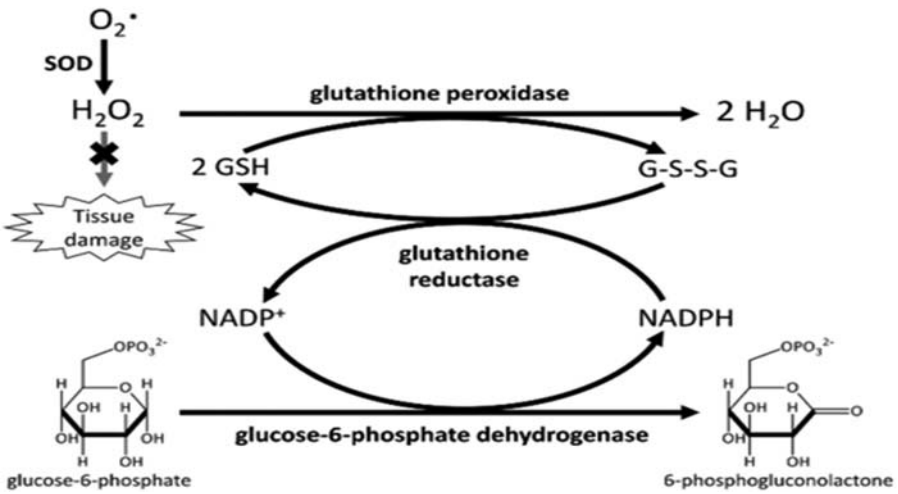


FIGURE 43.2 Free radical production and endogenous antioxidant defenses. *Modified from reference Sharifi-Rad M, Anil Kumar NV, Zucca P. Lifestyle, oxidative stress, and antioxidants: back and forth in the pathophysiology of chronic diseases. Front Physiol 2020. https://doi.org/10.3389/fphys.2020.00694.*

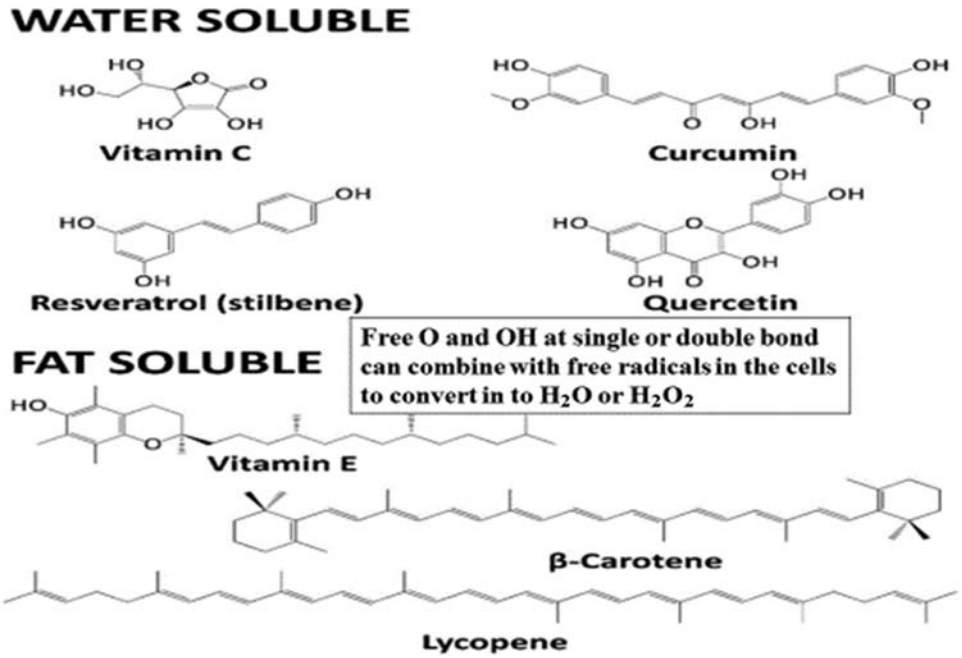


FIGURE 43.3 Chemical structure of nutraceuticals showing free O and OH group that neutralize free radicals to convert into water or oxygen.

B_{12} are chemically unrelated families of organic compounds that are essential for physiological function and metabolism. However, with the exception of vitamin D and CoQ10, they cannot be synthesized by humans; hence they need to be consumed in the diet to prevent disorders of metabolism. Vitamins should be distinguished from minerals, such as calcium, magnesium, and iron, some of which are essential micronutrients [5–8]. However, all the nutrients that provide benefits in the body can also be called nutraceuticals. Epidemiological studies indicate that the prevalence of vitamin deficiencies among people who consume a typical Western diet, particularly older adults and individuals with undernutrition, is significantly greater than that in the general population [5–8]. Pregnancy and alcoholism may also increase the requirements for certain vitamins and minerals. In cohort studies, subclinical deficiencies in multiple vitamins have been found to be associated with NCDs, such as cancer, atherosclerosis, and osteoporosis [1–3]. The vitamins could be fat soluble, such as vitamins E, beta-carotene, and lycopene, or water soluble, such as vitamin C and B-complex vitamins (Fig. 43.3).

Cohort studies and randomized, controlled trials indicate that the role of vitamin therapy in prevention or reversal of many chronic diseases is less well established. Results of studies evaluating the effects of vitamin supplementation have been variable; randomized trials often fail to demonstrate the associations seen in observational studies.

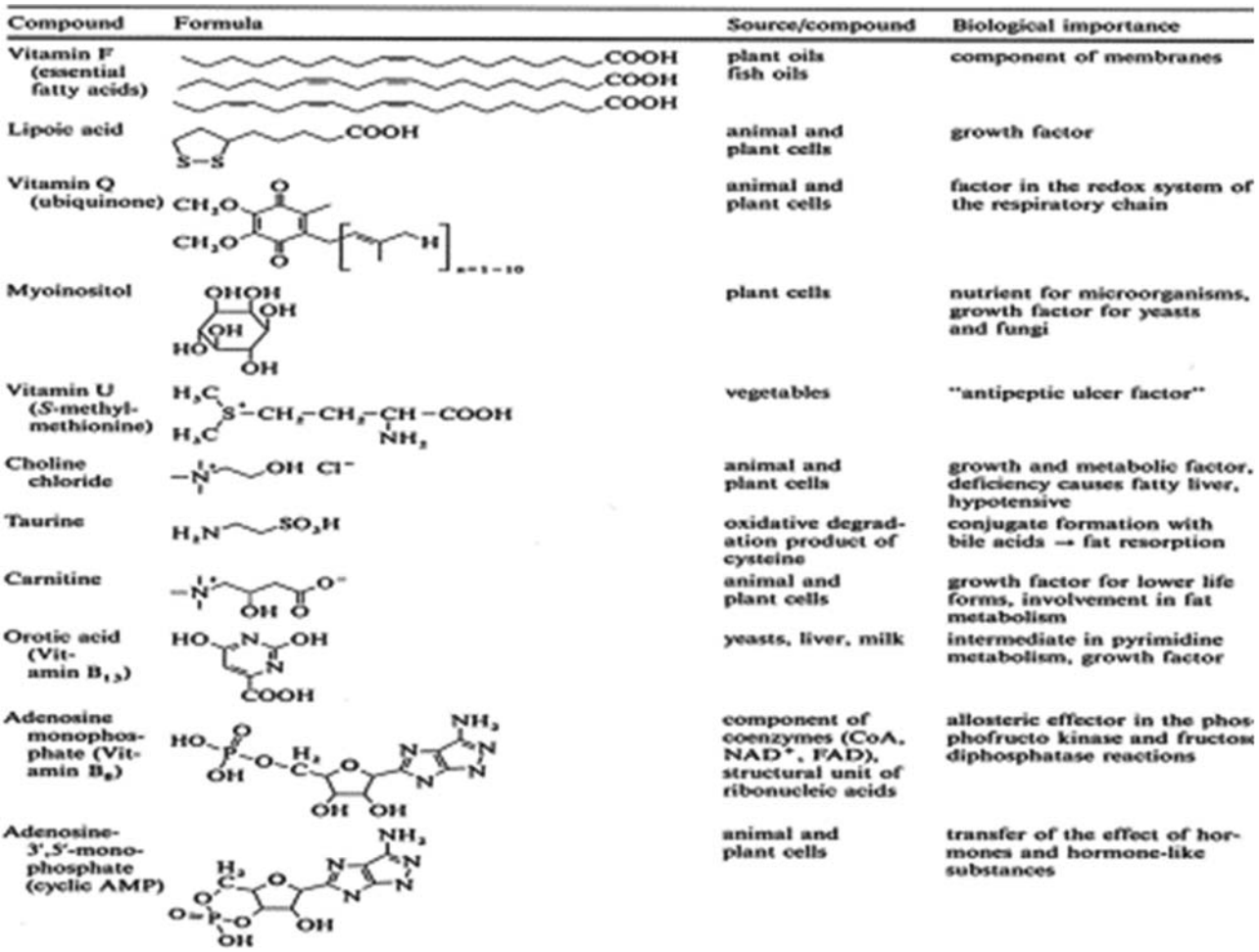


FIGURE 43.4 Chemical structure and effects of vitamins and other nutrients on risk of diseases. *Modified from references Sharifi-Rad M, Anil Kumar NV, Zucca P. Lifestyle, oxidative stress, and antioxidants: back and forth in the pathophysiology of chronic diseases. Front Physiol 2020. https://doi.org/10.3389/fphys.2020.00694.*

Apart from these problems, flaws in methodology, including lack of standardization of baseline vitamin status and dose, may contribute to inconsistent results in various studies [1]. Preconception and periconception factors as well as nutritional status in the newborn and infant may also determine, how vitamins are metabolized and the consequences of supplementation in various clinical situations [11–17]. There are gaps in the knowledge about how to use epigenetic profile and genetic factors to guide clinical decisions about vitamin deficiencies (e.g., vitamin B_{12}, pyridoxine, betaine) and therapeutic doses. However, this information is likely to become available in the near future from clinical trials in humans showing the effects of nutrients on the epigenome and genome [11].

It seems that vitamins and minerals have not been investigated as thoroughly as drugs with an equal level of scrutiny, and the evidence of cardiovascular benefit remains elusive [14]. Micronutrients are the most popular over-the-counter supplements in Western countries despite the lack of clear benefit on primary or secondary prevention of CVDs and diabetes and cancer [14]. Recent studies indicate a possible role of multivitamins in secondary prevention when concomitantly administered with chelation therapy. Apart from this, clinical trials and observational studies have shown preliminary evidence of cardiovascular protection with dietary supplements such as carnitine, arginine, and CoQ10 [14,18–20] (Fig. 43.4).

Epidemiological evidence

Among the most dramatic achievements in the history of medicine, in particular nutritional sciences, during the last 250 years is the management of micronutrient deficiencies with vitamins and minerals [1,8]. The British Naval Surgeon

James Lind in 1747 was perhaps the first who examined the role of citrus fruit (vitamin C) among 12 sailors in the treatment of scurvy [21].

Recently, our interest in micronutrients has shifted from prevention of classic deficiency states to prevention of possible subclinical deficiencies that can be repaired by the use of supplements [8,22]. The National Health and Nutrition Examination Survey data (1999–2012), including 37,958 adults, revealed that therapy with supplements was high in 2012, with up to 52% of the population taking supplements [22]. Intake of multivitamins was observed in 31% of the population, vitamin D in 19%, calcium in 14%, and vitamin C in 12% [22].

In Europe during this period, the European Prospective Investigation into Cancer and Nutrition data on 36,034 men and women revealed a wide range of supplement use [23]. There was a strong north-south gradient that was highest in the north (e.g., Denmark: 51% men, 65.8% women) and lowest in the south (e.g., Greece: 2.0% men, 6.7% women), and there was higher supplement use by women [23]. The Canadian Cancer Society recommends a supplement (1000 IU) vitamin D to be taken in fall and winter to maintain physiological levels [24]. Interestingly, majority of the health agencies, recommend increased consumption of a healthy Mediterranean-style diet as part of a healthy lifestyle [5,24]. The U.S. Dietary Guidelines Advisory Committee, also concerned with CVD risk reduction, recommended three dietary patterns: (1) a healthy American diet low in saturated fat, trans fat, and red meat but high in fruit and vegetables; (2) a Mediterranean-type diet; and (3) a Western vegetarian diet [25]. The Mediterranean-type diets, with their accompanying recommendations, may move toward more plant-based diets, which are relatively rich in all the micronutrients. Such diets satisfy daily requirements and are still below the tolerable upper levels of intake of the recommended range in which adverse effects may be seen. Therefore for the general public the focus has been on meeting requirements through diet rather than supplements. Interestingly, the evidence for supplement use over the years since publication of the evidence and guidelines for supplement use of the U.S. Preventive Services Task Force (USPSTF) [25,26].

Despite high supplement use by the general public, there is no general agreement on whether individual vitamins and minerals or their combinations should be taken as supplements for prevention of CVDs. In a metaanalysis, including 179 individual studies, 15 of which were published after the USPSTF assessment, data were provided for the four common supplements taken (multivitamins, vitamin D, calcium, and vitamin C) and also for those that were significant for any of the following: all-cause mortality, CVD mortality, and total CVD risk or related outcomes (e.g., myocardial infarction, stroke), provided that GRADE was more than low-quality evidence, and that more than one controlled trial was available for assessment (Fig. 43.5). Among four commonly used nutraceuticals (vitamin D, calcium, multivitamins, and vitamin C), none had a significant effect on risk for incidence of CVDs [8]. The forest plot for vitamin D, the most studied nutrient, with 43 randomized, controlled trials, shows a lack of harm or benefit, with 2908 deaths in 18,719 examined subjects and 2968 deaths in 18,831 control subjects. The point estimates were divided evenly in favor of vitamin D (16 trials) and in favor of control treatment (17 trials), with 10 trials on the unity line. The overall relative risk (RR) was 0.99 ($P = .58$), without any heterogeneity ($I^2 = 0$), high-quality evidence, showing a null effect. The micronutrients with significant effects included folic acid and B-complex vitamins for stroke reduction and niacin and antioxidants, which were associated with an increase in all-cause mortality.

Effects of nutraceutical folic acid on stroke risk

In a metaanalysis involving 12,268 subjects, intake of folic acid in two of seven randomized, controlled trials showed a decreased risk for stroke (RR: 0.80; $P = .003$), with no heterogeneity and moderate-quality evidence [27–35]. The total metaanalysis of the seven studies showed a benefit for folic acid driven by the China Stroke Primary Prevention Trial study. CVD was also declined in the metaanalysis of five trials (RR: 0.83; $P = .002$) (Fig. 43.6) [28–35].

The results show a RR of 0.80 in favor of folic acid. It seems that the 20% reduction in stroke risk was driven by the highly influential Chinese folic acid supplementation study, which was done in a community without folic acid fortification but is the major supplement finding of the last 6 years. The number needed to treat (NNT) for folic acid supplementation and stroke risk is 167.

Effects of nutraceutical folic acid on cardiovascular diseases risk

The results of the metaanalysis mentioned above showed that nutraceuticals provided a 17% reduction in CVD risk. This result was driven by the Chinese folic acid supplementation study, which was done in a community without folic acid fortification but is the major supplement finding of the last 6 years. The NNT for folic acid supplementation and CVD risk. The results show a RR of 0.83 in favor of folic acid (Fig. 43.7).

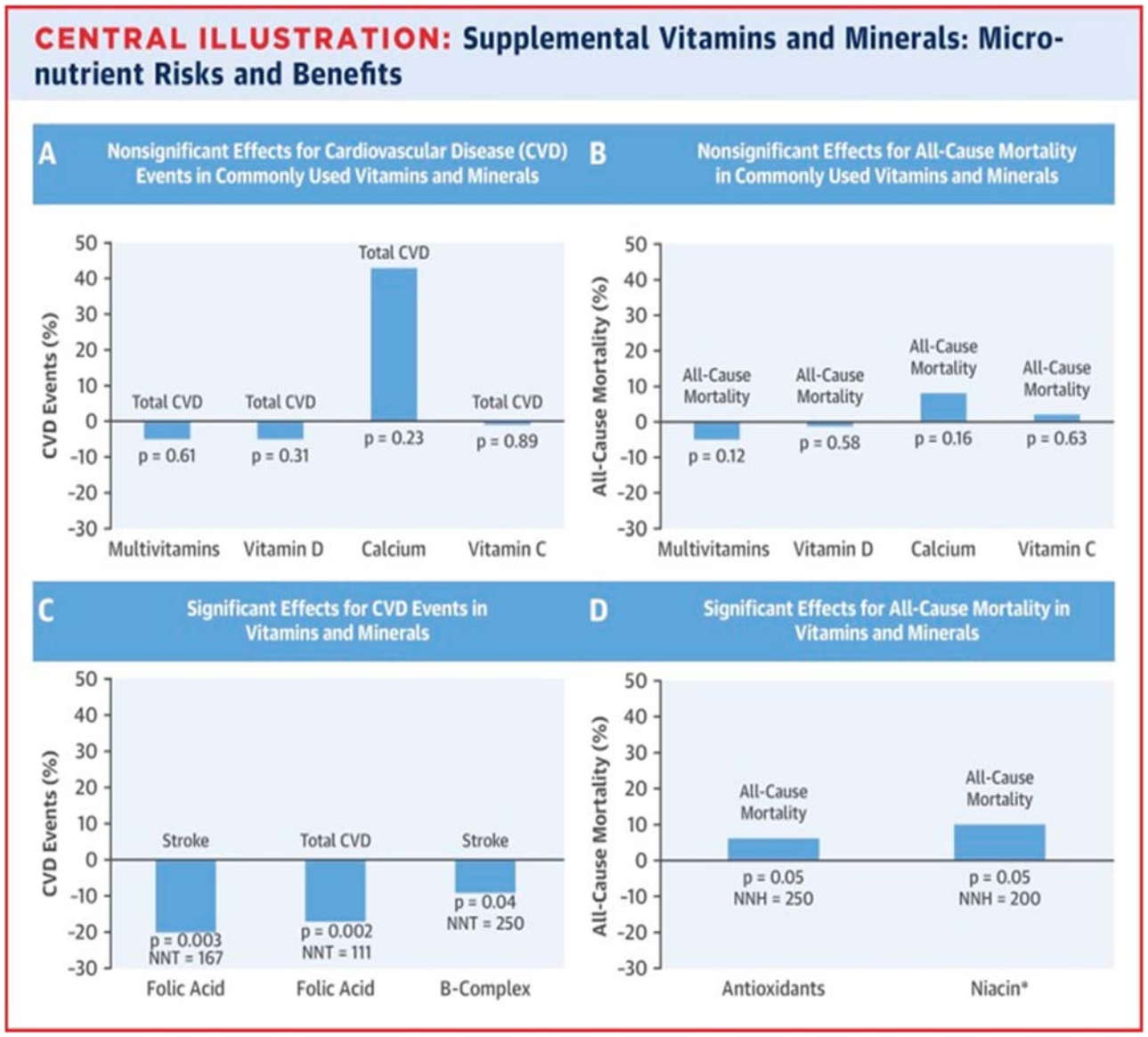


FIGURE 43.5 Main figure showing effects of supplemental vitamins and minerals; Risks and benefits of intake of micronutrients. (A and B) Effects of commonly used vitamins and minerals. (C and D) Vitamins with significant effects derived from summary plot estimates of risk ratios expressed as percentages. Popular supplements were without demonstrable effects on cardiovascular disease (CVD) or all-cause mortality. Both folic acid and B-complex vitamins showed benefits for stroke, whereas antioxidants and niacin showed a marginally significant increase in all-cause mortality. These data highlight the lack of effect of popular supplements on CVD and all-cause mortality but demonstrate potential benefits of folic acid supplementation for stroke. * indicates slow-release niacin with background statins. *NNH*, Number needed to harm; *NNT*, number needed to treat. *Modified from Jenkins DJA, Spence JD, Giovannucci EL. Supplemental vitamins and minerals for CVD prevention and treatment. J Am Coll Cardiol 2018;71:2570–84.*

Effects of B-complex vitamins on stroke risk

In 9 of 12 studies in a metaanalysis of 12 trials (RR: 0.90; $P < .04$), B-complex vitamins reduced the risk of stroke with no heterogeneity ($I^2 < 16\%$; $P < .28$) and moderate-quality evidence (Fig. 43.8) [36–47].

The 10% reduction in stroke comes from trials that also included folic acid and from areas with folic acid fortification. These results also support the conclusion that B-complex supplementation and folic acid have positive effects in stroke prevention. The NNT for vitamin B-complex supplementation and stroke risk is 250.

With background statin intake, niacin (nicotinic acid) or vitamin B_3, taken at pharmacological doses (1–3 g/day) in three trials and assessed in both the test and control groups with extended-release niacin, was associated with a 10% increase in all-cause mortality ($P < .05$) with no heterogeneity and moderate-quality evidence (Fig. 43.9) [48–51].

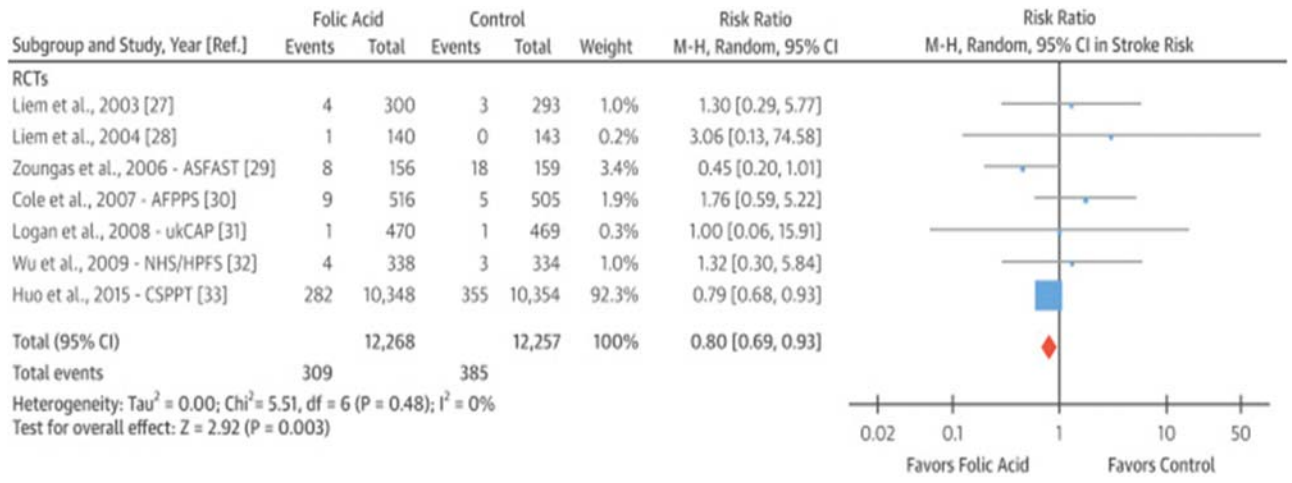


FIGURE 43.6 Forest plot of folic acid supplementation and stroke risk. The diamond represents the pooled risk estimate. Interstudy heterogeneity was tested by using the Cochran Q test (chi-square) at a significance level of $P < .10$ and quantified by the I^2 statistic. *df*, Degree of freedom; *M-H*, Mantel–Haenszel. *Modified from Jenkins DJA, Spence JD, Giovannucci EL. Supplemental vitamins and minerals for CVD prevention and treatment. J Am Coll Cardiol 2018;71:2570–84.*

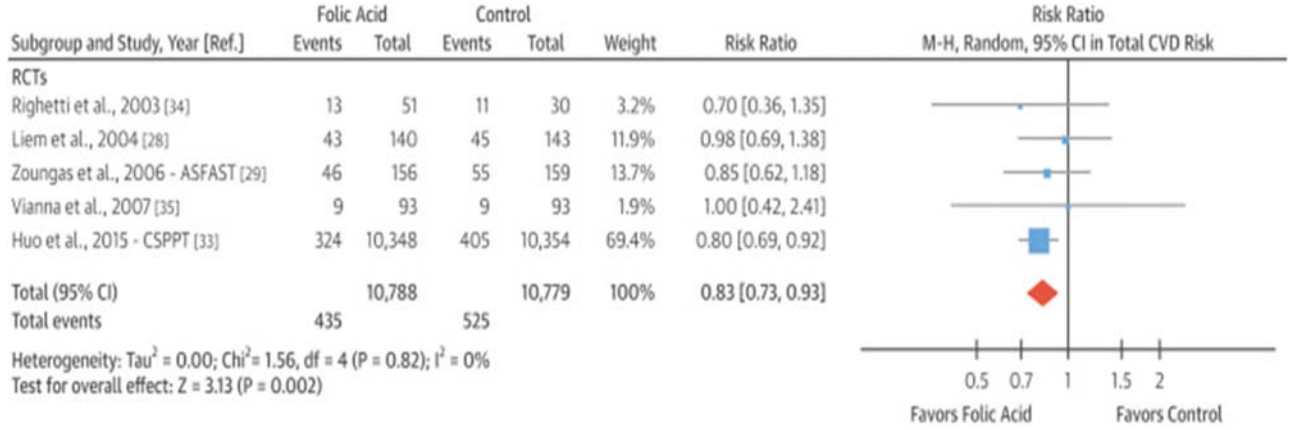


FIGURE 43.7 Forest plot of folic acid supplementation and CVD risk. The diamond represents the pooled risk estimate. Interstudy heterogeneity was tested by using the Cochran Q test (chi-square) at a significance level of $P < .10$ and quantified by the I^2 statistic. *df*, Degree of freedom; *M-H*, Mantel–Haenszel. *Modified from Jenkins DJA, Spence JD, Giovannucci EL. Supplemental vitamins and minerals for CVD prevention and treatment. J Am Coll Cardiol 2018;71:2570–84.*

The findings indicate that taking slow-release niacin to lower the level of low-density lipoprotein (LDL) cholesterol further in those already taking a statin appears to provide no additional benefit in CVD outcomes but has a marginally adverse effect on all-cause mortality (Fig. 43.9). The NNT for niacin without background statin use and all-cause mortality is 100; the number needed to harm (NNH) with background statin use and all-cause mortality is 200.

A combination of antioxidants found no effect on outcomes of CVD, but resulted in an increase in all-cause mortality in the metaanalysis of 21 randomized trials (Fig. 43.10), with a small but significant increase in RRs (1.06; $P < .05$), no heterogeneity, and with moderate-quality evidence for the randomized, controlled trials [53–73]. The use of vitamins A, B_6, E; beta-carotene; iron, zinc, magnesium, selenium and multivitamin supplements was associated with no significant effect on CVD outcomes and all-cause mortality.

The NNH for antioxidant supplementation and all-cause mortality risk is 250 (Fig. 43.11).

Studies in which selenium was administered were excluded from the metaanalysis of antioxidants because of the high percentage of these studies on the left side of the unity line versus the right side of the unity line in the antioxidant forest plot (83% vs 7%) compared with the other components of antioxidant mixtures. Exclusion of the selenium studies showed a significant increase in all-cause mortality (RR: 1.09; $P < .0002$ to $I^2 < 0\%$) [53,54,57–59,61–69,73].

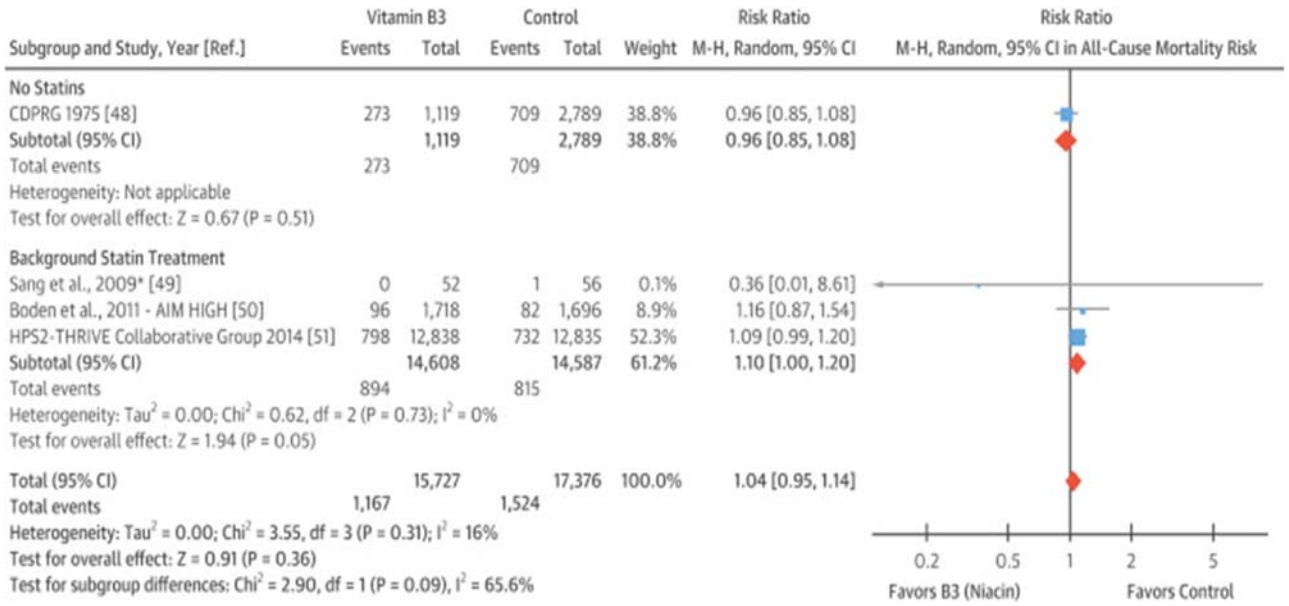


FIGURE 43.8 Forest plot of vitamin B-complex supplementation and stroke risk. The diamond represents the pooled risk estimate. Interstudy heterogeneity was tested by using the Cochran Q test (chi-square) at a significance level of $P < .10$ and quantified by the I^2 statistic. *Data for folic acid, vitamin B_6, and B_{12} versus placebo are from Bønaa et al. [36]. †Data for folic acid, B_6, and B_{12} versus placebo are from Ebbing et al. [38]. *df*, Degree of freedom; *M-H*, Mantel−Haenszel. *Modified from Jenkins DJA, Spence JD, Giovannucci EL. Supplemental vitamins and minerals for CVD prevention and treatment. J Am Coll Cardiol 2018;71:2570−84.*

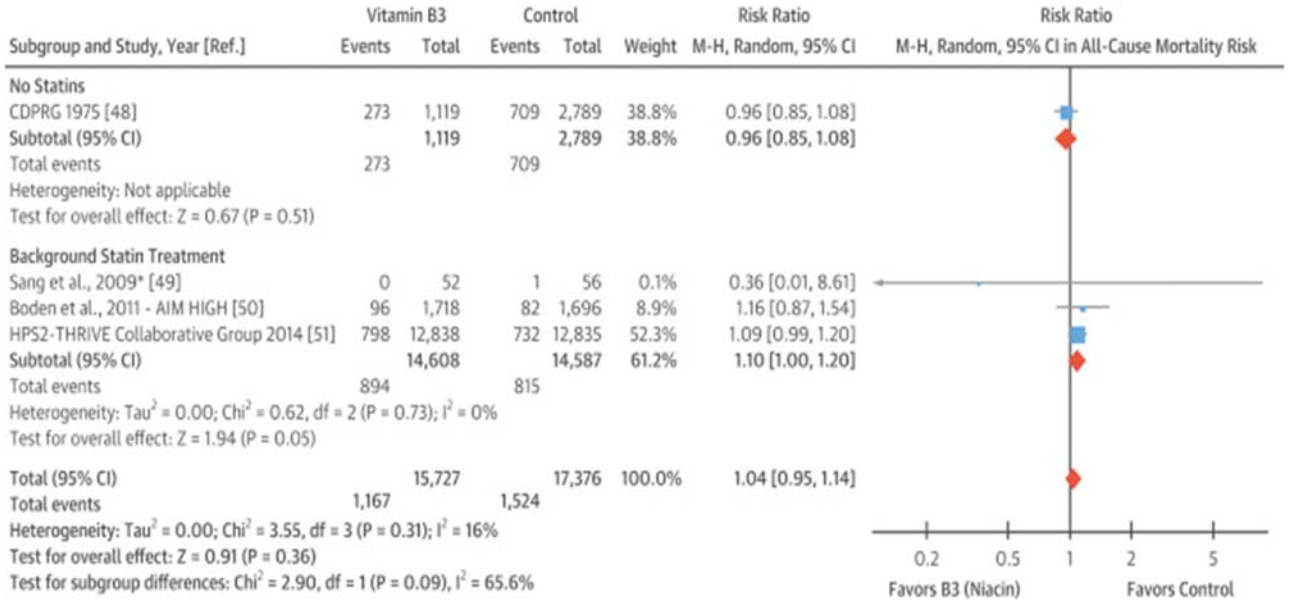


FIGURE 43.9 Forest plot of niacin (B_3) supplementation and all-cause mortality risk in controlled trials with and without background statin treatment. The diamond represents the pooled risk estimate. Interstudy heterogeneity was tested by using the Cochran Q test (chi-square) at a significance level of $P < .10$ and quantified by the I^2 statistic. *Sang et al. [49]; data taken from the metaanalysis in Keene et al. [52]. *df*, Degree of freedom; *M-H*, Mantel−Haenszel. *Modified from Jenkins DJA, Spence JD, Giovannucci EL. Supplemental vitamins and minerals for CVD prevention and treatment. J Am Coll Cardiol 2018;71:2570−84.*

Many studies also examined the association between nutraceutical intake and risk for cancers, showing positive association in a few studies and a negative association in other studies [26,52,74−78] (Fig. 43.12).

It is clear from these studies that use of these supplements cannot be advised for reduction of risk due to CVDs. The NNH for antioxidant supplementation and all-cause mortality risk is 127. In view of the lack of benefits, these

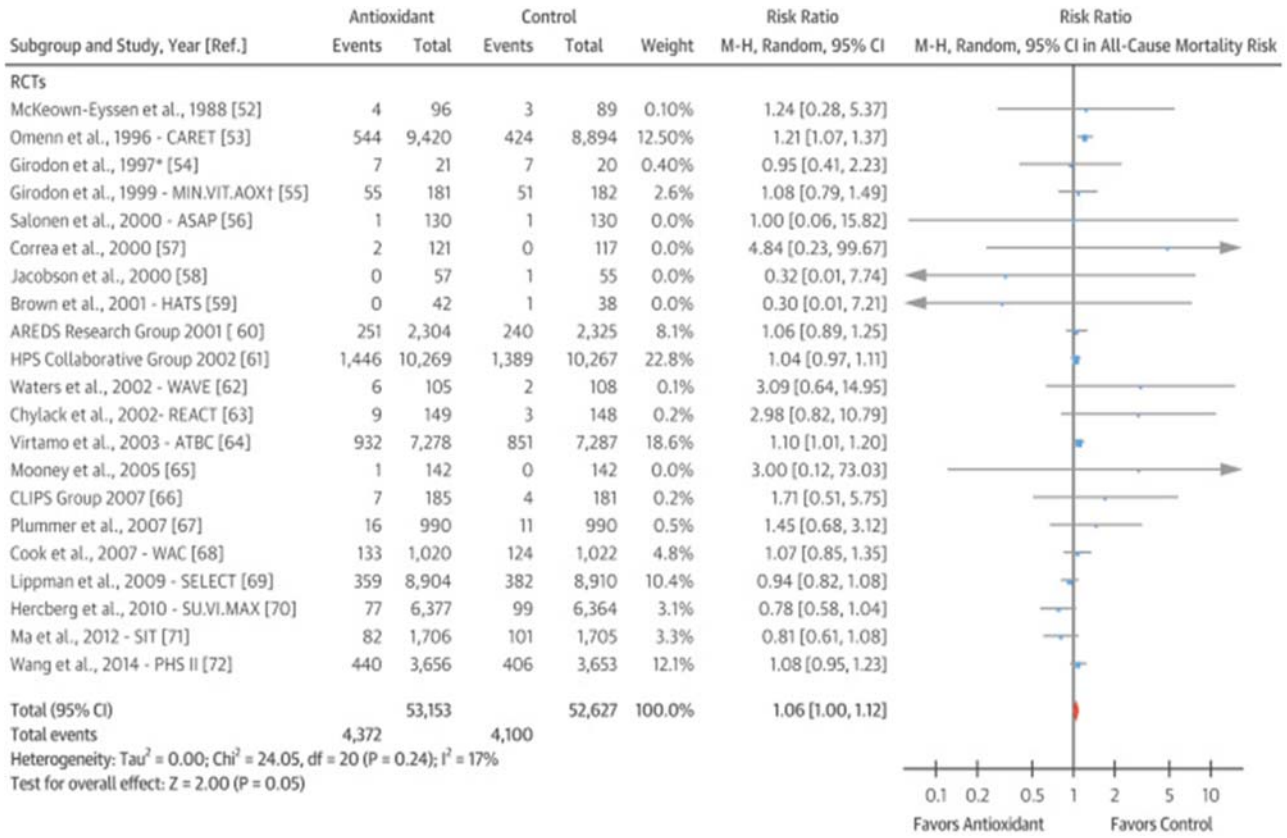


FIGURE 43.10 Forest plot of antioxidants supplementation and all-cause mortality risk in randomized trials. The diamond represents the pooled risk estimate. Interstudy heterogeneity was tested by using the Cochran Q test (chi-square) at a significance level of $P < .10$ and quantified by the I^2 statistic. *Data for vitamin C, vitamin E, beta-carotene, selenium, and zinc versus placebo are from Girodon et al. [55]. †Data for vitamin C, vitamin E, beta-carotene, selenium, and zinc versus placebo are from Girodon et al. [56]. *df*, Degree of freedom; *M-H*, Mantel−Haenszel. *Modified from Jenkins DJA, Spence JD, Giovannucci EL. Supplemental vitamins and minerals for CVD prevention and treatment. J Am Coll Cardiol 2018;71:2570−84.*

supplements were associated with no significant effect on CVD outcomes and all-cause mortality: vitamins A, B_6, and E; beta-carotene; zinc; iron; magnesium; selenium; and multivitamins.

Comments

This review shows that supplementation with vitamin D, multivitamins, magnesium, calcium, and vitamin C had no consistent benefit for the prevention of CVD, stroke, or myocardial infarction. The use of these nutraceuticals also found no benefit for all-cause mortality, including deaths due to cancers [8,26,52,74−77]. However, treatment with folic acid alone and treatment with folic acid with B_6 and B_{12} were associated with declines in stroke, whereas treatment with niacin and treatment with antioxidants were associated with increased risks of all-cause mortality. The overall effects of nutraceuticals were small, with lack of benefit of vitamin D on all-cause mortality. The effects of folic acid administration in reducing the risk of stroke are also convincing, with a 20% reduction.

A recent nationwide, randomized, placebo-controlled trial (known as VITAL) of omega-3 fatty acids (1 g/day) and vitamin D_3 (2000 IU/day) in the primary prevention of CVD and cancer included 25,871 subjects aged 50 years and older [78]. After a follow-up with a median of 5.3 years, supplemental omega-3 fatty acids revealed no significant reduction in the primary cardiovascular endpoint of major CVDs [composite of myocardial infarction, stroke, and CVD mortality; hazard ratio (HR): 0.92] but were associated with significant declines in total myocardial infarction (HR: 0.72), percutaneous coronary intervention (HR: 0.78), and fatal myocardial infarction (HR: 0.50) but not stroke or other cardiovascular endpoints [78]. A treatment benefit was observed for major CVD events in subjects with dietary fish intake below the cohort median of 1.5 servings/week (HR: 0.81) but not in those with intake above the median (P interaction = .045). Interestingly, the greatest risk reductions for myocardial infarctions were in Blacks

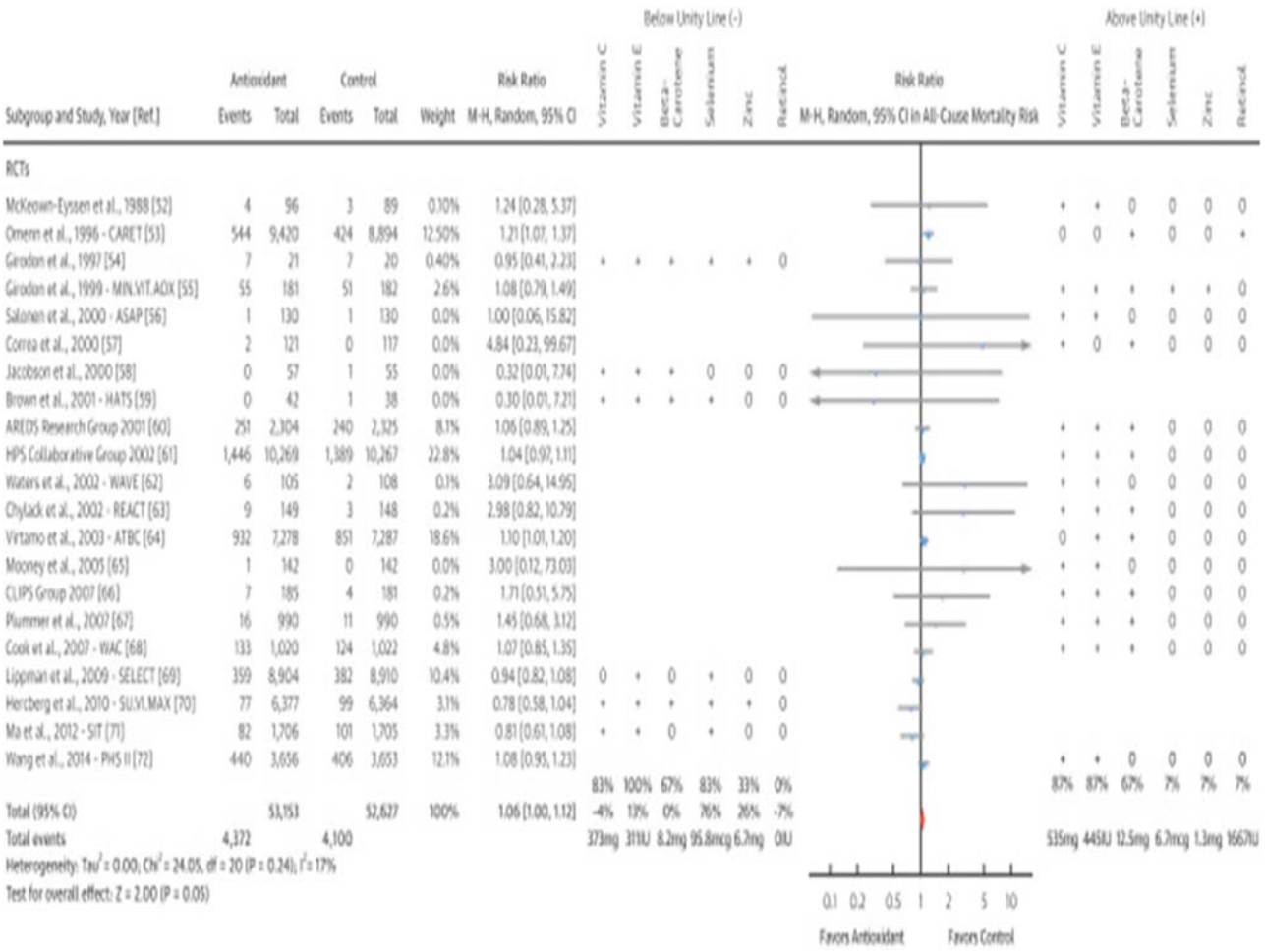


FIGURE 43.11 Forest plot of antioxidants supplementation and risk for all-cause mortality. The forest plots show whether the combination of antioxidant contained a specific antioxidant (+) or not (0), with data on the right or left side of the forest plot depending on whether the point estimate lies to the right (harm) or left (benefit) side of the unity line. The first line at the bottom shows the percentage of studies with point estimates on the right and left sides of the unity line for the antioxidant component, and the next line on the left is the difference between the left and right sides. The line at the bottom shows the average dosage of the antioxidant used on that side of the unity line (milligrams, micrograms, or international units). *Modified from Jenkins DJA, Spence JD, Giovannucci EL. Supplemental vitamins and minerals for CVD prevention and treatment. J Am Coll Cardiol 2018;71:2570–84.*

(HR: 0.23; *P* interaction by race = .001). However, treatment with vitamin D did not reduce major CVD events (HR: 0.97) or other cardiovascular endpoints. A metaanalysis that included VITAL and other recent trials documented a significant reduction in coronary risk from supplemental marine omega-3 fatty acids but no clear decline in CVD risk from supplemental vitamin D [78].

Magnesium levels have also been associated with cardiovascular health [15]. In this analysis, 1754 subjects from the Observatorio Nacional de Atherosclerosis en Nefrologia cohort were included. The interactions in linear regression analysis showed that magnesium was an effect modifier on the influence of lipid parameters. The carotid intima media thickness–predicted values were higher when magnesium levels were low and triglycerides or LDL levels were higher. Interestingly, when magnesium levels were high, this effect disappeared. It is possible that magnesium may act as a beneficial nutraceutical for its influence on lipid-related parameters and atherosclerotic CVD [15]. Dietary and serum levels of antioxidant, vitamin and mineral deficiency, and oxidative stress have been observed in patients with CVDs and other chronic diseases, and nutraceuticals have been administered for the treatment of these patients with some benefits [3,6,7,18–20]. Effects of other nutraceuticals such as CoQ10, L-carnitine and antioxidants such as resveratrol on risk of atherosclerosis and CVDs among patients with recent myocardial infarction have also been found to be beneficial [18–20,79]. However, the current clinical evidence based on metaanalysis is insufficient to assess the benefits and risks of taking multivitamins or single or paired nutrient supplements for the prevention of CVDs or cancer [77].

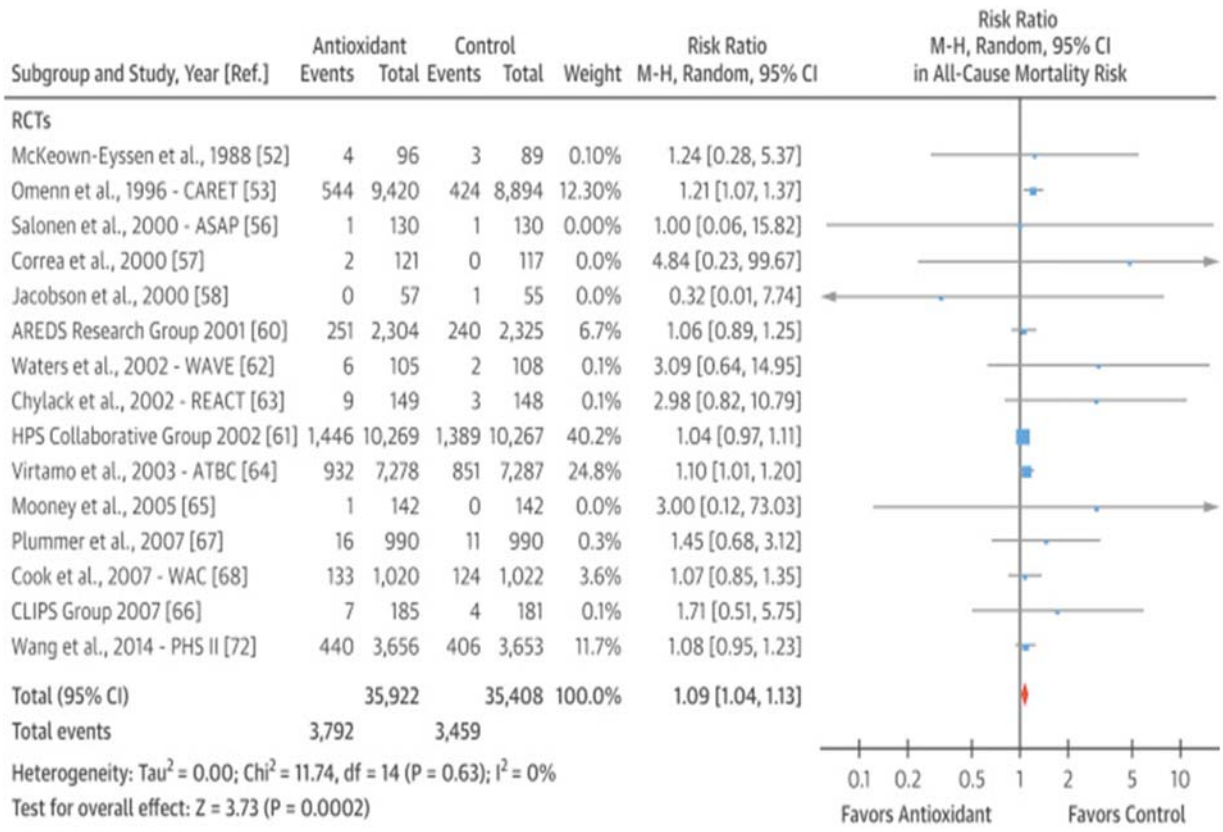


FIGURE 43.12 Forest plot of antioxidants supplementation and all-cause mortality risk in randomized trials with exclusion of studies on selenium. The diamond represents the pooled risk estimate. Interstudy heterogeneity was tested by using the Cochran Q test (chi-square) at a significance level of $P < .10$ and quantified by the I^2 statistic. Combination of antioxidants mixtures showed no benefit on CVD outcomes, but many had a marginally deleterious effect on all-cause mortality. *Modified from Jenkins DJA, Spence JD, Giovannucci EL. Supplemental vitamins and minerals for CVD prevention and treatment. J Am Coll Cardiol 2018;71:2570–84.*

CoQ10 is a vitamin-like molecule that is normally present in the inner side of the mitochondrial cell membranes. It is a potential antioxidant that is involved the cell energy production [20]. CoQ10 has been found to be important in hypertension, insulin resistance, heart failure, and decreasing lipoprotein(a) [80–83]. Population studies have reported an inverse association of serum magnesium and antioxidant vitamins status with risk of complications of aging in an elderly urban population [84]. Diet, antioxidants, and risk of cancer have been reported in a case study [85]. Association of low plasma concentration of antioxidant vitamins, magnesium, and zinc with a high body fat percentage has been observed among men [86]. There may be a circadian rhythmicity of circulating vitamin concentrations showing lower levels in the morning due to increased consumption to fight the circadian oxidative stress [87]. In an experiment in rabbits, antioxidant effects of lovastatin and vitamin E on experimental atherosclerosis have been demonstrated [88]. In the present review, we examine the available evidence about the beneficial and adverse effects of vitamins in CVDs

There is a critical gap in the evidence due to lack of studies on multivitamin combinations in groups that are generalizable to various social groups in the population. Research among individuals with high risk for nutrient deficiency may be the best target to produce scientific evidence. These subgroups may be individuals with undernutrition, pregnant women, and elderly subjects. CVDs and cancer are public health problems, and deficiencies in antioxidant vitamins and minerals were associated with blood vessel changes suggestive atherosclerosis [26,89–96]. It is possible that supplementation with these nutraceuticals may decrease the risk of CVDs and cancer [26,89–96]. The evidence against the use of beta-carotene or vitamin E is stronger, and these supplements cannot be used for preventing CVDs or cancer in smokers and in the general population [26,89–91]. CVDs and cancer continue to be the largest contributors to the burden of chronic diseases in the developed world, despite enormous use of vitamins; in 2011 these diseases accounted for 23.7% and 22.8% of all deaths in the United States, respectively [92].

There is strong evidence with which to estimate the overall net benefit or risk for beta-carotene and vitamin E due to higher lung cancer risk with beta-carotene in smokers [90]. There is a large and consistent body of evidence

showing that vitamin E supplements have no effect of on CVDs, cancer, or all-cause mortality [90]. Similar is the conclusion regarding the use of minerals or multimineral combinations [26,77,89–91]. It seems that the vitamin and mineral pharmacology is quite complex. Numerous clinical trials with single vitamins, including vitamins A, C, and D, and selenium have all shown negative results or, as is the case with vitamin A, have shown the potential to cause harm [26,89–91].

Multivitamin pharmacology is complex and it remains a difficult task to study this area of medicine. However, other vitamin and mineral studies, particularly, patients in the Trial to Assess Chelation Therapy (TACT) undergoing chelation were given large doses of oral vitamins and minerals, nearly all of which exceeded the daily recommended values. High doses of 1200 mg of vitamin C, 25,000 IU of vitamin A, 400 IU of vitamin E, 200 mg of niacin, and 800 μg of folate were prescribed in the TACT, which are more than necessary to replace nutrient deficiency [92]. In the TACT, there was a nonsignificant 11% reduction in the risk of CVDs. It is possible that other high-dose multivitamin and multimineral studies might be worth a second look because bioactivity of any agent may depend on doses of the agent and on the time of administration. The pharmacological properties of aspirin change when it is used at different doses. Aspirin is used at 81 mg an antiplatelet agent, at 650 mg as a treatment to reduce fever, and when 1–2 g/day are prescribed, it can be used to treat rheumatoid arthritis.

Studies on the associations between particular vitamins and CVD and cancer vary in quality, and their results often conflict. In 2003 the USPSTF recommended that people should not take beta-carotene supplements to decrease their chances of CVD or cancer because vitamins A, C, or E; multivitamins with folic acid; or combinations of these vitamins showed no evidence for the primary purpose of preventing CVD or cancer [77]. Recently, a review using large, high-quality studies showed that vitamin E supplements have no effect on CVD, cancer, or death rates [77]. In this review by the USPSTF, four randomized, controlled trials and one cohort study assessing health outcomes of a multivitamin supplement were included in which the studies varied in the nutrients and doses used [77]. However, there was no effect on all-cause mortality in the three trials that assessed this outcome or in the two trials that assessed CVDs outcomes. Overall, there was no effect on incidence of CVD events, but one trial reported a borderline-significant decrease in fatal myocardial infarctions [77].

The Physicians' Health Study II [91] and the SU.VI.MAX (Supplementation in Vitamins and Mineral Antioxidants) study conducted in France involving 13,017 men and women with an average age of 49 years [93] revealed a decrease in overall cancer incidence in men [pooled unadjusted RR: 0.93; 95% confidence interval (CI): 0.87–0.99] [77]. The Physicians' Health Study II included 14,641 male U.S. physicians with an average age of 64.3 years. Only commercially available multivitamins that contained 30 ingredients were used as intervention in this study. The unadjusted RR for total cancer incidence was 0.94 (95% CI: 0.87–1.00) after 11.2 years of follow-up. The intervention supplement included nutritional doses of vitamins C and E plus beta-carotene, selenium, and zinc. Outcomes were reported for the end of the intervention phase at 7.5 years and again at 12.5 years after randomization. During the supplementation period, overall cancer incidence was not affected in women but decreased by 31% in men (adjusted RR: 0.69). The lack of effect in women and the use of different supplement formulations in the two trials make it difficult to extrapolate these findings to the general population.

Individual vitamins and minerals

There are only a limited number of studies for most individual nutrients, and differences in study designs make pooling effects across supplements difficult [77,93–95]. It is therefore difficult to conclude with certainty that there is no effect. Hence evidence for each individual nutrient should be evaluated.

Vitamin A and C

Of three randomized trials and two cohort studies of vitamin A, none of the studies reported CVD incidence [77]. One good-quality trial showed an increased risk for lung cancer and related death. The baseline population (smokers and workers who had been exposed to asbestos) was at high risk for lung cancer, so the increased mortality may be attributable to the beta-carotene component. No significant difference was observed between the intervention and control groups at the longest follow-up in the two trials reporting all-cause mortality, but a greater risk for hip fractures was observed in one large prospective cohort study of postmenopausal women. Regarding vitamin C, three randomized trials studied the effects of vitamin C, either alone or in combination with other supplements, and found no statistically significant effect on CVD, cancer, or all-cause mortality [77].

Vitamin E and selenium

Of six randomized trials, three trials reported CVD incidence and mortality [77]. A lower CVD mortality rate in the intervention group was observed in one trial, but mortality rates for myocardial infarction and stroke did not differ statistically. One trial found an increased risk for hemorrhagic stroke in the intervention group. In the four randomized trials reporting cancer incidence, there was no significant effect on incidence of all types of cancer or on cancer mortality rates [77,90]. No effect on all-cause mortality was observed in the five trials reporting this outcome. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study [90] reported a decreased incidence of prostate cancer, but the effect did not persist with longer follow-up. Vitamin E was not found to have any effect on site-specific cancer incidence, although the results for prostate cancer were mixed. Similarly, SELECT (Selenium and Vitamin E Cancer Prevention Trial) observed a greater risk for prostate cancer after extended follow-up [97]. Two trials studied selenium alone or in combination with other nutrients and found no effect on CVD or all-cause mortality, and the effect on cancer was mixed [77]. One trial found a decrease in risk for cancer incidence and mortality; the other found no significant difference. Although no differences in all-cause mortality were found in either trial, further analysis showed a decrease in cancer incidence only in men with the lowest levels of selenium, suggesting a potential effect resulting from treatment of selenium deficiency.

Beta-carotene and folic acid

There is evidence from six clinical trials indicating that beta-carotene supplementation does not decrease the risk for CVD events, overall cancer incidence, or cancer mortality [77]. However, the ATBC study [90] and the Carotene and Retinol Efficacy Trial [94] showed an increased risk for lung cancer incidence and mortality and all-cause mortality in participants with a high baseline risk for lung cancer. A metaanalysis of beta-carotene trials reported an increased risk for lung cancer (pooled odds ratio: 1.24; 95% CI: 1.10−1.39) in current smokers [95]. Folic acid had no effect on CVD incidence or all-cause mortality [77]. There was an increased incidence of cancer, attributed to an excess number of deaths from prostate cancer in the intervention group. The multivitamin combination used in the brand Centrum Silver (Pfizer) failed to reduce the risk of myocardial infarction, stroke, or CVD mortality in one study. However, this company and others continue to publicize multivitamins as a heart-healthy supplement. In the United States, dietary supplements sale is a big business: Americans spent $28.1 billion on them in 2010 alone. The industry, doctors, and patients continue to believe that vitamins and minerals may be useful, and many physicians and nurses continue to recommended multivitamins to their patients for health and wellness [77,98,99].

However, important adverse effects have been observed with the use of beta-carotene in persons who smoke tobacco or have an occupational exposure to asbestos. Moderate doses of vitamin A supplements may reduce bone mineral density, and high doses may be hepatotoxic or teratogenic. Since many of these vitamins are fat soluble, the lifetime effect of high doses should be taken into consideration. The Food and Nutrition Board emphasized that vitamins A and D cause known harm at doses exceeding the tolerable upper intake levels, and the potential for harm from other supplements at high doses should be carefully considered [100].

Variability in the composition of dietary supplements makes extrapolating results obtained from controlled clinical trials challenging. These recommendations focus only on healthy adults without special nutritional needs and do not apply to children, women who are or may become pregnant, or people who are chronically ill or have a known nutritional deficiency [98−100]. It is important that vitamins and minerals be considered pharmacological agents and be available only with a physician's prescription, preventing their availability over the counter. A more recent study, on resveratrol levels and all-cause mortality in older community-dwelling adults, reported no benefit of this polyphenol during a follow-up of several years [101]. The researchers published 9-year follow-up data of 783 men and women aged 65 years and older living in two small towns in the Chianti wine−producing region of Tuscany. After 9 years, 34.2% of the participants had died. After adjustment for multiple variables, including age, sex, body mass index, lipid levels, and comorbidities, among others, total urinary resveratrol concentrations were not associated with mortality. Across the quartiles of resveratrol concentrations, ranging from lowest to the highest, the incidence of CVDs was 22.3%, 29.6%, 28.4%, and 28.0% ($P = .44$). Similarly, there was no association between resveratrol concentrations and cancer risk, nor was there any association with inflammatory markers such as C-reactive protein, tissue necrosis factor, interleukin-6, and interleukin-1β. This prospective study of older community-dwelling adults showed no association between urinary resveratrol metabolites and longevity. The study suggests that dietary resveratrol from Western diets in community-dwelling older adults does not have a substantial influence on inflammation, CVD, cancer, or longevity [101]. There were no studies on CoQ10, carnitine, and flavonoid intake in this analysis on micronutrients and risk of CVDs.

