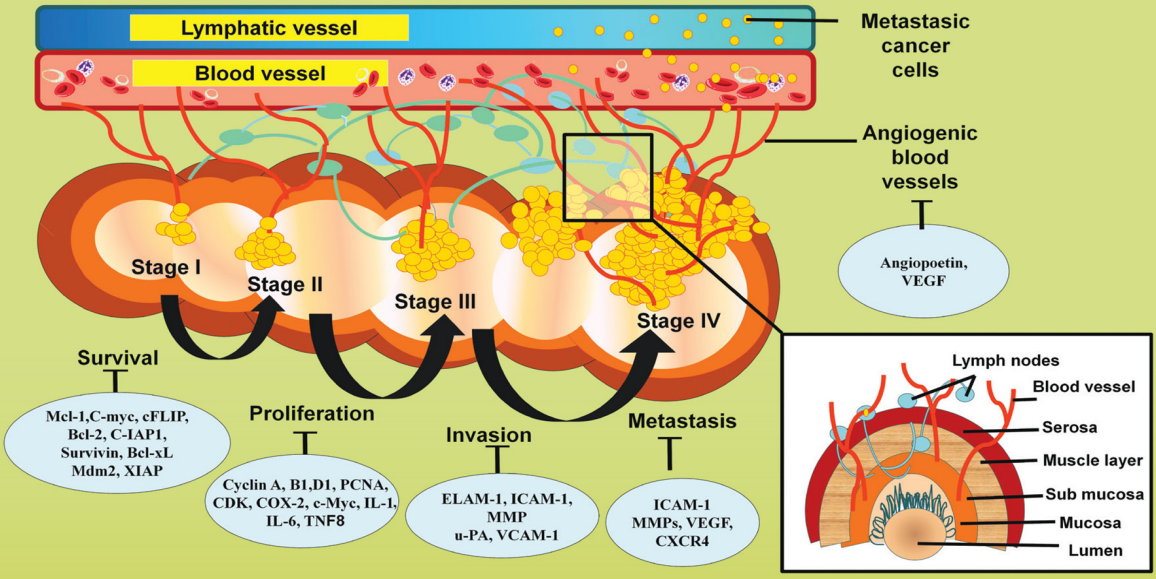
NUTRACEUTICALS Basic Research/Clinical Applications

ADVANCES IN NUTRACEUTICAL APPLICATIONS IN CANCER

RECENT RESEARCH TRENDS AND CLINICAL APPLICATIONS



Edited by
Sheeba Varghese Gupta
Yashwant V. Pathak

CRC Press
Taylor & Francis Group

Advances in Nutraceutical Applications in Cancer

Nutraceuticals: Basic Research and Clinical Applications

Series Editor: Yashwant V. Pathak, PhD

Herbal Bioactives and Food Fortification: Extraction and Formulation, *D. Suresh Kumar*

Nanotechnology in Nutraceuticals: Production to Consumption, *edited by Shampa Sen and Yashwant V. Pathak*

Handbook of Metallonutraceuticals, *edited by Yashwant V. Pathak and Jayant N. Lokhande*

Nutraceuticals and Health: Review of Human Evidence, *edited by Somdat Mahabir and Yashwant V. Pathak*

Marine Nutraceuticals: Prospects and Perspectives, *Se-Kwon Kim*

Nutrigenomics and Nutraceuticals: Clinical Relevance and Disease Prevention, *edited by Yashwant V. Pathak and Ali M. Ardekani*

Food By-Product Based Functional Food Powders, *edited by Özlem Tokuşoğlu*

Flavors for Nutraceuticals and Functional Foods, *M. Selvamuthukumaran and Yashwant V. Pathak*

Antioxidant Nutraceuticals: Preventive and Healthcare Applications, *Chuanhai Cao, Sarvadaman Pathak, and Kiran Patil*

Advances in Nutraceutical Applications in Cancer: Recent Research Trends and Clinical Applications, *edited by Sheeba Varghese Gupta and Yashwant V. Pathak*

For more information about this series, please visit:
https://www.crcpress.com/Nutraceuticals/book-series/CRCNUTBASRES

Advances in Nutraceutical Applications in Cancer

Recent Research Trends and Clinical Applications

Edited by
Sheeba Varghese Gupta
Yashwant V. Pathak

CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Printed on acid-free paper

International Standard Book Number-13: 978-1-1385-9391-6 (Hardback)

Library of Congress Cataloging-in-Publication Data

Names: Gupta, Sheeba Varghese, editor. | Pathak, Yashwant, editor.
Title: Advances in nutraceutical applications in cancer : recent research trends and clinical applications / edited by Sheeba Varghese Gupta and Yashwant V Pathak.
Description: Boca Raton : CRC Press, [2018] | Series: Nutraceuticals : basic research/clinical applications series | Includes bibliographical references and index. | Summary: "This book provides a comprehensive view of historic, current, and technological advances of nutraceuticals' applications in cancer. In case of cancer, it describes how nutraceuticals act as a preventive agent and integrative therapy with the main stream anticancer therapy"-- Provided by publisher.
Identifiers: LCCN 2019023906 (print) | LCCN 2019023907 (ebook) | ISBN 9781138593916 (hardback) | ISBN 9780429489129 (ebook)
Subjects: LCSH: Cancer--Diet therapy. | Functional foods--Therapeutic use. | Cancer--Prevention.
Classification: LCC RC271.D52 A38 2018 (print) | LCC RC271.D52 (ebook) | DDC 616.99/40654--dc23
LC record available at https://lccn.loc.gov/2019023906
LC ebook record available at https://lccn.loc.gov/2019023907

Visit the Taylor & Francis Web site at
http://www.taylorandfrancis.com

and the CRC Press Web site at
http://www.crcpress.com

Contents

Preface

Nutraceuticals are the blended products that possess both nutritional and the medicinal value and formulated in the form of various dosage forms such as tablets, capsules including other dosage forms. These products are designed to help in improving the physical health, immunity, increase longevity, and fight against day-to-day challenges such as stress.

The popularity of nutraceuticals in society as well as healthcare providers has been increasing due to its complimentary role in enhancing the positive effects of medicines and health supplements. There are nutraceutical products with a wide variety of therapeutic values such as immunity booster, antidiabetic, anticancer, antimicrobial, and gastroprotective.

Dietary supplements and nutraceuticals such as vitamin A and D, omega-3, and probiotics are used as part of the cancer treatment as complimenting the main therapy. Regulatory T cells (Tregs) are a heterogeneous T-cell subpopulation that regulates the immune system in various ways. T cells protect us from infections and tumors. Recent report published in *Science* (March 29, Volume 363, issue 6434, 2019, 1395–1396) in which Baixaulli et al. have proposed that reduced nutrient uptake in T cells in high potassium concentrations induces a state of functional caloric restriction. This extends life span, induces autophagy, increases mitochondria quality control, supports optimal stem cell activity, improves immunological functions, and improves malignant transformation. Vodnala et al. showed that elevated potassium triggers a starvation response of T cells with engagement of autophagy and metabolic modeling that involves a reduction of mTOR signaling, activation of the energy sensors, AMPK (adenosine monophosphate-activated protein kinase), and enhanced mitochondrial metabolism (SK Vodnala et al., *Science*, 363, 6434, 1417, 2019). There can be new therapeutic strategies using nutraceuticals, herbal drugs, and minerals to metabolically induce stemness programs in antitumor T cells that enhance cancer immunotherapies.

In this scenario, nutraceuticals and dietary supplements may play a significant role. Valenzuela et al. (*J. Immunol*., April 1, 2009, 182 (1 Supplement) 90.30) tested the nutraceuticals resveratrol and cycloastragenol for their ability to enhance T-cell functions in vitro. In this study, they evaluated the effect of these compounds on cellular proliferative capacity, levels of telomerase activity, surface markers, and cytokine secretion of human CD4 and CD8 T cells. They reported that cycloastragenol moderately increase telomerase activity and proliferative capacity of both CD4 and CD8 T cells. These preliminary results suggest that nutraceuticals inhibit the onset of CD4 and CD8 cellular senescence and can be a good complimentary medicine with anticancer drugs.

Several nutraceuticals have shown to boost the immune responses such as beta-glucans, echinacea, astragalus, selenium, and many more. Emerging clinical studies and research suggests that some plant-based agents may, indeed, impact late-stage cancer, influencing molecular processes corrupted by tumor cells to evade detection, expand clonally, and invade surrounding tissues.

This book is an attempt to collect evidence and related clinical information of application of nutraceuticals to be used in cancer treatment or compliment the cancer treatment. It contains 16 chapters written by experts in related field's and covers many different aspects of the formulation and development of nutraceuticals for cancer applications. It covers efficacy, safety, and toxicological aspects of nutraceuticals. Details about novel drug delivery systems of nutraceuticals as anticancer agents or supplements used for cancer prevention or treatment are also covered.

Nutraceuticals can alter the gut microbiota. Gut microbiome undergoes changes during the disease status and followed by the cancer treatment. Nutraceutical's role in proliferation and prevention of gynecological cancers, nutraceutical's role in proliferation and prevention of prostate cancer, and role of micronutrients in cancer prevention pros and cons, are some of the topics discussed in various chapters in this book.

We think this will be a very good reference book for the readers and scientists and students who are working in the area of nutraceutical applications in cancer treatment.

We express our sincere thanks to Dean College of Pharmacy at USF health to encourage us to work on this project as well as our colleagues at CRC Press who helped us to make this book marketable. If you find any challenges in this book information, kindly do bring it to our notice and we will update it in the next edition.

We also would like to express our sincere thanks Mr Steve Zollo, and others from Taylor and Francis who helped through the publication of this book.

Sheeba Varghese Gupta and Yashwant V. Pathak

Editors

Sheeba Varghese Gupta, MPharm, PhD, is an associate professor, Department of Pharmaceutical Sciences, College of Pharmacy, University of South Florida, Tampa, Florida. She received her PhD at Wayne State University, Michigan, and earned her MS in Pharmaceutical Chemistry from Bharati Vidhya Peeth Poona College of Pharmacy, University of Pune, Maharashtra, India. Her research interests are novel drug delivery systems, improving oral absorption of poorly absorbed drugs, and patient outcomes. She has authored many peer-reviewed publications, book chapters and abstracts.

Dr. **Yashwant V. Pathak** completed his PhD in Pharmaceutical Technology at Nagpur University, India, and EMBA and MS in Conflict Management at Sullivan University. He is professor and associate dean for Faculty Affairs at Taneja College of Pharmacy, University of South Florida. Tampa, Florida. With extensive experience in academia as well as industry, he has more than 200 research publications, including research papers; chapters and reviews; 2 patent and 2 patent application; and 28 edited books published, including 12 books in nanotechnology and 10 in nutraceuticals and drug delivery systems. He has several books in cultural studies and conflict management. He has received several national and international awards. Dr. Pathak was a recipient of Fulbright Senior Scholar award for Indonesia in the year 2016–2017. Dr. Yashwant V. Pathak is also an adjunct professor at Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Contributors

Sadaf Aslam
Division of Infectious Diseases and International Medicine
Department of Internal Medicine
USF Health
Tampa, Florida

Priyanka Bhatt
Department of Pharmaceutical Sciences
College of Pharmacy
University of South Florida
Tampa, Florida

Andréa Burgess
College of Pharmacy
University of South Florida
Tampa, Florida

Beata Casanas
Division of Infectious Diseases and International Medicine
Department of Internal Medicine
USF Health
Tampa, Florida

Anjelika Chatwal
College of Pharmacy
University of South Florida
Tampa, Florida

Brianna Choyce
College of Pharmacy
University of South Florida
Tampa, Florida

Rajiv Dahiya
School of Pharmacy
Faculty of Medical Sciences
The University of the West Indies
St. Augustine, Trinidad & Tobago

Sunita Dahiya
Department of Pharmaceutical Sciences
School of Pharmacy
University of Puerto Rico
San Juan, Puerto Rico

Richa Dayaramani
Tolani Institute of Pharmacy
Adipur, India

Aaishwarya B. Deshmukh
Department of Pharmacology
Shankersinh Vaghela Bapu Institute of Pharmacy
Gandhinagar, India

Sheeba Varghese Gupta
College of Pharmacy
University of South Florida
Tampa, Florida

Rohan Lalani
Department of Pharmacy
Faculty of Pharmacy
The Maharaja Sayajirao University of Baroda
Vadodara, Gujarat, India

Nicholas Micciche
College of Pharmacy
University of South Florida
Tampa, Florida

Bharat Mishra
Department of Pharmacology
Nirmala College of Pharmacy
Muvattupuzha, India

Kimberly Padawer
College of Pharmacy
University of South Florida
Tampa, Florida

Komal Parmar
Department of Pharmaceutics
ROFEL Shri G M Bilakhia College of Pharmacy
Vapi, India

Anita Patel
Nootan Pharmacy College
Sankalchand Patel University
Visnagar, India

Jayvadan K. Patel
Faculty of Pharmacy
Nootan Pharmacy College
Sankalchand Patel University
Visnagar, India

Mayur M. Patel
Department of Pharmaceutics
Institute of Pharmacy
Nirma University
Ahmedabad, India

Yashwant V. Pathak
College of Pharmacy
University of South Florida
Tampa, Florida

Vasudha Pritipaul
College of Pharmacy
University of South Florida
Tampa, Florida

Shruti U. Rawal
Department of Pharmaceutics
Institute of Pharmacy
Nirma University
Ahmedabad, India

Asra Sami
College of Pharmacy
University of South Florida
Tampa, Florida

Donald Sikazwe
Department of Pharmaceutical Sciences
Feik School of Pharmacy
University of the Incarnate Word
San Antonio, Texas

Imran Vhora
Ascension Bioceuticals Inc
Burnaby, Canada

Raghunandan Yendapally
Department of Pharmaceutical Sciences
Feik School of Pharmacy
University of the Incarnate Word
San Antonio, Texas

1 Role of Micronutrients in Cancer Prevention and Intervention—Pros and Cons

Anjelika Chatwal and Yashwant V. Pathak

CONTENTS

1.1 INTRODUCTION

By the end of the twenty-first century, cancer, a noncommunicable disease, will be the leading cause of death among both men and women, surpassing the most common causes: heart disease and stroke. Of roughly 18 million incidences, approximately 9 million will lead to death [1]. With the rising incidences of cancer in both developing and advanced countries, the necessity for alternative types of therapies for prevention and intervention before and during treatments has grown immensely. There have been countless promising theories and hypotheses that have been developed to evaluate the efficiency of altering one's diet to include micronutrients and antioxidants to contribute to the prevention of cancer [2]. While other factors, such as alcohol consumption and smoking, act on cancer amplification, eventually leading to death, it has been suggested that preventing cancer through the diet has accounted for a percentage of those who have cancer [2]. Since any food that a person eats can

have direct impact on their health, patients tend to gravitate toward popular diets, such as the vegan, ketogenic, Paleolithic, and alkaline, that might contribute to their survival [3]. Some believe that combined with general treatments, natural substances can target cells within the body to elicit effects [4].

However, the efficacy of these alternate diets and supplemental treatments has been doubted, as the use of either could promote unrealistic outcomes and properties relating to cancer recovery [3]. Even worse, patients who rely on these diets for an alternative without consulting their physicians can become nutrient deficient, which can further compromise their treatments [3]. The role of adding micronutrients in the diet in order to prevent cancer from developing and becoming malignant has been controversial in cancer research. Most studies regarding this area of research express the need for further experiments to be done in order to establish more concrete conclusions and results about the varying micronutrients that can contribute potential effects on cancer. Some papers suggest that efforts to study the potential treatments for cancer prevention should begin with high-risk groups through different levels of population so that a broader scope is defined [5]. Does implementing these necessary dietary factors truly contribute to preventing diseases such as cancer? We will first need to understand the classification and characteristics of micronutrients to have a better insight of how our bodies utilize and metabolize these factors and what they can potentially do in the cancer mechanisms.

1.1.1 Micronutrient Background

Micronutrients are classified as elements that we cannot synthesize in our bodies [6]. Certain metabolic and biosynthetic pathways in our bodies require a variety of nutrients, antioxidants, and phytochemicals that have properties necessary for these pathways and mechanisms to function properly. What makes micronutrients special is that in order to maintain these processes, our systems only need small amounts for adequate growth and development—hence their name, micronutrients. Antioxidants, on the other hand, are substances that can delay or prevent the oxidation of a substrate when present in low concentrations, in comparison to substrates that are more likely to be oxidized [7]. These are also helpful in preventing more oxidative damages from occurring in the body, as they, themselves, are redox-active substances that can act as catalyzers and active cofactors for enzymes [8]. Some others act as stabilizing proteins and enzyme activators [8].

Since we cannot physically develop these factors in our bodies, we must ingest them through foods that are rich in vitamins A, B12, C, D, and E and various other substances and through supplements [9]. Micronutrients can be found as part of specific substances, such as antioxidant enzymes, which include superoxide dismutase and glutathione peroxidase. In layman's terms, superoxide dismutase includes elements such as manganese, copper, and zinc, while glutathione peroxidase includes selenium [10]. Additionally, phytochemicals, which are described as plant-based nutrients that are not essential for our overall diets, include carotenoids, flavonoids, curcumins, and resveratrol [11]. While these substances may seem far-fetched for the common person, they are actually found in most of the everyday foods. Carotenoids

are typically found in carrots, flavonoids in fruits, wine, green tea, and other dietary factors, and curcumin in turmeric [12].

The various metabolic processes within our bodies can generate chemical errors or toxic by products, such as superoxide, reactive oxygen, reactive nitrogen, or reactive chlorine species [10]. Although some parts of our body systems function by utilizing these reactive species in beneficial ways, like killing bacterial organisms, uncontrolled production of these species can spark the need for substances that act as defenses to protect the body's normal processes from spiraling out of control. Micronutrients, as part of antioxidants, work to recycle, protect against, or remove certain reactive species that build up past their needs [10]. These substances all have their own unique mechanisms of action that work on the cellular processes in order to protect against oxidative and environmental stressors [13]. For instance, selenium deficiencies can contribute to diseases like cancer, indicating that researching its molecular processes is significant in determining how implementing selenium in the diet can help prevent illnesses [14]. Selenoproteins, proteins that contain selenium, have important physiological roles in the body. These are redox-active proteins that have roles of repairing oxidatively damaged proteins, quality control, and protein folding and can act as targets for new therapies for a number of diseases [14].

1.1.2 The Cell Cycle and Tumor Growth

Comprehending how micronutrients affect the cellular processes within our bodies is essential to realizing the role they have in cancer prevention and intervention. Normally, the cells in our bodies undergo cell cycles, in which they grow, replicate their DNA, and divide. However, cancerous cells undergo these cycles without proper signaling pathways and mechanisms that regulate errors and uncontrolled proliferation [15]. The cycle includes four phases as explained below. There are the checkpoints and signaling pathways involving regulatory mechanisms that are meant to prevent unnecessary cell growth and encourage apoptosis of cells that are damaged. If genetic mutations arise, these mechanisms or proteins found at the regulatory checkpoints can malfunction, causing cell proliferation of potential tumor-causing cells [15].

G1—the gap phase, involving cell growth and preparation to synthesize DNA
S—synthesis phase, where the cell synthesizes DNA
G2—second gap phase, involving preparation for division
M—mitosis phase, where cell division finally occurs

The various micronutrients studied are likely to target various regulatory proteins, checkpoints, and signaling pathways that are found within the cell cycle, as well as other metabolic processes, such as glycolysis [16]. For instance, if vitamin A was to impact the cell cycle, it would most likely induce apoptosis or encourage cell differentiation, which would in turn limit cell proliferation [17]. This means that the G1 phase would be affected, as cell growth would shut down. Looking at the micronutrients in this manner, we can assess the ability of these factors and substances to limit tumor growth in individuals, and therefore the most effective ways they can be implemented in research and treatments.

1.2 USE OF MICRONUTRIENTS PROS VS CONS

1.2.1 Accessibility to Micronutrients

An obvious benefit of utilizing micronutrients as supplements to chemotherapy is the fact that they are widely accessible in the market. Vitamins and minerals can be found in varying doses over the counter. In this way, studies that demonstrate how micronutrients are involved in cancer prevention and alleviation, biologically, are significant so that people can understand that, if needed for treatments, these supplements are readily available to them.

With the development of evidence suggesting the powerful anticancer effects that micronutrients and phytochemicals carry through their cell signaling pathways, newer methods of incorporating these into the everyday lives of individuals combatting cancer are being tested. General plans may not have a strong effect for all patients, as they would have differing symptoms and reactions to their treatments. However, creating personalized supplements for patient according to their necessary clinical treatments and needs is a leading goal in terms of utilizing phytochemicals for clinical use [18]. Once the molecular actions of phytochemicals on specific cancer cell targets are proven, the next step of assessing the proper phytochemicals to use as supplemental treatments for each clinical case would introduce the ease of accessing these supplements for the diet. This study, expanding on previous studies of the usefulness of phytochemicals in health, demonstrates how healing supplements can be developed in a personalized manner to make it easier for those who have these illnesses to acquire the nutrients they need to act as anticancer agents. Thus, personalized evaluations based on the evidence are more useful for these kinds of treatments [19].

Apart from micronutrients available in the market as dosed supplements, the necessary vitamins and minerals that are studied in relation to certain types of cancers can be acquired through dietary intake. In fact, the lack of a proper diet can be a risk factor for some cancers, highlighting the significance of micronutrients stemming from a person's diet [20]. The quality of a patient's diet is studied in order to assess how their food intake affects mechanisms of their chemotherapy, if it does at all. Therefore, the accessibility one has to micronutrients, such as vitamins and minerals, is significant, as they can be found in most foods.

For instance, vitamin C is a powerful antioxidant that is commonly found in our everyday lives. Apart from being an antioxidant, vitamin C, also known as ascorbic acid, is classified as a "functional food." Functional foods refer to those that are natural or processed and contain biologically active substances that are proven to have some benefit for chronic illnesses [7]. Most people think of orange juice, since the citrus contains this valuable essence, but there is a variety of foods, including fresh greens, fruits, and vegetables, that allow for more absorption of this vitamin and other vitamins beyond that of just orange juice, especially compared to supplemental pills and tablets. Since this antioxidant is water soluble, it is eliminated quickly and is not able to be stored in our bodies. Aside from this, our bodies are unable to produce this vitamin naturally due to an absent catalyzer, gulonolactone oxidase, for the an enzyme in the last step in the biosynthesis pathway, so incorporating more

vitamin C-rich foods into our diets is the most significant way for us to gain its effects [7]. As mentioned, many foods contain numerous vitamins and minerals, and the best way our bodies can absorb the nutrients from the vitamins is in combination with others. For example, vitamins C and E inhibit oxidation together, and vitamin C helps to reestablish vitamin E levels if they start to decline [7].

1.2.2 Alleviation of Chemotherapy-Induced Symptoms and Influence of Response to Chemotherapeutic Agents

Physicians tend to lean on more tangible therapeutics when it comes to certain diseases, such as cancer. Their primary focus would be to utilize chemotherapy and drugs targeted for the specific kinds of cancers that they see, but newer studies are demonstrating a shift to incorporating micronutrients in diets, which could potentially enhance the efficacy of some of the drugs used in chemotherapeutic treatments and the outcomes of patients. While other factors, such as genetic instability, can affect how tumor cells replicate and proliferate, studies indicate that the intake of vitamins, minerals, certain antioxidants, specific natural phenols, such as resveratrol, and carotenoids, can in some way influence how tumor cells respond to antitumor drugs [20]. For instance, green leafy vegetables and fruits can impact responses, in that they are associated with low levels of cytogenetic damage [20], which occurs in cells when they are exposed to ionizing radiation with changing dose rates [21].

A number of cancer treatments can result in various diseases that affect all parts of one's body. One example is Chemotherapy-Induced Peripheral Neuropathy or CIPN, which is a frequently occurring effect of cancer treatments [22]. Two specific chemotherapy agents, taxane and platinum, are known to be both primary choice treatments and lead to neurological symptoms, such as neuropathies. Apart from the tiring effects of the chemotherapy treatments themselves, these treatments can induce these symptoms of neuropathy, including cognitive function impairments and a worsening of the quality of life [22]. The nerve damage was enhanced due to the low nutrition levels found in patients who were treated with taxane and platinum [22]. However, this study done by Velasco et al. suggests that vitamin E deficiency can be a culprit to the worsening effects of nerve damage after chemotherapy treatments. Results from the blood samples that they took before and after treatments demonstrated that axon regeneration coincides with more vitamin E in the diet, though it is not completely certain how the micronutrients and antioxidants are involved in the nerve-regeneration process.

Other antioxidants have shown to have some effects during chemotherapy, such as selenium, which has been shown to decrease blood toxicity. Antioxidant supplementation effects are not widely known as of yet and have been shown more in short-term rather than long-term studies, but some studies describe how the addition of antioxidants in the diet can decrease adenomas, for example, in patients with colon cancer who do not smoke but are drink alcohol [23].

Moreover, micronutrients and antioxidants are significant for a person's overall health maintenance, even more so for someone who is undergoing chemotherapy treatments. Since chemo can be so detrimental to a person's body, weakening their

immune systems, for instance, it is important that an adequate diet, supplemented with micronutrients, is maintained. Therapies are not as effective and may reduce tolerance, while also increasing the possible adverse effects and complications after treatments [24].

Patients who must receive surgery are also at risk of weight loss and postoperative decline in nutritional status. By admitting nutrition to them preoperatively, physicians can alleviate some of the postoperative changes that might occur and increase their tolerance [25]. As this study by Liu et al. explores, postsurgery in colorectal patients, cytokine responses can change and become detrimental to the body. Inflammatory reactions are more likely to occur in those patients who are poorly nourished before they had their surgery [25]. Intake of some vitamins and minerals, however, can alleviate these inflammatory responses. Having a deficiency of vitamin A, for example is associated with more prominent inflammatory responses, while a deficiency in vitamin D can increase the risk of inflammatory and infectious diseases associated with the immune cells [25]. Additionally, vitamin E is associated with a defect in naïve T cells, while zinc can affect the production of cytokines within the body. More specifically, when zinc supplements are administered, cytokines in plasma respond on a dose-dependent basis [25]. In the cases of malnourishment, a method of providing supplemental nutrients to the body, called total parenteral nutrition (TPN), is utilized. This is a preferred method preoperatively over enteral feedings for extremely malnourished patients who are receiving abdominal surgery. The solution typically includes a fat emulsion, vitamins, and elements that offer a broad range of nutrition to compensate for what the patients were lacking. While this can pose risks, such as infections, pneumothorax, or hemothorax, the amount of energy this method delivers is far greater than other methods that can potentially be used [25].

A study performed by Hansen et al. investigates the relationship between antioxidant consumption and the risk of colorectal cancer for both smokers and nonsmokers. While their findings had a stronger indication for a risk of colorectal cancer in individuals who smoked, little evidence suggested that the consumption of antioxidants or micronutrients posed an effect along with this [26]. It is possible that antioxidants alone might have a greater effect on the risk of this type of cancer, but in combination with numerous years of smoking, it is difficult to determine how helpful the antioxidants and micronutrients are. A separate study, on the other hand, following the relationship between diet and colorectal cancer shows that there is considerable evidence for promising, protective effects of vitamin D, fruits, vegetables, and folate, while red and processed meats are associated with increasing the risk for the disease [27]. The interaction of nutrients and foods within the body can also create an effect that can influence cancer cell generation through effects on inflammation and overnutrition [27].

A specific study by Tayyem et al. involving micronutrient consumption among Jordinians and the risk of colorectal cancer, 169 participants previously diagnosed with colorectal cancer were tested for the association between total energy and nutrient intake and the potential risk for the development of colorectal cancer. The results demonstrated that total energy ingestion, along with increased saturated fat, cholesterol, and sodium, was significantly correlated with a higher risk of developing the disease [28]. On the other hand, vitamin E and caffeine showed a more protective outcome against colorectal cancer [28].

The mangosteen fruit, widely popular in Asian countries, contains gamma-mangostin, a micronutrient. Evidence was found that showcased antiinflammatory and antibrain tumor actions of the gamma-mangostin micronutrient. A study by Chang and Yang expanded on this development further by researching the relationship between apoptosis and colorectal adenocarcinoma cells, made possible by the gamma-mangostin. The viability of this micronutrient was tested on the HT29 cells specific to the colorectal adenocarcinoma, showing that when treated with differing concentrations of the micronutrient, the HT29 cells experienced a substantial concentration-dependent inhibition in viability [29]. Due to the promising findings from this study regarding the decreased cell viability due to the apoptotic effects of gamma-mangostin and the inhibition of the colorectal adenocarcinoma cell proliferation, there seems to be enough evidence for developing anticancer drugs using xanthones and micronutrients that have similar properties as this one. This evidence is substantiated by previous discoveries of the antiinflammatory characteristics of the mangosteen plant as well [29].

When studying cancer prevention and the role of micronutrients, it is important to understand the mechanisms involved of specific transcriptional factors. Nuclear factor-like 2 boosts antioxidant enzyme and phase-2-detoxifying enzyme levels through mechanisms that could help to reduce oxidative stress and chronic inflammation that contribute to the development of carcinogenesis [30]. The significance of this involves the actions of antioxidant enzymes and phase-2-detoxifying enzymes. The former works to abolish the work of free radicals through catalysis, while the latter changes carcinogens to risk-free substances that are able to be eliminated from the body [30]. However, the enzymes cannot work alone, as their actions are not substantial enough on their own to produce an effect against highly oxidative environments. Simultaneous additions of dietary antioxidants are necessary to help activate the transcriptional factor that enhances these enzymes [30].

Lycopene, a particular kind of carotenoid found in tomatoes, also regulates transcriptional factors in a way that is involved with cancer prevention, specifically in terms of sex hormone-dependent cancers, like breast cancer, which is estrogen-dependent, and androgen-dependent prostate cancer [31]. The study found that, in general, a high intake of vegetables and carotenoids were associated with a lower risk for breast cancer, linked to the limitation of estrogen activity, since higher levels of estrogen contributed to increased breast cancer incidence [31]. Since it was shown that carotenoids impede on estrogen signaling and cell proliferation, lycopene and other tomato-containing foods are useful in obstructing tumor growth in these tissues [31].

Moreover, in terms of prostate cancer, the most common cancer found in males in the United States, androgens contribute to the advancement of this disease, and treatment involves blocking the action of this hormone or castrating it [31]. Lycopene also slowed the development of the disease in a study, meaning these compounds help to regulate carcinogenesis in the prostate.

A mixture of natural substances, such as quercetin, curcumin, green tea, cruciferex, and resveratrol, showed a pronounced inhibition of growth head and neck squamous cell carcinoma and cell proliferation [32]. This further enhances the idea that combinations of substances seem to combat the illnesses more effectively than

when individually supplied to the body, as also demonstrated by the combination of vitamin A and beta-carotene for lung cancer. Research involving the alpha-tocopherol, beta-carotene study also explores the involvement of vitamin D, as the lipid metabolites of this compound provide evidence that serum 25-hydroxy vitamin D is associated with certain health benefits, particularly with cancer, though results are mixed [33].

Retinoids in general have been shown to decrease and go against the typical process of detrimental transformation in epithelial tissues. In terms of skin squamous cell carcinomas and cervical cancer, a specific retinoic acid, 1,3-*cis*-retinoic acid, demonstrated the most prominent results when utilized in treatment [34]. Moreover, this same study researched a number of factors with their association to cancer and carcinogenesis. It was found that a typical outcome of developing infections had a significant negative correlation with nutritional status, influencing the idea of recommending nutritional support for children with cancer [34].

1.2.3 Overconsumption of Nutrients Affecting Cancer Prognosis and Mortality

Just as is common with any other drugs or prescription medications, treatments involving supplements of micronutrients can have associated risks. Depending on the type of cancer an individual has and the specific micronutrient that works best for them, overconsumption of these nutrients can interfere with the normal processes of the body, leading to worsening effects of the cancer. Furthermore, other factors, such as genetic instability and variability, aging, and overall health, can come into play when assessing how effective micronutrients and antioxidants are in a body with a chronic illness, like cancer.

Aging, for instance, increases the vulnerability of the body, making it more difficult for substances and supplements, such as micronutrients, to combat the disruptive actions occurring on our bodies. The sensory, physical, and psychosocial aspects that are altered in the body as the aging process occurs creates an environment that is more susceptible to damage and risk for increasing diseases [35]. Incorporating antioxidants and micronutrients in the diet before the aging process is amplified ensures that these nutrients are absorbed more efficiently and are actually being metabolized effectively for our bodies to utilize, whereas in bodies that are older, the processes can be slower and less effective [36].

In this way, having a middle ground in terms of the amount of micronutrient that is ingested during treatment is a significant aspect to understand when considering these supplemental nutrients. There are optimal levels at which these substances are more useful than detrimental for the body, and several studies have described that, at higher than optimal levels, the body's normal functions can deteriorate. As we explored, some antioxidants and micronutrients are protective, in that they limit the amount of oxidation occurring on substrates. However, even ingesting too much of any vitamin or mineral, especially with addition of supplementation and fortified foods on top of dietary intake, can leave a lasting impact on the functions of our bodies [37]. Guidelines and safe limits for the optimal amounts of the vitamins and minerals are provided by the Institute of Medicine.

Although more studies and research need to confirm, several studies have demonstrated positive associations between various types of cancers and the intake of differing micronutrients associated with those cancers. For instance, micronutrients seem to have some kind of positive impact on lung cancer, but more studies need to validate these findings further, as oxidative stress and physical activity can affect the outcomes [38]. Primarily, there have been mixed results in terms of the efficacy of micronutrients in decreasing the risk of cancer or having a definitive protective role, but there are promising findings that indicate statistically significant results in terms of reductions of outcomes [39]. The amount and type of micronutrient changes the effect on the cancer and its mechanisms on the body. One study from the American Society for Nutrition found that vitamin A had a 16% increased risk for cancer, while calcium supplements showed a decreased risk of cancer and no effect was shown for selenium, zinc, vitamin D, beta-carotene, vitamin C, folic acid, and vitamin K [40].

In patients with the highest intake of phosphorus and lowest intake of vitamin D, researchers found patients to have higher odds of getting bladder cancer [41]. Due to the processes of the bladder system, nutrients and dietary factors are metabolized and broken down in the urinary tract. Therefore, these micronutrients or their metabolites can potentially affect carcinogenesis, in that they can act as either inhibitory or promotive factors [41]. An important aspect of this study to consider is the idea that micronutrients such as calcium, phosphorus, magnesium, and vitamin D metabolically work in conjunction with each other and are derived from similar food sources. Results for intake of micronutrients separately did not show statistically significant results. However, when studied together, as metabolically interactive minerals, results showed statistically significant outcomes for the odds of bladder cancer [41].

Past observational studies and randomized clinical trials show opposing results in terms of whether antioxidants and micronutrient supplements actually make a difference in prolonging life and improving the overall health of patients. However, more recent studies describe the more lasting effects of supplements like these. Vitamins A and E and beta-carotene might have an adverse effect, as they are linked to an increased mortality rate [42]. It seems that a noteworthy key to supplementing diets with antioxidants and micronutrients is that they should arise from natural sources, and not pills or tablets. Ingesting antioxidant- and micronutrient-rich foods tends to show better effects, as they are maintained in a balanced diet, while supplemental pills can come in unmanageable doses that our bodies cannot process adequately [42].

While beta-carotene has mostly been shown to have a positive effect on cancer prevention, especially in terms of the effect on reactive oxidative species (ROS), in terms of head and neck cancer, preventative intake of beta-carotene poses an increased risk for cancer development [43]. Specifically, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trail (ATBC) provided the data that showed an increased incidence of lung cancer in men who smoke who were also taking alpha-tocopherol and beta-carotene compared to those who were getting placebo administrations. Beyond this, combining vitamin A and beta-carotene showed an increased risk of lung cancer for both men and women [43]. A distinct, 18-month study involving alpha-tocopherol and beta-carotene, specifically with ATBC, showed that in terms of lung cancer, alpha-tocopherol did not have an effect, while beta-carotene increased the cancer incidence by just shy of 20% during the intervention period [44]. The difference

was eliminated after the postintervention period began [44]. This chapter also studied the combination of vitamin A and beta-carotene and its effect on lung cancer. There was an approximate 30% increase of a lung cancer incidence, and it was found that the beta-carotene contributed to the elevated growth of preclinical tumors through supplements and the fact that this substance could improve the lung's function, allowing for better inhalation of the carcinogens from smoking [44].

The combination of beta-carotene and vitamin A was tested with prostate cancer as well, as previous studies showed inconsistencies in this area. Stemming from the Prostate Cancer Prevention Trial, serum retinol and carotenoid levels were tested against low- and high-grade risk for prostate cancer [45]. A positive correlation was discovered between serum retinol and high-grade prostate cancer, along with serum alpha-carotene and total prostate cancer [45].

A mixture of natural substances, such as quercetin, curcumin, green tea, cruciferex, and resveratrol, showed a pronounced inhibition of growth head and neck squamous cell carcinoma and cell proliferation [32]. This further enhances the idea that combinations of substances seem to combat the illnesses more effectively than when individually supplied to the body, as also demonstrated by the combination of vitamin A and beta-carotene for lung cancer. Research involving the Alpha-Tocopherol, Beta-Carotene study also explores the involvement of vitamin D, as the lipid metabolites of this compound provide evidence that serum 25-hydroxy vitamin D is associated with certain health benefits, particularly with cancer, though results are mixed [33].

In a separate study by Brasky et al., an association between lung cancer and long-term (10 years) supplemental use of vitamin B was investigated. Their hypothesis suggested that the long-term intake would disturb the natural balance of the vitamins in the body, leading to a substantial consequence on the cellular mechanisms and physiology of the cells involved, leading to potential cancer cell generation [46]. The baseline characteristics of the participants with and without lung cancer were assessed to compare to their characteristics after the long-term supplementation. Based on the results, there was an approximate 30% increase in the risk for lung cancer amongst men who took supplements of vitamins B6 and B12, while an association between women and a risk for lung cancer was not found [46]. There was also a more significant effect on men who were also smokers, as the mutated cells that were also present could be amplified from the high doses of B vitamins that would promote cell growth and carcinogenesis [46]. This study further describes how the mechanisms of B vitamins should, in theory, contribute to the prevention of cancer through carbon metabolism, but this is only beneficial when the intake is in the recommended levels and when patients are deficient of the vitamins. The negative effects, such as DNA damage and carcinogenesis, are more pronounced when intake exceeds the recommended amounts [46].

1.2.4 Specific Micronutrients Affect Certain Cancers

A drawback of utilizing micronutrients in treatments is that, while supported by evidence of beneficial characteristics, they can be specific to certain cancers, and may affect one type of cancer differently than another. This is why studying these

micronutrients in regards to a variety of cancers can allow physicians to understand which ones have a better overall outcome for their patients and which ones may be potentially more harmful in combination with the chemotherapeutic agents. A full dietary assessment is necessary to evaluate what kinds of food patients are consuming, how these foods are processed and cooked, and how the chemicals in these foods can affect aspects of treatments. For example, in the case of bladder cancer, it was found that the deficiency of vitamin B12, found in meat, poultry, milk products, eggs, and fish products, results in a risk for cancer. Since this micronutrient is necessary for the methylation of DNA, a deficiency might lead to uracil coming into the DNA and the ensuing chromosomal breakage, which can be avoided with adequate amount of vitamin B12 [47].

Similarly, folate, a type of B vitamin, is required for DNA methylation as well, and can be found in citrus, green vegetables, and liver. Since this micronutrient is involved in one-carbon reactions during DNA synthesis and methylation, a deficiency could promote cancer growth in normal tissue, specifically ovarian cancer in this study. However, it was also found that having too much folate in the body could also lead to adverse effects, such as the development of tumors or a decline in the survival rate after the cancer has already been established [48].

In studies involving lung cancer, there have been repeated studies that show fruits and vegetables defending against the harmful effects [49]. Specifically, the beta-carotene that can be found within these food sources can have both beneficial and harmful effects on lung cancer.