However, a systematic review and metaanalyses revealed moderate or low-quality evidence of benefits for folic acid for total CVDs, folic acid and B-complex vitamins for stroke, and no effect for calcium, multivitamins, vitamins C and D, beta-carotene, and selenium [8]. There was an increased risk for antioxidant mixtures and for niacin with a statin for all-cause mortality. There was no conclusive evidence for the benefit of any supplement across all dietary backgrounds (including deficiency and sufficiency); therefore any benefits that are seen should be balanced against possible risks. This is true in particular for the role of vitamins and mineral supplements, multivitamins, vitamin D, calcium, and vitamin C on the components of CVD and all-cause mortality [8].

Fig. 43.13 shows summary data for the risk ratios derived from metaanalyses of randomized trials of the four most commonly consumed vitamins and mineral supplements (multivitamins, vitamin D, calcium, and vitamin C) on the components of CVD and all-cause mortality. Of note, none of these popular supplements had an effect on CVD or all-cause mortality.

Fig. 43.14 shows summary data derived from forest plot metaanalyses of randomized, controlled trials that demonstrate positive effects of folic acid and B-complex vitamin supplements (of which folic acid is a component) on stroke

Comparison	RCTs	N	Events	Pooled Effect Estimates RR (95% CIs)	I^2	*p*-value
Multivitamins						
Total CVD	2	16,349	1,941	0.95 [0.77, 1.17]	62%	0.61
MI	3	16,414	772	0.95 [0.82, 1.09]	0%	0.43
Stroke	2	16,349	666	0.86 [0.46, 1.62]	59%	0.64
Total CVD mortality	3	17,351	984	0.94 [0.83, 1.06]	0%	0.30
MI mortality	1	14,641	70	0.63 [0.39, 1.02]	N/A	0.06
Stroke mortality	3	18,055	233	0.88 [0.51, 1.51]	55%	0.63
All-cause mortality	10	22,869	3,633	0.95 [0.90, 1.01]	0%	0.12
Vitamin D						
Total CVD	6	6,546	1,037	0.95 [0.86, 1.05]	0%	0.31
Total CHD	3	434	6	0.97 [0.22, 4.22]	0%	0.97
MI	12	11,081	643	0.95 [0.83, 1.10]	0%	0.52
Stroke	11	11,173	479	1.12 [0.94, 1.34]	0%	0.20
Total CVD mortality	2	3,907	219	0.86 [0.66, 1.10]	0%	0.23
Total CHD mortality	2	225	4	0.41 [0.06, 2.72]	0%	0.35
MI mortality	4	2,873	94	0.85 [0.57, 1.26]	0%	0.41
Stroke mortality	2	2,773	60	1.13 [0.68, 1.87]	0%	0.63
All-cause mortality	43	37,550	5,876	0.99 [0.95, 1.03]	0%	0.58
Calcium						
Total CVD	3	3,328	364	1.43 [0.79, 2.59]	80%	0.23
Total CHD	2	3,171	166	1.16 [0.87, 1.56]	0%	0.32
MI	4	5,387	231	1.69 [0.94, 3.04]	69%	0.08
Stroke	3	3,861	178	1.29 [0.96, 1.72]	0%	0.09
Total CVD mortality	2	2,931	47	1.24 [0.27, 5.65]	53%	0.78
Total CHD mortality	1	5,292	338	1.15 [0.94, 1.41]	N/A	0.18
MI mortality	1	1,460	22	1.44 [0.62, 3.36]	N/A	0.39
Stroke mortality	1	1,460	14	0.75 [0.26, 2.15]	N/A	0.59
All-cause mortality	6	9,765	1,084	1.08 [0.97, 1.21]	0%	0.16
Vitamin C						
Total CVD	2	15,497	1,459	0.99 [0.90, 1.10]	0%	0.89
Total CHD	1	8,171	999	1.04 [0.93, 1.17]	N/A	0.49
MI	2	15,497	545	0.96 [0.81, 1.14]	6%	0.62
Stroke	2	15,497	525	0.92 [0.78, 1.09]	0%	0.33
Total CVD mortality	2	15,497	646	1.07 [0.92, 1.25]	0%	0.35
MI mortality	1	8,171	34	0.79 [0.40, 1.55]	N/A	0.49
Stroke mortality	1	8,171	33	0.83 [0.42, 1.65]	N/A	0.60
All-cause mortality	4	16,004	1,819	1.02 [0.94, 1.11]	0%	0.63



FIGURE 43.13 Summary plots of commonly used vitamins and minerals. *CHD*, Coronary heart disease; *CI*, confidence interval; *MI*, myocardial infarction; *RR*, risk ratio. *Modified from Jenkins DJA, Spence JD, Giovannucci EL. Supplemental vitamins and minerals for CVD prevention and treatment. J Am Coll Cardiol 2018;71:2570–84.*

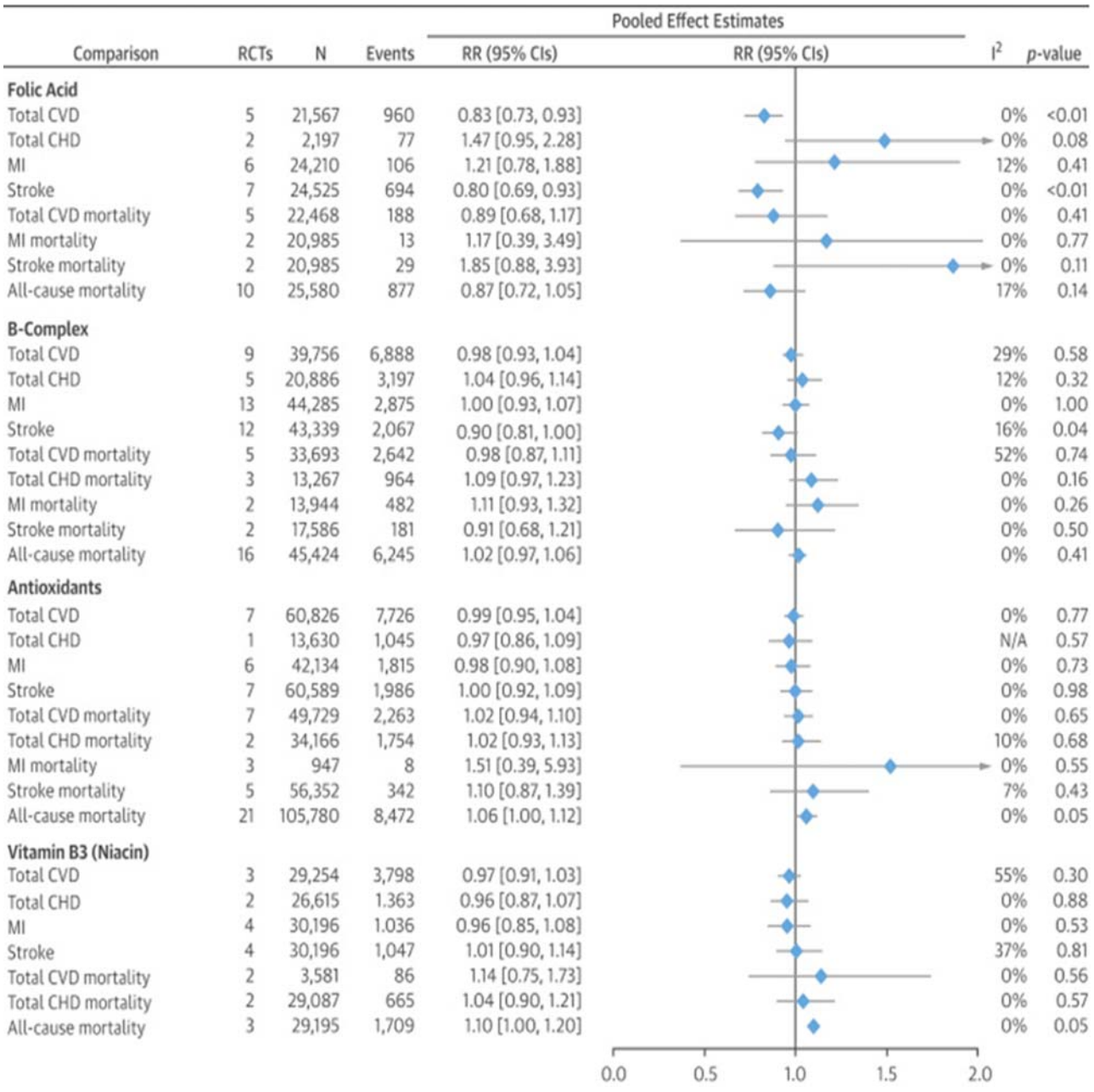


FIGURE 43.14 Summary plots of vitamins and minerals with significant effects. *CHD*, Coronary heart disease; *CI*, confidence interval; *MI*, myocardial infarction; *RR*, risk ratio. *Modified from Jenkins DJA, Spence JD, Giovannucci EL. Supplemental vitamins and minerals for CVD prevention and treatment. J Am Coll Cardiol 2018;71:2570–84.*

and marginally significant adverse effects of antioxidants on stroke and niacin and all-cause mortality. Folic acid and stroke prevention (especially in areas without folic acid fortification) is one of the most conclusive findings in this area over the last 6 years.

Metaanalysis of a large number of studies may have problems due to heterogeneity is studies [8]. Therefore results of large cohort studies are considered more meaningful [78]. In two large trials ($N = 27{,}658$) a lower incidence of cancer was observed in men who had taken a multivitamin for more than 10 years (pooled unadjusted RR: 0.93) [78]. However, in the study including women, no such effect was reported. High-quality studies ($k = 24$; $N = 324{,}653$) of single and paired nutrients (e.g., vitamins A, C, or D; folic acid; selenium; or calcium) were

scant and heterogeneous and showed no clear evidence of benefit or harm. The supplementation of beta-carotene increased lung cancer risk in smokers, and neither vitamin E nor beta-carotene prevented CVD or cancer [78]. The study had limitations because analysis included only primary prevention studies in adults without known nutritional deficiencies. Most studies were conducted in older subjects and included various supplements and doses under the set upper tolerable limits. The duration of most studies was less than 10 years. These two trials found a small, borderline-significant benefit from multivitamin supplements on cancer in men without any effect on CVD.

Another potential limitation may be that there is an unmet need to find nutraceuticals that can target specific molecular mechanisms such as beta cells of pancreas, proinflammatory cytokines, or endothelial cells. In type 2 diabetes, higher dietary inflammation and hyperinsulinemia may be targets of choice for prevention of diabetes and its complications [102].

In a recent population-based cohort study of 5571 adults, higher plasma concentrations of vitamin B_{12} were associated with a 25% increased adjusted risk of all-cause mortality [103]. In a previous cohort study of 75,864 postmenopausal women in the United States, median age 75.8 years, 2304 had a hip fracture during the follow-up from June 1984 through May 2014. A combined high dietary intake of vitamins B_6 and B_{12} was associated with an increased risk of hip fracture [104]. These findings suggest that caution should be used in vitamin administration when there is no apparent deficiency in these vitamins. The cost-benefit ratio of the use of drug therapy in the treatment of patients with high normal blood pressure is not yet clear, although it is associated with an increased risk of CVDs [105]. It is possible that either dietary components or natural products may be able to lower blood pressure with additional beneficial effects, such as a decline in blood glucose or blood lipid levels, without significant adverse effects. Guava fruit and beetroot juice have shown the most convincing evidence of blood pressure−lowering effect. It has also been observed that flavonoid-rich food and beverages (e.g., cocoa, teas, coffee) could be considered [105]. Supplementation of magnesium, potassium, vitamin C, and calcium in pregnancy may improve blood pressures. Among nonnutrient nutraceuticals, flavonols and soy isoflavones may be administered to perimenopausal women, resveratrol to insulin-resistant patients, and melatonin to subjects with nondipping blood pressure in the night [105]. A recent metaanalysis of randomized clinical trials of vitamin D alone, comprising 11 randomized clinical trials with 34,243 subjects, revealed no significant association with risk of any fracture or of hip fracture [106]. However, combined therapy with both vitamin D and calcium (six randomized clinical trials with 49,282 participants) was associated with a 16% lower risk of hip fracture. It seems that standard doses of vitamin D alone were associated with reduced risk of fracture, but daily treatment with both vitamin D and calcium was a more promising strategy [106]. Another systematic review and metaanalysis of randomized controlled trials, comprising 20 studies with 1141 subjects, was conducted to evaluate the effects of zinc administration on risk factors of cardiometabolic diseases [107]. The findings showed that zinc administration significantly reduced plasma levels of triglyceride standardized mean difference (SMD): 0.66, very LDL (SMD: 1.59), and total cholesterol (SMD: 0.65). Zinc therapy also significantly decreased fasting blood glucose (SMD: 0.52; 95% CI: −0.96 to −0.07) and HbA1c (SMD: 0.64; 95% CI: −1.27 to −0.02) [107]. The effects of zinc supplementation on blood pressure and anthropometric indices were not statistically significant ($P > .05$). Zinc supplements had beneficial effects on glycemic indices and lipid profile.

In brief, this systematic review and metaanalyses revealed that there is moderate or low-quality evidence of benefits for folic acid with regard to total CVDs and for folic acid and B-complex vitamins with regard to stroke. No effects were found for calcium, magnesium, multivitamins, vitamins C and D, beta-carotene, and selenium. The increased risk for combination of antioxidants and for niacin with a statin with regard to all-cause mortality was also observed. There seems to be no benefit of any supplement across all dietary backgrounds, including deficiency and sufficiency. Therefore any benefits that are reported should be balanced against possible risks from using the particular nutraceuticals. This is true in particular for the role of vitamins and mineral supplements, multivitamins, vitamin D, calcium, and vitamin C on the components of CVD and all-cause mortality. Vitamin D and calcium administered in combination have beneficial effects on the risk for fractures. However, intake of vitamins B_{12} and B_6 is associated with an increased risk for fractures. More studies are needed to determine the roles of magnesium, resveratrol, CoQ10, and L-carnitine, as well as those of organic calcium, vitamin D, multivitamins, and selenium in nutrient-rich foods.

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Chapter 44

Polyphenolics and flavonoids in health and diseases

Sergey Chibisov[1], Elena Kharlitskaya[10], Ram B. Singh[2], Arunporn Itharat[3], Ekasit On-Saard[4], Hyun-Ryul Park[5,6], Jayeeta Chaudhury[7], Saibal Chakravorty[8], Om Kumari Gupta[8] and Manal M.A. Smail[9]

[1]Faculty of Medicine, People's Friendship University of Russia, Moscow, Russia, [2]Halberg Hospital and Research Center, Civil Lines, Moradabad, India, [3]Department of Applied Thai Traditional Medicine, Thammasat University, Kluangnueng, Thailand, [4]Department of Agro-Industry, Faculty of Agriculture, Ubon Ratchathani University, Ubon Ratchathani, Thailand, [5]Emeritus of Chung-Ang University, Seoul, South Korea, [6]International Society for Heal-Being Studies, Seoul, South Korea, [7]Center of Nutrition Research, Ahmedabad, India, [8]Metro Group of Hospitals, Noida, India, [9]University of Central Lancashire, Preston, United Kingdom, [10]People's Friendship University of Russia, Moscow, Russia

Introduction

Polyphenols and flavonoids can regulate cellular activity by inhibiting free radicals, which are known to cause oxidative stress in the body tissues [1−3]. It seems that because of the presence of these molecules in the body tissues, the body can perform all the physiological and metabolic functions more efficiently while being protected against environmental toxins and risk factors [3−5]. Polyphenols and flavonoids, which are found in abundance in vegetables, fruits, whole grains, seeds, and herbs, provide their beneficial effects as a result of powerful antioxidant effects, which are known to decrease inflammation in the tissues and improve the function of the concerned organs [5−10].

Despite numerous advances in the management of cardiovascular diseases (CVDs) and diabetes, and cancer, corresponding decline in mortality attributed to these diseases remain the major concern [11,12]. Among all the non-communicable diseases (NCDs), the risk of coronary artery disease (CAD) and type 2 diabetes is significantly higher in southwest Asia than in all other countries of the world [12]. More than 17 million deaths each year may be due to CVD, accounting for 30% of all deaths, and CVD incidence continues to increase in low- and middle-income countries, where 80% of CVD deaths occur [11,12]. The International College of Nutrition expert group considers that dietary factors, including flavonoids and omega-3 fatty acids, are critical in the pathogenesis and prevention of deaths due to CVDs [13]. Improvements in US diet helped in reducing the disease burden and lowering premature deaths during 1999−2012 [13]. However, overall, diets remain poor in most countries of the world [13,14]. Increased consumption of fruits, vegetables, nuts, whole grains, and olive oil and mustard oil is an important part of diets associated with lower CVD risk [13,14]. Since these foods are rich in antioxidant flavonoids, omega-3 fatty acids, fiber, vitamins, and both essential and nonessential amino acids, the mechanism relating intake of these foods to CVD risk is still uncertain [13,14]. Epidemiological studies indicate that dietary flavonoids, a class of polyphenols found in a large array of plant foods and herbs, have been examined as potential components associated with risk of CVDs and diabetes [15−22]. This review aims to highlight the pertinent studies showing the role of polyphenolics and flavonoids in NCDs.

Antioxidants in the prevention of cell damage

The body's cells are continuously open to free radical−induced damage, owing to environmental factors such as a Western-type diet, pollution, tobacco, alcoholism, and radiation [1,2]. Excess oxygen may also damage the cells if there is a deficiency in endogenous antioxidants in the tissues. After being inhaled, oxygen is metabolized to split into single atoms with unpaired electrons. The electrons have the tendency to be in pairs, so these atoms, called free radicals, scavenge the body cells to seek out other electrons so that they can become part of a pair [2]. In this process, there may be damage to cells, proteins, and DNA in the tissues, in particular if there are deficiencies in the endogenous antioxidants

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superoxide dismutase, catalase, and ceruloplasmin. Vitamins E, C, A, and D and beta-carotene and the minerals selenium, copper, zinc, and magnesium as well as omega-3 fatty acids are potential antioxidants that have to be supplied from the diet or in nutraceuticals. Coenzyme Q10 is a highly potential antioxidant that is synthesized in the muscles of the body and acts in the mitochondrial cell membranes and is helpful in energy generation. Apart from these antioxidants, diet also supplies additional antioxidants: polyphenols and flavonoids that are generated by plant cells to fight the oxidative stress to protect from environment factors [1−8].

In the human body, a majority of these antioxidants are present in cell membranes to protect the cells from free radicals and reactive oxygen species (ROS) [2]. The common route of O_2 metabolism is through its complete reduction to H_2O by accepting four electrons [2]. However, with a single electron reduction, several free radicals and hydrogen peroxide (H_2O_2), are formed which may cause overproduction of free radicals and tissue damage. The overproduction of free radicals and ROS becomes more pronounced and damaging to tissues if there is a deficiency in endogenous antioxidants along with lower levels of vitamins, minerals, polyphenols, and flavonoids in the tissues [1−8].

Polyphenolics and flavonoids

Polyphenols are naturally present in plant foods, such as fruits, vegetables, herbs, spices, tea, dark chocolate, and wine, but the content may decrease as a result of food processing [3−8]. These agents are capable of neutralizing free radicals that would otherwise damage the cells and tissues in the body by producing inflammation [2]. The grade and amount of inflammation may depend on the acuteness and amount of free radical production as well as on available antioxidant defenses in the body [1−3]. An increase in free radical−induced inflammation damages the beta cells of the pancreas, endothelial cells, smooth muscle cells, cardiomyocytes, neurons, nephrons, and osteocytes, leading to increased risk of related diseases: diabetes mellitus, endothelial dysfunction and atherosclerosis, hypertension, cardiomyopathy, neurodegenerative diseases, chronic kidney disease, osteoporosis, and cancer [1−3]. Since polyphenols and flavonoids have been found to inhibit free radical generation and reduce inflammation, it is possible that dietary deficiency of these agents is the root cause of many NCDs [3−8].

Plants and herbs are rich sources of phytonutrient compounds synthesized in the plants themselves for their protection. These bioactive substances are responsible for the plant's antioxidant and medicinal values [3−6]. Flavonoids are considered as health promoting and disease preventing dietary supplements. Flavonoids are an essential group of naturally occurring polyphenolic compounds, that are characterized with its flavan nucleus. It is one of the most common classes of compounds available in vegetables, fruits, nuts, seeds and plant-derived beverages. It is now considered as an indispensable component in a variety of nutraceutical, pharmaceutical, medicinal, cosmetic and other applications [5−8]. Flavonoids produce a series of subclass compounds, such as flavones, flavonols, flavanones, isoflavones, flavanols, or catechins and anthocyanins [5]. Many flavonoid compounds have been shown to have an antioxidative activity, free radical−scavenging capacity, and are cardioprotective, antidiabetic, antiinflammatory, and antiallergic, while some other flavonoid compounds exhibit potential antiviral activities [2−5]. Recent studies have indicated that flavonoids are the most effective as an anticancer agents through apoptosis by induction of cell cycle arrest and inhibition of key enzymes involved in tumor promotion. Their basic structures consist of C6-C3-C6 rings with different substitution patterns (Fig. 44.1).

Types of polyphenols

The flavonoids can be subdivided into different subgroups depending on the carbon of the C ring on which B ring is attached and the degree of unsaturation and oxidation of the C ring [5,8] (Fig. 44.2). Flavonoids in which the B ring is linked in position 3 of the C ring are called isoflavones; those in which the B ring is linked in position 4 are called neoflavonoids; and those in which the B ring is linked in position 2 can be further subdivided into several subgroups on the

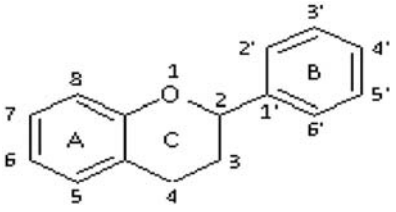


FIGURE 44.1 Chemical structure of flavonoids showing free oxygen at single bond to react with oxygen radical produced in the cell membrane. *Modified from reference Castro MC, Villagarcía H, Nazar A, Arbeláez LG, Massa ML, Del Zotto H, et al. Cacao extract enriched in polyphenols prevents endocrine-metabolic disturb- ances in a rat model of prediabetes triggered by a sucrose rich diet. J Ethnopharmacol. 2020;247:112263. Epub 2019 Sep 30.*

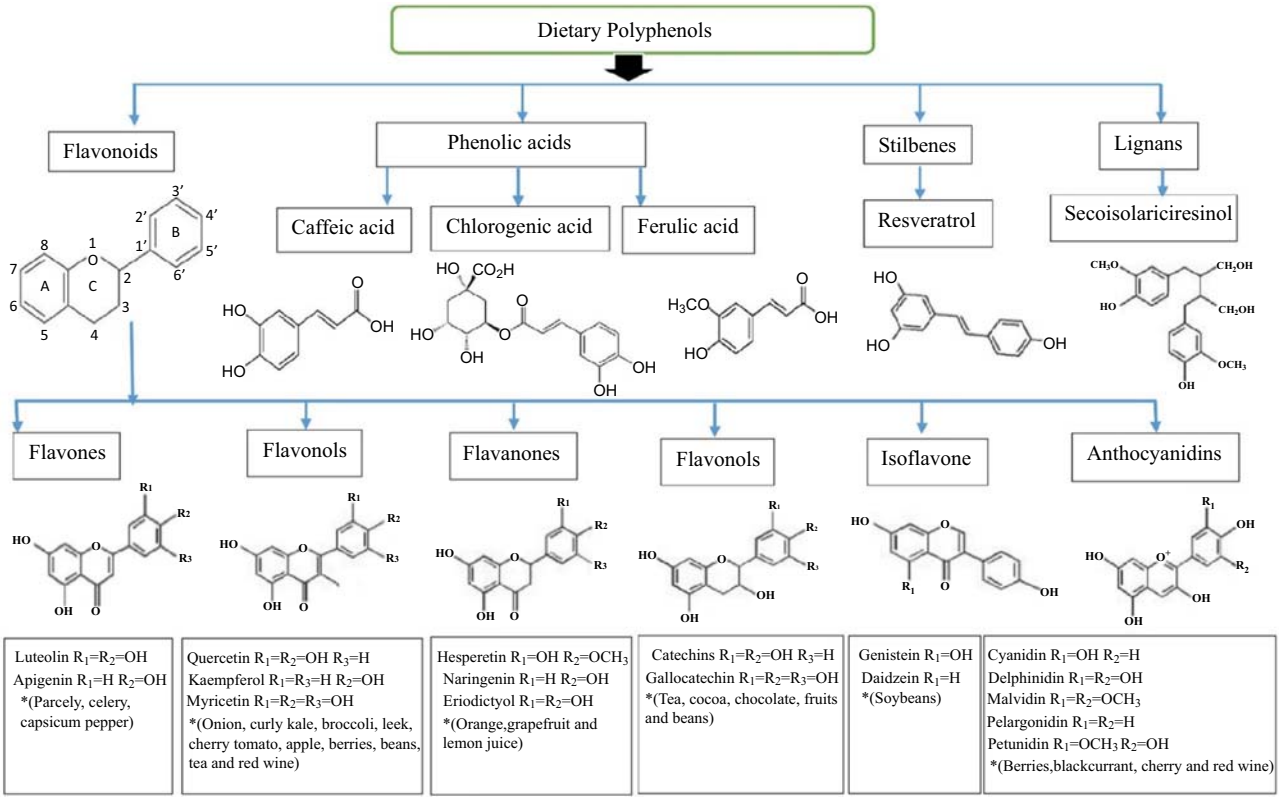


FIGURE 44.2 Chemical structures of different groups of polyphenols and flavonoids. *Modified from reference Karak P. Biological activities of flavonoids: an overview. Int J Pharm Sci Res 2019;10 <https://ijpsr.com/bft-article/biological-activities-of-flavonoids-an-overview/?view = fulltext>.*

basis of the structural features of the C ring. This subgroup is flavones, flavonols, flavanones, flavanonols, flavanols or catechins, and anthocyanins. The flavonoids with an open C ring are called chalcones.

Approximately, 8000 types of polyphenols have been identified that can be further categorized into four main groups [5–7]:

- Phenolic acids account for around 30% of all polyphenols. These are stilbenes and lignans, which are mostly found in fruits, seeds, vegetables, and whole grains [6–8].
- Flavonoids account for around 60% of all polyphenols and include quercetin, kaempferol, catechins, and anthocyanins, which are found in foods like apples, onions, dark chocolate, and red cabbage.
- Polyphenolic amides include capsaicinoids in chile peppers and avenanthramides in oats.
- Other polyphenols include resveratrol from grapes in red wine, ellagic acid in berries, curcumin in turmeric, and lignans in flax seeds, sesame seeds, and whole grains [5–9].

The amount, potency, and type of polyphenols in foods depend on the food, including its origin, its ripeness, and how it was farmed, transported, stored, and prepared [8,9]. The various types and classes of polyphenolics and flavonoids are shown in Fig. 44.2.

Flavonoids are most abundant in four groups of dietary polyphenols and share a basic structure. Among all flavonoids, resveratrol is most popular; it is one of a subclass of stilbenes. Some phenolic acids are caffeic acid, chlorogenic acid, and ferulic acid [5–9]. The main subclasses of flavonoids are flavones, flavonols, flavanones, flavanols, isoflavone, and anthocyanidins [9]. The chemical compound of those are characterized in accordance with the arrangement and number of hydroxyl groups and their extent of alkylation and/or glycosylation [9]. Typically, quercetin is found in abundance in onions, tea, and apples. Hesperetin is found in citrus fruits, and genistein and daidzein are found in soybeans. Anthocyanins, including cyanidins, contribute color to many red fruits such as strawberries, raspberries, and blackcurrants. The intake of polyphenols and flavonoids by various populations varies between 54.6 mg/day in Brazil to 889 mg/day in European countries (e.g., Poland). In the United States, the intake is 250–400 mg/day [15,16] (Table 44.1).

TABLE 44.1 Flavonoid intake and main food sources worldwide (average intake 150–600 mg/day).

Continent	Country	Intake (mg/dL)	Subclass	Food sources
Asia	Korea	107	Protanthocyanidins > flavonols >isoflavones > flavan-3-ols >anthocyanidins > flavanones > flavones	Tangerines, radishes, tofu, onions, soybeans, persimmons, green tea, persimmons, kimchi
	China	318	Protanthocyanidins > flavonols >isoflavones > flavan-3-ols >anthocyanidins > flavanones > flavones	Chinese cabbage, eggplant, leeks, soybean sprouts, celery, tomatoes, apples, oranges, lettuce, potatoes, tea
	Middle East*	1650	Flavan-3-ols > flavones	Black tea
Europe	Southern Europe	313.26	Proanthocyanidins > flavanones >flavan-3-ols > flavonols > anthocyanidins >flavones > isoflavones	Apples, red wine, oranges, beans, pears, peaches
	Northern Europe	348	Flavan-3-ols > flavones > anthocyanidins >flavonols > flavanones > isoflavones	Tea, citrus fruits, berries
	Central Europe	506	proanthocyanidins > flavanones > flavonols > flavones > isoflavone	Tea, noncitrus fruits, wine
	Eastern, Europe, Poland	~600	Flavan-3-ols	Tea, coffee, corn, cocoa,
Oceania	Australia	351–700	Flavan-3-ols > anthocyanidins > flavonols >flavanones > isoflavones > flavones	Black tea, green tea, oranges, grapes, wine, apples, beans, stalk vegetables, broccoli, onions
America	North and South America	250–400	Flavan-3-ols > flavanones > flavonols >anthocyanidins > flavones > isoflavones	Apples, wine, citrus fruit, berries, citrus fruit juices, tea
America	Mexico*	150	Isoflavones	Beans
	Brazil**	50	Flavan-3-ols > flavanones > flavonols >anthocyanidins > flavones	Citrus juices, cocoa, tea, coffee
Asia	India	150–620	Gallic acid protocatechuic acid, chlorogenic acid, ferulic acid, resveratrol, phenolic acids, flavonoids, carotenoids anthocyanidins (cyanidin; delphinidin; and pelargonidin, 0.02 mg), the flavan-3-ol (+)-catechin)	Turmeric, cumin, coriander, fenugreek, cinnamon, chiles, green leaves, fruits, mangos, bananas, citrus fruits, apples, grapes, vegetables, whole grains, wheat, corn, pulses, peanuts and other nuts, tea, herbs

*Highest average intake, **Lowest average intake.
Source: Modified from reference Rodriguez-Garcia C, Sanchez-Quesada C. Dietary flavonoids as cancer chemopreventive agents: an updated review of human studies. Antioxidants 2019;8:137; Escobar-Cevoli R, Castro-Espin C, Beraud V, Buckland G, Zamora-Ros R. An overview of global flavonoid intake and its foods sources. In: Escobar-Cévoli R, Castro-Espín C, Béraud V, Buckland G, Zamora-Ros R, editor. Flavonoids—biosynth hum health. Intech Publishers; 2017, https://doi.org/10.5772/67655.

The intake of whole grains, such as corn, wheat, rice, and pulses, varies between 50 and 200 g/day in various populations. Whole grains are rich sources of phenolic acid as well as free phenolic acids, which are known to inhibit glucose absorption as well as protect the microbiome, owing to their high content of fiber and flavonoids [6] (see Table 44.2).

Beneficial effects of polyphenols and flavonoids

Polyphenols and flavonoids may provide beneficial effects against all the conditions and diseases in which oxidative stress is important in the physiopathology and development of these diseases. [17–20]. The beneficial effects may depend on the class and subclass of the flavonoid as well as on the source. Polyphenols and flavonoids are natural products that are well known for their beneficial effects on health, and efforts are being made to isolate the ingredients from plants [17–20]. Flavonoids are now used as important components in a variety of products made by the nutraceutical, medicinal, pharmaceutical, and cosmetic industries. The current trends of research and development activities on flavonoids are concerned with isolation, identification, characterization, and functions of classes of flavonoid and subclasses and their therapeutic use for health benefits [20] (Fig. 44.3).

TABLE 44.2 Composition and existing forms of phenolic acids in whole grains.

Cereal type	Free phenolic acid combined with phenolic acid
Wheat	Gallic acid, protocatechuic acid, chlorogenic acid, caffeic acid, syringic acid, ferulic acid, vanillic acid, p-coumaric acid, p-hydroxybenzoic acid, isoferulic acid
Brown rice	Ferulic acid, caffeic acid, syringic acid, protocatechuic acid, chlorogenic acid, coumaric acid, salicylic acid, o-coumaric acid, syringol, 2−4-dihydroxybenzaldehyde, sinapic acid, 2-hydroxycinnamic acid, vanillic acid, p-coumaric acid, p-hydroxybenzoic acid
Oats	Chlorogenic acid, caffeic acid, syringic acid, vanillic acid, p-coumaric acid, p-hydroxybenzoic acid, 2−4-dihydroxybenzaldehyde, sinapic acid, ferulic acid, chlorogenic acid
Corn	Ferulic acid, caffeic acid, gallic acid, p-coumaric acid, o-coumaric acid, p-hydroxybenzoic acid, syringic acid, protocatechuic acid

Source: Modified from references Tian S, Sun Y, Chen Z, Yang Y, Wang Y. Functional properties of polyphenols in grains and effects of physicochemical processing on polyphenols. J Food Qual 2019, Article ID 2793973, 8 pages <https://doi.org/10.1155/2019/2793973>.

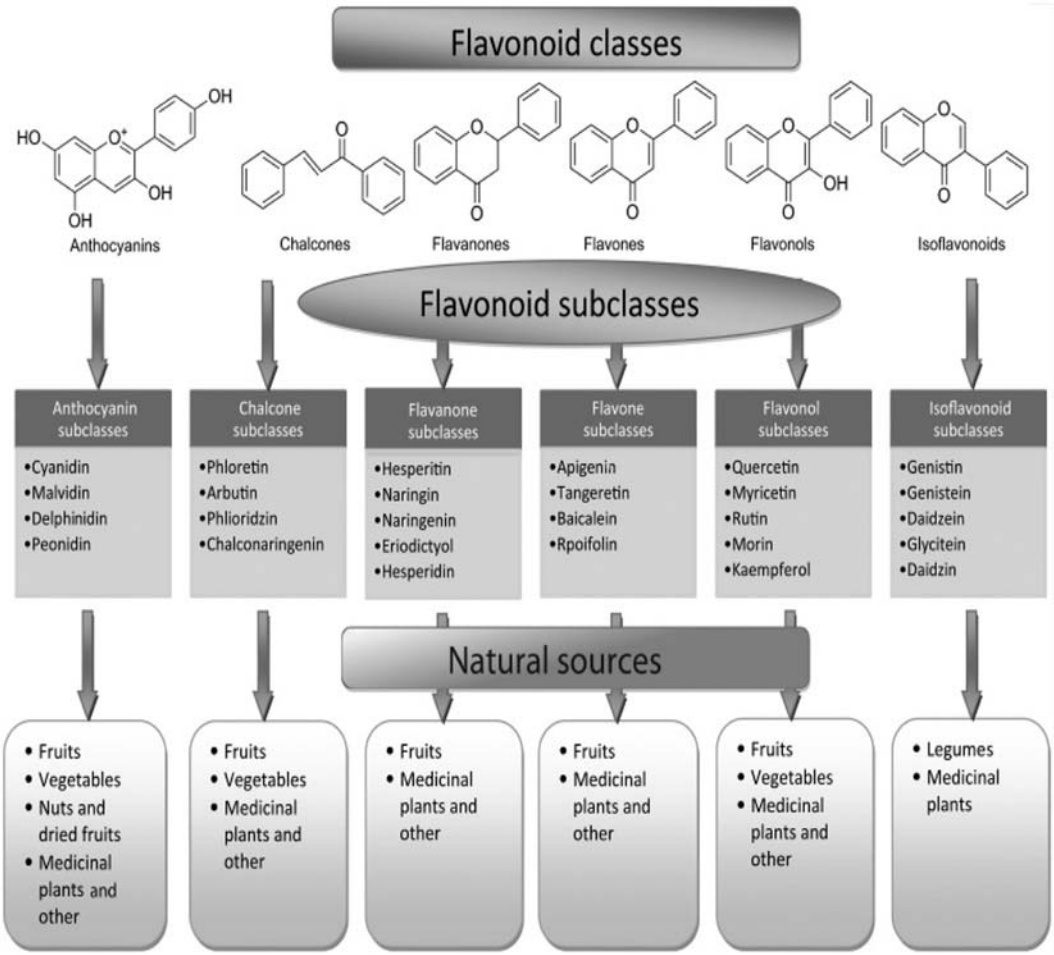


FIGURE 44.3 Flavonoid classes, subclasses, and natural sources. *Modified from reference Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. J Nutr Sci 2016;5:e47. Published 2016 Dec 29. doi:10.1017/jns.2016.41.*

Mechanism of action of flavonoids

The use of flavonoids is based on their mechanisms of actions—antioxidative, antiviral, antiinflammatory, antimutagenic, and anticarcinogenic—coupled with their capacity to modulate key cellular enzyme function [20–30]. (Fig. 44.4).

The hypoglycemic effects of dietary polyphenolic compounds may be related to inhibition of carbohydrate digestion by inhibiting salivary and pancreatic alpha-amylase and alpha-glucosidase enzymes in the small intestinal brush border, inhibition of glucose absorption, and stimulation of insulin secretion and protection of pancreatic beta cells against glucotoxicity [17,18]. Polyphenols are capable of suppressing release of glucose from the liver and improving glucose uptake in the peripheral tissues by modulating intracellular signaling.

Flavonoids are known to prevent oxidation of low-density lipoprotein (LDL) cholesterol and other lipoproteins that become more atherogenic after oxidation. Beta cells of the pancreas and endothelial cells are highly susceptible to damage from free radical–induced inflammation, resulting into insulin resistance and diabetes as well as atherosclerosis [17,18]. Flavonoid intake may bring about a decrease in endothelial damage, which may be associated with increased bradykinin and nitric oxide release and decrease in platelet aggregation. Nicotinamide adenine dinucleotide (NAD) is found in all living cells in an oxidized form (NAD^+) and a reduced form (NADH) [16,19]. The main function of NAD in cells is modulating cellular redox status by carrying electrons from one reaction to another. Hyperglycemia decreases NAD^+ concentrations, which is important in oxidative metabolism, by activation of the polyol pathway and by overactivation of poly(ADP-ribose)-polymerase (PARP). The protective role of three structurally related flavonoids (rutin, quercetin, and flavone) was examined during high-glucose conditions in an in vitro model using human umbilical vein endothelial cells. This study provides evidence that flavonoids are able to protect endothelial cells against a high glucose–induced decrease in NAD [16,19]. Flavonoids are able to inhibit aldose reductase, the key enzyme in the polyol pathway. This protective effect of flavonoids on NAD^+ concentrations is a combination of the flavonoids' ability to inhibit both PARP activation and aldose reductase enzyme activity. The study also shows that flavonoids, by a combination of these effects, maintain the redox state of the cell during hyperglycemia, which can ameliorate vascular complications in diabetes [16]. Antioxidants such as flavonoids prevent the oxidation of cholesterol, which is important in the prevention of atherosclerosis [19]. Polyphenols and flavonols have antioxidant activity and can inhibit the formation of advanced glycation end product to protect the target vascular cells, leading to increased blood flow to heart, brain, and peripheral arterial system [30] (Fig. 44.5).

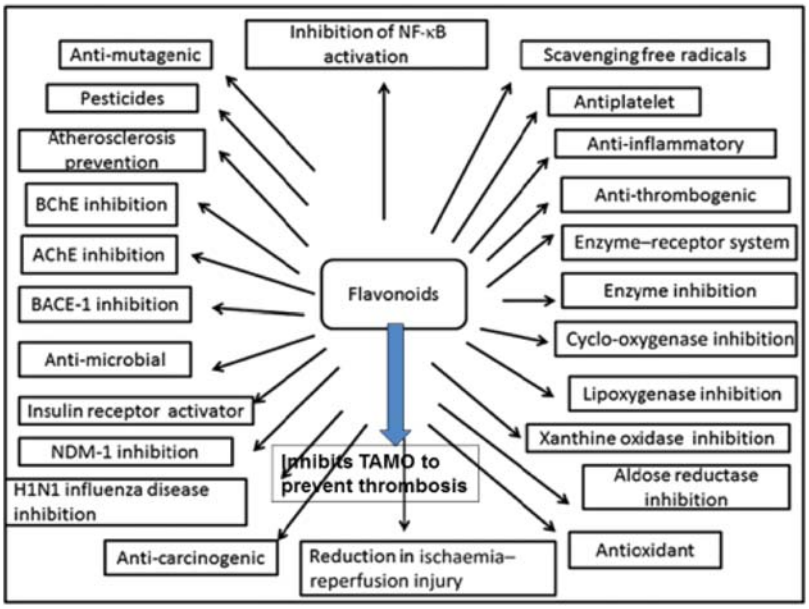


FIGURE 44.4 Beneficial effects and mechanisms of benefits of flavonoids. *Modified from references Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. J Nutr Sci 2016;5:e47. Published 2016 Dec 29. doi:10.1017/jns.2016.41; Bondonno NP, Lewis JR, Blekkenhorst LC et al. Association of flavonoids and flavonoid-rich foods with all-cause mortality: the Blue Mountains Eye Study. Clin Nutr 2020;39:141–150*

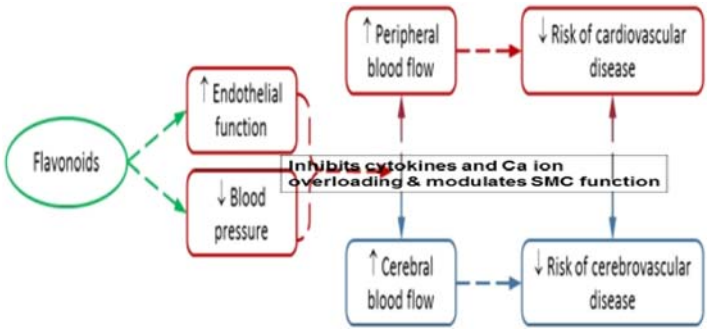


FIGURE 44.5 Mechanisms of action of flavonoids on vascular functions. *Modified from Rees A, Dodd GF, Spencer JPE. The effects of flavonoids on cardiovascular health: a review of human intervention trials and implications for cerebrovascular function. Nutrients 2018;10(12):1852. Published 2018 Dec 1. doi:10.3390/nu10121852.*

Effects of polyphenolics and flavonoids on mortality

There is controversy about the role of polyphenolics and flavonoids in prevention of CVDs and diabetes. Important causes of this controversy may be the type and quality of these agents, the lack of availability of a database for assessment of flavonoid intake, and differences in terminology used to identify flavonoids content [22–27]. The US Department of Agriculture (USDA) has the most comprehensive databases describing the flavonoid content of foods [23]. The Blue Mountains Eye Study, comprising 2349 subjects, with a mean ± standard deviation age of 64.7 ± 9.2 years and follow-up of 14 years [21]. There were 677 deaths during the follow-up years. In the whole cohort, the subjects in the highest tertile of anthocyanidin intake revealed a significantly lower risk of all-cause mortality [hazard ratio (HR): 0.76] when compared to those in the lowest tertile. In subjects with at least one early mortality risk factor (obesity, smoking, high alcohol consumption, no regular exercise), risk of all-cause mortality was lower in those in the highest intake tertile for total flavonoids (HR: 0.77), flavan-3-ols (HR: 0.75), anthocyanidins (HR: 0.70), and proanthocyanidins (HR: 0.69) compared to those in the lowest tertile [21]. Similarly, consumption of apples, tea, and the individual flavonoid compounds quercetin and epicatechin was associated with a lower risk of all-cause mortality among participants with at least one risk factor but not among other participants. It is possible that moderate to high intakes of flavonoids and certain flavonoid subclasses may provide health benefits, particularly for individuals with at least one early mortality risk factor.

In an earlier population-based study of elderly subjects, including 1063 randomly selected women older than 75 years of age, all-cause, cancer, and CVDs mortalities were assessed over 5 years of follow-up [25]. During the 5-year follow-up period, 129 (12%) deaths were documented. Subjects with high intake of total flavonoids were at lower risk of 5-year all-cause mortality (multivariate-adjusted HR: 0.37; 95% CI: 0.22, 0.58) than those with low total flavonoid consumption (HR: 0.36; CI: 0.22, 0.60). Similar beneficial relationships were observed for both CVD mortality (total flavonoid HR: 0.34; 95% CI: 0.17, 0.69; flavonoid HR: 0.32; 95% CI: 0.16, 0.61) and cancer mortality (total flavonoid HR: 0.25; 95% CI: 0.10, 0.62; flavonoid HR: 0.26; 95% CI: 0.11, 0.62). (See Fig. 44.6). It is possible that using the most comprehensive flavonoid databases will provide evidence that high intake of flavonoids is associated with lower risk of mortality in older women. The benefits of flavonoids may extend to the etiology of cancer and CVDs [25]

In a previous meta-analysis including ten studies, the relative risk (RR) of all-cause mortality for the highest category versus lowest category of total flavonoid intake was 0.82 (95% CI: 0.72–0.92) [26]. Subjects who took 200 mg/day of total flavonoids has the lowest risk of all-cause mortality. A marginally significant association was also found between dietary total flavonoids intake and risk of death from CVD (RR: 0.85; 95% CI: 0.70–1.03; $P = .099$) and CAD (RR: 0.74; 95% CI: 0.54–1.02; $P = .069$. This meta-analysis provides strong evidence for the recommendation of consuming flavonoids-rich food to reduce risks of mortality from all causes as part of a healthy diet for adults [26]. Diet quality index scores (DQIS) have traditionally been used to predict health outcomes. Dietary total antioxidant capacity (TAC), a useful tool for assessing total antioxidant power in the diet, may also be a novel predictor of risk [27]. This study evaluated the associations between dietary TAC and DQIS and all-cause mortality. The National Health and Nutrition Examination Survey (NHANES) 1988–1994 and 1999–2006, included 23 797 U.S. adults who were followed up until 2015, approximately 9–21 years. Dietary TAC and DQIS, including the Healthy Eating Index-2015 (HEI-2015), Alternative Healthy Eating Index-2010 (AHEI-2010), alternate Mediterranean Diet (aMED), and Dietary Approaches to Stop Hypertension (DASH), were calculated by using a one-day 24-hour dietary recall. The adult subjects in the highest quintiles of DQIS revealed reduced rates of all-cause mortality compared to those in the lowest quintiles (HEI-2015 HR: 0.87; AHEI-2010 HR: 0.84; aMED HR: 0.79; DASH HR: 0.80) [27]. Those in the highest

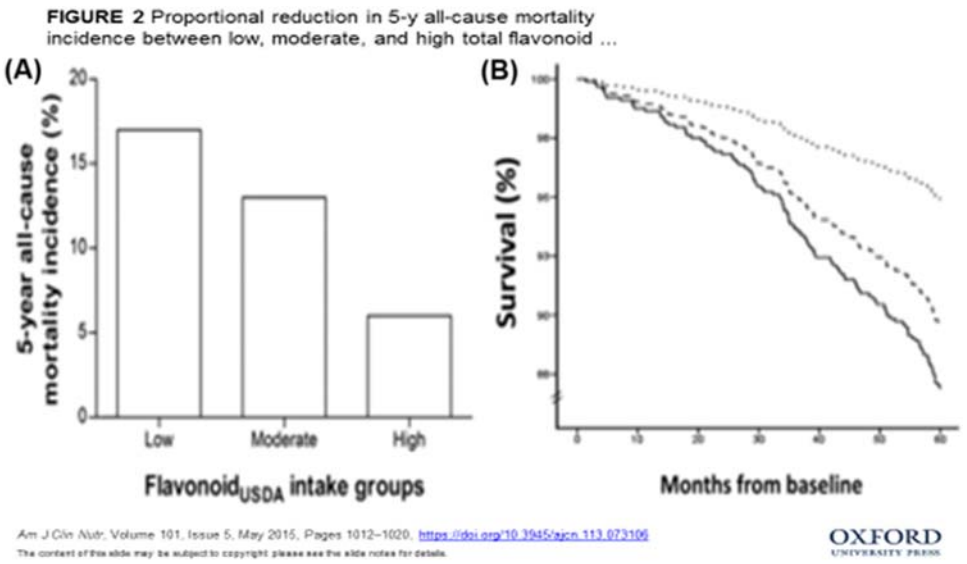


FIGURE 44.6 Proportional reduction in 5-year all-cause mortality incidence between low, moderate, and high total flavonoid consumption as estimated from the USDA database. (A) Low flavonoid USDA intake: <547 mg/day, $N = 354$; moderate flavonoid USDA intake: 547 to <813 mg/day, $N = 355$; high flavonoid USDA intake: ≥813 mg/day, $N = 35$). (B) Cox proportional hazard model survival curve from baseline to 5-year follow-up stratified by total flavonoid USDA consumption. Low flavonoid USDA intake (*solid line*): <605 mg/day, $N = 354$; moderate flavonoid USDA intake (*dashed line*): 605 to <915 mg/day, $N = 355$; high flavonoid USDA intake (*dotted line*): ≥915 mg/day, $N = 354$. *Modified from reference Ivey KL, Hodgson JM, Croft KD, Lewis JR, Prince RL. Flavonoid intake and all-cause mortality. Am J Clin Nutr 2015;101:1012−1020 [25].*

quintile of dietary TAC also showed a lower all-cause mortality than those in the lowest quintile (HR: 0.88). The results indicate that dietary TAC might be a relatively valid predictor of all-cause mortality in the US population compared to the DQIS [27].

The Zutphen Elderly Study, which was a prospective cohort study of 774 men aged 65−84 years in 1985, examined the association of epicatechin intake with risk of mortality due to CVDs [28]. The intake of epicatechin was, mean 15.2 ± 7.7 mg/day, and the major dietary sources were tea (51%), apples (28%), and cocoa (7%). After 25 years of follow-up, 329 men died from CVD, 148 died from CAD, and 72 died from stroke. CAD mortality risk was 38% lower in men in the top tertile of epicatechin intake than in men in the bottom tertile of epicatechin intake (HR: 0.62). Epicatechin intake was also significantly associated with a 46% lower risk of CVD mortality in men with prevalent CVD (HR: 0.54; 95% CI: 0.31, 0.96) but not in men who were free of CVD [28]. It is possible that epicatechin intake is inversely related to mortality due to CAD in elderly men and to CVD mortality in prevalent cases of CVD. More studies are needed before conclusions can be drawn. A systematic review provides an overview of the last ten years of literature on the evaluation of polyphenol intake and its association with specific disease markers and/or endpoints [29]. The mean total polyphenol intake was assessed by determining the food intakes pattern; tea, vegetables, fruits, red wine, and coffee were the main products providing polyphenols. The intake of flavonoids and specific subclasses, but not total polyphenols, has been associated with a low risk of diabetes, CVD events, and all-cause mortality [29]. The critical mass of available data strongly suggests the protective effect of a polyphenol-rich dietary pattern for prevention of CVDs [29].

Effects of flavonoids on cardiovascular diseases

Epidemiological studies have suggested that intake of flavonoids is associated with a decreased risk for CVD. However, the results of these studies remain controversial [22,30,31]. Consumption of foods rich in flavonoids (e.g., cocoa, apples, tea, citrus fruits, and berries) may provide beneficial effects from polyphenolics and flavonoids on cardiovascular risk factors such as high blood pressure, smooth muscle function, and endothelial dysfunction [30]. These effects are thought to have a significant impact on both vascular and cerebrovascular health, ultimately with the potential to prevent CAD, stroke, and hypertension as well as CVDs in diabetes and potentially neurodegenerative disease [30,31]. The current evidence indicates a consistent role for the effects of flavonoid supplementation on human endothelial function and both coronary and cerebral blood flow. There is evidence to indicate the potential to reduce blood pressure in hypertensive subjects and to increase peripheral blood perfusion [30]. A more recent meta-analysis of selected studies (published in 2020) comprised a total of 74 241 women from the Nurses' Health Study (1984−2012), 94 233 women from the Nurses' Health Study II (1991−2013), and 42 226 men from the Health Professionals Follow-Up

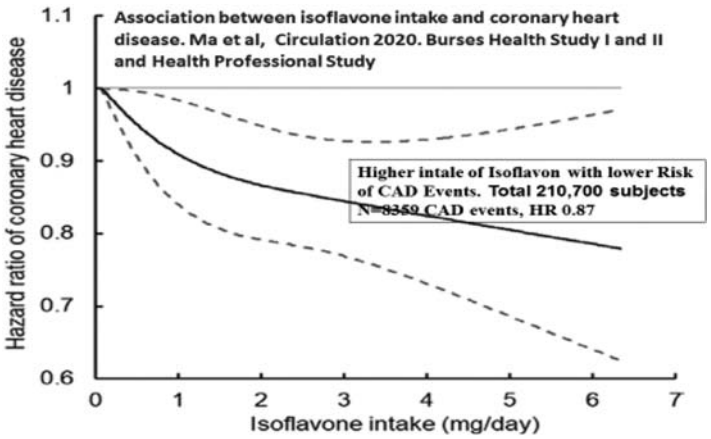


FIGURE 44.7 Association of isoflavone intake with risk of coronary artery disease. *Modified from Ma L, Liu G, Ding M, Zong G, Hu FB, Willet WC, et al. Isoflavone intake and the risk of coronary heart disease in United States Men and women, results from 3 Prospective Cohort Studies. Circulation. 2020;141:00–00. DOI: 10.1161/CIRCULATIONAHA.119.041306.*

Study (1986–2012) who were free of CVDs and cancer at baseline [22]. Of the total of 210 700 subjects, 8359 had incident CAD, documented during 4 826 122 person-years of follow-up. In multivariable-adjusted analyses, isoflavone intake was inversely associated with CAD (pooled HR: 0.87; [5% CI; $P = .008$) (see Fig. 44.7).

Intake of tofu, but not soy milk, was inversely associated with CAD risk, with pooled HRs (95% CIs) of 0.82 ($P = .005$) and 0.87 ($P = .41$), respectively, comparing one or more servings/week with fewer than one serving/month [22]. Further analyses showed that in women the favorable association of tofu was primarily driven by a stronger inverse association of tofu intake observed in younger women before menopause and in postmenopausal women without hormone use ($P_{\text{interaction}} = 0.002$). It is possible that higher intake of isoflavones and tofu was associated with a moderately lower risk of developing CAD, and in women the favorable association of tofu was more pronounced in postmenopausal women without hormone use and in young women [22].

In a systematic review of prospective cohort studies, the aim was to evaluate the association between dietary flavonoid intake and CVD risk [31]. The inclusion criteria were met by fourteen prospective cohort studies. The intakes of anthocyanidins (RR: 0.89), proanthocyanidins (RR: 0.90), flavones (RR: 0.88), flavanones (RR 0.88) and flavan-3-ols (RR: 0.87) were inversely associated with the risk of CVD on comparison of the highest and lowest consumption. A similar association was observed for flavonol intake and CVD risk. The summary RR for CVD for every 10 mg/d increment in flavonol intake was 0.95 (95% CI: 0.91, 0.99). It is possible that the dietary intakes of six classes of flavonoids, namely, flavonols, anthocyanidins, flavones, proanthocyanidins, flavanones, and flavan-3-ols, significantly decrease the risk of CVD [31].

Effects of flavonoids in hypertension

There is evidence that increased intake of flavonoids may be associated with vasodilation due to vascular relaxation [2–5,30–32]. Flavonoids are a type of polyphenol found in abundance in fruits, and a growing body of evidence indicates antihypertensive effects of the flavonoids due to its antioxidant properties. No systematic review has been conducted to collate the evidence on the effects of flavonoid-rich fruits among subjects with hypertension. This systematic review included only randomized controlled trials that compared the supplementation of any type of flavonoid-rich fruit or equivalent supplement with a placebo or other intervention in adults with hypertension [32]. Trials that did not specify the flavonoid component of the fruit or fruit supplement were excluded in the review. The subclasses of flavonoids included anthocyanins, naringin, narirutin, and flavan-3-ols. Secondary outcomes, including change in weight, blood glucose level, triglyceride level, and total blood cholesterol level, were also assessed. Fifteen randomized controlled trials comprising 572 subjects were included in the analysis.

A meta-analysis of five of the trials found no evidence of benefits of flavonoids on systolic or diastolic blood pressure when compared to placebo. The pooled results from two crossover trials with two-timed dosed interventions in a 24-hour period reported no evidence of benefits on a reduction in diastolic blood pressure ($P = .38$) but did reveal evidence of a reduction in systolic blood pressure ($P = 0$). A trial in which flavonoids were administered for more than four weeks ($N = 6$) and blood pressure was assessed after the flavonoid intervention reported no evidence of benefit for either systolic or diastolic blood pressures [32]. The results from this systematic review should be interpreted with caution, given that the results were obtained from single-center trials with small sample sizes. Many trials are conducted with support from the drug industry to demonstrate such effects of nonpharmacological interventions. Large, robust randomized controlled trials using sample sizes based on power calculations are needed to provide evidence for the use of flavonoid-rich fruits for the management of hypertension. This is important because flavonoid-rich diets have been

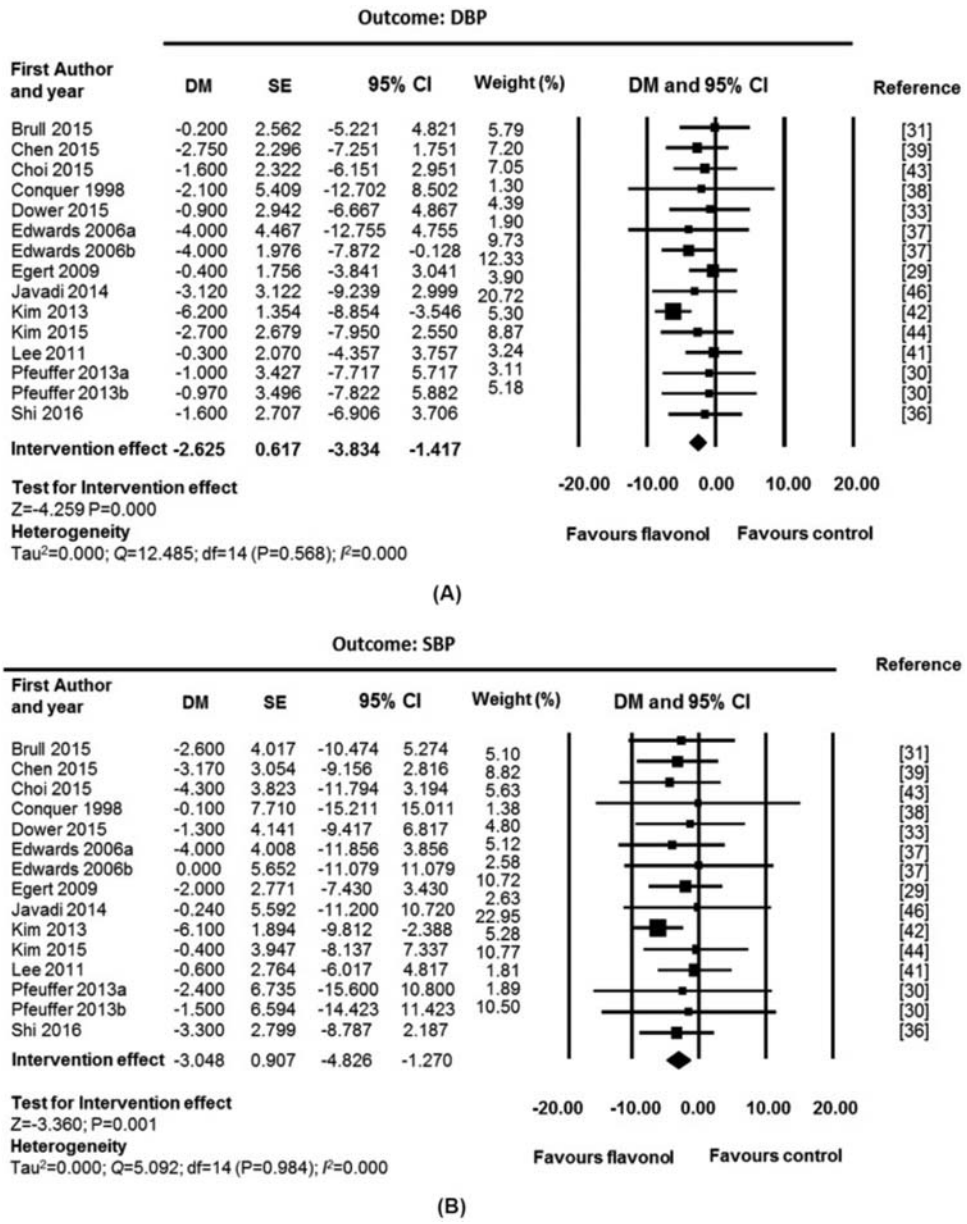


FIGURE 44.8 Effects of flavoids on blood pressures. *Modified from reference Menezes R, Rodriguez-Mateos A, Kaltsatou A, et al. Impact of flavonols on cardiometabolic biomarkers: a meta-analysis of randomized controlled human. Trials to explore the role of inter-individual variability. Nutrients 2017;9(2):117. Published 2017 Feb 9. doi:10.3390/nu9020117 [33].*

found to decrease CVD mortality [22]. In a meta-analysis of 18 studies, effects of polyphenol- and flavonoid-rich diets were assessed in 15 studies [33]. The results revealed that among subjects with hypertension there was no benefit for systolic and diastolic blood pressures (Fig. 44.8).

Effects of flavonoids on cardiometabolic risk factors

Several epidemiological studies have linked flavonols with decreased risk of CVD [30,31]. There may be some heterogeneity in the individual physiological responses to the consumption of these compounds [33]. This meta-analysis aimed to study the effect of flavonol therapy on biomarkers of CVD (blood lipids, blood pressure, and plasma glucose) as well as factors affecting their interindividual variability. The meta-analysis included 18 randomized controlled trials, which were pooled, and the effect was estimated by using fixed or random effects meta-analysis model and reported as difference in means (DM). Variability in the response of blood lipids to supplementation with flavonols was assessed by stratifying various population subgroups: age, sex, country, and health status. The findings revealed significant decreases in levels of total cholesterol (DM = −0.10 mmol/L), LDL cholesterol (DM = −0.14 mmol/L), and triacylglycerol (DM = −0.10 mmol/L) and a significant increase in levels of HDL cholesterol (DM = 0.05 mmol/L). A significant decrease was also reported in

fasting plasma glucose levels (DM = −0.18 mmol/L, and in blood pressure (systolic: DM = −4.84 mmHg; diastolic: DM = −3.32 mmHg) [33]. Interestingly, subgroup analysis revealed a more pronounced effect of flavonol intake in subjects from Asian countries and in subjects with dyslipidemia compared to healthy subjects with normal baseline values. It is possible that flavonol consumption improved biomarkers of CVD risk; however, country of origin and health status may influence the effect of flavonol intake on levels of blood lipids (Fig. 44.9).

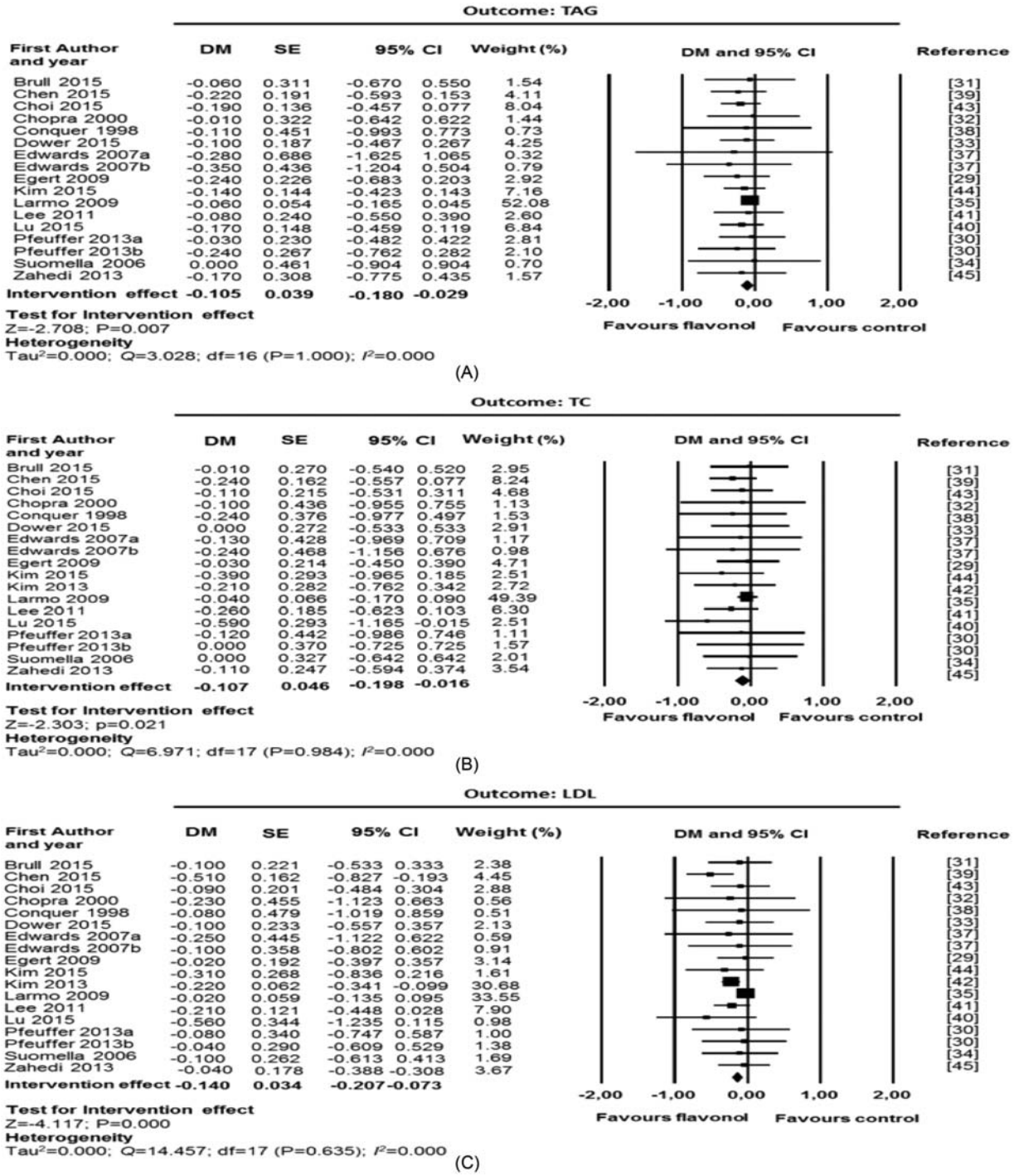


FIGURE 44.9 Effect of flavonol supplementation on measures of blood lipids (mmol/L): (A) Triacylglycerols (TAG); (B) Total cholesterol (TC); (C) LDL cholesterol (LDL); and (D) HDL cholesterol (HDL). *Modified from reference Menezes R, Rodriguez-Mateos A, Kaltsatou A, et al. Impact of flavonols on cardiometabolic biomarkers: a meta-analysis of randomized controlled human. Trials to explore the role of inter-individual variability. Nutrients 2017;9(2):117. Published 2017 Feb 9. doi:10.3390/nu9020117.*

Effects of polyphenols on diabetes

The prevalence of diabetes mellitus is rapidly increasing worldwide and has doubled in the last three decades in many countries [12]. The increased risk of diabetes is associated with increased intake of ready-prepared refined foods, red meat, and preserved meats with deficiency of micronutrients in the diet in conjunction with decreased physical activity [12–14]. Lack of treatment may lead to major microvascular and macrovascular complications, which will pose a major challenge for healthcare systems. Prevention of diabetes mellitus may be achieved via control of modifiable lifestyle factors, such as regular physical activity, a healthy diet, refraining from smoking, maintaining a healthy weight, and monitoring of blood pressure and total antioxidant status in the body [13,14]. One important component of a healthy diet is plant-based foods, particularly polyphenolics and flavonoids in the diets [18]. In a meta-analysis of 12 studies, increased supplementation of flavonoid-rich foods was associated with a significant decline in blood glucose levels [33] (Fig. 44.10).

In a meta-analysis including 18 studies, the association between polyphenols (51 different compounds in total) and type 2 diabetes was examined [34]. A comparison of extreme quantiles revealed inverse associations for intakes of polyphenols (HR: 0.56), flavonoids (HR: 0.88), flavonols (HR: 0.92), flavan-3-ols (HR: 0.89), catechins (HR: 0.86), anthocyanidins (HR: 0.86), isoflavones (HR: 0.92), daidzein (HR: 0.89), genistein (HR: 0.92), stilbenes (HR: 0.44), and biomarkers of daidzein (HR: 0.8) and genistein (HR: 0.79). Nonlinear associations were observed in the dose-response meta-analysis for intakes of polyphenols, flavonoids, flavanones, anthocyanidins, anthocyanins, and biomarkers of genistein [34]. A linear dose-response association was also observed for phenolic acids. It is possible that diets that are rich in polyphenols, particularly flavonoids, play a major role in the prevention of type 2 diabetes and all-cause mortality [21,22,25–27,34,35].

Effects of polyphenols and flavonoids on cancers

The prevalence of cancer is rapidly increasing in some populations, whereas in others there has been decline in the prevalence in the last three decades in many countries [12–14]. The increased risk of cancers is associated with increased intake of ready-prepared refined foods, red meat, and preserved meats with deficiencies in micronutrients in the diet in conjunction with decreased physical activity [12–15]. The risk of cancer is much lower among people who consume increased amount of vegetables, tea, coffee, wine, cocoa, fruits, and whole grains, which are the main dietary sources of polyphenolics and flavonoids [15,36,37]. Flavonoids have been shown to possess a wide variety of anticancer effects: they modulate ROS-scavenging enzyme activities, participate in arresting the cell cycle, induce apoptosis and autophagy, and suppress cancer cell proliferation and invasiveness. Flavonoids have dual action regarding ROS homeostasis: (1) They act as antioxidants under normal conditions and inhibit carcinogen initiated free radical damage, and (2) are potent prooxidants in cancer cells, triggering the apoptotic pathways and downregulating proinflammatory signaling pathways. It is possible that diets that are rich in polyphenols, particularly flavonoids, play a major role in the prevention of cancers and all-cause mortality [21,22,25–27].

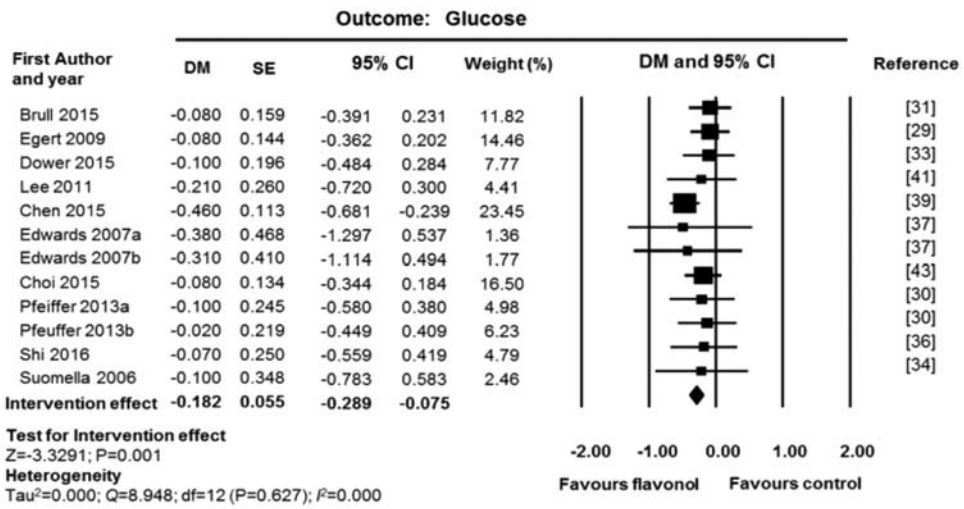


FIGURE 44.10 Effects of flavonoids on blood glucose. *Modified from reference Menezes R, Rodriguez-Mateos A, Kaltsatou A, et al. Impact of flavonols on cardiometabolic biomarkers: a meta-analysis of randomized controlled human. Trials to explore the role of inter-individual variability. Nutrients 2017;9(2):117. Published 2017 Feb 9. doi:10.3390/nu9020117.*

Randomized, controlled trials

There have been no large-scale trials using multiple polyphenols and flavonoids in the treatment of CVDs, diabetes mellitus, and cancers [32]. There is an unmet need for confirmation by adequately powered randomized controlled trials of the observed associations between increased intake of fruits and vegetables that are rich in flavonoids and vascular function or CVDs. In a randomized, controlled trial, the effect of increasing dietary polyphenol intake on microvascular function in hypertensive participants was examined [36]. Results of an analysis of the primary endpoint was obtained for 92 participants and indicated changes in maximum percent response to acetylcholine, revealing a significant improvement in the high-polyphenol group ($P = .02$). The levels of vitamin C, carotenoids, and epicatechin showed significantly larger increases in the high-polyphenol group (between-group difference $P < .001$; $P < .001$; $P = .008$, respectively) compared to the control group. It is possible that increasing the polyphenol content of the diet via consumption of high amount of berries and dark chocolate results in a significant improvement in an established marker of cardiovascular risk in hypertensive participants [36].

In a parallel dose-response dietary intervention study, subjects with a CVD RR of 1.5 assessed by risk scores were randomly assigned to one of the three groups: habitual (control group), high-flavonoid diet, or low-flavonoid diet [38]. The control group ($N = 57$) received their habitual diet, the high-flavonoid group ($n = 58$) and low-flavonoid group ($N = 59$) groups sequentially increased their daily intake of fruit and vegetables by an additional 2, 4, and 6 portions for six-week periods during the study duration of 18 weeks [38]. After the follow-up of 18 weeks, there was a dose-dependent increase in dietary and urinary flavonoids in the high-flavonoid group with no change in the other groups ($P = .0001$). Significantly higher dietary intakes of folate ($P = .035$), nonstarch polysaccharides ($P = .001$), vitamin C ($P = .0001$), and carotenoids ($P = .0001$) were observed in both intervention groups compared with the habitual diet group, findings that were broadly supported by nutrient biomarker analysis [38].

In a later single-blind, dose-dependent, parallel randomized controlled dietary intervention study, the role of low fruit and vegetable consumption (in subjects who had a $\geq$ 1.fivefold increased risk of CVD) was compared with high fruit and vegetable consumption [39]. All the volunteers ($N = 174$) were randomly assigned to receive a diet high in fruits and vegetables, a diet that was lower in fruits and vegetables, or a habitual diet. The amounts of fruits and vegetables and in the high and lower fruit and vegetable diets were sequentially increased by two, four, and six (+2, +4, and +6) portions/day every 6 weeks over habitual intakes. Arterial stiffness (pulse wave velocity measured by pulse wave analysis), microvascular reactivity (measured by laser Doppler imaging with iontophoresis), 24-hour ambulatory blood pressure, and biomarkers of nitric oxide, vascular function, and inflammation were determined at baseline and at 6, 12, and 18 weeks. In men the high fruit and vegetable diet increased endothelium-dependent microvascular reactivity ($P = .017$) with +2 portions/day (at 6 weeks) and reduced C-reactive protein ($P = .001$), E-selectin ($P = .0005$), and vascular cell adhesion molecule ($P = .0468$) with +4 portions/ay 12 week) [39]. High fruit and vegetable also increased plasma nitric oxide ($P = .0243$) with +4 portions/day (at 12 weeks) in the group as a whole. An increase in fruits and vegetables, regardless of flavonoid content in the groups as a whole, mitigated increases in arterial stiffness measured by pulse wave velocity ($P = .0065$) and decline in nitric oxide ($P = .0299$) in the control group. These results support recommendations to increase fruit and vegetable intake to six or more portions daily, with additional benefit from fruit and vegetables that are rich in flavonoids, particularly in men with an increased risk of CVD [39].

However, not all trial have found positive results. In a meta-analysis involving 15 randomized trials (mentioned earlier in the chapter in the discussion of hypertension) the subclasses of flavonoids (anthocyanins, naringin, narirutin, and flavan-3-ols) were administered [32]. Since these trials were small with treatment for 2−4 weeks, there was a nonsignificant reduction in blood pressures [32]. In another meta-analysis, 18 randomized controlled trials were pooled, and the effect of flavonols was estimated by using fixed or random effects meta-analysis model [32]. There was a significant DM of blood glucose and blood lipid levels as DM.

Effects of polyunsaturated fatty acid/flavonoid ratio on cardiovascular diseases

It is important to consider trials in which assessment of flavonoid intake was not done initially but the results showed beneficial effects on CVDs. In a meta-analysis including data from three earlier published, randomized, controlled single blind trials, the role of Indo-Mediterranean-style foods and nutrients in the prevention of CVDs, including heart failure was examined [35]. The intervention ($N = 1446$) and control groups ($N = 1320$) were compared for behavioral risk factors, food intake, fatty acid and flavonoid intake, and ratio of polyunsaturated fatty acid (PUFA) to flavonoid intake. The consumption of omega-3 fatty acids and consumption of flavonoids were significantly higher in the intervention group compared to the control group. The main flavonoids were carotenoids, flavonols, resveratrol, quercetin, gallic

acid, ferulic acid, anthocyanins, proanthocyanidins, and epicatechin. However, the PUFA/flavonoid ratio of the diets showed significant decrease on increased adherence to Indo-Mediterranean diets compared to the control group (Table 44.3). No such observation has been published to our knowledge. It is possible that increased intake of polyphenols and flavonoids along with high omega-3 fatty acids could be complementary to each agent by providing inhibition of lipid oxidation of fatty acids with synergestic antioxidant effects on various targets of body systems [35].

At entry to the study, all the parameters of heart failure revealed no significant differences between the intervention and control groups. However, after a follow-up of two years, incidences of left ventricular strain (odds ratio (OR): 0.57; CI:0.50−0.6;, $P < .01$), left ventricular hypertrophy (OR: 0.69, CI: 0.64−0.75, $P < .01$), and NYHA class II−IV heart failure (OR: 0.59; CI: 0.50−0.68; $P < .05$) were significantly lower in the intervention group compared to the control group [35]. The incidence of cardiac arrhythmias was also significantly lower in the intervention group compared to the control group (OR: 0.49; CI: 0.42−0.56; $P < .01$). Total mortality due to CVDs was significantly lower in the intervention group compared to control group (Table 44.4). The incidences of nonfatal and fatal myocardial infarctions were also significantly lower in the intervention group receiving a high-flavonoid diet compared to a low-flavonoid diet.

It seems that a high-flavonoid diet can prevent adverse effects of omega-6 fatty acids and inhibit adverse effects of choline and lecithin present in fish and meat, causing a significant decline in tri-amino-methyl-N oxide produced by these foods and nutrients [40]. It is possible that consumption of Indo-Mediterranean-style diets characterized by high amounts of omega-3 fatty acids and flavonoids and a low PUFA/flavonoid ratio can cause a significant decline in heart failure as well as in arrhythmias, possibly owing to the antiinflammatory effects of such diets. This may be an important mechanism for reduction in cardiovascular mortality in patients with recent myocardial infarction and high risk of

TABLE 44.3 Fatty acid consumption in the Indo-Mediterranean style diet group and standard diet group.

	Before entry	At entry		After 2 years	
Fatty acid (kJ/day)	All patients	Indo-Mediterranean ($N = 1446$)	Standard ($N = 1320$)	Indo-Mediterranean ($N = 1446$)	Standard ($N = 1320$)
Saturated	10.1 ± 2.43	7.1 ± 1.34*	9.2 ± 2.55	7.2 ± 0.24*	10.8 ± 0.36
Monounsaturated	9.4 ± 2.48	9.6 ± 2.42*	7.7 ± 2.36	8.0 ± 2.15	10.4 ± 3.22
Polyunsaturated	6.91 ± 1.72)	8.0 ± 2.04*	7.23 ± 2.42	8.8 ± 2.33*	7.11 ± 2.25
Omega-6	6.6 ± 1.36	6.2 ± 1.34	7.1 ± 2.31	7.1 ± 2.45	6.8 ± 2.23
Omega-3	0.31 ± 0.08	1.8 ± 0.24**	0.31 ± 0.095	1.7 ± 0.33**	0.31 ± 0.095
Omega-6/omega-3 ratio	21.3 ± 3.3**	3.4 ± 0.76**	22.9 ± 2.4	4.2 ± 0.76**	21.9 ± 4.3
Main dietary oil	Peanut	Mustard	Sunflower	Mustard	Sunflower, peanut
Flavonoids, g/day	0.62 ± 0.05	1.85 ± 0.066*	0.65 ± 0.12	1.88 ± 0.067*	0.66 ± 0.13
PUFA/flavonoid	11.12 ± 2.13	4.32 ± 0.67*	11.12 ± 2.34	4.68 ± 0.88*	10.77 ± 2.33

Values are mean ± standard deviation $^{**}P < .01$.
Source: From Singh RB, Takahashi T, Fatima G, Horuichi R, Fedacko J, Huzova Z, et al. Effects of antioxidant rich Indo-Mediterranean foods on pre-heart failure: results from the randomized controlled trials. Open Inflamm J 2020;8:1−10 [35].

TABLE 44.4 Numbers and percentages and rate ratios for endpoints in the Indo-Mediterranean-style diet group and standard diet group after two years of follow-up.

Events	Indo-Mediterranean-style diet ($N = 1446$)	Control diet ($N = 1320$)	Adjusted rate ratio (95% confidence interval)
Total cardiac mortality	77 (5.32)**	108 (8.18)	0.65 (0.57−0.70)**
Fatal myocardial infarction	57 (3.94)	64 (4.85)	0.81 (0.71−0.88)
Sudden cardiac death (<1 h)	20 (1.38)*	44 (3.33)	0.41 (0.31−0.53)**
Total cardiovascular mortality	86 (5.94)**	117 (8.86)	0.67 (0.61−0.73)*

Values are number (%), $^{**}P < .001$, $^{*}P < .01$. Total deaths; adjustment made for baseline age, gender, body mass index, cholesterol, and blood pressure.

CVDs [35]. The gut microbiome metabolizes choline and carnitine to release trimethylamine (TMA), which subsequently undergoes hepatic conversion to trimethylamine N-oxide (TMAO) [40]. Elevated TMAO levels are associated with increased risks of mortality due to CVDs and all-cause mortality. It is possible that dietary flavanols can modulate the composition and function of the gut microbiome, resulting in a decline in insulin resistance [41,42]. Therefore the possibility exists that these compounds could reduce intestinal TMA production with lower circulating TMAO on long-term administration [40]. Physiological characteristics do not appear to predict TMAO responsiveness to flavanol interventions. However, African-American subjects appeared less responsive compared to non-Hispanic white subjects for both green tea and high-cocoa treatments, and female subjects appeared less responsive than males for the high-cocoa treatment.

Effects of flavonoid intake and bioavailability

The highest concentration of plasma flavonoids in humans is usually reached 1−2 hour after the intake of flavonoid-rich foods [36,41−43]. The absorption of flavonoids depends on the type of flavonoid; for example, catechins and anthocyanins are characterized by a half-life elimination that is 5−10 times lower than that of flavonols. The levels of plasma quercetin metabolites are found to be 0.7−7.6 μM, since quercetin is the most abundant dietary flavonoid. Anthocyanins and proanthocyanidins have the lowest bioavailability, while quercetin glucosides, catechin, flavanones, isoflavones, and gallic acid have the highest bioavailability [41,42]. There may be an interaction of flavonoids with other nutrients [40−44]. These interactions may have adverse effects on the development of diseases such as diabetes and hypertension [45]. Some of the flavonoids may decrease glucose absorption, owing to suppression of carbohydrate-hydrolyzing enzymes (alpha-amylase and alpha-glucosidase) [17,18,45]. Increased consumption of fat may improve flavonoid bioavailability and increase their intestinal absorption via augmented secretion of bile salts, which increase micellar incorporation of flavonoids [41]. However, protein intake can decrease flavonoid bioavailability, affecting both antioxidant efficacy and protein digestibility [36,41]. The gut microbiome is very important for the absorption and metabolism of flavonoids. After consumption and prior to absorption, intestinal or colon microflora are able to hydrolyze glycosylated flavonoids, such as flavones, isoflavones, flavonols, and anthocyanins into their respective aglycones [43]. After absorption, flavonoids undergo metabolic transformations first in the small intestine, liver, and kidney. There is methylation, sulfation, or glucuronidation of flavonoids before they reach the circulation, and afterwards, the tissues could influence their biological activities [43,44]. Unabsorbed flavonoids remaining in the proximal intestine are further digested in the colon by microbes that are able to split their heterocyclic oxygen-containing ring, and the hydroxylated phenyl carboxylic acids formed could be absorbed.

Although dietary flavonoids are found mostly in their glucoside form (see Figs. 44.1−44.3), they are not found in plasma because once flavonoids enter the oral cavity, they begin to be hydrolyzed [45,46]. Apart from this action, the absorption of flavonoids occurs from throughout the digestive tract, which is associated with the hydrolyzing activity of different enzymes [47]. In the small gut, deglycosylation occurs in which two enzymes that act as beta-glucosidases are involved: lactase-phlorizin hydrolase (LPH) and cytosolic beta-glucosidase, which are located in the brush border of epithelial cells and enterocytes, respectively [45,46]. Interestingly, flavonoid-*O*-β-D-glucosides, for which LPH has high specificity, can enter into cells by passive diffusion, but the glucosides enter enterocytes via sodium-glucose cotransporter type 1 [45,47] Although beta-glucosidases cannot hydrolyze nonmonoglucosidic glycosides, gut microbiota compensate for this through the production of absorbable aglycon in the large intestine and cecum.

Selection of flavonoids for therapy

The most important polyphenols and flavonoids that have been selected for examination and found to have protective function are flavonols, anthocyanidins, proanthocyanidins, flavones, flavanones, flavan-3-ols, and flavonols [48,49]. Flavonoids, namely quercetin, kaempferol, myricetin, apigenin, and luteolin, which are found in abundance in various foods (tea, wine, vegetables, and fruits), have also been reported to protect against diseases [15,49]. Data on food consumption from the European Food Safety Authority and the FLAVIOLA Food Composition Database that were used to estimate flavonoids intake indicated that the main sources of anthocyanidins, flavanols, flavanones, flavones, flavonols, theaflavins proanthocyanidins, and thearubigins in the European Union are tea, fruits (apples, pears and grapes), broccoli, onions, cocoa, coffee, and spices [48]. Mean (± SEM) intake of total flavonoids in Europe was 428 ± 49 mg/day, of which 136 ± 14 mg/day were monomeric compounds. Gallated flavan-3-ols (53 ± 12 mg/day) were the main contributor [13,48]. In one estimate, the lowest flavonoid intake was observed in Mediterranean countries (monomeric compounds: 95 ± 11 mg/day), which may be because not all flavonoid-containing foods were assessed. However,

habitual consumption of flavonoids in Europe may be lower than the amounts that have been found to have a significant health effect.

Tropical plants could be major sources of certain flavonoids (myricetin, quercetin, kaempferol, luteolin, and apigenin), as revealed in a study of 62 edible tropical plants [49]. The highest total flavonoid content was in onion leaves (1497.5 mg/kg quercetin, 391.0 mg/kg luteolin, and 832.0 mg/kg kaempferol), followed by semambu leaves (2041.0 mg/kg), bird chile peppers (1663.0 mg/kg), black tea (1491.0 mg/kg), papaya shoots (1264.0 mg/kg), and guava (1128.5 mg/kg). The major flavonoid in these plant extracts is quercetin, followed by myricetin and kaempferol. Luteolin could be detected only in broccoli (74.5 mg/kg dry weight), green chile peppers (33.0 mg/kg), bird chile peppers (1035.0 mg/kg), onion leaves (391.0 mg/kg), belimbi fruit (202.0 mg/kg), belimbi leaves (464.5 mg/kg), French beans (11.0 mg/kg), carrots (37.5 mg/kg), white radishes (9.0 mg/kg), local celery (80.5 mg/kg), limau purut leaves (30.5 mg/kg), and dried asam gelugur (107.5 mg/kg). Apigenin was found only in Chinese cabbage (187.0 mg/kg), bell peppers (272.0 mg/kg), garlic (217.0 mg/kg), belimbi fruit (458.0 mg/kg), French peas (176.0 mg/kg), snake gourds (42.4 mg/kg), guavas (579.0 mg/kg), wolfberry leaves (547.0 mg/kg), local celery (338.5 mg/kg), daun turi (39.5 mg/kg), and kadok (34.5 mg/kg). In vegetables, quercetin glycosides predominate, but glycosides of kaempferol, luteolin, and apigenin are also present. Fruits contain almost exclusively quercetin glycosides; kaempferol and myricetin glycosides are found only in trace quantities. Flavonoids are present in the plant cells to protect the cells and in foods such as olive oil and flax seed oil to protect the foods from oxidation [44,48–53]. The calyces of *Hibiscus sabdariffa* contain a number of flavonoids, gossypetin, hibiscetine, and sabdaretine, ascorbic acid, mucilage, the calcium citrate, which have antihypertensive, hypoglycemic, and anti–heart failure effects as well as being beneficial in other CVDs [52]. In a clinical trial, *H. sabdariffa*, showed significant beneficial effects on blood pressures and blood lipids among 39 and 36 patients from the experimental and control groups, respectively [52].

In developed countries, blueberries, which are quite rich in flavonoids, have been found to decrease blood pressures and modulate blood lipids with release of nitric oxide [53]. In a randomized, double-blind, placebo-controlled eight-week-long clinical trial among 48 postmenopausal women with prehypertension and stage 1 hypertension, half of the subjects were randomly assigned to receive either 22 g freeze-dried blueberry powder or 22 g control powder [53]. After eight weeks, systolic blood pressure (131 $\pm$ 17 vs 138 $\pm$ 14 mmHg, $P < .05$) and diastolic blood pressure (75 $\pm$ 9 vs 80 $\pm$ 7 mmHg, $P < .01$) as well as brachial-ankle pulse wave velocity (1401 $\pm$ 1221 vs 498 $\pm$ 179 cm/second; $P < .01$) were significantly lower than the values at the start. Significant ($P < .05$) group time interactions were found in the blueberry powder group, whereas there were no changes in the group receiving the control powder. Nitric oxide concentrations were greater (15.35 $\pm$ 11.16 μmol/L, $P < .01$) in the blueberry powder group at eight weeks compared with values at entry (9.11 $\pm$ 7.95 μmol/L), whereas there were no changes in the control group. Daily blueberry consumption may reduce blood pressure and arterial stiffness, and the effect may be due in part to increased nitric oxide production by the flavonoid content of blueberries [53]. Selected foods that are rich in certain flavonoids, such as olive oil, apples, guavas, grapes, and berries, may be used to develop total diet score as a valid method of measuring diet quality among older adults, which may be important in determining their health score [44,53,54]. However, the presence of chronic diseases such as diabetes mellitus may decrease the health score [55].

Limitations

In many studies, the association of flavonoid intake with risk of CVDs was examined, but many of these studies had one or more limitations. Only a few flavonoid classes were examined in most of the studies. Diets that are high in flavonoids by their nature have higher nutritional quality, characterized by more fruits, vegetables, and legumes, such as the Indo-Mediterranean, Mediterranean, and Japanese diets [14]. In many studies, other nutrients have not been considered to account for possible confounding by overall diet quality, including fruit and vegetable intake, fiber, or other nutrients that may track with flavonoid intake with a better-diet quality [5–7]. In long-term follow-up studies, flavonoid intake was based on a single reference assessment, allowing the potential for regression dilution bias [1]. The relationship between incident CVD and CAD and long-term intake of individual flavonoid classes based on a more complete flavonoid database was not examined [1]. Most flavonoids are found in plant-based foods; hence the overall diet quality of people who ingest more flavonoids is likely to be better than that of people who consume fewer flavonoids. Flavonoid-rich foods are also rich in certain nutrients, such as potassium, magnesium, fiber, lignans, and phytosterols, which are known to reduce CVD risk [14]. These foods may be lower in other nutrients that have adverse effects, such as saturated fat, trans-fat, omega-6 fatty acid, and salt, which may increase CVD risk. Potential confounding by overall dietary quality or other specific dietary factors may be associated with flavonoid intake and may bring about false-positive associations.

In brief, increased consumption of polyphenols and flavonoids above 400 mg/day or more may be protective against CVDs and other chronic diseases. The polyphenols and flavonoids that have been selected for examination and found to have protective function are flavonols, anthocyanidins, proanthocyanidins, flavones, flavanones, flavan-3-ols, and flavonols. Flavonoids (quercetin, kaempferol, myricetin, apigenin, and luteolin) that are found in abundance in various foods (tea, vegetables, whole grains, nuts, and fruits) have also been reported to protect against diseases. Large-scale cohort studies and randomized, controlled intervention trials are necessary to confirm this finding.

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Chapter 45

Interactions of bioflavonoids and other polyphenolic-type nutraceuticals with drugs

Istvan G. Télessy
Department of Pharmaceutics, Faculty of Pharmacy, University of Pécs, Pécs, Hungary

Introduction

The term *nutraceuticals* is flexible, and its definition changes from country to country. Stephen DeFelice, who coined this word in 1989, gave the following (first) definition: "food or part of food, that provide medical or health benefits, including the prevention and treatment of disease." Since then, many interpretations have been published. We tend to understand this term to apply to medicinal foods, phytochemical-containing products, functional foods, and nutritional supplements including micronutrients (vitamins, trace elements), herbal remedies, prebiotics, and probiotics that are formulated as orally administered pharmaceuticals, that is, in tablets, capsules, solutions, sirups, powders, and the like.

Nutraceuticals are widely used even when medicines are prescribed for patients, and when consumed as foods, complementary and alternative medicines (CAMs), and herbs and dietary supplements (HDSs), they can interact with medicines. These interactions can result in positive and negative effects, that is, they can strengthen or weaken the preventive or therapeutic effect. These effects usually are not dangerous but may increase adverse effects of drugs. Therefore it is important to be familiar with the frequent consequences of certain combinations.

In this chapter we concentrate on the interactions of drugs and polyphenols, one of the most often used ingredients of plant origin, and on how these interactions may influence the preventive or therapeutic action of the nutraceuticals and/or the drugs.

Large quantities of scientific and lay publications have reported on the health benefits of polyphenols for prevention of cardiovascular and neurodegenerative diseases, cancer, obesity, type-2 diabetes, and metabolic syndrome [1]. Therefore more people are consuming fruits and vegetables, and over the last decades there has been more consumption of dietary supplements containing concentrated amounts of polyphenols or medicines with purified polyphenol ingredients [2]. Thus it is important to be familiar with the benefits and potential harms of the concomitant use of these substances. These interactions have impact especially in medical interventions in which the efficiency of a drug may be essential from the patient's point of view.

Interactions in general

In this chapter, discussions are restricted to interactions observed after oral administration of herbal and dietary supplements. Interactions occur when two or more substances (chemicals, biologicals, ingredients, etc.) influence the physiological processes of the body in such a way as to modify the properties or movement of each other or when the action of one participant modifies the effects of others. Interactions can be agonist type or antagonist type. Numerous factors contribute to the occurrence of interactions, and the results are various. There are pharmacokinetic (Pk) interactions, in which an ingredient interferes with the absorption, distribution, metabolism, or excretion (ADME) of another ingredient and this results in slowing down or acceleration of the movement of the other ingredient, resulting in reduced or increased efficacy or increased toxicity. But ingredients can also modify the pharmacological or physiological effects of

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other components (drug, nutrient, etc.). The impact of an interaction can also be different. Some interactions are serious, perhaps even life threatening; others are hardly or not perceptible. Others have short-term or long-term effects.

In the course of polypharmacy (concomitant use of multiple drugs), because of the high standards of drug evaluation conditions (stable components, lack of contaminants, carefully designed preclinical and clinical studies, postmarketing surveillance, etc.), most significant interactions are usually known, and doctors and patients can take them into consideration. This is not the situation with drug−food, drug−HDS, or drug−CAM interactions, in which the ingredients are not exactly known and the published information is not always reliable. Under such circumstances, one can only presume the potential interaction, but neither the quality nor the quantity of this interaction can be forecasted.

Half of the people in the United States regularly consume HDSs [3]. Often, they have been taking CAMs or HDSs for such long periods of time and in such a routine manner that they do not consider them to be remedies. Moreover, people also may think that products of herbal or other plant or natural origin are safe and cannot cause problems. Unfortunately, patients very often do not inform their doctors about taking HDSs; only 17% of those taking HDS said that they disclosed HDS use to their healthcare provider [4]. In Thailand, half of chronic kidney disease patients regularly take HDS, and 43% of them did not ask their doctor about them [5].

Apart from the unsupervised ingestion by children, 66% of emergency department visits per year were related to single-supplement products, and 31% were related to micronutrients [6]. There is another significant risk in HDS use: A recent U.S. survey demonstrated variable dietary supplement quality that consumers cannot control [7]. This is a problem all over the world, owing to the unregulated Internet commerce (e-commerce, e-business) in products with higher than indicated content as well as misleading indications [8]. Among the unsuitable products there are contaminations as well, which may induce unexpected reactions and interactions [9].

The most recognized herbal−drug interaction is the one between grapefruit and drugs metabolized via the 3A4 subgroup of cytochrome P450 [10]. As is known, grapefruit interaction is mediated via intestinal CYP3A4 and not via hepatic microsomal enzymes; that is, this interaction influences mainly the bioavailability of drugs. Today, many more or less important HDS−drug interactions have been identified, such as those with St. John's wort (*Hypericum perforatum*), ginkgo (*Gingko biloba*), garlic (*Allium sativum*), echinacea (*Echinacea angustifolia*, *Echinacea purpura*, etc.), goldenseal (*Hydrastis canadensis*), etc. Their mechanism of action is various but dominates the enzyme inhibitor or enzyme inductor property in the intestinal epithelium or in the liver, where the main biotransformation (detoxification) of the xenobiotics takes place. The main active ingredients of the above-mentioned herbs are hypericin and hyperforin (St. John's wort), flavones (gingko), allicin (garlic), pentadekans and alkilamides (echinacea), hydrastine, and berberine (hydrastis), but all of the mentioned herbs—as is usual in natural products—contain many more ingredients, which may contribute to their detectable collective pharmacological effect. In contrast, one specific interaction can usually be attributed to one or some well-defined ingredients. Thus in case of grapefruit the responsible ingredients for the drug interaction are furanocoumarins, hyperforin is responsible for the Pk interactions of St. John's wort, and so on [11,12].

Flavonoids, which are present in a great many plants and herbs, as well as citrus fruits and ginkgo, have many pharmacological effects and despite the low concentration in the circulation they exert interactions as well. For instance, according to the in vitro (HepG2) and ex vivo (HPH) experiments of Li, three types of ginkgo flavonoids (hPXR, hCar, and the hAhR) affect various receptors in HepG2 cells and exert hereby an inhibitory effect on human hepatic drug-metabolizing enzymes, for example, CYP1A2, CYP2B6, CYP3A4, UGT1A1, and the genes MDR1 and MRP2 [13].

Polyphenols, bioflavonoids, and main sources: a brief overview

Polyphenols are secondary metabolites of plants with health benefits for human beings mainly as a result of their antioxidant properties. They are naturally occurring compounds that are present in many daily diets, especially in fruits and vegetables but cereals and natural beverages also contain polyphenols. Several thousand polyphenols have been identified in plants, and the majority of them are present in edible plants. Major classes include flavonoids, phenolic acids (PAs), stilbenes, and lignans (Fig. 45.1).

Flavonoids are the largest group of polyphenolic phytochemicals produced by plants, especially in response to biotic and abiotic stress. Bioflavonoids are flavonoids that occur naturally in vegetables and fruits; artificially produced chemicals with flavonoid structure are not taken into consideration here. Bioflavonoids are natural compounds with high antioxidant properties that have great potential for health benefits. Nutraceuticals containing flavonoids are among the oldest representatives of this group of medicinal products. Flavonoids are the most studied group of polyphenols.

Chemically, flavonoids are gamma-benzopyrenes, and their subclasses differ in substitution of A and C benzene rings (Fig. 45.2). Most often, hydroxyl substituents are present in positions 2, 3, 5, and 7 of the A and C rings and in positions 3′, 4′, and 5′ in ring B. Flavonoids usually appear in glycoside format (bound to sugars, such as glucose,

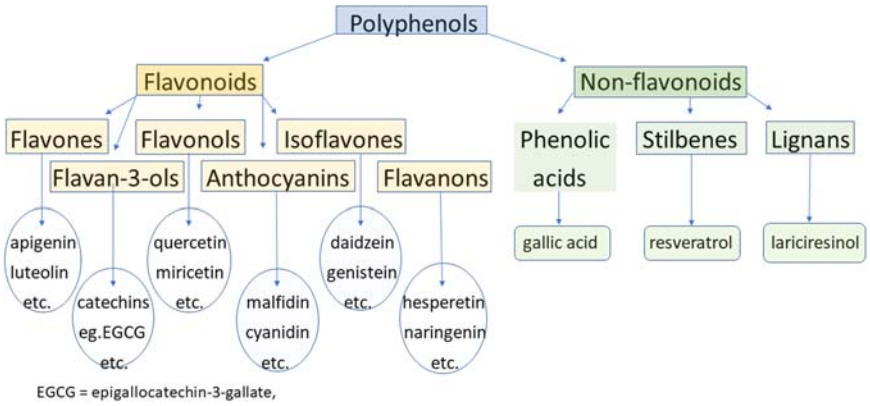


FIGURE 45.1 Classification of polyphenols with examples of classes.

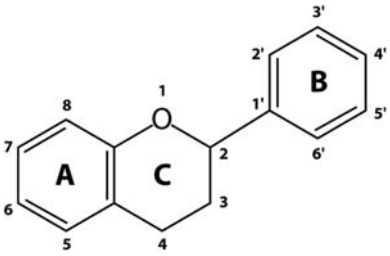


FIGURE 45.2 Basic structure of flavonoids.

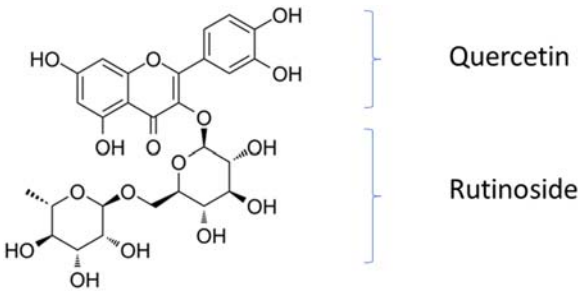


FIGURE 45.3 Rutin, an example of flavonoid glycosides (rutin = quercetin-3-rutenoside).

galactose, rhamnose, and arabinose) except catechins. Glycosidic linkage is normally located in position 3 or 7 (Fig. 45.3). The hydroxylic groups in position 3′-4′ (phenolic hydroxylic groups) are essential in the antioxidant effect of flavonoids. In a direct antioxidant effect, they either react with free radicals and can stop radical chain reactions or make chelates with metals needed in production of free radicals. In terms of an indirect effect, flavonoids induce expression of enzymes (e.g., catalase), increase activity of superoxide dismutase, and regulate protein synthesis and signaling pathways but inhibit other enzymes (e.g., xanthine oxydase, cyclooxygenase, lipoxigenase) [14,15]. The antioxidant potential of the group positively correlates with the number and arrangement of OH^- ions.

The flavonoid content of fruits depends on various factors, such as breed, soil, irrigation, and climatic conditions. Average flavonoid content is very variable even within vegetables; for example, the bell pepper contains approximately 4 mg QE (quercetin equivalent unit) per gram, the cherry tomato contains 1−2 mg QE/g, and leafy vegetables contain approximately 10−14 mg QE/g. Food and crop processing may decrease as well as increase the flavonoid content of fruits, vegetables, and products, depending on the method used. Moreover, as flavonoid synthesis is mainly reaction against stress (e.g., heat stress), plants can also multiply their flavonoid production under certain circumstances [16]. The great majority of flavonoids are hydrophobic weak acids. Owing to their low solubility, the short transit time in the small intestine, and the subsequent low absorption rate, the bioavailability of bioflavonoids is in general very poor; just 1%−10% of consumed polyphenols (flavonoids) will appear in the systemic circulation (blood concentration usually remains under 1 μmol/L) [17]. However, the bioavailability of the flavonoids (e.g., epicatechins) may differ within a wide range [18]. Absorption of a small proportion of flavonoids, such as the naturally aglicon catechins and the

hydrophilic glucoside quercetins, is much better [19]. Glycosides of flavonoids are absorbed well from gut lumen to epithelium and further into the circulation and the liver. Owing to the local hydrolysis (phase 1 metabolism and microbial fermentation), relatively large proportions of flavonoid glycosides—except anthocyanins—are cleaved to aglycone and sugar residues.

High doses of berries (containing anthocyanins) may prolong the pharmacological effects of CYP3A and CYP2C9 substrates (e.g., midazolam) because cranberry anthocyanins, for example, are as potent inhibitors as the well-known azole-type antifungal agents ketoconazole and fluconazole [20].

PAs are the second subclass of polyphenols. Representatives of this group are found in plant cell walls and play multifunctional roles. Among fruits, berries contain the most PAs (600−1000 mg/kg fresh fruit in total PA content). However, other fruits also contain remarkable quantities; for example, dark plums and cherries contain ca. 28 mg/kg or apple contains 56−618 mg/kg PAs [21,22]. PAs generally describes the phenolic phytochemicals having carboxylic acid group and are relatively resistant biochemical compounds. Well-known representatives are ferulic acid and caffeic acid (Fig. 45.4). In wheat ferulic acid is the most abundant free PA. PAs usually are present in the outer coverings of cereal grains in glucoside form; this version of PA is abundant, for example, in flax seed and barley grains. Caffeic acid is a widely studied PA derivative with biological effects that is present not only in coffee but in also berries, kiwi fruit, apples, and cherries. It is also derivative of curcumin. PAs exert antioxidant activity by scavenging various radicals, such as peroxyl-, hydroxyl-, superoxide-, and organic radicals and singlet oxygen.

Stilbenes consist of two phenolic rings bounded together with an ethylene group (Fig. 45.5). Stilbenes in plants act as antifungal phytoalexins that are synthesized only in response to infection or injury. The most studied stilbene is resveratrol (3,5,4′-trihydroxystilbene), which has significant health benefits and therefore is a common ingredient of dietary supplements. Resveratrol exists in two isomers. The trans isomer appears to be stable and can be found in red wine, dark chocolate, and nutraceuticals. Due to its lipophilic character, it is hardly soluble in water but much better in alcohol, and it has high affinity to lipids and phospholipids. Consequently, it has a relatively high absorption rate. However, its gastrointestinal absorption occurs by passive diffusion and complex formation with the membrane transporters [23]. Owing to backconversion of metabolites and the enterohepatic recirculation, its bioavailability is not as bad as is suggested by certain publications. Resveratrol has been declared to be safe and well tolerated in a single-dose as well as multiple-dose regimen up to 5 g/day [24]. Several health benefits are attributed to the molecule, as a result of free radical scavenging and antioxidant character; these include cardiovascular preventive, hepatoprotective, and neuroprotective effects and antimicrobial, antiinflammatory, and anticancer properties. However, according to certain researchers, there are also some risks, owing to the ROS-scavenging effect [25]. On the whole, a good many people consume resveratrol as a food ingredient (e.g., 1.7−1.9 mg/L in red wine) or as a dietary supplement for the expected positive health balance, and the potential for HDS−drug interaction exists on a dose-dependent manner.

Classical lignans are diphenolic compounds, usually variations of two substituted phenylpropanoid units (Fig. 45.6). The main sources of dietary lignans are, according to a recent summary from Durazzo, oilseeds (flax, soy, rapeseed, sesame), whole-grain cereals (wheat, oats, rye, barley), legumes, various vegetables and fruits (particularly berries), and beverages, such as coffee, tea, and wine [26]. Interest has been focused on lignans over the past decade, owing to their

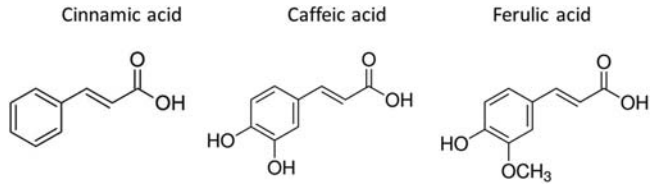


FIGURE 45.4 Structure of phenolic acids.

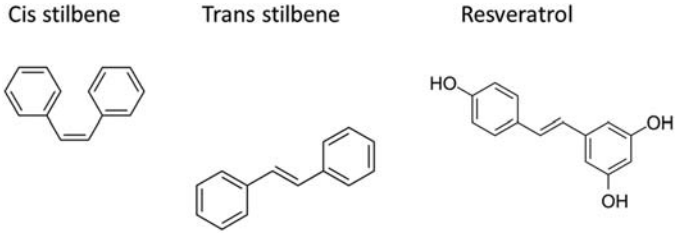


FIGURE 45.5 Basic structure of stilbenes.

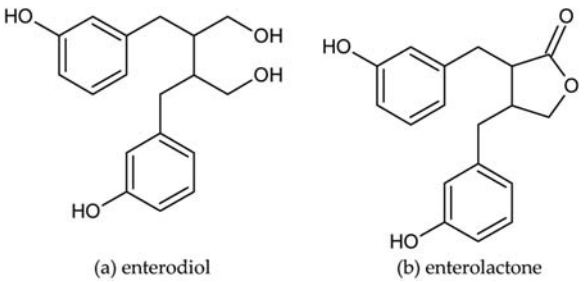


FIGURE 45.6 Two major forms of lignan structures.

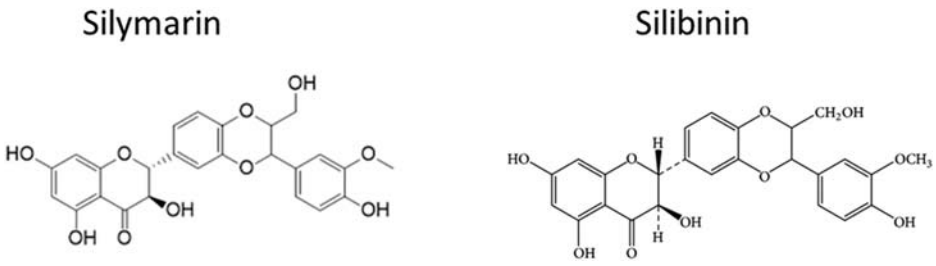


FIGURE 45.7 Structure of silymarin and its major active constituent, silibinin.

potent biological activities. Beside the classical lignans, there are six main subtypes of this structure of natural products, called neolignans (including flavonolignan, which will be discussed in the section on the flavonoid group later in the chapter). They have more varied structures and their biological activities are different, too. A Polish group recently revealed that certain Chinese plant extracts with high neolignan levels exert higher enzyme-inhibiting effects than ibuprofen [27]. Given these effects, their interaction potential is remarkable, especially since this ingredient is present in Asian dietary supplements and traditional Chinese medicine, and its interaction with tacrolimus has been confirmed in clinical studies [28].

Other polyphenolic-type compounds frequently used in nutraceuticals

Flavonolignans

Silymarin and silibinin are the main ingredients of several herbal supplements used as hepatoprotectors all over the world. They originate from the extract of seeds of *Silybum marianum*. Silymarin consists of several herbal components, but silibinin makes up approximately 70% of the extract and should be regarded as the primary molecule responsible for its pharmacological action (Fig. 45.7) [29]. *Silybum* extract reportedly inhibits CYP2D6, CYP2E1, and CYP3A4 hepatic isoenzymes in a concentration-dependent manner. Hydrogen bonding and van der Waals interactions are major contributors to interaction between silibinin and human serum albumin (HSA) [30]. Human studies performed with caffeine, tolbutamide, dextromethorphane, and midazolam as test drugs, however, suggest little potential for significant drug interactions of widely used drugs metabolized by the above-mentioned isoenzymes [31].

Catechins

Green tea contains an average of 126 mg catechins per 100 mL according to the European Food Safety Authority and 71 mg/100 mL according to the U.S. Food and Drug Administration. Epigallocatechin gallate (EGCG) is the most abundant flavonoid found in green tea (Fig. 45.8). This group of compounds is widely consumed as nutraceuticals. Catechins, especially EGCG, owing to its aggressive trihydroxyphenyl ring, can interact with molecular targets (proteins, phospholipids), regulate transduction pathways, and modulate enzymes as well as interacting with lipid bilayers and solvents [32]. Catechin and epicatechin have less radical scavenging potential than EGCG. Their mechanism of action has not yet been fully determined. However, exhaustive characterization of the catechins of green tea has revealed that this is the structure most disposed to interact with biological matters [33]. Green tea catechins exhibit

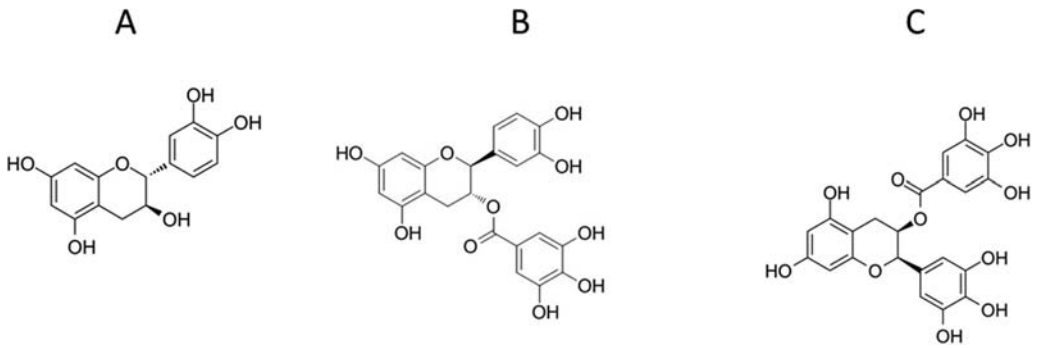


FIGURE 45.8 The structure of catechins. (A) Catechin. (B) Epicatechin gallate. (C) Epigallocatechin gallate.

antioxidant activity via blocking prooxidant enzymes. Moreover, radical scavenging activity is higher than that of ascorbic acid or beta-carotene [34]. While catechins influence most CYP and also UGT enzymes as drug transporters, EGCG is a far more potent inhibitor and/or inductor than the other catechins [35].

The main mechanisms of herbs and dietary supplements–drug interactions

In the course of Pk interactions, HDSs affect the ADME system of a drug; thus this type of interaction may modify the movement of the drug molecule. Most relevant Pk interactions are attributed to the HDS effects on active membrane transport and metabolizing enzymes, in particular the CYP enzyme system and also esterases. Recent modeling revealed that flavonoids (25 model ligands) competed with ATP for binding site of P-transmembrane glycoproteins [36]. This type of competitive interaction (usually inhibition) occurs with electrostatic and van der Waals bindings. As this results in altered absorption, distribution, biotransformation, and excretion of the drug, patients suffer from accelerated movement and/or decomposition of ingredients, or the ADME steps as well as inactivation or transformation slow down. From a therapeutic point of view, this means that Pk interactions can delay or accelerate the onset measure of action (T_{max} and C_{max}) or can shorten or prolong the duration of pharmacological effect. A number of studies have demonstrated induction or inhibition of the CYP450 system and drug transporters by polyphenols, but usually just speculations have been published about the real mechanisms. While experiments of the last decade revealed a lot of details of these interactions on the molecular level, there are still plenty of details to be determined.

In the formation of pharmacodynamic interactions, alterations in drug action occur via influencing the receptors [e.g., cell membrane proteins, such as P-glycoproteins (P-gp), or intracellular receptors controlling the DNA transcription] or nonreceptor targets (e.g., transmembrane carrier molecules). The binding of the agent and the receptor occurs via van der Waals forces, hydrogen bonds, ionic interactions, and/or covalent bindings. As pharmacodynamics is how the drug acts (or does not act) on the body or the target organ or cells, pharmacodynamic interactions cover the ways in which HDSs influence the pharmacological action of drugs.

On the basis of the myriad of publications in this field, we can assess that most therapeutic effects that are experienced as HDS–drug interactions are just the result of several small effects caused by the components in the organism. The most often referred physiological systems involved in the HDS–drug interactions are as follows.

The cytochrome P450 (CYP) system is a set of 57 terminal oxidase enzymes; nine of them (CYP1A2, -2B6, -2C8, -2C9, -2C19, 2D6, -2E1, -3A4, -3A5) are involved in the phase I metabolism of a large numbers of xenobiotics, including drugs. Principally, biotransformation takes place in the liver, but enzymatic metabolism is present in the intestine, the kidney, and the skeletal muscle as well. CYP3A4 is the most abundant CYP isoenzyme in the liver, which is responsible for the oxidative metabolism of two-thirds of all drugs [37]. Approximately 30% of all CYP enzymes are involved in the drug metabolism. Various CYP classes, families, and subfamilies are differently affected by xenobiotics. Moreover, the genotype is different in different people (polymorphism); therefore the different CYP isoenzymes may have individual levels of activity, affinity, and substrate specificity. Some of the phytochemicals inhibit and others induce the CYP families. The grapefruit juice flavonoid naringenin inhibits CYP1A enzymes in a competitive way and may increase the serum level of CYP1A2 the substrates theophylline, warfarin, and propranolol. By contrast, indole-3-carbinole, the main ingredient of cruciferous vegetables and an ingredient in dietary supplements, may induce the CYP1A enzymes [38]. Cranberry juice flavonoids (e.g., anthocyanins, proanthocyanidins, flavonols) have the potential to alter warfarin blood levels via inhibition of CYP2C9 and destabilize anticoagulant therapy, but the extent of the

effect depends on CYP polymorphism; therefore it is dangerous for some people but nor harmful for others. Of note, the chemicals belonging to one group may affect the CYP enzymes differently; in a recent study, tested flavonoids inhibited CYP1A2, CYP2A6, and CYP2C8 functions in different ways but did not affect CYP2D6 at all [39]. Flavonoids display both reversible and irreversible types of inhibition.

Special interest is focused on the prodrugs, which should be transformed from their inactive form into the active ingredient. For example, in case of codeine the pharmacologically inactive compound is converted by CYP2D6 to the active morphine via oxidative demethylation. (Tramadol is metabolized by the same pathway.) In this case, small alteration by concomitant use of enzyme inhibitors (e.g., the flavonoids luteolin and puerarin) may produce significant decreases in therapeutic efficacy [40].

The ABC superfamily, including P-gp, multidrug-resistant proteins (MDRp), multidrug-resistance-associated proteins (MDRAp), consists of ATP-energy-dependent transmembrane proteins that provide an active pump function into the cells (influx) and—predominantly—out of the cells (efflux) [41]. They have a broad substrate specificity. They are expressed mainly in the intestinal epithelial cells, in the hepatocytes and pancreas cells, in the brain capillary endothelium, and in the kidney, and they play a very active role in detoxification of the body. Unfortunately, cancer cells can express these proteins too. Thus they become able to pump out the anticancer drugs and make the cancer cell more multidrug resistant. The multiple binding sites of transmembrane domains of MDRp1 for dehydrosilybinin have been documented, for example, by Trompier et al. [42]. However, this property can also be seen in healthy cells (e.g., luminal cells of the short bowel) if drugs (xenobiotics) are administered (orally), and therefore these transport proteins are among others responsible for the quality and quantity of bioavailability of many drugs [43]. Should this transport function be disturbed by any HDS (which may be substrates of the proteins), the Pks and pharmacodynamics of certain drugs also can be altered. Examples for drug substrates in question are desloratadine, colchicine, quinidine, steroids (e.g., dexamethasone), and chemotherapeutic agents (etoposide, doxorubicin, vinblastine, gefitinib, sunitinib). Inhibitor natural products were recently exhaustively reviewed [44,45]. In the case of flavonoids, Xia and coworkers demonstrated a structure effectiveness correlation in the example of daunorubicin [46]. Further tests are being run to determine the feasibility of using flavonoid-induced reversal of P-gp-mediated MDR1 in cancer treatment because these transmembrane proteins as receptors may bind flavonoids [47]. The receptor-ligand binding is made by covalent binding of quercetin to serine and asparagine amino acids of the protein and by hydrogen bridges to phenylalanine, tyrosine, and alanine. This means that flavonoids may occupy one or some of the binding sites of P-gps and thus inhibit or modify the binding of pharmaceutical compounds to the receptor. In noncancer cells the enhancement of brain distribution of P-gp substrates is under evaluation by the help of flavonoids [48].