A study performed by O'Grady et al. explores the correlations between a variety of micronutrients and incidences of thyroid cancer. While there was no relationship found between selenium intake and the incidence of total thyroid cancer, there was a positive correlation found between an increasing intake of vitamin C and the risk of thyroid cancer or specific subtypes, particularly follicular and papillary [50]. Vitamin C tends to be associated with the improvement and mediation of unusual instances in terms of thyroid hormones. Additionally, no evidence of associations were observed among the risk for thyroid cancer and a number of other vitamins and minerals, such as calcium, vitamin E, vitamin D, folate, magnesium, and zinc [50]. This study, in particular, demonstrates the importance of the idea that micronutrients can affect cancers in diverse manners, as selenium, normally shown to have a preventative effect on most cancers, appears to have less of an effect on thyroid cancer and vitamin C intake tends to have both positive and negative correlations with thyroid cancer. Selenium actually aids in producing thyroid hormones and ensures the appropriate functions of these hormones, while also contributing its antioxidant effects [50].

In terms of breast cancer, the relationship between this specific disease and circulating levels of folic acid within the blood has been frequently studied, only to lead to inconclusive results. Aside from this, folate was perceived to have a preventative effect, and increased intake was associated with a lowered risk of having estrogen receptor negative breast cancer in premenopausal women [51]. Moreover, having higher plasma levels of vitamin B6 and riboflavin proved beneficial in combatting a risk of breast cancer for premenopausal women, while vitamin D allowed for lessened recurrence [51].

Although not studied thoroughly yet, some evidence suggests that the consumption of soya through the diet can have preventative effects for patients with triple negative breast cancer. The mechanism works on increasing the expression of tumor-suppressing genes, while decreasing expression of oncogenes [51]. More extensive research regarding this finding is necessary, but it does indicate that this specific food can have a protective measure against the risk for triple negative breast cancer.

Bladder cancer, developed from risk factors like smoking and the environment, has its own associated vitamins, particularly vitamins C, D, and E, investigated by Chen et al. in a study of close to 200,000 participants. This group studied three different focuses to determine the risk of bladder cancer in terms of the type of administration or delivery of the vitamins: diet with supplementation, supplementation only, or diet without supplementation. The background of this particular study suggested that vitamins C, D, and E have some individual protective effects against tumor development. Vitamin D supposedly inhibits the multiplication of cells and encourages apoptosis in human tumor cells from the bladder in in vitro experiments [52]. Vitamins C and E, as mentioned previously, tend to have better effects in combination. They protect against the development of cancer cells through their antioxidant properties [52]. Contingent on dose-dependent analysis, there was no association found between vitamin C and a risk for bladder cancer, while vitamins D and E from the diet had inverse relationships with the risk of bladder cancer, with an even stronger association among smokers. Conversely, γ-tocopherol, a prominent form of vitamin E found in plant seeds had a positive association with the risk of bladder cancer [52], as well as with lung, colon, prostate, and mammary [53]. Studies show that the gamma-tocopherol acts by trapping reactive oxygen species and creating "side-chain degradation products" that keep specific ring structure together [53].

While vitamin E had a more beneficial influence in the previous study, a few other findings suggest more variability when it comes to the vitamin E compounds. While a majority of vitamin E compounds have antitumorigenic properties for some cancers, such as prostate in this case, controlled trials have shown differing results. A Selenium and Vitamin E Cancer Prevention Trial (SELECT) explored the effects of selenium and vitamin E in respect to prostate cancer [54]. The trial demonstrated that there was a 17% higher incidence of prostate cancer in men who had these micronutrients supplemented daily compared to those who received a placebo [54]. Additional studies found no effect from administered drugs every other day while vitamin E indicated a reduced risk for prostate cancer, mainly among those who smoke. These trials illustrate that vitamins and minerals have varying effects; they can be both synergistic or antagonistic depending on the type of cancer they are associated with and the dosage given [54]. The results of the SELECT trial revealed a higher incidence of prostate cancer from supplemented alpha-tocopherol acetate, a compound of vitamin E, and the men with the highest level of plasma alpha-tocopherol were more likely to be diagnosed with prostate cancer with a selenium supplement [54]. High calcium doses on a daily basis also pose a risk for developing prostate cancer in a similar manner [55].

As mentioned previously, reactive oxygen species and oxidative stress are both factors in damaging cells. Skin cells are privy to these dangers, and UV exposure is a leading cause of skin cancer development, aside from other factors like genetics, as it

influences direct DNA oxidation and the formation of free radicals that can have lasting effects on the body despite their ability to recycle quickly [56]. These damaging effects can be repaired by the cells, themselves. The reactive oxygen species which are formed in the skin due to the oxidative stress is greater than the ability for the antioxidants to protect the body against these reactive oxidative species. Therefore, limiting the amount of UV exposure and increasing the amount of antioxidant intake can contribute to reducing the damage from oxidative stress [56]. Melanoma, basal cell carcinoma, and squamous cell carcinoma are the main types of skin cancers, which can be prevented by repair of damaged skin cells through endogenous antioxidants and antioxidants originating from the diet [56].

Several of the vitamins and antioxidants we have discussed for other types of cancers are relevant in terms of skin cancer as well. However, not all of these showed clear beneficial results for combatting the negative effects of UV exposure and other environmental dangers to skin cells. Vitamin C supplements taken for 8 weeks showed increased vitamin C content in the plasma and skin, with a reduction in the skin malonaldehyde amount, glutathione, and protein thiols [56]. This proves that vitamin C has a contradictory effect on the cells, as it was shown to increase collagen production, defend the body against UVA and UVB damage, and alleviate pigmentation and inflammation [56]. Vitamin E can get depleted from UV rays, which is one of the earliest signs of oxidative stress. A study indicated that treating with tocopherol can lead to shielding the cells from free radical damage and increased protection by increasing epidermal thickness [56]. However, topical application is not immune to UV rays as the alpha-tocopherol is decreased and its defenses are declined by the UVB rays [56].

Beyond these vitamins, beta-carotene, retinoids, coenzyme Q10, glutathione, and green tea all have an impact on skin cell damage. Coenzyme Q10 was shown to protect against cell death while also helping create the building blocks for dermal and epidermal cells [56]. In this case, the supplemental additions of these antioxidants need to exceed the amount of UV damage in order to have a worthy reverse on the effect on the skin cell damage already done. Folate is an additional target for cancer preventative agents, as it offers necessary factors and precursors for DNA repair and replication [57]. Folate also allows for control of gene expression by promoting the generation of methyl groups and was shown to have an involvement in the amplified risk of skin cancers for those who have low melanin pigmentations in areas of high UV exposures [57]. From studies that have already conducted on folate and skin cancers, the potential for folate deficiencies to contribute to the rising risk of skin cancer is evident, as there is evidence of topical application in helping prevent cancer development [57].

1.3 CONCLUSIONS

Alongside typical factors, such as genetic instability, diet plays a major role in cancer prevention and management. Specifically, micronutrients, elements that our bodies cannot synthesize on their own but require in small amounts, have been shown to assist in important cellular and biosynthetic processes. Antioxidants and phytochemicals are additional substances that our bodies utilize to limit the amount of oxidative stress that we might encounter, which can harm pathways, ultimately disrupting the normal functions.

These significant elements are ingested through our diets, making diet an extremely important factor for cancer patients to focus on. They can be found in fruits, vegetables, juices, teas, plants, and wine, among other foods. Therefore, having a balanced and well-maintained diet is a noteworthy topic that physicians can discuss as they assess their patients. The balance of these substances allows for proper functioning of the cell cycle, through each step and checkpoint, along with the appropriate actions of regulatory proteins. Some micronutrients, for example, can act on the cell cycle by inducing apoptosis of cells, which would limit the growth of malignant tumors.

It was found that most vitamin deficiencies tend to cause worsening side effects and symptoms of associated cancers, which led to the assessment that additional supplementation of these vitamins, such as vitamin E for chemotherapy-induced peripheral neuropathy, can repair some of the damage that was amplified by the deficiency. Vitamins A, B, C, and D also play important roles in maintaining prognoses postsurgery and reducing inflammation that could be typical in cancer treatments. Administering these nutrients with proper timing can help to avoid malnutrition and inflammation that might occur due to the fact that there is not enough baseline nutrients available for the body to utilize for its biosynthetic pathways when fighting against the tumors.

However, it was suggested that while micronutrients tend to be more helpful than not, the overconsumption of these substances can introduce adverse effects within the body, that coincide with normal aging processes, genetic instability, and deterioration of the body's normal functions. High intakes of phosphorus and vitamin D are associated with an increased risk for bladder cancer, while higher ingestion of vitamin A leads to an increased risk for cancer in general. Furthermore, combination studies were done to showcase the effects of combining certain elements versus administering them individually. In some cases, introducing another substance while administering one can augment its negative effects on the body, but in other cases, combing two substances amplifies the beneficial factors of each substance. Multiple elements can also affect cancer cells, as shown with skin cancer.

By understanding the specific mechanistic actions of these micronutrients with regard to how cancer cells develop through their cell cycles, we can analyze which specific vitamins are more likely to help in the prevention of cancer cell growth in general, and also which vitamins, in particular, target certain types of cancers. Vitamin B tends to work against DNA methylation in ovarian cancer, for instance, while vitamin D acts on cell proliferation in bladder cancer. However, these vitamins can also be combined with others to act on other cancers, while individually, they are more active. In this way, the micronutrients have specific mechanisms of action on the cellular processes, but work differently according to diverse illnesses, leading to little clarity [58]. Understanding how these micronutrients function is the key to incorporating them into further studies and treatments for cancer prevention and understanding the associated benefits and negative effects.

1.4 FUTURE TRENDS

With all this information presented, it is clear to note that more studies involving the use of micronutrients in cancer prevention need to be performed. While the functions of micronutrients in terms of cellular and biosynthetic processes have been evaluated

for some time, incorporating these findings into preventative therapies and treatments for cancer requires more concrete evidence. The distinctions of involvement for the micronutrients and substances discussed are unclear, since at some points certain vitamins can lead to apoptosis, while in other cases these same vitamins can cause tumor cell proliferation.

Future studies should include the micronutrient intake regulations that are established so that there is a reference of what the typical limit is. Without this information, it can be uncertain how much of these micronutrients is "too much" in terms of damaging cell processes and functions. Additionally, more conjunctive studies should be assessed, as they seem to be promising in terms of the results that were shown for combatting the risk for certain cancers. It was shown that skin cancer cells are affected by multiple elements, such as vitamin C, coenzyme Q10, retinoids, glutathione, beta-carotene, and green tea. Further studies should expand on this idea for other kinds of cancers by evaluating how multiple substances can contribute or have an effect. Additionally, since people are looking toward trending, natural food items, such as turmeric, teas, and superfoods, more research might be helpful to showcase the effects of the incorporation of these foods in cancer prevention. Lastly, larger sample sizes are necessary in order to eliminate any kind of recall bias when it comes to patients remembering their own dietary intake.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*. 2018;68(6):394–424. doi:10.3322/caac.21492.
2. Hennekens CH. Micronutrients and cancer prevention. *New England Journal of Medicine*. 1986;315(20):1288–1289. doi:10.1056/nejm198611133152009.
3. Zick SM, Snyder D, Abrams DI, Pros and cons of dietary strategies popular among cancer patients. *Integrative Oncology*. 2018;32(11).
4. Sharanova NE, Vasil'ev AV. Postgenomic properties of natural micronutrients. *Bulletin of Experimental Biology and Medicine*. 2018;166(1):107–117. doi:10.1007/s10517-018-4298-0.
5. Stewart BW, Bray F, Forman D, Ohgaki H, Straif K, Ullrich A, Wild CP. Cancer prevention as part of precision medicine: 'Plenty to be done'. *Carcinogenesis*. 2016;37(1):2–9. doi:10.1093/carcin/bgv166.
6. Opara EC, Rockway SW. Antioxidants and micronutrients. Disease-a-month. 2006;52(4):151–163. doi:10.1016/j.disamonth.2006.05.002.
7. Pacier CM, Danik M. Vitamin C: Optimal dosages, supplementation and use in disease prevention. *Function Foods in Health and Disease*. 2015;5(3):89–107.
8. Hänsch R, Mendel RR. Physiological functions of mineral micronutrients (Cu, Zn, Mn, Fe, Ni, Mo, B, Cl). *Current Opinion in Plant Biology*. 2009;12(3):259–266. doi:10.1016/j.pbi.2009.05.006.
9. Zhai T, Li S, Hu W, Li D, Leng S. Potential micronutrients and phytochemicals against the pathogenesis of chronic obstructive pulmonary disease and lung cancer. *Nutrients*. 2018;10(7):813. doi:10.3390/nu10070813.
10. Evans P, Halliwell B. Micronutrients: Oxidant/antioxidant status. *British Journal of Nutrition*. 2001;85(S2):S67–S74. doi:10.1049/BJN2000296.

11. Mathiesen S, Justesen US, Von Luttichau HR, Hansen AB. Genotyping of CYP2B6 and therapeutic drug monitoring in an HIV-infected patient with high efavirenz plasma concentrations and severe CNS side-effects. *Scandinavian Journal of Infectious Disease*. 2006;38(8):733–735. doi:10.1080/00365540500504109.
12. Torno MS, Witt MD, Saitoh A, Fletcher CV. Successful use of reduced-dose efavirenz in a patient with human immunodeficiency virus infection: Case report and review of the literature. *Pharmacotherapy*. 2008;28(6):782–787. doi:10.1592/phco.28.6.782.
13. Seifried RM, Harrison E, Seifried HE. Chapter 16—Antioxidants in health and disease. In: Coulston AM, Boushey CJ, Ferruzzi MG, Delahanty LM, editors. *Nutrition in the Prevention and Treatment of Disease*, 4th edition. Cambridge, MA: Academic Press, 2017, pp. 321–346.
14. Labunskyy VM, Hatfield DL, Gladyshev VN. Selenoproteins: Molecular pathways and physiological roles. *Physiological Reviews*. 2014;94(3):739–777. doi:10.1152/physrev.00039.2013.
15. Cyclacel. Cell Cycle in Cancer [cited 2018]. Available from: https://www.cyclacel.com/research_science_cell-cycle.shtml.
16. Ren J-G, Seth P, Ye H, Guo K, Hanai J-I, Husain Z, Sukhatme VP. Citrate suppresses tumor growth in multiple models through inhibition of glycolysis, the tricarboxylic acid cycle and the IGF-1R pathway. *Scientific Reports*. 2017;7(1):4537. doi:10.1038/s41598-017-04626-4.
17. Mondul AM, Weinstein SJ, Albanes D. Vitamins, metabolomics, and prostate cancer. *World Journal of Urology*. 2017;35(6):883–893. doi:10.1007/s00345-016-1878-3.
18. González-Vallinas M, González-Castejón M, Rodríguez-Casado A, Ramírez de Molina A. Dietary phytochemicals in cancer prevention and therapy: A complementary approach with promising perspectives. *Nutrition Reviews*. 2013;71(9):585–599. doi:10.1111/nure.12051.
19. Moyer VA. Risk assessment, genetic counseling, and genetic testing for BRCA-Related cancer in women: U.S. Preventive Services Task Force Recommendation Statement. *Annals of Internal Medicine*. 2014;160(4):271–281.
20. Paz MFCJ, Gomes Júnior AL, de Alencar MVOB. et al. Effect of diets, familial history, and alternative therapies on genomic instability of breast cancer patients. *Applied Biochemistry and Biotechnology*. 2018. doi:10.1007/s12010-018-2918-9.
21. Brehwens K, Staaf E, Haghdoost S, González AJ, Wojcik A. Cytogenetic damage in cells exposed to ionizing radiation under conditions of a changing dose rate: SPIE, *Radiation Research*; 2010. 7 p.
22. Velasco R, Santos C, Soler G, Gil-Gil M, Pernas S, Galan M, Palmero R, Bruna J. Serum micronutrients and prealbumin during development and recovery of chemotherapy-induced peripheral neuropathy. *Journal of the Peripheral Nervous System*. 2016;21(3):134–141. doi:10.1111/jns.12177.
23. Harvie M. Nutritional supplements and cancer: Potential benefits and proven harms. *2014 ASCO Annual Meeting 2014*.
24. Gröber U, Holzhauer P, Kisters K, Holick M, Adamietz I. Micronutrients in oncological intervention. *Nutrients*. 2016;8(3):163. doi:10.3390/nu8030163.
25. Liu M-Y, Tang H-C, Hu S-H, Yang H-L, Chang S-J. Influence of preoperative peripheral parenteral nutrition with micronutrients after colorectal cancer patients. *BioMed Research International*. 2015;2015:6. doi:10.1155/2015/535431.
26. Hansen RD, Albieri V, Tjønneland A, Overvad K, Andersen KK, Raaschou–Nielsen O. Effects of smoking and antioxidant micronutrients on risk of colorectal cancer. *Clinical Gastroenterology and Hepatology*. 2013;11(4):406–415.e3. doi:10.1016/j.cgh.2012.10.039.
27. Song M, Garrett WS, Chan AT. Nutrients, foods, and colorectal cancer prevention. *Gastroenterology*. 2015;148(6):1244–1260.e16. doi:10.1053/j.gastro.2014.12.035.

28. Tayyem R, Bawadi H, Shehadah I, Abu-Mweis S, Agraib L, Bani-Hani K, Al-Jaberi T, Al-Nusairr M, Heath D. Macro- and micronutrients consumption and the risk for colorectal cancer among Jordanians. *Nutrients*. 2015;7(3):1769. doi:10.3390/nu7031769.
29. Chang H-F, Yang L-L. Gamma-Mangostin, a micronutrient of mangosteen fruit, induces apoptosis in human colon cancer cells. *Molecules*. 2012;17(7):8010. doi:10.3390/molecules17078010.
30. Prasad KN. Simultaneous activation of Nrf2 and elevation of dietary and endogenous antioxidant chemicals for cancer prevention in humans. *Journal of the American College of Nutrition*. 2016;35(2):175–184. doi:10.1080/07315724.2014.1003419.
31. Sharoni Y, Linnewiel-Hermoni K, Zango G, Khanin M, Salman H, Veprik A, Danilenko M, Levy J. The role of lycopene and its derivatives in the regulation of transcription systems: Implications for cancer prevention. *The American Journal of Clinical Nutrition*. 2012;96(5):1173S–1178S. doi:10.3945/ajcn.112.034645.
32. Niedzwiecki A, Roomi M, Kalinovsky T, Rath M. Anticancer efficacy of polyphenols and their combinations. *Nutrients*. 2016;8(9):552. doi:10.3390/nu8090552.
33. Nelson SM, Panagiotou OA, Anic GM, Mondul AM, Männistö S, Weinstein SJ, Albanes D. Metabolomics analysis of serum 25-hydroxy-vitamin D in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study. *International Journal of Epidemiology*. 2016;45(5):1458–1468. doi:10.1093/ije/dyw148.
34. Pal D, Banerjee S, Ghosh AK. Dietary-induced cancer prevention: An expanding research arena of emerging diet related to healthcare system. *Journal of Advanced Pharmaceutical Technology & Research*. 2012;3(1):16–24. doi:10.4103/2231-4040.93561.
35. Jain R, Dotan E. Nutrition and aging: A practicing oncologist's perspective. *Current Oncology Reports*. 2017;19(11):71. doi:10.1007/s11912-017-0630-5.
36. Bogden JD, Louria DB. Micronutrients and immunity in older people. In: Bendich A, Deckelbaum RJ, editors. *Preventive Nutrition: The Comprehensive Guide for Health Professionals*. Cham, Switzerland: Springer International Publishing; 2015. pp. 531–550.
37. Datta M, Vitolins MZ. Food fortification and supplement use—Are there health implications? *Critical Reviews in Food Science and Nutrition*. 2016;56(13):2149–2159. doi:10.1080/10408398.2013.818527.
38. Filaire E, Dupuis C, Galvaing G, Aubreton S, Laurent H, Richard R, Filaire M. Lung cancer: What are the links with oxidative stress, physical activity and nutrition. *Lung Cancer*. 2013;82(3):383–389. doi:10.1016/j.lungcan.2013.09.009.
39. Fortes C, Boffetta P. Nutritional epidemiological studies in cancer prevention: What went wrong, and how to move forwards. *European Journal of Cancer Prevention*. 2011;20(6):518–525. doi:10.1097/CEJ.0b013e3283481e07.
40. Schwingshackl L, Boeing H, Stelmach-Mardas M, Gottschald M, Dietrich S, Hoffmann G, Chaimani A. Dietary supplements and risk of cause-specific death, cardiovascular disease, and cancer: A systematic review and meta-analysis of primary prevention trials. *Advances in Nutrition*. 2017;8(1):27–39. doi:10.3945/an.116.013516.
41. Brinkman MT, Buntinx F, Kellen E, Dagnelie PC, Van Dongen MCJM, Muls E, Zeegers MP. Dietary intake of micronutrients and the risk of developing bladder cancer: Results from the Belgian case–Control study on bladder cancer risk. *Cancer Causes & Control*. 2011;22(3):469–478. doi:10.1007/s10552-010-9718-z.
42. Bjelakovic G, Nikolova D, Gluud C. Antioxidant supplements and mortality. *Current Opinion in Clinical Nutrition & Metabolic Care*. 2014;17(1):40–44. doi:10.1097/mco.0000000000000009.
43. Leoncini E, Nedovic D, Panic N, Pastorino R, Edefonti V, Boccia S. Carotenoid intake from natural sources and head and neck cancer: A systematic review and meta-analysis of epidemiological studies. *Cancer Epidemiology Biomarkers & Prevention Biomarkers*. 2015;24(7):1003–1011. doi:10.1158/1055-9965.Epi-15-0053.

44. Virtamo J, Taylor PR, Kontto J, Männistö S, Utriainen M, Weinstein SJ, Huttunen J, Albanes D. Effects of α-tocopherol and β-carotene supplementation on cancer incidence and mortality: 18-Year postintervention follow-up of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *International Journal of Cancer*. 2014;135(1):178–185. doi:10.1002/ijc.28641.
45. Nash SH, Till C, Song X, Lucia MS, Parnes HL, Thompson IM, Lippman SM, Platz EA, Schenk J. Serum retinol and carotenoid concentrations and prostate cancer risk: Results from the prostate cancer prevention trial. *Cancer Epidemiology Biomarkers & Prevention Biomarkers*. 2015. doi:10.1158/1055-9965.Epi-15-0394.
46. Brasky TM, White E, Chen C-L. Long-term, supplemental, one-carbon metabolism-related vitamin B use in relation to lung cancer risk in the vitamins and lifestyle (VITAL) cohort. *Journal of Clinical Oncology*. 2017(Best of JCO 2018 Annual Meeting):51–59. doi:10.1200/JCO.2017.72.7735.
47. Wu JW, Cross AJ, Baris D. et al. Dietary intake of meat, fruits, vegetables, and selective micronutrients and risk of bladder cancer in the New England region of the United States. *British Journal of Cancer*. 2012;106:1891. doi:10.1038/bjc.2012.187. https://www.nature.com/articles/bjc2012187#supplementary-information.
48. Dixon SC, Ibiebele TI, Protani MM, Beesley J, deFazio A, Crandon AJ, Gard GB, Rome RM, Webb PM, Nagle CM. Dietary folate and related micronutrients, folate-metabolising genes, and ovarian cancer survival. *Gynecologic Oncology*. 2014;132(3):566–572. doi:10.1016/j.ygyno.2013.12.025.
49. Roswall N, Olsen A, Christensen J, Dragsted LO, Overvad K, Tjønneland A. Source-specific effects of micronutrients in lung cancer prevention. *Lung Cancer*. 2010;67(3):275–281. doi:10.1016/j.lungcan.2009.11.010.
50. O'Grady TJ, Kitahara CM, DiRienzo AG, Gates MA. The Association between selenium and other micronutrients and thyroid cancer incidence in the NIH-AARP diet and health study. *PLoS ONE*. 2014;9(10):e110886. doi:10.1371/journal.pone.0110886.
51. Horakova D, Bouchalova K, Cwiertka K, Stepanek L, Vlckova J, Kollarova H. Risks and protective factors for triple negative breast cancer with a focus on micronutrients and infections. *Biomedical Papers*. 2018;162(2):83–89. doi:10.5507/bp.2018.014.
52. Chen F, Li Q, Yu Y, Yang W, Shi F, Qu Y. Association of vitamin C, vitamin D, vitamin E and risk of bladder cancer: A dose-response meta-analysis. *Scientific Reports*. 2015;5:9599. doi:10.1038/srep09599. https://www.nature.com/articles/srep09599#supplementary-information.
53. Yang CS, Suh N. Cancer prevention by different forms of tocopherols. In: Pezzuto JM, Suh N, editors. *Natural Products in Cancer Prevention and Therapy*. Berlin, Germany: Springer; 2013. pp. 21–33.
54. Albanes D, Till C, Klein EA. et al. Plasma tocopherols and risk of prostate cancer in the selenium and vitamin E cancer prevention trial (SELECT). *Cancer Prevention Research*. 2014. doi:10.1158/1940-6207.Capr-14-0058.
55. Golabek T, Bukowczan J, Sobczynski R, Leszczyszyn J, Chlosta PL. The role of micronutrients in the risk of urinary tract cancer. *Archives of Medical Science: AMS*. 2016;12(2):436–447. doi:10.5114/aoms.2016.59271.
56. Godic A, Poljšak B, Adamic M, Dahmane R. The role of antioxidants in skin cancer prevention and treatment. *Oxidative Medicine and Cellular Longevity*. 2014;2014:6. doi:10.1155/2014/860479.
57. Williams JD, Jacobson EL, Kim H, Kim M, Jacobson MK. Folate in skin cancer prevention. In: Stanger O, editor. *Water Soluble Vitamins: Clinical Research and Future Application*. Dordrecht, the Netherlands: Springer; 2012. pp. 181–197.
58. Mayne ST, Playdon MC, Rock CL. Diet, nutrition and cancer; past, present and future. *Nature Reviews Clinical Oncology*. 2016;13:504–515.

2 Nutraceuticals as Supplements for Cancer Prevention

Nicholas Micciche, Brianna Choyce, and Yashwant V. Pathak

CONTENTS

According to the 1994 US Dietary Supplement Health and Education Act (DSHEA), a nutritional supplement is defined as a product (other than tobacco) intended to supplement the diet, which contains one or more dietary ingredients (vitamins, minerals, herbal supplements, or amino acids) and is intended to be taken orally as a pill, tablet, capsule, or liquid [1]. In 1989, Dr. Stephen DeFelice coined the term nutraceutical from the words nutrition and pharmaceutical. Nutraceutical is defined as a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease [2] (Table 2.1).

In the recent years, nutraceuticals and even medical condition-targeted nutraceuticals have exploded onto the market as over-the-counter products and are increasing in popularity. As the use of nutraceuticals has become more mainstream, there is a large push to filter through the evidence to evaluate their clinical utility and therapeutic appropriateness. What conditions can be treated with such supplements? What form results in the most appropriate bioavailability? Are these products safe? Are they efficacious?

The American Institute for Cancer Research estimated in the late 2000s that approximately 30%–40% of all cancers are preventable with appropriate food and nutrition, physical activity, and maintenance of healthy body weight [3]. Nutraceuticals have been shown to have benefits in numerous disease states and, with the broad disease

TABLE 2.1
Select Herbal Supplements and Their Plant Names

Herbal Supplement	Plant Name
Ginger	*Zingiber officinale*
Turkey tail mushroom	*Coriolus versicolor*
Maitake mushroom	*Grifola frondosa*
Turmeric	*Curcuma longa*
Garlic	*Allium sativum*
Ginseng	Korean ginseng: *Panax ginseng* American ginseng: *Panax quinquefolius* South China ginseng: *Panax notoginseng*
Green tea	*Camellia sinensis*
Bromelain (extract)	*Ananas comosus*
Licorice	*Glycyrrhiza* sp.
Red clover	*Trifolium pratense*
Milk thistle	*Silybum marianum*

TABLE 2.2
Most Common Nutraceutical Options in Various Types of Cancer

Type of Cancer	Breast	Skin	Colon	Lung	Liver
Common Nutraceuticals Used	Turmeric Ginger Garlic Green tea extract Ginseng Turkey tail mushroom Zinc Folate (B9) Cobalamin (B12) Vitamin E	Ginger Garlic Green tea extract	Turmeric Ginger Garlic Green tea extract Ginseng Turkey tail mushroom	Turmeric Ginger Garlic Green tea extract Ginseng Turkey tail mushroom Selenium Folate (B9) Cobalamin (B12)	Turmeric Ginseng

spectrum and ever-increasing average age of our population, cancer is one of the most targeted of these disease states. Table 2.2 identifies some nutraceuticals for cancer prevention and their corresponding cancer type. Both *in vitro* and *in vivo* evidence exists for nutraceutical options in many of our most common cancers. This chapter will discuss the proposed mechanisms for cancer prevention (Table 2.3).

TABLE 2.3
Proposed Mechanisms in Various Types of Cancer of Select Nutraceuticals

Nutraceutical Mechanisms for Cancer Prevention

Type of Nutraceutical	Proposed Mechanism
Garlic	Inhibits nitrosamine bioactivation
	Inhibits DNA alkylation
Ginseng	Inhibit proliferation
	Anti-inflammatory effects
Cannabidiol	Induce autophagy
	Induce intrinsic apoptosis
Curcumin	Anti-inflammatory effects
	Antioxidant effects
	Inhibit angiogenesis
	Inhibit metastasis
	Inhibit tumor initiation
	Induce apoptosis
Ginger	Induce apoptosis
	Anti-inflammatory effects
	Antioxidant effects
Green tea extract	Antioxidant effects
Resveratrol	Antioxidant effects
	Anti-inflammatory effects
	Inhibit tumor initiation
	Induce apoptosis
Selenium	Antioxidant effects
	Induce apoptosis
	Initiate DNA repair
Vitamin A	Antioxidant effects
Vitamin C	Induce apoptosis
	Anti-inflammatory effects
	Antioxidant effects
Vitamin D	Induce apoptosis
	Anti-inflammatory effects
	Inhibit angiogenesis
Vitamin E	Induce apoptosis
	Antioxidant effects
Molybdenum	Inhibit angiogenesis
Manganese	Induce apoptosis

2.1 NUTRACEUTICALS AND THEIR EVIDENCE IN CANCER PREVENTION

2.1.1 Green Tea Extract

Green tea is one of the most commonly consumed natural beverages and is known to have numerous and significant health benefits. Tea leaves of *Camellia sinensis* contain high levels of polyphenols, 40% of which is epigallocatechin gallate (EGCG), that have demonstrated efficacy in several health conditions. Green tea also contains catechins that possess several biological effects such as antioxidant, anticancer, and prevention of cardiovascular disease [4]. The various components of green tea possess several mechanisms in cancer prevention and treatment such as inducing apoptosis, inhibiting signaling molecules like NF-kappaB, producing antioxidant effects, and inhibiting metastasis [5,6].

Green tea extract has demonstrated efficacy in enhancing the cytotoxic effects of some chemotherapeutic agents, such as doxorubicin, but *in vivo* and *in vitro* evidence suggests that green tea may interact with bortezomib, which is used in treating multiple myeloma [7,8]. Green tea catechins are also able to target multiple pathways to address prostate carcinogenesis in men at high-risk of developing it, such as African American men, so they may be an ideal chemopreventive addition in those diagnosed with high-grade prostatic intraepithelial neoplasia [9].

2.1.2 Ginseng

Ginseng's pharmacological mechanisms are due to its biologically active constituents called ginsenosides [10]. Used historically for cardiovascular and cognitive benefits, ginseng has countless promising health benefits including cancer prevention and treatment. In fact, studies have even compared its use to traditional chemotherapeutic agents both alone and in conjunction [11–15]. Ginsenosides have been shown to mediate tumor cell cycles, including cyclin-dependent kinases (CDKs) and cyclins in the G0/G1 phase and induce endogenous apoptosis, as seen in Figure 2.1. Ginsenosides have also demonstrated ability to induce tumor cell differentiation, target tumor stem cells for autophagy, reduce the production of reactive oxygen species (ROS), suppress tumor angiogenesis, and downregulate the activity of matrix metalloproteinases (MMP) on tumor metastasis [16].

A meta-analysis review of PubMed, Ovid Technologies, Embase, The Cochrane Library, China National Knowledge Infrastructure, and Chinese VIP Information, from 1990 to 2014 was completed in 2016, titled, "Ginseng consumption and risk of cancer." Based on the data from these studies, there is a lower risk of cancer incidence with ginseng consumption. The studies included in the meta-analysis consisted of one randomized controlled trial and eight observational studies: five cohorts and three case–control studies [17–24]. The following Figure 2.2 shows the subgroup analysis from this meta-analysis [25].

2.1.3 Ginger

Ginger is a well-known herb that is prevalent in foods of many cultures and has been used for centuries for its medicinal benefits in ailments such as nausea,

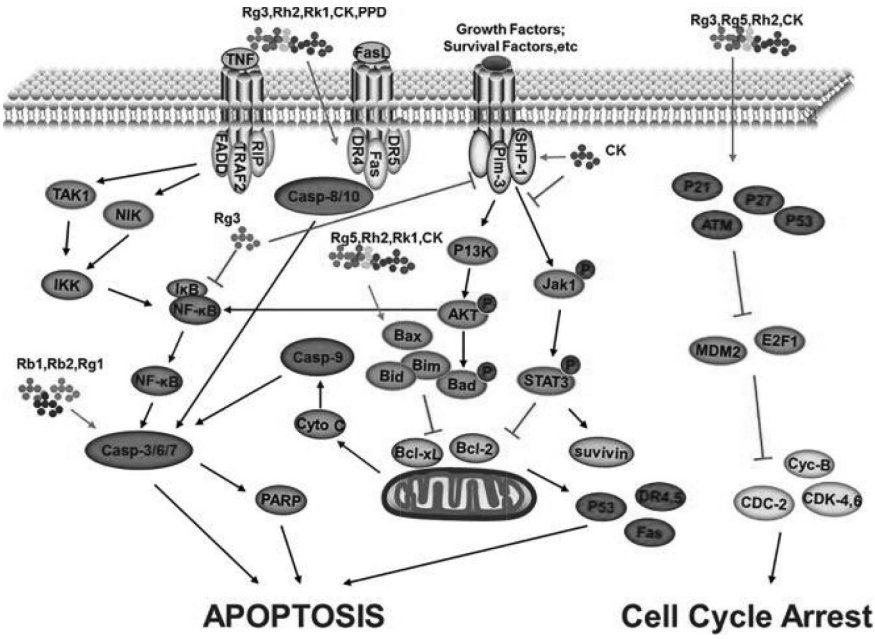


FIGURE 2.1 Mediation of cell cycle arrest and apoptosis: Some ginsenosides induce tumor apoptosis through tumor cell membrane proteins and block cell development via mediating cell cycle arrest. (From Chen, T. et al., *Saudi. J. Biol. Sci*., 25, 917–922, 2018.)

Group	Number of Studies	Risk Ratio (95% Confidence Interval)	*P*Heterogeneity	I^2, %
All	9	0.84 (0.76, 0.92)	0.0007	70
Type of cancer				
Colorectal cancer	3	0.76 (0.64, 0.90)	0.78	0
Lung cancer	4	0.78 (0.70, 0.87)	0.53	0
Gastric cancer	4	0.83 (0.75, 0.92)	<0.0001	88
Liver cancer	3	0.82 (0.73, 0.91)	0.41	0
Breast cancer	1	0.71 (0.54, 0.92)	—	—
Hematologic 35372 malignancies	1	0.75 (0.55, 1.03)	—	—
Prostate cancer	1	0.88 (0.70, 1.10)	—	—

FIGURE 2.2 Subgroup analyses of the risk ratio of different kinds of cancer in populations consuming ginseng. (From Jin, X., *J. Ginseng. Res*. 40, 269–277, 2015.)

gastrointestinal discomfort, and pain. The herb contains potent compounds called gingerols and other derivatives, most notably the dehydrated shogaols, that are being extracted and studied for their therapeutic properties. Studies have shown the benefits of using ginger and ginger derivatives in both prevention and treatment of several types of cancer [26–31].

Notch signaling, a protective biological mechanism, is a characteristic pathway of multicellular organisms. This pathway, which helps to regulate the fate of cells during the cell cycle, becomes active when signaled to renew stem cells. Genetic predispositions for notch receptor overactivation have been implicated in the formation of several types of cancers [32]. Ginger and many of its derivatives have been found to interfere with the notch signaling pathway by reducing its activity and the expression of target proteins [33]. This type of stop-it-before-it-starts mechanism makes notch signaling an important target in cancer prevention.

Along with cancer prevention, several studies have also confirmed that gingerols have anti-metastatic properties in several types of cancers including breast, lung, liver, skin, pancreas, prostate, and gastrointestinal tract [26–31]. Gingerols exhibit their anti-metastatic properties through the promotion of apoptosis by activating certain genes, downregulation of cancer-promoting genes, and by enhancing the body's cancer-killing defenses.

The parent generation of cancer cells make up less than 1% of the cells of most tumors but often prove to be the most virulent type of cancer cell due to their superior proliferative nature and genetic adaptations for survival. These parent cancer cells, known as cancer stem cells or CSCs, are blamed, at least in part, for tumor relapse and poor prognosis in various cancer types. It is notable that current chemotherapeutic agents have not demonstrated efficacy in killing of CSCs. The inhibitory activity of a specific gingerol compound, 6-shogaol, was investigated against CSCs in breast cancer. Therapy with 6-shogaol resulted in death of CSCs, as suggested by a reduction in CD44 and CD24 surface markers [26].

Besides its success in targeting CSCs, 6-shogaol has also shown potent anticancer activity against other cancer cells. Research shows that 6-shogaol has effectively reduced proliferation of cancer cells by suspending them in G1 and G2 of the cell cycle via damage to the microtubules. The compound 6-shogaol has demonstrated induction of apoptosis in mutated cells via a complex mechanism, even when those cells proved resistant to traditional chemotherapies. The first part of this mechanism includes the application of oxidative stress by creating excess reactive oxygen species. This is then followed by glutathione depletion and subsequent apoptosis resulting from a decline in mitochondrial transmembrane potential [28]. Another ginger derivative, 6-gingerol, has shown reduction in the viability of gastric cancer cells, subjecting them to apoptosis [27].

Other mechanisms by which ginger derivatives have induced apoptosis include induction of autophagy via inhibition of the Akt/mTOR pathway in nonsmall cell lung cancer (NSCLC) with alveolar basal epithelial cell mutation A-549 [29]. Similar results were seen in colon cancer cells with HCT-116, positive for transforming growth factor beta-1 and beta-2 [30]. Ginger derivative activation of peroxisomal proliferator activated receptor gamma (PPAR-γ) also resulted in apoptosis in MCF-7 breast and HT-29 colorectal cancer cells [31].

Research has shown that cancer stem cells are virulent and could be at least partially blamed for tumor relapse. Chemotherapy agents such as paclitaxel, doxorubicin, 5-fluorouracil, and the platinum drugs have not demonstrated efficacy in targeting CSCs [33,34]. One study revealed that ginger derivatives have potential therapeutic benefit in targeting CSCs up to 10,000 times greater than traditional

chemotherapy agents. The study demonstrated that 6-shogaol inhibits the CSC self-renewal pathway. Concentrations of the ginger-derived therapy that were found to be efficacious in reducing the number of CSCs in this study were also nontoxic to noncancerous cells [26].

Evidence points to ginger and the potential of its potent derivatives in fighting cancer. Numerous theories of just how ginger performs its anticancer activities have been researched and studied in human populations, as well as in other mammals. The mechanisms listed in this section are just a few among many that support the use of ginger extracts in the prevention and treatment of several types of cancer. Ginger, undoubtedly, has the ability to target CSCs and other tumor cells with genetic mutations resistant to traditional chemotherapies as well as reduce nausea caused by highly emetogenic chemotherapy regimens [33]. Past and current research studies provide an exciting perspective of how this natural herb may help with many common ailments including cancer.

2.1.4 Garlic

The *Allium* genus includes garlic, onions, leeks, shallots, and chives. These vegetables are popular worldwide and are valued for their potential medicinal benefits [35]. Garlic possesses cancer-preventive capacity and significant immune system-enhancing effects. The potential anticancer effects of garlic can be attributed to its metabolic organosulfur byproducts. Thiacremonone, one of the components, has been shown to inhibit the growth of lung tumor cells [36]. Numerous compounds extracted from garlic play important roles in the treatment of various other cancers. Ajoene, for example, was a potential candidate for the treatment of glioblastoma multiforme due to its ability to specifically target glioblastoma multiforme cancer stem cells. Garlic also plays various roles in upper digestive tract cancer, colorectal cancer, hematopoietic tumors, and breast cancer [36].