The solute carrier (SLC) superfamily, consisting of organic anion-transporting polypeptides (OATPs) and cation-transporting polypeptides (OCTs), is a family of secretory transporters in various organs. In this superfamily there are members for influx and efflux transport in more or less equal proportion. OATPs are present predominantly in the liver and are responsible for the hepatic uptake of large organic anions but also play a very important role in the gut and the kidney. OCTs take up small organic cations and anions in the liver and kidney. The efflux function for drugs is usually performed by MDRs; however, SLCs, to a smaller extent, are also capable of performing this function. HDSs are able to affect organic transporter proteins' function, as was demonstrated in an in vitro study by Wong et al., in which quercetin metabolites strongly inhibited OAT-mediated *p*-aminohippuric acid uptake in human embryonic kidney cells and decreased cytotoxicity of the drug that was the substrate of this transporter [49].

The last two systems belong to the active membrane transport proteins, most often influenced by polyphenols.

Following is a review of the interactions of bioflavonoids and nonflavonoid polyphenols with drugs with some selected examples.

Polyphenol natural molecules, after ingestion with foods and herbs or dietary supplements, are absorbed from the gastrointestinal tract and interact with numerous endogenous cell organelles and metabolites and with the lipid bilayer of every cell. They also interact with proteins, since hydrophobic benzene rings easily bind to proline residues, and the phenolic hydroxyl groups make hydrogen bridges. Polyphenols also interact with the gut microbiota, and they can metabolize one part of nonabsorbed polyphenolic compounds. This results in polyphenol metabolites that can be absorbed and may modify the functions of the microbiota as well. All these features of polyphenols also appear in interactions with drugs and drug mechanisms of actions.

There is accumulating evidence that many of the flavonoids and other polyphenolic compounds may interact with major transporter molecules and proteins and metabolizing enzymes participating in the fate of drugs. These reactions lead mainly to alteration in the Pks of the substrate drugs. Owing to the high number of studies in this field, we selected typical examples to demonstrate the possibilities of Pk and pharmacodynamic interactions.

Pharmacokinetic interactions

Pk interactions influence ADME processes of orally administered drugs. Therefore Pk interactions may affect the timing of appearance and conditions of circulation of drug molecules in the bloodstream as well as their biotransformation, thus influencing the therapeutic efficacy of the drug.

Absorption

Cyanidin-3-rutoside (anthocyanin) acts as a competitive inhibitor of pancreatic lipase, thus inhibiting absorption by mitigating micelle formation of cholesterol in the jejunum [50]. This effect is similar to that of ezetimibe, so administration of cyanidin-3 glucosides may result in a synergistic effect of cholesterol-lowering drugs.

Genistein (isoflavone) affects the function and mRNA of intestinal transporter P-gp, making possible drug interactions in the absorption phase [51]. This stimulation of the transport protein increases the efflux of P-gp substrates, such as digoxin.

Diadzein (isoflavone) significantly increased mRNA expression of MRDAp [51]. This is one reason for the development of resistance against oxaliplatin-derived platinum, for example, in oncology [52], and these proteins play a role in the disposition and efficacy of opioids, statins, antidepressants, and the like.

Biochanin A (O-methylated isoflavone) inhibited the liver-specific uptake transporter OATP1B1 [53]. Steroid hormone drugs are substrate of OATPs.

Diosmin (flavone) enhanced the bioavailability of fexofenadine due to the potent inhibition of P-gp-mediated drug efflux in the GI tract [54].

Quercetin (flavonol), which is a potent CYP3A4 and P-gp inhibitor, significantly enhanced the absorption and bioavailability of tamoxifen [55]. However, short-term quercetin administration decreased Area Under the Curve (AUC) and C_{max} of P-gp substrate talinolol in humans [56]. Owing to its competitive inhibitory properties on organic anion transporter 1B1, quercetin interacts with pravastatin and increased in human volunteers its C_{max} and AUC but decreased the clearance [57].

Naringin (flavonon) enhanced the bioavailability of paclitaxel by inhibition of gut CYP -metabolism and P-gp efflux [58].

Resveratrol (stilbenes) enhanced methotrexate intestinal absorption by inhibiting P-gp and MRP2. [59].

Green tea containing predominantly EGCG (catechins) decreased C_{max} of amoxicillin, which means that the absorption of amoxicillin was disturbed by coadministration of green tea [60].

EGCG (catechins) increased the C_{max} of amlodipine by 31% and AUC by 48% in rats after oral coadministration. This means that absorption of amlodipine was enhanced by the flavonoid [61].

Caffeic acid (PA) is able to sensitize MDR cancer cells toward chemotherapeutic drug treatment [62]. It has been demonstrated that through its inhibitory effects on P-gp efflux protein under in vitro conditions it can retard the pumping out of cells certain anticancer drugs.

Distribution and drug transport

Flavonoids bind to transport proteins, such as albumin. It has been documented that quercetin and its metabolites bind with high affinity to HSA and can displace drugs, such as warfarin. Poor and associates demonstrated that flavonoids displace warfarin from the surface of human serum albumin, but flavonones are much weaker competitors in this respect than flavones and flavonols [63]. By this interaction, free drug concentration in the blood increases and may augment adverse drug reactions; in extreme cases, even toxic reactions can be evoked [64]. A similar human serum albumin-binding displacement interaction was demonstrated in the quercetin−gliclazide relation [65] or quercetin−amlodipine relation [66].

Diosmin (flavone) and silibinin (flavonolignan) produce analogous effects [67,68].

Chrysin (dihydroxyflavone) and its main metabolite, chrysin-7-sulfate, bind to HSA and potentially compete for the binding site with several drugs that are transported in this way (e.g., warfarin, furosemide) and potentially increase circulating serum levels of the active ingredients [69].

Metabolism

In an ex vivo experiment, flavonolignans (silymarin constituents) significantly inhibited OATPs, which are responsible for cellular uptake of statins, for example [70].

Naringin (flavonon) as a CYP3A inhibitor substantially (by twofold) increased AUC and C_{max} of the cardiovascular drug diltiazem. The effect was attributed to obstructing metabolism [71].

Casticin (methoxylated flavonol) and resveratrol (trihydroxystilbene) inhibit CYP2C9 and CYP3A4. Thus under clinical conditions they may inhibit biotransformation of CYP2C9 substrates warfarin, diclofenac, phenytoin, and many more substrates regarding CYP3A4 isoenzymes [72].

Quercetin (flavonol) is a potent inhibitor of xanthine oxidase (XO) and therefore is able to hinder XO-mediated inactivation of the anticancer drugs 6-mercaptopurine and immunosuppressant azathioprine [73].

Chrysin (dihydroxyflavone) exerts a dominant reversible inhibition on CYP1A2 hepatic transformer, and this effect results in blocking the metabolism of phenacetin and other substrate drugs of this isoenzyme [74].

Silymarin (flavonolignan) basically modified the hepatic metabolism of simvastatin (HMG-CoA reductase inhibitor, prodrug) and after coadministration of silymarin and simvastatin AUC of the active metabolite simvastatin acid increased by 30%−90% in a simvastatin-dose dependent manner [75]. According to the suggestions of the authors, this interaction is due to the combined effect involving CYP (phase one metabolism) and UGT (phase two metabolism) and paraoxonase (hydrolysis) and P-gp (efflux protein).

Resveratrol (stilbene), studied in 42 healthy volunteers at a pharmacological dose (1 g/day for 4 weeks) exerted an inhibitory action on CYP3A4, CYP2D6, CYP2C9 and an inductive action on glutathione S-transferase and UDP-glucuronosyl transferase 1A1 enzymes of phase II hepatic metabolism [76].

Apigenin (flavone) inhibits carbonyl reductase 1 (CBR1) (short-chain dehydrogenase family) and in this way seems to be useful regarding the increased efficacy of anthracycline chemotherapy (doxorubicin, daunorubicin, epirubicin, etc.) [77].

Excretion

Flavonoid aglicones (especially morin and luteolin) but not glycosides are potent inhibitors of OAT1 transport proteins in the proximal tubular cells, and administration of dietary supplements containing these flavonoids hinder the uptake of OAT1-substrate drugs, such as cephaloridine, which may induce toxic reactions in the kidney [78].

Resveratrol, which inhibits OAT1 and OAT3 transporters localized mainly in the renal epithelium, decreases urinary excretion of methotrexate via influencing the functions of these active transport proteins [79].

Caffeic acid and, to a lesser extent, chlorogenic acid (phenolic compounds contained in coffee) have similar inhibitory effect on OAT1 and OAT3 and have similar inhibitory potential on renal excretion of their substrate drugs [80].

Pharmcodynamic interactions

Pharmacodynamic interactions occur when a chemical (even a phytochemical) modifies the effect of a pharmaceuticals ingredient. Because many polyphenols, including bioflavonoids, exert pharmacological action, they may modulate (e.g., increase or decrease) the effect of a drug that has a similar action mechanism. Here, we collected some types of interactions that have practical (therapeutic) impact. They are listed according to the four-stage partition of binding sites. It is important to note that membrane transport proteins, which serve as Pk regulators (mentioned before), can function as receptors as well; therefore phytochemicals that modify these transporters may exert pharmacodynamic interactions too. Sometimes this is due to the structural resemblance to endogenous substrates (e.g., hormones).

1. Ligand-gated ion channels (ionotropic receptors)
   - **a.** Flavones in general are ligands for benzodiazepine-binding sites on gamma-aminobutyric acid-A (GABA-A) receptors. This means that flavones are able to act synergistically to GABA-A receptor-ligand drugs having benzodiazepine structure and other hypnotics such as etomidate and propofol [81].
   - **b.** Flavonoids, owing to their high variance in structure, are substrates of GABA type A with very different affinity. Most in vitro and in vivo (mainly animal) studies have evaluated the binding of flavonoids and their metabolites to allosteric binding site of this receptor. One of the first documented specific ligands for the benzodiazepine-binding site was chrysin, but since then, several other flavonoids have been tested with various results [82].
2. Membrane transporters, such as G protein−coupled receptors (metabotropic receptors)
   - **a.** Flavonoids strongly inhibit breast cancer−resistant protein (BCRP) and increase the cytotoxicity of mitoxantron in BCRP-overexpressing breast cancer cells. Flavonoids—in this study, kaempheride, biochanin A, dimethoxyflavone, and methylflavone—exerted additive support to the chemotherapeutic effect in vitro [83].

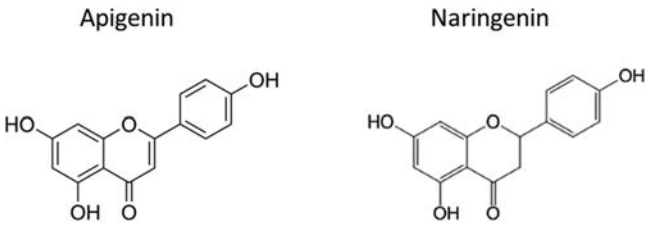


FIGURE 45.9 Structure of apigenin and naringenin. The difference is just a double bond.

b. Genistein (isoflavone) exerts inhibitory effects on lipopolysaccharide-induced expression of COX-2 and other enzymes; thus it exerts an additive antiinflammatory effect in microglial cells via G protein−coupled estrogen receptor activation [84].

c. Flavonoids (flavan-3-ols) increase plasma catecholamine (mainly adrenaline and noradrenaline) levels via upregulation of membrane-transporter uncoupling protein 1 [85]. In this way, the effect of all catecholamine receptor substrate drugs may be modulated by flavan-3-ols in a dose-dependent consumption of 25−40 g of dark chocolate.

d. Soy flavonoid (genistein, diadzein, glycitein) pretreatment unfavorably affects the concentration of the antiepileptic drug valproic acid via induction of UGT enzyme gene expression, resulting in pharmacodynamic effects of GABA concentration in the brain [86].

e. Flavonoids (quercetin) affect ATP-ase of P-gp. This transporter is responsible for the effects of several anticancer pharmaceuticals, such as daunomycin, doxorubicin, etoposide, taxol, and vinblastine. This interaction results in increase of the concentration of certain drugs, that is, it enhances the intensity of side effects of antineoplastic drugs, such as paclitaxel [87], or decreases the concentration of cyclosporine [88].

3. Kinase-linked receptors

a. EGCG (main polyphenol ingredient of green tea) act synergistic with tamoxifen in the treatment of estrogen receptor−positive breast cancer cells through tyrosine kinase suppression [89].

b. Icariin (prenylated flavonol) has fatty acid synthase gene (FASN) blocking properties beside other inhibitory activities [90]. The cell proliferation and chemoresistance to oxaliplatin by metastasis-associated colon cancer 1 oncogene (MACC1) upregulation can be attenuated by FASN blockade by using icaritin in vitro.

c. Apigenin and other polyphenols (luteolin, curcumin) have been shown to be very potent CBR1 inhibitors [77]. This enzyme induces important anthracycline-type antitumor drugs (daunorubicin, doxorubicin, epirubicin) and others (bupropion, dolasetron); therefore it has a potential pharmacodynamic role.

d. Apigenin (flavone) inhibits the production of 20-OH-eicosatetraenic acid in the arachidonic cascade by blocking cyclooxygenase enzymes. Theoretically, this means that it potentiates the efficacy of antiinflammatory COX-inhibitor drugs. Interestingly, the structurally similar naringenin (flavanone) (Fig. 45.9) does not inhibit COX enzymes [91]. The potency of this interaction is comparable with that of the well-known CYP-inhibitory interaction of ketoconazole.

4. Nuclear receptors

a. Nobiletin (hexamethoxyflavone) can sensitize adriamycin-induced cytotoxicity by inhibiting MRP1 expression. This means that nobiletin is a potent adjuvant in adriamycin-based chemotherapy [92].

b. Icariin (prenylated flavonol glycoside) dose-dependently reversed paclitaxel-induced SIRT1 downregulation and the H4 acetylation. In a rat experiment, icariin could antagonize neurological side effects of paclitaxel [93].

c. Flavonolignans competitively interact with active sites of cyclooxygenase enzyme, blocking the arachidonic acid pathway in platelets [94]. This means that flavonolignans are able to potentiate the activity of other COX-inhibitor drugs.

d. Green tea polyphenols and quercetin, via their multisignaling pathway properties, may enhance the therapeutic effect of anticancer drugs, including docetaxel [95].

e. Myrtus polyphenols modulate the expression of CYP3A4 and CYP27B1 genes [96].

Conclusions from the demonstrated examples

Different databases were searched to identify appropriate herbal and dietary supplement HDR−drug interactions. The most studied polyphenol compounds are potential modulators of transmembrane pumps and metabolizing enzymes. The activity profile of the various groups of polyphenols and members of the mentioned groups differ from one another,

suggesting that general rules cannot be drawn. As we can see in the unspecified details of the referred studies, interactions depend on several factors. Therefore the same flavonoid often demonstrates different behaviors with different drugs (e.g., EGCG and amlodipine or amoxicillin and others [35]) or with the same players but under different conditions (e.g., the effect of single or multiple doses [20,97]) or molecules and their metabolites (silybin vs 2,3-dehydrosilybin and Cu^{2+}, Fe^{2+} [98], etc.). It is also apparent that polyphenols that play an important role in the regulation of immunity by interfering with immune cell regulators and may affect pharmacological targets such as mTORC, XO, MAPK, COX, and others, may have pharmacodynamic agonistic and antagonistic interactions, depending on the actual drug or substrate of these proteins [99]. All these examples demonstrate that there is no one general rule to solve drug−HDS interactions, but there is a need for special knowledge to judge expected output of the interaction.

The physiological and therapeutic impact of herbs and dietary supplements−drug interactions

According to Goszcz et al., bioavailable concentrations of polyphenolic compounds are simply too low to mediate direct antioxidant activity in vivo [17]. This means that polyphenols in general are not able to exert a relevant physiological effect. This opinion is confirmed by the study of Hanley et al., who demonstrated that consumption of 300 mL of blueberry juice (a mixture of high levels of flavonoids) provided no evidence of clinically significant Pk interaction with CYP3A substrate buspirone and CYP2C9 substrate flurbiprofen [100]. Two very important factors should be pointed out here. The first one is that among dietary supplements, there are huge differences in recommended daily doses. For instance, Egert et al. demonstrated that the range of quercetin recommended in a daily dose was 200−1200 mg. The second is that interindividual differences may play a crucial role. According to the same authors, after a single dose of 150 mg quercetin, C_{max} varied between 180 and 600 nmol/L [101]. Dreiseitel et al. tested 12 anthocyanins and anthocyanidins and concluded that the low interaction potential is due to the low bioavailability because endothelial and intestinal tissues actively transport out these molecules, limiting the serum and brain levels [102]. In contrast, the ingredients of blueberry (anthocyanin flavonoids) had different effect on CYP1A1: 19 tested major anthocyanin did not affect CYP functions, but 2 anthocyanins displayed 79% and 65% inhibition at concentrations as low as 100 mM [103]. The above-mentioned statement of Goszcz et al. may be true for the majority of polyphenols but not for all, especially not for dietary supplements and nutraceuticals. This is partly, because the majority of nutraceuticals (herbal and dietary supplements) contains much higher doses than one can obtain by ingesting foods and partly because members of the polyphenols have very different chemical and biochemical aspects. Scholl et al. demonstrated in a study of 84 healthy participants that green tea extract capsules standardized to 150 mg EGCG taken twice a day for five days resulted in an AUC variability of more than fourfold and an AUC for metabolite of epigallocatechin more than 10-fold [104]. Maybe low bioavailability is true for some individual pharmacological effects and specific compounds, but the examples that we gave above support the hypothesis that polyphenolic components (including bioflavonoids and flavonolignans) have remarkable health benefit as well as occasionally health burdens with regard to HDS−drug interactions. One more important factor is the individual set of enzymes and transporters. This heterogeneity was highlighted by the randomized, controlled trial study of Curtis et al. After intake of 85 mg/day epicatechin for one year, urinary epicatechin (+ metabolite) excretion ranged from 9.6 to 327 μmol/day in 93 participants [105]. Moreover, even diversity of gut microbiota can results in further great differences in the biotransformation. The equol-producing ability of diadzein showed interindividual variability of 25%−30% in a Western population and 50%−70% in Asian people [106]. Similar ethnic differences were demonstrated by Wu et al. in the case of single nucleotide polymorphism of OATP1B1 transporters responsible for the quercetin−pravastatin interaction [57]. Fang and coworkers demonstrated recently the structure−permeability relationship of different groups of flavonoids, and these types of studies may help in selecting more effective flavonoids as well as in better prediction of their interaction potential [107]. If we consider the binding to human serum albumin or the effect on cytochrome P enzymes, we can conclude that the small amounts in the vegetarian diet and eating of food that are rich in plant origin ingredients need attention during acute drug therapy. Numbers of pharmacological publications depict weak research activities in the field of interactions. For the time being, only a few in vivo, ex vivo, or human studies have been performed to clear the impact of this type of interaction. Moreover, the preclinical and clinical studies are usually done with different test materials; therefore the results are not comparable. In other cases, in vitro and in vivo observations show ab ovo discrepancy [20]. In vitro quantification of receptor-ligand action is not enough. The motives of the discrepancy may originate in the low bioavailability of flavonoids or the faster clearance that results in shorter exposure of CYP enzymes to the inhibitor or inductor and the efficient protein binding and/or rapid tissue uptake of the interactor compound [20]. Sprouse and van Breemen

demonstrated in several examples that the prediction of drug−HDS interactions today can hardly be sure, for several reasons [108]. However, in certain instances, even in vitro studies may underpin the high probability. Before acute intravenous administration of a drug with a narrow therapeutic window, previous consumption of polyphenol-reach food supplements should be taken into consideration because, for example, silibinin significantly increases the plasma concentration of ivabradine [109]. The example of lignans schisandrin A and schisantherin A increasing the AUC of the narrow therapeutic index tacrolimus 1.34-fold and 1.77-fold, respectively, demonstrates the real impact of these interactions [28]. One should not forget the fact that HDS products are often used by frail persons, and higher than customary doses are frequently used. Moreover, elderly people as a rule have decreased or pathological organ functioning, which also influences the Pks and pharmacodynamics of the drug as well as the HDS and, of course, influences the potential interactions too. Additionally, in light of the advanced pharmaceutical research and development of the last decade [110−112], we can expect much higher bioavailability of the poor absorbing ingredients, and this increase the necessity of calculating interactions.

As one more aspect of this question, we demonstrated the results of several in vitro and ex vivo experiments as well. The translation to human individuals needs caution. Misaka et al. demonstrated in their experiment a significant inhibitory effect of EGCG on CYP2C9 isoenzyme (substrate sample: fluvastatin), but the human studies failed to show any influence in healthy human volunteers [113].

Finally, it is worth noting that nutraceuticals tend to contain specific and more purified ingredients of healthy vegetables and fruits than the combined extracts. Mixing of study results may lead to disputable translation to various nutraceuticals. This explains why nutraceuticals sometimes act differently from extracts or the opposite. For example, on the basis of human case studies, cranberry juice is highly likely to produce a significant increase in the (International Normalized Ratio (INR); measure of blood clotting time) of patients on warfarin therapy. However, flavonoid-containing dietary supplements (flavonoids are the main phytochemicals in cranberry) do not induce this reaction, just because the responsible compound for this type of interaction in the highly complex cranberry juice seems to be the hidden natural salicylate content of the juice [114].

Summary

Polyphenols, including bioflavonoids, are widely used phytochemicals in food as well as in dietary supplements. Therefore it is essential that they be safe to use. This safety should cover the use concomitantly with pharmacological therapy, especially in patients on polypharmacy. Polyphenols are a group of molecules that are prone to chemical reactions; therefore caution is reasonable.

It has been demonstrated that nutraceutical−drug interactions can intensify pharmacogenetic and pharmacodynamic differences among people. Dietary supplements usually contain concentrated amounts of natural ingredients; thus the effects of various substances are more pronounced than those in fruits or vegetables. In this chapter we reviewed several types of interference between bioactive components of herbal and dietary supplements and drugs, but it is important to remember that there are many more examples of positive and negative outcomes. Although HDS products in general serve our health, it is important to keep in mind that they sometimes carry risks as well, some of them in form of interactions.

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Chapter 46

Cardioprotective and neuroprotective effects of nutraceuticals derived from marine origin

Maushmi S. Kumar[1], Harpal S. Buttar[2], Yashodhara Dalal[1] and Ram B. Singh[3]

[1]Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM's NMIMS, Mumbai, India, [2]Department of Pathology & Laboratory Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada, [3]Centre of Nutrition and Heart, Medical Hospital and Research Centre, Moradabad, India

Introduction

Food is one of the most vital sources of energy for the human body. The different biochemical constituents of food aid the mental and physical growth of the body. Earlier research in medicine gave more importance to the activity and effects of food on various disease conditions and discovered that the complex nature of the human body may cause the functionality and nutrients possessed by food to be inaccurately and incompetently absorbed, leading to conditions such as malabsorption, heart palpitations, hair loss, brittle nails, digestive disorders, numbness, tingling, fatigue, bloating, swelling, muscle cramps, and weakness [1]. It has been understood through the years of medicine that as they age, most patients experience a decrease in nutrient absorption, leading to increases in the risk for contracting a related disease. To improve such conditions, special diets have been introduced containing a balance of meat and allied foods, dairy products, vegetables and fruits, bread and cereals, and fluids [2]. Furthermore, it is important to understand that a balanced and nutrient-rich diet improves homeostasis and the life span of the consumer [3]. Such a diet may result in a balance of nutrition supplied to the body, yet there are situations in which a diet of functional foods or nutraceuticals is needed to match the dietary requirements.

Functional foods have been identified as foods with high physiological benefits from health-promoting dietary components that aid in decreasing the risk of chronic diseases along with their normal activity as nutritional foods. Functional foods have been found to be similar in appearance to the conventional foods and may be ingested as part of a regular diet. The U.N. Food and Agriculture Organization[1] defines functional foods as follows:

> *Functional food can be defined as a food that satisfactorily demonstrates that it beneficially affects one or more target functions in the body, beyond adequate nutritional effects, in a way which is relevant to either an improved state of health and well-being or reduction of risk of disease.*

Diplock et al. [4] further defined functional food as follows:

> *A food can be regarded as functional if it is satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond adequate nutritional effects, in a way that is relevant to either an improved state of health and well-being and/or reduction of risk of disease. A functional food must remain food and it must demonstrate its effects in amounts that can normally be expected to be consumed in the diet: it is not a pill or a capsule, but part of the normal food pattern.*

Functional foods are often confused with functional components of food which are found as a natural part of food [5]. The emergence of the concept of physiologically functional food in 1993 in *Nature News* (Japan) led to a revolution

[1]Food and Agriculture Organization of the United Nations. Agenda Item 1: Overview of global developments in functional foods. (Conclusion and Recommendations From the Papers Presented and Discussed.) In: Report of the Regional Expert Consultation of the Asia-Pacific Network for Food and Nutrition on Functional Foods and their implications in the Daily Diet. Bangkok; 2004. http://www.fao.org/3/ae532e/ae532e00.htm#Contents.

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in the food industry, which brought to light a similar concept by Swinbanks and O'Brien in 1984 [6]. Research has proven the presence of immune-regulatory, antiaging, antifatigue, blood pressure−regulating, burning throat, improvement of bone calcification, antimutation, and antitumor properties (Yi et al., 1999). This has caused an increase in demand for functional foods as an approach to better health and longevity. Unfortunately, functional foods and nutraceuticals are often mistaken for one another.

Nutraceuticals can be alternatives to pharmaceuticals to provide not only active ingredients of medicinal composition, but also nutrition [7]. These food supplements contain vital amounts of minerals, vitamins, medicinal herbs or other botanicals, and amino acids. Although these supplements are found in our daily diet, they are given more importance as medicines to prevent and treat diseases over their activity of nutrient substitution [8−10]. Nutraceuticals have been identified as a rich source of dietary supplements. Although researchers and scientists have been able to define the term *nutraceutical*, the concept is still found in the gray area of food, supplements, and pharmaceuticals. The terminology of nutraceuticals originated through works of Stephen DeFelice, founder and chairman of the Foundation for Innovation in Medicine. The term *nutraceutical* is a combination of the terms *nutrition* and *pharmaceutical*. DeFelice defined a nutraceutical as "Food, or parts of food, that provide medical or health benefits, including the prevention and treatment of diseases" [11]. Furthermore, nutraceuticals are found in the form of the above nutrient metabolites, concentrates, extracts, constituents, or combinations of these [9]. As was previously mentioned, nutraceuticals are often mistaken for functional foods. Therefore a clear distinguishing of the two terms can be further understood through the following definition: "A diet supplement that delivers a concentrated form of a biologically active component of food in a nonfood matrix to enhance health" [9].

Marine source a rich source of functional foods and nutraceuticals

Functional foods and nutraceuticals have been found in land and sea ecosystems, mainly in foods from plants and animals. Because of the recent rise in isolation of active pharmaceuticals from marine sources, functional foods with an oceanic provenance have become a noteworthy topic of research and discussion. Functional foods have been isolated from quite a few marine organisms, including fish, marine mammals, algae, fungi, crustacean, mollusks, marine invertebrates, and cyanobacteria [12−15]. Similarly, fish, mollusks, crustaceans, algae, marine invertebrates, marine microorganisms, polysaccharides etc. have been found to be evident sources of nutraceuticals through research [16,17].

The main organisms and components leading to the production of the final functional food or nutraceutical are discussed in the following section.

Functional foods from marine source

Research and investigations have provided enough evidence to identify the true source of functional foods and their bioactivities. Each source is as vital as the next, owing to genetic composition, which may lead to a different set of bioactive components to be produced. Marine functional foods can be categorized on the basis of their inherent medicinal properties, the sources from which they can be isolated, or their functional food ingredients (Table 46.1).

Nutraceuticals from marine sources

Nutraceuticals derived from the marine source account for a large part of the global market, owing to the presence of a plethora of bioactive molecules [17]. The major reason to analyze them is their unique features, which are found particularly in molecules of marine origin [17]. They can be broadly classified as marine lipids of either animal or microalgal origin, polysaccharides from macroalgae, probiotics, natural pigments, chitin and related products, peptides/enzymes, and vitamins. They may also be classified on the basis of bioactive components, the medicinal properties, and related ingredients or type of nutraceuticals (Table 46.2).

Nutraceuticals as cardioprotective and neuroprotective agents

Cardioprotective activity

Cardiovascular diseases (CVDs) are the cause of a massive number of deaths around the world [48]. Although the traditional and clinical management of CVD is a matter of high importance, research has been limited by time and resources; as a result, marine sources have been explored for possible future cardioprotective agents [49,50]. The term

TABLE 46.1 Functional foods along with their sources and medicinal properties.

Functional food ingredients	Bioactive components	Functional foods	Medicinal property	References
Omega-3 fatty acids	DHA, DPA, EPA	Marine mammals, such as whale blubber and seal blubber; fungi; fish, such as tuna, salmon, sardines, mackerel, capelin, Pacific anchovy, krill, menhaden, herring, freshwater fish, cod, halibut; algae	Prevention and treatment of coronary artery disease, autoimmune disorders, cancer, diabetes, cardiovascular disease	[18–20]
			Development of retina and brain neuroprotective	[21]
			Antihypertensive	[22]
			Antioxidant	[23]
			Antiinflammatory	[24,25]
Carotenoids	Xanthophylls, such as capsanthin, flavoxanthin, rhodovibrin, violaxanthin, rhodoxanthin, crocetin, zeaxanthin, luteochrome, bixin, lutein, and cryptoxanthin, Lycopenes, alpha- and beta-carotenes	Corals, Atlantic herring, redfish, lobster, starfish, sponges, fungi, shrimp, algae, sea anemones, Pacific herring, crabs, red snapper, sea bream, crayfish, tuna, pink salmon, trout, mussels, salmon, squid, sea cucumber, sea urchin, octopus	Immunomodulatory Anticancer and antiviral Prevention of neurodegenerative and cardiovascular diseases	[18–20,24,25]
			Antioxidant	[23]
			Antiinflammatory	[24,25]
Proteins	Enzymes, bioactives, protein hydrolysates, peptides	Mollusks such as jumbo squid, mussels; cod, tuna, Pacific hake, conger eel, mackerel, dried bonito, oysters, prawns, nori, salmon, blue hoki, yellowfin sole, Alaska pollock, yellow stripe trevally, scad, krill, wakame, herring, capelinFish, crustaceans, algae	Antibacterial, antitumor, antithrombotic, anticoagulant ACE inhibitors, immunomodulatory, opioids	[18–20]
			Antioxidant	[23]
			Antiinflammatory	[24,25]
			Antihypertensive	[22]
Chitosan and chitin	HMW-; hetero-; sulfated hetero-; COS, heterochitosan, glucosamine, LMW chitosan/chitin	Krill, crawfish, prawns, crab, squid pen, clams, oysters, shrimp	Prevention and recovery of renal diseases, type 2 diabetes; dietary fiber Weight loss; decrease in total and LDL cholesterol levels Antimicrobial, antinuclear, anticarcinogenic	[18–20]
			Antioxidant	[23]
			Antiinflammatory	[24,25]
Phenolics and carbohydrates	Carrageenan, polyuronides, phlorotannins, furcellaran, laminarin, alginates, fucoidan, ascophyllan, agar, glutathione	Macroalgae such as seaweed, microalgae	Inhibition of HIV-1 reverse transcriptase and protease Cardioprotective and chemoprotective against vascular diseases Antidiabetic, antitumor, anticoagulant, antiallergic, antibacterial	[18–20]
			Antioxidant	[23]
			Antiinflammatory	[24,25]

(*Continued*)

TABLE 46.1 (Continued)

Functional food ingredients	Bioactive components	Functional foods	Medicinal property	References
Cyanobacteria and extremophiles		Polysaccharides such as carrageenan, algins, exopolysaccharides, agar, fucans	Antiinflammatory Antimicrobial and antiviral Anticoagulant	[26,27]
Polysaccharides	Dietary fibers	Crustaceans, algae	Antiviral and anticarcinogenic Cardioprotective	[26,27]
			Antioxidant	[28]
		Seaweeds	Antihepatic Antimicrobial	[29]
			Antiviral	[30]
			Antioxidative Antitumor	[31]
Peptides		Marine invertebrates, algae and protein waste, fish scales and collagen	Antimicrobial, anticoagulative, antidiabetic ACE inhibition	[26,27]
			Antioxidant	[28]
Polyphenols		Brown algae Algae	Antioxidative	[28]
			Antidiabetic	[27]
Chlorophyll		Algae	Anticarcinogenic	[32]

cardioprotection can be described as the mechanisms of the heart that lead to the development and maintenance of a healthy heart, thus reducing the risks of cardiac damage. Cardioprotection is known to include "all mechanisms and means that contribute to the preservation of the heart by reducing or even preventing myocardial damage" [51]. The main components from marine sources that have been identified as cardioprotective are omega-3 fatty acids, carotenoids, phenolics and carbohydrates, and polysaccharides (29.3−62.3 g/100 g of dietary fiber from seaweed) [52−54]. Cardioprotective functional foods and nutraceuticals have a wide range of activity, from healing acute CVD to managing chronic CVD [51].

Recent changes in the environment and the dietary habits of humans have led to an evolution of chronic ailments of the heart. CVDs have been reported as a major risk factor for deaths in the United States and European nations (one in three deaths and one in four deaths, respectively) [55]. Alongside the harm CVDs cause to the internal working balance of the body, issues such as disruption of the metabolic activities and metabolites associated with the normal functioning of the heart play an important role in understanding the relationship between targeted organ diseases with CVD. Furthermore, research has proven that the CVD and congestive heart disorders are more dependent on diastolic heart and less dependent on systolic heart failure [56]. Thus introducing the concept of cardioprotection in terms of not only cardiovascular system disorders but also the interconnected linkage of corresponding organ failure and disease is important and vital.

Quite a large number of drugs have been introduced into the market under the category of cardioprotection, including AT1 receptor blockers and angiotensin-converting enzyme (ACE) inhibitors, selective mineralocorticoid receptor antagonists, calcium channel blockers, thiazide diuretics, beta-adrenergic receptor blockers, nicorandil, thiazolidinediones, statins, fenofibrates, antiarrhythmic drugs (amiodarone, aprindine), class 1A antiarrhythmic agents (disopyramide), suppressors of ventricular premature complexes (ethmozin), and mexiletine [57−59]. These drugs are known to regulate the mechanism of the heart to ensure proper functioning and output. The ACE inhibitors work in harmony with ACE, which acts as a catalyst in the renin-angiotensin-aldosterone system. The main aim of these inhibitors is to regulate blood pressure and enhance vasodilation by protecting bradykinin from degradation [60]. Similarly, calcium channel blockers work on the negative inotropic effect of working atrial and ventricular

TABLE 46.2 Marine nutraceuticals along with their sources and medicinal properties.

Nutraceuticals	Bioactive component	Source	Medicinal property	References
Proteins and peptides	Collagen	Fish such as hake, brown-backed toadfish, albacore tuna, trout, catfish, common horse mackerel, silver-line grunt, lingcod, rainbow trout, yellow sea bream	Antihypertensive and antioxidant Antiaging (skin)	[33,34]
	Albumin	Mollusks, low fair fish, crustaceans	Antioxidant and anticoagulant	[35]
	Gelatin	Fish, especially cold-water (e.g., cod, cusk, haddock, pollock, hake)	Prevention and treatment of chronic atrophic gastritis	[36]
Fatty acids	Omega-3 fatty acids	Most marine sources	Mitigation of diseases such as hypertension, arthritis, cardiovascular disease Neurological and visual development	[37]
Vitamins and minerals	Vitamins such as zinc, manganese, iodine, iron (fat and water soluble)	Most marine sources, especially seaweeds	Used as a transport mediator within the host body cells Assist in the form of cofactors through metabolic processes	[38]
Polysaccharides	Chitosan, chitin, and their derivatives	Krill, prawn, crab, shrimp, lobster	Bactericidal and fungicidal Proliferate dietary fiber Reduce absorption of lipid Antitumor	[39]
	Agar agar	Red algae such as *Hypnea*, *Gelidium*, *Gigartina*, *Gracilaria*		[40]
	Carrageenan	Macroalgae such as *Betaphycus gelatinum*, *Eucheuma denticulatum*, *Kappaphycus alvarezii*	Anticoagulant Anti-HIV	[41]
	Fucans and fucanoids	Derived from the cell walls of sea cucumbers, sea urchin eggs, brown algae	Antiinflammatory, antiviral, anticoagulant, antithrombotic Proliferative	[42]
Enzymes	Lipases	Indian mackerel, salmon, Atlantic cod, sardine, red sea bream, seals	Although a variety of nutraceuticals have been identified and isolated from the given sources, confirmatory analysis is under way for the verification of the presence or absence of any medicinal properties	[43]
	Gastric proteases; pepsins, gastricsins, chymosins	Carp, tuna, Atlantic cod, harp seals (various body viscera)		[43]
	Transglutaminase	Pollock liver, atka mackerel, scallop, red sea bream, walleye, rainbow trout		[44]
	Serine and cysteine proteases	Mollusks, crustaceans, short-finned squid		[43]
Phenolics and pigments	Carotenoids such as lutein, beta-carotene	*Haematococcus pluvialis*, *Chlorella protothecoides*, *Sarcina maxima*, *Chlorella vulgaris*, *Dunaliella salina*	Anticarcinogenic, antiinflammatory, antioxidant Precursors of Vitamin A	[45]
	Phlorotannins	Brown algae	Antioxidant activity	[46]
	Chlorophyll	*Aphanizomenon flos-aquae*, *Spirulina platensis*	Natural pigmentation Anticancer activity	[47]
Polysaccharides	Dietary fibers	Seaweeds, algae	Antioxidative, antihepatic, antiviral, antimicrobial, antitumor	[29–31]

myocardial cells. Furthermore, these categories of drugs are known to regulate the impulse formation and partial conduction of the heart [61]. Diuretics indirectly affect the vasodilation of blood vessels, while antiarrhythmics regulate the sodium-potassium levels in the body [62,63]. One such nutraceutical, namely, the biofermented nutraceutical Fermented Papaya Preparation (FPP), was tested for its cardioprotective activity on the endothelial function of the heart. This nutraceutical was known to increase flow-mediated dilation by 3.1% from 4.2% to 7.3%. During this research, it was also observed that 4HNE levels were quite abnormal, which may cause inflammatory diseases. These levels were subdued by the FPP nutraceutical along with a rise in the plasma nitric oxide (NO) levels and a consequent decrease in the asymmetric dimethylarginine levels [64].

Neuroprotective activity

The neuronal system of the human body is reported to be quite unique and indeterminable at various standards. The more is learned about this system, the wider are the spectra of information required for a complete analysis. Neuroprotective agents work to protect the brain against any injury during or after a trauma or neuronal damage [65]. The term *neuroprotective* can be defined as "the strategies and relative mechanisms able to defend the central nervous system against neuronal injury due to both acute (e.g., stroke or trauma) and chronic neurodegenerative disorders (e.g., Alzheimer's disease and Parkinson's disease)" [66]. Neuroprotection can also be understood as "the preservation of the structure and function of neurons from insults arising from cellular injuries induced by a variety of agents or neurodegenerative diseases" [67]. The main components that have been identified as having neuroprotective properties are omega-3 fatty acids and carotenoids. Traditional medicines have been found to be a good alternative medicine that aids approximately 80% of healthcare systems in developing countries such as Ghana, India, China, and Nigeria. The lack of sources and limited technologies have led to the investigation of marine-based agents [68,69].

The central nervous system and peripheral nervous system are prone to a number of degenerative diseases that are highly progressive in nature and may lead to early senescence or death. In addition to the nerve-related disorders, which include epilepsy, multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's disease, stroke, transient ischemic attack, and subarachnoid hemorrhage, the constitution and nutrient balance of a human body and mind play an important role in the mental health of an individual [70]. One of the most common features of epilepsy is its direct relationship to the genetic and neuronal condition of the patient, which mainly focuses on the excessive, abnormal, and hypersynchronous electrical discharge of neurons through the brain [71]. Multiple sclerosis has been classified as relapse emitting, secondary progressive, primary progressive, and progressive relapsing, depending on the reoccurrence of relapse [72]. Although these two diseases are fatal, the most common neuronal degenerative disease id Alzheimer's disease, which is a dementia syndrome that causes episodic memory impairment in its early stages [73]. Similarly, conditions of stroke affect the cardiovascular system, which in turn may lead to hemorrhages of the brain in chronic stages [74]. Thus antiepileptic and antidepressant drugs are often used as primary medications. Chronic Alzheimer's disease may require combination therapies, owing to the lack of knowledge of the intricate mechanisms and the targets for the disease.

The antiepileptic drugs decrease GABA metabolism and increase chlorine influx. Drugs such as phenytoin are well-known voltage-regulated ion channel regulators that aid in the control of epileptic seizures, while quite a few drugs, such as valproate, have yet to be analyzed to understand their detailed mechanisms [75,76]. Antisclerotic drugs aim to reduce the duration of the acute exacerbations and decrease their frequency, which in turn provides symptomatic relief. Symptomatic treatments have been established for maintaining the proper functioning and quality of life. Similarly, drugs such as tacrine, donepezil, rivastigmine, galantamine (acetylcholinesterase inhibition), and memantine (N-methyl-D-aspartate (NMDA)-receptor antagonist) are used for symptomatic treatment for Alzheimer's disease [77]. Neuroprotective nutraceuticals such as curcumin have been reported to reduce the Aβ levels by inhibiting the formation of Aβ oligomers as well as decreasing oxidative stress and inflammation and attenuating microgliosis, oxidative injury, postsynaptic loss, and spatial memory deficits [78,79]. In Parkinson's disease, curcumin is also known to play an important role by defending against 6-OHDA-induced neural impairments in rats, thus enhancing the ability of the mind and memory. This also further elevates the superoxide dismutase (SOD) and GSH-Px levels and reduces concentration of malonaldehyde [80]. Treatment with apigenin showed an improvement in the memory of rats, reduced the fibrillar amyloid deposits, and protected the brain against the Aβ-induced toxicity [81,82]. Similar research and mechanisms have been reported in studies conducted on lipoid acid and epigallocatechin-3-gallate.

Supplements

Many nutraceuticals are commonly known as supplements because they act as nutrient and food replacements in the daily diet.

Omega-3 fatty acids

Omega-3 fatty acids, also known as omega-3 polyunsaturated fatty acids (omega-3 PUFAs), consist of three bioactive fatty acids, namely, docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), and eicosapentaenoic acid (EPA), which exhibit cardioprotective properties. Because they can be extracted from most marine organisms, the omega-3 PUFAs are among the most popular nutraceuticals. Omega-3 PUFAs also play an important role as the building blocks of cell membrane. They are biotransformed into endocannabinoids, eicosanoids such as thromboxanes (TX), prostaglandins (PGE2) and leukotrienes, and lipid-based signaling chemicals. These biotransformed products are involved in the important biochemical processes of the body, such as immune response, inflammation, and hypersensitivity. TX A3 and prostacyclin I3 can be classified as antineoplastic, antiinflammatory, vasodilatory, and antithrombotic eicosanoids [83].

Omega-3 PUFAs have been analyzed and reported to function as dietary supplements to reduce the morbidity and mortality rates caused by CVD [84] and to improve the risk factors affecting the cardiac hemodynamic factors such as blood pressure [85,86], endothelial function [87,88], left ventricular diastolic filling [89], and heart rate [90,91]. The cardioprotective nature of omega-3 PUFA extends to the prevention of arrhythmia [92], amelioration of vascular relaxation [87], inhibition of platelet aggregation [93], reduction in plasma triacylglycerols [94], enhancement of plaque stability [95], improvement in antiinflammatory responses [96], and antiatherosclerotic effects [97]. The mechanisms by which omega-3 PUFA work on CVDs and aid in the improvement of cardiac health are shown in Fig. 46.1 [98].

Nutraceuticals are increasingly used in the field of medicine. Recent advances in this field have given evidence of cardioprotective and neuroprotective activities. Certain bioactive components of nature, such as ubiquinone, curcumin, flavonoids, epigallocatechin gallate, omega-3 fatty acids and sterols, are well-known cardioprotective nutraceuticals that work in harmony with the body functions and improve the cardiovascular health of the body [99]. Similarly, nutraceuticals, including flavonoids, catechins, quercetin, anthocyanidins, resveratrol, zeaxanthin, beta-cryptoxanthin, alpha-carotene, crocin, vitamins, and diterpenes such as carnosic and rosmarinic acids, show great ability as neuroprotective agents [100].

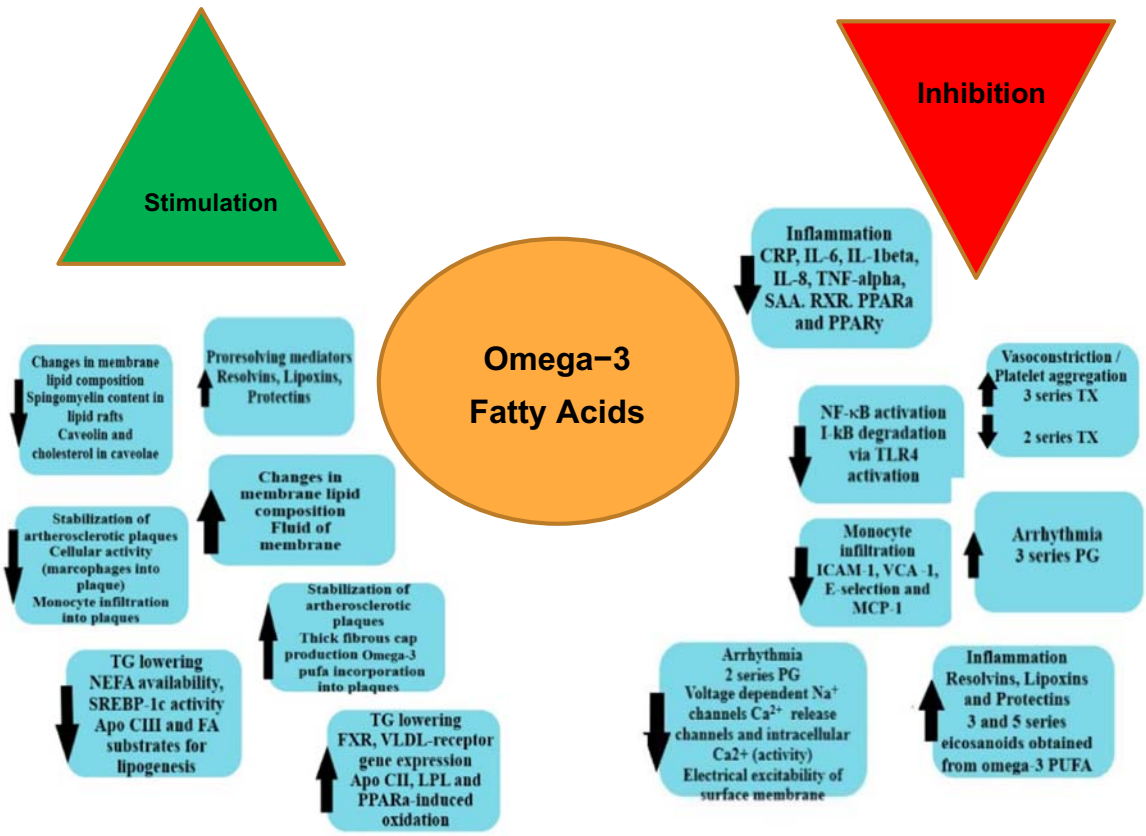


FIGURE 46.1 Mechanisms by which omega-3 fatty acids maintain cardiac health in human vascular cell adhesion molecule 1, intracellular cell adhesion molecule 1, macrophage chemoattractant protein-1, sterol regulatory element–binding protein (SREBP), TX, PGE2, nonesterified fatty acids (NEFAs), peroxisome proliferator-activated receptors (PPAR), apolipoprotein CIII (Apo CIII), farnesoid X receptor (FXR), lipoprotein lipase (LPL), and very low-density lipoprotein (VLDL).

TABLE 46.3 Neuroprotective activity of omega-3 PUFAs and related mechanisms.

Neuroprotective nature of omega-3 PUFAs	Mechanism		References
Ischemia	Decrease	Dopamine, norepinephrine, 3,4-dihydroxyphenylacetic acid Tumor necrosis factor alpha–induced immunopositive cells CA1, DG, CA3 Docosanoid neuroprotectin D1 Repress the proapoptotic genes such as *Bik*, *Bad*, and *Bax* triggered by beta-amyloid Postinfarct apoptosis (RGC model)	[32,107–111]
	Increase	Upregulate the antiproapoptotic genes such as Bcl-xl and Bcl-2 protein	[32]
	Preserves	Postinfarct survival (rat model) Visual function (rAION model)	
Central nervous system damage triggered by glutamate	Decrease	Excitotoxic processes	[112]
Neurotrauma such as excitotoxic	Decrease, block, inhibit	Glutamate efflux caused by depolarization Glutamate receptors activation Voltage-sensitive Ca^{2+} and Na^{+} channels	[113,114]
	Activation	K^{+} channels (two-pore domain background like TRAAK and TREK-1 channels)	
Inflammation	Decrease	Docosanoid neuroprotectin D1 Proinflammatory cytokine production	[108–111]
Oxidation	Decrease	Docosanoid neuroprotectin D1	[108–110]
Apoptosis	Decrease	RIPK-1	[115]
Memory	Decrease	Microglial activity and activation of sphingomyelinase, caspase-3	[116]
Neuronal differentiation	Increases	Hes6	[116]

The neuroprotective nature of omega-3 PUFAs has various factors such as acyl-CoA synthetase 6, which enhances its productivity and activity at the cellular level [101]. The hippocampus is known to be the target site of the brain for neurogenesis to take place, which leads to quite a few beneficial effects on mood, cognition, behavioral amelioration, chronic pharmacological treatment, enhanced synaptic plasticity and new spine formation [102]. Omega-3 PUFA regulate steroid hormone nuclear hormone isotypes of PPAR-α, PPAR-γ, and PPAR-δ/β as well as give rise to novel active metabolites like docosanoids and resolvins [103,104]. Moreover, the natural aging of the human body is known to affect the rate of neuronal degeneration and can be influenced by the intake of DHA and EPA supplements during adolescence or adulthood [105]. Omega-3 PUFAs are known to affect the neuroplasticity of nerve membranes, synaptic transmission, cognitive development, nervous system activity and synaptogenesis [106]. These fatty acids may also act as secondary messengers for inflammatory and proapoptotic events. Therefore any imbalance in the omega-3 PUFAs with any of it complementary components may lead to an increased susceptibility to the development of neurodegenerative diseases. The mechanisms related to the cellular structure of the nervous system especially the brain are not fairly clear and is being investigated to understand their level of activity [105]. The mechanisms by which omega-3 PUFAs work on neurodegenerative disorders are mentioned in Table 46.3.

Phenolics

Polyphenols are naturally occurring phytochemical compounds that have a large number of bioactivities, including antiallergic, antimicrobial, anticarcinogenic, antiinflammatory, antimutagenic, antiproliferative, antioxidant, antiviral, cardioprotective, and neuroprotective properties. Further, they are known to modulate cell-signaling pathways such as NF-κB

(nuclear factor kappa-B), activator protein-1 DNA binding, phosphoinositide 3, kinase/protein kinase B, extracellular signal-regulated protein kinase, nuclear factor erythroid 2−related factor 2 (Nrf2), and mitogen-activated protein kinases (MAPK) [117]. Polyphenols may be classified as hydroxycinnamic acid derivatives and hydroxybenzoic acid derivatives on the basis of their chemical structure [118]. These polyphenols may also be segregated as flavonoids, flavonols, lignans, stilbenes, and phenolic acids [119]. The bioavailability of polyphenols in the human body depends on quite a few factors, such as the absorption, metabolism, gastrointestinal digestion, and food preparation processes [120].

The cardioprotective nature of polyphenols extends to the regulation of hepatic metabolism, plasma lipids, and inflammatory cytokines [121]. Although polyphenols are known to reduce hypertension, blood pressure, and total cholesterol and to improve type 1 and 2 diabetes along with decreased insulin resistance and reduced metabolic syndrome and smoking effects [122], whether any marine-derived polyphenol has these bioactive activities remains under investigation. One of the major cardioprotective activities of polyphenols is observed through the investigation of Ahn et al. [123], who determined that the extracts of phlorotannins inhibited doxorubicin-induced cardiotoxicity by considerable reduction of myofibrillar bundle and lysis with the help of low- and high-dose sea polyols (SPN) derived from *Ecklonia cava* (brown algae). Although doxorubicin is found to damage 90% of mitochondrial cells, it is observed that the low and high doses of SPN reduced the mitochondrial damage to 50% and 30%, respectively. Low-dose SPN shows cardioprotective effects against adriamycin-induced and doxorubicin-induced cardiomyopathy [124,125]. In the future, the antihyperlipidemic activity of SPN may also aid in the control of the cholesterol levels of the heart [126].

Natural polyphenols have a variety of beneficial effects against CVD. A few of the key mechanisms that are part of the extensive cardiological care include antioxidant, anticholesterolemic, antifibrotic, antiapoptosis, antiinflammatory, vasodilation, and metabolic effects. These mechanisms are known to activate a number of signaling pathways, such as tumor necrosis factor (TNF), kinases, NO, antioxidant enzymes, heme oxygenase 1 (HO-1), ICAM, AMPK, STAT3, PGC-1, sirtuins, angiotensin II, IGFα, NF-κB, Bax, Bad, Bcl-2, adenosine receptors, prostaglandins, mKATP channels, and matrix metalloproteinase [122].

Unfortunately, only a few marine-derived polyphenols have been identified to have neuroprotective activity, although researchers are currently investigating the presence of any neuroprotective bioactive from marine sources.

One of the major categories of polyphenols is the carotenoids. Carotenoids are complex groups of naturally occurring chemicals [127] that are classified mainly on the basis of their bioactivity. A few are cardioprotective, preventing free radical oxidative damage, and some are neuroprotective and protective against cancer [128]. Quite a few carotenoids, especially beta-carotene, lycopene, lutein, and astaxanthin (AX), have been analyzed with the help of clinical trials. As was stated by Csepanyi et al. [129], beta-carotene is a double-edged sword; it is found to show slight cardioprotective activity only at low doses and is a causative agent for CVD at higher doses. This carotenoid, along with lycopene, is specifically correlated with the CVD, such as arteriosclerosis and oxidative stress [128]. Lycopenes increase the endothelial function while decreasing plasma cholesterol levels. Furthermore, lycopenes are known to show a number of cardioprotective activities that improve cardiovascular health. Lycopenes are also known to reduce the inflammatory response in allergies and to ameliorate intercellular communication and stimulate apoptosis. These nutraceuticals are also known to show antiangiogenic and reduced platelet aggregation, biomolecules oxidation, LDL levels, and lipid peroxidation [130,131].

Lutein and AX are known to be good cardioprotective agents. Lutein has been reported to reduce infarct size by 14%, lipid peroxidase product by 42%, apoptosis markers (caspase-3 and caspase-9) and production of cardiac markers such as LDH, cardiac troponin T, and creatine kinase-MB and inflammatory markers such as IL-6, TNF-α, NF-κB p65 (nuclear factor kappa-B p65 subunit), and IL-1β. Lutein is furthermore known to improve the antioxidant activity and increase the expression of proteins Nrf2 and HO-1 [132].

AX, a ketocarotenoid [133], targets different areas of the heart during the risks or exposure to CVD. This compound shows good bioavailability when loaded to the myocardium. The different effects that have been identified as the bioactivity and mechanism of AX in animal studies include reduction in the risk of secondary thrombosis [134,135], infiltration of macrophage into plaque, amelioration of plaque stability [136,137], reduced apoptosis, and considerable reduction in myocardial infarct size [138−141], reduction in the levels of 4-hydroxy-2-nonenal-modified protein and 8-hydroxy-2′-deoxyguanosine in cardiac and gastrocnemius muscle caused as a result of extensive exercise wall and lumen arterial ratio in coronary arteries [142], fasting blood sugar levels, complement activation, blood pressure, triglyceride and NEFA levels [137], apoptosis [143] and oxidative stress, lipid peroxidation products, NO end products, fat cell size, elastin bands in aorta, insulin resistance, and sensitivity. Furthermore, it delays the incidence of stroke, inhibits the activation of macrophages [143,144], increases the release of NO, decreases peroxynitrite levels, improves basal arterial blood flow, delays occlusive thrombosis after endothelial injury [145−147], and increases the myocardial mitochondrial membrane potential and contractility index.

The neuroprotective nature of polyphenols has been widely associated with inflammatory and cognitive disorders. Although there are quite a few neuroprotective polyphenols, we have focused mainly on AX, which is a recent topic of research and discussion. As was stated by Galasso et al. [148], AX shows attenuation of cognitive disorders in in vitro and in vivo models for neurodegenerative disorders [149−152]. A few of the neuroprotective activities associated with AX are improvement in the antioxidant status of erythrocytes in dementia, acting as a strong antiinflammatory agent by either suppressing or blocking the production of TNF-α, NO, PGE2 NF-κB-dependent signaling pathway, and IL-1β [153−155]. This nutraceutical also modulates the NF-κB cascade, such as p-IκBα, p-IKKα, and p-NF-κB p65, MAPK, and IL-6 for the antiinflammatory mechanism [156] as well as acting as a protection against neurotoxicity, which may be caused by beta-amyloid peptide [148]. AX also improves behavioral performance and promotes neurogenesis in tasks that are hippocampal dependent [151] and inhibits apoptosis [157,158]. Furthermore, it suppresses mitochondrial abnormalities [157,158] and oxidative stress and reduces levels of HO-1, Nrf2, NAD(P)H quinone oxidoreductase 1 [159,160], inducible NO synthase, heat shock protein 70, and heat shock protein 32 [161] and gene expression of mevalonate and proapoptotic factor Bcl-2-associated X (Bax) [159]. AX is also known to aid in the production of intracellular reactive oxygen species (ROS) [157,158], aid in the recovery of damaged neuronal cells [161], Increase the number of the hippocampus pyramidal cells, activate the Nrf2-antioxidant response element−signaling pathway [159] and increase of gene expression of SOD and antiapoptotic factor B cell lymphoma 2 (Bcl-2).

Polysaccharides and carbohydrates

Polysaccharides are combinations of sugar molecules that are currently being investigated for protection against CVD. Although the bioactive sulfated polysaccharides extracted from marine algae and seaweeds act as good cardioprotective functional foods and nutraceuticals, their bioactivity has been considerably undermined as a dietary fiber source for alternative medicines [162,163]. Alginate and fucoidans are a few of polysaccharides, as mentioned in Table 46.1 and 46.2, to possess cardioprotective activity. The remaining polysaccharides are reported to show hypocholesterolemic, hypolipidemic, and hypertriglyceridemia effects [162]; decreased LDL cholesterol levels [164]; and antilipidemic activities [165] that aid in the regulation of the CVD.

The sulfated derivatives of polysaccharides extracted from *Padina tetrastromatica* have been identified as rich functional foods and nutraceutical sources of cardioprotective agents such as fucoidan [166]. Polysaccharides such as carrageenan derived from *Mastocarpus stellatus* [167,168], sulfonated galactans from *Nemalion helminthoides* [169] and *Codium divaricatum* [170], ulvan from *Capsosiphon fulvescens* [171], and rhamnan sulfate from *Monostroma angicava* [172] are known anticoagulants that work as, or concurrently with, cardioprotective agents against CVD. Quite a few algae have been identified as good sources of cardioprotective and neuroprotective activity, including those belonging to the orders Dictyotales, Ectocarpales, Fucales, Laminariales, Bangiales, Ceramiales, Corallinales, Cryptonemiales, Gelidiales, and Gigartinales. The cardioprotective activity includes anticoagulant, antioxidant, antithrombotic, hypertensives, antiinflammatory, serum hypocholesterolemic, and antiangiogenic effects. The neuroprotective nature of polysaccharides is ideally as a peripheral antinociceptive [173].

Discussion

CVD are among the major causes for the rise in global mortality rate. Because of current food habits and fads, approximately 17.9 million people died from CVDs in 2016, which corresponded to 31% of global deaths. According to the World Health Organization, 85% of these deaths were caused by stroke and heart attack [174]. This number is expected to reach 23.6 million by 2030, according to a 2014 study [175]. Similarly, neurological diseases are associated with a large mortality rate due to the lack of a proper balanced diet and corresponding health disorders, and these diseases are the second leading cause of death [176]. These disorders are characterized as two segments of neuropsychiatric and neurological sequelae with maximum deaths in adults [68]. Approximately 276 million deaths (95% Uncertainty intervals (UI): 247−308) caused by neurological diseases were reported in the year 2016. An increase of 39% was observed in the combined neurological diseases followed by a 28% decrease in the age-standardized rate between the years 1990 and 2016 [176].

As the great Greek physician Hippocrates said, “Let food be thy medicine and medicine be thy food.” This has been the foundation for discovery and research in the field of functional foods and nutraceuticals. Although all foods are considered to be functional, because of their different genetic makeup and production of essential nutrients, the abnormalities in the genetic disposition of the human body lead to the identification, selection, and addition of functional foods and nutraceuticals in the daily balanced diet [177]. Functional foods are derived from animals, plants, and microorganisms.

They are known to show physiological health benefits along with reductions in the risks for chronic diseases. Ideally, this variety of food is cooked according to "scientific intelligence" [178]. The total number of manufacturers of functional foods and nutraceuticals was 935 in 2004 [179]. Nutraceuticals are known to be a subsequent part of extract derived from plants, animals, and algae. They aid in the amelioration of nutrient-deficiency diseases as well as the reduction in the risks for chronic disorders [180]. Although functional foods and nutraceuticals are found largely in land-based sources, the recent rise of interest in the marine biota has led to investigation of marine sources for these supplements.

The major functional foods and nutraceuticals that have shown potent cardioprotective and neuroprotective activity are omega-3 fatty acids, carotenoids (especially AX), polyphenols, and polysaccharides. Omega-3 PUFAs are among the major functional foods and nutraceuticals because of their cardioprotective and neuroprotective activity. Omega-3 PUFAs comprise of a group of fatty acids including EPA with 20 carbons and DHA with 22 carbons [181]. Omega-3 PUFAs, as was previously mentioned [93], inhibit the platelets from aggregating by prevention of vasoconstrictive behavior of the blood vessels. There are many mechanisms that work in harmony to enhance and provide a good cardioprotective nature. Furthermore, the neuroprotective nature of PUFAs extends not only to the protection against neurological disorders but also the maintenance of the cellular functional integrity [182,183]. As was previously mentioned, omega-3 PUFAs attenuated the ischemic effects of passive arterial occlusion, apoptosis caused by RIPK-1, and multiple diffuse infarcts [115].

AX is a major ketocarotenoid and has been widely investigated for its cardioprotective and neuroprotective activity. It has been reported to be a suppressant of the Bax/Bcl-2 ratio, infarct size, and thiobarbituric acid reactive substance and to attenuate mitochondrial dysfunction. AX is also known to possess cardioprotective activity similar to that of vitamin E [184]. Similarly, AX reduces the levels of serum cardiac enzymes and increases the antioxidant capacity in doxorubicin cardiotoxicity [185]. The bioactivities of AX are not limited to only cardioprotective activity, but also include neuroprotective activity. AX reduces oxidative stress by free radical absorption or by chemical bond formation and further reduces the ROS levels [186]. AX also effectively attenuates 6-hydroxydopamine and DHA hydroperoxide toxicity by the same mechanism of reducing ROS along with protein carbonylation, cytochrome C release, and mitochondrial membrane potential. This combination of mechanism ultimately inhibits the apoptosis of SH-SY5Y human neuroblastoma cells [186]. This carotenoid forms a major active component against the mitigation of Parkinson's disease and Alzheimer's disease.

Polysaccharides are a neglected source of pharmaceuticals, especially functional foods and nutraceuticals. Although these supplements are extracted from a large variety of algae, investigations of these components have been limited. Polysaccharides target not only the major sectors of the cardiovascular system but also any mechanism associated with it, thus enhancing the effectiveness and efficiency of the supplement. The neuroprotective nature of polysaccharides is still in investigational stages; as a result, only a certain amount of information has been reported, including their antinociceptive behavior [173].

Conclusion

Nutraceuticals are a leading strategy to improve health and reduce cardiovascular and neurological risks in the future. The major bioactive components of omega-3 fatty acids, carotenoids, and polyphenols, especially AX, have been investigated and reported to be cardioprotective and neuroprotective, while a few polyphenols and polysaccharides are yet in the investigational stage to be proven as neuroprotective. Although the bioactivity of the stated components may be portrayed as highly potent agents, they should be further analyzed to understand the effects of their biota and environment on their efficiency and effectiveness for the production of better and purified active ingredients.

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Section 14

Nutrients for metabolic diseases

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Chapter 47

Coenzyme Q_{10} in the pathogenesis and prevention of metabolic and mitochondrial non-communicable diseases

Anna Gvozdjáková[1], Jarmila Kucharská[1], Zuzana Sumbalová[1], Germaine Cornélissen[2], Viliam Mojto[3], Zuzana Rausová[1] and Ram B. Singh[4]

[1]Pharmacobiochemical Laboratory of 3rd Medical Department, Medical Faculty, Comenius University in Bratislava, Bratislava, Slovakia, [2]Halberg Chronobiology Center, University in Minnesota, Minneapolis, MN, United States, [3]3rd Department of Internal Medicine, Faculty of Medicine, Comenius University, Bratislava, Russia, [4]Halberg Hospital and Research Center, Civil Lines, Moradabad, India

Coenzyme Q_{10}

Frederick Loring Crane, the discoverer of coenzyme Q_{10}

Frederick Loring Crane (Fig. 47.1) was born in Bernardston, Massachusetts (United States), on December 3, 1925. He died in Metamora, Illinois (United States), on August 11, 2016. He attended the University of Michigan for one semester before entering the armed services in World War II. Returning to the University of Michigan after the war, he completed a PhD in botany 1953. He was at the University of Wisconsin Enzyme Institute as an assistant professor from 1957−59 and at the University of Texas from 1959−60. Then he was a Professor in the Biology Department of Purdue University in West Lafayette, Indiana, until 1994.

Professor Crane discovered CoQ in the respiratory chain of bovine heart mitochondria in 1957. His discovery opened the way toward determining the importance of CoQ in health and disease [1]. During his life he collaborated with many scientists around the world. In the last years of his life he demonstrated the importance of CoQ in the plasma membrane and its role in autism. Professor Crane collaborated with our team in our findings about the effect of



FIGURE 47.1 Frederick Loring Crane.

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ubiquinol in children with autism. On the basis of these results, Professor Crane hypothesized about a new CoQ binding site in the volt-dependent anion channel (VDAC) of outer mitochondrial membrane and about a possible alternative function of coenzyme Q_{10} in mitochondrial outer membrane permeability regulation, which depends on the VDAC (Fig. 47.2).

Professor Crane received many awards during his career, such as the American Chemical Society Eli Lilly Award in Biochemistry (1961), the Fulbright Award in Australia (1971), the NIH Career Award (1964–94), the Silver Medal in Biochemistry, University of Bologna (1989), Doctor *honoris causa* of Medicine in the Karolinska Institute (1989), and the Folkers Foundation Award for Research on Coenzyme Q (1996). He was among the pioneers who founded the International Coenzyme Q_{10} Association, where he was a Vice-Chairman (1997–2002). His last paper was published in May 2014 [3,4].

Characteristics of coenzyme Q_{10}

CoQ_{10} is found in all eukaryotic cells in all tissues of the body. Professor Crane isolated CoQ_{10} as the yellow golden substance from bovine heart mitochondria. The essential function of CoQ_{10} is in the mitochondrial respiratory chain for adenosine triphosphate (ATP) production and as an antioxidant (ubiquinol-ubiquinone).

In 1958, Professor Karl Folkers determined the chemical structure of CoQ [5]. The structure of CoQ_{10} is similar to that of vitamin K (chemical name: 2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzochinone). The benzoquinone ring is linked to the long side isoprenyl chain that in humans is composed of 10 isoprenyl units. CoQ_{10} occurs in all cellular membranes and in high- (HDL) and low-density lipoproteins (LDL). CoQ_{10} is a lipophilic antioxidant that is capable of recycling and regenerating other antioxidants, such as vitamin E and ascorbic acid.

Two major forms of CoQ_{10} are present in the body: the ubiquinone-oxidized form and the ubiquinol-reduced form. There is a dynamic balance between ubiquinone and ubiquinol. About 95% of circulating CoQ_{10} occurs as ubiquinol [6] (Fig. 47.3).

The content of CoQ_{10} in tissues and organs differs, being highest in the heart, and its concentration and biosynthesis rate depend on age and nutrition [7]. Of the total CoQ_{10} concentration in a cell, the mitochondria contain 40%–50%, the plasma membrane contains 25%–30%, the endoplasmic reticulum contains 15%–20%, and the cytoplasm contains 5%–10%.

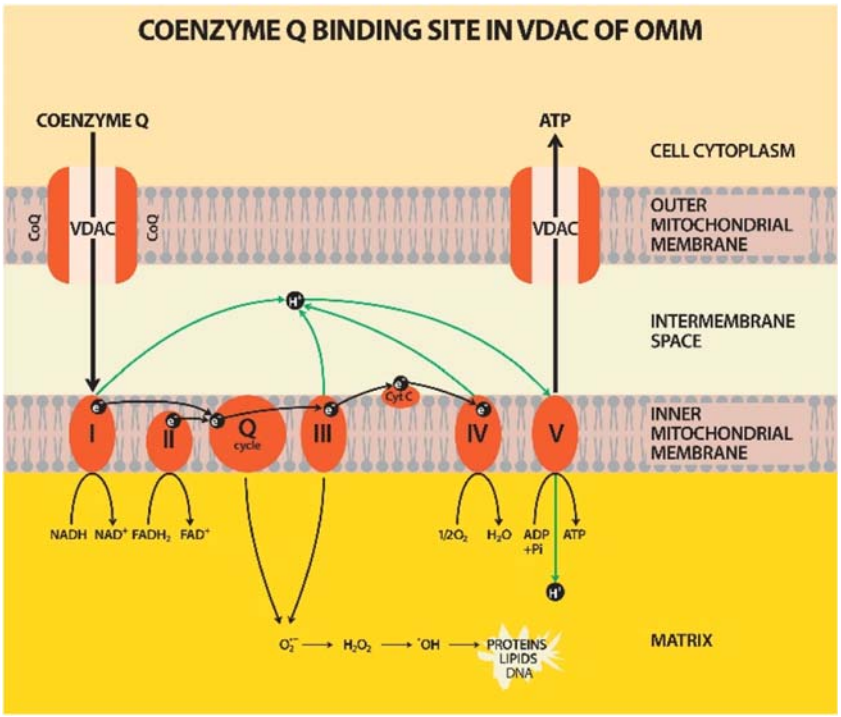


FIGURE 47.2 Proposed new coenzyme Q binding site in the VDAC outer membrane of mitochondria [2] *ADP*, adenosine diphosphate; *ATP*, adenosine triphosphate; *CoQ*, coenzyme Q; *Cyt c*, cytochrome c; *e*, electron; FAD^+, flavin adenine dinucleotide; $FADH_2$, reduced flavin adenine dinucleotide; H^+, proton; H_2O, water; H_2O_2, hydrogen peroxide; I, II, III, IV, V: respiratory chain complexes; NAD^+, nicotin adenine dinucleotide; *NADH*, reduced nicotin adenine dinucleotide; *OH*, hydroxyl radical; O_2, oxygen; O_2^-, superoxide radical; *Pi*, inorganic phosphorus; *Q-cycle*, coenzyme Q cycle; *VDAC*, voltage-dependent anionic channel.

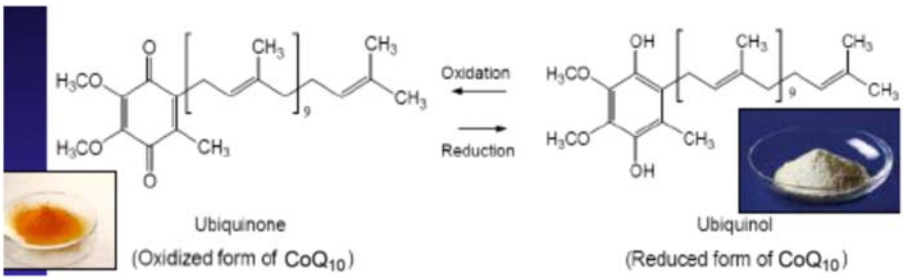


FIGURE 47.3 A dynamic balance between ubiquinone and ubiquinol. *P. Lambrechts, Kaneka, Brussels, 2011.*

Sources of coenzyme Q_{10}

Organisms receive CoQ_{10} from three main sources: endogenous, exogenous, and as a dietary supplement.

Biosynthesis of coenzyme Q_{10}: endogenous source

Under physiological conditions, sufficient CoQ_{10} is synthesized in all cells. Most CoQ_{10} comes from endogenous biosynthesis in all cells. Endogenous biosynthesis of CoQ_{10} occurs as a result of food ingestion via the mevalonate cycle, which involves acetyl-CoA as the initial substrate for cholesterol, dolichol, and CoQ_{10} production [8].

Exogenous sources and absorption of coenzyme Q_{10}

The human organism can acquire CoQ_{10} from exogenous sources, mainly in meals: red meats, such as pork and beef; some fish, such as mackerels and sardines: soy and peanuts; grains; nuts, such as almonds; spinach; broccoli; melon; red grapefruit; grapes; red wine; sunflower seeds; and beans. Daily CoQ_{10} intake from meal ranges from 3–5 mg, and only 10% of what is ingested is absorbed in the gastrointestinal tract.

CoQ_{10} is not soluble in water, so it is slowly absorbed from the small intestine and then transported to the liver, passed into the lymph, then into the blood and tissues. For this transport, CoQ_{10} is coupled to the chylomicrons, 58% is incorporated into LDL particles, and 26% into HDL particles. CoQ_{10} is than distributed to various organs, such as the spleen, adrenal glands, lungs, myocardium, brain, and kidney. The main elimination of CoQ_{10} is via the bile ducts and feces, and a small part is eliminated in urine [9].

Absorption of exogenous CoQ_{10} and its bioavailability depend on the type of CoQ_{10} preparation. Plasma CoQ_{10} levels increased 1–2 hours after oral intake, with maximum absorption within 6–10 hours. Several studies have found significantly better absorption of ubiquinol in comparison with ubiquinone. The absorption of ubiquinol was twice as high as that of ubiquinone in healthy subjects and four times higher in cardiac patients [10].

Coenzyme Q_{10} as dietary supplement

Several CoQ_{10} products are available as dietary supplements as powders, capsules in oil, or in oil- or water-soluble form. Solubilized CoQ_{10} formulations have greater bioavailability than powder or oil-soluble formulations. Ubiquinol is better absorbed in comparison with ubiquinone [6]. All supplemental CoQ_{10} products are better absorbed when taken with a meal. Improvements in the absorption of CoQ_{10} have been reported when it is consumed with grapefruit juice [11].

Functions of coenzyme Q_{10}

CoQ_{10} is a necessary component of the mitochondrial respiratory chain. It carries electrons from complex I and II to complex III of the respiratory chain and in this way participates in the process of energy production via oxidative phosphorylation. Other CoQ_{10} functions include regulation of the cytosolic ratio of NAD^+/NADH and the involvement in regulation of cell growth and differentiation. CoQ_{10} as a lipid-soluble antioxidant prevents oxidation of proteins, lipids, and DNA. By protecting LDL from oxidation, it has antiatherosclerotic properties [8].

According to the hypothesis of Linnane and Eastwood [12], the global functions of CoQ_{10} are in cellular bioenergetics (ATP production) and redox poise (ratio of ubiquinol to ubiquinone). The ratio of reduced to oxidized forms of CoQ_{10} has a key role in metabolic control, energy production, and gene regulation. As an antioxidant, CoQ_{10} reduces

the production of free oxygen radicals and modulates endothelial dysfunction [13–15]. The evidence on bioenergetics and antioxidant functions of CoQ_{10} was presented by several authors [16,17].

Chronobiology of coenzyme Q_{10}

The term *chronobiology* is based on Greek (*chronos* = time; *bios* = life; *logos* = science). Chronobiology is a computer-aided objective quantification, mapping, and investigation of mechanisms underlying biological rhythms, the fundamental mechanisms of life [18,19]. CoQ_{10} levels in the plasma, tissues, and mitochondria of various organs show biological circadian or circasemidian rhythms [20]. In 32 clinically healthy men, 18–61 years of age, plasma CoQ_{10} concentrations were found to be higher in the evening (determined between 17:00 and 20:00 hours) than in the morning (determined between 06:00 and 08:00 hours). The presence of a circadian rhythm in CoQ_{10} levels suggests that CoQ_{10} supplementation as an adjuvant therapy could be optimized by timing its administration along the 24-hour scale [21].

In an experimental study, the biological CoQ_{10} cycles of brain and myocardium in control rats were compared. Circadian rhythmicity in mitochondria of brain of control rats had the maximum CoQ_{10} (PEAK 1) at 07:28 hours and (PEAK 2) at 19:24 hours. The minima (NADIRS 1 and 2) were at 14:04 hours and at 01:03 hours. Nocturnal activity of the rats is between 22:00 hours and 10:00 hours, and inactivity is between 10:00 and 22:00 hours. Myocardial mitochondrial circasemidian (12 hours) and circadian (24 hours) rhythms showed statistically significant maxima (peaks) only for $CoQ_{10\text{-}OX}$ at 15:27 and 3:30 hours and minima (nadirs) for $CoQ_{10\text{-}OX}$ at 10:00 and 20:51 hours. $CoQ_{9\text{-}OX}$ peaks were without statistical significance. Nocturnal activity of rats (22:00–10:00 hours) was reflected in higher peaks versus diurnal peaks (10:00–22:00 hours). It is known that biorhythms in humans are opposite to those in rats (Fig. 47.4).

We assume that the biological Q_{10} clock plays an important role in the pathogenesis of altered cardiac function and can contribute to the understanding of acute attacks of heart muscle [22].

Coenzyme Q_{10} analysis

Determination of coenzyme Q_{10} in whole blood and plasma

The concentration of $CoQ_{10\text{-TOTAL}}$ (oxidized + reduced CoQ_{10}) in human blood and plasma was determined by a modified HPLC method with spectrophotometric detection [23,24]. For the oxidation of ubiquinol to ubiquinone, 100 μL of 1,4-benzoquinone (2 mg/1 mL double distilled water, daily fresh) was added to 500 μL of blood or plasma a vortexed for 10 seconds [25]. After 10 minutes incubation at room temperature, 2 mL of the mixture hexane/ethanol (5/2 v/v) was added, shaken for 5 minutes, and centrifuged at 1.000 g for 5 minutes. The hexane layer was separated, and the

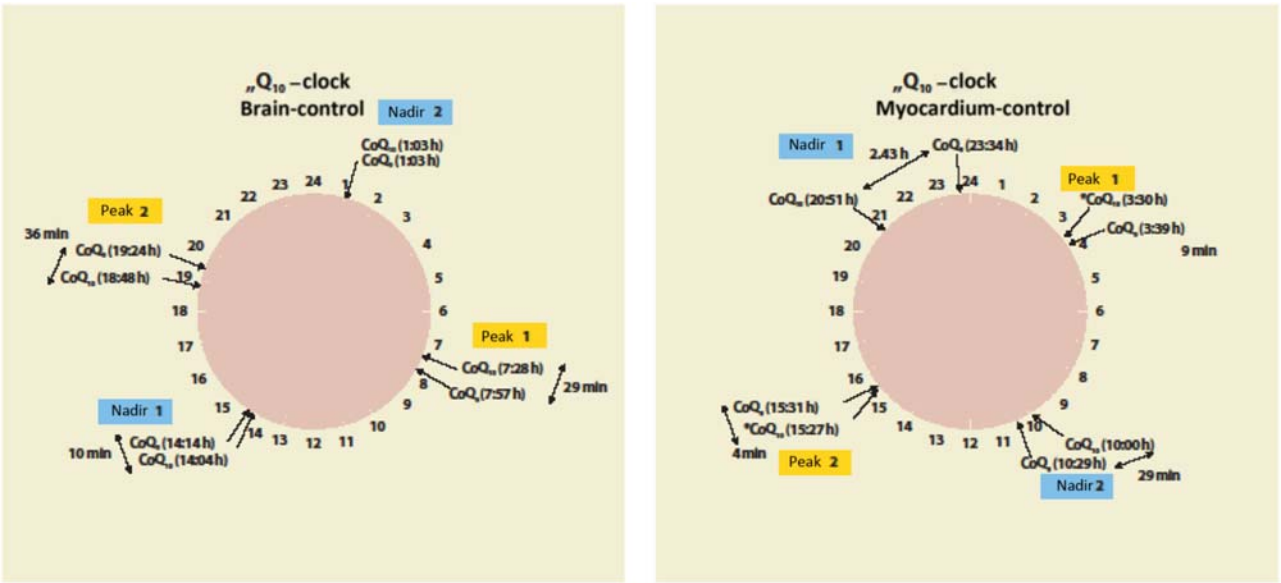


FIGURE 47.4 Biological Q_{10} clock of control rat brain and myocardial mitochondria.

extraction procedure was repeated with 1 mL of the extraction mixture. Collected organic layers were evaporated under nitrogen at 50°C. The residues were taken up in 99.9% ethanol and injected into a reverse-phase HPLC column (SGX C18, 7 μm, Tessek Ltd). Elution was performed with methanol/acetonitrile/ethanol (6/2/2, v/v/v) at a flow rate 0.9 mL/minute. The concentrations of $CoQ_{10\text{-TOTAL}}$ were measured by UV detector at 275 nm, with external standard. Data were collected and processed by using a CSW32 chromatographic station (DataApex Ltd). Concentrations of $CoQ_{10\text{-TOTAL}}$ in blood and plasma were calculated in micromoles per liter.

Determination of coenzyme Q_{10} in isolated human platelets

Isolated human platelets (100−200 μL) were disintegrated with 500 μL of cold methanol [26]. Oxidation of ubiquinol to ubiquinone was performed with 1,4-benzoquinone as described for plasma extraction. The cell suspension was extracted with 2 mL hexane by shaking for 5 minutes. After centrifugation at 1000 g for 5 minutes, the organic layer was separated and evaporated under nitrogen. The residue was taken up in ethanol and injected into an HPLC column. The concentrations of $CoQ_{10\text{-TOTAL}}$ were measured, and the data were processed as described above. Concentrations of $CoQ_{10\text{-TOTAL}}$ in platelets were calculated in picomoles per 10^9 cells.

Determination of coenzyme Q_{10} in human skeletal muscle biopsy

Biopsy samples from human skeletal muscle (5−15 mg) were homogenized by using an Ultra-Turrax in 1 mL of double distilled water for 10 seconds. The extraction mixture hexane/ethanol (5/2 v/v, 2 mL) and 1,4-benzoquinone (50 μL) were added, and samples were mixed and incubated at room temperature for 10 minutes. After shaking for 5 minutes and centrifuging, the organic layer was separated, evaporated, and measured by HPLC under conditions as described above. Concentrations of $CoQ_{10\text{-TOTAL}}$ were calculated in picomoles per milligram of wet weight tissue.

Diagnostic significance of coenzyme Q_{10}

CoQ_{10} deficiency impairs oxidative phosphorylation and causes clinically heterogeneous mitochondrial diseases. Primary CoQ_{10} deficiency is due to mutations in genes encoding proteins of the CoQ biosynthesis pathway (CoQ genes). The clinical phenotypes of primary CoQ_{10}-deficient patients include cerebellar ataxia, myopathy or encephalomyopathy, and nephrotic syndrome [27]. Secondary CoQ_{10} deficiency may be due to defects in genes unrelated to the CoQ_{10} biosynthesis complex [28].

The concentration of CoQ_{10} in blood plasma depends on the concentration of lipoproteins, which are its major carriers in the circulation. Approximately 58% of total plasma CoQ_{10} is associated with LDL cholesterol. The concentration of CoQ_{10} in plasma does not reflect CoQ_{10} concentration in tissues; a better parameter for CoQ_{10} deficiency is the ratio of CoQ_{10} to total cholesterol [29]. CoQ_{10} deficiency is usually determined by skeletal muscle biopsy and/or skin fibroblasts. Determination of CoQ_{10} in cerebrospinal fluid may be of diagnostic importance in patients with neurological dysfunction. In recent years, less invasive methods for evaluation of CoQ_{10} and mitochondrial bioenergetics have been used on isolated thrombocytes or leukocytes [30,31].

Metabolic mitochondrial non-communicable diseases and coenzyme Q_{10}

Metabolic syndrome is characterized by risk factors such as arterial hypertension, diabetic hyperglycemia, dyslipidemia, and abdominal obesity. Metabolic syndrome includes several factors that directly increase the risk of coronary heart disease, cardiovascular (CV) atherosclerotic diseases, and diabetes mellitus (DM) type 2. In recent years, other factors, such as chronic proinflammatory and prothrombotic states, nonalcoholic fatty liver disease, and sleep apnea have been added to metabolic syndrome [32].

Non-communicable diseases (NCDs) are closely related to metabolic syndrome. NCDs are noninfectious and nontranmissible; their origin is a combination of genetic, physiological, and lifestyle factors. NCDs are responsible for 71% of all deaths in the world. The most common causes of NCDs are CV diseases, cancers, respiratory tract disease, diabetes, and chronic kidney diseases (CKD). Annually, 17.9 million people become ill with CV diseases, 9 million people with cancers, 3.9 million people with respiratory tract diseases, and 1.6 million people with diabetes [33]. The prevalence, development, and progression of CKDs have reached epidemic proportions. In all NCDs, oxidative stress and mitochondrial dysfunction play crucial roles. Prevention of metabolic syndrome and mitochondrial NCDs is the one of the basic forms of protection of human health.

Coenzyme Q_{10} in prevention and development of mitochondrial cardiovascular diseases and statin-induced mitochondrial myopathy

Myocardial deficiency of CoQ_{10} has been demonstrated in endomyocardial biopsy samples in patients with cardiomyopathy [34] and in patients after heart transplantation in relationship with the degree of rejection development (Fig. 47.5) [35]. One of the main causes of CVD is oxidative stress and the decrease of mitochondrial ATP production in heart associated with low endogenous CoQ_{10} levels.

In 2019 the observations in the field of prevention of risk factors for CV disease were summarized with a focus on epidemiology, dyslipidemia, diabetes, and hypertension. The importance of early reduction in risk factors has been shown. Notably, reduction in LDL cholesterol to 1 mmol/L and reduction in blood pressure by 10 mmHg were associated with a 80% lower risk of CV disease. Higher levels of CV risk factors are associated with worse brain health, and dementia can develop in older adults [36].

Prevention of CV disease involve several factors, such as daily moderate intake of carbohydrates, lower body fat, sleep duration of 6−8 hours daily without disturbance, increased physical activity, less time spent being sedentary, and decreasing exposure to high noise levels, such as road traffic and railway noise. Decreased LDL cholesterol by ezetimibe had a lower risk for side effects in comparison with statin-induced myopathy [36]. Despite major advances in the treatment of CV diseases, the prevalence of hypertension, ischemic heart disease, and stroke is still on the rise.

For prevention and early treatment of the major CV risk factors, increased physical activities, a healthy diet, and natural products are important. One of the natural products for the enhancement of health and prevention of CVD is CoQ_{10} [37]. CoQ_{10} as a key component of the mitochondrial respiratory chain is necessary for ATP production [38]. CoQ_{10} in reduced form (ubiquinol) acts as an antioxidant, contributes to prevention of lipid peroxidation, and prevents LDL oxidation as a factor in the development of atherosclerosis [39]. CoQ_{10} is useful in preventing several CV diseases, as ischemic heart disease, chronic heart failure, hypertension, CV surgery, arrhythmias, and statin-induced cardiomyopathy. The possible mechanisms of CoQ_{10} in CVD include improvement of myocardial energy production, reduction of free radical production, increasing of myocardial CoQ_{10} content, and improvement in endothelial function by counteracting nitric oxide oxidation [40].

In 1981, Karl Folkers (known as the Father of Coenzyme Q_{10}) and Peter Langsjoen were among the first researchers to use CoQ_{10} as a supportive therapy in patients with dilated cardiomyopathies (CMPs). Patients with NYHA III and IV were stabilized by conventional therapy. Supportive therapy with a daily dose of 100 mg CoQ_{10} improved the patients' ejection fraction from 41% to 59% after 24 months of the treatment [41].

The effect of oral treatment with CoQ_{10} was studied in patients with acute myocardial infarction. A daily dose of 120 mg CoQ_{10} for 28 days was compared with placebo. In the CoQ_{10} group, symptoms were significantly ($P < .05$) reduced: angina pectoris (9.5% vs 25.3%), total arrhythmias (9.5% vs 25.3%), and poor left ventricular function (8.2% vs 22.5%). In the CoQ_{10} group, cardiac death and nonfatal infarction declined significantly in comparison with the placebo group (15.0% vs 30.9%, $P < .02$) [42]. In hypertensive patients with coronary artery disease, hydrosoluble CoQ_{10}

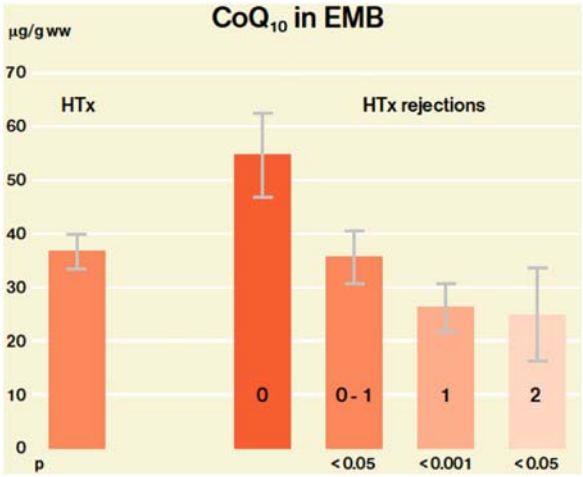


FIGURE 47.5 CoQ_{10} concentration in endomyocardial biopsy (EMB) is decreased with increased rejection degrees of patients after heart transplantation.

treatment caused a decline in insulin levels. CoQ_{10} treatment (60 mg twice daily) was compared with B-complex vitamin treatment in an eight-week randomized trial. In the CoQ_{10} group, systolic and diastolic blood pressure and fasting and 2-hour plasma insulin, glucose, triacylglycerol, lipid peroxides, malondialdehyde, and conjugated diene levels were reduced. CoQ_{10} treatment significantly ($P < .05$) increased levels of HDL cholesterol; vitamins A, C, and E; and beta-carotene. These finding indicate that CoQ_{10} treatment decreases blood pressure, possibly by improving insulin sensitivity by decreasing oxidative stress in hypertensive patients receiving conventional antihypertensive drugs [43]. In a randomized, double-blind, controlled trial, patients with heart failure were treated with CoQ_{10} and carnitine (Carni-Q-Gel). After 12 weeks of treatment, there was significant improvement in the ejection fraction. Serum concentrations of interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) showed significant reduction in the Carni-Q-Gel group compared to the control group [44]. CoQ_{10} increased extracellular superoxide dismutase activity in the endothelium in ischemic heart disease. This finding indicates that supplementary therapy with CoQ_{10} can improve endothelial dysfunction [40,45].

In a multicenter study, the two-year effect of daily doses of 3×100 mg CoQ_{10} was monitored in 420 elderly patients with dilated CMP and ejection fraction greater than 30% of the NYHA III functional class. The CV mortality of these patients was reduced from 16% to 9%, the functional NYHA class improved, and the number of hospitalizations was reduced by almost half. Several mechanisms are involved in improving the symptoms of patients with heart failure, especially energy metabolism and endothelial function [46].

Supportive therapy with CoQ_{10} in patients with heart failure is safe, well tolerated, and accompanied by a reduction of their subjective problems [47,48]. Mechanisms of CoQ_{10} effect in hypertension include improving diastolic function, decreasing blood viscosity, and contribution to the induction of vasodilation. CoQ_{10} decreased systolic and diastolic blood pressure with CoQ_{10} dosage from 30 to 360 mg/day for 13 months [49] and improved insulin sensitivity in diabetic hypertensive patients [50]. The beneficial effect of hydrosoluble CoQ_{10} was demonstrated in daily doses of 2×60 mg for eight weeks by lowering of both systolic and diastolic blood pressure, concentrations of glucose, conjugated dienes, oxidative stress, and triacylglycerols in hypertensive patients. CoQ_{10} stimulated HDL cholesterol production [43] and contributed to the regulation of plasma insulin, lipoproteins, blood pressure, IL-6, TNF-α in acute myocardial infarction [44].

The benefit of CoQ_{10} has also been shown in patients who received 100 mg of CoQ_{10} for 14 days prior to surgery (bypass grafting and valve replacement). After the surgical procedure, patients took 100 mg of CoQ_{10} daily for 30 days. The result was increased mitochondrial CoQ_{10} content, increased mitochondrial energy production, and improved contractile function of the left ventricle [46], and the postoperative time was reduced from 15−30 days to 5 days [50]. Patients with low serum CoQ_{10} concentrations have a poorer prognosis from chronic heart failure, and when they are on long-term statin therapy, these patients may require supplementation with CoQ_{10} to reduce risk of statin-induced mitochondrial myopathy. Although conflicting conclusions are connected to CoQ_{10} treatment in patients with statin-induced mitochondrial myopathy, a recent metaanalysis suggests a benefit of CoQ_{10} in preventing statin myopathy [51]. It has been suggested that CoQ_{10} may be used for reduction of cardiotoxicity induced by anticancer drugs [52].

In recent years, a reduced form of CoQ_{10}-ubichinol (Ubiquinol, Kaneka, Japan) has been shown to be three times more bioavailable. In patients with heart failure, enormous daily doses of CoQ_{10}, namely, 150−600 mg of ubiquinol (332 mg of ubiquinol on average) for 9−20 months, improved both systolic and diastolic heart function, improved NYHA classifications from NYHA IV to NYHA II, and increased the ejection fraction from 20% to 39% [53]. At present, the European Commission, the European Parliament, and the European Council have decided to identify Ubiquinol as a medicine for rare diseases under the European Commission's Regulation No. 141/2000, Brussels (14.10.2016). The rare diseases concern the primary deficiency of the coenzyme Q_{10} in serious rare diseases that can affect the muscular, nervous, and renal systems.

CoQ_{10} is a direct source of ATP production through OXPHOS stimulation in cardiac muscle mitochondria. Under physiological conditions, 90% of ubiquinol and 10% of ubiquinone are in the organism. On the basis of previous studies, several authors recommend CoQ_{10} administration as supportive treatment for mitochondrial CV diseases to reduce the degree of heart damage and improve the quality of life of patients with a certain type of CV pathology. Daily doses and the duration of CoQ_{10} treatment depend on the baseline therapy, the severity and type of the disease, and associated complications. Supportive therapy with coenzyme Q_{10} has a significant role in preventing the development of CV complications [54].

In the primary prevention of CV disease in patients with elevated cholesterol concentration, the beneficial effect of statins was documented as improving endothelial function by reducing oxidative stress; inhibiting inflammatory processes; reducing levels of C-reactive protein, IL-6, and TNFα; and preventing thrombus formation. In secondary

prevention, statins are used to reduce CV disease and death by lowering lipid levels, thus protecting the body from ischemia, myocardial infarction, and sudden stroke [55–57].

Statins are mostly well tolerated, but side effects have been found, such as coenzyme Q_{10} reduction, myopathy, myalgia or rhabdomyolysis, increased serum creatine kinase activity, increased risk of diabetes, rheumatoid arthritis development, oncological disease (if LDL cholesterol levels are low), elevations of transaminase levels (ALT, AST), memory impairment, and sexual dysfunction [58] if long-term use and higher daily doses of statins are used. Statins block CoQ_{10} synthesis in cancer cells, and reduced CoQ_{10} levels decrease ATP production via oxidative phosphorylation. The cells compensate the loss of ATP from the Krebs cycle by increasing glycolysis [59].

Statins are commonly used for the treatment of elevated cholesterol levels. They inhibit the activity of enzymes (3-hydroxy-3-methylglutaryl coenzyme A reductase-HMG-CoA reductase), important for mevalonic acid formation. Mevalonic acid is a precursor of cholesterol, dolichol, and coenzyme Q_{10}. Statins reduce the formation of mevalonic acid and the production of not only cholesterol but also dolichol and CoQ_{10} in serum as well as in muscles, which is associated with the impairment of skeletal muscle mitochondria. A deficiency in CoQ_{10} is considered to be one of the causes of myopathy formation during statin therapy, and myopathy may be induced; this is known as statin-induced mitochondrial myopathy [60,61].

The mechanism of action of statins on skeletal muscle mitochondria involves inhibition of complex I and IV of mitochondrial respiratory chain, reduction of CoQ_{10} concentration and energy production in skeletal muscle mitochondria, depolarization of the internal mitochondrial membrane, and fragmentation of mitochondrial DNA. As a result of these changes, Ca^{2+} is released from the mitochondria and the sarcoplasmic reticulum into the cytoplasm. Accumulated Ca^{2+} damages the skeletal muscle mitochondria [62].

Several clinical studies have confirmed the beneficial effect of CoQ_{10} on the reduction of statin-induced skeletal muscle pain and weakness. To reduce the intensity of muscular pain in statin therapy, different doses of CoQ_{10} were used: 2×50 mg CoQ_{10} daily for 30 days or 100 mg CoQ_{10} daily for 30 days. To improve the function of skeletal muscle mitochondria and decrease statin-induced myopathy doses of 200 mg CoQ_{10} daily or 60 mg ubiquinol daily for 3–6 months were used. The regeneration of skeletal muscle mitochondria biogenesis with CoQ_{10} in statin-induced myopathy has been demonstrated [61].

The conclusions of some studies did not confirm the beneficial effect of CoQ_{10} on the reduction of muscular pain in statin therapy. In 2015 the results of seven extensive studies on the effect of CoQ_{10} on statin therapy were evaluated. In four studies, the CoQ_{10} was shown to be beneficial for muscle pain; in three studies the beneficial effect of CoQ_{10} on muscle pain in patients with statin myalgia was not confirmed. These different results are explained by the different types and daily doses of statins, the duration of their use, and the daily doses and duration of CoQ_{10} treatment [63].

In view of the controversial results on the effect of CoQ_{10} on reducing the side effects of statins, the European Atherosclerotic Society points to possible prospective studies with two types of LDL cholesterol–lowering and HDL cholesterol–elevating drugs in patients with statin-related muscular problems (PSCK9 and CEPT inhibitor) [64].

Currently, there is no clear guideline for recommending CoQ_{10} supplementation with statin therapy, yet it is one of the most effective nutritional supplements to reduce muscular pain caused by statin therapy. On the basis of our experience and the experiences of multiple authors, a supportive energy and antioxidant treatment with CoQ_{10} at daily doses of 60 mg-100 to 200 mg is recommended to reduce the side effects of statins, especially in patients with muscle pain and overall weakness, in patients with increased creatine kinase and transaminase activity, in CV disease and diabetes, in memory impairment, and in sexual dysfunction.

The recommended daily dose of CoQ_{10} in statin therapy depends on the patient's overall health status and metabolic parameters. The long-term ubiquinol intake improves the quality of human life [65]. Although conflicting conclusions have been reached about supportive therapy with coenzyme Q_{10} in statin therapy, the use of CoQ_{10} in patients with statin-associated myopathy is recommended [66].

Coenzyme Q_{10} in prevention and development of mitochondrial diabetes

The prevalence of diabetes is increasing. Globally, more than 452 million patients have diabetes, and the number is expected to increase to 629 million by 2045. Diabetes is a risk of CV disease. In diabetes care prior to glucose approaches is the aim to prevent cardiorenal complications [67].

DM is a chronic metabolic disorder associated with both impaired insulin release from pancreatic beta cells and impaired insulin action in insulin-sensitive tissues. Mitochondrial dysfunction and oxidative stress play roles in both processes as well as in the development of diabetic complications [68]. DM is associated with chronic hyperglycemia and disturbances in carbohydrate, lipid, and protein metabolism [69]. The CoQ_{10} concentration in serum of patients

with type 2 diabetes is often decreased but may be reversed by CoQ_{10} supplementation [70]. Clinical studies proved some beneficial effects of CoQ_{10} treatment in diabetic patients, assuming improved bioenergetic function and antioxidant protection. Dosing, bioavailability, and duration of treatment may be important factors in coenzyme Q_{10} effectiveness in the management of complications associated with diabetes. Increased effects can also be achieved by combining coenzyme Q_{10} with other antioxidants, vitamins, nutraceuticals, drugs, or application of polarized light [71–73]. In 2012 Hermanéz et al. demonstrated that 12-week supplementation with ubiquinone improved parameters of diabetic neuropathy and reduced oxidative stress without significant adverse effects [74].

Coenzyme Q_{10} is an electron carrier in the mitochondrial respiratory chain which may also account for circadian oscillations. Concentrations of CoQ_9 and CoQ_{10} in cardiac mitochondria are subject to variations for 24 hours a day. Every 12 hours they reach two maxima (peaks) and two minima (nadirs). These are circadian and circasemidian rhythms, which are different in control and diabetic experimental animals. CoQ_{10} maxima for controls are at 15:27 and 03:30 hours, in diabetic mitochondria maximum concentrations of CoQ_{10} occur earlier, at 13:09 and 02:33 hours (Fig. 47.6) [61].

Mitochondrial biological clocks of CoQ_{10} may be a key parameter for mitochondrial membrane regeneration and reenergization of the heart. Determining the differences in circadian and circasemidian rhythms of CoQ_{10} concentrations in the mitochondria of control and diabetic subjects may contribute to the understanding of the onset of acute myocardial infarction in diabetic patients [60,61,75].

Coenzyme Q_{10} in prevention and development of mitochondrial cancers

Otto Warburg, pioneer in the study of malignant cells metabolism, formulated a hypothesis for why malignant cells require a higher amount of glucose for increased lactate production without the requirement for oxygen delivery. Cancer cells preferred aerobic glycolysis to mitochondrial oxidative phosphorylation [76]. Warburg explained the glycolysis effect of malignant tumor cells by the dysfunctional mitochondria. The molecular mechanisms of pyruvate utilization include stimulation of glycolysis by the oncogenes, inhibition of pyruvate dehydrogenase, reduction of mitochondrial biogenesis, and inhibition of respiratory chain activity [77].

Coenzyme Q_{10} plays an important role in ATP synthesis and in the antioxidant defense against increased production of free radicals. Lower CoQ_{10} levels were detected in the plasma of patients with various cancers, such as breast cancers and malignant melanoma. Significantly reduced CoQ_{10}, alpha-tocopherol, and gamma-tocopherol concentrations were reported in patients with cervical carcinoma [78]. Higher plasma beta-carotene levels had a positive effect on the survival of patients with metastatic urothelial carcinoma who were treated with platinum-based therapy [79]. Cytostatics such as doxorubicin, methotrexate, camptothecin, and etoposide stimulated CoQ_{10} concentration in tumor cells lines. Increased CoQ_{10} levels resulted from increased regulation of expression of the CoQ genes that are involved in biosynthesis of CoQ_{10} (COQ4, CoQ7, CoQ8) [80]. The anthracycline antibiotics are used in cancer chemotherapy. Anthracyclines produce acute and chronic cardiotoxicity. Symptoms of acute cardiotoxicity, such as various EKG changes and depression of myocardial contractility, are common in patients during the first 24 hours after drug infusion. These effects are transient and resolve spontaneously [81]. Several studies suggest that anthracycline-induced

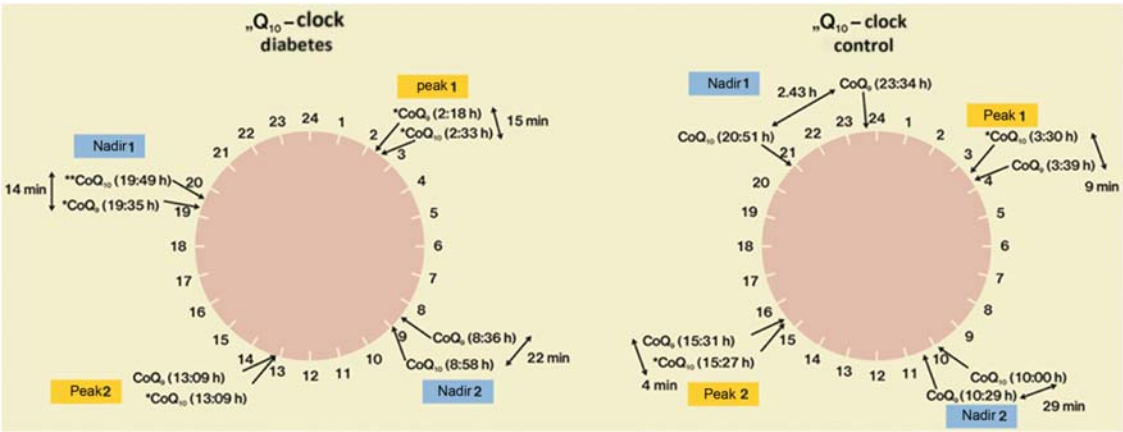


FIGURE 47.6 Biological Q_{10} clock in myocardial mitochondria of control and diabetic rats.

cardiotoxicity can be prevented by administration of CoQ_{10} during cancer chemotherapy. CoQ_{10} can prevent damage of myocardial mitochondria and prevent the development of anthracycline-induced cardiotoxicity [52]. Infusion of 1 mg CoQ_{10} per kilogram of body weight for four days before chemotherapy reduced EKG changes induced by doxorubicin or daunorubicin [82].

In the last four decades, the incidence of breast cancer has increased globally. The highest incidence is in developed countries, such as Australia, New Zealand, Canada, the United States, the United Kingdom, and Western Europe. The number of women diagnosed with breast cancer has also been increasing in the rest of the world. Also during the last four decades the use of complementary and alternative therapies has increased. Coenzyme Q_{10} is a specific alternative supplementary treatment for breast cancer. Women with breast cancer with lower plasma and tissue levels of CoQ_{10} have a worse prognosis. Supplementation with CoQ_{10} in combination with other nutrients has been associated with tumor regression and increased years of survival [83].

Ultraviolet (UV) radiation is an essential risk factor for the development of skin cancers. UV generates free oxygen radicals and directly oxidizes DNA. Supplementation with antioxidants, such as vitamin C, vitamin E, beta-carotene, vitamin A, glutathione, green tea, and CoQ_{10}, can prevent oxidative stress and reduce the harmful effects of UV in skin cancer [84]. CoQ_{10} protects against oxidative stress−induced dermal cell death and has a cutaneous healing effect [85].

The optimal CoQ_{10} daily dosage in patients with cancer can be established. Developing of a novel approach based on mitochondrial function will be important for improving the quality of human life [86]. Mechanisms of CoQ_{10} benefit in cancer may include antioxidant activity and immune system enhancement. Supplemental CoQ_{10} (100−200 mg/day) can prevent cardiac damage during chemotherapy treatment with high doses of doxorubicin [87]. CoQ_{10} provides protection against cardiotoxicity and liver toxicity in patients receiving anthracycline chemotherapy drugs [88].

Coenzyme Q_{10} in the prevention and development of mitochondrial chronic kidney diseases

CKD is characterized by a progressive loss of renal function caused by chronic inflammation, oxidative stress, vascular remodeling [89], changes in cellular energy metabolism, mitochondrial dysfunction, and reduced antioxidant protection, including coenzyme Q_{10} (CoQ_{10}) concentration. Damage to the balance between antioxidants and reactive oxygen species formation may accelerate renal disease progression and CV complications, atherosclerosis, and DNA damage and may contribute to clinical complications. All these factors contribute to CKD [90−92]. Mitochondrial dysfunction in the kidney, decreased CoQ_{10} level, and oxidative stress play critical roles in the pathogenesis of kidney diseases [93,94]. Development and progression of CKD are closely linked with NCDs, such as CV diseases, cancers, respiratory tract diseases, and diabetes [33]. Patients with CKD have a high risk of death from stroke or heart attack [89]. The mortality rate of patients with CKD increases with the decrease in glomerular filtration rate.

In our patients with CKD and combinations of CKD + AH (arterial hypertension) and CKD + AH + DM (DM) we found reduced endogenous $CoQ_{10\text{-TOTAL}}$ concentration (ubiquinol + ubiquinone) in isolated platelets and in plasma.

The concentration of $CoQ_{10\text{-TOTAL}}$ (ubiquinone + ubiquinol) in platelets of CKD-ALL patients significantly decreased ($P < .008$), by 73.8%; in the CKD + AH group, it decreased to 64.3% ($P < .00015$); in the CKD + AH + DM group, it decreased not significantly, to 85.1% of control values. The concentration of $CoQ_{10\text{-TOTAL}}$ in plasma of CKD-ALL patients significantly decreased ($P < .01$), to 69.8%; in the CKD + AH ($P < .016$) group, it decreased to 67.2%; in the CKD + AH + DM group, it decreased not significantly, to 71.5% of control values (Fig. 47.7) [95,96].

In CKD-ALL and the CKD + AH group, the concentrations of $CoQ_{10\text{-TOTAL}}$ in platelets and in plasma were significantly reduced in comparison with the control group. Insufficient CoQ_{10} concentration results in decreased mitochondrial ATP production [97]. The progression of CKD is associated with mitochondrial dysfunction. The decrease of complex IV activity was reported in peripheral blood mononuclear cells of patients with stage IV−V CKD [89,91]. In group of patients with CKD and diabetes the decrease in concentration of $CoQ_{10\text{-TOTAL}}$ in platelets and plasma was not significant. We suppose that higher levels of CoQ_{10} in DM patients could be an adaptation of the antioxidant defense system to chronic oxidative stress [95,96], and drugs or differences in dietary intake could participate on this effect.

A number of multicenter studies have confirmed the beneficial effect of CoQ_{10} in patients with CV diseases [49] and heart failure [54]. Sing's group has demonstrated for the first time that CoQ_{10} can modulate plasma insulin, lipoprotein(a), serum creatinine and albuminurea, serum IL-6, TNF-α, serum nitrite, blood pressure variability, and neuronal degeneration [98]. Patients with chronic renal failure were treated with 60 mg CoQ_{10} three times per day orally (Q-Gel) or with placebo for 12 weeks. Serum creatinine, blood urea, and nitrogen levels were significantly improved in comparison to the placebo group [99].

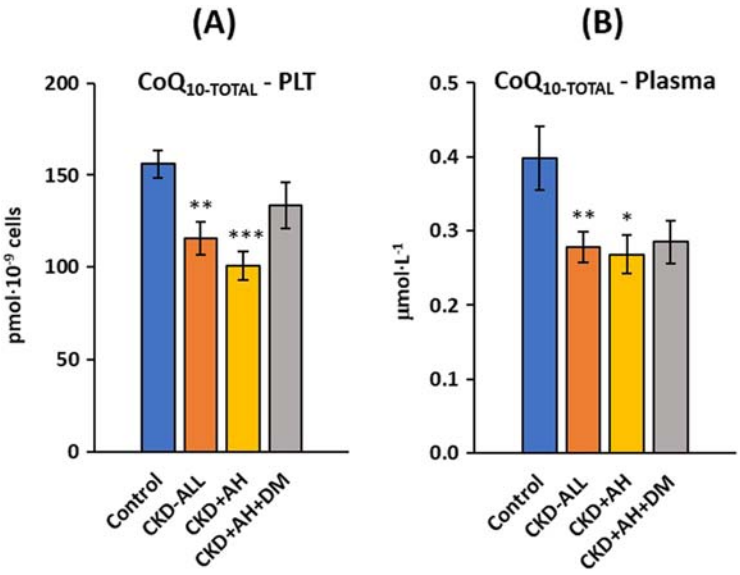


FIGURE 47.7 Endogenous $CoQ_{10\text{-TOTAL}}$ in platelets and plasma of patients with chronic kidney disease. (A) $CoQ_{10\text{-TOTAL}}$ in platelets (**$P < .008$, ***$P < .00015$). (B) $CoQ_{10\text{-TOTAL}}$ in plasma (*$P < .01$, **$P < .016$). *CKD-ALL*, all 27 CKD patients; *CKD + AH*, CKD patients with arterial hypertension ($N = 17$); *CKD + AH + DM*, CKD patients with AH + type w diabetes ($N = 10$).

Conclusion

CoQ_{10} as a key component of the mitochondrial respiratory chain is important for ATP production via oxidative phosphorylation. Ubiquinol acts as an antioxidant, reducing oxidative stress. Therefore CoQ_{10} supplementary therapy in NCDs could prevent development of NCD complications, such as mitochondrial CV diseases, mitochondrial diabetes, mitochondrial cancer, and mitochondrial CKDs. Among the main reasons for development of NCDs are mitochondrial dysfunction and oxidative stress.

Up to now, there has been no guideline for CoQ_{10} treatment as supplementary therapy. Although there are discrepancies in the literature on CoQ_{10} supplementation in statin-induced mitochondrial myopathy and in CV diseases, many publications recommend CoQ_{10} treatment as supplementary therapy for the prevention and development of complications of mitochondrial NCDs.

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Chapter 48

Plants of the genus *Annona*: Source of potential anti-cancer therapeutics

Shalini Behl, Asha Inbanathan, Madhumitha Kedhari Sundaram and Arif Hussain
School of Life Sciences, Manipal Academy of Higher Education, Dubai, United Arab Emirates

Introduction

Cancer is a major health issue all over the world [1,2], in both developing and developed countries [3]. In the 21st century, it is the second leading cause of death globally [3]. It is caused by uncontrolled and abnormal cell division [4]. According to the World Health Organization (WHO), 85 million deaths due to cancer were reported between 2005 and 2015 [1,2]. The number of people being diagnosed with cancer is also increasing each year. In 2018 Globocan reported that 18.4% of the total deaths worldwide were caused by lung cancer [5]. Globocan also reported that gastric cancer was the third leading cause of cancer death worldwide [6–8]. Cervical cancer is the fourth major cause of death in females [9,10].

Dysregulation of the cell cycle and increase in telomerase activity are among the reasons for the increased proliferation and achievement of cellular immortality in cancer cells. Another important hallmark of cancer cells, including ovarian, breast, colorectal and pancreatic cancers, is their ability to evade apoptosis [2,11–13]. Breast cancer cells are associated with improper functioning of the intrinsic pathway [2], improper cytochrome release [2,14], non-formation of apoptosome [2,15], and lack of activation of caspases [2,16]. Lung cancer cells also show resistance to apoptosis [17,18].

WHO statistics show that more than 80% of the world's population uses medicines prepared from natural products to treat diseases [19,20]. Natural products that are known to block the progression of the cell cycle in cancer cells have the potential to function as effective anticancer agents [2,21]. Plant-based compounds that are cytotoxic to cancer cells can be used as complementary and alternative medicines [2].

Family Annonaceae, genus *Annona*

The components of the *Annona* species that have anti-cancer properties are known as acetogenins [7]. Acetogenins have been reported to demonstrate anticancer activity against various cancer cells. The bis-adjacent tetrahydrofuran (THF) α,α'-dihydroxylated acetogenins, such as squamocin, asimicin, and panalicin, are the most effective acetogenins against the MCF-7 human breast cancer cell line, the A-549 human lung cancer cell line, and the HT-29 human colon cancer cell line [22]. The THF Annonaceous acetogenins are the most effective against the A-498 human kidney carcinoma cell line, the MIA PaCa-2 human pancreatic carcinoma cell line, and the PC-3 human prostrate adenocarcinoma cell line [22,23]. Various cancer cell lines show different susceptibilities to the same acetogenins [22,24]. Acetogenins also show antitumor effects in ovarian cancer, liver cancer, lymphoma, and leukemia cell lines [22,25]. They are effective even at very low doses, but their efficiency varies depending upon the number of hydroxyls and their position in the chain and the number of THF rings in their structures [22,25]. Acetogenins act as anticancer agents by inhibiting mitochondrial complex I [26,27] and nicotinamide adenine dinucleotide oxidase [2,28]. They also block the production of adenosine triphosphate in mitochondria, which stops the cancer cells from growing [2]. Acetogenins are anti-neoplastic agents [29] or chemopreventive agents. Certain compounds are also effective in treating multidrug-resistant cancer by inhibiting the P-glycoprotein [27,30]. Interestingly, acetogenins are toxic only to cancer cells and have no toxic effect on normal cells [31]. Furthermore, analogs of acetogenins that were synthesized in vitro were found to be toxic to the

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human colorectal cancer cell lines HT-29 and HCT-8 and non-toxic to human embryonic lung fibroblasts, which is a normal lung human cell line [31].

Annona atemoya

The compounds squamostatin-D, 12,15-cis-squamostatin-D, desacetyluvaricin, neoannonin, bullatacin, and squamocin, which were isolated from *Annona atemoya* extract by bioactivity-guided chromatographic fractionation, were cytotoxic to the human nasopharyngeal cancer cell line KB, human hepatoblastoma cell line Hep 2.2.15, human liver cancer cell line HepG2, human lymphoblastic leukemia cell line CEM, and human colon cancer cell line CCM2 [32]. Another study showed that bullatacin had anti-proliferative and pro-apoptotic effect on 2.2.15, a hepatitis B virus DNA-transfected human hepatocarcinoma cell line [33].

Annona bullata

Annona bullata shows selective cytotoxicity and has anti-tumoral effect on the A-549, HT-29, MCF-7/Adr, and MCF-7/wt cancer cell lines [22,34–39]. The acetogenins obtained from *A. bullata* ethanolic extract are 2,4-cis- and trans-28-hydroxybullatacinone, 2,4-cis- and trans-30-hydroxybullatacinone, 2,4-cis- and trans-31-hydroxybullatacinone, 2,4-cis- and trans-32-hydroxybullatacinone, bullatacinone, bullatacin, diterpene 16 alpha-hydroxy-(-)-kauranoic acid, 30-hydroxybullatacin, 31-hydroxybullatacin, 32-hydroxybullatacin, uvariamicins, bullatencin, and 4-deoxyasimicin [22]. Isoquinolin alkaloids, such as liriodenine and (R)-annonain, are also obtained from this extract [22]. When mice with L-1210 leukemia were treated with bullatacinone and bullatacin, there was an increase in their life spans [40]. Bullatalicin and bullatacin were cytotoxic to the A-2780 line of human ovarian cancer in athymic mice [40]. These mice did not show weight loss, which indicated that the drugs were tolerated favorably in the animals [40]. Another compound derived from *A. bullata*, bullatacin was shown to be cytotoxic to the ovarian cancer cell lines, OVCAR-3, OC-222, A-2780, and OC-194 [41]. However, it had no effect on murine ovarian teratocarcinoma in C3HeB/FeJ mice [41]. Furthermore, bullatacin can activate apoptosis [42].