Nitrosamines and heterocyclic amines (HCAs) are considered potential dietary carcinogens that are not normally found in food but may arise in the preservation or cooking processes [37]. There is evidence showing the ability of allyl sulfur compounds of *Allium* vegetables to suppress the spontaneous formation of nitrosamines [38]. Liquid and powder formations of garlic, as well as onion, decrease nitrosamine formation [39]. This reduction in nitrosamine formation may be a result of nitrosothiol formation, limiting the amount of available nitrites [40]. HCAs arise on the surface of well-done meats, and the addition of some *Allium* vegetables decreases HCAs [41]. The addition of onion powder on hamburger meat prior to cooking decreased HCAs 2-amino-3,8-dimethylimidazo(4,5-f)quinoxaline (MeIQx) and 2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine (PhIP) by 73% and 94.3%, respectively [41]. The addition of garlic powder to the hamburger meat reduced MeIQx and PhIP levels by 66.2% and 85%, respectively [41]. Aqueous garlic extracts also reduce the mutagenicity of ionizing radiation, peroxides, and Adriamycin [42]. The observed protection from garlic may also involve other enzymes that are involved in the bioactivation or the removal of carcinogenic substances. There is evidence showing that the efficacy of various organosulfides to suppress tumorigenesis of benzo(a)pyrene was correlated with their ability to

induce NAD(P)H:quinone oxidoreductase (NQO1) [43]). This NQO1 enzyme has been shown to be involved in the removal of quinones associated with benzo(a) pyrene. Diallyl sulfide (DAS), diallyl disulfide (DADS), and diallyl trisulfide (DATS) mediate garlic's antioxidant effects, and DADS and DATS also increase the activity of glutathione-S-transferases (GSTs), the enzymes responsible for toxin protection [44,45].

2.1.5 Curcumin

Curcumin (diferuloylmethane) is the major active component in the Indian spice turmeric (*Curcuma longa*). It is found in most dishes in India and is also used as a coloring additive in food. Epidemiological evidence has shown that the incidence of certain cancers is less in people who consume curcumin than in those who do not [46]. While this may be circumstantial, this does point us to a correlation.

Curcumin has been shown to prevent a large number of cancers in animal studies and data has shown that curcumin can inhibit tumor initiation, promotion, invasion, angiogenesis, and metastasis [47–50]. Curcumin has been shown to interfere with multiple cell signaling pathways, as seen in Figure 2.3 including cell cycle (cyclin D1 and cyclin E), apoptosis (activation of caspases and downregulation of antiapoptotic gene products), proliferation (HER-2, EGFR, and AP-1), survival (PI3K/AKT pathway), invasion (MMP-9 and adhesion molecules), angiogenesis (VEGF), metastasis (CXCR-4), and inflammation (NF-kappaB, TNF-alpha, IL-6, IL-1, COX-2, and 5-LOX) [51].

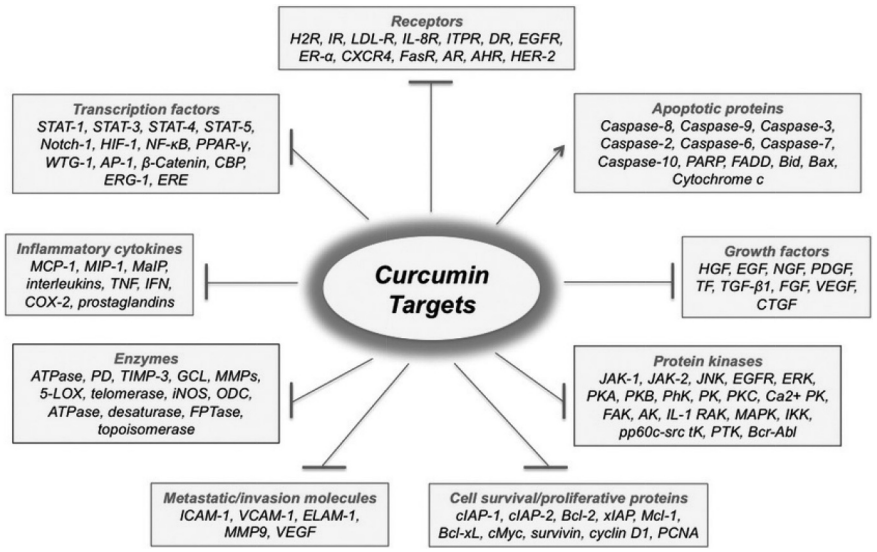


FIGURE 2.3 Molecular targets of curcumin. (From Prasad, S. et al., *Biotechnol. Adv.*, 32, 1053–1064, 2014.)

Not only has curcumin demonstrated cancer prevention, it has also been shown to act as a chemosensitizing and radiosensitizing agent for some types of tumors. Curcumin can also be used to protect healthy organs such as the kidneys, heart, liver, and oral mucosa from adverse effects caused by many chemotherapeutic agents as well as radiotherapy [53]. Curcumin's broad range of activity on various cancers such as gastrointestinal cancers, ovarian cancers, breast cancers, melanoma, neurological cancers, sarcoma, pancreatic cancers, leukemia, and lymphoma demonstrate its ability to affect multiple pathways and targets [54,55]. Generally recognized as safe by the US Food and Drug Administration (FDA), curcumin has been used for centuries as a spice with minimal adverse effects [56]. The most common adverse effect of curcumin is upset stomach (usually only in people taking high doses or in patients who take curcumin over a long period of time), but it also can stimulate menstrual flow (caution during pregnancy) and exacerbate gallbladder problems [57]. Some of the issues with curcumin are its poor solubility and bioavailability, which is why scientists have researched and devised ways to increase them. Curcumin is rapidly metabolized in the liver and intestinal wall, so some have combined piperine with curcumin to increase its bioavailability [58]. Another advancement to increasing curcumin's bioavailability has been the technique of ingesting curcumin with a high-fat meal or foods such as olive oil, fish oil, or milk. These advancements have allowed us to demonstrate the true therapeutic effects of curcumin and to further explore its role in cancer treatment and prevention.

2.1.6 Milk Thistle

Milk thistle, *Silybum marianum*, has been used for centuries for various health conditions such as liver and biliary disorders. The main active components of milk thistle, flavonoids and flavonolignans, can be found in dried milk thistle. Silymarin, a combination of flavonolignans and one flavonoid, constitutes up to 80% of milk thistle extract [59]. Silymarin has been studied extensively in clinical trials in patients with hepatitis and cirrhosis and is the only known drug that is effective in protecting the liver from the *Amanita phalloides* toxin that targets the organ [60–62]. Silymarin has also demonstrated efficacy in preventing chemotherapy-induced adverse effects such as hand–foot syndrome and oral mucositis [63,64].

Silibinin, a flavonolignan isolated from the seeds of milk thistle, is considered a very promising chemopreventive agent based on clinical studies showing efficacy of silibinin in various epithelial cancers, including colorectal cancer [65]. Using azoxymethane and 1,2-dimethylhydrazine as potential carcinogens to induce colorectal cancer in rodents, several trials have demonstrated the potential of silibinin to reduce the number of carcinogen-induced aberrant crypt foci (ACF), as well as colonic tumors [66]. Studies looking at both the short- and long-term effects of silibinin have confirmed that intestinal polyps are significantly reduced in number and in size by consumption of silibinin [67–69]. The anticancer effects of silibinin (Figure 2.3) can be attributed to its ability to cause cell cycle arrest, which decreases proliferation,

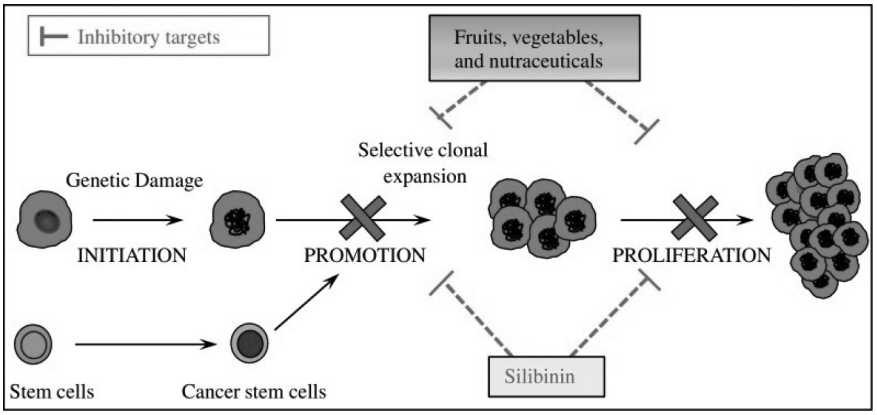


FIGURE 2.4 Silibinin can reduce the incidence of lesions that are pro-neoplastic in nature by targeting the CSCs and proliferating bulk tumor cells to prevent disease progression. (From Raina, K., et al., *J Biomed Res*., 30, 452–465, 2016.)

induce apoptosis, interfere with cellular metabolism to decrease tumor cell energy, and inhibit various pathways involved in tumorigenesis, inflammation, and angiogenesis [66] (Figure 2.4).

2.1.7 Cannabinoids

Cannabinoids belong to a class of molecules that are lipophilic ligands for two G protein-coupled cannabinoid receptors (CB). The class consists of three main groups: endo-, phyto-, and synthetic cannabinoids. Endocannabinoids are endogenous agonists of CB receptors. Phytocannabinoids mimic endogenous ligand action at the CB receptors, namely, CB1 and CB2. CB1 receptors are largely present in several brain regions and in lower amounts in other organs and periphery. These receptors mediate many of the psychoactive effects of cannabinoids. CB2 receptors are concentrated on immune cells and exist in lower amounts in neurons. Numerous phytocannabinoids, which are found in *Cannabis* plants, have been identified, including Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Many preclinical and clinical studies have studied the therapeutic potential of cannabis and cannabinoids. THC is especially psychoactive and specifically causes euphoric effects of *Cannabis*. This has limited its clinical application. CBD, on the other hand, has low affinity for CB receptors and exerts effects on other receptors including transient receptor potential channel subfamily V member 1 (TRPV1), orphan G-protein coupled receptor (GPR55), and peroxisome proliferator-activated receptors (PPARs) [70]. The anticancer action of cannabinoids includes modulation of cell signaling pathways controlling the cell cycle, proliferation, and survival. *In vitro* and *in vivo* experiments have shown antitumorigenic and anticancer effects of cannabinoids demonstrating decreased viability of certain cancer cell lines, inhibition of cancer cell proliferation, stimulation of

apoptosis, and prevention of angiogenesis and metastasis [71–79]. A systematic review published in *Cancer Medicine*, a peer-reviewed, interdisciplinary journal with current research from global biomedical researchers in the areas of cancer biology, clinical cancer research, and cancer prevention, presented the current state of knowledge regarding the molecular mechanisms of cannabinoids' anticancer action. The review, titled "The current state and future perspectives of cannabinoids in cancer biology," identified the specific antitumor mechanism of CBD in numerous cell lines and in animal models of cancer, some of which are listed in Table 2.4 [70].

The mechanism of cannabinoids in cancer prevention is predominantly attributed to the inhibition of cancer cell proliferation and the induction of apoptosis. Agonism of CB1 and CB2 receptors cause apoptosis by stimulating ceramide synthesis. Increases in ceramide concentration causes activation of the endoplasmic reticulum (ER) stress-related signaling pathway, an evolutionarily conserved

TABLE 2.4
Overview of Cannabinoids' Actions in Cancer Cell Lines

Compound	Type of Cancer	Observed Changes	Reference
THC CBD	Melanoma • CHL-1, A375, SK-MEL-28	• Reduction in the growth of tumors treated by THC+CBD *in vivo*	Armstrong et al. [71]
CBD	Breast adenocarcinoma • MDA-MB-231 • SKBR3 Invasive ductal carcinoma • MCF-7 • ZR-75-1	• Decrease in the viability of cells • Coexistence of apoptosis and autophagy • Endoplasmic reticulum stress • Inhibition of Akt/mTOR/4EBP1 • Decrease in expression of cyclin D1 • Mitochondrial depolarization • Translocation of BID to the mitochondria • Release of cytochrome c to cytosol • Activation of the intrinsic apoptotic pathway • Increase in the generation of ROS	Shrivastava et al. [72]
CBD	Glioblastoma • U251 Primary glioma stem cells (GSC) lines	• Decrease in the viability of cells • Increase in the generation of ROS • Increase in the survival rate of mice bearing GSC xenografts • Inhibition of GSC self-renewal • Activation of p-p38 pathway • Downregulation of Sox2, Id1, and p-STAT3 • Adaptation of a subset of GSC and tumor regrowth • Therapeutic resistance mediated by enhanced expression of xCT and by PN–MES transition	Singer et al. [73]

(*Continued*)

TABLE 2.4 (*Continued*)
Overview of Cannabinoids' Actions in Cancer Cell Lines

Compound	Type of Cancer	Observed Changes	Reference
CBC, CBD, CBG, CBN, CBDA, CBGA, CBDV, CBGV, THC THCA, THCV, THCVA, BDS	Prostate carcinoma • LNCaP • 22RV1 • DU-145 • PC-3	• Decrease in viability of cells • Increase in effects of bicalutamide and docetaxel (standard drugs for the treatment of prostate cancer) in the presence of CBD • Reduction of the LNCaP xenograft growth and increase in effects of bicalutamide and docetaxel against LNCaP and DU-145 xenograft • Activation of the intrinsic apoptotic pathway • Cell cycle arrest at the G1-S transition • Downregulation of AR, p53 activation, and elevation of reactive oxygen species in LNCaP cells	De Petrocellis et al. [74]
THC CBD	Neuroblastoma • SK-N-SH • IMR-32 • NUB-6 • LAN-1	• Decrease in viability of the cells • Cell cycle arrest at G1/G0 phase • Decrease in cell invasiveness • Reduction in growth of tumors *in vivo*	Fisher et al. [75]
CBD	Breast carcinoma • SUM159 • MDA-MB-231-SCP2 • MVT-1 Murine breast carcinoma • 4T1.2 • Murine leukemia • RAW264.7	• Inhibition of EGF-induced cell proliferation, migration, and invasion • Inhibition of the EGF-induced activation of EGFR, ERK, AKT and NF-κB signaling pathways • Inhibition of MMP2 and MMP9 secretion • Reduction in the growth of tumors and inhibition of metastasis *in vivo* • Inhibition of the recruitment of tumor-associated macrophages in primary tumor stroma and secondary lung metastases	Elbaz et al. [76]
CBD	Lung adenocarcinoma • A549 Large cell lung carcinoma • H460 Primary non-small-cell lung carcinoma cells	• Decrease in the viability of cells • Upregulation of COX-2 and PPAR-γ expression • Upregulation of PGE_2, PGD_2, and 15d-PGJ_2 • Inhibition of cannabidiol-induced viability loss by NS-398 (COX-2 inhibitor) and GW9662 (PPAR-γ antagonist) • Inhibition of cannabidiol-induced viability loss by transfection of cells with COX-2 and PPAR-γ siRNA • Reduction in growth of tumors *in vivo* • Reduction of tumor-regressive action of cannabidiol by pretreatment with GW9662	Ramer et al. [77]

(*Continued*)

TABLE 2.4 (*Continued*)
Overview of Cannabinoids' Actions in Cancer Cell Lines

Compound	Type of Cancer	Observed Changes	Reference
CBD	T acute lymphoblastic leukemia • Jurkat	• Decrease in viability of the cells • Resistance of the cells cultured in physiological conditions to CBD (up to 40 μM) • Increase in the number of cells in G1 phase • Inhibition of Akt/mTOR and ribosomal protein S6	Kalendero-glou et al. [78]
CBG CBD CBDV CBC	Colon adenocarcinoma • Caco-2 • HCT 116	• Decrease in viability of the cells • Promotion of apoptosis • Increase in the generation of ROS • Upregulation of CHOP expression • Reduction in the growth of tumors *in vivo*	Borrelli et al. [79]

Source: Śledziński, P. et al., *Cancer Med*., 7, 765–775, 2018.

Definitions: 4EBP1, 4E-binding protein 1; 15d-PGJ_2 -15-Deoxy-Delta-12,14-prostaglandin; Akt, protein kinase B; AR, androgen receptor; BDS, biological drug substance, extracts from *Cannabis sativa* L.; BID, BH3 interacting-domain death agonist; CBC, cannabichromene; CBD, cannabidiol; CBDA, cannabidiolic acid; CBDV, cannabidivarin; CBG, cannabigerol; CBGA, cannabigerol acid; CBGV, cannabigevarin; CBN, cannabinol; CHOP, C/EBP homologous protein; COX-2, cyclooxygenase-2; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinases; Id1, inhibitor of DNA binding 1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; MMP2, matrix metalloproteinase-2; MMP9, matrix metallopeptidase 9; mTORC1, mammalian target of rapamycin C1; PN–MES transition, upregulation of mesenchymal (MES) markers with concomitant downregulation of proneural (PN) markers; p53, tumor protein p53; PGD_2, prostaglandin D2; PGE_2, prostaglandin E2; PPAR-γ, peroxisome proliferator-activated receptor gamma; p-p38, p38 mitogen-activated protein kinases; p-STAT3, phosphorylated signal transducer and activator of transcription 3; ROS, reactive oxygen species; siRNA, small interfering ribonucleic acid; Sox2, SRY (sex-determining region Y)-box 2; THC, Δ^9 -tetrahydrocannabinol; THCA, tetrahydrocannabinolic acid; THCV, Δ9-tetrahydrocannabivarin; THCVA, Δ9-tetrahydrocannabivarinic acid; xCT, antioxidant response system X catalytic subunit.

response, termed the unfolded protein response (UPR). This pathway, when activated, causes increased expression of the highly mobile transcriptional regulation factor, p8. The p8 is a key player in the cellular stress response [80]. The expression of p8 mediates early cancer development by stopping the translation of cancer cells and degrading mutated proteins. Activation of p8 results in activation of downstream targets including activating transcription factor 4 (ATF4), C/EBP homologous protein (CHOP), and tribbles homologue 3 (TRIB3). Activation of TRIB3 specifically causes inhibition of Akt, subsequent inhibition of mTORC1, and finally autophagy [70,81] (Figure 2.5).

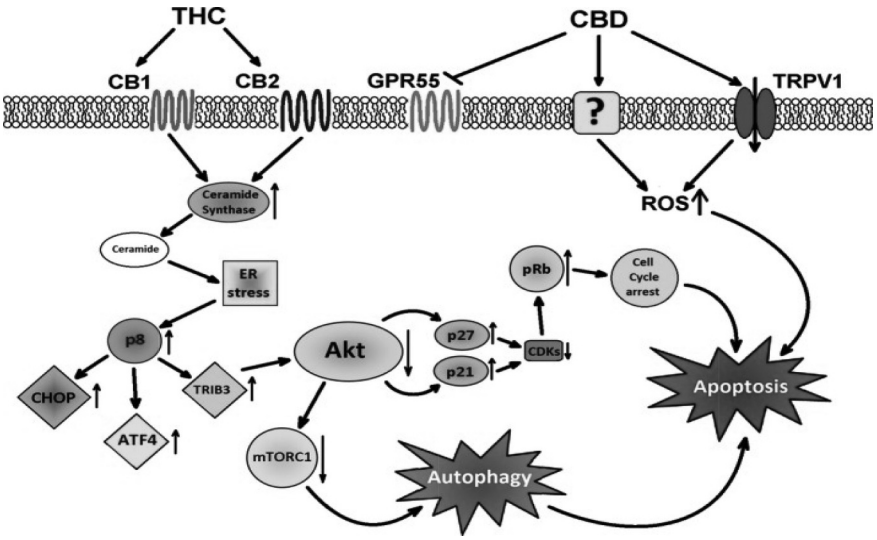


FIGURE 2.5 Cannabinoids and autophagy and apoptosis: This figure depicts the mechanisms responsible for the induction of autophagy and apoptosis by cannabinoids. (From Śledziński, P., et al., *Cancer Med*., 7, 765–775, 2018.) Definitions: Akt, protein kinase B; ATF4, activating transcription factor 4; CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; CBD, cannabidiol; CDK, cyclin-dependent kinase; CHOP, CCAAT/-enhancer-binding protein homologous protein; ER, endoplasmic reticulum; GPR55, orphan G-protein coupled receptor 55; mTORC1, mammalian target of rapamycin C1; p21, cyclin-dependent kinase inhibitor 1; p27, cyclin-dependent kinase inhibitor 1B; p8, protein p8 (nuclear protein 1, NUPR1); pRb, retinoblastoma protein; ROS, reactive oxygen species; THC, Δ9-tetrahydrocannabinol; TRIB3, tribbles pseudokinase 3; TRPV1, receptor potential channel subfamily V member 1.

2.1.8 Selenium

Selenium is an essential trace mineral involved in various biological processes including immune function and gene expression [82]. Low levels of selenium have been shown to have negative effects on overall health including the occurrence of certain cancers [83]. Higher selenium exposure, such as regular dietary intake of fish and selenium supplementation, has been suggested to protect against certain types of cancer, although there are conflicting studies [84–87]. The EPIC-Heidelberg cohort followed patients for 10 years and found that prostate cancer risk was significantly decreased for those with higher blood selenium concentration [85]. The VITAL prospective study with 35,342 male patients showed there was no association between selenium supplementation and prostate cancer risk [86]. Also, the Selenium and Vitamin E Cancer Prevention Trial, a phase 3, randomized, placebo-controlled human trial of vitamin E and selenium in 35,533 men, ended early after the supplements were found not to be effective and demonstrated a statistically insignificant increased risk of prostate cancer risk [87].

While there is conflicting evidence in regards to prostate cancer, selenium has been extensively studied and has promise as a chemopreventive agent in breast,

colorectal, and thyroid cancers [88–90]. A meta-analysis of eight randomized controlled trials also showed that supplementation with selenium alone significantly reduced the overall risk of gastrointestinal cancer as well as liver cancer [91]. Further research needs to be conducted on the use of selenium and which form of selenium is appropriate as a chemopreventive agent.

2.1.9 Resveratrol

Resveratrol is a naturally occurring polyphenolic compound found in blueberries, cranberries, nuts, red grapes, and wine. It has been demanding a lot of attention in oncology due to its potent antioxidant and anti-inflammatory properties. Resveratrol was first recognized for its chemoprevention attributes in 1997, when it was discovered to intervene at all three stages of carcinogenesis: initiation, promotion, and progression in HL-60 cells [92]. Studies in human populations have shown that there is at least 50% reduction in the risk of breast cancer among women who consume grapes rich in the compound [93].

Studies have further evaluated the implications of these findings, investigating the cancer-preventive potential of resveratrol in various forms of cancer. Results show anticancer effects of resveratrol supplementation in breast, liver, prostate, esophageal, and colon cancers [94–98]. The ability of resveratrol to inhibit the cellular events associated with tumor initiation, promotion, and progression is attributed to its ability to inhibit cyclooxygenase-1 (COX-1) activity [99]. Tumor cells, treated with resveratrol, exhibited a dose-dependent increase in externalization of the inner membrane phosphatidylserine and in cellular content of subdiploid DNA. These results indicate a loss of membrane symmetry and fragmentation of DNA. This resveratrol-induced cell death is mediated by intracellular caspases as evidenced by the dose-dependent increase in proteolytic cleavage of caspase substrate poly (ADP-ribose) polymerase (PARP) and the ability of caspase inhibitors to block the cytotoxicity caused by resveratrol. Resveratrol treatment was also shown to enhance CD95L expression on HL-60 cells and that the resveratrol-induced cytotoxicity was dependent on CD95 signaling [99].

Additional research suggests that resveratrol can also provide benefits in autoimmune diseases and conditions related to aging including Alzheimer's, diabetes, liver disease, and cardiovascular diseases. This same mechanism for chemoprevention of some cancers, the inhibition of COX-1, as well as the antioxidant properties is thought to be the mechanisms behind some of the benefits of resveratrol in these other health conditions.

As cancer awareness among the public increases, so does the number of individuals who are seeking preventative measures. Since these products are available over the counter, there is a dire need for more clinical evidence to help guide their use. Healthcare professionals, who generally rely on well-designed clinical trials and evidence-based medicine often, find it challenging to recommend the use of products that are not FDA-approved, nor proven to treat and/or prevent certain medical conditions such as cancer. If you are willing, however, and have much patience, there is a lot of evidence to be considered supporting the use of nutraceuticals for general well-being and cancer prevention.

REFERENCES

1. Dietary Supplement Health and Education Act of 1994. Pub. L. No. 103–417. 103rd Congress. October 25, 1994.
2. Brower V. Nutraceuticals: Poised for a healthy slice of the healthcare market? *Nat Biotechnol*. 1998;16(8):728–731.
3. World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. Washington, DC: AICR; 2007.
4. Tsai YJ, Chen BH. Preparation of catechin extracts and nanoemulsions from green tea leaf waste and their inhibition effect on prostate cancer cell PC-3. *Int J Nanomedicine*. 2016;11:1907–1926. doi:10.2147/IJN.S103759.
5. Khan N, Muktar H. Multitargeted therapy of cancer by green tea polyphenols. *Cancer Lett*. 2008;269:269–280.
6. Khan N, Muktar H. Cancer and metastasis: Prevention and treatment by green tea. *Cancer Metastasis Rev*. 2010;29:435–445.
7. Liang G, Tang A, Lin X, et al. Green tea catechins augment the antitumor activity of doxorubicin in an in vivo mouse model for chemoresistant liver cancer. *Int J Oncol*. 2010;37:111–123.
8. Golden EB, Lam PY, Kardosh A, et al. Green tea polyphenols block the anticancer effects of bortezomib and other boronic acid-based proteasome inhibitors. *Blood*. 2009;113:5927–5937.
9. Kumar NB, Pow-Sang JM, Spiess PE, et al. Chemoprevention in African American men with prostate cancer. *Cancer Control*. 2016;23(4):415–423.
10. Tode T, Kikuchi Y, Kita T, Hirata J, Imaizumi E, Nagata I. Inhibitory effects by oral administration of ginsenoside Rh2 on the growth of human ovarian cancer cells in nude mice. *J Cancer Res Clin Oncol*. 1993;120(1–2):24–26.
11. Mochizuki M, Yoo YC, Matsuzawa K, et al. Inhibitory effect of tumor metastasis in mice by saponins, ginsenoside-Rb2, 20(R)- and 20(S)-ginsenoside-Rg3, of red ginseng. *Biol Pharm Bull*. 1995;18(9):1197–1202..
12. Zhu JH, Takeshita T, Kitagawa I, Morimoto K. Suppression of the formation of sister chromatid exchanges by low concentrations of ginsenoside Rh2 in human blood lymphocytes. *Cancer Res*. 1995;55(6):1221–1223.
13. Yun TK, Choi SY. Preventive effect of ginseng intake against various human cancers: A case-control study on 1987 pairs. *Cancer Epidemiol Biomarkers Prev*. 1995;4(4):401–408.
14. Kim YS, Kim DS, Kim SI. Ginsenoside Rh2 and Rh3 induce differentiation of HL-60 cells into granulocytes: Modulation of protein kinase C isoforms during differentiation by ginsenoside Rh2. *Int J Biochem Cell Biol*. 1998;30(3):327–338.
15. Yang J, Yuan D, Xing T, et al. Ginsenoside Rh2 inhibiting HCT116 colon cancer cell proliferation through blocking PDZ-binding kinase/T-LAK cell-originated protein kinase. *J Ginseng Res*. 2016;40(4):400–408.
16. Chen T, Li B, Qiu Y, Qiu Z, Qu P. Functional mechanism of ginsenosides on tumor growth and metastasis. *Saudi J Biol Sci*. 2018;25(5):917–922.
17. Yun TK, Choi SY. Non-organ specific cancer prevention of ginseng: A prospective study in Korea. *Int J Epidemiol*. 1998;27:359–364.
18. Kamangar F, Gao YT, Shu XO, et al. Ginseng intake and gastric cancer risk in the Shanghai Women's Health Study Cohort. *Cancer Epidemiol Biomarkers Prev*. 2007;16:629–630.
19. Satia JA, Littman A, Slatore CG, Galanko JA, White E. Associations of herbal and specialty supplements with lung and colorectal cancer risk in the VITamins and Lifestyle study. *Cancer Epidemiol Biomarkers Prev*. 2009;18:1419–1428.

20. Brasky TM, Kristal AR, Navarro SL, et al. Specialty supplements and prostate cancer risk in the VITamins And Lifestyle (VITAL) cohort. *Nutr Cancer*. 2011;63:573–582.
21. Walter RB, Brasky TM, Milano F, White E. Vitamin, mineral, and specialty supplements and risk of hematologic malignancies in the prospective VITamins And Lifestyle (VITAL) study. *Cancer Epidemiol Biomarkers Prev*. 2011;20:2298–2308.
22. Yun TK, Choi SY. A case-control study of ginseng intake and cancer. *Int J Epidemiol*. 1990;19:871–876.
23. Rebbeck TR, Troxel AB, Norman S, et al. A retrospective case-control study of the use of hormone-related supplements and association with breast cancer. *Int J Cancer*. 2007;120:1523–1528.
24. Yun TK, Zheng S, Choi SY, et al. Non-organ-specific preventive effect of long-term administration of Korean red ginseng extract on incidence of human cancers. *J Med Food*. 2010;13:489–494.
25. Jin X, Che DB, Zhang ZH, Yan HM, Jia ZY, Jia XB. Ginseng consumption and risk of cancer: A meta-analysis. *J Ginseng Res*. 2015;40(3):269–277.
26. Ray A, Vasudevan S, Sengupta S. 6-Shogaol inhibits breast cancer cells and stem cell-like spheroids by modulation of notch signaling pathway and induction of autophagic cell death. *PLoS One*. 2015;10(9):e0137614. doi:10.1371/journal.pone.0137614.
27. Ishiguro K, Ando T, Maeda O, et al. Ginger ingredients reduce viability of gastric cancer cells via distinct mechanisms. *Biochem Biophys Res Commun*. 2007;362(1):218–223.
28. Chen CY, Liu TZ, Liu YW, et al. 6-shogaol (alkanone from ginger) induces apoptotic cell death of human hepatoma p53 mutant Mahlavu subline via an oxidative stress-mediated caspase-dependent mechanism. *J Agric Food Chem*. 2007;55(3):948–954.
29. Hung JY, Hsu YL, Li CT, et al. 6-Shogaol, an active constituent of dietary ginger, induces autophagy by inhibiting the AKT/mTOR pathway in human non-small cell lung cancer A549 cells. *J Agric Food Chem*. 2009;57(20):9809–9816. doi:10.1021/jf902315e.
30. Gan FF, Nagle AA, Ang X, et al. Shogaols at proapoptotic concentrations induce G(2)/M arrest and aberrant mitotic cell death associated with tubulin aggregation. *Apoptosis*. 2011;16(8):856–867. doi:10.1007/s10495-011-0611-3.
31. Tan BS, Kang O, Mai CW, et al. 6-Shogaol inhibits breast and colon cancer cell proliferation through activation of peroxisomal proliferator activated receptor γ (PPARγ). *Cancer Lett*. 2013;336(1):127–139. doi:10.1016/j.canlet.2013.04.014.
32. Dontu G, Jackson KW, McNicholas E, Kawamura MJ, Abdallah WM, Wicha MS. Role of Notch signaling in cell-fate determination of human mammary stem/progenitor cells. *Breast Cancer Res*. 2004;6(6):R605–R615.
33. Artavanis-Tsakonas S, Rand MD, Lake RJ. Notch signaling: Cell fate control and signal integration in development. *Science*. 1999;284(5415):770–776.
34. Pillai AK, Sharma KK, Gupta YK, Bakhshi S. Anti-emetic effect of ginger powder versus placebo as an add-on therapy in children and young adults receiving high emetogenic chemotherapy. *Pediatr Blood Cancer*. 2011;56(2):234–238. doi:10.1002/pbc.22778.
35. Nicastro HL, Ross SA, Milner JA. Garlic and onions: Their cancer prevention properties. *Cancer Prev Res (Phila)*. 2015;8(3):181–189. doi:10.1158/1940-6207.CAPR-14-0172.
36. Zheng J, Zhou Y, Li Y, Xu DP, Li S, Li HB. Spices for prevention and treatment of cancers. *Nutrients*. 2016;8(8). pii: E495. doi:10.3390/nu8080495.
37. Jakszyn P, Agudo A, Ibanez R, et al. Development of a food database of nitrosamines, heterocyclic amines, and polycyclic aromatic hydrocarbons. *J Nutr*. 2004;134:2011–2014.
38. Milner JA. Mechanisms by which garlic and allyl sulfur compounds suppress carcinogen bioactivation—Garlic and carcinogenesis. *Adv Exp Med Biol*. 2001;492:69–81.
39. Dion ME, Agler M, Milner JA. S-allyl cysteine inhibits nitrosomorpholine formation and bioactivation. *Nutr Cancer*. 1997;28:1–6.

40. Williams DLH. Nitrosation mechanisms. *Adv Phys Org Chem*. 1983;19:381–428.
41. Rounds L, Havens CM, Feinstein Y, Friedman M, Ravishankar S. Plant extracts, spices, and essential oils inactivate Escherichia coli O157:H7 and reduce formation of potentially carcinogenic heterocyclic amines in cooked beef patties. *J Agric Food Chem*. 2012;60:3792–3799.
42. Knasmuller S, de Martin R, Domjan G, Szakmary A. Studies on the antimutagenic activities of garlic extract. *Environ Mol Mutagen*. 1989;13:357–365.
43. Singh SV, Pan SS, Srivastava SK, et al. Differential induction of NAD(P)H:quinone oxidoreductase by anti-carcinogenic organosulfides from garlic. *Biochem Biophys Res Commun*. 1998;244:917–920.
44. Chen C, Pung D, Leong V, et al. Induction of detoxifying enzymes by garlic organosulfur compounds through transcription factor Nrf2: Effect of chemical structure and stress signals. *Free Radic Biol Med*. 2004;37:1578–1590.
45. Munday R, Munday CM. Relative activities of organosulfur compounds derived from onions and garlic in increasing tissue activities of quinone reductase and glutathione transferase in rat tissues. *Nutr Cancer*. 2001;40:205–210.
46. Frenkel M, Abrams DI, Ladas EJ, et al. Integrating dietary supplements into cancer care. *Integr Cancer Ther*. 2013;12(5):369–384. doi:10.1177/1534735412473642.
47. Gupta SC, Kim JH, Kannappan R, Reuter S, Dougherty PM, Aggarwal BB. Role of nuclear factor-κB-mediated inflammatory pathways in cancer-related symptoms and their regulation by nutritional agents. *Exp Biol Med (Maywood)*. 2011;236:658–671.
48. Karin M, Greten FR. NF-kappaB: Linking inflammation and immunity to cancer development and progression. *Nat Rev Immunol*. 2005;5:749–759.
49. Shishodia S, Chaturvedi MM, Aggarwal BB. Role of curcumin in cancer therapy. *Curr Probl Cancer*. 2007;31: 243–305.
50. Kunnumakkara AB, Anand P, Aggarwal BB. Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. *Cancer Lett*. 2008;269:199–225.
51. Anand P, Sundaram C, Jhurani S, Kunnumakkara AB, Aggarwal BB. Curcumin and cancer: an "old-age" disease with an "age-old" solution. *Cancer Lett*. 2008;267:133–164.
52. Prasad S, Gupta SC, Tyagi AK, Aggarwal BB. Curcumin, a component of golden spice: From bedside to bench and back. *Biotechnol Adv*. 2014;32(6):1053–1064. doi:10.1016/j.biotechadv.2014.04.004.
53. Goel A, Aggarwal BB. Curcumin, the golden spice from Indian saffron, is a chemosensitizer and radiosensitizer for tumors and chemoprotector and radioprotector for normal organs. *Nutr Cancer*. 2010;62:919–930.
54. Sharma RA, McLelland HR, Hill KA, et al. Pharmacodynamic and pharmacokinetic study of oral Curcuma extract in patients with colorectal cancer. *Clin Cancer Res*. 2001;7:1894–1900.
55. Dhillon N, Aggarwal BB, Newman RA, et al. Phase II trial of curcumin in patients with advanced pancreatic cancer. *Clin Cancer Res*. 2008;14:4491–4499.
56. US Food and Drug Administration. Center for Food Safety and Applied Nutrition, Office of Premarket Approval. EAFUS: A food additive database. http://www.usc.es/caa/ EdulcWeb/EAFUS.pdf. Accessed December 27, 2012.
57. Rasyid A, Rahman AR, Jaalam K, Lelo A. Effect of different curcumin dosages on human gall bladder. *Asia Pac J Clin Nutr*. 2002;11:314–318.
58. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Med*. 1998;64:353–356.
59. Kroll DJ, Shaw HS, Oberlies NH. Milk thistle nomenclature: Why it matters in cancer research and pharmacokinetic studies. *Integr Cancer Ther*. 2007;6:110–119.
60. Tamayo C, Diamond S. Review of clinical trials evaluating safety and efficacy of milk thistle (*Silybum marianum* [L.] Gaertn.). *Integr Cancer Ther*. 2007;6:146–157.

61. Enjalbert F, Rapior S, Nouguier-Soule J, Guillon S, Amouroux N, Cabot C. Treatment of amatoxin poisoning: 20-year retrospective analysis. *J Toxicol Clin Toxicol*. 2002;40:715–757.
62. Hruby K, Csomos G, Fuhrmann M, Thaler H. Chemotherapy of *Amanita phalloides* poisoning with intravenous silibinin. *Hum Toxicol*. 1983;2:183–195.
63. Elyasi S, Shojaee FSR, Allahyari A, Karimi G. Topical silymarin administration for prevention of capecitabine-induced hand-foot syndrome: A randomized, double-blinded, placebo-controlled clinical trial. *Phytother Res*. 2017;31(9):1323–1329. doi:10.1002/ptr.5857.
64. Elyasi S, Hosseini S, Niazi Moghadam MR, Aledavood SA, Karimi G. Effect of oral silymarin administration on prevention of radiotherapy induced mucositis: A randomized, double-blinded, placebo-controlled clinical trial. *Phytother Res*. 2016;30(11):1879–1885. doi:10.1002/ptr.5704.
65. Derry MM, Raina K, Agarwal C, Agarwal R. Identifying molecular targets of lifestyle modifications in colon cancer prevention. *Front Oncol*. 2013;3:119. doi:10.3389/fonc.2013.00119.
66. Raina K, Kumar S, Dhar D, Agarwal R. Silibinin and colorectal cancer chemoprevention: A comprehensive review on mechanisms and efficacy. *J Biomed Res*. 2016;30(6):452–465. doi:10.7555/JBR.30.20150111.
67. Rajamanickam S, Kaur M, Velmurugan B, et al. Silibinin suppresses spontaneous tumorigenesis in APCmin/+ mouse model by modulating beta-catenin pathway. *Pharm Res*. 2009;26(12):2558–2567.
68. Rajamanickam S, Velmurugan B, Kaur M, et al. Chemoprevention of intestinal tumorigenesis in APCmin/+ Mice by Silibinin. *Cancer Res*. 2010;70(6):2368–2378.
69. Verschoyle RD, Greaves P, Patel K, et al. Evaluation of the cancer chemopreventive efficacy of silibinin in genetic mouse models of prostate and intestinal carcinogenesis: Relationship with silibinin levels[J]. *Eur J Cancer*. 2008;44(6):898–906.
70. Śledziński P, Zeyland J, Słomski R, Nowak A. The current state and future perspectives of cannabinoids in cancer biology. *Cancer Med*. 2018;7(3):765–775.
71. Armstrong JL, Hill DS, McKee CS, et al. Exploiting cannabinoid-induced cytotoxic autophagy to drive melanoma cell death. *J Invest Dermatol*. 2015;135:1629–1637.
72. Shrivastava A, Kuzontkoski PM, Groopman JE, and Prasad A. Cannabidiol induces programmed cell death in breast cancer cells by coordinating the cross-talk between apoptosis and autophagy. *Mol Cancer Ther*. 2011;10:1161–1172.
73. Singer E, Judkins J, Salomonis N, et al. Reactive oxygen species-mediated therapeutic response and resistance in glioblastoma. *Cell Death Dis*. 2015;6:e1601.
74. De Petrocellis L, Ligresti A, Schiano Moriello A, et al. Non-THC cannabinoids inhibit prostate carcinoma growth in vitro and in vivo: Pro-apoptotic effects and underlying mechanisms. *Br J Pharmacol*. 2013;168:79–102.
75. Fisher T, Golan H, Schiby G, et al. In vitro and in vivo efficacy of non-psychoactive cannabidiol in neuroblastoma. *Curr Oncol Tor Ont*. 2016;23:S15–S22.
76. Elbaz M, Nasser MW, Ravi J, et al. Modulation of the tumor microenvironment and inhibition of EGF/EGFR pathway: Novel anti-tumor mechanisms of Cannabidiol in breast cancer. *Mol Oncol*. 2015;9:906–919.
77. Ramer R, Heinemann K, Merkord J, et al. COX-2 and PPAR-γ confer cannabidiol-induced apoptosis of human lung cancer cells. *Mol Cancer Ther*. 2013;12:69–82.
78. Kalenderoglou N, Macpherson T, Wright KL. Cannabidiol reduces leukemic cell size—But is it important? *Front Pharmacol*. 2017;8:144.
79. Borrelli F, Pagano E, Romano B, et al. Colon carcinogenesis is inhibited by the TRPM8 antagonist cannabigerol, a Cannabis-derived non-psychotropic cannabinoid. *Carcinogenesis*. 2014;35:2787–2797.
80. Xu C, Bailly-Maitre B, Reed JC. Endoplasmic reticulum stress: Cell life and death decisions. *J Clin Invest*. 2005;115(10):2656–2664.