Annona cherimola (cherimoya, custard apple)

The anti-proliferative activity of the ethanol macerate extract, which was obtained from *Annona cherimola* seeds, was studied by Macuer-Guzmán et al. on the AGS cell line, which is a human stomach gastric adenocarcinoma cell line. The main metabolites that were present in the extract were coumarins, flavonoids, sterols, terpenes, alkaloids, and acetogenins (gamma-lactones) [7]. After the AGS cells were exposed to the extract for 7 hours, over-expression of PUMA, a proapoptotic gene, was observed along with significant activation of the pro-apoptotic enzymes caspase-3 and caspase-7 [7]. Haykal et al. studied the anti-cancer effects of *A. cherimola* Mill ethanolic seed extract (ASEE) on Mono Mac 1, KG-1, and U937 acute myeloid leukemia cell lines in vitro and found that the extract decreased cell proliferation. Further, it was found to induce apoptosis with accumulation of sub-G1 population [43]. High concentrations of ASEE activated both the intrinsic and extrinsic pathways of apoptosis [43], with a crucial role played by the P53-dependent pathway. Upregulation of the proapoptotic proteins P53 and cleaved poly (ADP-ribose) polymerase 1 (PARP-1) was observed upon treatment with ASEE extract along with an increase in the apoptotic agents cleaved caspases-8 and 9 and an increase in the ratio of pro-apoptotic Bax to anti-apoptotic Bcl-2 protein. It was noticed that there is a link between anti-oxidative properties and anti-cancer properties. The reactive oxygen species (ROS) produced by tert-butyl hydrogen peroxide could be quenched by ASEE, emphasizing its anti-oxidative properties. The compounds that were identified in ASEE were phytosterols, namely, beta-stigmasterol, beta-sitosterol, methylene di-tert-butyl cresol, and dihydrobrassicasterol [43]. A number of mono-THF acetogenins, such as motrilin, cherimolin-1, annomolin, laherradurin, annomocherin, annocherimolin, annomontacin, annonacin, and *cis*-annonacin, have been isolated from *A. cherimola* seeds. Bis-THF acetogenins such as tucumanin; mixtures of epimers, such as 34-epiannomolon A, annomolon A, 34-epiannomolon B, and annomolon B; and mixtures of (2,4)-cis- and trans-isoannonacins have also been isolated from these seeds. These compounds are selectively toxic to various cancer cell lines and cause the mitochondrial complex I to be inhibited [22,44–50]. The above-mentioned acetogenins were isolated from a methanolic or ethanolic extract and were seen to be cytotoxic to various cancer cell lines and were equally or more effective than the approved anti-cancer drug, doxorubicin [22]. Annomolin showed cytotoxicity to the HT-29 colon cancer cell line, the PC-3 human prostate cancer cell line, and the MCF-7 breast cancer cell line and was seen to be more effective than the

anti-cancer drug doxorubicin [51]. Cherimolacyclopeptide C, another phytochemical obtained from a methanolic extract of *A. cherimola* seeds, a cyclic heptapeptide, is cytotoxic to KB cells in vitro, with an IC_{50} value of 0.072 μM [52].

Annona crassiflora (araticum)

The seed extract and methanolic leaf extract of *Annona crassiflora* were shown to have anti-proliferative properties in vitro in a number of cancer cell lines such as leukemia, glioblastoma, and colorectal, ovarian, and lung cancer cell lines [9,53]. The ethanolic extract of the wood of *A. crassiflora* is rich in acetogenins and has been shown to have anti-tumor activity on Ehrlich tumors [9,54]. The apoptotic and cytotoxic properties of *A. crassiflora* were studied by Silva et al., on seven immortalized human cervical cancer cell lines: HR5, HtTA-1, SiHa, HeLa, HR5-CL11, CaSki, and BU25TK. The crude extract of *A. crassiflora* caused a significant reduction in cell viability, reduced migration, and caused cell death in the SiHa human cervical cancer cell line [9]. This may have been achieved via reduction in the activity of the protein AKT, thereby inhibiting the PI3K-AKT pathway [9]. The components present in the hexane partition derived from the crude extract of *A. crassiflora* are alkaloids, palmitate, octadecatrienoic acetogenins, and acids [9]. The hexane portion was cytotoxic both in vivo and in vitro and caused a reduction in the proliferation of the seven cervical cancer cell lines [9]. The hexane partition from *A. crassiflora* modulated the intracellular signaling pathways and increased ERK activity. It promoted DNA damage, apoptosis by intrinsic pathway via cleavage of procaspases 3 and 9 and PARP, polarization of the mitochondrial membrane, and reduction in the expression of p21 by the ubiquitin proteasome pathway [9]. The hexane partition also promoted a reduction in the perimeter of the SiHa tumor in vivo in chicken embryo [9].

Annona glabra (pond apple)

Ethanolic extracts of the fruit pulp, leaves, and seeds of *Annona glabra* was prepared by Cochrane et al. These extracts showed high cytotoxicity to drug-sensitive (CEM) and multidrug-resistant leukemia (CEM/VLB) cell lines. The seed extract was seen to be more effective than the pulp and leaf extracts. The extract from *A. glabra* seeds resulted in an increase in the percentage of G_0/G_1 and sub-G_0/G_1 cell population in a concentration-dependent manner, which contributed to its cytotoxic effect [27]. Treatment of the CEM and CEM/VLB cell lines with the seed extract induced necrosis and apoptosis in a concentration-dependent manner. The expression of the cyclin kinase inhibitor (WAF1/p21) was upregulated, which contributed to the arrest of cells at the G_0/G_1 phase of the cell cycle. The seed extract contains compounds that modulate the MDR1/P-glycoprotein, which may help to overcome drug resistance in tumor cells [27]. The antiproliferative effects of an alcoholic extract of *A. glabra* leaves on MC-1010 human monocytic leukemia cells were studied by Liu et al. Glycosides, flavonoids, steroids, terpenoids, tannins, saponins, acidic compounds, and anthraquinones were seen to be present in this extract [55]. Treatment with the plant extract reduced viability of leukemia cells by 28%, inhibited colony formation, restricted migration, and promoted apoptosis [55]. A significant increase in the free radical reducing power and scavenging activity was also observed [55].

Annona glauca

Glaucacylopeptide A, a compound that was obtained from *A. glauca* seeds, was seen to be cytotoxic to the KB tumoral cell line [56].

Annona jahnii

Extracts of *Annona jahnii* were seen to be selectively cytotoxic and to have anti-tumoral effects on the human kidney cancer cell line A-498, the human lung cancer cell line A-549, the human breast cancer cell line MCF-7, the human colon cancer cell line HT-29, the human pancreatic cancer cell line PACA-2, and the human prostate cancer cell line PC-3 [22,57]. The compounds annojahnin, its racemic alcohol, its acetonide, annomontacin, and semisynthetic acetogenins 4-deoxy-18/21-cis-annomontacin-10-one and 4-deoxy-18/21-trans-annomontacin extracted from *A. jahnii* were found to be toxic to the MCF-7 breast cancer cell line, the A-549 human lung cancer cell line, the A-498 kidney cancer cell line, the HT-29 colon cancer cell line, the PACA-2 pancreatic cancer cell line, and the PC-3 prostate cancer cell line [57]. Annojahnin was seen to be cytotoxic to the PACA-2 human pancreatic carcinoma cell line, while 4-deoxy-18/21-trans-annomontacin was more cytotoxic than 4-deoxy-18/21-cis-annomontacin-10-one [57]. In another study, acetogenins jahnonacin and annodienin, which were isolated from the ethanolic twig extract of *A. jahnii*, were seen to be

cytotoxic to the human prostate cancer cell line PC-3, the human kidney cancer cell line A-498, the human colon cancer cell line HT-29, the human pancreatic cancer cell line PACA-2, the human breast cancer cell line MCF-7, and the human lung cancer cell line A-549 [58].

Annona montana

The acetogenin cis-annoreticuin was isolated from *Annona montana*. It has been seen to be cytotoxic to Hep G2, a human hepatoma carcinoma cell line [59,60]. *A. montana* contains monotetrahydrofuranic acetogenins, which have toxicity to liver cancer in Hep G2 cells [61,62]. High-performance liquid chromatography was used to isolate the monotetrahydrofuranic Annonaceous acetogenins, monlicins A and B, and montalicins G and H; linear acetogenins, (−)-monhexocin, and (+)-monhexocin; and muricatacin, murisolin, and 4-deoxyannomontacin from the seeds of *A. montana*. Monlicins A and B, montalicins G and H, and (−)-monhexocin and (+)-monhexocin were cytotoxic to Hep G2 hepatoma cells, which are liver cancer cells. Monlicins A and B were cytotoxic to the 1A9 ovarian cancer cell line [61]. Acetogenin montanacin F, obtained from *A. montana* leaves, was cytotoxic to the Lewis lung carcinoma (LLC) tumor cell lines. Acetogenin annonacin was also cytotoxic to this cell line [63]. An acetogenin annomontacin was isolated from *A. montana* seeds. Annonacin, annonacinone, and annomontacin were seen to be cytotoxic to the MDA-MB-231 human breast adenocarcinoma cell line, the L-1210 murine leukemia cell line, and the MCF-7 human breast carcinoma cell line [64]. The acetogenins annonacin, gigantetrocin A, gigantetrocin B, and montanacin C, which were isolated from the fruits and leaves of *A. montana*, are strongly cytotoxic to human lung cancer LLC cells [42]. Liaw et al. isolated 17 acetogenins from the methanolic extract of *A. montana* seeds [65]. The acetogenins, namely, cis-annoreticuin, and montalicins A, B, C, D, E, F, I and J were cytotoxic to the HepG2 hepatoma cell line but less cytotoxic to the Hep 3B hepatoma cell line [65]. Montalicin C, E, and I were cytotoxic to the MCF-7 breast cancer cell line, the A-549 lung cancer cell line, the KB epidermoid nasopharyngeal carcinoma cell line, and the KB-VIN vincristine-resistant KB and 1A9 ovarian cancer cell line. Montalicin C was also shown to be cytotoxic to and inhibited the growth of the U-87-MG glioblastoma cell line, the HCT-8 ileocecal cell line, the PC-3 prostate cancer cell line, and the 1A9 PTX10 ovarian cancer cell line with beta-tubulin mutation [65]. The acetogenins cis-annonacinone, annonacin, and xylopianin were cytotoxic to the 1A9 ovarian cancer cell line [65]. The other acetogenins that were isolated from the extract are annonacinone, gigantetronenin, cis-annonacin, goniothalamicin, and annoreticuin [65]. The compounds annoquinone-A and beta-sitostenone, which were isolated from the stem bark of *A. montana*, were shown to be cytotoxic to KB cells [66]. Other compounds that were isolated from the same plant part were parietin (physcion) and phenanthrene-l-quinone [66]. Cytotoxic phenanthrene alkaloid, annoretine [3-hydroxy-4-methoxy-*N*-methyl-tetrahydropyrido(4,3-α) phenanthrene], and cytotoxic alkaloids Liriodenine and argentinine, were isolated from the methanolic extract of the leaves of *A. montana*. These compounds were cytotoxic to the L-1210 lymphocytic leukemia cell line, the KB human cancer cell line, the P-388 murine cancer cell line, the HT-29 colon cancer cell line, and the A-549 lung carcinoma cell line [67]. Using crystal violet assay, it was shown that the ethyl acetate extract of *A. montana* fruit was most cytotoxic and the methanolic extract of the fruit was least cytotoxic to the human A-549 lung cancer cell line, the D-384 astrocytoma cell line, the MCF-7 breast cancer cell line, the PC-3 prostate cancer cell line, and the RKO colon cancer cell line [68]. Wang et al. isolated acetogenins from the leaves of *A. montana*. These compounds are montanacin G, an isoacetogenin, and acetogenins montanacin H, montanacin I, montanacin J, 34-epi-montanacin H, 34-epi-montanacin I, 34-epi-montanacin J, annonacin, giganterocin A, giganterocin B, and cis-annonacin. The cytotoxic effect of these acetogenins and montanacin B and montanacin C on the LLC and Meth-A mouse tumor cell lines was investigated. All the investigated acetogenins showed higher cytotoxicity to the LLC tumor cell line than to the Meth-A tumor cell line. Out of the investigated acetogenins, annonacin, was seen to have the most cytotoxic effect on both the cell lines [69]. In three-day cytotoxicity bioassays, acetogenins cis-montacin, and montacin, which were isolated from *A. montana* seeds, were seen to be cytotoxic to the MCF-7 breast, SK-MEL-2 melanoma, A-549 lung, KB epidermoid nasopharyngeal carcinoma, and HCT-8 ileocecal cancer cell lines. These acetogenins showed more cytotoxicity to 1A9 ovarian cancer and 1A9 PTX10 ovarian cancer with alpha-tubulin mutation cell lines in the six-day assay compared to the three-day assay. More cell growth was inhibited in 1A9 and 1A9 PTX10 cell lines when calcium ions were included in the bioassays along with the acetogenins [70].

Annona muricata (soursop or graviola)

The name "cancer killer" has been given to the leaves of *Annona muricata*, which is used to treat cancer, in traditional medicine [2,71]. Annomuricin A, muricatocin, and annonacin are acetogenins that were isolated from *A. muricata*

leaves and have been most widely studied. These acetogenins have anti-tumoral activity. It was seen that annomuricin A and muricatocin A showed significant cytotoxicity to the A-549 human lung cancer cell line [22]. Moghadamtousi et al. evaluated the molecular mechanisms involved in the cytotoxic effect of *A. muricata* leaves ethyl acetate extract (AMEAE) on the A-549 lung cancer cell line [18]. Apoptosis was induced by the leaf extract through the mitochondrial-mediated pathway and by involvement of nuclear factor kappa B (NF-κB). AMEAE showed cytotoxicity to the A-549 cells, and leakage of lactate dehydrogenase leakage and externalization of phosphatidyl serine were observed. AMEAE caused G0/G1 arrest, increased levels of ROS, disrupted mitochondrial membrane potential (MMP), down-regulated Bcl-2, and upregulated Bax, along with the release of cytochrome c and caspase activation [18]. When the A-549 cells were incubated with catalase and superoxide dismutase, there was attenuation in the cytotoxic effect of AMEAE, indicating that intracellular ROS increase plays a significant role in cell death. Additionally, the translocation of NF-κB from the cytoplasm to the nucleus was suppressed by AMEAE [18]. *A. muricata* extracts were shown to have antiproliferative effects on the NCI-H292 lung cancer cell line and the HEp-2 laryngeal cancer cell line [72]. Annonacin from *A. muricata* could be a topoisomerase poison [42].

A. muricata leaves were seen to be cytotoxic to MCF-7 breast cancer cells [73]. Another study using the leaf extract of *A. muricata* showed that the extract was toxic to the 4 TI, MCF-7, and MDA-MB-231 breast cancer cell lines but was less toxic to MCF10A normal breast cells [74]. This signifies that the cancer cells were specifically targeted by the acetogenins present in the leaf extract [2,74]. The aqueous leaf extract in the *A. muricata* crude extract (AMCE) that was most effective against cancer was B1 AMCE [74]. B1 AMCE caused apoptosis of the breast cancer cell lines in vitro. Female BALB/c mice were injected with 4 TI breast cancer cells, which caused tumors to form in the mice. B1 AMCE was administered to these mice. B1 AMCE was seen to decrease the weight and size of the tumor in vivo and caused apoptosis and antimetastasis. It also caused the levels of malondialdehyde and nitric oxide to decrease in the tumors. An increase in the levels of natural killer cells, T cells, and white blood cells was observed [74]. In another study, Rachmani et al. demonstrated that the ethanol extracts as well as the methanol extracts of the *A. muricata* leaves were cytotoxic to the MCF-7 cells [75]. The methanolic extract was shown to decrease the levels of Bcl-2 protein in these cells [75]. Gavamukulya et al. conducted another study that demonstrated that ethanol extract of the *A. muricata* leaves was cytotoxic to SKBR3 and MDA breast cancer cell lines [76] and Ehrlich ascites carcinoma cells in vitro [76]. Another study showed that *A. muricata* ethanol leaf extract was cytotoxic to and causes apoptosis in the T47D human breast cancer cell line [62]. The ethyl acetate fraction from this extract showed the best cytotoxicity to the cell line [62]. The aqueous extract of *A. muricata* leaves caused the highest inhibition of proliferation compared to that caused by extracts of seeds or fruits. *A. muricata* extracts in combination with the chemotherapeutic drug capecitabine was seen to be effective in stabilizing metastatic breast cancer in a 66-year-old woman [77].

The chloroform extract of *A. muricata* leaves induced apoptosis in cervical cancer HeLa cells [78]. Another study showed that the growth of HeLa cells could be decreased by a synergistic interaction between doxorubicin and polyketide derivatives isolated from *A. muricata* leaves [79]. These polyketide derivatives are seen to increase the level of p53 in the nucleus and activate the process of apoptosis in the HeLa cells. The derivatives could be used as chemotherapeutic agents to treat cervical cancer and could stabilize p53 [79].

The ethanolic extract of *A. muricata* could inhibit the growth of tumor in two-stage skin papillomagenesis in mice [80].

The ethanol extract of *A. muricata* leaves was cytotoxic to HepG2 liver cancer cells by inducing apoptosis by means of ROS production [81]. Liu et al. showed that when HepG2 cells were treated with *A. muricata* leaf extracts, the protein disulfide isomerase 5 (PDI-related protein 5), glucose-regulated protein 94, and heat shock protein 70 were upregulated [82]. This meant that apoptosis was triggered by endoplasmic reticulum (ER) stress, as was indicated by bioinformatic analysis as well [82]. There was also an upregulation in the expression levels of DNA damage inducible transcript 3 protein C/EBP homologous protein (CHOP) and heat shock protein family A member 5 Bip and in the phosphorylation of eukaryotic translation initiation factor 2 alpha (eIF2α) and eukaryotic translation initiation factor 2 alpha kinase 3 PERK. This shows that ER stress was mediated by the Bip-PERK-eIF2α-CHOP pathway [82]. Cis-annomontacin, muricin H, and muricin I are annonaceous acetogenins that were isolated from the leaves of *A. muricata* and have been seen to have significant cytotoxicity in vitro to the Hep G2.2.15 and Hep G2 human hepatoma cell lines. Annocatalin, another annonaceous acetogenin that was isolated from the leaves of *A. muricata*, was seen to be highly cytotoxic to the human hepatoblastoma Hep 2.2.15 cell line [83].

A decrease in the viability of HCT-116 colon cancer cells was observed upon treatment with ethanol extract of *A. muricata* leaves [82]. *A. muricata* leaves are also cytotoxic to the HT-29 colon adenocarcinoma cell lines [75]. *A. muricata* leaf extracts can also cause G1 cell cycle arrest [71]. Moghadamtousi et al. demonstrated that when HT-29 and HCT-116 cells were treated with *A. muricata* extracts, the apoptotic pathway was induced, as evidenced by increased ROS production, increased cytochrome c levels, increased Bax levels, and increased levels of executioner caspases

[71]. Another study investigated the chemopreventive properties of an ethyl acetate extract of *A. muricata* leaves (EEAML) on azoxymethane-induced colonic aberrant crypt foci (ACF) in rats. The extract decreased the formation of colonic ACF with down-regulation of Bcl-2 proteins and proliferating cell nuclear antigen and simultaneous up-regulation of Bax protein [84]. Enzymatic anti-oxidant levels increased, while malondialdehyde levels decreased in the homogenates of colon tissue, which suggests lipid peroxidation suppression [84]. A bioassay-guided approach was used to evaluate cytotoxicity and apoptosis induced on the HT-29 colon cancer cell line by annomuricin E, which was isolated from EEAML [84]. Annomuricin E caused inhibition of cell growth, early apoptosis, and G1 cell cycle arrest in the HT-29 cells via activation of caspases 3, 7, and 9; cytochrome c release; Bax upregulation; and Bcl downregulation [84]. Another study evaluated the in vivo anti−colon cancer effect of ethanolic extract of *A. muricata* leaves on colon cancer that was induced in Wistar albino rats by 1,2-dimethyl hydrazine [3]. The extract significantly reduced ACF formation, hematological parameters, and individual organ weight and increased weight gain and apoptotic index compared to the control. A significant decrease was observed in the level of total cholesterol as compared to disease controls [3]. Another study investigated the anticancer effect of *A. muricata* extract supplement on the colorectal cancer cell line by exposing the cell line to the serum of patients who had taken the supplement for eight weeks [85]. This study was a randomized, double-blind, placebo-controlled pre-post trial, and the 30 colorectal cancer patients who participated in the trial had undergone primary tumor resection. When the cell line was treated with the patient serum, it was seen that serum from patients who had taken the *A. muricata* supplement was cytotoxic to the cell line, as compared to the placebo control group. The investigators concluded that the extract's bioavailability was sufficient for it to reach the blood and cause the cancer cells to be inhibited [85].

A. muricata leaves are also cytotoxic to the PACA-2 pancreatic carcinoma cell lines [75]. Torres et al. showed that treatment of pancreatic cancer cells with *A. muricata* extract led to decreased migratory capacity of these cells and inhibited the protumorigenic Akt and ERK pathways [86]. *A. muricata* extracts disrupt the microtubule and cortical actin network, which is involved in metastasis, and thereby inhibit cancer cell motility [86]. This could also play a role in inducing apoptosis [86]. *A. muricata* hexane and commercialized leaf extracts were also shown to be mildly cytotoxic to Capan-1 pancreatic cancer cells [87].

Various studies showed that *A. muricata* extracts cause the inhibition of multiple signaling pathways, such as those that regulate the cell cycle, survival, metabolism, and metastatic properties in various prostate cancer cell lines [22,88]. Sun et al. showed that the acetogenins muricin J, K, and L that were obtained from *A. muricata* fruit pulp using bioassay-guided fractionation were cytotoxic to the PC-3 human prostate cancer cell line [88]. A study by Yang et al. was found that the constituents of the graviola leaf extract (GLE) have phytochemical synergy among themselves [89]. The acetogenin-enriched fraction (AEF) and the flavonoid-enriched fraction (FEF) were compared in prostate cancer. The concentrations of quercetin-3-glucoside and rutin were higher in FEF than in GLE, but GLE showed higher inhibition than FEF in human prostate tumor xenograft action. AEF demonstrated superior efficacy both in vivo and in vitro, resulting in the death of the mice due to its toxicity. GLE consists of acetogenins and other phytochemical compounds. All these compounds could act synergistically to optimize the effectiveness of GLE [89]. The study showed that extracts of *A. muricata* could inhibit prostate cancer. It also demonstrated that it was important to use whole-leaf extracts to effectively inhibit cancer [89].

Annoreticuin-9-one, an acetogenin, was obtained from the di-chloromethane extract of *A. muricata* seeds [59]. This acetogenin is cytotoxic to the A-549 human lung carcinoma cell line, the PC-3 human prostate adenocarcinoma cell line, and the PACA-2 human pancreatic cancer cell line [59]. Another acetogenin, cis-annoreticuin, which was obtained from the flesh of the *A. muricata* fruit, is cytotoxic to the HepG2 human hepatoma cell line [59]. Murihexocin C and muricoreacin are annonaceous acetogenins that are present in *A. muricata* leaves. These acetogenins are cytotoxic to the PACA-2 human pancreatic carcinoma cell line and the PC-3 human prostate adenocarcinoma cell line [90].

A study by Pieme et al. showed that ethanol extracts of the roots, leaves, and twigs of *A. muricata* contained different concentrations of flavonols, phenols, and flavonoids, based on plant part [20]. All three extracts had antiproliferative effects on the HL-60 human leukemia cell line in a dose-dependent manner [20]. Inhibition of cell growth was observed with G0/G1 cell cycle arrest and could be attributed to generation of ROS and G_0/G_1 cell cycle arrest [20]. Apoptosis was induced by MMP loss and arrest of the cell cycle in the G0/G1 phase. The growth of cells was seen also to be inhibited [20].

An n-butanolic extract of *A. muricata* was cytotoxic to human immortalized keratinocyte cell line HaCaT and human breast cell line MDA-MB-435S and moderately cytotoxic to the normal human hepatic cell line WRL-68 [91].

The ethyl acetate−soluble fraction of *A. muricata* leaves, which contains acetogenins, can be used as adjuvant cancer therapy on the basis of the MTT assay results obtained by testing it on HeLa cells [92]. The suggested dose is 23 g of *A. muricata* leaves three to four times a day for therapeutic efficacy [22,88].

Annona reticulata

The acetogenin annoreticuin-9-one obtained from *Annona reticulata* is cytotoxic to the PC-3 human prostate adenocarcinoma cell line, the A-549 human lung carcinoma cell line, and the PACA-2 human pancreatic tumor cell line [59]. Another acetogenin, annonacin, was purified from *Annona reticulata* seeds. Annonacin was found to be cytotoxic to T24 bladder cancer cells and caused G1 arrest with p53-independent activation of p21 [29]. It promoted the expression of Bax protein and increased the activity of caspase 3, resulting in apoptosis [29]. This acetogenin was also shown to be cytotoxic to other cancer cell lines, such as the HeLa and HeLa S3 cervical cancer cell lines, the SKOV3 and PA-1 ovarian cancer cell lines, the BCC-1 skin cancer cell line, and the MCF-7 breast cancer cell line [29]. Annonacin inhibited the mitochondrial complex I [22,29]. The ethanolic extract of *A. reticulata* roots has been shown to stop the proliferation of the K-562 human chronic myelogenous leukemia cell line, the A-549 human lung cancer cell line, the MDA-MB human breast cancer cell line, and the HeLa human cervical cancer cell line [51]. Bullatacin and squamocin from *A. reticulata* cause activation of apoptosis [42]. Annonacin from *A. reticulata* could function as topoisomerase poison [42].

Annona senegalensis

The compound C/M_2, which was isolated from the bark of the roots of *Annona senegalensis*, was shown to be cytotoxic to sarcoma 180 ascites (S180A) tumor cells [93]. Another study reported that when 100 mg/kg of the compound was given intraperitoneally to mice sarcoma daily for seven days, tumor cell growth was inhibited completely, and no toxic effects were observed in the mice [93]. Durodola et al. showed that when a dilution of 1 mg/mL of C/M_2 was incubated with the tumor cells, more than 70% of the cells become nonviable within two hours of incubation, and a tumor could not be produced when these cells were transplanted into mice. The minimum incubation period required to render tumor cells incapable of tumor induction when transplanted into the mice was inversely proportional to the drug concentration in the medium of incubation [93]. (−)-Roemerine is an aporphine alkaloid that was isolated from *A. senegalensis* leaves [79]. It improved the cytotoxic response of the drug vinblastine to multidrug-resistant KB-V1 cells via inhibition of P-glycoprotein [79]. On its own, this alkaloid was not significantly cytotoxic to KB-3 or KB-V1 multidrug-resistant cells [79].

Annona squamosa (sugar apple)

The crude and ethyl acetate extracts of *Annona squamosa* were seen to be cytotoxic to the HCT-116 human colon cancer cell line and the KB-3-1 human epidermoid cancer cell line [22]. Acetogenins that have a mono-tetrahydrofuran ring, such as annoreticuin-9-one, mosin B, mosin C, and 2,4-cis- and trans-mosinone A, and acetogenins that have a bis-adjacent THF ring and other acetogenins, such as squamatocin, molvizarin, and bullatacin, have been isolated from the bark of *A. squamosa* [94,95]. These acetogenins are more effective as anticancer agents than the drug doxorubicin and are cytotoxic to the PACA-2, A-498, PC-3, A-549, HT-29, and MCF-7 cancer cell lines [94,95]. The aqueous and ethanolic extracts of *A. squamosa* bark were found to reverse the genotoxicity caused by the carcinogen 7,12-dimethylbenz(a)anthracene in golden Syrian hamsters [96]. The ethyl acetate extract of the pericarp of *A. squamosa* was seen to show cytotoxicity to the SMMC-7721 hepatoma cell lines [97].

Chen et al. evaluated the safety and anticancer effect of extract of *A. squamosa* seeds, which contained bullatacin and 12,15-cis-squamostatin-A [98]. It was observed that this extract was significantly cytotoxic to the HepG2 and MCF-7 cell lines. The growth of H_{22} hepatoma cells in mice in vivo was also inhibited by this extract, and there were no side effects in the mice. Because the extract was significantly cytotoxic to hepatoma cells in vitro and in vivo, it could be used as an anti−liver cancer drug [98]. The acetogenin squamocin in organic, and aqueous extracts of defatted *A. squamosa* seeds cause apoptosis in the tumor cells by oxidative stress [99−101]. The aqueous *A. squamosa* seed extracts also show antitumor activity in vivo against the AD-5 tumor [99−101]. The aqueous and organic extracts of defatted *A. squamosa* seeds were also seen to induce apoptosis in K-562 erythroleukemic cells and the MCF-7 breast carcinoma cell line, as evidenced by DNA fragmentation, formation of apoptotic bodies, and externalization of phosphatidyl serine [101]. This was accompanied by the generation of ROS, decrease in the levels of glutathione in the cells, condensation of nuclear material, and decrease in Bcl-2 levels in the K-562 and MCF-7 cells [101]. However, these extracts did not induce apoptosis in the COLO-205 human colon cancer cell line; only externalization of PS was observed, and there was no change in the levels of glutathione and ROS in these cells. This shows that the extracts of *A. squamosa* seeds are selectively cytotoxic to certain cancer cell lines [101].

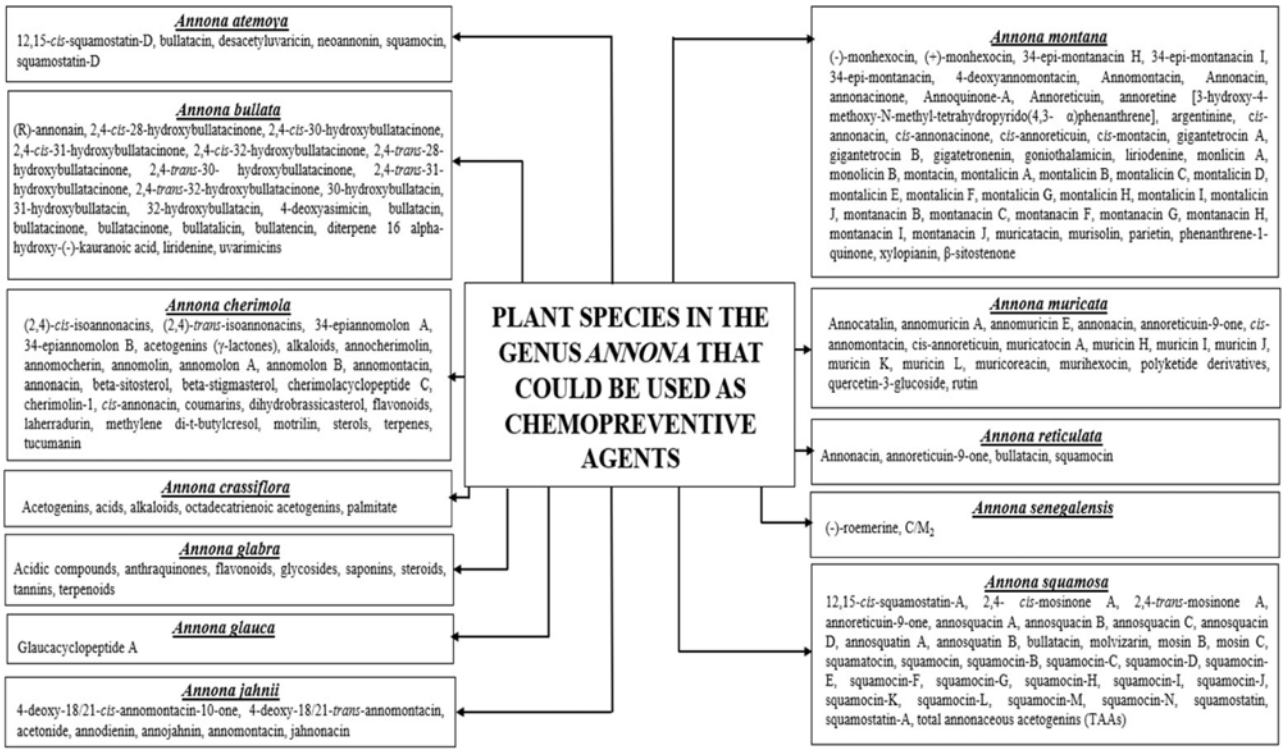


FIGURE 48.1 Plant species of the genus *Annona* that are used as chemopreventive agents.

The crude extract of *A. squamosa* seeds, containing the ribosome-inactivating protein, may be used as an immunotoxins for cancer therapy [62,102]. At low concentrations, this extract can cleave supercoiled double-stranded DNA [102]. The acetogenins squamostatin and squamocin have been isolated from the petroleum ether extract of the seeds of *A. squamosa* [103]. Squamocin is cytotoxic to L-1210 cells [103]. Squamocin had antiproliferative effect on HL-60 cells and promoted apoptosis in these cells by caspase 3 activation [100]. Sahai et al. isolated various acetogenins from the petroleum ether extract of the seeds of *A. squamosa*, namely, squamocin, squamostatin-A, squamocin-B, squamocin-C, squamocin-D, squamocin-E, squamocin-F, squamocin-G, squamocin-H, squamocin-I, squamocin-J, squamocin-K, squamocin-L, squamocin-M, and squamocin-N [104]. The acetogenins annosquacin A, annosquacin B, annosquacin C, annosquacin D, annosquatin A, and annosquatin B were isolated from the ethanol fraction of the seeds of *A. squamosa* [105]. All the six mentioned acetogenins were cytotoxic to the cervical cancer cell line HeLa, the gastric adenocarcinoma cell line MKN-45, the human lung cancer cell line A-549, the breast carcinoma cell line MCF-7, and the hepatoma cell lines SMMC-7721 and HepG2. Annosquatin A and annosquatin B showed increased cytotoxicity to the A-549 and MCF-7 cancer cell lines as compared to the other acetogenins [105]. Total annonaceous acetogenins found in the ethyl acetate−soluble fraction obtained from the ethanol extract of the seeds of *A. squamosa* have anticancer effects on human hepatocarcinoma cell lines by arresting the cell cycle at the G1 phase and inducing apoptosis through mitochondrial, intrinsic, and extrinsic apoptotic pathways [106]. *A. squamosa* seed oil was seen to suppress the growth of the H22 solid hepatoma tumor in mice [107].

Silver nanoparticles prepared by using the extract of *A. squamosa* leaves have anticancer effect on MCF-7 cells [108]. Another study showed that silver nanoparticles prepared by using the extract of *A. squamosa* leaves were cytotoxic to HeLa cells [109]. Chitosan nanoparticles were prepared from the leaf extract of *A. squamosa*. These nanoparticles were seen to be cytotoxic to WiDr human colon cancer cell lines, with apoptosis following the increase in caspase 3 expression and G2/M cell cycle arrest [110].

Conclusion

In this chapter, the anti-cancer properties of compounds isolated from genus *Annona*, namely, *A. atemoya*, *A. bullata*, *A. cherimola*, *A. crassiflora*, *A. glabra*, *A. glauca*, *A. jahnii*, *A. montana*, *A. muricata*, *A. reticulata*, *A. senegalensis*, and *A. squamosa*, were reviewed (Fig. 48.1). Extracts prepared from various parts of these plants, such as leaves, bark,

seeds, fruit pulp, and roots were found to have anticarcinogenic potential against various cancer cell lines. The main anticancer compounds that were isolated from these plants are acetogenins. These compounds showed antiproliferative, proapoptotic, and antimigration potential against several cancers, including breast, cervical, colon, gastric, kidney, laryngeal, liver, lung, nasopharyngeal, ovarian, pancreatic, prostate, and skin cancer and leukemia. Further, the mechanisms of action of several of these compounds were identified. They were found to modulate genes belonging to the apoptotic pathway, including the bcl-2 family [18,75,84,101], p53 [43,79], and the PERK pathway [82]. They were also found to increase ROS levels [18,20,43,71,81,101] in many cancers selectively. These compounds were also selectively cytotoxic and did not affect normal cells [31,74].

It can therefore, be concluded that the plants belonging to the genus *Annona* have the potential to provide effective anti-cancer agents. There is a need to evaluate the nature of interactions between the phytochemicals in *Annona* extracts in order to develop proper dose regimens to achieve optimal therapeutic benefits in the management of cancer.

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Section 15

Amino acids, cortisol and hydrogen

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Chapter 49

Molecular hydrogen as a nutraceutical for extending the health span

Alex Tarnava[1,2] and Tyler W. LeBaron[3,4,5]

[1]Drink HRW, New Westminster, BC, Canada, [2]Natural Wellness Now Health Products Inc., New Westminster, BC, Canada, [3]Molecular Hydrogen Institute, Enoch, UT, USA, [4]Centre of Experimental Medicine, Institute for Heart Research, Slovak Academy of Sciences, Bratislava, Slovak Republic, [5]Department of Kinesiology and Outdoor Recreation, Southern Utah University, Cedar City, UT, United States

Introduction

Advancements in medical care and geriatrics over the last century have increased the human life span in most developed countries. Concurrent with the extension of the life span, the prevalence of chronic non-communicable diseases has risen. Many factors have contributed to this epidemic, including the extended life span itself, with significant influence from a sedentary lifestyle combined with access to many foods that are high in both sugars and fats. Numerous nonprescription molecules available as supplements have emerged as candidates to combat these consequences. Notably, sirtuin activators, such as resveratrol, have been proposed as potent caloric restriction mimetics with the potential to improve health and extend the life span [1]. Promising results in fruit flies and rodents have been followed by disappointing results in humans, albeit with some observed benefits [2].

While many other molecules have gained widespread media attention with little human evidence, the field of molecular hydrogen (H_2) therapy has rapidly gained interest despite sparse media coverage. Following the seminal 2007 article in *Nature Medicine* detailing the ability of H_2 to selectively scavenge peroxynitrite and hydroxyl radicals in vitro, research in the health benefits of H_2 continues to gain momentum. There are currently over 2000 publications on H_2 as a therapeutic agent, including over 120 studies in humans that either have been published or are in manuscript preparation or review phases. There are numerous beneficial observations, including favorable alterations in gene expression [3] and the activation or inhibition of various signaling pathways [4]. Furthermore, a hypothesis has emerged that partially explains a mechanism of action through hormesis [5,6]. However, elucidating the exact molecular mechanisms remains elusive. Increased evidence of efficacy has inspired more researchers around the world to begin studying molecular hydrogen, although the research varies in direction. As the therapeutic evidence of molecular hydrogen grows, research efforts should be dedicated to further understanding hydrogen's exact mechanisms of action and its optimal dosing and administration protocols in order to best address real world challenges.

Human research progression

The first human study specific to hydrogen water was published in 2006, a year before the seminal article in *Nature Medicine*. Although, this short-term study in young healthy adults did not demonstrate an antioxidant activity in vivo, it did report that H_2 has an antioxidant effect in vitro [7]. Two more human studies were published in 2008, and the human research has steadily increased. The growth of human research on molecular hydrogen has increased at a rate of progression similar to that of the trajectory of overall hydrogen publication growth. Between 2006 and 2012, the first seven years of research concerning humans, 16 papers were published. In the next seven years, between 2013 and 2019, there were 64 published papers.

Administration methods for hydrogen gas have varied throughout the research. The various methods include oral consumption of hydrogen dissolved into water, hydrogen inhalation, hydrogen dissolved into saline, topical application of hydrogen dissolved into water, and products designed to create hydrogen gas internally. It is reasonable to initially suspect that molecular hydrogen would best be administered via gaseous inhalation, since this is typically how medicinal gases are

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administered and the relatively poor solubility of molecular hydrogen in water significantly decreases the total dosage of H_2 that can be effectively delivered. However, the majority of publications, including those in humans, administer hydrogen dissolved in water, which trend has remained relatively constant. As illustrated in Table 49.1, there are currently 80 publications as of 2019, some of which have used the same group to report different clinical findings, thus arising in additional publications. Therefore a total of 76 groups of study participants have been evaluated. Additionally, in some trials, researchers experimented on different administration methods (e.g., water and saline) on the same or different subjects, thus resulting in 81 total methods of hydrogen administration. Of these methods used in humans, oral consumption of hydrogen water accounted for 62.5% of the studies between 2006 and 2012 and 55% of the published work between 2013 and 2019. Hydrogen-rich saline and hydrogen inhalation have maintained a constant share of the research interest, while hydrogen-rich water (HRW) has decreased in relative interest. The decrease in HRW, which is still the statistically preferred method, can be accounted for by an increase in hydrogen-rich hydrotherapy and formulations to create hydrogen gas internally. Between 2006 and 2012, only a single publication used a different administration method in the form of topical application, accounting for 6.3% of total publications. During 2013−2019, nine publications used either topical H_2 water or some method of orally administered drug or tablet for internal consumption, totaling 14% of the total publication share (see Table 49.1).

Saline and H_2 inhalation remain the favored administration routes for critical care models in which incapacitated patients are unable to consume water. However, despite those methods being favored under those conditions, they may not be the most effective. For example, one rodent model of Parkinson's disease demonstrated that hydrogen dissolved in water is as effective at 1% the dosage as when inhaled [8]. In some models, inhalation may be less effective than drinking hydrogen water and may even not be effective at all [8]. This realization, with the added convenience, cost-effectiveness, and ease of blinding for proper placebo-control trials, has likely contributed to the high rate of publications choosing H_2 water as the preferred delivery method.

Despite 75 of 79 publications on H_2 therapy reporting beneficial outcomes, little replication work has been done. The replication studies that do exist differ in methods from previous work. Nevertheless, trends are emerging with many publications highly supporting one another even if they are not truly replicative. Potentially attributable to relatively few industry-funded studies compared to those conducted by public teams, research progress has been conducted

TABLE 49.1 Advancement of human research on hydrogen per year and administration method.

Year	Hydrogen-rich water	Hydrogen-rich saline	Hydrogen inhalation	Oral tablet or internal production	Topical	Yearly total
2006	1	-	-	-	-	1
2008	2	-	-	-	-	2
2009	-	1	-	-	-	1
2010	1	1	-	-	-	2
2011	2	1	-	-	-	3
2012	4	1	1	-	1	7
2013	5	2	-	-	1	8
2014	1	1	-	-	-	2
2015	4[a]	1[a]	1[a]	2[b]	1[b]	9[c], 6[d]
2016	4	1	1	-	1	7
2017	9	1	2	-	-	12
2018	6	1	3	1	2	13
2019	7[e], 6[f]	-	6	-	1	14,13[d]
Total methods	46	11	14	3	7	81
Total publications			80			
Total study groups			76			

[a] *Same publication in which hydrogen-rich saline and hydrogen-rich were both used on different participants.*
[b] *Topical hydrogen-rich medium and an orally ingested hydrogen-producing tablet were used.*
[c] *The total methods utilized in this year.*
[d] *Total publications of this year.*
[e] *Two publications were released in the same year using the same group of study participants.*
[f] *Total amount of study groups.*

to further understand the H_2 molecule and its potential benefits rather than to fast-track status toward approved health claims. As H_2 emerges as a strong candidate for clinical application, the need to expand the research into larger and well-controlled trials that attempt to replicate early results is imperative (Table 49.2).

As of January 2020, there were ten registered clinical trials on the U.S. National Library of Medicine's ClinicalTrials.gov website. It is unclear how many clinical trials are currently underway or recruiting, as many trials are potentially only registered with their own country or are not registered at all. From personal correspondence with some of the H_2 researchers, it is known that many other clinical trials are indeed currently underway that are not registered at least in that database.

Amelioration of age-related markers and stressors

A main criticism of research into H_2 as a therapeutic agent is the wide array of outcomes with limited replication work. Paradoxically, this also points to one of the biggest strengths of H_2 in terms of therapeutic potential, as it combats or alleviates biological functions observed in several disease models, including metabolic [9] and neurodegenerative disorders [10,11].

Sirtuins

Sirtuins (SIRT), the SIRT1 isoform specifically, has been extensively linked to aging and extending the life span [12], and molecules acting as SIRT1 activators have been linked to extending the life span in rodents [13]. Hydrogen water is able to mitigate SIRT1 inhibition in the presence of biological assaults [14], suggesting that H_2 dampens SIRT1 inhibition rather than targeting its activation.

Nicotinamide adenine dinucleotide

Raising nicotinamide adenine dinucleotide (NAD^+) levels is associated with extending both health and the life span [15]. Alterations in the ratios of NAD^+ to NADH occur during the so-called normal aging process, with levels of NAD^+ decreasing and levels of NADH increasing [16]. H_2 was able to prevent a decrease in the NAD^+/NADH ratio while alleviating cellular senescence in endothelial cells via activation of nuclear factor erythroid 2−related factor 2 (NRF2) in a cell culture models incubated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) [17]. TCDD is a persistent organic pollutant and carcinogen present in Agent Orange, which was used in the chemical warfare program during the Vietnam War, as well in incidents such as the Seveso disaster.

TABLE 49.2 Publications on molecular hydrogen as sorted by condition and administration method.

Research area	H_2 water	H_2 inhalation	H_2 saline	Internally producing hydrogen substance	Topical hydrogen, water, and gel	Total
Exercise	15	1	-	1[a]	2[a]	19[a], 18[e]
Metabolic and mitochondria	8[b]	1	-	2	-	11[b], 10
Neurodegenerative and traumatic brain injury	5	5	2	-	-	12
Skin issues	3[c]	1[c]	2[c]	-	5	11[c], 9[e]
Dialysis	-	-	6[d]	-	-	6[d], 5[e]
Cancer	-	3	-	-	-	3
Cancer treatment adjuvant	2	-	-	-	-	2
Antioxidant capacity	4	-	-	-	-	4
Rheumatoid arthritis	1	-	1	-	-	2
Other	8	3	-	-	-	10
Total	46	14	11	3	7	81, 76[e]

[a] *Same study participants.*
[b] *Same study participants for two papers.*
[c] *Same group study participants two methods.*
[d] *Same study participants for two papers.*
[e] *Total number of study groups.*

Inflammatory markers

Inflammation plays a critical role in disease and aging pathogenesis. One study following 1554 individuals [684 centenarians and semisupercentenarians, 167 pairs of centenarian offspring and spouses, and 536 community-living elderly people (aged 85−99 years)] found only inflammation, and not telomere length, predicted the remaining life span [18]. Despite the strong association that chronically elevated inflammatory markers have on aging and remaining life span prediction in the elderly, no antiinflammatory drug has been shown to significantly extend the human life span or health span. On the contrary, recommendations exist to limit and moderate the use of all three approved classes of antiinflammatory drugs in the elderly population, owing to their side effects [19].

Strategies for regulating the inflammatory process may be preferred over administering antiinflammatory drugs in managing chronic inflammation. Hormesis plays a role in inflammation, with acute spikes in proinflammatory cytokines resulting in lasting mobilization of antiinflammatory cytokines. For example, in exercise, interleukin 6 (IL-6) is excreted as a myokine from skeletal muscle, leading to a stronger antiinflammatory response and the mobilization of the antiinflammatory cytokine IL-10 [20]. H_2 indirectly regulates the production of proinflammatory cytokines, such as tumor necrosis factor alpha and IL-6 in a selective manner [9].

H_2 can attenuate excessive inflammation via the same mechanisms as other hormetic agents while not blunting it beyond normal function. In addition, H_2 activates heat shock proteins [3], which tend to regulate inflammatory responses toward a homeostatic function [21]. The role of H_2 during the inflammatory response needs further research, with better-controlled studies elucidating the mechanisms by which H_2 regulates inflammatory cytokine production. To further gain understanding of molecular hydrogen's therapeutic potential and clarity regarding appropriate applications of use, it is important to understand whether and how H_2 increases cytokines (such as IL-6) in their beneficial myokine role when other stressors are not present.

Regulation of redox status

Excess oxidative stress, such as chronic inflammation, is a causative factor in the development and progression of countless disease models. Despite this, high-dose antioxidant therapy has been shown to have no benefits in many cases and to lead to an increase in all-cause mortality in others [22]. Recent evidence suggests that maintaining homeostatic cellular redox status and function is critical for optimal cellular health [23].

H_2 has been demonstrated to acutely raise oxidative stress in cells to levels that are not physiologically harmful, similar to levels induced during light exercise and other forms of hormesis [5]. This leads to a stronger antioxidant response, mobilizing increased endogenous production of glutathione, superoxide dismutase (SOD), and catalase via the NRF2 pathway. Many trials, from cell culture studies to human population studies, have demonstrated this improvement in redox status as well as protection from free radical damage. These antioxidant-like functions of H_2 are perhaps the most replicated in H_2 research [5,6].

Regulation of autophagy

Autophagy is the natural process of recycling or removing damaged components of cells. The importance of autophagy's role in aging and physiology earned Dr. Yoshinori Ohsumi the 2016 Nobel Prize in Physiology or Medicine. Autophagy is implicated in both cell survival and cell death [24]. Additionally, it both suppresses and promotes cellular senescence [25], the phenomenon in which cells stop dividing. While senescence is considered detrimental to health in oncogene-induced senescence, promotion of cellular senescence could be advantageous in the reduction of cancer risk or tumor growth cessation [26]. Cellular senescence can be a protective barrier to cancer [27]. However, dysfunction can promote cancer progression by contributing to a chronic inflammatory state [28]. In a similar manner, autophagy seems to prolong cancer cell survival when apoptosis is impaired, even leading to the reemergence of cancers thought to have been eradicated. However, impaired autophagy increases the rate of tumor growth. Evidence also suggests that autophagy is protective in limiting tumor necrosis and inflammation as well as mitigating genomic damage in tumor cells in response to metabolic stress [29].

H_2 has been shown to regulate autophagy rather than simply activating or suppressing it. In some cases, H_2 activates autophagy for a beneficial outcome [30,31]; in other cases, the beneficial effects of H_2 were attributed to inhibiting autophagy [32]. Furthermore, H_2 inhibits cellular senescence [17] and apoptosis [30]. Critically short telomeres lead to telomere crisis, which occurs when the ends of chromosomes significantly erode and the DNA is no longer protected. Telomere crisis activates autophagy as a last line of defense [33]. However, when this protection occurs, health

outcomes are already in a less than favorable state. The ability of H_2 to regulate autophagy while protecting against senescence and apoptosis independent of telomere crisis is an important distinction and potentially very beneficial toward longevity. In fact, hydrogen water has been shown to significantly increase telomerase activity in vitro, suggesting that it may play a role in protecting against telomere shortening [34].

Relevance in human diseases

The mechanisms by which H_2 seem to operate differentiate it from other molecules that have been shown to have similar benefits. In other words, the beneficial outcomes are indirect with a tendency toward regulation rather than direct interaction with a specific target. For example, as was previously described, hydrogen regulates, rather than activates or inhibits, various cellular processes, including autophagy, apoptosis, cellular senescence, and the inflammatory and antioxidant responses.

Cancer

H_2 has distinct advantages over other molecules that act as Nrf2 activators, or those with direct antioxidant roles, particularly regarding potential uses as adjuvant cancer therapy. In some cases, antioxidant therapy may increase the spread of cancer throughout the body, as indicated in metastatic melanoma in mice [35]. These findings, as well as problematic trends that began to emerge in the human research, have caused several large-scale clinical trials using high-dose antioxidant therapy to be aborted [36]. Additionally, Nrf2 activation in some cases has shown to be oncogenic as well as potentially contributing to chemotherapy resistance [37].

Hyperbaric hydrogen therapy was studied as a potential cancer therapy in 1975 by a team from Baylor and Texas A&M, who found potent antitumor capacities in rodents [38]. There were no human studies specifically targeting cancer until 44 years later, when in 2019, three publications emerged demonstrating that hydrogen inhalation may be effective at slowing the progression of certain cancers. These publications have important limitations, as none were double- or single-blinded. The first publication was a case study of a single participant in which the authors hypothesized that hydrogen may have an inhibitory effect on programmed cell death protein 1 (PD-1) expression [39]. This was due to a pseudo-progression followed by remission, which is similar to what would be expected from typical antiPD-1 treatment [39]. The next study article was an open-label study on 55 patients with stage IV colorectal cancer; the authors stated that H_2 reversed imbalances toward PD-1^+ $CD8^+$ T cells to provide an improved prognosis [40]. The third report was a 2019 observational study that followed 82 patients for periods of 3−46 months. It reported that hydrogen inhalation improved numerous outcomes starting at four weeks, such as fatigue, insomnia, anorexia, and pain. Moreover, in 36.2% of cases in which tumor markers were abnormally elevated, hydrogen inhalation decreased the markers in 13−45 days (median: 23 days). The researchers noted that hydrogen therapy is a low-cost procedure that demonstrates the capacity to improve patient quality of life while also controlling cancer progression [41]. Of significant note, rather than contributing toward chemotherapy resistance, H_2 has been shown to mitigate the side effects of chemotherapy and radiotherapy, such as suppressing the cytotoxic effects of drugs such as fluorouracil (5FU) and cisplatin in several rodent studies and in one human study [42].

Radiation damage

Radiation damage is a topic that is discussed less frequently in terms of aging, but it can be a significant contributor. Indeed, high-dose radiation has numerous known negative side effects, including death. However, low-dose ionizing radiation has been suggested to have potential benefits, including life span extension by acting as a form of hormesis [43]. As is true for overexposure to other forms of hormesis, such as exercise and alcohol, H_2 has been shown to protect against the damaging effects of radiation. This protection has been observed in rodent models with full body damage, as well as the healing of postradiation burns in rats. Several mechanisms in which H_2 assists in these models have been described in great detail in two review papers. One paper provided original results with a rodent model in which elevated levels of SOD and phosphorylated-AKT, a cell growth and survival signaling molecule, were observed [9,44]. The radioprotective effect of H_2 prompted NASA scientists to hypothesize that hydrogen, either dissolved in water and/or inhaled, could protect astronauts from excessive radiation exposure [45].

In addition to the basic scientific evidence, an early human study used hydrogen water to mitigate the side effects of radiation therapy in cancer patients ($N = 49$, 6 weeks). The researchers observed strong improvements in various quality-of-life scores as well as markers of oxidative stress [46]. Despite these positive benefits, additional human

studies have not yet been conducted. However, there is currently an ongoing trial, as listed on the ClinicalTrials.gov website, by Stony Brook Medicine. The trial will follow 15 patients with high-grade gliomas receiving radiation therapy and chemotherapy while simultaneously providing hydrogen therapy for 1 year, and it will measure changes in quality of life.

Metabolic disorders

Metabolic disorders are a cluster of issues and classifications, including metabolic syndrome and nonalcoholic fatty liver disease (NAFLD), that increase the risks for heart disease, stroke, and type 2 diabetes. A recently published article suggests that hydrogen administration can prevent vascular aging of the aorta in low-density lipoprotein receptor−deficient mice that are fed a high-fat diet to simulate atherosclerosis [47]. This may be an important contributor in hydrogen's promising ability to mitigate symptoms of metabolic syndrome.

Currently, there are nine studies in humans depicting beneficial responses in outcomes that can be classified under metabolic disorders. Metabolic dysfunction may be the best example of a dose- and time-dependent response observed in the human literature. Unfortunately, there is very limited crossover of markers in the human publications measuring the various metabolic-related study groups. Further confounding the ability to directly compare results, groups had a wide difference in initial measurements, and the parameters that are measured throughout many publications use inconsistent biomarkers to determine beneficial outcome. These inconsistencies allow for only relative comparisons, such as rate of significant findings against null findings. Two open-label studies and one double-blinded, placebo-controlled study have shown limited beneficial responses in a few of the measured outcomes at relatively low dosages. For example, the first open-label study ($N = 20$) showed that 0.5 mg H_2/day for eight weeks significantly improved 38% biomarkers (5 of 13) [48]. The other open-label study ($N = 20$) reported that 0.5 mg H_2/day for ten weeks improved 59% of biomarkers (13 of 22) [49]. Similarly, another group found that 1 mg H_2/day for eight weeks showed improvement in 13% of biomarkers ($N = 30$) of metabolic syndrome (3 of 23) [50]. Replicative work shows more prominent results in longer studies with higher doses. For example, 1 mg H_2/day for ten weeks showed improvement in 75% of biomarkers (9 of 12) with two markers showing a strong trend, although not statistically significant ($N = 68$) [51]. Finally, 12 mg H_2/day for 24 weeks showed significant improvement in 90% of biomarkers (18 of 20) with another marker showing a strong trend ($P = .06$) ($N = 60$) [52]. The replicative work has found significantly better results than the early work, despite the replicative trials being randomized, double-blinded, and placebo-controlled designs with larger study groups.

Hydrogen concentrations given to mice and humans have been similar across research projects. However, as was shown earlier in the chapter, a dose-dependent response in humans compared to what is observed to be beneficial in rodents has started to emerge. This makes sense because of the dramatic difference in volumes of water consumed relative to weight between humans and rodents. For example, based on body weight, mice drink significantly more water than humans. For example, a 25-g mouse will consume roughly 4 mL/day of water [53], whereas the average person with a body weight of 80 kg [54] is recommended to consume 3.2 L/day (2.7 L for women, 3.7 L for men) [55]. This is four times less than the 12.8 L based a direct weight to volume conversion from mice to humans. Moreover, most human studies typically provide 300 mL to 1 L of hydrogen water per day, whereas the mice are provided hydrogen water ad libitum. Therefore drinking the same concentration of hydrogen water, mice are getting between 13 and 26 times more hydrogen relative to body weight in comparison to humans in the clinical studies.

For typical pharmaceuticals it typically takes larger dosages of molecules to work in mice than in humans, a standard conversion being roughly 12 times more needed in mice [56]. This second conversion would suggest that concentration should remain constant between mice and humans when factoring in total water dosage. That said, this conversion is likely not applicable, since unlike drugs, the half-life and actual cellular concentration of H_2 in the cells is similar in rodents and humans. Therefore the 13−26 times the hydrogen dosage given in mice is significant and should not be easily dismissed. In a mouse model study of NAFLD, 0.8 mg/L was effective, whereas 0.3 mg/L was not [57]. This study was conducted after an initial study by the same investigators found that electrolyzed alkaline water with a high pH of 11, an oxidation-reduction potential of -495 mV, and a concentration of 0.2 mg/L of H_2 was not effective (see Fig. 49.1). The mouse model would suggest that a human would gain no therapeutic benefit from ingesting 3.84 mg of H_2 by either drinking 1 L of 3.84 ppm or 2 L of 1.92 ppm hydrogen water. The observed benefits were noted only at comparative dosages of 10.24 mg of hydrogen (e.g., 2 L of 5.12 mg/L hydrogen water) for a human.