81. Goruppi S, Iovanna JL. Stress-inducible protein p8 is involved in several physiological and pathological processes. *J Biol Chem*. 2009;285(3):1577–1581.
82. Prostate Cancer, Nutrition, and Dietary Supplements. Health Professional Version. October 21, 2015. Available from: http://www-ncbi-nlm-nih-gov.ezproxy.lib.usf.edu/books/NBK83261/?report=printable.
83. Rayman MP. The importance of selenium to human health. *Lancet*. 2000;356:233–241.
84. Vinceti M, Filippini T, Del Giovane C, et al. Selenium for preventing cancer. *Cochrane Database Syst Rev*. 2018;1:CD005195. doi:10.1002/14651858.
85. Steinbrecher A, Meplan C, Hesketh J, et al. Effects of selenium status and polymorphisms in selenoprotein genes on prostate cancer risk in a prospective study of European men. *Cancer Epidemiol Prev Biomark*. 2010;19(11):2958–2968.
86. Kenfield SA, Van Blarigan EL, DuPre N, Stampfer MJ ELG, Chan JM. Selenium supplementation and prostate cancer mortality. *J Natl Cancer Inst*. 2015;107(1):360.
87. Ledesma MC, Jung-Hynes B, Schmit TL, Kumar R, Mukhtar H, Ahmad N. Selenium and vitamin E for prostate cancer: Post-SELECT (Selenium and Vitamin E Cancer Prevention Trial) status. *Mol Med*. 2011;17(1–2):134–143.
88. Fontelles CC, Ong TP. Selenium and breast cancer risk: Focus on cellular and molecular mechanisms. *Adv Cancer Res*. 2017;136:173–192. doi:10.1016/bs.acr.2017.08.001.
89. Thompson PA, Ashbeck EL, Roe DJ, et al. Selenium supplementation for prevention of colorectal adenomas and risk of associated type 2 diabetes. *J Natl Cancer Inst*. 2016;108(12). pii: djw152. doi:10.1093/jnci/djw152.
90. Glattre E, Nygård JF, Aaseth J. Selenium and cancer prevention: Observations and complexity. *J Trace Elem Med Biol*. 2012;26(2–3):168–169. doi:10.1016/j.jtemb.2012.04.021.
91. Lee EH, Myung SK, Jeon YJ, Kim Y, Chang YJ, Ju W, Seo HG, Huh BY. Effects of selenium supplements on cancer prevention: Meta-analysis of randomized controlled trials. *Nutr Cancer*. 2011;63(8):1185–1195. doi:10.1080/01635581.2011.607544.
92. Jang M, Cai L, Udeani GO, et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science*. 1997;275(5297):218–220.
93. Chikara S, Nagaprashantha LD, Singhal J, Horne D, Awasthi S, Singhal SS. Oxidative stress and dietary phytochemicals: Role in cancer chemoprevention and treatment. *Cancer Lett*. 2018;413:122–134. doi:10.1016/j.canlet.2017.11.002.
94. Fernandez SV, Russo IH, Russo J. Estradiol and its metabolites 4-hydroxyestradiol and 2-hydroxyestradiol induce mutations in human breast epithelial cells. *Int J Cancer*. 2006;118(8):1862e1868.
95. Cao L, Chen X, Xiao X, Ma Q, Li W. Resveratrol inhibits hyperglycemia-driven ROS-induced invasion and migration of pancreatic cancer cells via suppression of the ERK and p38 MAPK signaling pathways. *Int J Oncol*. 2016;49(2):735–743. doi:10.3892/ijo.2016.3559.
96. Li W, Cao L, Chen X, Lei J, Ma Q. Resveratrol inhibits hypoxia-driven ROS-induced invasive and migratory ability of pancreatic cancer cells via suppression of the Hedgehog signaling pathway. *Oncol Rep*. 2016;35(3):1718–1726. doi:10.3892/or.2015.4504.
97. Chen CY, Jang JH, Li MH, Surh YJ. Resveratrol upregulates heme oxygenase-1 expression via activation of NF-E2-related factor 2 in PC12 cells. *Biochem Biophys Res Commun*. 2005;331(4):993–1000.
98. Singh B, Shoulson R, Chatterjee A, et al. Resveratrol inhibits estrogen-induced breast carcinogenesis through induction of NRF2-mediated protective pathways. *Carcinogenesis*. 2014;35(8):1872–1880.
99. Clément MV, Hirpara JL, Chawdhury SH, Pervaiz S. Chemopreventive agent resveratrol, a natural product derived from grapes, triggers CD95 signaling-dependent apoptosis in human tumor cells. *Blood*. 1998;92(3):996–1002.

3 Nutraceutical's Role in Proliferation and Prevention of Prostate Cancer

Raghunandan Yendapally and Donald Sikazwe

CONTENTS

3.1 INTRODUCTION

This chapter outlines the role of nutraceuticals in mitigating against cell proliferation and potential chemoprevention in prostate cancer. The probability of developing prostate cancer rapidly increases in men after 50 years of age [1]. According to the American Cancer Society, one in every nine men is at risk of being diagnosed with prostate cancer in his lifetime [2]. About 60% of all prostate cancer cases are diagnosed in men older than 65 years of age. Therefore, age is one of the important risk factors [2]. In the United States, prostate cancer is the second leading cause of cancer deaths in men, accounting for 29,430 deaths in 2018 [2]. Epidemiological, environmental, and dietary factors appear to play an important role in prostate cancer. In a study conducted by Shimizu et al., Japanese men who migrated to the United States were at a higher risk of developing prostate cancer than their homeland men probably due to environmental and lifestyle differences [1]. As a result, prevention strategies of prostate cancer may include myriad factors in patients' lifestyle, including diet [3].

Many natural foods or food products have anticancer properties. Recently, there has been a tremendous interest in evaluating the beneficial effects of nutraceuticals in prostate cancer. Since most of the research studies are focused on retrospective studies and due to limited number of large randomized clinical trials, the beneficial effects of

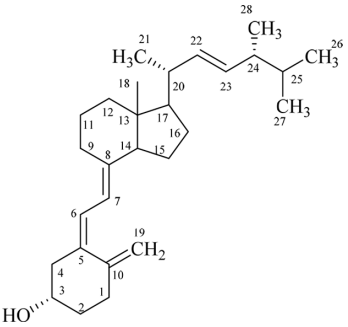
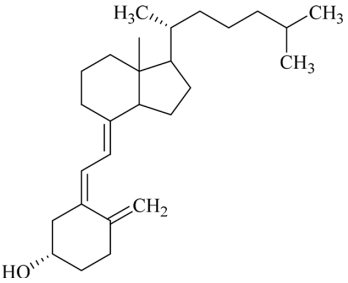
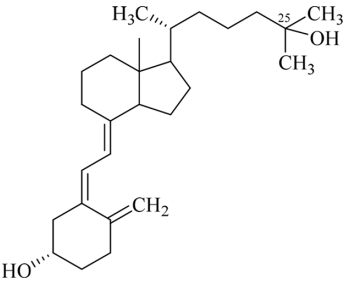
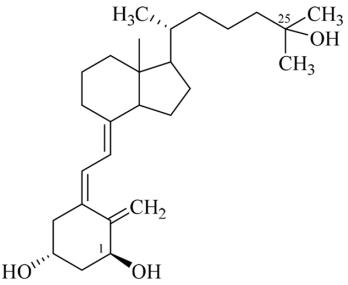
nutraceuticals described in this chapter should not be viewed as clinical guidelines [3]. However, most of the compounds described are considered to be relatively safe, and dietary changes may be beneficial in patients with prostate cancer or who are at risk of developing this disease [3]. Nutraceuticals discussed in this chapter include vitamin D, green tea polyphenols, sulforaphane, lycopene, genistein, resveratrol, and several other molecules. Some nutraceuticals reduce the levels of prostate-specific antigen (PSA), a specific biomarker that is elevated in prostate cancer.

3.2 VITAMIN D

The two major forms of vitamin D include vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) [4]. Structurally, ergocalciferol differs from cholecalciferol in its side chain by the presence of a double bond between C_{22} and C_{23} carbons and an additional methyl (C_{28}) group at C_{24} carbon [5] (Table 3.1). Vitamin D is a secosteroid fat-soluble vitamin biosynthesized in the human body sequentially in the skin, liver, and kidneys [6]. In the presence of sunlight's ultraviolet radiation, 7-dehydrocholesterol is converted to cholecalciferol (vitamin D_3) in the skin [7,8]. Cholecalciferol is metabolized to 25-hydroxy-cholecalciferol [$25(OH)D_3$ or calcidiol] (Table 3.1) in the liver by the enzyme vitamin D-25-hydroxylase, which is further converted into 1,25-dihydroxy-cholecalciferol [$1,25(OH)_2D_3$ or calcitriol] (Table 3.1) in the kidneys by the enzyme 1α-hydroxylase [7,8]. The major circulating form of vitamin D in the blood is calcidiol [9]. However, calcitriol is about 500 times more potent than calcidiol and is considered to be the active form of vitamin D_3 [7,8]. Since sunlight is one of the key factors for vitamin D biosynthesis, lack of exposure to sunlight may lead to the vitamin D deficiency [8]. It was estimated that on average, about 5–10 minutes exposure of arms and legs to direct sunlight may produce 3000 IU of Vitamin D [8]. However, this is dependent on several factors including skin sensitivity, latitude, time, and season [8]. Vitamin D_2 is biosynthesized in plants and fungi by ultraviolet irradiation on ergosterol [4,5,8]. Even though both vitamin D_2 and D_3 are commercially available as supplements, they are no longer considered as equivalent and thus not interchangeable [4]. Vitamin D_2, when taken as a supplement, results in shorter plasma clearance than vitamin D_3 [5]. Natural sources rich in vitamin D include salmon, sardines, mackerel, tuna, shiitake mushrooms, and egg yolk. Fortified foods such as milk, cheese, yogurt butter, and orange juice also contain vitamin D [8].

Vitamin D binds to vitamin D receptors (VDRs), which are present in most of the tissues and influence several biochemical processes [5]. Vitamin D plays a key regulatory role in bone metabolism and maintains homeostasis calcium and phosphorus [7]. Skowronski et al. have experimentally shown that VDRs are present in human prostate cancer cell lines (LNCaP, PC-3, and DU-145) and the antiproliferative effect of $1,25(OH)_2D_3$ was also demonstrated against these cell lines [10]. Vitamin D and its analogues exhibit antiprostatic mechanistic effects by multiple mechanisms [11]. Calcitriol inhibits tumor-derived endothelial cells (TDECs) and thereby has antiangiogenic effects [12]. Calcitriol is shown to arrest the G_1 phase of the cell cycle, thereby decreasing the cell proliferation [13]. In preclinical studies, it was demonstrated that calcitriol, when combined with taxane derivatives

TABLE 3.1
Vitamin D Forms, Common Names, Chemical Structures, and Sources

Vitamin D Form	Common Name	Chemical Structures	Sources
Vitamin D_2	Ergocalciferol		Biosynthesized in plants and fungi
Vitamin D_3	Cholecalciferol		Biosynthesized in animals from 7-dehydrocholesterol
25-Hydroxyvitamin D_3	Calcidiol (25-hydroxy-cholecalciferol)		Produced as a metabolite of vitamin D_3 in the liver by vitamin D-25-hydroxylase
1,25-Dihydroxy-vitamin D_3	Calcitriol (1,25-dihydroxy-cholecalciferol)		Produced as a metabolite of 25-hydroxy-vitamin D_3 in the kidneys by 1α-hydroxylase

(e.g., paclitaxel, docetaxel) and platinum compounds (e.g., cisplatin, carboplatin), enhances anticancer properties of these agents by upregulating proapoptic signaling molecule mitogen-activated protein kinase (MEKK-1)/tumor suppressor p73 protein, and decreases the prosurvival signals via Erk/Akt pathways [14].

In a study conducted by Marshall et al., supplementation of 4000 IU of vitamin D_3 soft gels did not lead to any serious toxic effects and provided beneficial effects in low-risk prostate cancer individuals under surveillance [15]. Veldhuizen et al. observed a vitamin D deficiency in patients with advanced hormone refractory prostate cancer. In this study, daily supplementation of 2,000 IU of vitamin D by oral route for 12 weeks was shown to be beneficial for pain alleviation, enhancing muscle strength and improving quality of life [16]. In a study conducted by Gross et al., daily administration of calcitriol for 6–15 months starting at 0.5 μg and gradually increasing it to 2.5 μg led to a decrease in the elevation rate of PSA in prostate cancer patients after radiation or surgery [17].

In a study conducted by Ahonen et al., in Finland, it was concluded that low levels of serum 25-hydroxyvitamin D (<16 ng/mL) were associated with an increased risk of aggressive prostate cancer and an early onset [18,19]. On the contrary, in a prospective study conducted by Park et al. in a multiethnic cohort did not find an increased risk with low serum 25-hydroxyvitamin D (<20 vs. 30–<50 ng/mL) [20]. However, it was found that there was an increased risk with higher concentrations (≥50 ng/mL) [20]. Therefore, further studies must be conducted to unequivocally establish the significance of levels of circulating 25-hydroxyvitamin D in prostate cancer.

3.3 GREEN TEA POLYPHENOLS

Routine consumption of green tea (GT) from *Camellia sinensis* plant leaves may be chemopreventive against or provide a dietary treatment option for male prostate cancer. Although not all studies conclusively agree on GT's antiprostate cancer effects, the aforementioned proposal continues to attract increasing research attention driven by several evidentiary lines. Epidemiological data indicate that the low rates of prostate cancer diagnosis seem more prevalent in Asian men who ritually or habitually consume GT as part of their daily diet versus high rates in Western men (Caucasians, African Americans, Hispanic, etc.) who mostly consume black tea [21–26]. Apparently, the world market is dominated by black tea (obtained from fully fermented or oxidized tea leaves and makes up 78% of all teas produced) that is mostly consumed by people residing in Western countries. On the other hand, green tea (i.e., unoxidized tea from steamed leaves—steaming, in this case, deactivates the oxidizing polyphenol oxidase enzymes) only accounts for 20% of the world tea market and is primarily consumed by Asian people of Chinese, Japanese, and Indian descent. The rest is oolong tea (sourced from partially oxidized tea leaves) whose market share is the lowest, less than 2%, and its use is mainly confined to China and Taiwan [21–26].

Chemical and pharmacological data suggest that the antiprostate cancer effects arise from the presence of catechin polyphenols, which account for slightly over 30% of the dried green tea leaves total chemical extracts by weight [26–29]. Data indicate that (−)-epigallocatechin-3-gallate or EGCG, which is GT's major and most active polyphenol, was chemopreventive in animal models and exhibited selective antiproliferative

effects in prostate cancer cells via a variety of mechanisms, including dose-dependent induction of apoptosis, cell-cycle inhibition, and urokinase and cyclin-dependent kinase enzyme inhibitions [26,30,31]. In DU145 prostate cancer cells, GT potentiated the antiproliferative effects of radiation treatment and stimulated apoptotic events [32].

The chemical composition of green tea is not only limited to polyphenols (i.e., catechins, flavanols, and depsides), rather it is a diverse and complex mixture, which includes vitamins, minerals, carbohydrates, xanthines (caffeine, theobromine, theophylline, etc.), phenolic acids [23]. Relevant to prostate cancer, however, is the fact that green tea provides four catechin polyphenols of clinical chemotherapeutic significance, viz-a-vis: (–)-epicatechin or EC, (–)-epigallocatechin or EGC, (–)-epicatechin-3-gallate or ECG, and (–)-epigallocatechin-3-gallate or EGCG [29]. Out of the above-stated compounds, EGCG is reportedly the most pharmacologically active catechin extractable by water and predominant polyphenol representing ≥60% of overall catechin amounts [28,29]. Structurally, these natural compounds are small molecules (FWs or formula weights <500), which can be subdivided into the biphenol (i.e., EC and EGC) and esterified triphenol (i.e., ECG and EGCG) classes illustrated in Figure 3.1. As observed for EGCG, the phenolic polar hydroxy (–OH) groups are hydrogen-bond donors having antioxidant or radical-scavenging actions and interact with specific receptors (nucleic acids and proteins) via hydrogen bonding [33]. Apparently, the catechins are unstable under basic conditions (pH >7, they may form dimers or irreversibly oxidize to yield colored compounds) or even in neutral environments [27].

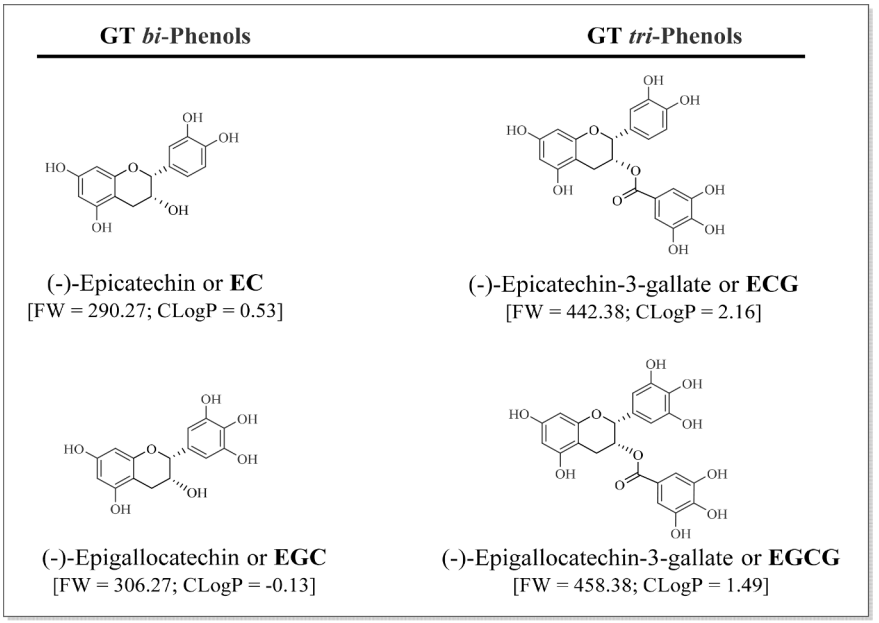


FIGURE 3.1 EC, EGC, ECG, and EGCG—the commonest green tea polyphenols. FW denotes formula weight. CLogP denotes the calculated Log partition coefficient. FWs and CLogP were calculated using ChemDraw Professional 16.0 software.

Pharmacokinetic and safety characterizations of the above polyphenols indicate that they exhibit low oral bioavailabilities perhaps due to presystemic intestinal metabolism, possess low (CLogP: −0.13–0.53) to moderate lipophilicities (CLogP: 1.5–2.2), do not alter the activities of cytochrome P450s (1A2; 2C9; 2D6; 3A4), and possess no observable toxicities at the study doses used [25]. Note that key CYPs (i.e., 3A4 and 2D6) are implicated in metabolism related drug interactions. A cup or 240 mL of brewed green tea yields approximately 100–200 mg (these numbers vary depending on the sources cited) EGCG whose oral bioavailability is then impacted by metal ions, catechol methyl transferase (COMT), uridine glucuronosyltransferases (UGTs), and sulfotransferase (STs) activities and can be toxic at higher doses [21,25,27,29].

Although these catechins are potent antioxidants, they seem to exhibit multitarget pharmacologic activities. Antiprostate cancer mechanisms of representative GT polyphenol currently include [25,34,35]:

1. apoptosis and cell-cycle arrest via selective induction and activation of prostate cells apoptotic caspase cascades
2. direct antioxidant activity via hydroxyl group neutralization of reactive oxygen species or ROS and chelation of metal ions
3. indirect antioxidant effects via induction of antioxidant enzymes (superoxide dismutase or SOD, catalase or CAT, glutathione peroxidase or GPx) and suppression of both prooxidant enzymes (nicotinamide adenine dinucleotide phosphate oxidase or NADPH-oxidase, cyclooxygenase or COX, lipoxygenase, xanthine oxidase or XO, inducible nitric oxide synthase or iNOS) and signaling proteins (e.g., tumor necrosis factor alpha or TNF-α, and nuclear factor kappa-B or NF-κB)
4. anti-inflammation via inhibitions of NF-κB and COX-2
5. anti-androgenic via 5-α-reductase inhibition (an enzyme that converts testosterone into a much more active androgen called 5-α-dihydrotestosterone in the prostate tissue)
6. insulin growth factor modulation via inhibition of insulin-like growth factor binding proteins (IGFBP)
7. modulation of mitogen-activated protein (MAP) kinase signaling and suppression of DNA replication evidenced by prostate cancer's minichromosome maintenance complex component 7 (MCM7) biomarker levels

Using EGCG, the above preclinical mechanisms and cancer targets have been further investigated *in vitro* (involving pull-down experiments) as well as *in silico* (via modeling for protein interactions) by Saeki et al. [36]. The above tools have been deployed in the attempt to unravel EGCG's active site interactions including relevant molecular binding or induced conformations at a variety of protein targets for potentially beneficial antiprostate cancer outcomes.

The clinical trial landscape of GT in prostate cancer has thus far yielded a mixed bag of results and begs for more standardized studies using perhaps larger sample populations with the additional aim of establishing a consensus on effective doses

(600 mg GT per day has been used in several clinical studies). The statements below represent proof of concept and other clinical studies versus placebo, which shed some light on the potential effectiveness of using GT for chemoprevention or treating prostate cancer.

- Bettuzzi et al. conducted a one-year proof-of-principle clinical trial to determine the safety and efficacy of catechin polyphenols in 60 patients with high-grade prostate intraepithelial neoplasia (HGPIN) for prostate cancer chemoprevention [31]. They administered 200 mg GT (containing 52% EGCG) three times a day and observed a 90% prostate cancer chemoprevention and no toxicity.
- A systematic database review by Jacob et al. indicated that only 5 out of the 11 total studies were supportive of prostate cancer chemoprevention by GT [37]. Aside from the chemopreventive effect demonstrated in premalignant HGPIN patients using 400–600 mg of EGCG daily for a year, the report also showed that only one phase II trial out of the four conducted, on GT as a treatment for prostate cancer, showed significant declines in biomarkers: 69% decline for prostate-specific antigen, 40% for hepatocyte growth factor, and 24% for serum vascular endothelial growth factor.
- On the contrary, a study by Micali et al. did not observe any chemoprevention using 600 mg of GT in their HGPIN patient cohort of 55–65-year-old men [38].
- Guo et al.'s meta-analysis of seven randomized controlled trials found a dose-dependent effect of GT, and that consumption of over seven cups each day seemed to significantly minimize the prostate cancer risk in either HGPIN or atypical small acinar proliferation (ASAP) cases [39].

3.4 SULFORAPHANE

The 2015–2020 dietary guidelines for Americans advocate that adults consume one and half to two and a half cup-equivalents of dark-green vegetables (including cruciferous vegetables) every week [40]. Besides being a good source of fiber and nutrients (minerals, vitamins C/E/K, beta-carotene, lutein, zeaxanthin, folate, etc.), potential chemoprevention by cruciferous vegetables is the next frontier being investigated. From the cancer perspective, animal and epidemiological studies already indicate that high consumption of cruciferous vegetables may decrease the risk (e.g., by 40%) and progression of prostate cancer [41,42]. The implied antiprostate cancer pharmacological actions are linked to the presence of sulfur phytochemicals called glucosinolates or β-thioglucoside N-hydroxysulfates in cruciferous vegetables. More than 120 glucosinolates exist in nature, and the commonly occurring compounds may be organized based on their aliphatic, aromatic, and indole structural motifs (Figure 3.2) [43,44].

It is suggested that glucosinolate amounts in cruciferous vegetables vary (for instance, 2–10 μmol/g amounts per dry mass) mainly due to plant genetics, growth, and food preparation conditions [42]. Among the currently known

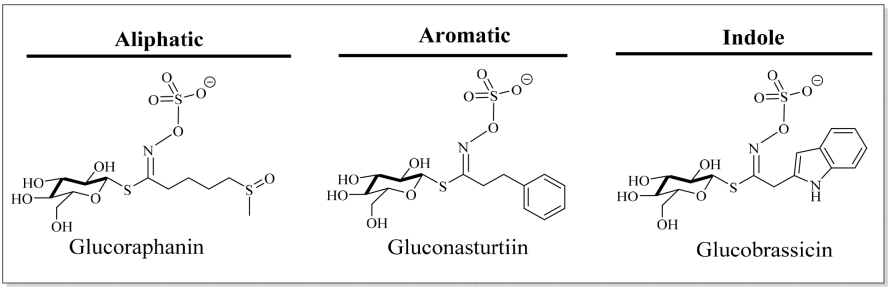


FIGURE 3.2 Representative aliphatic, aromatic, and indole glucosinolates.

glucosinolates, special attention has been paid to aliphatic glucoraphanin, which exists in the brassica or cabbage-type vegetables (brussels sprouts, broccoli, cauliflower, kale, etc.), and glucoraphanin accounts for >50% of the total glucosinolate content in broccoli [42,45]. Glucoraphanin undergoes metabolic conversion to sulforaphane (SFN, Figure 3.3), a bioactive compound, which has been correlated to the antiprostate cancer effects of cruciferous vegetables.

SFN itself is a naturally occurring biologically active isothiocyanate (ITC) that is hydrolytically obtained from an inactive precursor molecule called glucoraphanin [i.e., 1-isothiocyanato-(4R)-(methylsulfinyl)butane]. SFN is a small polar molecule (FW <500, CLogP = 0.68). Among all brassica vegetables, the highest levels of SFN in the form of glucoraphanin are found in fresh broccoli sprouts, followed by mature broccoli [45]. Essentially, glucoraphanin in these vegetables is hydrolyzed by thioglucosidase enzymes in the form of plant myrosinases or is present in human colon/gut flora to release SFN [45–47]. Myrosinases are activated by physical/mechanical manipulation, like chewing, and are deactivated by high-temperature cooking, which results ultimately in decreased SFN bioavailability. In fact, raw broccoli SFN is better absorbed and more bioavailable than that from the cooked vegetables [48]. In other words, *fresh salad* type preparations of cruciferous vegetables may be better sources of dietary SFN.

The growing appeal for SFN as a nutraceutical is supported by confirmatory research data indicating that the molecule has promising pharmacological activity in prostate cancer as well as other disease states [49,50]. For prostate cancer, reports

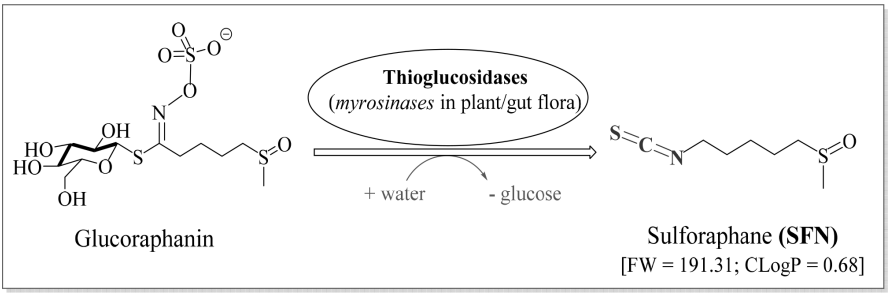


FIGURE 3.3 Glucoraphanin conversion by myrosinase or human gut flora into sulforaphane. FWs and CLogP were calculated using ChemDraw Professional 16.0 software.

indicate that consumption of foods high in SFN levels led to reductions in aggressive forms and could be chemopreventive in nature [47]. The antiprostate cancer molecular mechanisms for SFN are indeed multifactorial and currently include [50–52]:

1. Inhibition of cytochrome P450 enzymes (e.g., 1A1, 2B1, 2B2, 3A4), thereby preventing the bioactivation of molecules to carcinogenic intermediates capable of forming DNA adducts.
2. Epigenetics—suppressing histone deacetylase (HDAC, which is overly active in prostate cancer) to promote cell cycle arrest (e.g., G_2/M phase) and apoptosis.
3. Promoting cancer cell cytotoxic ROS formation.
4. Stimulating the nuclear factor erythroid-2-related factor 2 (Nrf-2) resulting in antioxidant response gene elevations (e.g., glutathione peroxidase and glutathione reductase), and increased phase II metabolic activity (e.g., NAD(P)H: quinone reductase or NQO1, GSTs, UDP-glucuronosyltransferases or UGTs) for detoxifying the carcinogens.
5. Decreasing NF-κB signaling, thereby modulating the associated deleterious cascade biochemistries. NF-κB is upregulated in prostate cancer.
6. Antiangiogenesis through its inhibition of such transcription factors as the hypoxia inducible factor-1α (HIF-1α), vascular endothelial growth factor (VEGF), and matrix metalloproteinase-9 (MMP-9).

In terms of pharmacokinetics, SFN is a rapidly absorbed polar molecule (CLogP = 0.681) that undergoes glutathione-S-transferase (GST)/N-acetyl transferase (NAT) mediated metabolism and is mostly eliminated as mercapturic acids in urine (Figure 3.4) [49,51]. Glutathione (GSH) conjugation occurs because SFN's isothiocyanate (**–N=C=S**) moiety is electron deficient and GSTs (especially the isoforms of GSTP1-1 and GSTM1-1 isoforms) preferentially deactivate molecules containing electrophilic centers. Conversely, excessive or overdose SFN can lead to GSH depletion and cellular toxicity through electrophilic center attacks on protein nucleophiles and adduct formation. Additional details related to isothiocyanate metabolism and toxicity are provided elsewhere [53].

Albeit studies (observational, epidemiological, and clinical) on the efficacy of cruciferous vegetables have thus far yielded inconclusive results, a number of clinical trials (ended and ongoing) continue to shed more light on the chemopreventive

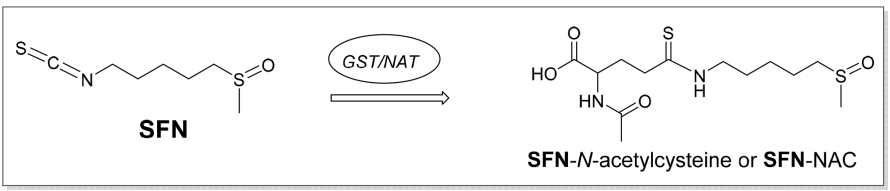


FIGURE 3.4 SFN metabolic pathway to its mercapturic acid (SFN-*N*-acetylcysteine). The GST conjugation reaction involves proteolytic steps (via γ-glutamyl-transpeptidase and cysteinyl-glycinase) and then *N*-acetylation by NAT.

potential of dietary vegetable or supplementary SFN (broccoli and watercress dietary capsules are now available over the counter, in the United States) against prostate cancer [54]. The following are representative antiprostate cancer clinical studies.

- A 4.2 years prospective study involving 29,361 men previously screened for PSA levels indicated that high broccoli and cauliflower consumption was inversely correlated to the risk of developing metastatic prostate cancer [55]. Significant inverse correlations were recorded with more than 1 serving of weekly consumption of either broccoli or cauliflower in aggressive prostate cancer.
- Alumkal et al. recently demonstrated that 200 μmoles/daily of SFN-rich broccoli sprout extracts were safe to administer, although this dose did not significantly lower the PSA levels in majority of their phase II clinical study involving 20 patients [56]. On the other hand, a randomized clinical trial using higher daily supplementation with 60 mg SFN (three times/day for six months) lowered the PSA levels in 78 patients with recurrent prostate cancer after prostate gland removal [57].
- Peisch et al. report that men who consumed more than 5.7 servings of cruciferous vegetables daily following their diagnosis of nonmetastatic prostate cancer exhibited a 59% lower risk of prostate cancer progression versus men who consumed 1.4 or less servings [58].
- The *European prospective investigation into cancer and nutrition (EPIC)-Heidelberg's* 9.4-year follow-up study revealed an inverse relationship between the nonadvanced/low-grade prostate cancer risk using 7.9 mg daily glucosinolate supplementation [59].

3.5 LYCOPENE

Lycopene (Figure 3.5) belongs to a chemical class of compounds known as carotenoids (a type of phytochemicals) and is predominantly present in tomatoes (*Solanum lycopersicum*) [60]. In fact, it has been estimated that about 85% of lycopene is obtained by consuming tomato-based products in Western diet [61]. The deep characteristic red color of tomatoes is largely attributed to the lycopene [62]. Lycopene is also present in other fruits such as watermelon, papaya, grape fruit, and apricots [63]. Lycopene in fresh tomatoes primarily exists in all-*trans* configuration [62] (Figure 3.5). However, processing the tomatoes, especially with heat, leads to isomerization, transforming the all-*trans* to *cis* configuration [62]. Interestingly, the *cis* form is more well-absorbed than the *trans* form [62,64]. Lycopene has the highest singlet oxygen-quenching capacity, making it an attractive nutrient to protect against certain types of cancer [65].

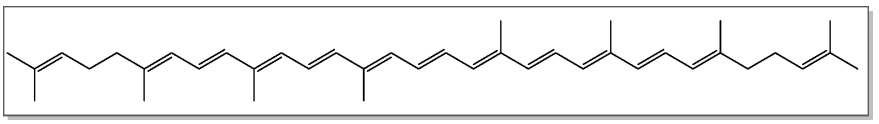


FIGURE 3.5 Structure of all-*trans* lycopene.

The conjugated polyene structure of lycopene makes it an electron-rich molecule and scavenges reactive free radicals and oxygen [63]. Lycopene is well-distributed and present in significant concentrations in human serum, milk, and prostate [66].

Lycopene induces substantial apoptosis in prostate cancer LNCaP cell lines by inhibiting signaling and proliferative effects of phosphatidylinositol 3-kinase and causes arrest of G0/G1 cell cycle [67]. Goo et al., by using proteomic analysis software, determined that lycopene-treated LNCaP cell lines were shown to increase the levels of detoxifying enzymes such as superoxide dismutase-1 and epoxide hydrolase 1 [68]. Lycopene possess greater growth-inhibitory effect in DU145 prostate cancer cell lines, expressing high insulin-like growth factor I receptor (IGF-IR), and in combination with docetaxel, it is found to be more effective and increases docetaxel's efficacy than when docetaxel is used alone in high IGF-IR cancer cells [69].

Several studies, including the Health Professionals Follow-Up Study (HPFS) have shown that lycopene, tomatoes, and tomato-based products are beneficial in prostate cancer [70–72]. Giovannucci et al. conducted a prospective study and on the basis of the analyzed results from the HPFS suggested that frequent consumption of tomato products rich in lycopene may reduce the risk associated with prostate cancer, a greater risk reduction was seen with primarily bioavailable tomato sauce [70]. Based on the studies conducted by Tonucci et al., it is evident that lycopene in thermally processed tomato paste, tomato sauce, tomato puree, and ketchup is present in excess quantities than in fresh tomatoes due to the removal of water during the processing of food products [73]. A prospective cohort study conducted by Zu et al., involving 49,898 US male health professionals indicated that the higher consumption of lycopene was associated with the lowered risk of total prostate cancer risk and most importantly a strong correlation with a reduced risk for lethal prostate cancer [74]. Further, one of the risk factors for progression of prostate cancer is benign prostatic hyperplasia (BPH), a common disease in older men [75]. In a study conducted by Schwarz et al., subjects were instructed to take one capsule of lycopene supplementation consisting of 77% all-*trans* and 23% *cis*-lycopene once daily for 6 months [75]. The group taking lycopene supplementation had a higher lycopene concentration in the plasma and reduced serum PSA levels than the placebo group [75]. Most importantly, the prostate enlargement did not occur in the lycopene group, whereas it was noted that prostate was enlarged in the placebo group, indicating that lycopene inhibited the advancement of BPH [75]. In a randomized controlled trial conducted on prostate cancer patients, Paur et al. showed that nutritional intervention with tomato-based products rich in lycopene (30 mg daily) either alone or in combination with omega-3 fatty acids and selenium reduced serum PSA levels in nonmetastatic prostatic cancer patients [76].

3.6 GENISTEIN

Genistein (Figure 3.6) is an isoflavone polyphenolic chromone derivative [77] Genistein is present in good quantities in soy and soy-based products (soy beverages, soy cheese, soy soups) [78]. According to the US Department of Agriculture (USDA) 100 mg of soy flour contains 85–98 mg of genistein [78]. Genistein has bitter taste and poor aqueous solubility, which limit its oral bioavailability [77]. Further, genistein undergoes extensive metabolism [77].

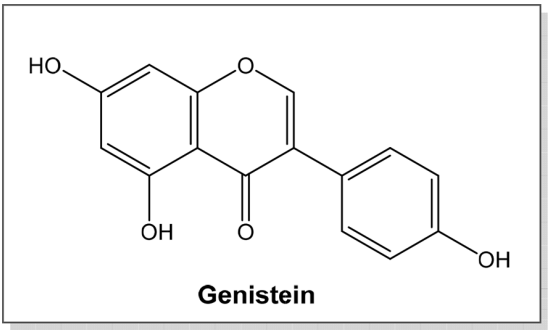


FIGURE 3.6 Structure of genistein.

Genistein has structural similarity to estradiol and has weak estrogenic properties due to its ability to bind to estrogen receptors [77,79]. Genistein antiprostatic effects are mediated by various cell signaling pathways [80]. Genistein suppresses vascular endothelial growth factor (VEGF), thereby inhibiting angiogenesis in prostate cancer [81]. In human prostate cell lines, genistein was shown to inhibit p38 mitogen-activated protein kinase (MAPK) and matrix metalloproteinase type 2 (MMP-2) in the nanomolar range, which corresponds to its dietary intake, blood concentrations [82]. In androgen-independent prostate cancer PC3 and DU145 cell lines microRNA-151 (miR-151) are upregulated [83]. It was demonstrated that genistein inhibits oncogenic miR-151 in both PC3 and DU145 cell lines [83]. It was also demonstrated that genistein treatment with radiation in PC-3 prostate cancer cells promotes apoptosis and arrests G_2/M cell cycle by inhibiting radiation-induced NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) activation [84]. It is evident that genistein has antimetastatic effect and also modulates the metastatic potential markers [85].

In a randomized double-blind clinical trial conducted by Lazarevic et al., administration of 30 mg of synthetic genistein prior to radical prostatectomy decreased the serum PSA and PSA levels in tumor tissue compared to the patients receiving placebo [86]. The adverse effects at this dose were mild [86]. In a study conducted by Dalais et al., soy-containing high-phytoestrogen diet (genistein, daidzein, and glycitein) is shown to favorably influence PSA levels in prostate cancer patients [87]. In vitro studies indicate that isoflavones have the potential to cause genetic damage [88]. However, in a study conducted by Miltyk et al., 20 prostate cancer patients were administered genistein at a dose of 300 mg for 28 days and an increase to 600 mg for another 56 days did not cause genotoxicity [88].

3.7 RESVERATROL

Resveratrol (Figure 3.7) is a polyphenol derivative extracted in 1940s from the roots of white hellebore (*Veratrum grandiflorum*) [89,90]. Specifically, it is a *trans*-3,5,4′-trihydroxy stilbene [89]. Resveratrol was later identified in various plants such as grapes, berries, and peanuts [89,90]. It is considered as a phytoalexin, which is biosynthesized in plants due to ultraviolet irradiation, stress, injury, or as a defense

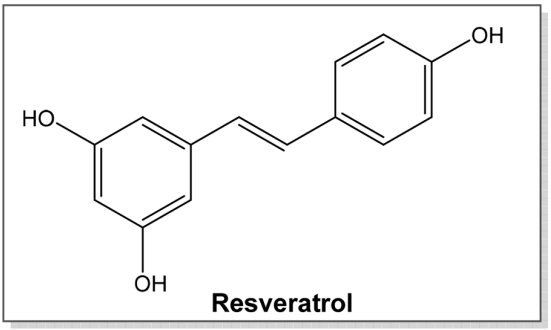


FIGURE 3.7 Structure of resveratrol.

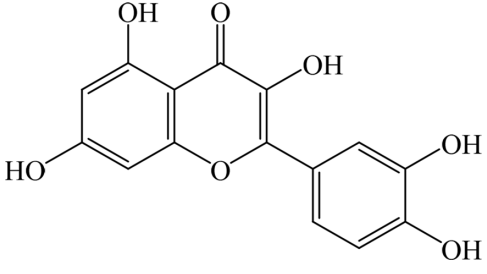
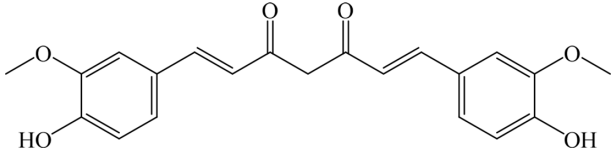
mechanism in response to fungal infections [89]. One gram of fresh grape skins contains about 50–100 mg of resveratrol [89]. Approximately 0.2–7.7 mg/L of resveratrol is present in wine, although the content levels depend on several factors including climatic conditions and the type of wine [89]. For instance, wines from colder regions tend to have higher resveratrol concentrations than wines from warmer climates, while red wine has higher resveratrol concentrations than white wine [91,92]. Studies indicate that resveratrol may have potential clinical benefits in cancer (prostate, breast, colorectal), neurologic disorders such as Alzheimer's and stroke, fatty liver disease (nonalcoholic), type 2 diabetes, and cardiovascular disorders [93].

Resveratrol has poor oral bioavailability because it undergoes extensive first pass metabolism in the intestine and liver predominantly by sulfate conjugation [94]. To improve its bioavailability and cellular penetration, resveratrol-loaded polylactic-co-glycolic acid (PLGA) nanoparticles are currently being investigated [95]. Jang et al. made a breakthrough by demonstrating that resveratrol inhibits cyclooxygenase enzymes and therefore possesses anti-inflammatory properties [96]. With regard to the prostate cancer, studies have demonstrated that resveratrol inhibits cellular events associated with tumor initiation and tumor promotion and exhibits antimutagenic and antiproliferative properties [96]. Resveratrol at 2.5×10^{-5} M concentration was shown to have significant antiapoptic effect against LNCaP prostate cell lines [97]. Sheth et al. demonstrated that resveratrol suppresses microRNA-21 (miR-21) expression by inhibiting akt pathway in PC-3M-MM2 aggressive human prostate cancer lines [98]. Kjaer et al. conducted a randomized clinical trial in middle-aged men with metabolic syndrome by administering resveratrol for 4 months with a daily dose of 150 mg or 1000 mg. Resveratrol at the highest dose decreased the serum levels of androgen precursors such as androstenedione, dehydroepiandrosterone, and dehydroepiandrosterone-sulfate; however, it did not alter the PSA levels, prostate size, testosterone, and dihydrotestosterone levels [99].

3.8 OTHER AGENTS

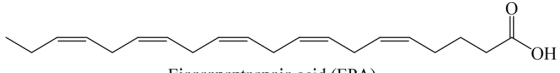
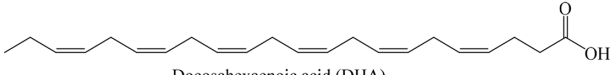
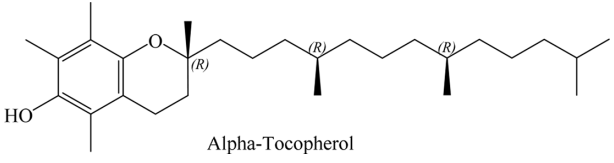
Refer to Table 3.2 for details regarding other agents that may have variable effects on prostate cancer.

TABLE 3.2
Chemical Structure, Natural Sources, Chemical Class, and Key Information About Agents That have Variable Effects in Prostate Cancer

Other Agents	Chemical Structure	Natural Sources	Chemical Class	Comments
Quercetin		Various vegetable and fruits including onions, grapes, apples, tea, berries, shallots [100]	Flavonoid	Quercetin acts by multiple mechanisms and is shown to induce apoptosis, inhibit proliferation, and inhibit angiogenesis in prostate cancer [101]. Xing et al. demonstrated that quercetin in a dose-dependent manner inhibits androgen receptor expression in LNCaP prostate cancer cells [102]. New quercetin formulations are currently being investigated such as nanomicelle drug delivery due to its poor water solubility and bioavailability [103]
Curcumin		Rhizome of turmeric (*Curcuma longa*)	Polyphenol containing bis-α,β-unsaturated β-diketone [104]	Curcumin is shown to significantly inhibit cell proliferation and induce apoptosis in LNCaP prostate cell lines [105]. In a randomized double-blind study combined supplement of curcumin and soy isoflavones was shown to inhibit PSA levels [106]

(*Continued*)

TABLE 3.2 (*Continued*)
Chemical Structure, Natural Sources, Chemical Class, and Key Information About Agents that have Variable Effects in Prostate Cancer

Other Agents	Chemical Structure	Natural Sources	Chemical Class	Comments
Omega-3 fatty acids	 Eicosapentaenoic acid (EPA)  Docosahexaenoic acid (DHA)	Animal omega-3 fatty acids are found in fishes and other marine organisms	Polyunsaturated fatty acids	While some studies suggest Omega-3 poly unsaturated fatty acids, especially EPA may decrease the risk of prostate cancer [107–109]. On the contrary, there are reports that indicate omega-3 fatty acids may be associated with greater risk [109,110]. Other data suggest there is insufficient data to support it one way or the other [111]. More studies must be conducted to clearly understand the role of omega-3 fatty acids in prostate cancer
Vitamin E (alpha, beta, gamma, and delta tocopherol and tocotrienol) [112]	 Alpha-Tocopherol	Vegetable oils such as wheatgerm, sunflower, and soybean oil [112]	Fat-soluble vitamin containing chromanol ring	While some reports suggest that vitamin E and selenium may be beneficial in prostate cancer, other findings are contradictory to these effects. In a long-term follow-up "Selenium and Vitamin E Cancer Prevention Trial" (SELECT) in relatively healthy men indicates that supplementation of vitamin E and/or selenium leads to an increased risk of prostate cancer [113]
Selenium	Element symbol: Se Atomic number: 34	Brazil nuts, eggs, and fish [114]	Nonmetal	

REFERENCES

1. Shimizu H, Ross RK, Bernstein L, Yatani R, Henderson BE, Mack TM. Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County. *Br J Cancer*. 1991;63(6):963–966.
2. American Cancer Society. Key Statistics for Prostate Cancer. https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html.
3. Trottier G, Bostrom PJ, Lawrentschuk N, Fleshner NE. Nutraceuticals and prostate cancer prevention: A current review. *Nat Rev Urol*. 2010;7(1):21–30.
4. Houghton LA, Vieth R. The case against ergocalciferol (vitamin D2) as a vitamin supplement. *Am J Clin Nutr*. 2006;84(4):694–697.
5. Bikle DD. Vitamin D metabolism, mechanism of action, and clinical applications. *Chem Biol*. 2014;21(3):319–329.
6. Perez-Lopez FR. Vitamin D: The secosteroid hormone and human reproduction. *Gynecol Endocrinol*. 2007;23(1):13–24.
7. Cesari M, Incalzi RA, Zamboni V, Pahor M. Vitamin D hormone: A multitude of actions potentially influencing the physical function decline in older persons. *Geriatr Gerontol Int*. 2011;11(2):133–142.
8. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357(3):266–281.
9. Gupta D, Lammersfeld CA, Trukova K, Lis CG. Vitamin D and prostate cancer risk: A review of the epidemiological literature. *Prostate Cancer Prostatic Dis*. 2009;12(3):215–226.
10. Skowronski RJ, Peehl DM, Feldman D. Actions of vitamin D3, analogs on human prostate cancer cell lines: Comparison with 1,25-dihydroxyvitamin D3. *Endocrinology*. 1995;136(1):20–26.
11. Trump DL, Aragon-Ching JB. Vitamin D in prostate cancer. *Asian J Androl*. 2018;20(3):244–252.
12. Bernardi RJ, Johnson CS, Modzelewski RA, Trump DL. Antiproliferative effects of 1alpha,25-dihydroxyvitamin D(3) and vitamin D analogs on tumor-derived endothelial cells. *Endocrinology*. 2002;143(7):2508–2514.
13. Verlinden L, Verstuyf A, Convents R, Marcelis S, Van Camp M, Bouillon R. Action of 1,25(OH)2D3 on the cell cycle genes, cyclin D1, p21 and p27 in MCF-7 cells. *Mol Cell Endocrinol*. 1998;142(1–2):57–65.
14. Johnson CS, Muindi JR, Hershberger PA, Trump DL. The antitumor efficacy of calcitriol: Preclinical studies. *Anticancer Res*. 2006;26(4A):2543–2549.
15. Marshall DT, Savage SJ, Garrett-Mayer E, et al. Vitamin D3 supplementation at 4000 international units per day for one year results in a decrease of positive cores at repeat biopsy in subjects with low-risk prostate cancer under active surveillance. *J Clin Endocrinol Metab*. 2012;97(7):2315–2324.
16. Van Veldhuizen PJ, Taylor SA, Williamson S, Drees BM. Treatment of vitamin D deficiency in patients with metastatic prostate cancer may improve bone pain and muscle strength. *J Urol*. 2000;163(1):187–190.
17. Gross C, Stamey T, Hancock S, Feldman D. Treatment of early recurrent prostate cancer with 1,25-dihydroxyvitamin D3 (calcitriol). *J Urol*. 1998;159(6):2035–2039; discussion 9–40.
18. Ahonen MH, Tenkanen L, Teppo L, Hakama M, Tuohimaa P. Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland). *Cancer Causes Control*. 2000;11(9):847–852.
19. Chen TC, Holick MF. Vitamin D and prostate cancer prevention and treatment. *Trends Endocrinol Metab*. 2003;14(9):423–430.
20. Park SY, Cooney RV, Wilkens LR, Murphy SP, Henderson BE, Kolonel LN. Plasma 25-hydroxyvitamin D and prostate cancer risk: The multiethnic cohort. *Eur J Cancer*. 2010;46(5):932–936.

21. Posadino AM, Phu HT, Cossu A, et al. Oxidative stress-induced Akt downregulation mediates green tea toxicity towards prostate cancer cells. *Toxicol In Vitro*. 2017;42:255–262.
22. Mukhtar H, Ahmad N. Tea polyphenols: Prevention of cancer and optimizing health. *Am J Clin Nutr*. 2000;71(6 Suppl):1698S-1702S; discussion 703S–704S.
23. Namal Senanayake SPJ. Green tea extract: Chemistry, antioxidant properties and food applications—A review. *J Funct Foods*. 2013;5(4):1529–1541.
24. Sanlier N, Gokcen BB, Altuğ M. Tea consumption and disease correlations. *Trends Food Sci Technol*. 2018;78:95–106.
25. Rady I, Mohamed H, Rady M, Siddiqui IA, Mukhtar H. Cancer preventive and therapeutic effects of EGCG, the major polyphenol in green tea. *Egyptian J Basic Appl Sci*. 2018;5(1):1–23.
26. Johnson JJ, Bailey HH, Mukhtar H. Green tea polyphenols for prostate cancer chemoprevention: A translational perspective. *Phytomedicine*. 2010;17(1):3–13.
27. Peter B, Bosze S, Horvath R. Biophysical characteristics of proteins and living cells exposed to the green tea polyphenol epigallocatechin-3-gallate (EGCg): Review of recent advances from molecular mechanisms to nanomedicine and clinical trials. *Eur Biophys J*. 2017;46(1):1–24.
28. Tachibana H. Green tea polyphenol sensing. *Proc Jpn Acad Ser B Phys Biol Sci*. 2011;87(3):66–80.
29. Zaveri NT. Green tea and its polyphenolic catechins: Medicinal uses in cancer and noncancer applications. *Life Sci*. 2006;78(18):2073–2080.
30. Adhami VM, Mukhtar H. Polyphenols from green tea and pomegranate for prevention of prostate cancer. *Free Radic Res*. 2006;40(10):1095–104.
31. Bettuzzi S, Brausi M, Rizzi F, Castagnetti G, Peracchia G, Corti A. Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplasia: A preliminary report from a one-year proof-of-principle study. *Cancer Res*. 2006;66(2):1234–1240.
32. Schroeder AC, Xiao H, Zhu Z, et al. A potential role for green tea as a radiation sensitizer for prostate cancer. *Pathol Oncol Res*. 2017.
33. Yang CS, Wang X, Lu G, Picinich SC. Cancer prevention by tea: Animal studies, molecular mechanisms and human relevance. *Nat Rev Cancer*. 2009;9(6):429–439.
34. Grzesik M, Naparlo K, Bartosz G, Sadowska-Bartosz I. Antioxidant properties of catechins: Comparison with other antioxidants. *Food Chem*. 2018;241:480–492.
35. Bernatoniene J, Kopustinskiene DM. The role of catechins in cellular responses to oxidative stress. *Molecules*. 2018;23(4).
36. Saeki K, Hayakawa S, Nakano S, et al. In vitro and in silico studies of the molecular interactions of epigallocatechin-3-O-gallate (EGCG) with proteins that explain the health benefits of green tea. *Molecules*. 2018;23(6).
37. Jacob SA, Khan TM, Lee LH. The effect of green tea consumption on prostate cancer risk and progression: A systematic review. *Nutr Cancer*. 2017;69(3):353–364.
38. Micali S, Territo A, Pirola GM, et al. Effect of green tea catechins in patients with high-grade prostatic intraepithelial neoplasia: Results of a short-term double-blind placebo controlled phase II clinical trial. *Arch Ital Urol Androl*. 2017;89(3):197–202.
39. Guo Y, Zhi F, Chen P, et al. Green tea and the risk of prostate cancer: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2017;96(13):e6426.
40. US Department of Health and Human Services and US Department of Agriculture. 2015–2020 Dietary Guidelines for Americans. 8th ed., 2015. https://health.gov/dietaryguidelines/2015/resources/2015-2020_Dietary_Guidelines.pdf.
41. Ramirez CN, Li W, Zhang C, et al. In vitro-in vivo dose response of ursolic acid, sulforaphane, PEITC, and curcumin in cancer prevention. *AAPS J*. 2017;20(1):19.

42. Jeffery EH, Brown AF, Kurilich AC, et al. Variation in content of bioactive components in broccoli. *J Food Compos Anal*. 2003;16(3):323–330.
43. Hayes JD, Kelleher MO, Eggleston IM. The cancer chemopreventive actions of phytochemicals derived from glucosinolates. *Eur J Nutr*. 2008;47(Suppl 2):73–88.
44. Shapiro TA, Fahey JW, Wade KL, Stephenson KK, Talalay P. Human metabolism and excretion of cancer chemoprotective glucosinolates and isothiocyanates of cruciferous vegetables. *Cancer Epidemiol Biomarkers Prev*. 1998;7(12):1091–1100.
45. Herr I, Buchler MW. Dietary constituents of broccoli and other cruciferous vegetables: Implications for prevention and therapy of cancer. *Cancer Treat Rev*. 2010;36(5):377–383.
46. Ho E, Clarke JD, Dashwood RH. Dietary sulforaphane, a histone deacetylase inhibitor for cancer prevention. *J Nutr*. 2009;139(12):2393–2396.
47. Traka MH, Melchini A, Mithen RF. Sulforaphane and prostate cancer interception. *Drug Discov Today*. 2014;19(9):1488–1492.
48. Vermeulen M, Klopping-Ketelaars IW, van den Berg R, Vaes WH. Bioavailability and kinetics of sulforaphane in humans after consumption of cooked versus raw broccoli. *J Agric Food Chem*. 2008;56(22):10505–10509.
49. Tortorella SM, Royce SG, Licciardi PV, Karagiannis TC. Dietary Sulforaphane in cancer chemoprevention: The role of epigenetic regulation and HDAC inhibition. *Antioxid Redox Signal*. 2015;22(16):1382–1424.
50. Bayat Mokhtari R, Baluch N, Homayouni TS, et al. The role of sulforaphane in cancer chemoprevention and health benefits: A mini-review. *J Cell Commun Signal*. 2018;12(1):91–101.
51. Clarke JD, Dashwood RH, Ho E. Multi-targeted prevention of cancer by sulforaphane. *Cancer Lett*. 2008;269(2):291–304.
52. Cheung KL, Kong AN. Molecular targets of dietary phenethyl isothiocyanate and sulforaphane for cancer chemoprevention. *AAPS J*. 2010;12(1):87–97.
53. Veeranki OL, Bhattacharya A, Tang L, Marshall JR, Zhang Y. Cruciferous vegetables, isothiocyanates, and prevention of bladder cancer. *Curr Pharmacol Rep*. 2015;1(4):272–82.
54. Palliyaguru DL, Yuan JM, Kensler TW, Fahey JW. Isothiocyanates: Translating the power of plants to people. *Mol Nutr Food Res*. 2018;62(18):e1700965.
55. Kirsh VA, Peters U, Mayne ST, et al. Prospective study of fruit and vegetable intake and risk of prostate cancer. *J Natl Cancer Inst*. 2007;99(15):1200–1209.
56. Alumkal JJ, Slottke R, Schwartzman J, et al. A phase II study of sulforaphane-rich broccoli sprout extracts in men with recurrent prostate cancer. *Invest New Drugs*. 2015;33(2):480–489.
57. Cipolla BG, Mandron E, Lefort JM, et al. Effect of sulforaphane in men with biochemical recurrence after radical prostatectomy. *Cancer Prev Res (Phila)*. 2015;8(8):712–719.
58. Peisch SF, Van Blarigan EL, Chan JM, Stampfer MJ, Kenfield SA. Prostate cancer progression and mortality: A review of diet and lifestyle factors. *World J Urol*. 2017;35(6):867–874.
59. Steinbrecher A, Nimptsch K, Husing A, Rohrmann S, Linseisen J. Dietary glucosinolate intake and risk of prostate cancer in the EPIC-Heidelberg cohort study. *Int J Cancer*. 2009;125(9):2179–2186.
60. Gerster H. The potential role of lycopene for human health. *J Am Coll Nutr*. 1997;16(2):109–126.
61. Fraser ML, Lee AH, Binns CW. Lycopene and prostate cancer: Emerging evidence. *Expert Rev Anticancer Ther*. 2005;5(5):847–854.
62. Shi J, Le Maguer M. Lycopene in tomatoes: Chemical and physical properties affected by food processing. *Crit Rev Biotechnol*. 2000;20(4):293–334.

63. Holzapfel NP, Holzapfel BM, Champ S, Feldthusen J, Clements J, Hutmacher DW. The potential role of lycopene for the prevention and therapy of prostate cancer: From molecular mechanisms to clinical evidence. *Int J Mol Sci*. 2013;14(7):14620–14646.
64. Unlu NZ, Bohn T, Francis DM, Nagaraja HN, Clinton SK, Schwartz SJ. Lycopene from heat-induced cis-isomer-rich tomato sauce is more bioavailable than from all-trans-rich tomato sauce in human subjects. *Br J Nutr*. 2007;98(1):140–146.
65. Di Mascio P, Kaiser S, Sies H. Lycopene as the most efficient biological carotenoid singlet oxygen quencher. *Arch Biochem Biophys*. 1989;274(2):532–538.
66. Khachik F, Carvalho L, Bernstein PS, Muir GJ, Zhao DY, Katz NB. Chemistry, distribution, and metabolism of tomato carotenoids and their impact on human health. *Exp Biol Med (Maywood)*. 2002;227(10):845–851.
67. Ivanov NI, Cowell SP, Brown P, Rennie PS, Guns ES, Cox ME. Lycopene differentially induces quiescence and apoptosis in androgen-responsive and -independent prostate cancer cell lines. *Clin Nutr*. 2007;26(2):252–263.
68. Goo YA, Li Z, Pajkovic N, et al. Systematic investigation of lycopene effects in LNCaP cells by use of novel large-scale proteomic analysis software. *Proteomics Clin Appl*. 2007;1(5):513–523.
69. Tang Y, Parmakhtiar B, Simoneau AR, et al. Lycopene enhances docetaxel's effect in castration-resistant prostate cancer associated with insulin-like growth factor I receptor levels. *Neoplasia*. 2011;13(2):108–119.
70. Giovannucci E, Rimm EB, Liu Y, Stampfer MJ, Willett WC. A prospective study of tomato products, lycopene, and prostate cancer risk. *J Natl Cancer Inst*. 2002;94(5):391–398.
71. Giovannucci E, Ascherio A, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Intake of carotenoids and retinol in relation to risk of prostate cancer. *J Natl Cancer Inst*. 1995;87(23):1767–1776.
72. Graff RE, Pettersson A, Lis RT, et al. Dietary lycopene intake and risk of prostate cancer defined by ERG protein expression. *Am J Clin Nutr*. 2016;103(3):851–860.
73. Tonucci LH, Holden JM, Beecher GR, Khachik F, Davis CS, Mulokozi G. Carotenoid content of thermally processed tomato-based food products. *J Agric Food Chem*. 1995;43(3):579–586.
74. Zu K, Mucci L, Rosner BA, et al. Dietary lycopene, angiogenesis, and prostate cancer: A prospective study in the prostate-specific antigen era. *J Natl Cancer Inst*. 2014;106(2):djt430.
75. Schwarz S, Obermuller-Jevic UC, Hellmis E, Koch W, Jacobi G, Biesalski HK. Lycopene inhibits disease progression in patients with benign prostate hyperplasia. *J Nutr*. 2008;138(1):49–53.
76. Paur I, Lilleby W, Bohn SK, et al. Tomato-based randomized controlled trial in prostate cancer patients: Effect on PSA. *Clin Nutr*. 2017;36(3):672–679.
77. Spagnuolo C, Russo GL, Orhan IE, et al. Genistein and cancer: Current status, challenges, and future directions. *Adv Nutr*. 2015;6(4):408–419.
78. Bhagwat S, Haytowitz, DB, Holden, JM. USDA Database for the Isoflavone Content of Selected Foods, Release 2.0. U.S. Department of Agriculture, Agricultural Research Service, Nutrient Data Laboratory. https://data.nal.usda.gov/dataset/usda-database-isoflavone-content-selected-foods-release-20.
79. Vitale DC, Piazza C, Melilli B, Drago F, Salomone S. Isoflavones: Estrogenic activity, biological effect and bioavailability. *Eur J Drug Metab Pharmacokinet*. 2013;38(1):15–25.
80. Adjakly M, Ngollo M, Boiteux JP, Bignon YJ, Guy L, Bernard-Gallon D. Genistein and daidzein: Different molecular effects on prostate cancer. *Anticancer Res*. 2013;33(1):39–44.

81. Guo Y, Wang S, Hoot DR, Clinton SK. Suppression of VEGF-mediated autocrine and paracrine interactions between prostate cancer cells and vascular endothelial cells by soy isoflavones. *J Nutr Biochem*. 2007;18(6):408–417.
82. Huang X, Chen S, Xu L, et al. Genistein inhibits p38 map kinase activation, matrix metalloproteinase type 2, and cell invasion in human prostate epithelial cells. *Cancer Res*. 2005;65(8):3470–3478.
83. Chiyomaru T, Yamamura S, Zaman MS, et al. Genistein suppresses prostate cancer growth through inhibition of oncogenic microRNA-151. *PLoS One*. 2012;7(8):e43812.
84. Raffoul JJ, Wang Y, Kucuk O, Forman JD, Sarkar FH, Hillman GG. Genistein inhibits radiation-induced activation of NF-kappaB in prostate cancer cells promoting apoptosis and G2/M cell cycle arrest. *BMC Cancer*. 2006;6:107.
85. Pavese JM, Farmer RL, Bergan RC. Inhibition of cancer cell invasion and metastasis by genistein. *Cancer Metastasis Rev*. 2010;29(3):465–482.
86. Lazarevic B, Boezelijn G, Diep LM, et al. Efficacy and safety of short-term genistein intervention in patients with localized prostate cancer prior to radical prostatectomy: a randomized, placebo-controlled, double-blind phase 2 clinical trial. *Nutr Cancer*. 2011;63(6):889–898.
87. Dalais FS, Meliala A, Wattanapenpaiboon N, et al. Effects of a diet rich in phytoestrogens on prostate-specific antigen and sex hormones in men diagnosed with prostate cancer. *Urology*. 2004;64(3):510–515.
88. Miltyk W, Craciunescu CN, Fischer L, et al. Lack of significant genotoxicity of purified soy isoflavones (genistein, daidzein, and glycitein) in 20 patients with prostate cancer. *Am J Clin Nutr*. 2003;77(4):875–882.
89. Aggarwal BB, Bhardwaj A, Aggarwal RS, Seeram NP, Shishodia S, Takada Y. Role of resveratrol in prevention and therapy of cancer: Preclinical and clinical studies. *Anticancer Res*. 2004;24(5A):2783–2840.
90. Gueguen N, Desquiret-Dumas V, Leman G, et al. Resveratrol directly binds to mitochondrial complex I and increases oxidative stress in brain mitochondria of aged mice. *PLoS One*. 2015;10(12):e0144290.
91. Goldberg DM, Yan J, Ng E, et al. A global survey of trans-resveratrol concentrations in commercial wines. *Am J Enol Viticult*. 1995;46(2):159–165.
92. Kopp P. Resveratrol, a phytoestrogen found in red wine. A possible explanation for the conundrum of the 'French paradox'? *Eur J Endocrinol*. 1998;138(6):619–620.
93. Berman AY, Motechin RA, Wiesenfeld MY, Holz MK. The therapeutic potential of resveratrol: A review of clinical trials. *NPJ Precis Oncol*. 2017;1.
94. Walle T, Hsieh F, DeLegge MH, Oatis JE, Jr., Walle UK. High absorption but very low bioavailability of oral resveratrol in humans. *Drug Metab Dispos*. 2004;32(12):1377–1382.
95. Nassir AM, Shahzad N, Ibrahim IAA, Ahmad I, Md S, Ain MR. Resveratrol-loaded PLGA nanoparticles mediated programmed cell death in prostate cancer cells. *Saudi Pharm J*. 2018;26(6):876–885.
96. Jang M, Cai L, Udeani GO, et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science*. 1997;275(5297):218–220.
97. Hsieh TC, Wu JM. Differential effects on growth, cell cycle arrest, and induction of apoptosis by resveratrol in human prostate cancer cell lines. *Exp Cell Res*. 1999;249(1):109–115.
98. Sheth S, Jajoo S, Kaur T, et al. Resveratrol reduces prostate cancer growth and metastasis by inhibiting the Akt/MicroRNA-21 pathway. *PLoS One*. 2012;7(12):e51655.
99. Kjaer TN, Ornstrup MJ, Poulsen MM, et al. Resveratrol reduces the levels of circulating androgen precursors but has no effect on, testosterone, dihydrotestosterone, PSA levels or prostate volume. A 4-month randomised trial in middle-aged men. *Prostate*. 2015;75(12):1255–1263.

100. Li Y, Yao J, Han C, et al. Quercetin, inflammation and immunity. *Nutrients*. 2016;8(3):167.
101. Yang F, Song L, Wang H, Wang J, Xu Z, Xing N. Quercetin in prostate cancer: Chemotherapeutic and chemopreventive effects, mechanisms and clinical application potential (Review). *Oncol Rep*. 2015;33(6):2659–2668.
102. Xing N, Chen Y, Mitchell SH, Young CY. Quercetin inhibits the expression and function of the androgen receptor in LNCaP prostate cancer cells. *Carcinogenesis*. 2001;22(3):409–414.
103. Zhao J, Liu J, Wei T, et al. Quercetin-loaded nanomicelles to circumvent human castration-resistant prostate cancer in vitro and in vivo. *Nanoscale*. 2016;8(9):5126–5138.
104. Stanic Z. Curcumin, a compound from natural sources, a true scientific challenge—A review. *Plant Foods Hum Nutr*. 2017;72(1):1–12.
105. Dorai T, Cao YC, Dorai B, Buttyan R, Katz AE. Therapeutic potential of curcumin in human prostate cancer. III. Curcumin inhibits proliferation, induces apoptosis, and inhibits angiogenesis of LNCaP prostate cancer cells in vivo. *Prostate*. 2001;47(4):293–303.
106. Ide H, Tokiwa S, Sakamaki K, et al. Combined inhibitory effects of soy isoflavones and curcumin on the production of prostate-specific antigen. *Prostate*. 2010;70(10):1127–1133.
107. Reese AC, Fradet V, Witte JS. Omega-3 fatty acids, genetic variants in COX-2 and prostate cancer. *J Nutrigenet Nutrigenomics*. 2009;2(3):149–158.
108. Moreel X, Allaire J, Leger C, et al. Prostatic and dietary omega-3 fatty acids and prostate cancer progression during active surveillance. *Cancer Prev Res (Phila)*. 2014;7(7):766–776.
109. Liang P, Gao M. Fish oil and prostate cancer: Effects and clinical relevance. *Cancer Transl Med*. 2017;3(3):80–86.
110. Dahm CC, Gorst-Rasmussen A, Crowe FL, et al. Fatty acid patterns and risk of prostate cancer in a case-control study nested within the European Prospective Investigation into Cancer and Nutrition. *Am J Clin Nutr*. 2012;96(6):1354–1361.
111. Aucoin M, Cooley K, Knee C, et al. Fish-derived omega-3 fatty acids and prostate cancer: A systematic review. *Integr Cancer Ther*. 2017;16(1):32–62.
112. Rizvi S, Raza ST, Ahmed F, Ahmad A, Abbas S, Mahdi F. The role of vitamin e in human health and some diseases. *Sultan Qaboos Univ Med J*. 2014;14(2):e157–e165.
113. Klein EA, Thompson IM, Jr, Tangen CM, et al. Vitamin E and the risk of prostate cancer: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA*. 2011;306(14):1549–1556.
114. National Institutes of Health. The Office of Dietary Supplements. Selenium. https://ods.od.nih.gov/factsheets/Selenium-HealthProfessional/#h3.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

4 Nutraceutical's Role in Proliferation and Prevention of Colorectal Cancer

Mayur M. Patel, Shruti U. Rawal, and Jayvadan K. Patel

CONTENTS

4.1 INTRODUCTION

Cancer rates are tolling high constantly worldwide. High life expectancy, environmental changes, urbanization, and changing lifestyles have been vital contributive factors for the hike in carcinogenesis. Carcinogenesis is a complex process that involves numerous pathways that bring oncogenetic transformation in the normal

cells and render them unassailably viable. The cancer cells undergo unlimited replication due to growth signal autonomy, evasion of growth and inhibitory signals, evasion of apoptosis, invasion, metastasis, and sustained angiogenesis [1]. The fact that cancer cells are very similar to the normal human cells makes them a very difficult target. In spite of extensive research and development in the field of oncology, it still remains a big challenge to prevent, treat, or mitigate this disease. Among several cancer subtypes, one of the highly incidental and preventive cancer is the colorectal cancer (CRC). As per American Cancer Society's (ACS) statistical data, CRC is the third most common cancer worldwide. CRC is one of the most lethal cancers contributing to about 7,000,000 annual cancer-related deaths [2]. The ACS has estimated an astounding statistics that claims 97,220 new cases of colon and 43,030 new cases of rectal cancer present every year. Their extrapolated estimates for 2018 presented a lifetime risk of about 1 in 22 men and 1 in 24 women to be suffering from CRC. The global burden of CRC is expected to increase by 60 % till 2030; expecting about 2.2 million new cases and about 1.1 million deaths. Out of several risk factors that are believed to contribute to the pathogenesis of this lethal disease, diet and lifestyle have been realized to have a principal role. Lifestyle was identified to be a leading cause, with contribution to etiology of about 90%–95% of all cancers, while only 5%–10% was found to be due to genetic fault [3,4]. The latest CRC report 2017, generated by World Cancer Research Fund International in coalition with the American Institute of Cancer Research has emphasized the role of diet, weight, and physical activity in the prevention and control of CRC [5]. A global scientific research was undertaken by World Cancer research fund international as a part of Continuous Update Project (CUP) to establish the association of the above-mentioned factors in the development and prevention of CRC. The study has underpinned the research findings from over 99 worldwide studies, comprising of more than 29 million adults and over 2,47,000 cases. The incidence and death statistics results were found to vary by about 10-fold worldwide owing to regional and lifestyle disparities. Surprisingly, the trends and patterns of CRC were found to strongly corelate with food and lifestyles. For instance, the incidental rates of CRC in Indian subcontinent (30 cases per million) was radically less than the incidental rates of CRC worldwide (530 cases per million). This striking difference in the incidence rates was a subject of several research works that tried to explore the underlying reasons. Indian environment, lifestyle, and diet were the common reasons that justified the low CRC rates in India. Indian diet in contrast to the Western diet was found to be rich in dietary fiber, probiotics, and spices that might play a vital role in CRC epidemiology. Also, vegetarianism and lower red meat intake were found to have been linked to the prevention of the CRC incidence in the Indian subpopulation [6].

The concept of use of food as medicine has been in applied since the maxim "let food be thy medicine and medicine be thy food" was introduced by Hippocrates almost 25 centuries ago [6]. Increased awareness about association of dietary habits and lifestyle in prevention and treatment of CRC has led to establish a strong foundation for the use of nutraceuticals as complementary and alternative medicine. Several bioactive dietary elements/"functional foods"/"nutraceuticals" have been identified to have chemopreventive and chemotherapeutic roles in CRC. The term " nutraceutical" was coined by Dr. Stephen De Felice in 1989, who defined them

to be bioactive natural foods/food ingredients/dietary supplements having nutritive and therapeutic values [7,8]. To be precise, any extracted and purified biomolecule derived from plant/animal/marine/microbial or mineral food sources with nutritive and therapeutic value is known as "nutraceutical." On the contrary, any semi-purified or crude source of nutrition, consumed as a regular food, that supports human health and welfare and provides health benefits beyond basic nourishment and nutrition is termed as "functional food." The line of differentiation between a nutraceutical and functional food can further be explained in terms of the volume of consumption. Nutraceuticals being concentrated forms need to be consumed in smaller amounts in contrast to the functional foods that need to be consumed in large amounts. Nutraceuticals mainly comprise of dietary fibers, probiotics, prebiotics, polyunsaturated fatty acids (PUFA), antioxidants, vitamins, polyphenols, and spices [9,10]. Nutraceuticals have grabbed attention of the scientific community as an alternative to the existing oncotherapy owing to several outweighing benefits over it.

4.2 COLORECTAL CANCER CLASSIFICATION, ETIOLOGY, AND LEADING RISK FACTORS

Colorectal carcinoma is the cancer that starts in distal alimentary canal (large intestine) involving colon and/or rectum. Most of the CRC initiate with the development of "polyps," which are small growth on the inner lining (mucosa) of colon or rectum. Some of these polyps are precancerous and may progress to the development of cancer. Polyps that are flat or have raised growths are termed as sessile polyps, and those having a growth on short stalks are termed as pedunculated polyps. The presence of polyps, however, does not always indicate a cancerous or even precancerous condition. Noncancerous polyps include small hyperplastic polyps, inflammatory polyps, and hamartomatous polyps, which are not part of an inherited polyp syndrome. Cancerous polyps are hyperplastic polyps and adenomas. Polyps have to be extracted during colonoscopy in order to determine their nature and prevent CRC incidence [11].

4.2.1 Classification of CRC

According to the site of origin of carcinogenesis in colon or rectal tissues, CRC has been classified into the following four categories:

1. **Colorectal adenocarcinoma**: carcinoma that starts in the goblet cells (cells making mucus) that constitutes about 96% of all CRC cases. Other subtypes of this type of CRCs, viz., signet ring and mucinous adenocarcinoma exhibit poor prognosis.
2. **Gastrointestinal carcinoid tumors/carcinoid tumors**: carcinoma that develops in the diffuse neuroendocrine cells (special hormone making cells of intestine).
3. **Gastrointestinal stromal tumors**: the cancer that develops in specialized colon cells called interstitial cells of Cajal.

4. **Lymphomas**: When there is carcinogenic mutation in the immune cells/lymph nodes, it is called lymphoma. When such type of cancer starts developing in the colon or rectum or any other organ, it is called non-Hodgkin lymphoma.

4.2.2 Etiology of CRC

About 70%–80% of the CRCs have sporadic origin (no hereditary cause). While there is a possibility of about 20%–30% of the CRC cases having a hereditary disposition, only 5% of the cases have been observed to be due to genetic cause [11]. Sporadic forms of CRC develop in the form of polyps, most of which disappear spontaneously. But about 10% of these may develop into adenomas or special kind of hyperplastic polyps within 8–10 years.

Cancer is one of the diseases having a strong genetic basis that basically develops due to an imbalance of tumor suppressor gene and the oncogene DNA expressions. Many research works have evidenced some genetic mutations to be contributive to the development of CRC. The hereditary forms of CRCs are familial adenomatous polyposis (FAP) and Lynch syndrome. FAP is a condition caused by inherited changes in the *APC* gene, subclassified as attenuated FAP (AFAP), Gardner syndrome, and Turcot syndrome. These patients are at a higher risk of developing CRC. Turcot syndrome develops due to mutations in the *STK11 (LKB1)* gene and may be subclassified into Peutz–Jeghers syndrome and MYH-associated polyposis. The patients suffering from this condition tend to have freckles around the mouth with different type of polyp called hamartomas in their alimentary canal. Lynch syndrome (hereditary nonpolyposis colon cancer, or HNPCC) is caused by mutation in one of the DNA repair enzyme genes like MLH1, MLH3, MSH2, PMS1, MSH6, and PMS2, which can allow DNA errors to go unrectified. This condition can predispose to the development of CRC in later stages of life. Except these, there are several acquired genetic mutations that may be held responsible for the development of CRC [11].

The entire mechanism of the pathogenesis of CRC oncogenesis can be explained by any one of the following four carcinogenic pathways: “adenocarcinoma sequence type,” “de novo type,” “HNPCC type,” and “colitic cancer type.” The details on each of these molecular pathways are given elsewhere [12].

4.2.3 Risk Factors Associated with CRC Development and Progression

Several risk factors have been identified to be majorly responsible for the development of CRC. Being overweight or obese, being physically inactive, consuming high-fat diet, red/processed meat diet, tobacco, alcohol, and smoking are probable high-risk factors leading to CRC. Patients with inflammatory bowel disease (IBD) also have a higher risk of developing CRC in later stages of life. Some of the iatrogenic causes may be radiation therapy and NSAIDs administration. Both preventive and contributive factors to CRC have been demonstrated in Figure 4.1.

Also, it has been a common observation from many researchers that a diet rich in vegetables, fruits, and whole grains may lower the risk of developing CRC. A diet rich

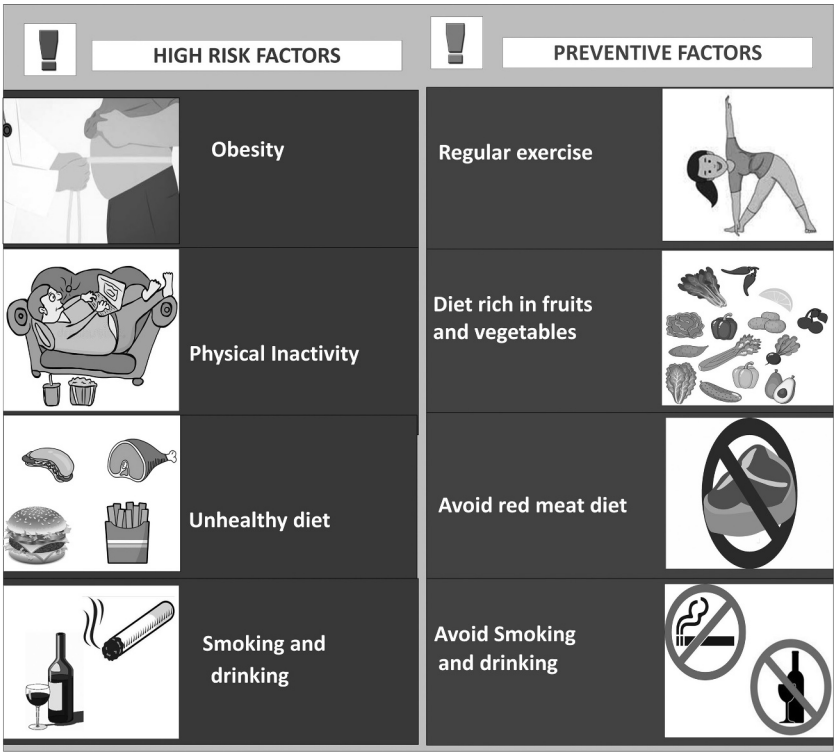


FIGURE 4.1 High risk factors and preventive factors for CRC.

in micronutrients such as vitamins, calcium, iron, and selenium have also been associated with lowering the risk of developing CRC. Hormone replacement therapy in postmenopausal women has also been associated with lowered risk of CRC development.