In the pilot NAFLD study using a high-dose hydrogen water tablet, a strong benefit was observed in a randomized double-blinded, placebo-controlled crossover design ($N = 12$) [58]. The concentration was reported at 6 mg/L, and subjects ingested 1 L for a dosage of 6 mg H_2, which surpasses the 3.84-mg ineffective dose conversion from the NAFLD

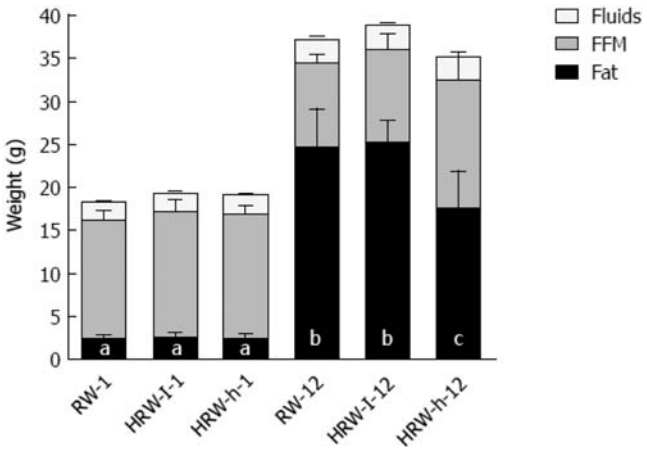


FIGURE 49.1 Body composition following regular water, low-dose hydrogen water and high-dose hydrogen water treatment. Fat, fluids, and free fatty mass at weeks 1 (first three columns) and 12 (last three columns) ($N = 8$). Data are expressed as mean ± standard deviation. Different letters show a significant difference in fat content (Mann Whitney and Kurskal-Wallis $P <$ .05) [57]. *HRW-h*: hydrogen-rich water high concentration; *HRW-l*: hydrogen-rich water low concentration; *RW*: regular water. *Jackson K, Dressler N, Ben-Shushan RS, Meerson A, LeBaron TW, Tamir S. Effects of alkaline-electrolyzed and hydrogen-rich water, in a high-fat-diet nonalcoholic fatty liver disease mouse model. World J Gastroenterol. 2018;24(45):5095–5108.*

mouse model. This study saw clinically significant reductions in liver fat, a 10% drop in aspartate transaminase, and an 11% improvement in insulin sensitivity measured via HOMA2 analysis. These results were reported for a short 28-day observation period, which is significantly shorter than any of the previously mentioned trials on hydrogen therapy exploring metabolic outcomes. It is of note that the $N = 20$ open label on metabolic syndrome dosing at 0.5 mg/day observed no significant improvements at week 4, but by week 8, 5 of 13 biomarkers were significantly improved. In one study, in which middle-aged overweight women consumed 6 mg of molecular hydrogen per day, their body composition and metabolic profiles improved with significant findings in 5 of 20 outcomes and strong trends in two outcomes along with weak trends in seven outcomes [59]. In another study using a single acute dosage of high-concentrations hydrogen water, 500 mL of 7 mg/L (3.5 mg H_2), H_2 immediately improved vascular endothelial function ($N = 34$) [60]. As research on H_2 for metabolic dysfunction progresses, this early trend of higher doses and longer duration leading to better outcomes should be noted.

Neurological disorders

Age-related neurological disorders, such as dementia and Parkinson's disease, have significant impacts on the population. Despite massive worldwide research efforts, there are few potential candidates to improve outcomes. For many molecules, strong early research in rodents has been followed by disappointing results in humans. In contrast, hydrogen water has shown largely positive results in human research after strong results in rodents. Hydrogen has shown promise in rodent models in addressing many of the current targets of various neurological diseases, such as reducing the cytotoxic effects of amyloid beta, tau entanglements, neuroinflammation, and excessive oxidative stress [10].

Parkinson disease

Research on H_2 in Parkinson's disease has had mixed results, with two negative studies in humans ($N = 178$, 72 weeks and $N = 20$, 8 weeks) [61,62] and a single study demonstrating significant benefits ($N = 17$, 48 weeks) [63]. Caveats maintain plausibility for the treatment. The smaller study ($N = 20$) used hydrogen gas inhalation, which according to a rodent model of Parkinson's disease, may not be as effective as hydrogen water [64]. In the larger ($N = 178$) study using high-concentration hydrogen water providing 5 mg H_2/day, the placebo, unfortunately, also contained dissolved hydrogen of up to $\approx$ 0.5 mg/L. Interestingly, however, both the high and low (placebo) hydrogen concentrations showed significant improvements over other placebo groups of similar trials, as they experienced less deterioration in total disease score according to the Unified Parkinson's Disease Rating Scale. Stony Brook Medicine has registered a 52-week clinical trial ($N = 70$) using high-dose hydrogen-creating tablets and placebo tablets. Results of this study are urgently needed to clarify the discrepancies in the previously published data.

Alzheimer disease

Results from research on H_2 in Alzheimer's disease and dementia have shown slightly better indications in humans than the results from the Parkinson's disease research. Several reviews on the topic cover early rodent research that is

promising and one human publication using low-dose hydrogen water for mild cognitive impairment [10,11]. A 2018 human study on advanced dementia utilizing inhaled hydrogen gas showed a significant benefit overall ($N = 11$, 4- to 7-month duration) [65]. In contrast, when low-concentration hydrogen water was used, the benefits were observed only in patients with at least one *APOE4* allele ($N = 73$, 52 weeks) [66]. The exact dosage conversions between hydrogen dissolved in water and inhalation do not yet exist. However, the dosage provided in the water study was reported to be 0.36 mg/day, which is below the recommended minimum therapeutic benefit advised by the International Hydrogen Standards Association, a group of international researchers focused on H_2 as a therapeutic agent. This same publication [66] also released results from a concurrently run rodent study, in which mice received the same hydrogen water concentration as the human patients did, but the mice drank ad libitum in comparison to a set amount (average 300 mL/day) for the human participants. The mice were observed to have significant improvement in cognitive function and memory, decreased oxidative stress in the brain, and increased recovery from neurodegeneration, and they experienced a significant increase in mean life span (see Fig. 49.2A and B).

Sleep deprivation alters brain energy metabolism [67] and has been linked to the development of neurodegenerative diseases [68]. Interestingly, a recent study demonstrated that high-dose hydrogen water was noninferior to 100 mg of caffeine at improving alertness as measured via the visual analog scale and the Attention Network Test [69]. Future research targets of molecular hydrogen could potentially include regulation of brain energy metabolism as well as mitigation of impairments induced by sleep deprivation. For models with already advanced or progressing deteriorative states, future research on cognitive decline should first identify the optimal relative dose, based on body weight from the positive rodent studies, before commencing human clinical trials.

Emergency medicine

H_2 has received significant attention for its potential in mitigating damage from acute stress in emergency medicine. Following published evidence in rats and dogs on myocardial infarction, a small pilot study was undertaken to explore the potential of inhaled hydrogen gas in out-of-hospital cardiac arrest. Positive results in this trial led to the approval of inhaled hydrogen as an advanced medical technique in Japan in order to start a large multicenter clinical study exploring this application [70].

Research in rodents as well as early clinical research has demonstrated that molecular hydrogen is a safe and potentially effective treatment for acute neurological episodes, such as cerebral ischemia and infraction [71]. Some results

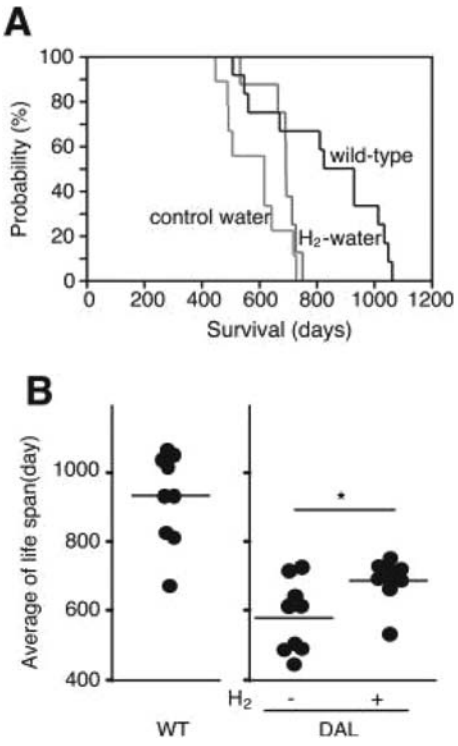


FIGURE 49.2 Extension of average life span by continuous H_2 water drinking. (A) Kaplan-Meier curve representing the survival of female C57BL/6 mice (wild-type), female DAL101 mice drinking control water, and H_2 water. (B) Life span of each mouse ($N = 9$). The bars indicate the average life span of each group. $*P < .05$ ($P = .036$) by Student's *t*-test [66]. *Nishimaki K, Asada T, Ohsawa I, Nakajima E, Ikejima C, Yokota T, et al. Effects of molecular hydrogen assessed by an animal model and a randomized clinical study on mild cognitive impairment. Curr Alzheimer Res. 2018;15(5):482–492.*

have demonstrated that molecular hydrogen is more effective than the free radical scavenger edaravone [71]. Additional results in humans have shown that the combined therapy of edaravone and hydrogen is more effective than edaravone alone [71]. These promising results, along with the high safety profile of hydrogen, have led to another clinical trial, utilizing hydrogen water and minocycline, to be registered by Stony Brook Medicine. In this study, 100 patients recovering from postacute ischemic stroke will be observed. In an acute traumatic brain injury model, a promising case study was published on concussion recovery [72], which corroborates earlier rodent work on recovery from traumatic brain injury [73]. Additionally, a human study demonstrated that hydrogen water significantly protected against damage from hypoxic-ischemic encephalopathy in newborn babies ($N = 40$) [74].

Exercise performance and protection from exercise-induced stress

Exercise is widely considered one of the best preventive strategies for maintaining health and staving off age-related decline. Aging results in several complications, including the tendency of older individuals to develop sarcopenia, lose lean body mass during inactivity, be more prone to injury, and take longer to recover from exercise [75]. As has been covered extensively in a recent review [5], H_2, administered via various methods, has demonstrated rescuing from the effects of exercise-induced damage, such as attenuating impaired redox status and preventing decreased exercise performance. Furthermore, hydrogen gas administered topically has shown to accelerate the healing of soft tissue injuries and reduce delayed onset muscle soreness. Drinking hydrogen water has also been shown to significantly improve fitness in middle-aged overweight women compared to placebo in a double-blinded, placebo-controlled, crossover design, as detailed in the cited review [5]. A registered clinical trial exploring topical hydrogen water versus the RICE protocol (rest, ice, compression, and elevation) for grade 2 ankle tears was recently completed is and now in manuscript preparation. It found that hydrogen-rich hydrotherapy was noninferior to the standard RICE protocol when applied during the first 24 hours after injury for reducing joint swelling and pain while regaining range of motion and balance [76]. A target of future studies using hydrogen-rich hydrotherapy could be to evaluate differences in healing time compared to standard protocols such as RICE. H_2 appears to have the potential to mitigate age-related declines in exercise performance and speed recovery from injury and exercise-induced damage.

Rescuing effects from toxicity

H_2 has shown more prominent effects in rescuing functions from artificial damage. There is early evidence that H_2 can also mitigate damage from molecules taken by participants electively, such as illegal and legal substances, although aside from chemotherapy drugs, this has been observed only in rodent studies. H_2 appears to have protective effects against aspirin-induced gastric damage [77], acetaminophen-induced hepatoxicity [78], ethanol-induced hangovers [79], and methamphetamine-induced neurotoxicity [80]. In a rodent study published in 2020, molecular hydrogen restored the redox status, suppressed oxidative damage, and improved kidney function induced by long-term cyclosporin A administration [81]. Human trials utilizing H_2 against artificial damage from toxic substances, taken either electively or accidentally, should be explored in the future.

Adverse events

From the 79 human studies published by 2019 on molecular hydrogen, totaling 1676 subjects, nine total adverse events potentially attributable to molecular hydrogen have been reported. These were observed in only seven subjects. One study, following 81 stage III and IV cancer patients, cited “minor events” that “spontaneously resolved” but did not specify what types of events they were. The only adverse event that has been observed in more than one participant is loose stool/diarrhea (four events, 0.2% frequency) (see Table 49.3). Larger trials are needed to determine whether molecular hydrogen will have any contraindications in specific populations or if administered with any prescribed medications. No contraindications have currently been identified.

Safety

Molecular hydrogen is commonly used in deep-sea diving because it is far less narcotic than nitrogen gas or even helium gas. Data from mixed-gas sea diving has revealed that hydrogen is very well tolerated by the body, and only at very high pressures will hydrogen narcosis occur [82]. Fortuitously, even when hydrogen narcosis is present, it has been observed that hydrogen-containing mixes may suppress high-pressure neurological symptoms [83]. Importantly,

TABLE 49.3 Assessment of patients experiencing adverse events across the human clinical literature.

Study	Subjects (total)	Loose stool	Hypoglycemia	Increased frequency of bowel movement	Headache	Heartburn	Cardiac failure
Nakao (2010)	20	3	0	1	1	1	0
Ito (2011)	5	0	1[a]	0	0	0	0
Nagatani (2013)	38	1	0	0	0	0	1
73 trials	1697	0	0	0	0	0	0
Total	1760	4	1	1	1	1	1

[a]*Corrected by lowering subject's insulin.*

the dosage of hydrogen needed under pressure to exhibit signs of narcosis is significantly higher than what any commercial method (such as via inhalation or dissolved in water) could deliver to consumers even in the most extreme circumstances. Thus hydrogen narcosis (which exhibits no known long-term damages, toxicity, or side effects) is of relatively small concern.

One hypothesis article makes conjectures about several concerns regarding hydrogen therapy involving hydrogen-induced ghrelin-mediated risks and benefits. For example, hydrogen may increase ghrelin excretion, which may increase cancer risk [84]. However, no such adverse events due to this hypothesized connection have been reported in either humans or animal models, and current evidence points to H_2 being a potentially beneficial adjuvant therapy for various cancer models. Finally, humans produce up to 12 L of molecular hydrogen gas per day through bacterial breakdown of carbohydrates in our digestive tract [85], so the relatively small volumes of exogenous supplementation should, and have thus far been demonstrated to, have a very high safety profile.

Commercially available options

Many commercial products have emerged for administering molecular hydrogen. HRW products can be classified as ready-to-drink products, which already contain hydrogen gas that is delivered to consumers in cans, bottles, and pouches, or on-demand products, including reactive tablets, magnesium sticks, and machines to create HRW. Various products may dramatically differ in concentration and dosage. Machines tend to use electrolysis, whereas reactive sticks and tablets tend to use elemental magnesium, hydrides, or, in one case, aluminum. Delivered concentration and dosage, based on manufacturer recommendation, can vary by a factor of 100 or more for HRW products. Similarly, topical HRW products use the same technologies as those intended to make hydrogen-rich drinking water, with the same variance in delivered dose.

Hydrogen inhalation units tend to use electrolysis to produce H_2 gas. Machines differ in both flow rate and concentration of H_2. For example, flow rates of the delivered gas via cannula vary between 20 and 600 mL/min of 99.99% H_2 gas, which would equate to an inhaled concentration of less than 0.25%−12% after being diluted by normal human breathing at rate of 5−8 L/min. Other units are able to deliver a consistent H_2 concentration (1%−4%) based on human breathing rate. As such, delivered dosage can vary by a factor of 40 or more, and recommended session times also vary, thus blurring the distinction between high-dose intermittent and continuous exposure.

There are also tablets and capsules that are intended to create H_2 gas internally. However, other than acarbose, a prescribed drug, which works by slowing down carbohydrate breakdown and as such increases the volume of H_2 bacterial production, the remainder rely on reactive metals to produce gas internally. These do not have approved status regarding safety and often have adulterated labels to obfuscate the actual reactive material. For all technologies, some products may be clinically validated with approved regulatory status, while many others are neither clinically validated nor have proper regulatory status with the governmental departments that are tasked with overseeing the respective industries.

Conclusion

Research on molecular hydrogen therapy has been advancing at an exponential rate in recent years. Basic research conducted in cell culture and animals has demonstrated wide-ranging implications. The early human evidence has likewise been overwhelmingly positive with a very high safety threshold. Despite these positive results, translational limitations

from animals to human application have begun to emerge. This may be partly due to inconsistencies in dosage, duration, and administration methods. Future research should focus on ascertaining the appropriate dose, duration, and method of hydrogen gas administration. Additionally, research needs to identify priorities pertaining to models in which hydrogen therapy is or is not effective, either on its own or as an adjuvant therapy. Molecular hydrogen therapy is a novel, safe, and potentially effective approach to mitigating many stressors that develop throughout life, both externally and internally. Moreover, it holds the possibility of significantly benefiting the human health span while protecting against many age-related, genetic, and environmentally induced non-communicable diseases.

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Glossary

Apoptosis: A form of programmed cell death. Apoptosis differs from necrosis, which happens from trauma, as apoptosis is highly regulated and may confer advantages to the organism. Excessive apoptosis can lead to damaging effects, such as neurological disorders.

Atherosclerosis: A condition in which plaque builds up inside arteries.

Catalase: An enzyme capable of breaking down H_2O_2 to water and oxygen, preventing cellular damage from excess H_2O_2 within the cell.

Cellular Senescence: The loss of a cell's ability to divide. All cells reach a limit of divisions. Cellular senescence can be prematurely initiated by a variety of stressors, both internal or environmental. Cellular senescence both inhibits carcinogenesis and contributes to numerous deleterious physiological outcomes and has been implicated as having a causative role in aging.

Cytokines: A broad category of small proteins excreted from cells that affect cellular signaling.

Glutathione: A naturally produced antioxidant found in plants and animals that can protect against excessive oxidative stress.

Heat Shock Proteins (HSPs): Heat shock proteins are released in response to many physiologically stressful conditions. HSPs act as a "supervisor" or "chaperone" during protein folding to ensure proper folding.

Hydroxyl: A free radical and highly reactive oxygen species that can oxidize DNA (remove electrons).

Interleukin 6 (IL-6): IL-6 is promptly produced in response to acute stress, in which it acts as a proinflammatory cytokine in functions such as playing a critical role in increasing body temperature to fight off infection.

Insulin Sensitivity: Denotes the effect that the hormone insulin has on cells to take in glucose from the blood.

Low-Density Lipoprotein (LDL): One of the five major groups of lipoproteins, which transport fat molecules around the body. Commonly known as cholesterol transporters. Oxidized LDL can lead to atherosclerosis.

Minocycline: A tetracycline antibiotic used to treat many different bacterial infections.

Molecular Hydrogen: Molecular hydrogen, or H_2, is a molecule formed by two hydrogen atoms that share electrons. It has recently been implicated as potentially having numerous beneficial physiological roles.

NAD^+: Nicotinamide adenine dinucleotide is a cofactor involved in redox reactions and is thus crucial for many metabolic enzymes. It exists in its oxidized form abbreviated as NAD^+ and in a reduced from abbreviated as NADH (H for hydrogen). It is also a cosubstrate for sirtuins and PARP-1.

Necrosis: The irreversible trauma in which tissue dies as a result of lack of oxygen flow to the tissue. It can be caused by many factors, such as radiation, injury, or chemical damage.

Peroxynitrite: A form of nitrosative stress, which as a free radical can damage DNA, such as inducing DNA strand breaks or base modifications.

Programmed Cell Death Protein 1 (PD-1): A cell surface protein that contributes to the regulation of the body's immune system. PD-1 downregulates the immune system and promotes self-tolerance by suppressing inflammatory T cell activity. This can prevent the immune system from killing cancer cells but also protects against autoimmune disease.

Redox: The redox status is the balance between prooxidants and antioxidants. Oxidants are constantly produced within the cell, some being beneficial at homeostatic levels and others being highly damaging during chronically elevated levels.

Resveratrol: A polyphenol found in certain plants and red wine that has been investigated for its ability to activate SIRT1.

Sarcopenia: A condition of significant skeletal muscle mass and function loss as part of the natural aging process.

Sirtuin (SIRT): A protein involved in regulating cellular processes, including aging, cell death, and resistance to stress. Sirtuins have been widely linked to both health span and life span.

Superoxide Dismutase (SOD): A naturally occurring enzyme capable of breaking down the damaging superoxide radical into either O_2 or H_2O_2. It plays a critical role in the antioxidant system.

Tumor Necrosis Factor Alpha (TNF-α): A proinflammatory cytokine produced by monocytes and subsequently macrophages during acute inflammation and responsible for many signaling events within cells. Excessive TNF-α leads to necrosis or apoptosis.

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Chapter 50

Nutraceuticals to decrease cortisol and hyperglycemia

Adrian Isaza
Alternative Medicine, Everglades University, Tampa, Fl, United States

Introduction

Cushing disease is characterized by the overproduction of endogenous glucocorticoids. In 2012 Feelders et al. carried out a review of the literature from 2000 to 2012. This study found that at the time of diagnosis, 58%−85% of patients have hypertension, 32%−41% are obese, 20%−47% have diabetes mellitus, and 38%−71% have dyslipidemia

Polyphenol-rich herbs have shown clinically meaningful benefits on fasting serum glucose reduction, antiinflammation properties, and antioxidation in patients with type 2 diabetes mellitus. Recent reviews have listed numerous herbs that have been clinically tested and have shown various degrees of effectiveness in preventing and managing type 2 diabetes mellitus. This chapter will examine whether some herbs can reduce both cortisol and hyperglycemia.

Tetrahydrocannabivarin

Tetrahydrocannabivarin is a nonpsychoactive phytocannabinoid that affects lipid and glucose metabolism. It is a propyl analog of tetrahydrocannabinol (Δ9-THC), which affects the endocannabinoid system, modulating food intake and energy homeostasis [1] (Fig. 50.1).

Effect on cortisol

In 2009 Ranganathan et al. showed that frequent cannabis users had blunted increases of cortisol in comparison to healthy controls [2].

Effect on glucose

The impact of tetrahydrocannabivarin on fasting plasma glucose was demonstrated in one randomized, double-blind, placebo-controlled study, which included 62 subjects with noninsulin-treated type 2 diabetes. In patients treated with tetrahydrocannabivarin, concentrations of fasting plasma glucose decreased, and patients had an improvement in pancreatic beta cell function compared with control subjects. Also, an increase in adiponectin and apolipoprotein concentration was seen after 13 weeks [3].

Tribulus terrestris

Effect on cortisol

In 2016 Yin et al. published the results of a study on overtrained rats and found that treatment of rats with *Tribulus terrestris* during overtraining led to a significant decrease in the serum level of corticosterone and a substantial increase in testosterone levels, increasing the testosterone/cortisol ratio compared to control rats [4].

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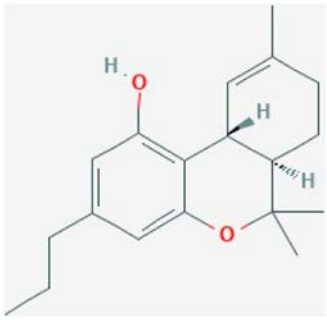


FIGURE 50.1 Chemical formula of tetrahydrocannabivarin. *From: https://pubchem.ncbi.nlm.nih.gov/compound/Tetrahydrocannabivarin.*



FIGURE 50.2 *Tribulus terrestris* plant. *Zhu W, et al. A review of traditional pharmacological uses, phytochemistry, and pharmacological activities of* Tribulus terrestris*. Chem Cent J 2017;11 (1):60.*

Effect on glucose

One human study has demonstrated the usefulness of *T. terrestris* in glucose regulation. In 2016 Samani et al. performed a double-blind, randomized, placebo-controlled clinical trial of 98 women with type 2 diabetes mellitus. The women who were treated with *T. terrestris* showed a significant decrease in fasting blood glucose, two-hour postprandial glucose, and glycosylated hemoglobin levels and an improvement in lipid levels compared to placebo [5] (Figs. 50.2 and 50.3).

Urtica dioica (common nettle)

Effect on cortisol

Two studies have been reviewed concerning the impact of *Urtica dioica* on cortisol concentrations. In 2014 Patel et al. experimented on dexamethasone-induced diabetic mice and found that *U. dioica* significantly reduced hyperglycemia and plasma corticosterone [6]. In a 2015 study conducted by Ngugi on fish, a decrease in plasma cortisol levels was found after administration of *U. dioica* [7].

Effect on glucose

For several years, the antiglycemic impact of *U. dioica* was speculative, but in 2013 Kianbakht et al. designed a randomized, double-blind, placebo-controlled clinical trial of 92 patients, which showed that *U. dioica* significantly lowered the blood levels of fasting glucose, two-hour postprandial glucose, and glycosylated hemoglobin A1c [8].

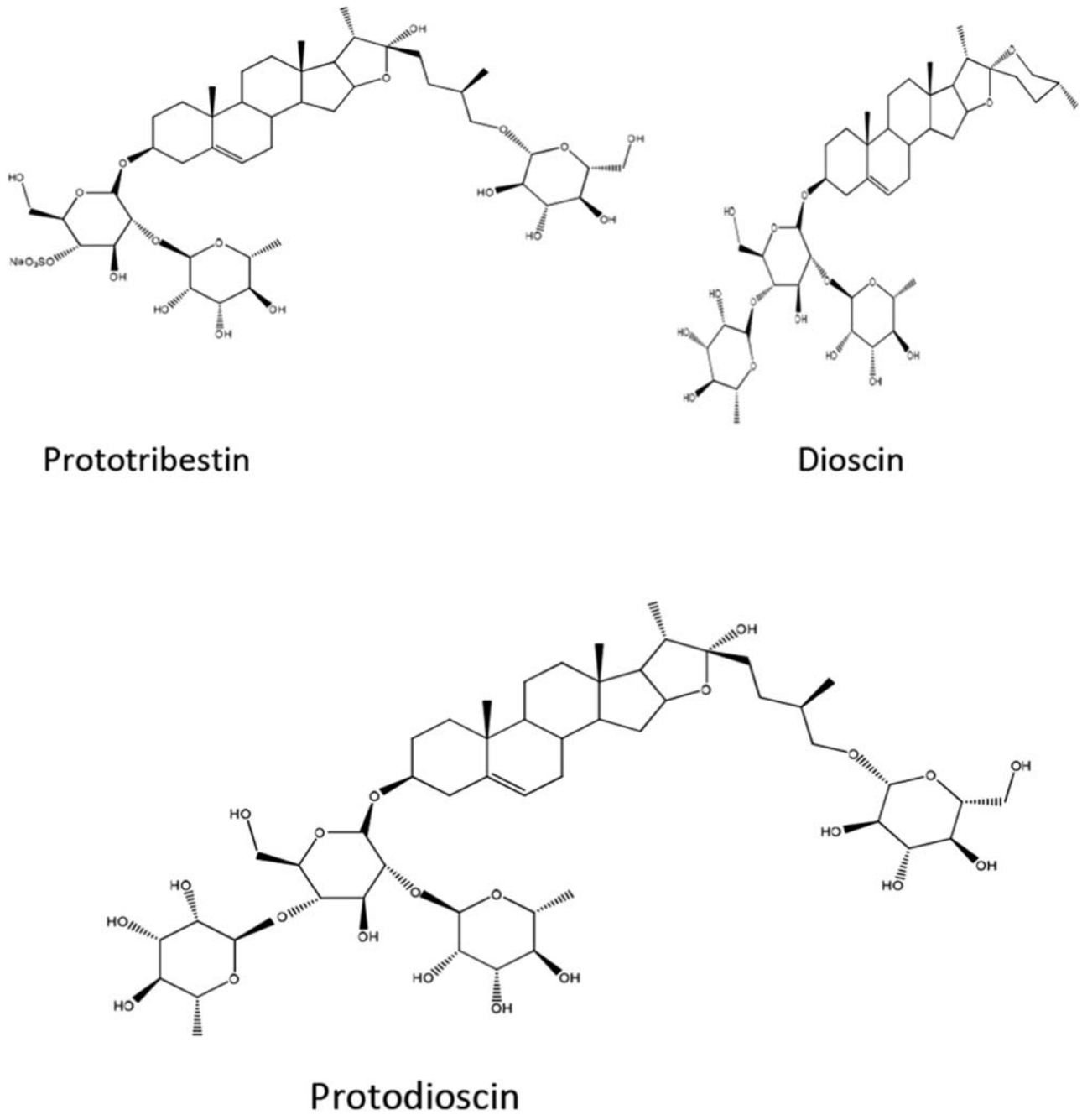


FIGURE 50.3 Chemical formulas of the principal saponins of *Tribulus terrestris*. *Semerdjieva IB, Zheljazkov VD. Chemical constituents, biological properties, and uses of tribulus terrestris: a review. Nat Prod Commun 2019;14(8):1934578X19868394.*

Momordica charantia (bitter melon)

Effect on cortisol

In 2011 Kavitha et al. tested albino rats that were given *Momordica charantia* and found that pretreatment with *M. charantia* attenuated the fluctuation on plasma corticosterone induced by chronic stress. This attenuation was found to be dose-dependent [9].

Effect on glucose

One study in humans has been evaluated regarding the utility of *M. charantia* in reducing glucose levels. In 2018 Cortez-Navarrete et al. carried out a randomized, double-blinded, placebo-controlled clinical trial involving 24 patients, which revealed a reduction in hemoglobin A1C and 2-hour postprandial glucose area under the curve after the administration of *M. charantia* [10] (Figs. 50.4 and 50.5).

Artemisia dracunculus (tarragon)

Effect on cortisol

Artemisia has a high concentration of eugenol, which has been found to reduce cortisol in at least two studies. In 2011, Renault et al. studied 20 yellow European eels that were subjected to eugenol and showed that eugenol reduced the release of plasma cortisol during anesthesia [11]. In another 2011 study, Garabadu et al. evaluated the antistress effect of eugenol in a four-hour restraint rat model and found that pretreatment with eugenol for seven days decreased the plasma corticosterone levels [12].

Effect on glucose

Concerning the impact on glucose plasma levels of *Artemisia dracunculus*, one study will be discussed. In 2016 Mendez del Villar et al. published the results of a randomized, double-blind, placebo-controlled clinical trial involving 24 patients with a diagnosis of impaired glucose tolerance, and its results showed a significant decrease in hemoglobin A1C, the area under the curve of insulin, and total insulin secretion [13].

Coccinia indica

Effect on cortisol

Coccinia indica has a high concentration of beta-sitosterol, which is known to lower cortisol plasma concentration.

Effect on glucose

In 1979, Azad et al. conducted a double-blind controlled trial in 16 patients, which demonstrated a marked improvement in glucose tolerance in 10 patients who had received a preparation of *C. indica* leaves. None of the 16 patients in the placebo arm showed such a marked improvement [14]. In 2008 Kuriyan et al. conducted a double-blind, placebo-controlled, randomized trial with 60 incident type 2 diabetic subjects, who were randomly given 1 g alcoholic extract of this herb for 90 days. Subjects who received this treatment showed a significant decrease in fasting blood glucose, postprandial blood glucose, and hemoglobin A1C concentrations compared with those of the placebo group [15] (Fig. 50.6).

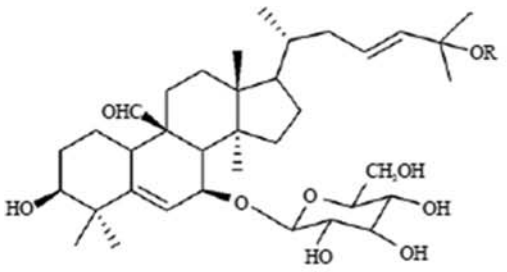
Salvia officinalis

Effect on cortisol

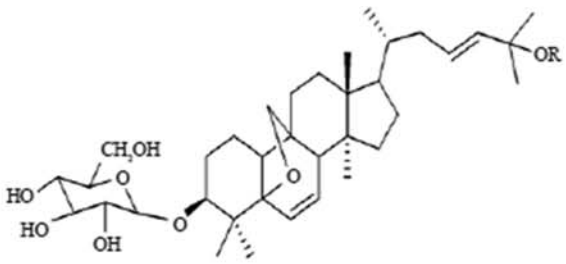
Salvia officinalis has a high concentration of linalool, which has been found to reduce cortisol. In 2018 a study was performed by Lee et al. to examine whether linalool elicited an antistress effect reversing the behavioral alterations observed in mice as rapid eye movement or sleep deprivation. In this study, those alterations were reduced, as were cortisol levels [16].

Effect on glucose

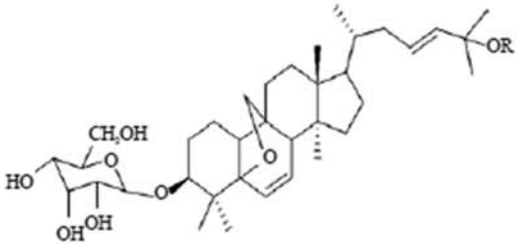
One double-blind trial was performed to determine the hypoglycemic results of *S. officinalis*. Behradmanesh et al. found that 80 patients with type 2 diabetes exhibited a significant decrease in two-hour postprandial blood sugar levels compared to the control group [17].



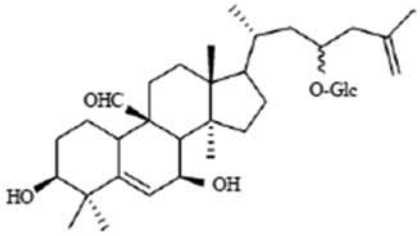
8 Momordicoside K R = CH_3



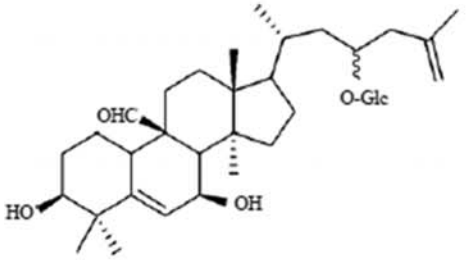
10 Momordicoside F1 R = CH_3
11 Momordicoside I R = H



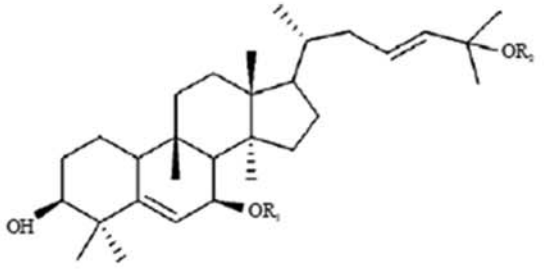
12 Momordicoside G R = CH_3
13 Momordicoside F2 R = H



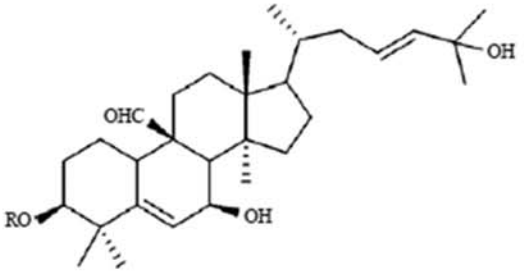
14 Momordicin I R = H
15 Momordicin II R = Glc



16 Momordicin III



17 3β,25-dihydroxy-7β-methoxy-cucurbita-5,23(E)-diene R_1 = Me, R_2 = H
18 3β-hydroxy-7β,25-dimethoxy-cucurbita-5,23(E)-diene $R_1 = R_2$ = Me



19 3-O-β-D-allopyranosyl 7β,25-dihydroxycucurbita-5,23(E)-dien-19-al R = All
20 3β,7β,25-trihydroxy-cucurbita-5,23(E)-dien-19-al R = H

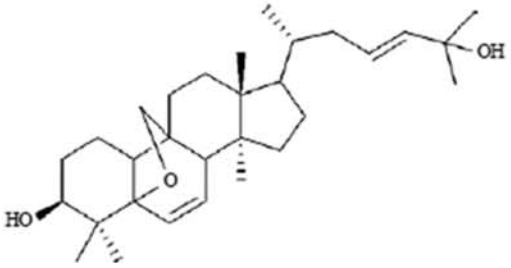


FIGURE 50.4 Chemical structure of saponins and triterpenes isolated from *Momordica charantia*.

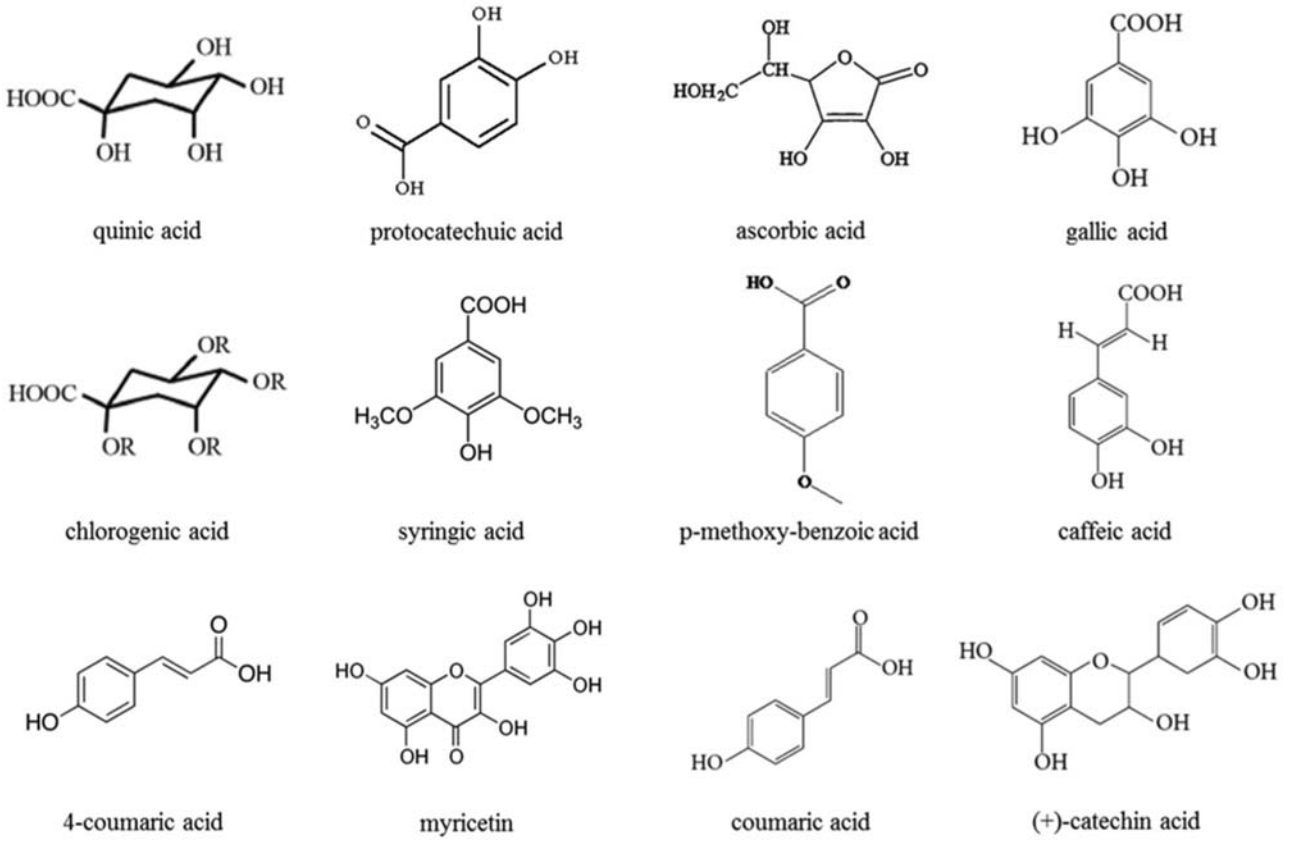


FIGURE 50.5 Chemical structure of phenolics and flavonoids isolated from *Momordica charantia*. *Fan M, et al. The role of Momordica charantia in resisting obesity. Int J Environ Res Public Health 2019;16(18):3251.*

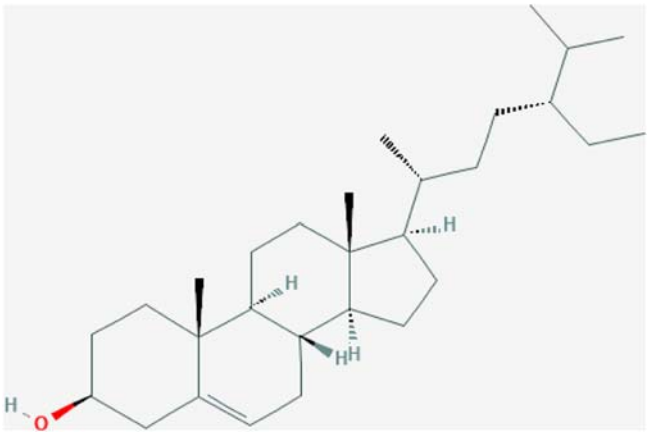


FIGURE 50.6 Beta-sitosterol, a component of *Coccicia indica*. *From: <https://pubchem.ncbi.nlm.nih.gov/compound/beta-Sitosterol>.*

Artichoke

Effect on cortisol

Artichoke has a high concentration of a prebiotic called inulin, and it was proved that inulin inhibit corticosterone. In 2004 Li et al. tested brain cells and found that an inulin-type hexasaccharide protected the cells from lesions induced by corticosterone [18].

Effect on glucose

In 2014, Rondanelli et al. published the results of a randomized, double-blind, placebo-controlled trial in which 55 overweight subjects with impaired fasting glucose were randomly given artichoke as a supplement. The supplemented group showed a significant decrease in fasting blood glucose, glycosylated hemoglobin concentrations, and A1C-derived average glucose [19].

Chamomile

Effect on cortisol

In 2006 Reis et al. examined the cortisol levels of stressed bovines, which were given *Matricaria chamomilla*. In this study, cortisol levels were significantly lower in animals fed with *M. chamomilla* [20].

Effect on glucose

Two studies were reviewed with regard to the effect of chamomile on glucose. In 2015 Rafraf et al. conducted a single-blind randomized controlled clinical trial involving 64 individuals with type 2 diabetes. They were given chamomile tea randomly. In this study, the authors concluded that chamomile tea significantly decreased hemoglobin A1C concentration, serum insulin levels, and insulin resistance [21]. In 2016 Zemestani et al. performed a single-blind, randomized, controlled clinical trial on 64 subjects with type 2 diabetes, similar to the study of Rafraf et al. In this study, the author got the same results as those of Rafraf's study [22].

Sumac bran

Effect on cortisol

Sumac bran has a high concentration of myricetin, which was proved to reduce corticosterone. In 2015 Ma et al. investigated the possible impact of chronic administration of myricetin on depressive behaviors in mice that were subjected to repeated restraint stress. In this study, the myricetin treatment reduced the plasma corticosterone levels of the mice [23].

Effect on glucose

Two studies were published in 2014 on the use of sumac bran in diabetic subjects. One double-blind, randomized study conducted by Rahideh et al. involved 41 volunteers with type 2 diabetes. The subjects randomly received herbs, plants, and plant derivatives of sumac bran or placebo. Participants who were allocated to the treatment arm showed a significant decrease in insulin and insulin resistance [24]. The second study was done by Shidfar et al., who designed a similar study of 41 volunteers with type 2 diabetes. It was also a double-blind, randomized, controlled clinical trial, and subjects who received the nutraceutical showed significant reductions in their serum glucose and hemoglobin A1C concentrations [25].

Citrullus colocynthis

Effect on cortisol

Citrullus colocynthis has a high concentration of cucurbitacin R, which has been shown to lower cortisol levels. In 1987 Panosian et al. evaluated rats that had been injected with cucurbitacin R glucoside and exposed to immobilization stress. The level of corticosterone in the adrenal cortex and blood plasma was not increased in the rat group that had received the injection, in contrast to the control group [26].

Effect on glucose

A randomized, double-blind, placebo-controlled trial done by Huseini et al. in 2009 demonstrated hypoglycemic outcomes with *C. colocynthis*. It was performed in 50 subjects with type 2 diabetes. A significant decrease in

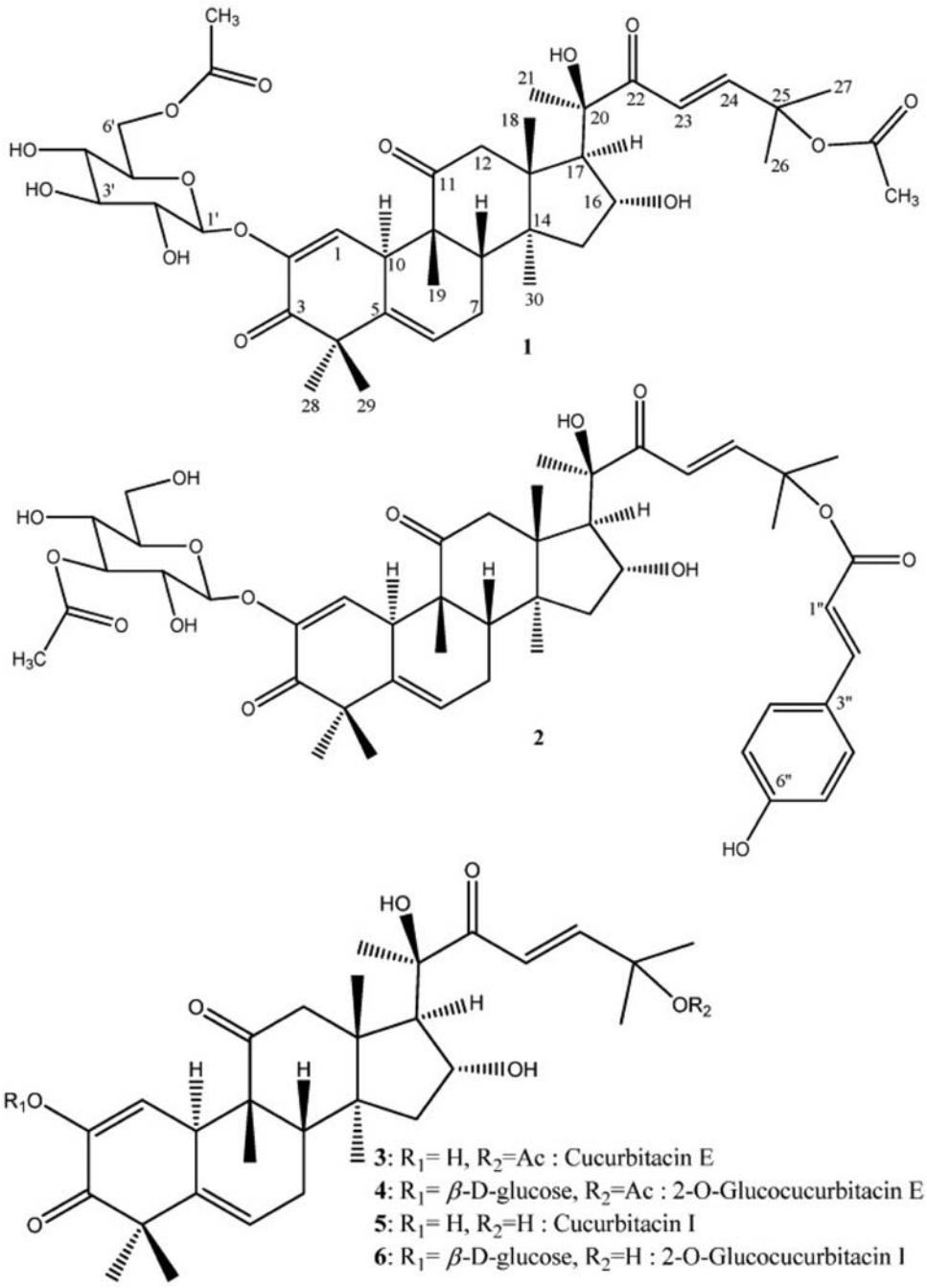


FIGURE 50.7 Cucurbitacin derivatives from *Citrullus colocynthis*: (**1**) 6′-acetyl-2-*O*-β-D-glucocucurbitacin E, (**2**) 25-*p*-coumaroyl-3′-acetyl-2-*O*-β-D-glucocucurbitacin I, (3) cucurbitacin E (also named α-elaterin), (**4**) 2-*O*-β-D-glucocucurbitacin E (colocynthin, elaterinide), (**5**) cucurbitacin I (elatericin B), and (**6**) 2-*O*-β-D-glucocucurbitacin I. *Chawech R, et al. Cucurbitacins from the leaves of* Citrullus colocynthis *(L.) schrad. Molecules 2015;20(10):18001–18015.*

hemoglobin A1C and fasting blood glucose levels was found in patients who were treated with *C. colocynthis* [27] (Fig. 50.7).

Cardamom

Effect on cortisol

In 2015 Bhat et al. evaluated the efficacy of cardamom on albino rats with dexamethasone-induced hyperglycemia. This study concluded that supplementation of the diet with cardamom was useful for fasting hyperglycemia caused by glucocorticoids excess [28].

Effect on glucose

Concerning the cardamom impact on glucose metabolism, results of one study were published in 2017. Fatemeh et al. performed a randomized, double-blind, placebo-controlled clinical trial on 80 overweight and obese prediabetic women. The author concluded that cardamom increased insulin sensitivity [29].

Chicory

Effect on cortisol

Chicory has a high concentration of inulin, which was discussed earlier in the chapter with regard to its cortisol-lowering effect.

Effect on glucose

Two clinical essays have been reviewed in regard with this topic. In 2015 Nishimura et al. published the results of a randomized, double-blind, placebo-controlled trial done with 47 healthy adult participants. The researchers found that hemoglobin A1C concentrations decreased with chicory root extract ingestion [30]. In 2018 Lightowler et al. carried out a double-blind, randomized, controlled crossover study involving 40 healthy adults. They confirmed that substitution of inulin or oligofructose from chicory for glycemic sugars might be an effective strategy to reduce postprandial blood glucose response to foods [31].

Schisandra

Effect on cortisol

Two studies were reviewed with regard to the cortisol-reducing effect of schisandra. In 2009 Sunet et al. investigated the impact of schisandra on the function of the pituitary-adrenal cortex and carbohydrate metabolism in male rats undergoing experimental psychological chronic stress. The results of this experiment were that both the glucose and corticosterone levels were significantly reduced in the rat group that received Schisandra [32]. In 2015 Li et al. investigated the outcomes of herbs, plants, and plant derivatives containing *Schisandra chinensis* in rats with type 2 diabetes mellitus. The authors characterized the glucose metabolism and the pituitary-adrenal axis of rats after strenuous navigation and exercise. The results revealed that *S. chinensis* could reduce serum corticosterone and blood glucose levels in those rats [33].

Effect on glucose

Concerning the antidiabetic effect of schisandra, in 2015, Song et al. conducted a randomized, double-blind, placebo-controlled study of 28 obese women who were given *S. chinensis* fruit or placebo for 12 weeks. The *S. chinensis* group tended to show a more significant decrease in fasting blood glucose levels compared to the placebo group [34] (Fig. 50.8).

Carob

Effect on cortisol

Carob has a high concentration of inositol, which has been demonstrated to reduce cortisol concentrations.

Effect on glucose

Regarding the impact of carob on glucose concentrations, in 2016, Banuls et al. performed a 12-week double-blind, randomized clinical trial involving 44 subjects with impaired fasting glucose metabolism. They were randomly given a carob pod inositol-enriched beverage, and subjects who consumed that beverage exhibited a significant decrease in insulin and glucose levels during the postprandial state and nocturnal fasting compared with the control group [35].

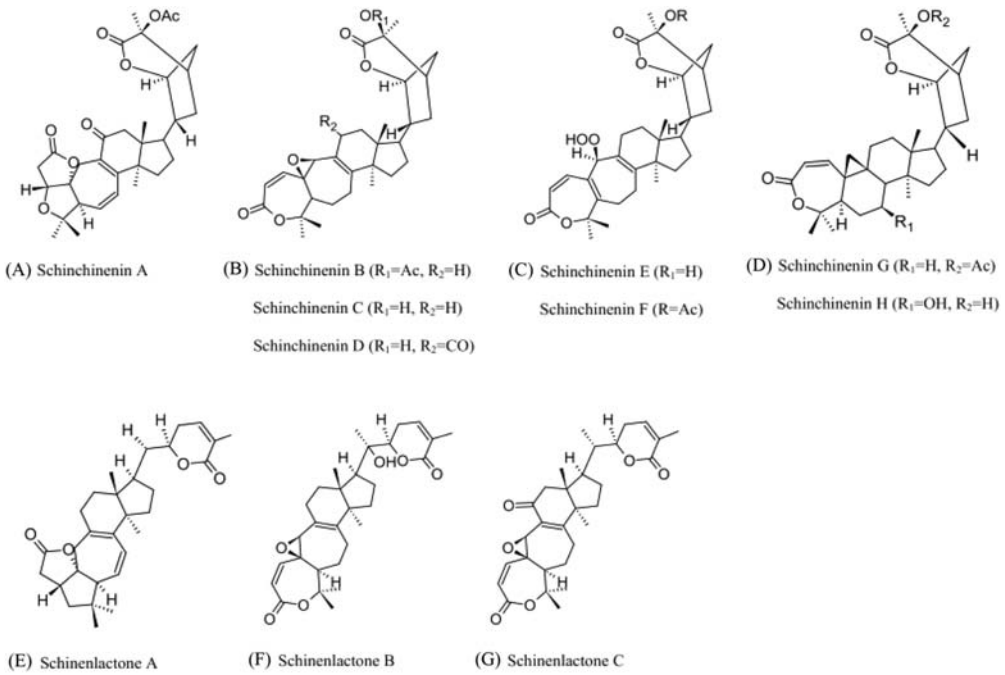


FIGURE 50.8 Examples of recently identified triterpenoids from *Schisandra chinensis*. (A–D) Schinchinenins A–H. (E–G) Schinenlactones A–C. *Song QY, Jiang K, Zhao QQ, et al. Eleven new highly oxygenated triterpenoids from the leaves and stems of* Schisandra chinensis*. Org Biomol Chem 2013;11:1251–1258. https://doi.org/10.1039/c2ob27115j.*

Discussion

All these nutraceuticals could be used as supplements or coadjutants for diet and exercise treatment in patients with type 2 diabetes mellitus and hypercortisolemia. They could help to improve glucose metabolism and insulin response and to prevent insulin resistance in patients with hypercortisolemia or Cushing syndrome.

Several nutraceuticals have components that might affect the gluconeogenesis pathway or glucose metabolism. For example, bitter melon, a well-known hypoglycemic plant, contains cucurbitane triterpenoids (glycosides) that have AMP-activated protein kinase activity, which is a crucial pathway modulating glucose uptake and fatty acid oxidation. Also, it was shown that stimulated GLUT4 translocation to the cell membrane facilitated glucose entry into cells [36]. Myricetin, a component of sumac bran, also enhances GLUT4 translocation, improving glucose plasma levels. This plant-derived flavonoid not only decreases hyperglycemia but also increases hepatic glycogen and glucose-6-phosphate content in hepatic cells [37]. Another nutraceutical that was demonstrated to modulate glucose metabolism was *T. terrestris*, in which its gross saponins showed inhibitory activity against alpha-glucosidase that led to modulation of the levels of postprandial blood glucose and improvement in insulin-dependent diabetes symptoms [38].

These nutraceuticals were shown to decrease cortisol plasma concentrations by different mechanisms. For example, myricetin (sumac bran) was proven to lower cortisol levels by reducing depression [23]. By contrast, *Schisandra* affects the pituitary-adrenal cortex, thus lowering cortisol concentrations and carbohydrate metabolism [32]. However, each mechanism led to less plasma cortisol concentration or a better regulation of its levels, which may have an indirect impact on glycemic levels. There seems to be a causal relationship between increased cortisol levels and insulin resistance, especially in the case of Cushing disease. It is probably a cause of being a constant stimulus for gluconeogenesis in chronic hypercortisolemia. Thus it has as consequences a poor management of glucose metabolism and a decrease in cell response to insulin, provoking hyperinsulinemia and insulin resistance and consequently type 2 diabetes mellitus.

In addition to Cushing disease, it is essential to examine the effect of exogenous glucocorticoids on insulin resistance. In a literature review including articles from 1950 to 2009, Clore et al. affirmed that the odds ratio for new-onset diabetes mellitus in patients treated with glucocorticoids ranges from approximately 1.5 to 2.5 [39]. Another review that included scientific studies from 1980 to 2012 concluded that the odds ratio for the development of new-onset diabetes mellitus had been reported to be 1.36–2.31 in patients undergoing glucocorticoid treatment [40]. Finally, a meta-analysis performed by Liu et al. in 2014, which involved 13 studies, found that the risk for patients developing glucocorticoid-induced hyperglycemia or diabetes was 32.3% [41].

Furthermore, glucocorticoids are associated with blood pressure increase and weight gain. In a 2016 systemic review of 22 randomized, controlled trials, including over 3000 children, Aljebab et al. found that 144 of 369 patients showed increased blood pressure, and 21 of 75 patients showed weight gain. So it may be crucial to evaluate the causal relationship between hypercortisolemia and metabolic syndrome in further studies.

However, helping to lower cortisol and control glucose levels might be necessary in those patients to prevent insulin resistance, type 2 diabetes mellitus and maybe metabolic syndrome. All the nutraceuticals discussed in this chapter could be excellent tools to decrease plasma cortisol concentrations and to regulate glucose metabolism.

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Chapter 51

Biochemical and dietary functions of tryptophan and its metabolites in human health

Bichitra N. Nayak[1], Ram B. Singh[2] and Harpal S. Buttar[3]

[1]Department of Human Nutritional Sciences, University of Manitoba, Winnipeg, MB, Canada, [2]Internal Medicine (Cardiology), Hallberg Hospital and Research Institute, Moradabad, India, [3]Department of Pathology & Laboratory Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada

Background information

L-tryptophan (hereinafter referred to as tryptophan) is an indole-containing essential amino acid that is necessary for normal development and growth of children, and for maintaining nitrogen balance in adults [1,2]. Tryptophan was first isolated in 1901 from the milk protein casein, by Sir Frederick Gowland Hopkins and Sydney W. Cole by feeding mice a diet devoid of tryptophan. The principal role of tryptophan in the human body is synthesis of proteins and muscle tissues. It is also the precursor of several bioactive molecules needed for vital physiological and neurological functions. Dietary sources of tryptophan in adult humans are dairy products including whey alpha-lactalbumin, meats, fish, eggs, bananas, oats, pumpkin and sesame seeds, chocolate, dried dates, soy, tofu, tree nuts, peanuts, and peanut butter (Table 51.1). Tryptophan occurs in L- and D-isomeric forms with an indole ring and aromatic side chain that form the glucogenic product alanine and acetyl coenzyme A (acetyl-CoA). The D-form is confined to some bacterial cell wall proteins and peptide antibiotics. Tryptophan is the precursor of serotonin (5-hydroxytryptamine, 5-HT), tryptamine, melatonin, L-kynurenines, anthranilic acid, 3-hydroxykynurenine, kynurenic acid, 3-hydroxyanthranilic acid, quinolinic acid, niacin, acetyl-CoA, and alanine [4] Serotonin, melatonin, and tryptamine contain an indole ring that imparts antioxidant properties to these molecules.

Tryptophan has a complex metabolism (Fig. 51.1) is involved in two synthetic pathways: i) proteins, ii) serotonin/melatonin (Fig. 51.2) and a catabolic kynurenine pathway (Figure 51.3). Tryptophan metabolism through the kynurenine pathway is involved in the regulation of immunity, neuronal function, and gastrointestinal (GI) homeostasis. The indole molecule is an important structure that is responsible for the production of physiologically active metabolites in the kynurenine pathway. The presence of an indole ring in tryptophan, tryptamine, serotonin, and melatonin provides the antioxidant, antiinflammatory, and other bioactive properties to these molecules [1,2,4,5]. Tryptophan administration reduced the severity of lipopolysaccharide-induced acute lung injury in rats [40]. However, it is not known whether long-term repeated administration of L-tryptophan will cause any harmful effects in humans. Tryptophan is the sole precursor of brain serotonin. Enterochromaffin cells in the GI tract can produce about 95% of serotonin in the gut, and about 5% of serotonin is produced in the brain [6]. Serotonin is an important monoamine neurotransmitter that is involved in mood, behavior, and cognition [5–8]. It has been reported that gut-derived serotonin inhibits bone formation, whereas brain-derived serotonin enhances bone formation and decreases bone resorption [9]. Serotonin, quinolinic acid, and kynurenic acid are involved in neurodevelopment and synaptogenesis [40]. A study by Deac et al. indicated that tryptophan catabolism status is affected by gender and lifestyle factors in healthy young adults [10]. This shows that the concentrations of tryptophan catabolites from kynurenine pathway can be altered by environmental factors besides the metabolic dysfunction of kynurenine pathway.

Melatonin (*N*-acetyl-5-methoxy tryptamine) is a neurohormone consisting of acetamide-substituted indole. It is produced by the modified neurons pinealocytes in pineal gland in the brain in humans and other mammalian species and

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TABLE 51.1 Tryptophan amounts in common foods.