4.3 MOLECULAR PATHWAYS AND TARGETS FOR NUTRACEUTICALS-MEDIATED ANTICANCER ACTION

Dysregulation of gene products has been identified to be the root cause of most of the cancers, irrespective of whether it has a genetic origin or not. As many as 500 gene products including but not limited to proapoptotic proteins (e.g., TNF, Fas, TRAIL), protein kinases (e.g., Src), growth factors (e.g. EGF, VEGF, and IGF-1), inflammatory enzymes (e.g., COX-2, 5-LOX, and PLA-2), inflammatory cytokines (e.g., TNF, Ire4L-1, and IL-6), tumor suppressors (e.g., p53 and Rb), antiapoptotic proteins (e.g., Bcl-2, Bcl-xL, cFLIP, IAP-1, IAP-2, and survivin), and transcription factors (e.g., NF-κB, AP-1, STAT3, HIF-1, and PPARγ) get deregulated in cancerous condition [13]. Among several molecular pathways contributing to the development of CRC, proinflammatory pathway activated via transcription factor NF-κB is vital. Association of the NF-κB activation with the pathogenesis of CRC has been well-established. NF-κB has been found to be activated by several risk factors like

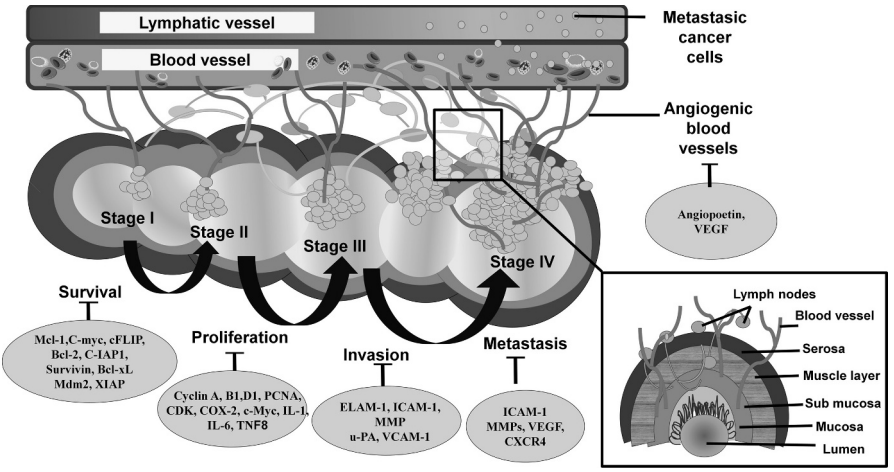


FIGURE 4.2 Molecular targets of several nutraceuticals that play an imperative role in CRC pathogenesis.

chemical and physical stress, environmental pollutants, and diet including grilled meat, fried foods, and saturated fatty acids. NF-κB plays an important role in regulating the gene expression of genetic products that mediate cell survival (e.g., antiapoptotic proteins like Bcl-2, cFLIP, Bcl-xL, survivin, IAP-1, and IAP-2), cell proliferation (e.g., c-myc, cyclin D1, and COX-2), cell invasion (e.g., MMP-9, ELAM-1, ICAM-1, 5-LOX, and VCAM-1), and neo-angiogenesis (e.g., IL-8, TNF, VEGF, and IL-1) [14]. Due to the involvement of multiple gene products in CRC pathogenesis, it is postulated that a multitargeted approach is better suited for its treatment rather than a specifically targeted approach. Nature has bestowed several miraculous nutraceuticals that can be used to downregulate several of these molecular targets participating in CRC pathogenesis [13]. Figure 4.2 illustrates important molecular targets involved in CRC pathogenesis that are modulated by several nutraceuticals.

4.4 FUNCTIONAL FOODS AND NUTRACEUTICALS IN COLORECTAL CANCER: PREVENTION AND TREATMENT

Several types of nutraceuticals have been identified to play a vital role in the inhibition of growth and spread of CRC. Anticancer potential of these nutraceuticals can be conferred to their antimutagenic, immunity-enhancing, antiangiogenic, and antioxidant properties. Besides being cost-effective and having multimolecular targeting ability, numerous nutraceuticals have been established for their chemopreventive and anticancer activity in several cancers including CRC. Nutrients have a vital role in carrying out the normal activities in cells and suffice a proper body functioning. All cellular activities are regulated through genetic expression of DNA. Realization of the role of genomics in directing nutrient functionality and their biochemical pathway intervention has laid the foundation for the development of a field termed as "nutrigenomics" [15,16]. Nutrigenomics is a science that correlates plant

biochemistry, genomics, and human nutrition [17]. Nutrigenomics has been applied to establish novel molecular targets that can be targeted by novel nutraceuticals.

According to the estimates of ACS and National Cancer Institute (NCI), inclusion of fruits and vegetables in diet can reduce the incidence of CRC by about 35%. Also, there has been a considerable rise in the FDA approval of either natural products, natural product derivatives, compounds based on natural products, or mimics of natural products for their anticancer activity within last four decades [18]. Several nutraceuticals like allicin, alpha-tocopherol, acetoxychavicol acetate (ACA), anacardic acid, acetylapoaranotin, avenanthramides, apigenin, anethole, astaxanthin, anthocyanidins, betulinic acid, butein, berberine, beta-carotene, boswellic acid, β-escin, biochanin, capsaicin, catechins, casein, caffeic acid, cardamonin, conjugated linolenic acid, celastrol, curcumin, chrysin, cryptoxanthin, and carotenoids like lycopene, oxycarotenoids like lutein, and zeaxanthin, daidzein, diosgenin, deguelin, diallyl sulfide, deoxyelephantopin, dietary fibers, epigallocatechin gallate (EGCG), ellagic acid, embelin, evodiamine, eugenol, fucoxanthin, fucoxanthinol, fisetin, flavopiridol, flavonoids, ferulic acid, folic acid, gambogic acid, garcinol, gossypol, guggulsterone, gingerol, genistein, galangin, honokiol, hesperitin, halocynthiaxanthin, indirubin, indole-3 carbinol, isorhamnetin, isoflavones, kaempferol, laminarin, luteolin, myricetin, morin, magnolol, naringenin, noscapine, nimbolide, oleuropein, omega-3 fatty acid, omega-6 fatty acid, piperine, piceatannol, pinitol, plumbagin, pterostilbene, perillyl alcohol, phytic acid, procyanidins, prebiotics, probiotics, quercetin, rhizochalin, resveratrol, rosmarinic acid, scallian, salograriolide A, sanguinarine, sulphoraphane, siphonaxanthin, sesamin, silibinin, secoisolariciresinol diglucoside (SDG), sphingadiene, selenium, tocotrienol, triptolide, thymoquinone, taxol, ursolic acid, vanillin, withanolides, xanthohumol, zeaxanthin, and zerumbone have been explored for the treatment of CRC (Table 4.1). These nutraceuticals act through modulation of several molecular targets that are proactive in CRC development.

Nutraceuticals have been classified in diverse ways depending upon the source of origin (plant, animal, mineral, microbial or marine), stage of acceptance (potential, established), chief applications (dietary supplement, nutritive supplement, herbal) and their chemical nature.

Harborne has widely classified the nutraceuticals according to their chemical nature into terpenoids that include monoterpenoids, iridoids, sesquiterpenoids, sesquiterpene, lactones, diterpenoids, steroid saponins, triterpenoid saponins, cardenolides, bufadenolides, cucurbitacins, phytosterols, nortriterpenoids, other triterpenoids, and carotenoids.

Polyphenolic compounds, viz., anthochlors, anthocyanins, chromones, benzofurans, coumarins, flavonoids (anthocyanins, flavanols, flavanones, flavones, flavonols, and isoflavonoids), phenolic acids, lignans, stilbenes, phenylpropanoids, phenolic ketones, quinonoids, stilbenoids, tannins, and xanthones.

The alkaloids are broadly categorized into diterpenoid, betalain, isoquinoline, indole, peptide, pyrrolidine and piperidine, pyrrolizidine, lycopodium, quinoline, quinolizidine, steroidal, and tropane alkaloid compounds.

Amino acids, proteins, nonprotein amino acids, fatty acids, cyanogenic glycosides, amines, purines, pyrimidines, glucosinolates, carbohydrates, and minerals are also widely used anticancer agents against CRC. Considering the limitation of

TABLE 4.1
Nutraceuticals Having Chemopreventive and Anticancer Activity Against CRC

Nutraceutical	Nutritional Sources	Molecular Targets	Cell Line[s]/Animal Model	References
Allicin	Garlic, onions, shallots, Chinese chives and leeks	Nrf2-mediated luciferase transactivation activity	HT-29, SW480 [human colon cancer], HT-9/HL-60, LS174T, HCT-116, HT-29, Caco-2 (human colon cancers)	[125,126]
Acetoxychavicol acetate	*Alpinia galangal*, blue ginger	NAD(P)H, GST, GSH, NQO1, p21, Nrf2	IEC6	[127]
Anacardic acid	Cashew, semecarpus anacardium	Histone modifications p300, PCAF, and Tip60 HATs modification, NF-κB, p65 inhibition	HCT-8	[128–130]
Acetylapoaranotin	Aspergillus	Bcl-2, caspase-3, -8, -9, Bax, Bcl-xL, and cleavage-mediated apoptosis	HCT116	[131]
Apigenin	Parsley, celery, celeriac, and chamomile tea	Cell-cycle inhibitor (p21) and NAG-1 and p53 (proapoptotic proteins)	SW480, HCT-116, LoVo and HT-29 cell lines	[132,133]
Andrographolides	*Andrographis paniculata*	ROS generation mediating the caspase activation, nuclear condensation, DNA fragmentation, and mitochondrial membrane depolarization	HT-29	[134]
Anethole	Anise, liquorice, camphor, star anise, myrtle, and fennel	NF-κB, AP-1, JNK, MAPK	HCT 116 cell line	[135,136]
Astaxanthin	*Haematococcus pluvialis*, crab, and marine sources	NF-κB, MMP-9, COX-2, TNF-α, IL-8, iNOS like apoptotic proteins	dextran sulfate sodium [DSS]-induced colitis male ICR rat model and inflammation-related mouse colon cancer model	[137–139]

(*Continued*)

TABLE 4.1 (*Continued*)
Nutraceuticals Having Chemopreventive and Anticancer Activity Against CRC

Nutraceutical	Nutritional Sources	Molecular Targets	Cell Line[s]/Animal Model	References
Berberine	Barberry, *Berberis aristata*, *Tinospora cordifolia*, Oregon, grape goldenseal, yellowroot, Amur cork tree, Chinese goldthread, prickly poppy, and Californian poppy	NF-κB, COX-2, VEGF, p21, Bcl-2, survivin	SW480	[140]
		Survivin	HT-29	[141]
		MAPK, BID, Bcl-xL, c-IAP1, Bcl-2, JNK, FasL, p38	SW620	[142]
		IL-6	Colon 26	[143]
		Cyclin B1, cdc2 kinase	HCT116	[144]
		Pgp-170	COLO 205, CT26	[145]
		COX-2	DLD-1	[146]
Betulinic acid	White birch, *Ancistrocladu heyneaus*, rosemary, diospyros leucomelas, ber tree, selfheal, jambul, and flowering quince	Glyco-genes	Colo-205	[147]
		Sp3, Sp1, Sp4, survivin, VEGF, EGFR, NF-κB, PTTG-1, cyclin D1	RKO, SW480	[148]
		Topoisomerase I and IIα	SW948, HCT116	[149]
		CYP1A2	PTC	[150]
		Bad, Bcl-2	SNU-C5	[151]
		PPARγ, KLF4, Caveolin-1,	SW480	[152]
		Bcl-2, cyclin D1, Bax	HT29	[153]
		p17	Colo-205	[147]
Boswellic acid	*Boswellia serrata*	Decrease in cyclin D1 expression, 5-lipoxygenase and nuclear factor-kappaB	HT-29 cell line	[154–156]
Butein	Cashew nuts	ERK-1/-2, NF-κB, IAP-2, Bcl-xL, Bcl-2, cyclin-D1, c-Myc	CCL 220.1	[157]
β-Escin	Horse chestnut	p21waf1/cip1-mediated G1-S phase arrest and apoptosis	HT-29	[158]

(*Continued*)

TABLE 4.1 (*Continued*)
Nutraceuticals Having Chemopreventive and Anticancer Activity Against CRC

Nutraceutical	Nutritional Sources	Molecular Targets	Cell Line[s]/Animal Model	References
Beta carotene	Sweet potato, carrot, spinach, cantaloupe, butternut squash, lettuce, apricots, red bell pepper	G2/M phase apoptosis by Bcl-2, Bcl-xl family, and cyclin A downregulation	LS 180, SW620, and HCT-15	[159]
Biochanin	Red clover, soyabean	Caspase-3 and poly[ADP ribose] polymerase [PARP] activation	HCC-44B2, HCC-50D3	[160]
Casein	Milk and milk-derived products	Bacteria-mediated deconjugation of procarcinogenic glucuronides to carcinogens, L type calcium channel activation mediated apoptosis and growth suppression	HT-29 cells	[161]
Catechins [EGCG]	Red pine, *Pinus resinosa*	MMP-2, MMP-9, Notch signaling pathway	HT-29 cells, HCT-8 cells, LoVo, and SW480 cells	[162,163]
Capsaicin	Pepper, red chilli, and paprika	tNOX	HCT116	[164]
		Bax, Bcl-2	Colo 205	[165]
		Mdm2, p53, Fas (CD95), DR4, Bax, Bcl-2	HCT116	[166]
		ACC, PPARγ, AMPK	HT29	[167,168]
Cardamonin	Cardamom and *Alpinia* species	B-catenin degradation, G2/M cell-cycle arrest mediated by cyclin D1 and c-myc suppression	SW480 colon cancer cells	[169]
		DR4, DR5, DcR1, CHOP	HCT116	[169]
Celastrol	Chinese thunder of God vine	CXCR4	HCT116	[170]
		TRAIL/APO-2L	SW620	[171]
Chrysin	Passionflower, honey, and propolis	Caspase-3, -9, Bax, and Sall4	CT26	[172]
Conjugated linoleic acids [CLA]	Probiotic bacteria, eggs, mutton, beef, and mushrooms	PPARγ, CDK inhibitor $p21^{CIP1/WAF1}$ induced apoptosis	Caco-2	[173]
Caffeic acid	Coffee, *Coffea arabica*	(−) Cell growth; (−) colony formation ↑ ROS and apoptosis	HCT15	[174]

(*Continued*)

TABLE 4.1 (*Continued*)
Nutraceuticals Having Chemopreventive and Anticancer Activity Against CRC

Nutraceutical	Nutritional Sources	Molecular Targets	Cell Line[s]/Animal Model	References
cyanidins	Hawthorn, apples, bilberry, grapes, blackberry, blueberry, cranberry, loganberry, cherry, elderberry, raspberry, and açai berry	Oxidative stress-mediated apoptosis	LoVo/ADR cells	[175]
Cryptoxanthin	Black olives, orange and orange juice, mangoes, peaches, watermelon, papayas, nectarines fruit cocktail, plums, and grapefruit	Antioxidant action of β-cryptoxanthin-mediated stimulation of DNA oxidation damage repair of in human cells	MNU-induced colon cancer in F344 rats	[176,177]
Curcumin	Turmeric	p53, p21	HCT116	[178]
		CD133, CD44, CD166, ALDH	HT29, HCT116	[179]
		P-gp	Caco2	[180]
		IDPm	HCT116	[181]
		ABCG2, EGFR, IGF-1R, NF-κB, β-catenin, COX-2, c-myc, Bcl-xL, Bax	HCT116	[182]
		STAT3	HCT116	[183]
		ERK1/2, p38 MAPK, JNK	HCT116	[184]
		EGFR, HER-2, IGF-1R, Akt, COX-2, cyclin D1	HCT116	[185]
		E2F4, cyclin A, p21, p27	HCT116	[186]
		p53, p21, PUMA	HCT116, HT29	[187]
		NF-κB, EGFR, IGF-1R	HCT116	[188]
		CD44, CD166, EGFR	HT29, HCT116	[189]
		VDRE, GR, CYP3A4, CYP24, p21, TRPV6	Caco2	[190]

(*Continued*)

TABLE 4.1 (*Continued*)
Nutraceuticals Having Chemopreventive and Anticancer Activity Against CRC

Nutraceutical	Nutritional Sources	Molecular Targets	Cell Line[s]/Animal Model	References
		p53, p21 (CIP1/WAF1)	HCT116	[191]
		NF-κB, Akt, Bcl-2, Bcl-xL, IAP-2, COX-2, cyclin D1	HCT116	[192]
		Akt, COX-2, AMPK	HT29	[193]
		SW480 20S and 26S proteasome	HCT116	[194]
		PCNA, CDK2, CDK4, cyclin B, p21, p27, p53, NF-κB, Akt	HCT116	[195]
		DNA methylation, histone modifications, miRNA	HuTu 80, Caco-2	[196]
		HSP70	HCT116	[197]
Daidzein	Soyabean, fruit, and nuts	HT29 colon cancer cells: BIRC5 (surviving), expression of CTNNBIP1 (β-catenin) and APC (adenomatous polyposis coli)	LoVo HT29 colon cancer cells	[198]
Deoxyelephantopin	*Elephantopus scaber*	activation of caspase-3 and PARP cleavage	HCT-116	[199]
Deguelin	Plants of Fabaceae or Legume family like *Derris*, *Tephrosia*, and *Lonchocarpu*	Ki-67, NF-κB, VEGF	COLO 205	[200]
Diosgenin	Fenugreek, crape ginger	Activation of p38 pathway, TRAIL-induced apoptosis and death receptor-5 activation, COX-2 and 5-LOX mediated apoptosis	HT-29 and HCT-116	[201–204]
Emodin	Aloe, buckthorn, rhubarb, and Japanese knotweed	Bcl-2, Bax, downregulating MMP-2/9, RhoB, and VEGF via reduced DNA-binding activity of NF-κB	LS1034	[205–209]
		MMP-2, MMP-9, RhoB, NF-κB, VEGF PRL-3, ezrin SOD, GST, tGPx, LDH VEGFR-1, VEGFR-2	WiDr, HCT116, DLD-1,DLD-1, HT2	

(*Continued*)

TABLE 4.1 (*Continued*)
Nutraceuticals Having Chemopreventive and Anticancer Activity Against CRC

Nutraceutical	Nutritional Sources	Molecular Targets	Cell Line[s]/Animal Model	References
Escin	Horse chestnuts	p21 (WAF1/CIP1)	HT29	[210]
Embelin	Embelicaribes	IL-6/STAT3 signaling inhibition for apoptosis induction	HCT116	[211,212]
Ellagic acid	Pomegranate, grapes, berries, walnuts, chocolate, wine, and green tea	Caspase-8 activation, cell-cycle modulation, Bax translocation to mitochondrial fraction of cells, ↓ PCNA expression	CaCo-2 cell line HCT 116	[213]
Evodiamine	*Evodia fructans*, *Evodia* spp.	Downregulation of IGF-1/HIF-1α	LoVo cells	[214]
Eugenol	Clove, nutmeg, cinnamon, basil, bayleaf, coriander, honey, Flos, balm, Magnolia, clove oil, and cinnamon	p53 activation and proline-rich acidic protein (PRAP) cleavage, apoptosis signal transducer	HT-29 and HCT-15 cell line	[215]
Fisetin	Smoke tree	Bak, TRAIL, p53, Bim, EGFR, Bcl-xL, p53, Bcl-2, FasL, COX-2, β-catenin, DR5, MMP-7, Wnt NF-κB, PGE2, cyclin D1, CDK2, cyclin E CDC25C, CDK4, p21 [CIP1/WAF1]	HCT116, HT29	[216–219]
Ferulic acid	*Ferula foetida*, peanut and nuts rice, grains, wheat, oats, pineapple, vegetables, coffee seeds, and artichoke	Decreased cell viability and colony formation, COX-1 and COX-2 inhibition, inhibits peroxidation in vitro	SW 480 colon cells HCT 15	[220,221]
Fucoxanthin, fucoxanthinol	Marine micro and macroalgae and diatoms like *Phaeodactylum tricornutum*	Induce apoptosis	Caco-2, HT-29	[222]
Flavopiridol	*Dysoxylum binectariferum*	p21, p53, Cdk9, Rad51, Cdc2, XIAP, survivin, cAMP and Rb	HCT116, T84	[223–228]

(*Continued*)

TABLE 4.1 (*Continued*)
Nutraceuticals Having Chemopreventive and Anticancer Activity Against CRC

Nutraceutical	Nutritional Sources	Molecular Targets	Cell Line[s]/Animal Model	References
Garcinol	*Garcinia indica*, *Garcinia huillkensis*, and *Garcinia cambogia*	MMP-7, Akt, Bcl-2, Bax, DR4, XIAP, Bid, DR5, survivin, Src, cFLIP, ERK1/2, FAK, MAPK and PI3K	HCT116, HT29	[229–231]
Genistein	Soybean	miR-95, Akt, and SGK1 mRNA	HCT-116	[232]
Galangin	Propolis, *Alpinia officinarum*, galangal root	Activation of caspase-3 and -9, release of apoptosis inducing factor from the mitochondria into the cytoplasm, mitochondria membrane potential alteration and dysfunction	HCT-15 and HT-29	[233]
Gambogic acid	*Garcinia hanburyi*	JNK signaling pathway, p38 pathway, PI3K, Akt, Bad	HCT-15R, LOVO	[234]
6-Gingerol	Ginger	AP-1, chemokines, cyclin D1, VEGF, COX-2,D1NF-κB, growth factors, iNOS, MAPK, p53 and pathways, β-catenin translocation inhibition	Rat azoxymethane [AOM] model	[235–237]
Gossypol	Cottonseed oil	Bcl-2, Bcl-xL	CT26	[238]
		Bcl-2, cFLIP, Bcl-xL, XIAP, survivin, ERK1/2, and CHOP	HCT116, DR5	[239]
		p53, LoVo, Bax, and Bcl-2	HT29	[240]
		Bak, Mcl-1, Bcl-2, Bcl-xL, p21, cyclin D1, Bag-1,	HT29	[241]
Guggulsterone	Guggulipid from Commiphora mukul (also known as *Commiphora wightii*)	ARNT, c-Jun, IGF1-Rβ , CBR3, p21, cIAP-1, cIAP-2, Bcl-2, Fas, Bid, p-JNK, MMP-2,VEGF, STAT3, MMP-9	HT29	[242,243]
Hesperitin	Oranges and mandarin	CDK4 and p21cip1 mediated G1 phase cell-cycle arrest, prooxidant and antiangiogenic effects	DMH-induced colon cancer rat model	[244]
Honokiol	*Magnolia obovata*, *Magnolia grandiflora*	↓ed transcriptional activity of NF-κB-responsive promoters, ↑ed cytoplasmic accumulation of NF-κB, ↓ed phosphorylation of inhibitor of kappa B alpha (IαB-α), G1 phase cell-cycle arrest, inducing apoptosis	SW620 and HCT116	[245]

(*Continued*)

TABLE 4.1 (*Continued*)
Nutraceuticals Having Chemopreventive and Anticancer Activity Against CRC

Nutraceutical	Nutritional Sources	Molecular Targets	Cell Line[s]/Animal Model	References
Halocynthiaxanthin	Oysters and sea squirts	nuclear condensation, induction of caspase inhibitors, poly(ADP-ribose) and polymerase cleavage	DLD-1 colon cancer	[246]
Indirubin	*Indigofera tinctoria* L. and *Isatis tinctoria* L.	Induction of proapoptotic Bcl-2 family members Bid and Bax	HCT116.	[247]
Indole-3 carbinol	kale, broccoli, cauliflower, Brussels sprouts, and cabbage	↑ed cytotoxicity owing to intracellular spermine levels	HT29 and SW480	[248]
Isorhamnetin	Red turnip, golden rod, mustard leaf, almonds, chives, dill weed, fennel leaves, and ginkgo biloba	↓ed phosphorylation levels of Akt (ser473), cell arrest at G2/M phase, suppression of phosph–p70S6 kinase and phosph–4E–BP1 (t37/46) protein, inhibition of PI3K–Akt–mTOR pathway-mediated proliferation suppression, enhanced the expression of cyclin B1 protein	HT–29, HCT116, and SW480	[249]
Isoflavones	Soyabean, tofu, soy protein, miso, genistein, phytoestrogen, and natto	Estrogen receptor (ER)-mediated anticancer effect on colon cancer cells	—	[250]
Japanese quince extract	*Chaenomeles japonica* fruit extract	NF-κB inhibition, ↓ed expression of metalloproteinase-9 and cyclooxygenase-2	SW-480 cells	[251]
Kaempferol	Apples, spinach grapes, tomatoes, raspberries, green tea, green beans, peaches cucumbers potatoes, onions, broccoli, brussels sprouts, squash, lettuce, and blackberries	CDK2-, CDK4-, and Cdc2-mediated G1 and G2/M cell-cycle arrest, depolarization of the mitochondria and the release of cytochrome C from the mitochondria	HT-29	[252,253]

(*Continued*)

TABLE 4.1 (*Continued*)
Nutraceuticals Having Chemopreventive and Anticancer Activity Against CRC

Nutraceutical	Nutritional Sources	Molecular Targets	Cell Line[s]/Animal Model	References
Laminarin	Brown algae, seaweeds such as *Sargassum fusiforme* and *Sargassum trichophyllum*	↓ed procaspase-8 and -3 expression levels, upregulated TRAIL/ DR4, DR5 pathway-mediated apoptosis, TRAIL and FADD expression levels, and ↑ed activity of caspase-8, -3, -6, and -7	LoVo cells	[254]
Luteolin	Broccoli, celery, onion leaves, apple skins parsley, carrots, peppers, cabbages, and chrysanthemum flowers	Cell-cycle arrest at G2/M phase	SW480 and Caco-2	[255]
		CDK2 and cyclin D1, Luteolin-induced apoptosis by activating caspase-3, -7, and -9	HT-29	[256]
		Inhibition of wnt/β-catenin/GSK-3β pathway	Azoxymethane induced colon cancer in Balb/C mouse	[257]
Nimbolide	Neem (*Azadirachta indica*)	NF-κB, ERK1/2, p38, JNK1/2, MMP-2, 9	WiDr	[258]
		DR4, DR5, ERK, p38 MAPK, I-FLICE, cIAP-1, cIAP-2, Bcl-2, Bcl-xL, survivin, XIAP, p53, Bax	HCT116	[259]
		p21, cyclin D2, Chk2, cyclin A, cyclin E, CDK2, Rad17	HT29	[260]
Noscapine	Poppy seeds	p53, p21, Bcl-2, Bax	HCT116	[261]
		Survivin, Bcl-2, Bax	LoVo	[262]
Morin	*Maclura tinctoria*, *Maclura pomifera*, and common guava	↓ed Bax, Bcl 2, ↑ed ROS generation, loss of mitochondrial membrane, ↑ed PARP, caspase caspase-8, -9, and -3 cleavage	SW480	[263]
Maslinic acid	Olives (*Olea europaea* L.)	Inhibits Bcl-2 expression, ↑ed Bax expression, caspase-9 and caspase-3 activation, and release of mitochondrial cytochrome-c	HT29	[264]
Myricetin	Various berries, herbs, and walnuts	↑ed BAX/BCL2 ratio, release of AIF from mitochondria to cytosol	HCT-15 human colon cancer	[265]

(*Continued*)

TABLE 4.1 (*Continued*)
Nutraceuticals Having Chemopreventive and Anticancer Activity Against CRC

Nutraceutical	Nutritional Sources	Molecular Targets	Cell Line[s]/Animal Model	References
Magnolol	*Magnolia officinalis*	G0/G1 phase cell arrest, AMP-activated protein kinase signaling pathway	COLO-205, HCT-116	[266]
Naringenin	Grapefruit	↑ed ATF3 expression and apoptosis in human colon cancer cells	SW480, HT-29, HCT116 and Lovo cells	[267]
Noscapine	*Papaver rhoeas*	COX-2 and Bcl-2	LoVo cells	[268]
Oleuropein	Olive tree leaves	Prevents DNA damage through COX-2 mediation, antioxidant, antiapoptotic, and antiangiogenic roles	Azoxymethane [AOM]-induced colon cancer	[269]
Omea-3 and 6 fatty acid	Marine fishes, microalgae, seaweeds, fish oil, algae oils, eggs	Chemopreventive action in CRC progression, anticatabolic action, and apoptotic activity	Azoxymethane or 1,2-dimethylhydrazine rat models	[270]
Phytic acid	Cereals, fruits	↓ed ROS production , mostly chemopreventive	-	[271]
Pinitol	Soybean, *Bougainvillea* flower, and ice plant	NF-κB suppression, cyclooxygenase-2 inhibition, cyclin D1, inhibition of c-myc, vascular endothelial growth factor, matrix metalloproteinase-9, X-linked inhibitor, cell cIAP1, cIAP2 inhibition, Bcl-2, and Bcl –xL inhibitor	Azoxymethane [AOM] rat model	[272,273]
Pterostilbene	Blueberries, almonds, red wine, mulberries, red grapes, cocoa	NF-E2-related factor 2 (Nrf2)-mediated antioxidant signaling pathway	Azoxymethane [AOM]-induced mice model	[274,275]
Piceatannol	passion fruit, red wine, white tea, grapes, and Japanese knotweed	miR-129-mediated pro-apoptotic effects	HCT116 and HT29	[276]
Perillyl alcohol	Cranberries, spearmint, peppermint, cherries, lavender, sage, celery	Stimulated the Ang2 expression of by ECs Decreased VEGF release from cancer cells	AOM-induced colon cancer rat model	[277]

(*Continued*)

TABLE 4.1 (*Continued*)
Nutraceuticals Having Chemopreventive and Anticancer Activity Against CRC

Nutraceutical	Nutritional Sources	Molecular Targets	Cell Line[s]/Animal Model	References
Piperine	Long pepper and black pepper	Endoplasmic reticulum stress-induced apoptosis and G1 phase arrest	HT-29 cells	[278]
Plumbagin	*Plumbago zeylinica*	Suppression of cyclins D1 and B1, ↑ed p21WAF1/CIP1; induction of apoptosis through the involvement of mitochondrial pathways	HCT116	[279]
Procyanidins	Cinnamon, sorghum, grapes, berries	Caspase-3- and caspase-8-mediated apoptosis at G2/M phase of cell cycle	SW620	[280]
Quercetin	Broccoli, red onions, peppers, apples, grapes, black tea, green tea, red wine, and some fruit juices	Downregulation of Bcl-2, upregulation of Bax responsible for apoptosis induction and mitochondrial dysfunction	CACO-2 and SW-620 cells	[281]
Reserpine	*Rauwolfia serpentina*	CYP3A5	LS180	[282]
		β-catenin, cyclin D1, c-myc, Siah-1	HCT116	[283]
Rhizochalin	*Rhizochalina incrustata*	AMPK activation, mTOR-p70S6K inhibition *via* phosphorylation of raptor, resulting in inhibition of ERK1/2 phosphorylation and AP-1 activity	HT-29	[284]

(*Continued*)

TABLE 4.1 (*Continued*)
Nutraceuticals Having Chemopreventive and Anticancer Activity Against CRC

Nutraceutical	Nutritional Sources	Molecular Targets	Cell Line[s]/Animal Model	References
Resveratrol	Cranberries, blueberries, peanuts, red and white wine, pistachios, grapes, cocoa, and dark chocolate	STAT3, Akt	SW480, HT29	[285]
		TLR-4, IκB, iNOS	SW480, Caco-2	[286]
		Lysosomal cathepsin D-mediated colon cancer cell death	DLD1 and HT29	[287]
		p38, JNK	HCT116	[288]
		JNK, ERK, FAK, Akt, Grb2, Fyn, Ras, SOS	HT29, SW480	[289]
		Bcl- 2, Bax, p53	HCT116	[290]
		FADD, Bak	Caco-2	[291]
		Mdm2, Bax, DR4, p53, Fas, and [CD95]	HCT116	[292]
		HIF-1α , MMP-9, and VEGF	Lovo	[293]
		SMADs, TGFβR, PDCD4, and PTEN	SW480	[294]
		XBP1, GRP-78,	CHOP, HT29	[295]
		IGF-1R, EGFR, NF-κB	HCT116	[296]
		Wnt, p27, p53, cyclin D1, IGF-1R, Akt	HT29	[297]
		CYP1A1	Caco-2	[297]
		β-Catenin	RKO	[298]
		PGE2 and COX-2	HT29	[299]
Rosmarinic acid	Peppermint, lemon, marjoram, basil, holy basil, rosemary, balm, thyme, and sage	AMPK pathway activation	CT26 cells and HCT116	[300]
Scallian	*Allium fistulosum*	COX-2 and iNOS, and suppressed expression of cyclin D1 and c-Myc, VEGF and HIF-1a, MMP-9, and ICAM-1	CT-26	[301]
Sesamin	Sesame seeds	Reduction of tyrosine phosphorylation of EphA1 and EphB2	HT29 and LS180	[302]

(*Continued*)

TABLE 4.1 (*Continued*)
Nutraceuticals Having Chemopreventive and Anticancer Activity Against CRC

Nutraceutical	Nutritional Sources	Molecular Targets	Cell Line[s]/Animal Model	References
Secoisolariciresinoldiglucoside	Flaxseeds, wheat bran	beta-glucuronidase activity, phase 2 detoxification enzyme NADPH:quinone reductase induction, apoptotic and cytostatic potential	SW480 cancer cells	[303]
Salograriolide A	*Centaurea aintensis*	Reduce colon tumor formation	HCT-116	[304]
Sanguinarine	Bloodroot	Bax, Bcl-2	HT29	[305]
		Akt, mTOR, PP2Ac, β-catenin, IGF-1Rβ, ILGBP-1, GSK-3β, PKB/Akt	CSLC	[306]
Silibinin	Milk thistle plant	XIAP, Mcl-1, DR4, DR5	SW480	[307]
		β-Catenin, GSK3β, cyclin D1, VEGF, iNOS, c-myc, survivin	SW480	[308]
		Flt-1	LoVo	[309]
		Cyclin B1, cyclin D1, CDK2, p21, p27, COX-2	HCT116	[310]
Siphonaxanthin	Marine green algae *Codium fragile*	Caspase-3 activation, enhancement of GADD45α and DR5 expression levels, suppression of Bcl-2 expression	induces apoptosis in HL- 60	[311,312]
Sulphoraphane	Broccoli and other cruciferous vegetables	Epigenetic modulation of microRNA-21 and Downregulation of human telomerase reverse transcriptase [hTERT] enzyme	HT-29 cells	[313]
Triptolide	*Tripterygium wilfordii*	↓ed mRNA expression of the positive cell cycle regulatory genes *c-myc,* and A, B, C, and D-type cyclins, ↓ed VEGF and COX-2 expression, inhibited expression of TNF receptors, thrombin receptor and CXCR4 and TGF-β receptors	HT29 and HCT116	[314]
		Inhibiting transcriptional activation of E2F	HCT116 and HT29	[315]

(*Continued*)

TABLE 4.1 (*Continued*)
Nutraceuticals Having Chemopreventive and Anticancer Activity Against CRC

Nutraceutical	Nutritional Sources	Molecular Targets	Cell Line[s]/Animal Model	References
Tocotrienol	Wheat germ oil, palm oil, rice bran oil, barley, and certain types of grains and nuts	HMG-CoA reductase, RhoA	HT29, HCT116	[316]
		Bcl-xL, ERK1, DR4, DR5, Bax	HCT116	[317]
		c-IAP2, WAF1/p21, p53, Bcl-2	RKO	[318]
		Wnt-1, β-catenin, c-jun, MMP-7 and cyclin D1	SW620	[319]
		Bax, Bcl-2, NF-κB	HT29	[320]
Theaflavin	Black tea	NF-κB, ICAM-1, TNFα, COX-2	Caco-2	[321]
Thymoquinone	Black seed	HDAC2	HT29	[322]
		p53, CHEK1	HCT116	[323]
		p53, p21WAF1, Bcl-2	HCT116	[324]
Ursolic acid	Lavender, oregano, prunes, hawthorn, thyme, peppermint, cranberries, elder flowers, bilberries, rosemary, basil, and apples	JNK, DcR2, DR4 and DR5	HCT116	[325]
		Sphingomyelinase	HCT116	[326]
		Bcl-2, ERK1, ERK 2, Bcl-xL EGFR, JNK, and p38 MAPK	HT29	[327]
		Bcl-2, Bcl-xL, survivin	SW480	[328]
		Bcl-xL, Bcl-2, cFLIP, survivin, cyclin D1, MMP-9, VEGF, ICAM-1	HCT116	[329]
Vanillin	Vanilla pods	G0/G1 arrest at 200 μg/mL G2/M arrest at 1000 μg/mL	HT-29	[330]
Withanolide	Ashwagandha *Withania somnifera*	NF-κB, COX-2	HCT116	[331]
Xanthohumol	Hop plant	DNA topoisomerase I, MDR1	HCT15	[332]
		CXCR4	HCT116	[333]
		Bcl-2	HCT116	[334]
Zeaxanthin	Carrots, lettuce, corn bread, romaine, oranges, eggs, and orange juice, green peas, peaches, spinach, and corn	Apoptosis induction	HT-29 cells	[335]
Zerumbone	Ginger	DR4, DR5, cFLIP, ERK1/2, p38 MAPK, p53, Bax, p21	HCT116	[336]
		IL-1α, IL-1β, IL-6, TNFα	Caco-2, Colo320	[337]

discussion, only the nutraceuticals that have been extensively studied for the prevention and treatment of CRC will be detailed in the present chapter. The other numerous nutraceuticals that have emerged as potential anti-CRC agents, but not extensively researched to prove their efficacy, have been briefed in Table 4.1.

4.4.1 Polyphenols for the Chemoprevention and Treatment of CRC

Natural polyphenols are secondary plant metabolites with one aromatic ring attached to a single or multiple hydroxyl group(s) in their structure [18]. This class of phytochemicals include small molecules as well as highly polymerized compounds that are widely present in foods and beverages of plant origin like fruits, vegetables, spices, soy, nuts, tea, and wine [19,20]. Chemically, natural polyphenols can be divided into flavonoids, phenolic acids, lignans, stilbenes, and phenylpropanoids.

1. **Flavonoids**: These are the commonest forms of polyphenolic phytonutrients present in numerous plants. Flavonoids of various types are well-known for their anticancer activity. A representative of each of the subclass of flavonoid that has been researched in detail has been discussed in the following section [21]. Flavonoids can be subclassified into the categories like anthocyanins, flavanols, flavanones, flavones, flavonols, and isoflavonoids.
   a. **Anthocyanins**: Anthocyanins are the most ubiquitous form of flavonoids that confer bright attractive colors to many fruits and vegetables. Anthocyanins usually occur in their glycosylated form with glucose, galactose, arabinose, rutinose, and so on. Aglycone part of anthocyanins is known as anthocyanidin. This group of phytonutrients includes delphinidin, cyanidin, petunidin, pelargonidin, peonidin, malvidin, and so on that are obtained from berries, grapes, cherries, plums, and pomegranate. Delphinidin is one of the most important anthocyanidin that has exhibited strong anticancer activities owing to its apoptotic and cell-cycle-arrest ability through NF-κB suppression [22,23]. Cyanidin and delphidin exhibit oxidative stress-based cytotoxicity to CRC cells [24]. Anthocyanins also have a chemopreventive action against the CRC cells. Systematic study of the effect of chemical structure on their chemopreventive activities has also been carried out to confirm the role of nutraceuticals in the treatment of CRC. Monoglycosylated nonacylated anthocyanins were found to be more cytotoxic to cancer cells than their anthocyanin counterparts [25].
   b. **Flavanols (flavan-3-ols)**: These are among the most complex flavonoid subclass. These include simple monomers like catechins, oligomers like proanthocyanidins, and polymers known as condensed tannins. Examples of anticancer flavanols include epicatechin, epigallocatechin, EGCG, and procyanidins obtained from apples, pears, legumes, tea, cocoa, and wine. EGCG is one of the most profound antioxidant in green tea. It has been found to affect multiple signaling pathways that play an important role in colon carcinogenesis. EGCG is also known to exert chemopreventive action by affecting extracellular signal-related kinase

(ERK)1/2, Akt, and alternative p38MAPK signaling pathways [26]. EGCG has been found to induce apoptosis in HCT116, SW480, SW837, HT-29, and Caco2 colon cancer cells through epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor-2 inhibition. HT-29 cells when treated with EGCG were found to induce apoptosis via G1 phase stasis. Transcriptional activity of the activator protein 1 (AP-1), NF-κB, cyclinD1, and c-fos promoters were found to be inhibited by EGCG. Synergism of 10 mg/mL of EGCG with 1 mg/mL of epicatechin was reported in one research, which indicates the possibility of synergism between several other catechins with EGCG [27,28].

c. **Flavanones**: These polyphenolics are most commonly found in the solid parts of citrus fruits like orange, lemon, sweet lime, and grapefruit. Naringenin, a flavanone constituent present in grapefruit, is found to induce apoptosis and inhibit cancer cell proliferation, invasion, and migration in several cancer cell lines [29]. Activation of pro-apoptotic p38-dependent pathway by naringenin was studied in a research study performed by Song et al. [30]. Naringenein was found to induce cell apoptosis and reduce the cell viability in CRC cells. The mechanism of action was believed to be PARP cleavage and p38-dependent ATF3 overexpression at mRNA and protein levels in a dose-dependent pattern [30]. Hesperetin is the commonest form of flavanone present in fruits like orange. It has been found to decrease cancer cell proliferation and induce apoptosis by promoting intracellular ROS accumulation and inducing mitochondria-mediated cell apoptosis at a dose of 100–400 μM. Oral administration of hesperetin (20 mg/kg/day) has been found to reduce the formation of aberrant crypt foci and proliferating cell nuclear antigen in 1,2-dimethylhydrazine (DMH)-induced colon cancer rat model [31]. Besides its chemopreventive action, it also showed antiproliferative and growth suppression effect in xenograft mice models as well as chemical-induced colon carcinogenesis models at a dose of 20–40 mg/kg thrice a week on intraperitoneal administration.

d. **Flavones**: These are mainly glycosides of apigenin, chrysin, and luteolin that are obtained from parsely, celery, orange, onions, tea, honey, and other spices. Luteolin is an important flavone that is abundantly available from edible vegetables and plants such as artichoke, celery, perilla, and spices like thyme, green pepper, oregano, and sage. Anticancer activity of naturally extracted luteolin against CRC is clinically proven [32]. Luteolin has been reported to induce apoptosis in several cell line studies in vitro [33,34]. Luteolin is found to exert anticancer activity against colon cancer cells due to decreased IGF-II production and the resultant downregulation of IGFR-I receptor signaling, mediating the PI3K/Akt and ERK1/2 pathways in HT-29 human colon cancer cells, resulting in the suppression of sphingosine-1-phosphate synthesis and ceramide trafficking [35]. The research work of Abdel et al. has held sphingosine kinase 2 and ceramide transport to be the focal targets for luetolin's ability to induce apoptosis in colon cancer

cells [35,36]. Moderate luteolin concentrations in a range of 20–100 μM has been evidenced to induce apoptosis and cell arrest in several colon cancer cell lines with no toxic effects on normal differentiated enterocytes. It has been found to suppress the overexpression of several anti-apoptotic proteins and regulate the cyclin B1 and CDC2 (CDK1) kinase activity to cause G2/M transition cell-cycle phase arrest. Considerable reduction in tumor growth was observed in a human gastric xenograft model on luteolin treatment at a dose of 10 mg/kg/day (i.p.). The in vivo study found no apparent toxicity or weight loss following the luteolin therapy [37].

e. **Flavonols**: These are most widely distributed flavonoids present in numerous foods but in very low concentrations [38]. Quercetin, kaempferol, myricetin, isorhamnetin, and galangin are representative anticancer agents from this class of polyphenols. The anticancer activity of quercetin in CRC has been attributed to the AMPK pathway suppression. A dose of 50 mg/kg/day intraperitoneally was found to reduce tumor volume in the HCT116 cell colon cancer xenograft model. Quercetin supplementation in the dose of 25 mg/kg/day in a mouse model of colorectal carcinogenesis was found to alleviate signs and symptoms of cancer cachexia and improve grip strength, muscle mass, and body weight [39]. Moreover, the anticancer effect of quercetin was found to be markedly more in hypoxic conditions than in normoxic conditions as evidenced in the study on HCT116 colon cancer cell line [40].

   Kaempferol in 0–60 μM concentration range was found to induce apoptosis in HT-29 cancer cells due to death receptor pathway activation and mitochondrial pathway [41]. Myricetin, a flavonol present in berries, walnuts, and herbs, exhibits its antiproliferative effects by causing cell-cycle arrest and apoptosis through Bax/Bcl-2-dependent pathway in HCT-15 human colon cancer cells [42].

f. **Isoflavonoids**: Isoflavanoids is an important polyphenolic compound similar in structure to the phytoestrogen. Daidzein and genistein from soy are important representatives from this subclass of polyphenols [18]. Antiproliferative activity and proapoptotic effects were exhibited by genistein at a dose of 25–100 μM on colon cancer cells. The anticancer effects of genistein were observed due to the inhibition of oncogenic miR-95, Akt, and SGK, as well as phosphorylation of Akt. Oral administration of genistein was found to inhibit angiogenesis and metastasis to distant organs in mice [43].

2. **Phenolic acids**: These polyphenolic compounds are present in a few edible sources and are classified into two main categories like hydroxybenzoic acid and hydroxycinnamic acid [18]. Some important representative examples of hydroxybenzoic acids having anticancer activity against CRC are gallic acid and ellagic acid from grapes, pomegranate, walnuts, berries, chocolate, green tea, and wine. Ferulic acid and chlorogenic acid from coffee and cereal grains are the phenolic acids belonging to hydroxycinnamic

acids category. The proapoptotic effect of gallic acid was observed in HCT-15 colon cancer cells at the dose of 200 μM leading to reduced cell viability [44,45].

3. **Lignans**: These polyphenolic compounds, being structurally similar to estradiol, exert their anticancer activity in hormone-dependent cancers like breast, colon, and prostate cancer [46]. These phytonutrients are ubiquitously present in sesame, flaxseed, and seeds of *Arctium lappa*. Sesamin and seciosolariciresinol diglucoside (SDG) are representative lignans that possess a strong anticancer activity against the above-mentioned cancers. SDG is converted into biologically more active lignans, that is, enterodiol and enterolactone, by human colonic bacteria that induce cell-cycle arrest and apoptosis. SDG exhibits cell growth inhibition, cytotoxicity, and cell-cycle arrest at the S-phase [47,48].
4. **Stilbenes**: These polyphenolic compounds exist in a limited number of plant families and have nutritional and medicinal properties. Resveratrol, pterostilbene, and picetannol are some of the important stilbenes having anticancer efficacy.

   Resveratrol is an important polyphenolic present in red wine, grapes, and berries. Resveratrol has been known to induce its anticancer action through modulation of varied targets, thereby inducing apoptosis. Resveratrol was found to induce its anticancer activity in HT-29 and COLO 201 human colon cancer cells (IC50 150 μM and 75 μM, respectively) through ROS-triggered autophagy mediated by caspase-3- and caspase-8-dependent apoptosis [49]. Other proposed mechanisms of anticancer action of resveratrol were reported to be indirect DNA-damaging effects due to ROS overgeneration and topoisomerase II poisoning [50,51]. Resveratrol has also been reported for being chemopreventive against CRC. The chemopreventive role of resveratrol was found to be mediated by K-ras protein suppression. A dietary supplementation of resveratrol (equivalent to 105 and 210 mg daily for humans) was found to prevent K-ras mutation and thereby the development of sporadic colorectal cancer [52]. In addition to its chemopreventive and anticancer activity, resveratrol has also been known to prevent MDR1-mediated drug efflux and emergence of resistance in CRC [53]. Resveratrol conjugates, viz., RSV-3-*O*-glucuronide, RSV-3-*O*-sulfate, and RSV-4′-*O*-glucuronide, formed on resveratrol metabolism after its oral administration were found to exert synergistic anticancer action via the induction of DNA damage and thereby cell apoptosis in human CRC. This fact supported the high anticancer activity of resveratrol despite its low oral bioavailability and extensive first pass metabolism [54].
5. **Phenylpropanoids**: Phenylpropanoids are a cluster of organic compounds synthesized by plants from phenylalanine and tyrosine amino acids [55].

   1′-Acetoxychavicol acetate (ACA) is an important phenylpropanoid obtained from the rhizomes of blue ginger, that is, *Alpinia galanga*, which is a component of many traditional Asian condiments. ACA has been extensively explored for its chemopreventive and chemotherapeutic action in several in vitro models of CRC and in animals. ACA has been found to

inhibit DNA synthesis and cell proliferation in several CRC cell lines [56]. ACA was found to upregulate intranuclear Nrf2 and cytosolic p21 and promote glutathione-S-transferase (GST) and NAD(P)H:quinone oxidoreductase 1 activity, which resulted in increased intracellular glutathione levels in rat intestine epithelial cells (IEC6). ACA exhibited its anticancer action in azoxymethane (AOM)-induced colon cancer in rat model through suppression of proliferation biomarkers like ornithine decarboxylase and colonic mucosal polyamine content [57].

6. **Other polyphenols**: Curcumin, a polyphenolic compound, is a bright yellow colored diferuloylmethane that is produced by *Curcumn longa* belonging to Zingiberaceae family. Curcumin has exhibited anticancer activity against several types of cancers including CRC. Besides its anticancer property, it contributes to prevent CRC through its anti-inflammatory activity in ulcerative colitis, Crohn's disease, tropical pancreatitis, and FAP, thus diminishing the risk factors that promote development of CRC. In a clinical study on five patients with FAP, treatment with curcumin was found to reduce the polyp size by 50% and reduce their incidence by about 60% [58]. Curcumin has been extensively explored for its anticancer mechanism [59]. Out of several molecular targets of curcumin, downregulated activation of NF-κB is claimed to be the chief one. Curcumin has been known to have antiapoptotic, antiproliferative activity on cancer cells in addition to its antiangiogenic, antimetastatic, and anti-invasive action [59,60]. Other important targets that are responsible for the anticancer effect of curcumin are STAT3 [61], HIF-1 [62], and PPARγ [63]. It is known to downregulate the expression of inflammatory mediators like 5-lipoxygenase (5-LOX), cyclooxygenase-2 (COX-2), IL-1, TNF, and IL-6 expression in cancer cells in addition to the inhibition of antiapoptosis-activating transcription factor [64], and EGF receptor signaling [65].

The safety of this nutraceutical was reflected through pharmacological observations from several articles that showed very high maximum tolerance dose [66]. In a clinical trial undertaken by Sharma and colleagues [67], pharmacokinetic and pharmacodynamic effects of orally administered curcuma extract in patients with advanced CRC were observed. The study was conducted in 15 patients with advanced CRC, refractory to the standard chemotherapies. The patients were treated with curcuma extract daily for a period of 4 months and observed for its therapeutic effect, adverse effect, and side effects. There were no signs of dose-limiting toxicity or drug intolerance. Significantly high, that is, about 59% reduction in lymphocytic glutathione-S-transferase (GST), activity was observed on administration of 440 mg of curcumin extract for 29 days. In yet another trial conducted by the same group of researchers, a radiologically stable disease was observed in patients with advanced CRC when treated with curcumin. A daily dose of 3.6 g of curcumin was found to reduce the inducible PGE2 production in blood samples by about 62% (1 day after dosing) and 57% (29 days after dose). In a pilot scale study by Plummer et al., a standardized curcuma extract formulation was orally administered and evaluated in 15 patients with advanced CRC.

Reduced basal and lipopolysaccharide-mediated PGE2 production, signifying a dose-dependent COX-2 inhibition, revealed its anticancer efficacy [68].

However, curcumin still needs to be further explored for ensuring a clinically assuring molecule. Most challenging issues faced by curcumin are poor bioavailability and biodistribution [69]. The fact that turmeric and not curcumin is consumed in countries having low CRC incidence rates, consumption of turmeric and not curcumin in combination with other anticancer spices like *Piper nigrum* (black pepper) and *Zingiber officinale* (ginger) question the efficacy of curcumin alone. The pharmacological activity of turmeric is different from that of curcumin alone when compared to the synergistic pharmacology of curcumin with tumerones and other phytoconsituents of turmeric [70,71]. Garcea et al. undertook a pilot trial in 12 patients with hepatic metastasis from CRC who were treated with 450–3500 mg of curumin daily for 1 week prior to surgery in order to investigate the dose essential for eliciting pharmacological activity [72]. Their findings concluded that the dose sufficient to exert pharmacological activity was not feasible to be administered to humans. To solve the above problems related to anticancer activity of this molecule, many combinations of curcumin with nanoformulations and other oncotherapeutics have been hypothesized.

4.4.2 Terpenoids (Terpenes)

Terpenes/isoprenoids are major phytoconsituents present in plant resin and essential oils. Terpenes are composed of a mixture of isomeric hydrocarbons having a general molecular formula of $(C_5H_8)_n$, where "n" refers to the number of isoprene units. They are classified as mono, di, oligo, and polyterpenes. This class is the largest class of phytonutrients that is present in green foods, soy plants, and grains. Terpenes exert antioxidant activity by partitioning themselves into fatty membranes with the help of their long carbon side chain and react with free radicals to inactivate them [73]. Some important terpenes having potent anticancer activity in CRC are tocotrienols and tocopherols, carotenoids, limonoids, phytosterols triterpene, and steroidal saponins.

1. **Tocotrienols and tocopherols**: These terpenes, in addition to their vitamin role, have potent antioxidant and anticancer actions. These terpenes are widely found in edible oils like palm tree oil, vegetable oils, wheat germ oil, barley, certain types of nuts, and grains.

   They were reported to induce a p53-independent death pathway in human colon cancer RKO cells [74]. In a study by Eitsuka et al., tocotrienol (δ-tocotrienol) was found to inhibit the growth of human colon adenocarcinoma cells through anti-telomerase downregulation. Wnt signal pathways, the β-catenin/Tcf pathways, were held responsible to execute the anticancer activity in HT-29 cells by Xu and colleagues. Paraptoptosis-like death was observed on treating SW620 colon cancer cells due to its activity on Wnt signaling pathways [75]. γ-Tocotrienol was found to chemosensitize CRC cells to capecitabine and inhibit their growth through NF-κB pathway modulation in a xenograft mice model [76].

2. **Carotenoids**: These well-known antioxidants are highly pigmented secondary terpene metabolites that are ubiquitously present in numerous fruits, vegetables, and marine sources [77,78]. Their anticancer activity on colon cancer cells have been conferred to free radical scavenging ability and ability to maintain the integrity of cell membrane in addition to its antimutagenic potential [79].

   Carotenoids have been classified into two broad categories such as hydrocarbon carotenoids (alpha-carotene, beta-carotene, lycopene) and oxycarotenoids (halocynthiaxanthin, beta-cryptoxanthin, lutein, zeaxanthin, and astaxanthin).

   Lycopene, a hydrocarbon carotenoid derived from tomatoes, grapes, and papaya, has been known to exert anticancer action in colon cancer via suppression of phosphoinositide 3-kinase/Akt survival signaling pathway and downstream molecular targets. Besides this, lycopene was found to increase nuclear cyclin-dependent kinase inhibitor p27 (kip) abundance and inhibit retinoblastoma tumor suppressor protein in human colon cancer cells. Lycopene treatment in colon cancer cell line HT-29 was found to exert anticancer activity through increased phosphorylated form of beta-catenin proteins and reduced promoter activity and cyclin D1 expression. The IC_{50} value of lycopene was found to be 10 μM for HT-29 cells [80]. Halocynthiaxanthin, a dietary carotenoid in combination with tumor necrosis factor related apoptosis inducing ligand (TRAIL), has been found to exert anticancer activity by interfering with microtubule formation and inducing apoptosis in DLD-1 colon cancer cells. Other apoptosis inducing mechanisms activated by halocynthiaxanthin in colon cancer cells are mediated by poly(ADP-ribose)polymerase cleavage, nucleus condensation, and caspase inhibition.

   Astaxanthin, yet another carotenoid produced by an unicellular green algae, *Haematococcus pluvialis*, crabs, and other marine animals, is known to exert anticancer activity on colon cancer cells. The anticancer potential of astaxanthin was pharmacologically established in a mice model wherein it was shown to induce apoptosis and inhibit proliferation of colon cancer cells by normalizing expression of inflammatory mediators like NF-κB, MMP, IL-6, TNF-α, and COX-2. Supplementation of astaxanthin was observed to suppress the formation of colonic mucosal ulcers and dysplastic crypts in animal model through its NF-κB-regulating ability. Astaxanthin has specific functional groups that target NF-κB. Post-transcriptional function of NF-κB signaling pathways is critical in the process of carcinogenesis in various organs including the CRC. In DMH-induced colon cancer rat model, astaxanthin was found to have chemopreventive action that was reflected by regulation of lipid peroxidation, enhanced antioxidant activity, reduction in the total number of aberrant crypt foci (ACF), cell proliferation, and diminished histological lesions [81].

   Siphonaxanthinis is another such marine algae (*Codium fragile*) derived anticancer agent that mediates its action through induction of

apoptosis in HL-60 cells via caspase-3 activation, Bcl-2 suppression, and increased GADD45α, and DR5 expression.

3. **Limonoids**: These terpenes are present in citrus fruits and appear to exert their anticancer activity through phase I enzyme inhibition and induction of phase II detoxification enzyme activity in liver [82,83]. They are found to inhibit N-methyl-N′-nitro-N-nitrosoguanidine-induced gastric cancer in rats and have been employed for treatment of CRC too. Nimbolide is an important triterpene limonoid derived from the leaves and flowers of neem (*Azadirachta indica*). It was found to induce apoptosis and inhibit cell proliferation in CRC cells via NF-κB and NF-κB-regulated tumorigenic proteins suppression. NF-κB inhibition was found to affect downstream signaling via NF-κB kinase (IKK) activation, IκBα phosphorylation, and p65 nuclear translocation. In vivo anticancer action of limonoids was observed after intraperitoneal injection of nimbolide at (5 and 20 mg/kg body weight) in a xenograft model of CRC, wherein it was found to down-regulate tumor cell survival proteins like (Bcl-2, Bcl-xL, c-IAP-1, survivin, Mcl-1), proliferation mediators (c-Myc, cyclin D1), and invasion proteins like (MMP-9, ICAM-1). It was also observed for its antimetastatic effect through (CXCR4) inhibition and inhibition of angiogenesis through its effect on VEGF proteins. Limonoids have been found to exert inhibitory action on CXCR4 protein and VEGF proteins through which it was established to have an antimetastatic potential [84].
4. **Phytosterols**: Phytosterols/phytosterolids are plant-derived sterols and stanols that share a structure that is similar to that of cholesterol. Phytosterols have been known for various health benefits in addition to their role in chemopreventive action in CRC. Basker et al. have reported β-sitosterol to be effective in the treatment of DMH-induced colon carcinogenesis in rats [85]. Various studies have been conducted by several research groups in order to demonstrate the association of dietary phytosterol intake and CRC incidence [86].
5. **Triterpene and steroidal saponin**: These terpene derivatives are triterpene glycosides that bear sapogenein in their aglycone part that is attached to a polar glycone (sugar) via an ether linkage. Diosgein and tubeimoside are the two most important anticancer agents belonging to this class of nutraceuticals having a proven activity against CRC [87,88].

4.4.3 Alkaloids

Several nutraceuticals are important sources of many antiproliferative and antimetastatic alkaloids. Camptothecin and vinblastine are plant-derived alkaloids having anticancer activity against several types of malignancies including CRC. Berberine, evodiamine, matrine, piperine, sanguinarine, and tetrandrine are some other important alkaloids having anticancer action [89].

Berberine is an isoquinoline alkaloid that is derived from roots, rhizomes, stems, and bark of goldenseal, barberry, and oregon grape. Several clinical studies have exhibited the application of berberine in treatment and prevention of CRC. Berberine

was found to execute its anticancer activity by inducing apoptosis through cell-cycle arrest at G2/M phase, loss of mitochondrial membrane potential, cyt *c* release, Bcl-2, Bcl-xL, and c-IAP1 suppression, activation of caspases, and PARP cleavage [90,91]. JNK and p38 MAPK phosphorylation, increase in FasL and t-BID levels, and ROS generation also contribute to its apoptotic activity. Moreover, it was found to reduce incidences of drug resistance by inhibition of P-gp 170 expression and inhibition of arylamine N-acetyltransferase activity in a human colon tumor cell line [92,93]. Berberine was observed to inhibit increment in lipid peroxidation and protein-bound carbohydrate levels in addition to its enhanced antioxidant status in an AOM-induced colon cancer rat model [94]. Berberine also selectively inhibited COX-2-activity-mediated neoplastic transformation in AOM-induced rat colon carcinogenesis without affecting COX-1 activity [95].

4.4.4 Organosulfur Compounds

Naturally occurring sulfur-containing organic compounds are known as organosulfur compounds. Isothiocyanates, indoles, allylic sulfur compounds, and sulfur-containing amino acids are some of the important dietary organosulfur compounds that are essentially active against colon cancer cells. Diallyl disulfides like allicin from garlic and sulforaphane from broccoli are important organosulfur compounds that are active against CRC cells. Besides this, acetylapoaranotin, a diketopiperazine disulfide derived from marine *Aspergillus* sp., is also an important anticancer agent [96]. These organosulfur compounds exhibit their anticancer activity through various modes of action that target molecules playing an important part in survival, proliferation, invasion, angiogenesis, and metastasis of the CRC cells.

4.4.5 Fatty Acids and Structural Lipids

Long-chain hydrocarbons with 10–30 "C" that are constituents of lipids are defined as fatty acids. Fatty acids are classified as saturated and unsaturated fatty acids that are constituent of many marine fishes, microalgae, seaweeds, fish oils, algae oil, and eggs. Eicosapentanoic acids (EPA) and docosahexanoic acids (DHA) are essential fatty acid supplementations that have proven their chemopreventive action against colon and breast cancer [97]. Omega-3 fatty acids reduce polyp formation and colon cancer progression in high-risk population. Tumor metastasis and growth have been demonstrated to be inhibited by regular supplementation with fatty acids. N-3 PUFA, conjugated linoleic acid (CLA), MUFA, sphingolipids, and lecithin are some of the important fatty acids that have chemopreventive and anticancer activity in CRC.

4.4.6 Micronutrients and Minerals

Amino acids like methionine, arginine, and glutamine, and microelements like calcium, selenium, potassium, copper, and zinc are vital in the development and progression of CRC [98]. Besides these, vitamins like B6, B12, folic acid, ascorbic acid, A, D, and E have also been researched to possess anticolorectal cancer activity by several research groups [99,100]. Selenium is a trace element that is found in many

foods including sea food, lean meats, pork, beef, turkey, chicken, fish, shellfish, eggs, legumes (beans and peas), nuts, and seeds. The North Carolina Colon Cancer Study has depicted significant reduction in colorectal cancer development with higher selenium and folate consumption. A strong association of calcium administration and vitamin D has been highlighted in many of the in vitro studies [101]. Calcium and vitamin D consumption has been found to reduce the fatty acids and secondary bile acid concentrations, thereby lowering their cytotoxicity in vitro. A blinded study has also proved their protective effect in subjects with higher risks of FAP, thereby reducing the recurrence of adenomatous polyps. Ascorbic acid (vitamin C) is an important dietary supplement that plays several pharmacological actions including anticancer and apoptotic actions. The anticancer role of ascorbic acid was made evident in the study by Kim et al., wherein it was found to induce apoptosis in HCT-8 colon cancer cell line through enhanced translocation of Bcl-2-associated death promoter protein (BAD) to mitochondria, increased Bcl-2-associated X protein (BAX) expression, and calcium influx in endoplasmic reticulum [102].

4.4.7 Probiotics

The strong association of gut microbiota and colon cancer has been established since long. Several mechanisms that lead to prophylactic and therapeutic anti-CRC activity have been discussed in detail by Uccello et al. [103].

Probiotics are basically living microorganisms like bacteria and yeasts that are acclaimed to have health benefit on their consumption, mainly by restoring gut microflora balance and avoiding dysbiosis. Some of the important strains of bacteria and yeasts that have been established for their probiotic property are *Bacillus*, *Lactobacillus*, *Enterococcus*, *Bifidobacterium*, *Streptococcus*, *Saccharomyces*, *Pediococcus*, *Escherichia coli*, and *Leuconostoc*. Several mechanisms that have been proposed for the anticolorectal property of probiotics are undigested food fermentation, carcinogen inactivation, improved host immunoresponse against pathogenic and putrefactive microbes, altered intestinal microfloral metabolism, antiapoptotic and antiproliferative activity, and tyrosine kinase signaling pathway inhibition [104].

4.4.8 Prebiotics

Prebiotics are dietary fibers comprising mostly complex carbohydrates, oligosaccharides, dietary fibers, and resistant starch that are undigestible and beneficial for host due to their stimulatory effect on the growth of one particular species or a group of bacterial species in the colon [105]. Unlike the probiotics that include the intake of exogenous bacteria, prebiotics enhance the proliferation of selective existing commensal flora [106].

Consumption of whole grains, vegetables, and fruits containing high fiber content has been associated in reducing CRC risks in several research works (plants, fiber, and colon cancer). There are several proposed mechanisms that are believed to be responsible for their chemopreventive action. Dietary fibers help in increasing fecal weight while reducing gastric transit time to reduce the carcinogen-mucosal lining contact time [107]. In addition to this, they prevent polyp recurrence and tumor

promoter gene expression. Soluble fibers enhance the excretion of tumor promoters like the secondary bile acids. Besides this, short chain fatty acids are formed on the digestion of dietary fibers that induce differentiation and apoptosis of colon tumor cells via decrease in fecal pH, which in turn affects bile acid conversion [107]. The prebiotics and probiotics are collectively referred as "synbiotics." They help in the recuperation of patients with CRC [103].

4.5 FORMULATION ASPECTS FOR DELIVERY OF NUTRACEUTICALS

Many of the nutraceuticals in spite of having high anticancer potential in vitro fail to be successful in vivo due to their poor bioavailability. Poor bioavailability can be attributed to several factors like (i) hampered drug release from the constitutional food matrix [108], (ii) interaction with the components of GIT to form insoluble or less bioavailable complexes, and (iii) enzymatic biotransformation or metabolism in the GIT rendering many nutraceuticals inactive [109–111]. Recent advances in the delivery of nutraceutical have led to development of a classification system called nutraceutical biopharmaceutical classification scheme (NuBACS) that is akin to the biopharmaceutical classification system (BCS) [112]. The main objective of development of this system was to realize and characterize the factors impeding the bioavailability of different types of nutraceuticals. Colon-targeted drug delivery system is yet another prevalent approach that has provided promising therapeutic outcomes for the treatment of CRC [113,114]. The application of such an approach for nutraceutical delivery in CRC is still being envisaged.

Out of several pharmaceutical approaches, nanotechnology is one of the most advanced approaches that can be used to solve the above-mentioned problems. Nanocarriers have unique colloidal properties due to their high surface-to-volume ratio, nanoscale size, and favorable physicochemical characteristics [115]. Nanoscale drug delivery systems have been applied to enhance the aqueous solubility, extend shelf-life, modify drug release, taste masking, flavor enhancement, and nutraceutical stability against various environmental factors, and biological milieu. Modified nanocarriers have been applied to modulate the pharmacokinetics as well as pharmacodynamics profiles of several nutraceuticals [115].

Nanocarriers exhibit an effect termed as "enhanced permeation and retention (EPR)" that facilitates selective passive targeting of the payload to the tumor site. This passive targeting of nanocarriers is based on the fundamental of leaky tumor vasculature that facilitates nanocarrier entry selectively into these "leaky" endothelial gaps [115]. Also, these nanocarriers may be surface modified to be applied for active drug targeting via overexpressed receptors like the hyaluronic acid, folic acid, RGD peptides, and so on [116–119].

Nanocarriers of several types like polymeric nanoparticles, micelles, liposomes, lipid nanocarriers, dendrimers, metal-based nanoparticles, phytosomes, and so on have been employed for the delivery of several types of nutraceuticals. Some nutraceuticals like albumin, chitosan, vitamin E, fatty acids, and so on that are used as excipients for nanoparticle fabrication also can modify anticancer nutraceutical's bioavailability by enhancing its physicochemical properties. D-α-Tocopheryl

polyethylene glycol 1000 succinate (Vitamin E TPGS) is one such nutraceutical-derived nonionic surfactant that modulates the pharmacokinetics of many P-gp substrate drugs by ATP-mediated P-gp inhibition [120]. Several researchers have reported the use of nanocarriers to increase the nutraceutical bioavailability. To confine to the limitations of the present chapter, only few such examples have been discussed below.

Nanoliposomes composed of phospholipids, cholesterol, and Tween 80 encapsulating EGCG were found to reduce its degradation in simulated intestinal fluid by almost 10 folds due to extensive protection offered by its constituents against the adverse GI interactions [121]. Several nanoformulations of curcumin have been devised for facilitating the delivery of this molecule, thereby solving issues related to its safety and bioavailability. Curcumin nanocrystals and conjugates, curcumin emulsions, liposome, and phospholipid formulations, curcumin-encapsulated polymer NPs, curcumin self-assemblies, and nanogel, in addition to several other novel nanoformulations, have been developed by several research groups [122]. A wealth of relevant literatures reporting use of nanotechnology for nutraceutical delivery exists. The details of which have been described elsewhere [123].

4.6 FUTURE DIRECTIONS

Nutraceuticals derived from plant, microbial, marine, animal, and mineral sources have an added advantage of being relatively very less toxic over other anticancer medications. Several nutraceuticals have been researched extensively for their preventive and therapeutic applications in CRC till date. In spite of being explicit anticancer tools, most of the nutraceuticals have failed to reach the clinical trials with some exceptions. There are several encumbrances in the path of clinical approval of nutraceuticals, but it would be sufficient here to reiterate the following major ones. (i) Several nutraceuticals can act on a particular molecular target in opposite ways to cause complication in data interpretation so as to conclude its antitumor or tumorigenic property [124]. (ii) Concerns about tumor selective cytotoxicity of nutraceuticals, (iii) mere in vitro/preclinical evidence for anticancer efficacy renders it insufficient to count for clinical efficacy, (iv) formation of bioactive intermediates that may draw misleading conclusions and render the in vitro data unreliable, (v) low potency and poor bioavailability of nutraceuticals, and (vi) inability to confront tumor resistance due to ignorance about the molecular mechanism of action of nutraceuticals and pathological changes due to disruption of a particular pathway [124]. The issues enlisted above present a real challenge to bring bench-to-bedside transition in clinical application of nutraceuticals. Toiling to solve these issues can truly help transform the existing picture of CRC treatment.

In order to get an armada of natural, potent, relatively safe, and economical nutraceuticals approved for their anti-CRC activity, the scientific community should put efforts to elucidate their exact molecular mechanisms of action and establish their safety and efficacy through in vivo trials. Exploring, expanding, and assembling the pharmacological aspects of nutraceuticals can evidently emerge as an extremely powerful weapon to mitigate and treat several types of cancers

including the CRC. The use of several nutraceuticals in combination with existing chemotherapy has also been researched extensively as a better treatment option for CRC. Such a combination approach may help in reducing the dose of cytotoxic drugs while enhancing their efficacy. Furthermore, to enhance their clinical efficacy and safety, we may use several pharmaceutical technologies like nanotechnology. Appropriate efforts in this direction may vouch a better therapeutic development scenario, ameliorating the existent prevention and therapeutic strategies for several cancers including CRC.

ACKNOWLEDGMENTS

The authors are grateful to Nirma University for providing necessary facilities. Ms. Shruti Rawal is also thankful to Nirma University for providing Junior Research Fellowship.

REFERENCES

1. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell*. 2000;100(1):57–70.
2. https://www.cancer.org/cancer/colon-rectal-cancer/about/what-is-colorectal-cancer.html.
3. Anand P, Kunnumakara AB, Sundaram C, et al. Cancer is a preventable disease that requires major lifestyle changes. *Pharmaceutical Research*. 2008;25(9):2097–2116.
4. Aggarwal BB, Van Kuiken ME, Iyer LH, Harikumar KB, Sung B. Molecular targets of nutraceuticals derived from dietary spices: Potential role in suppression of inflammation and tumorigenesis. *Experimental Biology and Medicine*. 2009;234(8):825–849.
5. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, Nutrition, physical activity and colorectal cancer.
6. Aggarwal B, Prasad S, Sung B, Krishnan S, Guha S. Prevention and treatment of colorectal cancer by natural agents from mother nature. *Current Colorectal Cancer Reports*. 2013;9(1):37–56.
7. Kalra EK. Nutraceutical—definition and introduction. *AAPS PharmSciTech*. 2003;5(3):27–28.
8. Brower V. Nutraceuticals: Poised for a healthy slice of the healthcare market? *Nature Biotechnology*. 1998;16(8):728–731.
9. Kalia AN. *Textbook of Industrial Pharmacognosy*. New Delhi, India: CBS Publisher and Distributor 2005;204–208.
10. Kokate CK, Purohit AP. and Gokhale SB. *Nutraceutical and cosmeceutical. Pharmacognosy*, 21st edition, Pune, India: Nirali Prakashan, 2002;542–549.
11. https://www.cancer.org/cancer/colon-rectal-cancer/causes-risks-prevention/what causes.html.
12. Tanaka T, Oyama T, Yasui Y. Dietary supplements and colorectal cancer. *Current Topics in Nutraceutical Research*. 2008;6(4):165–188.
13. Aggarwal BB, Shishodia S. Molecular targets of dietary agents for prevention and therapy of cancer. *Biochemical Pharmacology*. 2006;71(10):1397–1421.
14. Gupta SC, Kim JH, Prasad S, Aggarwal BB. Regulation of survival, proliferation, invasion, angiogenesis, and metastasis of tumor cells through modulation of inflammatory pathways by nutraceuticals. *Cancer and Metastasis Reviews*. 2010;29(3):405–434.
15. Coyle CH, Philips BJ, Morrisroe SN, Chancellor MB, Yoshimura N. Antioxidant effects of green tea and its polyphenols on bladder cells. *Life Sciences*. 2008;83(1–2):12–18.

16. Adams LS, Phung S, Yee N, Seeram NP, Li L, Chen S. Blueberry phytochemicals inhibit growth and metastatic potential of MDA-MB-231 breast cancer cells through modulation of the phosphatidylinositol 3-kinase pathway. *Cancer Research*. 2010;3594–3605.
17. DellaPenna D. Nutritional genomics: Manipulating plant micronutrients to improve human health. *Science*. 1999;285(5426):375–379.
18. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: Food sources and bioavailability. *The American Journal of Clinical Nutrition*. 2004;79(5):727–747.
19. Zhou Y, Li Y, Zhou T, Zheng J, Li S, Li HB. Dietary natural products for prevention and treatment of liver cancer. *Nutrients*. 2016;8(3):156.
20. Fu L, Xu BT, Xu XR, Qin XS, Gan RY, Li HB. Antioxidant capacities and total phenolic contents of 56 wild fruits from South China. *Molecules*. 2010;15(12):8602–8617.
21. Deng GF, Lin X, Xu XR, Gao LL, Xie JF, Li HB. Antioxidant capacities and total phenolic contents of 56 vegetables. *Journal of Functional Foods*. 2013;5(1):260–266.
22. Yun JM, Afaq F, Khan N, Mukhtar H. Delphinidin, an anthocyanidin in pigmented fruits and vegetables, induces apoptosis and cell cycle arrest in human colon cancer HCT116 cells. *Molecular Carcinogenesis*. 2009;48:260–270.
23. Bin HB, Asim M, Siddiqui IA, Adhami VM, Murtaza I, Mukhtar H. Delphinidin, a dietary anthocyanidin in pigmented fruits and vegetables: A new weapon to blunt prostate cancer growth. *Cell Cycle*. 2008;7:3320–3326.
24. Cvorovic J, Tramer F, Granzotto M, Candussio L, Decorti G, Passamonti S. Oxidative stress-based cytotoxicity of delphinidin and cyanidin in colon cancer cells. *Archives of Biochemistry and Biophysics*. 2010;501(1):151–157.
25. Jing P, Bomser JA, Schwartz SJ, He J, Magnuson BA, Giusti MM. Structure–function relationships of anthocyanins from various anthocyanin-rich extracts on the inhibition of colon cancer cell growth. *Journal of Agricultural and Food Chemistry*. 2008;56(20):9391–9398.
26. Cerezo-Guisado MI, Zur R, Lorenzo MJ, Risco A, Martín-Serrano MA, Alvarez-Barrientos A, Cuenda A, Centeno F. Implication of Akt, ERK1/2 and alternative p38MAPK signalling pathways in human colon cancer cell apoptosis induced by green tea EGCG. *Food and Chemical Toxicology*. 2015;84:125–132.
27. Shimizu M, Shirakami Y, Moriwaki H. Targeting receptor tyrosine kinases for chemoprevention by green tea catechin, EGCG. *International Journal of Molecular Sciences*. 2008;9(6):1034–1049.
28. Jin H, Gong W, Zhang C, Wang S. Epigallocatechin gallate inhibits the proliferation of colorectal cancer cells by regulating Notch signaling. *OncoTargets and Therapy*. 2013;6:145–153.
29. Bao L, Liu F, Guo HB, Li Y, Tan BB, Zhang WX, Peng YH. Naringenin inhibits proliferation, migration, and invasion as well as induces apoptosis of gastric cancer SGC7901 cell line by downregulation of AKT pathway. *Tumor Biology*. 2016;37(8):11365–11374.
30. Song HM, Park GH, Eo HJ, Jeong JB. Naringenin-mediated ATF3 expression contributes to apoptosis in human colon cancer. *Biomolecules & Therapeutics*. 2016;24(2):140.
31. Aranganathan S, Nalini N. Antiproliferative efficacy of hesperetin (citrus flavanoid) in 1, 2-dimethylhydrazine-induced colon cancer. *Phytotherapy Research*. 2013;27(7):999–1005.
32. Palaniselvam K, Mashitah MY, Gaanty PM, Solachuddin JA, Ilavenil S, Natanamurugaraj G. Nutraceuticals as potential therapeutic agents for colon cancer: A review. *Acta Pharmaceutica Sinica B*. 2014;4(3):173–181.
33. Yoshida T, Maoka T, Das SK, Kanazawa K, Horinaka M, Wakada M, et al. Halocynthiaxanthin and peridinin sensitize colon cancer cell lines to tumor necrosis factor-related apoptosis-inducing ligand. *Molecular Cancer Research*. 2007;5:615–625.