Food	Tryptophan content (mg/100 g)
Cow's milk	42
Eggs	165
Wheat flour	110
Potato	28
Cheese	325
Beef	230
Bananas	10
Soybeans	160
Other beans (red, kidney, green, black)	160–200
Bread (oat bran, toasted)	140
Chia seeds (dried)	440
Chicken breast (skinless, boneless)	400
Salmon	335
Cocoa	290
Walnuts	318
Almonds	281
Pistachio	271
Cashew	287
Peanuts, ground nuts	200

Source: Modified from Kaluzna-Czaplinska et al., 2017 López A, García JA, Escames G, Venegas C, Ortiz F, López LC, et al. Melatonin protects the mitochondria from oxidative damage reducing oxygen consumption, membrane potential, and superoxide anion production. J Pineal Res 2009;46:188–198 [3].

provides a defense against oxidative stress. Melatonin is a potent anticancer and antioxidant agent and crosses the blood-brain barrier. It upregulates antioxidant enzymes and reduces mitochondrial electron leakage. Recent data show that melatonin is present in plant tissues and seeds as well as in nonvertebrate organisms [11]. The primary action of the melatonin molecule is induced through its high affinity for membrane-bound intracellular G-protein-coupled receptors and intranuclear targets. Melatonin is involved in the control of circadian rhythms and regulation of sleep-wakefulness timing, blood pressure regulation, and seasonal reproduction of domestic and wild animals. It is an antioxidant, anti-inflammatory, and immunomodulator [12]. Some products of melatonin are marketed for treating insomnia in humans. Tryptophan and some of its metabolic products, such as serotonin, melatonin, 3-hydroxyanthranilic acid, and niacin, have antioxidant and antiinflammatory properties [2,5,7]. On the other hand, 3-hydroxykynurenine, xanthurenic acid, and quinilinic acid may produce oxidative effects [13], while 3-hydroxyanthranilic acid exhibits prooxidant and antioxidant activities [9]. Indoleamine 2,3-dioxygenase, the first and rate-limiting step in tryptophan metabolism, seems to have an immunological role in regulating the T cell response [14]. Niacin (vitamin B_3) includes nicotinamide and nicotinic acid. Biochemically, niacin contributes to nicotinamide adenine dinucleotide (NAD) and NADH as electron acceptors. The niacin-related molecules are important for synthesis of nucleic acids, fatty acids, and cholesterol. Kynurenic acid is a N-methyl-D-aspartate (NMDA) receptor antagonist, and quinilinic acid is NMDA agonist. An increased quinilinic acid level in the brain may cause depression. Also, increased levels of quinolinic acid and 3-hydroxykynurenine are associated with anxiety. Quinolinic acid is an endogenous modulator with agonistic properties on N-methyl-D-aspartate. It also plays a role in neurodegenerative disorder. By contrast, kynurenic acid is a neuroprotective agent and is involved in immune system modulation, inflammation, and cancer. The gut microbiota is associated with kynurenic acid formation. Kynurenic acid uses receptors such as G-proteins, aryl-hydrocarbon, and GPR-35 [15].

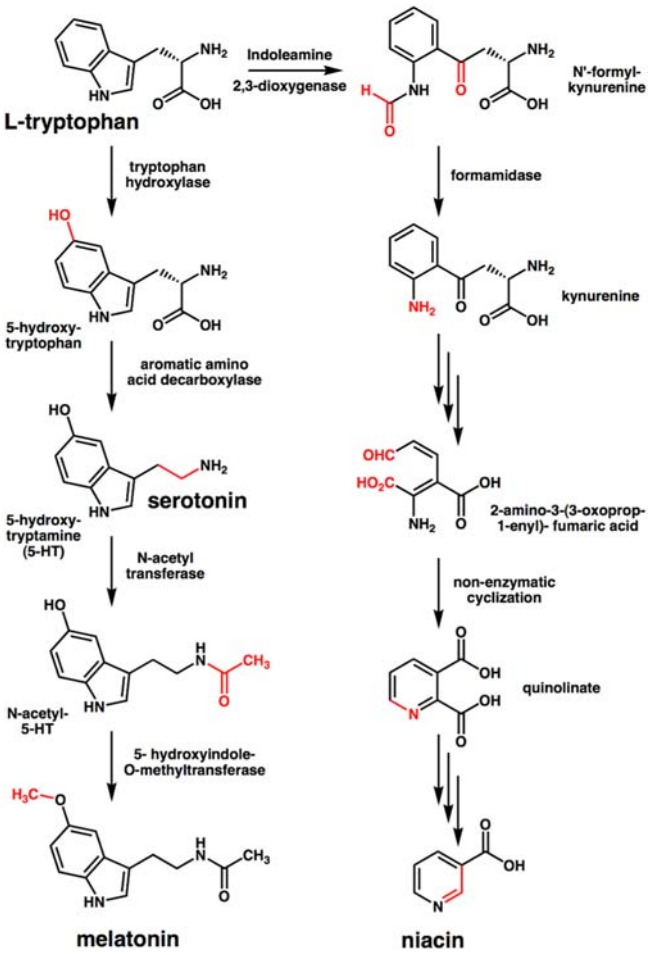


FIGURE 51.1 Enzymatic processes involved in the metabolism of tryptophan and key metabolites.

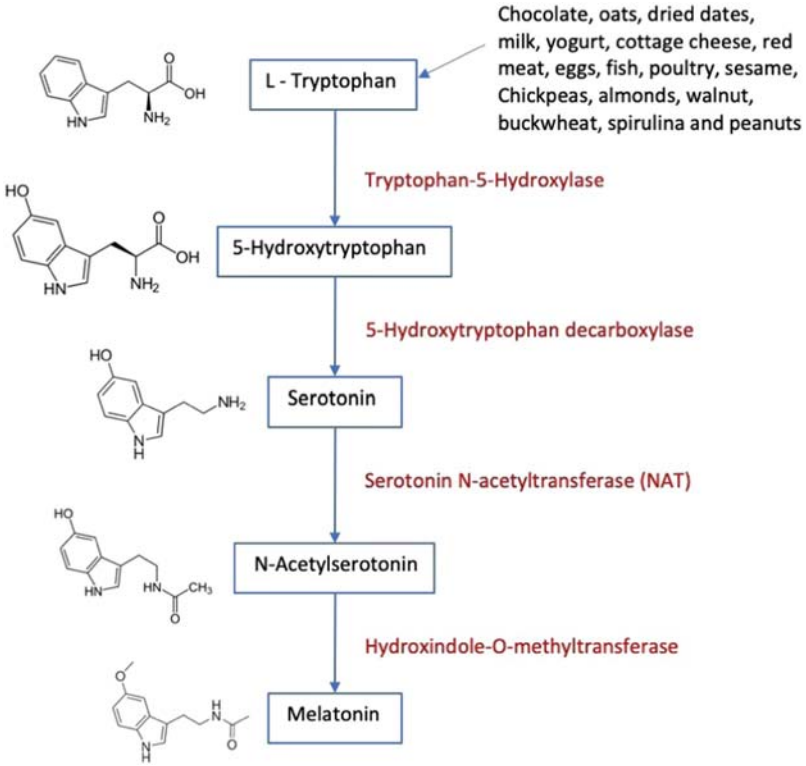


FIGURE 51.2 Dietary sources of tryptophan influence the level of tissue tryptophan, which is converted into serotonin and melatonin to regulate circadian clock functions. *Modified from Takahashi T, Toda E, Singh RB, De Meester F, Wilczynska A, Wilson D and et al. Essential and non-essential amino acids in relation to glutamate. Open Nutraceuticals J 2011;4:205–212.*

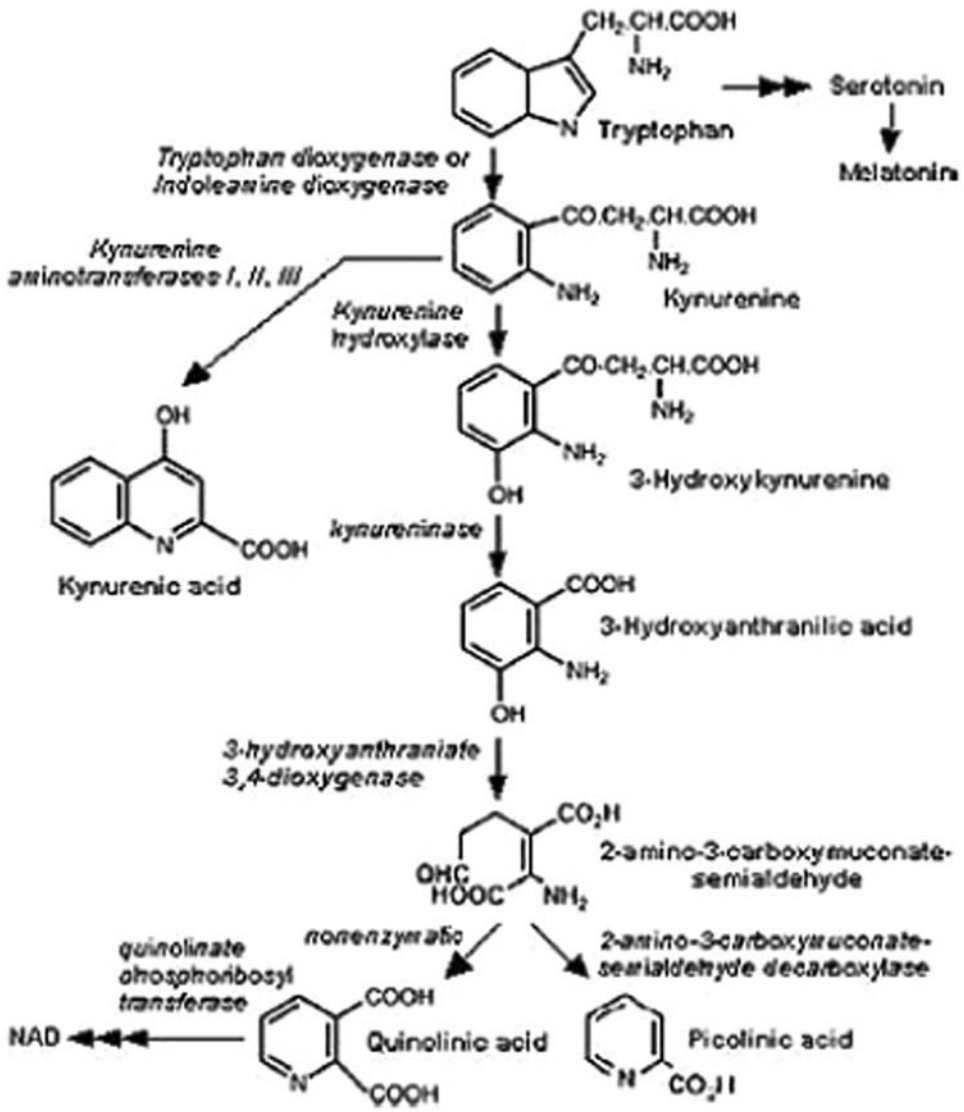


FIGURE 51.3 Tryptophan catabolites via kynurenine pathway.

Role of tryptophan in health and disease

As was alluded to earlier, the essential amino acid tryptophan is needed for normal growth and development in children and for maintaining the nitrogen balance in adults [2,5,16]. Decreased availability of tryptophan or its disturbed metabolism may alter brain development in children. Breast milk is the primary source of tryptophan in nursing infants. Tryptophan being the sole precursor of brain serotonin, is important for neurotransmission, neuronal development and synaptogenesis, neuroimmune activity, and mitochondrial function [5,17,18]. Melatonin is an important antioxidant and anti-inflammatory agent [19,20]. It plays a pivotal role in mood and sensory perception [3] as well in circadian rhythms of sleep-wakefulness timing, blood pressure regulation, and appetite [21]. It is now becoming clear that GI tract serotonin plays an important role in the brain-gut axis, and such serotonergic neurotransmission is influenced by the gut microbiota [21,22]. Serotonin synthesis occurs in the periphery within the gut neurons and enterochromaffin cells and centrally within the neurons of the raphe in the brain stem [21]. The developing serotonergic system in a child's GI tract may be vulnerable to differential microbial colonization patterns prior to the emergence of the stable microbiota that exists in the adult GI tract [7,17]. Melatonin produced either by tryptophan metabolism or by the pineal gland not only acts as a neurohormone but also has a powerful free-radical scavenger ability [20].

Dysregulation of the tryptophan-kynurenine pathway is linked to inflammation, oxidative stress, and the immunoactivation pathway in cardiovascular diseases [23]. Abnormal metabolic pathways of tryptophan or perturbed metabolism

of tryptophan may be involved in people with autism. The pathophysiological relevance of genetically altered tryptophan pathways in people with autism remains to be defined. Some emerging evidence from clinical trials suggests that tryptophan supplementation may be beneficial in treating psychiatric disorders, especially when used in combination with antipsychotic medications [5]. It is important to recognize that tryptophan may interact with lithium, monoamine oxidase inhibitors, and selective serotonin reuptake inhibitors.

Metabolic degradation of tryptophan yields both glucogenic alanine and ketogenic acetyl-CoA. Alanine enters gluconeogenesis, and acetyl-CoA is used for lipid synthesis. Tryptophan has also other metabolic role. Tryptophan donates its carbon after the removal of amino group for synthesis of acetyl-CoA which combines with oxaloacetate to form citrate in the citric acid cycle (Fig. 51.3) to generate high-energy electrons in the form of reduced nicotinamide adenine dinucleotide (NADH) and reduced flavin adenine dinucleotide for energy production in electron transport chain. The major metabolites of tryptophan, however, are serotonin, melatonin, kynurenines, 3-hydroxy-DL-kynurenine, 3-hydroxyanthranilic acid, and niacin. The metabolic fate of tryptophan by the kynurenine pathway is important to the pathogenesis of inflammatory and degenerative diseases. The 3-hydroxykynurenine of the kynurenine pathway is activated in macrophages by infection and inflammation. 3-hydroxyanthranilic acid, a product of 3-hydroxykynurenine, plays anti-inflammatory and neuroprotective roles during inflammation [13]. The kynurenine pathway is involved in the pathogenesis of inflammatory, infectious, and degenerative diseases, including Huntington's disease and stroke-induced brain disease [24]. The 3-hydroxykynurenine, a product activated in macrophages and microglia, leading to the generation of 3-hydroxykynurenine, 3-hydroxyanthranilic acid, and quinolinic acid, which are considered neurotoxic, owing to their free radical−generating action and N-methyl-D-aspartic acid receptor agonist activities.

The antioxidant potential of tryptophan isolated from human breast milk was analyzed for oxygen radical absorption capacity (ORAC) and its ability to mitigate the bacterial lipopolysaccharide-induced proinflammatory cytokines interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) using an in vitro cell-based assay. Tryptophan isolated from human breast milk showed nearly 99-fold higher ORAC capacity than that of whole human milk (7986 ± 468 μm Trolox equivalent (TE)/g versus 80.4 ± 13.3 μm TE/g) [2,16] (Table 51.2). These results suggest that tryptophan isolated from human milk is a powerful antioxidant, as can be seen from the ORAC values shown in Table 51.2.

As was mentioned earlier, the primary source of tryptophan in nursing infants is breast milk [16]. Tryptophan released from mother's milk has high antioxidant properties and free radical−scavenging activity. The antioxidant and antiinflammatory properties of breast milk may help in the normal development not only of the central nervous system (CNS) and the GI tract but also of other organ systems in newborns, especially preterm infants. Tryptophan supplements are recommended to relieve pain, depression, and insomnia. Tryptophan supplementation may improve pharmacotherapy in patients with anorexia nervosa by increasing serotonin content in the brain [25]. Daily adult dietary intake of tryptophan should not exceed 220 mg. However, doses of tryptophan in the range 225−425 mg daily have been used. Whey protein concentrate and isolates are good sources of tryptophan. These proteins are more water-soluble than casein. As an antioxidant, tryptophan supplementation is recommended in infant foods. To determine the free and total tryptophan levels in breast milk and plasma, a group of 30 healthy breastfeeding women received either 2−4 g/day of tryptophan, 20−40 g/day of alpha-lactalbumin, or no supplement. Total tryptophan concentration in breast milk remained unaffected by oral administration of tryptophan or alpha-lactalbumin, whereas the levels of free tryptophan and alpha-lactalbumin were significantly enhanced in breast milk [26]. Disruptions in tryptophan metabolism along the kynurenine path are associated with aging, psychiatric disorders, inflammation, cancer, Alzheimer's disease,

TABLE 51.2 Antioxidant abilities of tryptophan isolated from breast milk, whole breast milk, whole cow's milk, and whey for oxygen radical absorbance capacity (ORAC).

Test material	ORAC value
Tryptophan isolated from breast milk	7986 ± 468 μmol TE/g
Whole breast milk	80.4 ± 13.3 μmol TE/g[a]
Whole cow milk	[a]67.2 ± 7.5 μmol TE/g[a]
Whey isolated from cow milk	[a]13.1 ± 3.2 μmol TE/g[a]

[a]*P <.001 when compared with breast milk tryptophan values.*
Source: Nayak BN, Buttar HS. Evaluation of the antioxidant properties of tryptophan and its metabolites in vitro assay. J Complement Integ Med 2016;13:129−136; Nayak BN, Buttar HS. Health benefits of tryptophan in children and adults. J Pharm Sci Tech Mgmt 2015;1:8−12; Wu H, Gong J, Liu Y. Indoleamine 2,3-dioxygenase regulation of immune response. Mol Med Rep 2018;17:4867−4873 [1,2,16].

Parkinson's disease, Tourette's syndrome, and GI disorders [27]. Defects in tryptophan metabolism or the L-kynurenine pathway are implicated in several other human diseases, including chronic kidney disease; brain edema or injury; susceptibility to tuberculosis, malaria, and cancer; and neurodegenerative and autoimmune disorders [27]. Kynurenic acid is generally considered to have a positive impact on human health and well-being [28]. A markedly elevated content of kynurenic acid was reported in humans suffering from kidney disease [29].

Dietary requirements of tryptophan

The daily tryptophan requirement for adult humans has been set at around 4−5 mg/kg/day. A person weighing 70 kg (approx. 154 lb) would need about 280−350 mg of tryptophan per day from all consumable foods. Other investigators have suggested that the daily adult dietary intake of tryptophan should not exceed 220 mg. However, a higher dose in the range 225−425 mg daily has been reported [5]. Tryptophan is a nutritionally essential amino acid for monogastric animals (e.g., dogs, cats, and monkeys) and preweaning ruminants because it cannot be synthesized in the body. Besides serving as a building block for proteins, tryptophan is a critical nutrient for functioning of the CNS and the immune system. Over the past decades, much attention has been directed to study the role of tryptophan as a limiting amino acid in mammalian and avian nutrition. However, emerging evidence from recent studies shows that tryptophan and its metabolites (e.g., serotonin, 5-HT and melatonin) can regulate food intake, reproduction, immunity, neurological function, and antistress responses. Additionally, tryptophan may modulate gene expression and nutrient metabolism to affect whole-body homeostasis in mammalian organisms. Thus adequate intake of this amino acid from the diet is crucial for growth, development, and health promotion in animals and humans [30].

Oxidative stress, free radical production, and pathological changes

Free radicals are needed for cell-to-cell communication and for the intercellular and intracellular signaling systems [31,32]. Free radicals generated in aerobic metabolism are involved in a series of regulatory processes, such as cell proliferation, apoptosis, and gene expression [33]. However, during the process of oxidative stress, an excessive amount of highly reactive oxygen species (ROS) free radicals are generated in the cells by mitochondrial damage [32]. Sometimes the excess free radicals can overpower or counteract the defense capability of the cell's antioxidant system. The unabated ROS and reactive nitrogen species cause impairment of essential biomolecules in the cell membrane, including lipids, proteins, carbohydrates, metabolic enzymes, and DNA. Oxidative stress results in the production of cytotoxic compounds such as malonyl-dialdehyde-4-hydroxynonyal and alters the oxidant-antioxidant balance (redox homeostasis), disturbing normal cell function. When not adequately scavenged because of the lesser availability of antioxidants, the oxidative stress−related free radicals cause potential structural damage not only to the cell membrane, but also to its subcellular components, such as DNA [32,33]. Oxidative stress−induced ROS may cause amino acid oxidation, lipid peroxidation, oxidation of purine and pyrimidine, glycoxidative damage, disruption of redox signaling in cell control mechanisms [33]. Further, oxidative stress can activate a variety of transcription factors, causing inflammation, hypoxia, and mitochondrial damage, and consequently initiating the production of proinflammatory cytokines. Certain foods, drugs, tobacco, heavy alcohol intake, and environmental chemical pollutants may exacerbate the oxidative stress level. Higher dietary amount of lipids, glucose, and low-density lipoprotein cholesterol can also cause inflammation. Excessive production of stressor molecules beyond the threshold level and unresolved persistent inflammation can have pathological consequences. Friel et al. [34]. have shown that full-term healthy infants experience oxidative stress, and dietary tryptophan may alleviate this condition. Mitochondria act as the main sources of free radical production in diabetic patients and of disruption of blood flow in heart attack and stroke and reperfusion of blood vessels. Oxidative stress−induced pathology includes the occurrence of cancer, cardiovascular disease, Alzheimer's disease, cognitive impairment, Parkinson's disease, alcohol-induced liver disease, ulcerative colitis, atherosclerosis, osteoporosis, and aging [32,33].

Biochemistry of tryptophan

Tryptophan is an essential amino acid that generates several biologically active metabolites, which play a significant role in protein and enzyme syntheses, memory and cognition, and neurohormonal regulation. The indole ring of tryptophan gives tryptophan its ketogenic property, and the side chain forms alanine. Alanine is used in the biosynthesis of protein, and ketones produced through its ketogenic activity are further converted to acetyl-CoA, which enters the citric acid cycle and is oxidized in the mitochondria for energy production [4]. Melatonin and serotonin are two important tryptophan metabolites,

which are known to protect mitochondria from oxidative stress and enhance mitochondrial biogenesis and functions [6,20,35]. Tryptophan is metabolized in the peripheral tissues as well as in the brain [36]. It is transported to the CNS via a transporter molecule, 5-hydroxytryptophan, which can easily enter into the brain tissues to produce serotonin neurotransmitter. Serotonin is also synthesized in the enterochromaffin cells in the GI tract. Emerging evidence suggests that there is cross-talk between the gut microbiota and the brain that may influence tryptophan metabolism in the gut [22]. Tryptophan needs the transporter molecule tryptophan hydroxylase to cross the blood-brain barrier [37]. In humans, tryptophan is transported across the blood-brain barrier with the help of the large-neutral amino acid transporter. The large-neutral amino acid transporter is a sodium-independent exchanger found in the brain, testis, and placenta.

Biosynthesis and metabolism of tryptophan

Physiologically, tryptophan is used in the biosynthesis of proteins, muscle protein, neurotransmitter serotonin, the neurohormone melatonin, and niacin as well as in the production of the coenzyme nicotinamide adenine dinucleotide (NAD^+). Tryptophan also possesses glucogenic and ketogenic properties [4]. The indole ring is ketogenic, and the side chain forms the glucogenic product alanine. Tryptophan metabolites are produced mainly in the hepatocytes via the tryptophan-kynurenine pathway. Tryptophan 2,3-dioxygenase (TDO) is involved in hepatic degradation of tryptophan, whereas indoleamine 2,3-dioxygenase (IDO) enzyme is responsible for the production of tryptophan catabolites, including kynurines in nonhepatic tissues. IDO is expressed in fibroblasts, macrophages, microglia, monocytes, dendritic cells, neurons, and astrocytes, while TDO is expressed in the liver. IDO can be induced by lipopolysaccharide, TNF-α, transforming growth factor beta, IL-1, and IL-2. TDO can be induced by glucocorticosteroids, glucagon, and estrogens and via tryptophan-kynurenine pathway enzymes. IDO acts on L-tryptophan, whereas TDO can affect the L- and D-tryptophan, 5-hydroxytryptophan, and 5-hydroxytryptamine (5-HT or serotonin) pathways. Nearly 98% of dietary tryptophan is metabolized into niacin (nicotinic acid); only a very small amount is metabolized to serotonin via the intermediary stage of 5-hydroxytryptophan (5-HTP). Several dietary supplements containing tryptophan and its metabolic products (melatonin, niacin) are marketed for children and adults. Currently, synthetic tryptophan is used as a supplement in pig and poultry feed to reduce ammonia emission. Biosynthesis of tryptophan is done by chemical process or using genetically modified microbial strains, particularly *Escherichia coli*.

Kynurenine is the regulator of inflammation and the immune response. As is shown in Fig. 51.1, Fig. 51.3 kynurenine produces three metabolites: anthranilic acid, 3-hydroxykynurenine, and kynurenic acid. 3-Hydroxykynurenine further produces 3-hydroxyanthranilic acid and xanthurenic acid. 3-Hydroxyanthranilic acid generates quinolinic acid, which is involved in the synthesis of the coenzyme nicotinamide adenine dinucleotide (NAD^+). Kynurenine metabolites play multiple functions, such as host-microbiome signaling, immune cell response, and neuronal functions. Inflammation in peripheral tissues can contribute to the accumulation of kynurenine in the brain. Excess kynurenine in the CNS has been associated with depression and schizophrenia. Kynurenine accumulation can be suppressed by activating kynurenine clearance in physically exercised skeletal muscle.

Physiological functions of tryptophan

Tryptophan is the precursor of a wide array of metabolites which are involved in a variety of physiological and metabolic functions in the brain and GI tract. For instance, production of serotonin and other tryptophan metabolites, such as kynurenine, play an important role in regulating GI functions [38]. Tryptophan, serotonin, and melatonin are also antioxidant and antiinflammatory molecules. Tryptophan is the sole source for brain serotonin, which is a potent neurotransmitter that is involved in mood, behavior, and cognition [5]. Melatonin produced either by tryptophan metabolism or by the pineal gland (located in the epithalamus near the center of the brain) acts not only as a neurohormone but also as a powerful free radical scavenger [5]. Melatonin is involved in the regulation of circadian rhythms, such as sleep timing and blood pressure regulation [21]. Xia et al. [12] have reported that human monocytes challenged by lipopolysaccharide and thereafter exposed to melatonin suppress the cytotoxicity of proinflammatory cytokines. Decreased availability of tryptophan or its disturbed metabolism may alter brain development in children. Recently, it was reported that abnormal metabolic pathways of tryptophan or perturbed metabolism of tryptophan may be involved in autism [39]. Tryptophan anchors the membrane proteins within the cell membrane and may also play a role in signal transduction. The pathophysiological relevance of genetically altered tryptophan pathways in people with autism remains to be defined. Recent evidence from clinical trials suggests that tryptophan supplementation may be beneficial in treating psychiatric disorders, especially when used in combination with antipsychotic medications [5]. It is important to monitor interactions and adverse reactions as well as dose effects. Higher doses may result in toxic effects. Niacin produced in

the kynurenine pathway is converted to nicotinamide, which is used in the body to form the coenzymes NAD^+ and nicotinamide adenine dinucleotide phosphate ($NADP^+$) for mitochondrial oxidative phosphorylation and energy production. The metabolic fate of tryptophan by the kynurenine pathway is important to the pathogenesis of inflammatory and degenerative diseases. The 3-hydroxykynurenine that is produced in the kynurenine pathway is activated in macrophages as a result of infection and inflammation. 3-Hydroxyanthranilic acid, a product of 3-hydroxykynurenine, plays antiinflammatory and neuroprotective roles during inflammation [13]. The kynurenine pathway is involved in the pathogenesis of inflammatory, infectious, and degenerative diseases, including Huntington's disease and stroke-induced brain disease [24]. The 3-hydroxykynurenine that is generated via the kynurenine pathway is activated in macrophages and microglia, leading to the production of 3-hydroxykynurenine, 3-hydroxyanthranilic acid, and quinolinic acid, which are considered neurotoxic, owing to their free radical−generating action and N-methyl-D-aspartic acid receptor agonist activities. Serotonin is a neurogenic molecule that plays an important role in mood, anxiety, aggression, sleep, appetite, and sexual function [40,41]. Long-term treatment with antidepressant drugs induces significant changes in serotonergic receptor sensitivity [6]. It has been reported that serotonin plays a role in bone metabolism and in maintaining a balance between the action of bone-forming osteoblasts and bone-resorbing osteoclasts [9]. Gut-derived serotonin inhibits bone formation, whereas brain-derived serotonin enhances bone formation and decreases bone resorption [9]. Melatonin has been reported to increase the differentiation of human mesenchymal stem cells into the osteoblastic cell lineage [9]. Although many of the tryptophan metabolites show antioxidant activity, 3-hydroxyanthranilic acid exhibits prooxidant and antioxidant activity. Research also shows that the tryptophan transport system is commonly overexpressed in tumor cells. The exact mechanism is not well understood. Functions of tryptophan have also been discussed in relation to a possible role of the gut-brain axis [7,17,22].

Antioxidant properties of tryptophan and possible mechanisms of action

Tryptophan is an alpha amino acid with an indole ring and an aromatic side chain. Indole compounds are potent free radical scavengers. Aromatic side chains react freely with hydroxyl radicals. The cleavage of the indole ring of tryptophan by hydroxy radical attack or one-electron oxidation creates two important molecules: kynurenine and N-formyl-kynurenine. Further catabolic action generates two potent antioxidant molecules: 3-hydroxykynurenine, 3-hydroxyanthranilic acid, niacin, and serotonin. Tryptophan isolated from human milk possesses nearly 99-fold higher ORAC capacity than that of whole human milk (7.986 ± 468 μm TE/g versus 80.4 ± 13.3 μm TE/g) [1,2,16], suggesting the powerful antioxidant property of tryptophan (see Table 51.2). As was mentioned earlier in the chapter, the primary source of tryptophan in nursing infants is breast milk [2,16]. The antioxidant and antiinflammatory properties of breast milk may help in the normal development not only of the CNS and GI tract, but also of other organ systems in newborns, especially preterm infants. Tryptophan supplements are recommended to relieve pain, depression, and insomnia. Tryptophan supplementation may improve pharmacotherapy in patients with anorexia nervosa by increasing serotonin content in the brain [25]. Melatonin (N-acetyl-5-methoxy tryptamine) is known to protect mitochondria from oxidative damage [20]. Serotonin facilitates the development of platelets with increased procoagulant activity [42]. The antioxidant properties of tryptophan and some of its oxidative metabolites were examined by measuring how efficiently they inhibited peroxyl radical−mediated oxidation of phosphatidylcholine liposomes and B-phycoerythrin. Low micromolar concentrations of 5-hydroxytryptophan, 3-hydroxykynurenine, xanthurenic acid, or 3-hydroxyanthranilic acid, but not their corresponding nonhydroxylated metabolic precursors, scavenged peroxyl radicals with high efficiency. 3-Hydroxykynurenine and 3-hydroxyanthranilic acid protected B-phycoerythrin from peroxyl radical−mediated oxidative damage more effectively than equimolar amounts of either ascorbate or Trolox (a water-soluble analog of vitamin E). Enzyme activities involved or related to oxidative tryptophan metabolism, as well as endogenous concentrations of tryptophan and its metabolites, were determined within tissues of mice suffering from acute viral pneumonia. Infection resulted in a 100-fold induction of pulmonary indoleamine 2,3-dioxygenase [43]. This was accompanied by 16-fold and 3-fold increases in the levels of lung kynurenine and 3-hydroxykynurenine, respectively. In contrast, endogenous concentrations of tryptophan and xanthurenic acid did not show similar increases. The activity of the superoxide anion ($O2^-$)−producing enzyme xanthine oxidase increased 3.5-fold during infection, while that of the O_2-removing superoxide dismutase decreased to 50% of control levels. These results plus the known requirement of indoleamine 2,3-dioxygenase for superoxide anion for catalytic activity suggest that viral pneumonia is accompanied by oxidative stress and that induction of indoleamine 2,3-dioxygenase may represent a local antioxidant defense against this and possibly other types of inflammatory diseases [18]. Tryptophan has low tissue storage, and it is needed in the body at a much lower amount than other amino acids. Higher amounts of tryptophan and its metabolites may cause tissue toxicity. Tryptophan is shown to be CNS-toxic in rats. The toxicity may be dose-related and species-specific or due to unique cytocellular environment in rat brain tissues. Quinolinic acid is neurotoxic and acts at the N-methyl-D-aspartate receptor [44].

Anti-inflammatory properties of tryptophan

Inflammation is an innate response to harmful stimuli, such as pathogens, injury, and metabolic stress. Tryptophan is known to upregulate the IL-10 cytokine, an antiinflammatory cytokine, thus acting as an antiinflammatory agent. Tryptophan inhibited proinflammatory cytokines Il-6 and TNF-α in mouse macrophage (RAW 164.7) and human glioma U 251 cells [1]. Peptides derived from human milk did not show much effect on IL-6, while peptide 1 stimulated TNF-α. Peptide 1 also had the lowest ORAC value. This may suggest an inverse relationship between high ORAC values estimated in vitro and low TNF-α-inducing capacity. The measurement of TNF-α was carried out by a cell-based assay. Tryptophan showed an inhibitory effect on TNF-α. Interferon (IFN) is an inflammatory cytokine that acts on enzyme indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO), and melatonin acts on cytokine IFN and IDO [41]. Melatonin has been reported as an antiinflammatory agent modulating inflammasome activation [19]. Deregulation of the tryptophan-kynurenine pathway is linked to inflammation, oxidative stress, and immune activation pathway [23]. Increased tryptophan metabolism is associated with activity of inflammatory bowel diseases [45]. Crohn's disease is associated with lower serum tryptophan and an elevated kynurenine/tryptophan ratio [46]. Tryptophan metabolites modulate the activity of CNS-resident cells and suppress neuroinflammation [47]. We examined tryptophan and several of its metabolites (e.g., xanthunuric acid, L-kynurenine, 3-OH anthranilic acid, serotonin hydrochloride, 3-hydroxy-DL-kynurenine, and melatonin) in RAW 164.7, U251 (human glioma), and CCL 127 (human neuroblastoma) cells. Melatonin was found to be a strong inducer of TNF-α in mouse macrophage RAW cells, suggesting that it acts as an inflammatory agent for mouse macrophage cells.

Distortion of tryptophan metabolism and occurrence of non-communicable diseases

Biochemical disruptions in tryptophan metabolism and kynurenine pathway are associated with early aging, psychiatric disorders, Alzheimer's disease, Parkinson's disease, Tourette's syndrome, GI disorders, inflammation, and cancer [5,27]. Defects of tryptophan metabolism in the L-kynurenine pathway are implicated in several human diseases, including chronic kidney disease, brain edema or injury, tuberculosis, malaria, cancer, and neurodegenerative and autoimmune disorders [27]. Involvement of kynurenines in Huntington's disease and stroke-induced brain damage has been reported by Stone et al. [24]. Kynurenic acid is generally considered to have a positive impact on human health and well-being [28]. However, markedly elevated levels of kynurenic acid were reported in humans suffering from kidney disease [29]. Kynurenic acid and 3-hydroxykynurenine display a spectrum of neuroprotective properties, since they are potent free radical scavengers and antagonists of excitatory amino acid receptors. Free radicals generated in aerobic metabolism are involved in series of cellular regulatory processes, such as cell proliferation, apoptosis, and gene expression. When generated in excess, free radicals can counteract the defense capability of the antioxidant system, impairing the functions of essential biomolecules in cells by oxidizing the membrane lipids, proteins, carbohydrate, DNA, and enzymes. Uncompromised oxidative stress can result in the production of cytotoxic compounds, such as malonyl dialdehyde and 4-hydroxynonenal, and alter DNA protein cross-links, thereby causing chromosomal breakage, oxidation of purine and pyrimidine bases and deoxyribose moiety, glycoxidative damage, altered glycosylation, and perturbation of cellular redox status Figure 51.4.

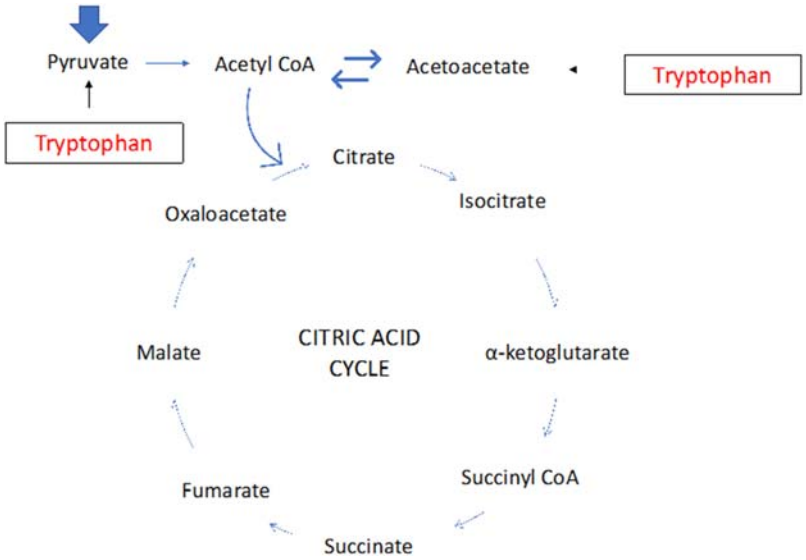


FIGURE 51.4 Entry of tryptophan into the citric acid cycle.

Overwhelming evidence suggests that oxidative stress may be involved in the pathogenesis of several human non-communicable diseases, including cancer, cardiovascular diseases, neural disorders, Alzheimer's disease, cognitive impairments, Parkinson's disease, alcohol-induced liver disease, ulcerative colitis, atherosclerosis, cataract, and accelerated aging. L-tryptophan has been used to treat mental depression. L-tryptophan and lithium have been used to treat bipolar disorder. Low plasma concentrations of tryptophan have been associated with clinical observation of insomnia, anxiety, and depression. In children, tryptophan is used for treating autism. Glutaric acidemia and type 1 autosomal-recessive disorder of tryptophan and lysine metabolism are caused by deficiency of glutaryl-CoA dehydrogenase. Tryptophan and some of its metabolites may protect from the harmful effects of oxidative stress. It is important to point out that the kynurenine pathway takes place mainly in the liver, and in case of liver diseases, the efficiency of this pathway will be challenged, and tryptophan metabolism will be adversely affected, resulting in tryptophan deficiency. As was pointed out earlier in the chapter, dietary sources of tryptophan in adult humans are whole milk, chicken, turkey, fish, eggs, bananas, oats, pumpkin and sesame seeds, chocolate, dried dates, soy, tofu, tree nuts, peanuts, and peanut butter. The enzyme indoleamine 2,3-dioxygenase is induced by proinflammatory cytokines and may form a link between immune functioning and altered neurotransmission, which results in depression. Increased indoleamine 2,3-dioxygenase activity may cause both tryptophan depletion and increased neurotoxic metabolites in the kynurenine pathway, and these metabolic alterations have been hypothesized to cause depression [48]. Animal studies suggest that 5-HT is an important neurotransmitter that is involved in the control of food intake, aggression, and pain perception [49]. In Canada, tryptophan is marketed to treat mood disorders (such as bipolar disorder and depression). It may be combined with other antipsychotic medicines. Tryptophan helps to makes mood more stable and causes behavioral changes by restoring the balance of serotonin and melatonin in the brain. Tryptophan is a natural substance (amino acid) found in high-protein foods and milk. In the United States, tryptophan is sold as a dietary supplement. It has been used to support mood, relaxation, and restful sleep. A patient who takes other medications that enhance the serotonin level in the brain (e.g., SSRI antidepressants) should not take tryptophan without consulting the doctor. Very serious, possibly life-threatening, drug-tryptophan interactions may occur in some patients.

It was mentioned earlier in the chapter that tryptophan is one of the essential amino acids that cannot be synthesized in the human body and must be provided in the diet. In the body, tryptophan is involved in the formation of the vitamin niacin and the neurotransmitter serotonin. Tryptophan is available in Canada as a prescription drug for use in combination with antidepressant drugs to enhance the activity of the antidepressants. Tryptophan is also sold in combination with other amino acids for kidney dialysis patients. Low plasma concentration of tryptophan has been associated with clinical observation of insomnia, anxiety, and depression. Tryptophan plus lithium is used to treat bipolar disorder. Melatonin is used to have a calming effect when other medications may produce a stimulatory effect. Tryptophan has also been used to treat pain, insomnia, premenstrual syndrome, bipolar disorder, autism, attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder, and schizophrenia and to bring relaxation with other drugs with stimulatory effects. Nicotinamide appears to play a role in protecting neurons from traumatic injury, ischemia, and stroke, as well as being implicated in three key neurodegenerative conditions: Alzheimer's disease, Parkinson's disease, and Huntington's disease [50].

Role of microbial tryptophan catabolism in the gut

Agus et al. [51]. have discussed the importance of gut bacterial metabolism of tryptophan, leading to the production of serotonin, kynurenine, and indole derivatives. They have reported that the production of serotonin, kynurenine, and indole derivatives are under the direct or indirect control of the microbiota. It therefore appears that the gut microbes play an important role in host-microbial cross-talk [52]. The gut-produced metabolites may activate the immune system through binding to the aryl-hydrocarbon receptor and enhance the intestinal epithelial barrier, stimulate GI motility, cause secretion of gut hormones, and exert antioxidant and antiinflammatory or toxic effects [52]. A few investigators have suggested that the serotonin produced in the GI tract may be functionally different from brain serotonin [7]. It is likely that the gut microbiota may affect intestinal gluconeogenesis (IGN). The IGN is believed to have beneficial effects on glucose and energy homeostasis.

Clinical studies done with tryptophan and 5-hydroxytryptophan

Turner et al. [6]. reviewed the preclinical and clinical evidence regarding the use of the dietary supplement 5-HTP for the treatment of depression. According to the authors, in the absence of supplementation with exogenous 5-HTP, the amount of endogenous 5-HTP available for serotonin synthesis depends on the availability of tryptophan and on the

activity of various enzymes, especially tryptophan hydroxylase, IDO, and TDO. The amount of 5-HTP reaching the CNS is affected by the extent to which 5-HTP is converted to serotonin in the periphery. This conversion is controlled by the enzyme amino acid decarboxylase, which, in the periphery, can be blocked by peripheral decarboxylase inhibitors, such as carbidopa. Safety issues with 5-HTP are also reviewed, with an emphasis on eosinophilia myalgia syndrome and serotonin syndrome. Clinical studies of 5-HT function using intravenous L-tryptophan have been reported [35]. The aryl-hydrocarbon receptor (AHR) is a ligand-dependent transcription factor that has been implicated in a range of key cellular events. In the gut, AHR is crucial for maintaining intestinal barrier immune homeostasis. The physiology of the AHR, however, is not completely understood; its precise gut luminal activators and functional consequences are unknown. Some AHR ligands originate from the diet. Commensals play crucial roles in metabolizing tryptophan and other amino acids, such as tyrosine, with the subsequent production of tryptophan metabolites. Previous studies have shown that patients with inflammatory bowel disease have impaired production of AHR agonists by the microbiota. Furthermore, dietary supplementation with tryptophan ameliorates clinical parameters of colitis in rodent models. Whether these findings translate into human pathophysiology has not been explored. In the present study, the investigators will evaluate the effect of a high-tryptophan diet versus a low-tryptophan diet on AHR activation in healthy participants. Briefly, participants will be instructed to follow a standardized low-tryptophan diet and will be randomized to a three-week L-tryptophan supplement or placebo. Later, after a two-week washout period, participants will cross over to the other arm. In addition, the effect of tryptophan and microbiota-derived metabolites on AHR activation will be analyzed The National Research Agency and the National Cancer Institute (2012) are studying the side effects and optimal doses of 1-methyl-D-tryptophan in treating patients with metastatic or refractory solid tumors that cannot be removed by surgery [53,54]. Kahn and Westenberg [54] found that ten patients with anxiety disorders who were treated for 12 weeks with 300 mg/day of 5-HTP (with 50 mg of carbidopa TID) exhibited significant reductions in anxiety. The authors then performed a double-blind study with 45 patients and found that the group taking 5-HTP exhibited a reduction in anxiety similar to that of the group taking clomipramine, a tricyclic anxiolytic [54]. A double-blind study compared the effects on 14 children with ADHD of one-week trials of tyrosine (140 mg/kg/day), tryptophan (100 mg/kg/day), dextroamphetamine (5 mg/day or 10 mg/day), and placebo. Parent and teacher ratings and measures of attention were obtained at baseline and at the end of each trial. Tyrosine was not significantly different from placebo on any of the variables measured. Tryptophan, while not significantly different from placebo on teachers' ratings, was significantly better by parents' ratings. This suggests that tryptophan may have some benefit in selected cases of ADD, primarily with home behavior problems [55].

Preclinical studies done with tryptophan

In monogastric animals and preweaning ruminants (e.g., cow or buffalo calves), tryptophan is a nutritionally mandatory amino acid because it cannot be synthesized in their bodies. As was mentioned earlier in the chapter, besides serving as a building block for the synthesis of proteins, tryptophan is a critically important nutrient for the development and function of nervous and immune systems in newborn animals. Over the past few decades, much attention has been focused on studying the role of tryptophan in mammalian and avian nutrition. Emerging evidence from several studies suggests that tryptophan and its metabolites (serotonin and melatonin) regulate food intake, reproduction, immune modulation, neurological function, and antistress responses in animal species. Tryptophan has been used in dogs and cats for calming effects. Additionally, tryptophan may modulate gene expression and nutrient metabolism to affect whole-body homeostasis in mammals and birds. Thus adequate intake of this essential amino acid from the diet is crucial for growth, development, and health promotion in animals [30]. A study in rats showed that tryptophan and its metabolites are associated with an analgesic effect [56].

Toxicity of tryptophan and its metabolites

It has also been reported that 3-hydroxykynurenine and 3-hydroxyanthranilic acid can produce oxygen radicals [28]. Quinolinic acid toxicity is a result of NADA receptor agonist activity [28]. Kynurenic acid increased the lethality of pupae of *Drosophila melanogaster* (wild type). This is believed to be due to the interaction of kynurenic acid with downstream kynurenic acid metabolites 3-hydroxykynurenine and or xanthurenic acid [29]. Kynurenic acid and quinolinic acid are metabolites produced in the degradation of tryptophan and have important neurological activities. Changes in the ratio of kynurenic acid to quinolinic acid are known to be associated with CNS disorders, such Alzheimer's disease, Parkinson's disease, and Huntington's disease.

Antioxidant capacity of stored breast milk

For maximal antioxidant benefit to babies, breast milk should be stored at 4°C for up to 24 hours. The antioxidant capacity of breast milk may be markedly reduced if stored at 4°C for more than 3−4 days. Storing at −80°C seems to be better than storing at −20°C or 4°C. Dried milk powder may be stored at −80°C, but the thawing process may decrease the antioxidant capacity and limit its immediate use for infants.

Platelet-derived serotonin

Platelets do not synthesize serotonin but act as a reservoir for serotonin in their dense granules. Serotonin is synthesized in duodenal enterochromaffin cells and secreted into the blood. About 95% of total serotonin is present in the periphery, and the majority of peripheral serotonin is present in platelets. A small part of total serotonin in the periphery is synthesized in the neuronal cells associated with the GI. Platelets enhance the inflammatory response to infections, injury, and allergens by releasing serotonin with neutrophil recruitments. Neutrophils are inflammatory cells that produce toxins and cytokines, such as IFN-γ, IL-17, TNF-α, and other molecules. They help in the immune response and wound repair. Serotonin and neutrophil interaction can induce inflammation. A reduced synthesis of peripheral serotonin may lower the amount of serotonin in the circulation and affect the normal activity of the heart. Cloutier et al. [57]. suggested that during immunoglobulin G−mediated immune complex formation in the circulation, platelets are activated and release serotonin with inflammatory properties and actions.

Chronobiology and chronomedicine of tryptophan

Tryptophan, being an essential amino acid and precursor of serotonin and melatonin, must be supplied from the diet [1,2,4]. After ingestion, tryptophan binds with blood albumin for transportation across the blood-brain barrier by a specific carrier for neutral amino acids in competition with the rest of large neutral amino acids (tryptophan, tyrosine, phenylalanine, leucine, isoleucine, and valine) [1,2,4]. After reaching the brain, tryptophan is converted into the neurotransmitter serotonin (5-HT) through a two-step synthesis process that is limited by the availability of this amino acid in the plasma [4]. The biosynthesis of most serotonin takes place in the raphe nucleus, whose neurons innervate widespread areas of the brain, such as the striatum, cerebellum, hippocampus, and pineal gland [4]. Serotonin is responsible for the modulation of some developmental events, such as neuron migration, cell differentiation, cell division, and synaptogenesis. Serotonin is also involved in the control of appetite, sleep, memory and learning, temperature regulation, mood, behavior (including sexual function), and cognition or mental disorders [4].

The major sources of tryptophan are most protein-based foods or dietary proteins. As alluded to earlier, tryptophan is particularly plentiful in oats, dried dates, milk, yogurt, cottage cheese, red meat, eggs, fish, poultry, chocolate, sesame, chickpeas, almonds, sunflower seeds, pumpkin seeds, buckwheat, spirulina, and peanuts [2,4]. Walnuts are also a good source of tryptophan but have lower tryptophan content than almonds.

Tryptophan's role in circadian rhythm sleep disorders

Tryptophan is a sleep-enhancing amino acid and makes serotonin and melatonin, which are like circadian clocks that set sleep-wakefulness cycles or day-night cycles [1,2,4]. A majority of the physiological and metabolic processes that take place in the body have a circadian rhythm that is controlled by an internal biological clock located in the suprachiasmatic nucleus [1,2,4]. The pineal gland synthesizes the indole melatonin, which synchronizes these biological rhythms, and melatonin is synthesized and released according to a circadian rhythm. An experimental study analyzed the levels of melatonin over a 24-hour period in Wistar rats in both basal and control conditions and after oral administration of 125 mg/kg tryptophan, the amino acid that is the precursor of this indole, for seven days [1] (Sanchez S et al., 2008, J App Biomed 6:177-186). The findings showed that the tryptophan administration provoked higher levels of melatonin at all time periods in both plasma and the pineal gland. There were increases in the levels of the melaton in MESOR (circadian rhythm adjusted mean) in comparison to the values obtained in the basal and control groups (the respective increases being 45% and 52% in plasma and 46% and 47% in the pineal gland), as well as an advanced acrophase with respect to the basal and control groups [1]. (Sanchez et al., 2008). Tryptophan intake one hour before lights-off increased melatonin levels in both plasma and the pineal gland over a 24-hour period, as well as advancing the peak of its synthesis. The melatonin and serotonin rhythms, which exhibit a close association with the endogenous circadian component of sleep, are attenuated with increasing age, which seems to be linked to sleep alterations in the elderly [4].

Chrononutrition is a field of chronobiology that establishes the principle of consuming foodstuffs at times of the day when they are most useful for improving health as well as biorhythms and physical performance.

In a clinical study done in elderly subjects, consumption of cereals enriched with tryptophan was found to help in the reconsolidation of the sleep-wakefulness cycle and counteracted depression and anxiety in 35 volunteers aged 55−75 years in a simple-blind assay. The intake of cereals containing the higher dose of tryptophan increased sleep efficiency, actual sleep time, and immobile time and decreased total nocturnal activity, sleep fragmentation index, and sleep latency. Urinary levels of 6-sulfatoxymelatonin and 5-hydroxyindoleacetic acid and total urinary antioxidant capacity also increased after tryptophan-enriched cereal ingestion with improvement in anxiety and depression. It is possible that cereals enriched with tryptophan may be useful as a chrononutrition tool for changing the sleep-wakefulness cycle in the elderly [58].

Aging may be associated with decreased levels of serotonin and melatonin in the blood and CNS, and the sleep problems among the elderly may be a consequence of age-related impairment in the biosynthesis and secretion of both these neurotransmitters [4−7]. It has been reported that advanced age causes reduction in the transport of tryptophan across the blood-brain barrier and tryptophan hydroxylase, which catalyzes the rate-limiting step in the biosynthetic pathway of serotonin and melatonin in cells. The resulting reduction of serotonin and melatonin with aging and decreased scavenging ability of ROS produces alterations in the phosphorylation cascade that modulates enzyme activity [5−7]. Distortion in the serotonin level is more common among Western populations, owing to foods that produce less serotonin, whereas a Mediterranean diet that is rich in nuts, seeds, whole grains, and dairy products may be neuroprotective and sleep enhancer [1,2,4]. Novel efficacious therapies are needed for the restoration of the circadian rhythm of the sleep-wakefulness cycle and treatment of chronic insomnia.

Briefly, the serotonergic system is deeply involved in sleep, mood, and cognition functions. It has been shown that age provokes changes in the biosynthesis and secretion of serotonin. Dysfunction in the metabolic pathways of this neurotransmitter can predispose an individual to depression and anxiety disorders, cognitive malfunction, bipolar disorders, and obsessive-compulsive abnormalities [6−8].

Discussion and conclusions

The essential amino acid tryptophan is a pivotal dietary nutrient for neonates, children, and adults. It is required primarily for the synthesis of proteins and several key biomolecules, such as serotonin, melatonin, tryptamine, niacin, quinoline, kynurenic acid, and NAD^+. Tryptophan, serotonin, melatonin, and 3-hydroxyanthranilic acid show antioxidant and antiinflammatory properties, whereas 3-hydroxykynurenine, xanthurenic acid, and quinilic acid can generate oxygen radicals [59]. Kynurenic acid has a neuroprotective role [60]. The presence of an indole ring in tryptophan, serotonin, melatonin, and tryptamine may be responsible for the antioxidant property of these molecules. Tryptophan is necessary for mental health, gut health, bone health, and immune health. The antioxidant and antiinflammatory properties of human milk−derived peptides indicate that the peptides possess moderate degrees of antioxidant and antiinflammatory activities. In the antioxidant in vitro assay, the ORAC values that were found in the presence of tryptophan isolated from human milk were significantly higher ($P < .01$) than those found in whole human milk (see Table 51.2). Overall, studies indicate that the essential amino acid tryptophan and its metabolites have important roles in health and disease, in particular as an antiinflammatory and antioxidant nutrient in breast milk [34]. Breast milk feeding supplemented with tryptophan may prevent or ameliorate some of the conditions that very low birth weight infants experience, such as reduced gut microbiome, GI dysfunction, necrotizing enterocolitis, and oxygen toxicity [61]. The application of matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry milk profiling may be useful to monitor the quality of breast milk and banked milk [62]. Critical functional analysis of the dose-response relationship between donor human milk, preterm formula, and neonatal growth outcomes is an important consideration [63]. It is important to recognize that recent research findings indicate that some of the tryptophan metabolites that are produced in the kynurenine pathway may act as oxidants [64].

Fig. 51.2 shows the dietary sources of tryptophan that influence the level of tissue tryptophan, which is converted to serotonin and melatonin to regulate circadian clock function. Both melatonin and serotonin exhibit a close association with the endogenous circadian component of sleep that is attenuated with increasing age and seems to be linked to sleep alterations in the elderly [58]. Chrononutrition is a field of chronobiology that establishes the principle of consuming foodstuffs at times of the day when they are most useful for improving health as well as biorhythms and physical performance.

Neurodegenerative diseases (e.g., dementia, depression, insomnia, Alzheimer's disease) are quite prevalent globally and adversely affect the quality of life of millions of people. Many pharmacotherapies are used for treating sleep

problems (e.g., chronic insomnia) and depression; these include herbal remedies, dietary interventions, acupuncture and yoga. However, evidence of their effectiveness and safety is lacking. In a clinical study performed with elderly subjects, consumption of cereals enriched with tryptophan was found to help in reconsolidation of the sleep-wakefulness cycle and to counteract depression and anxiety in 35 volunteers aged 55−75 years in a single-blind assay. The intake of cereals containing the higher dose of tryptophan increased sleep efficiency, actual sleep time, and immobile time and decreased total nocturnal activity, sleep fragmentation index, and sleep latency. Urinary 6-sulfatoxymelatonin and 5-hydroxyindoleacetic acid levels and urinary total antioxidant capacity also increased after the ingestion of tryptophan-enriched cereal, with improvement in anxiety and depression. It is possible that cereals enriched with tryptophan may be useful as a chrononutrition tool for alterations in the sleep-wakefulness cycle due to age.

Aging may be associated with a decline in the circulating levels and neuronal synthesis of serotonin and melatonin. The age-related impairment in the synthesis and secretion of these neurotransmitters may cause chronic sleep problems in the elderly [58,65−67]. It has been reported that advanced age impairs the transport of tryptophan across the blood-brain barrier and tryptophan hydroxylase, which is the rate-limiting enzyme in the biosynthesis of both serotonin and melatonin in cells. Age-related oxidative stress appears to cause excessive production of ROS and alterations in the phosphorylation cascade that modulation of enzyme activity [65−67]. Disturbance in the serotonin levels is more common among Western populations, owing to the consumption of foods that produce less serotonin, whereas Mediterranean-type diets that are rich in nuts, seeds, whole grains, omega-3 fatty acids, poultry, and dairy products may be neuroprotective and enhance sleep in older adults [1,2,4]. In brief, the serotonergic system is implicated in sleep, mood, and cognition functions. It has been shown that age also causes changes in the synthesis and secretion of serotonin. Dysfunction in the metabolic pathways of this neurotransmitter can predispose humans to anxiety and depression, cognitive dysfunction, bipolar behavior, and obsessive-compulsive disorders [31,66,67].

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Ziziphus acidojujuba, 87
Ziziphus jujube. *See* Chinese jujube (*Ziziphus jujube*)
Ziziphus mauritiana. *See* Indian jujube (*Ziziphus mauritiana*)

FUNCTIONAL FOODS AND NUTRACEUTICALS IN METABOLIC AND NON-COMMUNICABLE DISEASES

EDITED BY
RAM B. SINGH, SHAW WATANABE AND ADRIAN A. ISAZA

Functional Foods and Nutraceuticals in Metabolic and Non-Communicable Diseases presents strategies for the prevention of non-communicable diseases and undernutrition through the use of functional foods and nutraceuticals.

Research has shown that the use of certain functional foods and nutraceuticals, including spices, herbs, and millets, animal foods and plant foods can play a role in the treatment and prevention of various diseases and in health promotion.

Functional Foods and Nutraceuticals in Metabolic and Non-Communicable Diseases explores epigenetic modulation as a new method for the development of functional foods and functional farming.

Intended for nutritionists, food scientists, and those working in related health science professions, this book contributes to the discussions focused on nutritional transition, globalization, and how to administer foods in the treatment of metabolic syndrome, hypertension, diabetes, heart attacks, neuropsychiatric disorders, bone and joint diseases and carcinogenesis.

Key Features

- Places emphasis on food diversity to provide perfect combinations of nutritional ingredients
- Presents the utility and necessity of functional food production for health promotion
- Offers suggestions to increase functional food production while simultaneously decreasing production costs

Dr. Ram B. Singh is president of the Tsim Tsoum Institute in Krakow, Poland. He's an honorary fellow of the Halberg Chronobiology Centre, a member of the Russian Academy of Medical Sciences, a fellow of the International Academy of Cardiovascular Sciences, and former president and founder of the Indian Society of Hypertension, International College of Cardiology, and International College of Nutrition. He is the editor of the World Heart Journal and former professor of medicine at Subharti Medical College. He has contributed over 500 research papers to peer reviewed journals and has edited seven books.

Dr Shaw Watanabe is the chief editor of the Clinical and Functional Nutriology and the Life Science in Japan. 渡邊 At Present, he is the President of Life Science Promoting Association since 2009. He is also the President of the Society of National Integrated Medicine (2011-Present). He was the President of APCCN 2014 in Tokyo in 2013 and the Chairman of the East Asia Conference on Standardization of Rice Function in Kyoto in 2014. He is the chief editor of the Clinical and Functional Nutriology and the Life Science in Japan. He has published several hundred papers in refreed journals and written book chapters for international books.

Dr Adrian A. Isaza is a Professor of Alternative Medicine at Everglades University, Tampa. He is also a Diplomate of the American Clinical Board of Nutrition, Item writing committee for the American Clinical Board of Nutrition, CLINICAL ATTACHMENT in Palmer College of Chiropractic, Daytona Florida (2014), Registered with American Public health Association. Dr Isaza has contributed to a number of publications having numerous citations.

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