34. Lim DY, Jeong Y, TynerAL, Park JHY. Induction of cell cycle arrest and apoptosis in HT-29 human colon cancer cells by the dietary compound luteolin. *American Journal of Physiology-Gastrointestinal and Liver Physiology*. 2007;292:G66–G75.
35. Lim DY, Cho HJ, Kim J, Nho CW, Lee KW, Park JHY. Luteolin decreases IGF-II production and downregulates insulin-like growth factor-I receptor signaling in HT-29 human colon cancer cells. *BMC Gastroenterology*. 2012;12:9.
36. Hadi LA, Di Vito C, Marfia G, Ferraretto A, Tringali C, Viani P, Riboni L. Sphingosine kinase 2 and ceramide transport as key targets of the natural flavonoid luteolin to induce apoptosis in colon cancer cells. *PloS One*. 2015;10(11):e0143384.
37. Lu J, Li G, He K, Jiang W, Xu C, Li Z, Wang H, Wang W, Wang H, Teng X, Teng L. Luteolin exerts a marked antitumor effect in cMet-overexpressing patient-derived tumor xenograft models of gastric cancer. *Journal of Translational Medicine*. 2015;13(1):42.
38. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: Food sources and bioavailability. *The American Journal of Clinical Nutrition*. 2004;79(5):727–747.
39. Velazquez KT, Enos RT, Narsale AA, Puppa MJ, Davis JM, Murphy EA Carson JA. Quercetin supplementation attenuates the progression of cancer cachexia in ApcMin/+ mice. *Journal of Nutrition*. 2014;144:868–875.
40. Kim HS, Wannatung T, Lee S, Yang WK, Chung SH, Lim JS, Choe W, Kang I, Kim SS, Ha J. Quercetin enhances hypoxia-mediated apoptosis via direct inhibition of AMPK activity in HCT116 colon cancer. *Apoptosis*. 2012;17(9):938–949.
41. Lee HS, Cho HJ, Yu R, Lee KW, Chun HS, Park JH. Mechanisms underlying apoptosis-inducing effects of Kaempferol in HT-29 human colon cancer cells. *International Journal of Molecular Sciences*. 2014;15(2):2722–2737.
42. Kim ME, Ha TK, Yoon JH, Lee JS. Myricetin induces cell death of human colon cancer cells via BAX/BCL2-dependent pathway. *Anticancer Research*. 2014;34(2):701–706.
43. Xiao X, Liu Z, Wang R, Wang J, Zhang S, Cai X, Wu K, Bergan RC, Xu L, Fan D. Genistein suppresses FLT4 and inhibits human colorectal cancer metastasis. *Oncotarget*. 2015;6(5):3225.
44. Subramanian AP, Jaganathan SK, Mandal M, Supriyanto E, Muhamad II. Gallic acid induced apoptotic events in HCT-15 colon cancer cells. *World Journal of Gastroenterology*. 2016;22(15):3952.
45. Russell LH, Mazzio E, Badisa RB, Zhu ZP, Agharahimi M, Oriaku ET, Goodman CB. Autoxidation of gallic acid induces ROS-dependent death in human prostate cancer LNCaP cells. *Anticancer Research*. 2012;32(5):1595–1602.
46. Barzi A, Lenz AM, Labonte MJ, Lenz HJ. Molecular pathways: Estrogen pathway in colorectal cancer. *Clinical Cancer Research*. 2013;19(21):5842–5848.
47. Delman DM, Fabian CJ, Kimler BF, Yeh H, Petroff BK. Effects of flaxseed lignan secoisolariciresinol diglucosideon preneoplastic biomarkers of cancer progression in a model of simultaneous breast and ovarian cancer development. *Nutrition and Cancer*. 2015;67(5):857–864.
48. Xiong XY, Hu XJ, Li Y, Liu CM. Inhibitory effects of enterolactone on growth and metastasis in human breast cancer. *Nutrition and Cancer*. 2015;67(8):1326–1334.
49. Miki H, Uehara N, Kimura A, Sasaki T, Yuri T, Yoshizawa K, Tsubura A. Resveratrol induces apoptosis via ROS-triggered autophagy in human colon cancer cells. *International Journal of Oncology*. 2012;40(4):1020–1028.
50. Colin DJ, Limagne E, Ragot K, Lizard G, Ghiringhelli F, Solary E, Chauffert B, Latruffe N, Delmas D. The role of reactive oxygen species and subsequent DNA-damage response in the emergence of resistance towards resveratrol in colon cancer models. *Cell Death & Disease*. 2014;5(11):e1533.
51. Demoulin B, Hermant M, Castrogiovanni C, Staudt C, Dumont P. Resveratrol induces DNA damage in colon cancer cells by poisoning topoisomerase II and activates the ATM kinase to trigger p53-dependent apoptosis. *Toxicology in Vitro*. 2015;29(5):1156–1165.

52. Saud SM, Li W, Morris NL, Matter MS, Colburn NH, Kim YS, Young MR. Resveratrol prevents tumorigenesis in mouse model of Kras activated sporadic colorectal cancer by suppressing oncogenic Kras expression. *Carcinogenesis*. 2014;35(12):2778–2786.
53. Wang Z, Zhang L, Ni Z, Sun J, Gao H, Cheng Z, Xu J, Yin P. Resveratrol induces AMPK-dependent MDR1 inhibition in colorectal cancer HCT116/L-OHP cells by preventing activation of NF-κB signaling and suppressing cAMP-responsive element transcriptional activity. *Tumor Biology*. 2015;36(12):9499–9510.
54. Aires V, Limagne E, Cotte AK, Latruffe N, Ghiringhelli F, Delmas D. Resveratrol metabolites inhibit human metastatic colon cancer cells progression and synergize with chemotherapeutic drugs to induce cell death. *Molecular Nutrition & Food Research*. 2013;57(7):1170–1181.
55. Barros J, Serrani-Yarce JC, Chen F, Baxter D, Venables BJ, Dixon RA. Role of bifunctional ammonia-lyase in grass cell wall biosynthesis. *Nature Plants*. 2016;2(6):16050.
56. Zheng Q, Hirose Y, Yoshimi N, Murakami A, Koshimizu K, Ohigashi H, et al. Further investigation of the modifying effect of various chemopreventive agents on apoptosis and cell proliferation in human colon cancer cells. *Journal of Cancer Research and Clinical Oncology*. 2002;128(10):539–546.
57. Tanaka T, Kawabata K, Kakumoto M, Makita H, Matsunaga K, Mori H, et al. Chemoprevention of azoxymethane-induced rat colon carcinogenesis by a xanthine oxidase inhibitor, 1′-acetoxychavicol acetate. *Japanese Journal of Cancer Research*. 1997;88(9):821–830.
58. Cruz-Correa M, Shoskes DA, Sanchez P, Zhao R, Hylind LM, Wexner SD, et al. Combination treatment with curcumin and quercetin of adenomas in familial adenomatous polyposis. *Clinical Gastroenterology and Hepatology*. 2006;4(8):1035–1038.
59. Aggarwal BB, Sundaram C, Malani N, Ichikawa H. Curcumin: The Indian solid gold. *Advances in Experimental Medicine and Biology*. 2007;595:1–75.
60. Aggarwal S, Ichikawa H, Takada Y, Sandur SK, Shishodia S, Aggarwal BB. Curcumin (diferuloylmethane) down-regulates expression of cell proliferation and antiapoptotic and metastatic gene products through suppression of I kappa B alpha kinase and Akt activation. *Molecular Pharmacology*. 2005;69(1):195–206.
61. Aggarwal BB, Singh S, Aggarwal BB. Activation of transcription factor NF-kappaB is suppressed by curcumin (diferuloylmethane). *Journal of Biological Chemistry*. 1995;270(42):24995–25000.
62. Bharti AC, Donato N, Aggarwal BB. Curcumin (diferuloylmethane) inhibits constitutive and IL-6-inducible STAT3 phosphorylation in human multiple myeloma cells. *Journal of Immunology*. 2003;171(7):3863–3871.
63. Bae MK, Kim SH, Jeong JW, Lee YM, Kim HS, Kim SR, et al. Curcumin inhibits hypoxia-induced angiogenesis via downregulation of HIF-1. *Oncology Reports*. 2006;15(6):1557–1562.
64. Xu J, Fu Y, Chen A. Activation of peroxisome proliferator activated receptor-gamma contributes to the inhibitory effects of curcumin on rat hepatic stellate cell growth. *American Journal of Physiology-Gastrointestinal and Liver Physiology*. 2003;285(1):G20–G30.
65. Yan C, Jamaluddin MS, Aggarwal B, Myers J, Boyd DD. Gene expression profiling identifies activating transcription factor 3 as a novel contributor to the proapoptotic effect of curcumin. *Molecular Cancer Therapeutics*. 2005;4(2):233–241.
66. Dorai T, Gehani N, Katz A. Therapeutic potential of curcumin in human prostate cancer. II. Curcumin inhibits tyrosine kinase activity of epidermal growth factor receptor and depletes the protein. *Molecular Urology*. 2000;4(1):1–6.
67. Lao CD, Ruffin MT, Normolle D, Heath DD, Murray SI, Bailey JM, et al. Dose escalation of a curcuminoid formulation. *BMC Complementary and Alternative Medicine*. 2006;6:10.

68. Sharma RA, McLelland HR, Hill KA, Ireson CR, Euden SA, Manson MM, et al. Pharmacodynamic and pharmacokinetic study of oral Curcuma extract in patients with colorectal cancer. *Clinical Cancer Research*. 2001;7(7):1894–1900.
69. Ireson C, Orr S, Jones DJ, Verschoyle R, Lim CK, et al. Characterization of metabolites of the chemopreventive agent curcumin in human and rat hepatocytes and in the rat in vivo, and evaluation of their ability to inhibit phorbol ester-induced prostaglandin E2 production. *Cancer Research*. 2001;61:1058–1064.
70. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: Problems and promises. *Molecular Pharmaceutics*. 2007;4(6):807–818.
71. Deshpande SS, Ingle AD, Maru GB. Inhibitory effects of curcumin free aqueous turmeric extract on benzo[a]pyrene-induced forestomach papillomas in mice. *Cancer Letters*. 1997;118 (1):79–85.
72. Deshpande SS, Ingle AD, Maru GB. Chemopreventive efficacy of curcumin-free aqueous turmeric extract in 7,12-dimethylbenz[a]anthracene-induced rat mammary tumorigenesis. *Cancer Letters*. 1998;123(1):35–40.
73. Garcea G, Jones DJ, Singh R, Dennison AR, Farmer PB, et al. Detection of curcumin and its metabolites in hepatic tissue and portal blood of patients following oral administration. *British Journal of Cancer*. 2004;90:1011–1015.
74. Dillard CJ, German JB. Phytochemicals: Nutraceuticals and human health. *Journal of Science of Food and Agriculture*. 2000;80:1744–1756.
75. Agarwal MK, Agarwal ML, Athar M, Gupta S. Tocotrienol-rich fraction of palm oil activates p53, modulates Bax/Bcl2 ratio and induces apoptosis independent of cell cycle association. *Cell Cycle*. 2004;3(2):205–211.
76. Zhang JS, Li DM, He N, Liu YH, Wang CH, Jiang SQ, et al. A paraptosis-like cell death induced by delta-tocotrienol in human colon carcinoma SW620 cells is associated with the suppression of the Wnt signaling pathway. *Toxicology*. 2011;285(1–2):8–17.
77. Prasad S, Gupta SC, Tyagi AK, Aggarwal BB. γ-Tocotrienol suppresses growth and sensitises human colorectal tumours to capecitabine in a nude mouse xenograft model by down-regulating multiple molecules. *British Journal of Cancer*. 2016;115(7):814.
78. Wolf G. Is dietary beta carotene an anticancer agent? *Nutrition Reviews*. 1982;40(9):257–261.
79. Liebler DC. Antioxidant reactions of carotenoids. *Annals of the New York Academy of Sciences*. 1993;691(1):20–31.
80. Miller EC, Hadley CW, Schwartz SJ, Erdman JW, Boileau TWM, Clinton SK. Lycopene, tomato products, and prostate cancer prevention. Have we established causality? *Pure and Applied Chemistry*. 2002;74:1435–1441.
81. Tang FY, Shih CJ, Cheng LH, Ho HJ, Chen HJ. Lycopene inhibits growth of human colon cancer cells via suppression of the Akt signaling pathway. *Molecular Nutrition & Food Research*. 2008;52(6):646–654.
82. Prabhu PN, Ashokkumar P, Sudhandiran G. Antioxidative and antiproliferative effects of astaxanthin during the initiation stages of 1,2-dimethylhydrazine induced experimental colon carcinogenesis. *Fundamental & Clinical Pharmacology*. 2009;23:225–234.
83. Nakaizumi A, Baba M, Uehara H, Iishi H, Tatsuta M. d-Limonene inhibits N-nitrosobis (2-oxopropyl) amine induced hamster pancreatic carcinogenesis. *Cancer Letters*. 1997;117(1):99–103.
84. Uedo N, Tatsuta M, Iishi H, Baba M, Sakai N, Yano H, Otani T. Inhibition by d-limonene of gastric carcinogenesis induced by N-methyl-N′-nitro-N-nitrosoguanidine in Wistar rats. *Cancer Letters*. 1999;137(2):131–136.
85. Gupta SC, Prasad S, Sethumadhavan DR, Nair MS, Mo Y-Y, Aggarwal BB. Nimbolide, a limonoid triterpene, inhibits growth of human colorectal cancer xenografts by suppressing the proinflammatory microenvironment. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*. 2013;19(16):4465–4476.

86. Ramprasath VR, Awad AB. Role of phytosterols in cancer prevention and treatment. *Journal of AOAC International*. 2015;98(3):735–738.
87. Rao AV, Janezic SA. The role of dietary phytosterols in colon carcinogenesis. *Nutrition and Cancer*. 1992;18(1):43–52.
88. Lepage C, Léger DY, Bertrand J, Martin F, Beneytout JL, Liagre B. Diosgenin induces death receptor-5 through activation of p38 pathway and promotes TRAIL-induced apoptosis in colon cancer cells. *Cancer Letters*. 2011;301(2):193–202.
89. Lu JJ, Bao JL, Chen XP, Huang M, Wang YT. Alkaloids isolated from natural herbs as the anticancer agents. *Evidence-Based Complementary and Alternative Medicine*. 2012;2012.
90. Chidambara Murthy KN, Jayaprakasha GK, Patil BS. The natural alkaloid berberine targets multiple pathways to induce cell death in cultured human colon cancer cells. *European Journal of Pharmacology*. 2012;688(1–3):14–21.
91. Hsu WH, Hsieh YS, Kuo HC, Teng CY, Huang HI, Wang CJ, et al. Berberine induces apoptosis in SW620 human colonic carcinoma cells through generation of reactive oxygen species and activation of JNK/p38 MAPK and FasL. *Archives of Toxicology*. 2007;81(10):719–728.
92. Wu K, Yang Q, Mu Y, Zhou L, Liu Y, Zhou Q, et al. Berberine inhibits the proliferation of colon cancer cells by inactivating Wnt/beta-catenin signaling. *International Journal of Oncology*. 2012;41(1):292–298.
93. Lin HL, Liu TY, Wu CW, Chi CW. Berberine modulates expression of mdr1 gene product and the responses of digestive track cancer cells to Paclitaxel. *British Journal of Cancer*. 1999;81(3):416–422.
94. Thirupurasundari CJ, Padmini R, Devaraj SN. Effect of berberine on the antioxidant status, ultrastructural modifications and protein bound carbohydrates in azoxymethane-induced colon cancer in rats. *Chemico-Biological Interactions*. 2009;177(3):190–195.
95. Fukutake M, Yokota S, Kawamura H, Iizuka A, Amagaya S, Fukuda K, et al. Inhibitory effect of coptidis rhizoma and scutellariae radix on azoxymethane-induced aberrant crypt foci formation in rat colon. *Biological and Pharmaceutical Bulletin*. 1998;21(8):814–817.
96. Barrow C, Shahidi F. *Marine Nutraceuticals and Functional Foods*. Boca Raton, FL, CRC Press;2007:237–289.
97. Larsson SC, Kumlin M, Ingelman-Sundberg M, Wolk A. Dietary long-chain 3 fatty acids for the prevention of cancer: Are view of potential mechanisms. *The American Journal of Clinical Nutrition*. 2004;79:935–945.
98. Järvinen R, Knekt P, Hakulinen T, Rissanen H, Heliövaara M. Dietary fat, cholesterol and colorectal cancer in a prospective study. *British Journal of Cancer*. 2001;85(3):357.
99. Lee KW, Lee HJ, Surh YJ, Lee CY. Vitamin C and cancer chemoprevention: Reappraisal. *The American Journal of Clinical Nutrition*. 2003;78:1074–1078.
100. Tangpricha V, Flanagan JN, Whitlatch LW, Tseng CC, Chen TC, Holt PR, et al. 25 Hydroxyvitamin D-1α-hydroxylase in normal and malignant colon tissue. *Lancet*. 2001;357:1673–1684.
101. Holt PR. Dairy foods and prevention of colon cancer: Human studies. *Journal of the American College of Nutrition*. 18:sup5, 379S–391S.
102. Kim JE, Kang JS, Lee WJ. Vitamin C induces apoptosis in human colon cancer cell line, HCT-8 via the modulation of calcium influx in endoplasmic reticulum and the dissociation of bad from 14-3-3β. *Immune Network*. 2012;12(5):189–195.
103. Uccello M, Malaguarnera G, Basile F, D'agata V, Malaguarnera M, Bertino G, Vacante M, Drago F, Biondi A. Potential role of probiotics on colorectal cancer prevention. *BMC Surgery*. 2012;12(1):S35.

104. Fijan S. Microorganisms with claimed probiotic properties: An overview of recent literature. *International Journal of Environmental Research and Public Health*. 2014,11:4745–4767.
105. Raman M, Ambalam P, Kondepudi KK, et al. Potential of probiotics, prebiotics and synbiotics for management of colorectal cancer. *Gut Microbes*. 2013;4(3):181–192.
106. Ferguson LR, Chavan RR, Harris PJ. Changing concepts of dietary fiber: Implications for carcinogenesis. *Nutrition and Cancer*. 2001;39:155–169.
107. Liong MT. Roles of probiotics and prebiotics in colon cancer prevention: Postulated mechanisms and in-vivo evidence. *International Journal of Molecular Sciences*. 2008;9(5):854–863.
108. Moelants KRN, Lemmens L, Vandebroeck M, Van Buggenhout S, Van Loey AM, Hendrickx ME. 2012. Relation between particle size and carotenoid bioaccessibility in carrot- and tomato-derived suspensions. *Journal of Agricultural and Food Chemistry*. 60:11995–12003.
109. D'Ambrosio DN, Clugston RD, Blaner WS. Vitamin A metabolism: An update. *Nutrients*. 2011,3:63–103.
110. Fernández-García E, Carvajal-Lérida I, Jarén-Galán M, Garrido-Fernández J, Pérez-Gálvez A, Hornero-Méndez D. Carotenoids bioavailability from foods: From plant pigments to efficient biological activities. *Food Research International*. 2012;46(2):438–450.
111. Hurst NG, Stocken DD, Wilson S, Keh C, Wakelam MJ, Ismail T. Elevated serum matrix metalloproteinase 9 (MMP-9) concentration predicts the presence of colorectal neoplasia in symptomatic patients. *British Journal of Cancer*. 2007,97:971–977.
112. McClements DJ, Li F, Xiao H. The nutraceutical bioavailability classification scheme: Classifying nutraceuticals according to factors limiting their oral bioavailability. *Annual Review of Food Science and Technology*. 2015;6:299–327.
113. Patel MM, Getting into the colon: Approaches to target colorectal cancer. *Expert Opinion on Drug Delivery*. 2014;11:1343–1350.
114. Patel MM, Amin A. Recent trends in microbially and/or enzymatically driven colon-specific drug delivery systems. *Critical Reviews in Therapeutic Drug Carrier Systems*. 2011;28(6).
115. Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nature Biotechnology*. 2015;33(9):941–951.
116. Saneja A, Dubey RD, Alam N, Khare V, Gupta PN. Co-formulation of P-glycoprotein substrate and inhibitor in nanocarriers: An emerging strategy for cancer chemotherapy. *Current Cancer Drug Targets*. 2014;14(5):419–433.
117. Jain AK, Thanki K, Jain S. Co-encapsulation of tamoxifen and quercetin in polymeric nanoparticles: Implications on oral bioavailability, antitumor efficacy, and drug-induced toxicity. *Molecular Pharmaceutics*. 2013;10(9):3459–3474.
118. Sutradhar KB, Amin ML. Nanotechnology in cancer drug delivery and selective targeting. *ISRN Nanotechnology*. 2014;2014.
119. Zhong Y, Meng F, Deng C, Zhong Z. Ligand-directed active tumor-targeting polymeric nanoparticles for cancer chemotherapy. *Biomacromolecules*. 2014;15(6):1955–1969.
120. Collnot EM, Baldes C, Schaefer UF, Edgar KJ, Wempe MF, Lehr CM. Vitamin E TPGS P-glycoprotein inhibition mechanism: Influence on conformational flexibility, intracellular ATP levels, and role of time and site of access. *Molecular Pharmaceutics*. 2010;7(3):642–651.
121. Radhakrishnan R, Kulhari H, Pooja D, Gudem S, Bhargava S, Shukla R, Sistla R. Encapsulation of biophenolic phytochemical EGCG within lipid nanoparticles enhances its stability and cytotoxicity against cancer. *Chemistry and Physics of Lipids*. 2016;198:51–60.

122. Yallapu MM, Nagesh PK, Jaggi M, Chauhan SC. Therapeutic applications of curcumin nanoformulations. *AAPS*. 2015;17(6):1341–1356.
123. Sen S, Pathak Y. *Nanotechnology in Nutraceuticals: Production to Consumption*, CRC Press; 2016.
124. Aggarwal BB, Van Kuiken ME, Iyer LH, Harikumar KB, Sung B. Molecular targets of nutraceuticals derived from dietary spices: Potential role in suppression of inflammation and tumorigenesis. *Experimental Biology and Medicine (Maywood, NJ)*. 2009;234(8):825–849.
125. Mo SJ, Son EW, Rhee D K, Pyo S. Modulation of TNF-α-induced ICAM expression, NO and H2O2 production by alginate, allicin and ascorbic acid in human endothelial cells. *Archives of Pharmacol Research*. 2003;26:244–251.
126. Gruhlke MCH, Nicco C, Batteux F, Slusarenko AJ. The effects of allicin, a reactive sulfur species from garlic, on a selection of mammalian cell lines. Jacob C, Giles GI, eds. *Antioxidants*. 2017;6(1):1.
127. Xu S, Kojima-Yuasa A, Azuma H, Huang X, Norikura T, Kennedy DO, et al. (l'S)-Acetoxychavicol acetate and its enantiomer inhibit tumor cells proliferation via different mechanisms. *Chemico-Biological Interactions*. 2008;172:216–223.
128. Balasubramanyam K, Swaminathan V, Ranganathan A, Kundu TK. Small molecule modulators of histone acetyltransferase p300. *Journal of Biological Chemistry*. 2003;278(21):19134–19140.
129. Sun Y, Jiang X, Chen S, Price BD. Inhibition of histone acetyltransferase activity by anacardic acid sensitizes tumor cells to ionizing radiation. *FEBS Letters*. 2006;580(18):4353–4356.
130. Hamad F, Mubofu E. Potential biological applications of bio-based anacardic acids and their derivatives. *International Journal of Molecular Sciences*. 2015 16;16(4):8569–8590.
131. Choi EJ, Park JS, Kim YJ, Jung JH, Lee JK, Kwon HC, et al. Apoptosis inducing effect of diketopiperazine disulfides produced by *Aspergillus* sp. KMD901 isolated from marine sediment on HCT116 colon cancer cell lines. *Journal of Applied Microbiology*. 2011;110:304–313.
132. Xu M, Wang S, Song Y, Yao J, Huang K, Zhu X. Apigenin suppresses colorectal cancer cell proliferation, migration and invasion via inhibition of the Wnt/β-catenin signaling pathway. *Oncology Letters*, 2016:11:3075–3080.
133. Zhong Y, Krisanapun C, Lee S-H, et al. Molecular targets of apigenin in colorectal cancer cells: Involvement of p21, NAG-1 and p53. *European Journal of Cancer (Oxford, England : 1990)*. 2010;46(18):3365–3374.
134. Khan I, Khan F, Farooqui A, Ansari IA. Andrographolide exhibits anticancer potential against human colon cancer cells by inducing cell cycle arrest and programmed cell death via augmentation of intracellular reactive oxygen species level. *Nutrition and Cancer*. 2018:1–7.
135. Jaganathan SK, Mazumdar A, Mondhe D, Mandal M. Apoptotic effect of eugenol in human colon cancer cell lines. *Cell Biology International*. 2011;35(6):607–615.
136. Chainy GB, Manna SK, Chaturvedi MM, Aggarwal BB. Anethole blocks both early and late cellular responses transduced by tumor necrosis factor: Effect on NF-kappaB, AP-1, JNK, MAPKK and apoptosis. *Oncogene*. 2000;19(25):2943–5290.
137. Yasui Y, Hosokawa M, Mikami N, Miyashita K, Tanaka T. Dietary astaxanthin inhibits colitis and colitis-associated colon carcinogenesis in mice via modulation of the inflammatory cytokines. *Chemico-Biological Interactions*. 2011;193:79–87.
138. Yang Y, Kim B, Lee JY. Astaxanthin structure, metabolism, and health benefits. *Journal of Nutrition and Food Sciences*. 2013;1:1003–1014.

139. Nagendraprabhu P, Sudhandiran G. Astaxanthin inhibits tumor invasion by decreasing extracellular matrix production and induces apoptosis in experimental rat colon carcinogenesis by modulating the expressions of ERK-2,NF-κB and COX-2. *Invest New Drugs*. 2011;29:207–224.
140. Chidambara Murthy KN, Jayaprakasha GK, Patil BS. The natural alkaloid berberine targets multiple pathways to induce cell death in cultured human colon cancer cells. *European Journal of Pharmacology*. 2012;688(1–3):14–21.
141. Hu W, Yu L, Wang MH. Antioxidant and antiproliferative properties of water extract from *Mahonia bealei* (Fort.) Carr. leaves. *Food and Chemical Toxicology*. 2011;49(4):799–806.
142. Hsu WH, Hsieh YS, Kuo HC, Teng CY, Huang HI, Wang CJ, et al. Berberine induces apoptosis in SW620 human colonic carcinoma cells through generation of reactive oxygen species and activation of JNK/p38 MAPK and FasL. *Archives of Toxicology*. 2007;81(10):719–728.
143. Iizuka N, Hazama S, Yoshimura K, Yoshino S, Tangoku A, Miyamoto K, et al. Anticachectic effects of the natural herb Coptidis rhizoma and berberine on mice bearing colon 26/clone 20 adenocarcinoma. *International Journal of Cancer*. 2002;99(2):286–291.
144. Li XK, Motwani M, Tong W, Bornmann W, Schwartz GK. Huanglian, A Chinese herbal extract, inhibits cell growth by suppressing the expression of cyclin B1 and inhibiting CDC2 kinase activity in human cancer cells. *Molecular Pharmacology*. 2000;58(6):1287–1293.
145. Lin HL, Liu TY, Wu CW, Chi CW. Berberine modulates expression of mdr1 gene product and the responses of digestive track cancer cells to paclitaxel. *British Journal of Cancer*. 1999;81(3):416–422.
146. Fukuda K, Hibiya Y, Mutoh M, Koshiji M, Akao S, Fujiwara H. Inhibition by berberine of cyclooxygenase-2 transcriptional activity in human colon cancer cells. *Journal of Ethnopharmacology*. 1999;66(2):227–233.
147. Basu S, Ma R, Boyle PJ, Mikulla B, Bradley M, Smith B, et al. Apoptosis of human carcinoma cells in the presence of potential anti-cancer drugs: III. Treatment of Colo-205 and SKBR3 cells with: Cis-platin, tamoxifen, melphalan, betulinic acid, L-PDMP, L-PPMP, and GD3 ganglioside. *Glycoconjugate Journal*. 2004;20(9):563–577.
148. Chintharlapalli S, Papineni S, Lei P, Pathi S, Safe S. Betulinic acid inhibits colon cancer cell and tumor growth and induces proteasome-dependent and -independent downregulation of specificity proteins (Sp) transcription factors. *BMC Cancer*. 2011;11:371.
149. Bar FM, Khanfar MA, Elnagar AY, Liu H, Zaghloul AM, Badria FA, et al. Rational design and semisynthesis of betulinic acid analogues as potent topoisomerase inhibitors. *Journal of Natural Products*. 2009;72(9):1643–1650.
150. Rajendran P, Jaggi M, Singh MK, Mukherjee R, Burman AC. Pharmacological evaluation of C-3 modified betulinic acid derivatives with potent anticancer activity. *Investigational New Drugs*. 2008;26(1):25–34.
151. Jung GR, Kim KJ, Choi CH, Lee TB, Han SI, Han HK, et al. Effect of betulinic acid on anticancer drug-resistant colon cancer cells. *Basic & Clinical Pharmacology & Toxicology*. 2007;101(4):277–285.
152. Chintharlapalli S, Papineni S, Liu S, Jutooru I, Chadalapaka G, Cho SD, et al. 2-cyano-lup-1-en-3-oxo-20-oic acid, a cyano derivative of betulinic acid, activates peroxisome proliferator activated receptor gamma in colon and pancreatic cancer cells. *Carcinogenesis*. 2007;28(11):2337–2346.
153. Rzeski W, Stepulak A, Szymanski M, Sifringer M, Kaczor J, Wejksza K, et al. Betulinic acid decreases expression of bcl-2 and cyclin D1, inhibits proliferation, migration and induces apoptosis in cancer cells. *Naunyn-Schmiedeberg's Archives of Pharmacology*. 2006;374(1):11–20.

154. Liu JJ, Duan RD. LY294002 enhances boswellic acid-induced apoptosis in colon cancer cells. *Anticancer Research*. 2009;29(8):2987–2991.
155. Liu JJ, Huang BH, Hooi SC. Acetyl-keto-β-boswellic acid inhibits cellular proliferation through ap21-dependent pathway in colon cancer cells. *British Journal of Pharmacology*. 2006;148:1099–1107.
156. Takahashi M, Sung B, Shen Y, Hur K, Link A, Boland CR, Aggarwal BB, Goel A. Boswellic acid exerts antitumor effects in colorectal cancer cells by modulating expression of the let-7 and miR-200 microRNA family. *Carcinogenesis*. 2012;33(12):2441–2449.
157. Yit CC, Das NP. Cytotoxic effect of butein on human colon adenocarcinoma cell proliferation. *Cancer Letters*. 1994;82(1):65–72.
158. Beta-escin inhibits colonic aberrant crypt foci formation in rats and regulates the cell cycle growth by inducing p21(waf1/cip1) in colon cancer cells. *Molecular Cancer Therapeutics*. 2006;5(6):1459–1466.
159. Iftikhar S, Helen L, Sohrab M, Thomas O. Frommel. In vitro β-carotene toxicity for human colon cancer cells. *Nutrition and Cancer*. 1996;25(3):221–230.
160. Yanagihara K, Ito A, Toge T, Numoto M. Antiproliferative effects of isoflavones on human cancer cell lines established from the gastrointestinal tract. *Cancer Research*. 1993;53(23):5815–5821.
161. Casein phosphopeptides modulate proliferation and apoptosis in HT-29 cell line through their interaction with voltage-operated L-type calcium channels. *The Journal of Nutritional Biochemistry*. 2012;23(7):808–816.
162. Lee SJ, Lee KW, Hur HJ, Chun JY, Kim SY, Lee HJ. Phenolic Phytochemicals derived from red pine (*Pinus densiflora*) inhibit the invasion and migration of SK-Hep-1 human hepatocellular carcinoma cells. *Annals of the New York Academy of Sciences*. 2007;1095(1):536–544.
163. Jin H, Gong W, Zhang C, Wang S. Epigallocatechin gallate inhibits the proliferation of colorectal cancer cells by regulating Notch signaling. *OncoTargets and Therapy*. 2013;6:145–153.
164. Aggarwal BB, Shishodia S. Suppression of the nuclear factor-κB activation pathway by spice-derived phytochemicals: Reasoning for seasoning. *Annals of the New York Academy of Sciences*. 2004;1030(1):434–441.
165. Lu HF, Chen YL, Yang JS, Yang YY, Liu JY, Hsu SC, et al. Antitumor activity of capsaicin on human colon cancer cells in vitro and colo 205 tumor xenografts in vivo. *Journal of Agricultural and Food Chemistry*. 2010;58(24):12999–13005.
166. Kim MY, Trudel LJ, Wogan GN. Apoptosis induced by capsaicin and resveratrol in colon carcinoma cells requires nitric oxide production and caspase activation. *Anticancer Research*. 2009;29(10):3733–3740.
167. Kim YM, Hwang JT, Kwak DW, Lee YK, Park OJ. Involvement of AMPK signaling cascade in capsaicin-induced apoptosis of HT-29 colon cancer cells. *Annals of the New York Academy of Sciences*. 2007;1095:496–503.
168. Kim CS, Park WH, Park JY, Kang JH, Kim MO, Kawada T, et al. Capsaicin, a spicy component of hot pepper, induces apoptosis by activation of the peroxisome proliferator-activated receptor gamma in HT-29 human colon cancer cells. *Journal of Medicinal Food*. 2004;7(3):267–273.
169. Park S, Gwak J, Han SJ, Oh S. Cardamonin suppresses the proliferation of colon cancer cells by promoting β-catenin degradation. *Biological and Pharmaceutical Bulletin*. 2013;36(6):1040–1044.
170. Sung B, Park B, Yadav VR, Aggarwal BB. Celastrol, a triterpene, enhances TRAIL-induced apoptosis through the downregulation of cell survival proteins and upregulation of death receptors. *Journal of Biological Chemistry*. 2010:jbc-M109.

171. Yadav VR, Sung B, Prasad S, Kannappan R, Cho SG, Liu M, et al. Celastrol suppresses invasion of colon and pancreatic cancer cells through the downregulation of expression of CXCR4 chemokine receptor. *Journal of Molecular Medicine (Berl)*. 2010;88(12):1243–1253.
172. Anticancer Properties of Chrysin on Colon Cancer Cells, In vitro and in vivo with Modulation of Caspase-3, -9, Bax and Sall4. *Iranian Journal of Biotechnology*. 2016;14(3):177–184.
173. Tanaka T, Hosokawa M, Yasui Y, Ishigamori R, Miyashita K. Cancer chemopreventive ability of conjugated linolenic acids. *International Journal of Molecular Sciences*. 2011;12(11):7495–7509.
174. Jaganathan SK. Growth inhibition by caffeic acid, one of the phenolic constituents of honey, in HCT 15 colon cancer cells. *The Scientific World Journal*. 2012;2012.
175. Choy YY, Fraga M, Mackenzie GG, Waterhouse AL, Cremonini E, Oteiza PI. The PI3K/Akt pathway is involved in procyanidin-mediated suppression of human colorectal cancer cell growth. *Molecular Carcinogenesis*. 2016;55(12):2196–2209.
176. Lorenzo Y, Azqueta A, Luna L, Bonilla F, Domínguez G, Collins AR. The carotenoid β-cryptoxanthin stimulates the repair of DNA oxidation damage in addition to acting as an antioxidant in human cells. *Carcinogenesis*. 2008;30(2):308–314.
177. Narisawa T, Fukaura Y, Oshima S, Inakuma T, Yano M, Nishino H. Chemoprevention by the oxygenated carotenoid β-Cryptoxanthin of N-Methylnitrosourea-induced colon carcinogenesis in F344 Rats. *Japanese Journal of Cancer Research: Gann*. 1999;90(10):1061–1065.
178. Mosieniak G, Adamowicz M, Alster O, Jaskowiak H, Szczepankiewicz AA, Wilczynski GM, et al. Curcumin induces permanent growth arrest of human colon cancer cells: Link between senescence and autophagy. *Mechanisms of Ageing and Developmen*. 2012;133(6):444–455.
179. Nautiyal J, Kanwar SS, Yu Y, Majumdar AP. Combination of dasatinib and curcumin eliminates chemo-resistant colon cancer cells. *Journal of Molecular Signaling*. 2011;6:7.
180. Yue GG, Cheng SW, Yu H, Xu ZS, Lee JK, Hon PM, et al. The role of turmerones on curcumin transportation and P-glycoprotein activities in intestinal Caco-2 cells. *Journal of Medicinal Food*. 2012;15(3):242–252.
181. Jung KH, Park JW. Suppression of mitochondrial NADP(+)-dependent isocitrate dehydrogenase activity enhances curcumin induced apoptosis in HCT116 cells. *Free Radical Research*. 2011;45(4):431–438.
182. Kanwar SS, Yu Y, Nautiyal J, Patel BB, Padhye S, Sarkar FH, et al. Difluorinated-curcumin (CDF): A novel curcumin analog is a potent inhibitor of colon cancer stem-like cells. *Pharmaceutical Research*. 2011;28(4):827–838.
183. Lin L, Liu Y, Li H, Li PK, Fuchs J, Shibata H, et al. Targeting colon cancer stem cells using a new curcumin analogue, GOY030. *British Journal of Cancer*. 2011;105(2):212–220.
184. Lee YJ, Kim NY, Suh YA, Lee C. Involvement of ROS in Curcumin-induced Autophagic cell death. *The Korean Journal of Physiology & Pharmacology*. 2011;15(1):1–7.
185. Patel BB, Gupta D, Elliott AA, Sengupta V, Yu Y, Majumdar AP. Curcumin targets FOLFOX-surviving colon cancer cells via inhibition of EGFRs and IGF-1R. *Anticancer Research*. 2010;30(2):319–325.
186. Kim KC, Lee C. Curcumin induces downregulation of E2F4 expression and Apoptotic cell death in HCT116 human colon cancer cells; involvement of reactive oxygen species. *The Korean Journal of Physiology & Pharmacology*. 2010;14(6):391–397.
187. Watson JL, Hill R, Yaffe PB, Greenshields A, Walsh M, Lee PW, et al. Curcumin causes superoxide anion production and p53-independent apoptosis in human colon cancer cells. *Cancer Letters*. 2010;297(1):1–8.

188. Majumdar AP, Banerjee S, Nautiyal J, Patel BB, Patel V, Du J, et al. Curcumin synergizes with resveratrol to inhibit colon cancer. *Nutrition and Cancer*. 2009;61(4):544–553.
189. Yu Y, Kanwar SS, Patel BB, Nautiyal J, Sarkar FH, Majumdar AP. Elimination of colon cancer stem-like cells by the combination of curcumin and FOLFOX. *Translational Oncology*. 2009;2(4):321–328.
190. Bartik L, Whitfield GK, Kaczmarska M, Lowmiller CL, Moffet EW, Furmick JK, et al. Curcumin: A novel nutritionally derived ligand of the vitamin D receptor with implications for colon cancer chemoprevention. *The Journal of Nutritional Biochemistry*. 2010;21(12):1153–1161.
191. Basile V, Ferrari E, Lazzari S, Belluti S, Pignedoli F, Imbriano C. Curcumin derivatives: Molecular basis of their anti-cancer activity. *Biochemical Pharmacology*. 2009;78(10):1305–1315.
192. Sandur SK, Deorukhkar A, Pandey MK, Pabon AM, Shentu S, Guha S, et al. Curcumin modulates the radiosensitivity of colorectal cancer cells by suppressing constitutive and inducible NFkappaB activity. *International Journal of Radiation Oncology, Biology, Physics*. 2009;75(2):534–542.
193. Lee YK, Park SY, Kim YM, Park OJ. Regulatory effect of the AMPK-COX-2 signaling pathway in curcumin-induced apoptosis in HT-29 colon cancer cells. *Annals of the New York Academy of Sciences*. 2009;1171:489–494.
194. Milacic V, Banerjee S, Landis-Piwowar KR, Sarkar FH, Majumdar AP, Dou QP. Curcumin inhibits the proteasome activity in human colon cancer cells in vitro and in vivo. *Cancer Research*. 2008;68(18):7283–7292.
195. Giri B, Gomes A, Sengupta R, Banerjee S, Nautiyal J, Sarkar FH, et al. Curcumin synergizes the growth inhibitory properties of Indian toad (*Bufo melanostictus* Schneider) skin-derived factor (BM-ANF1) in HCT-116 colon cancer cells. *Anticancer Research*. 2009;29(1):395–401.
196. Ahmad A, Wang Z, Ali R, Maitah MY, Kong D, Banerjee S, et al. Apoptosis-inducing effect of garcinol is mediated by NF-kappaB signaling in breast cancer cells. *Journal of Cellular Biochemistry*. 2010;109:1134–1141.
197. Kwon Y, Magnuson BA. Age-related differential responses to curcumin-induced apoptosis during the initiation of colon cancer in rats. *Food and Chemical Toxicology*. 2009;47(2):377–385.
198. Guo JM, Xiao BX, Liu DH, Grant M, Zhang S, Lai YF, Guo YB, Liu Q. Biphasic effect of daidzein on cell growth of human colon cancer cells. *Food and Chemical Toxicology*. 2004;42(10):1641–1646.
199. Chan CK, Supriady H, Goh BH, Kadir HA. *Elephantopus scaber* induces apoptosis through ROS-dependent mitochondrial signaling pathway in HCT116 human colorectal carcinoma cells. *Journal of Ethnopharmacology*. 2015;168:291–304.
200. Choi KC, Jung MG, Lee YH, Yoon JC, Kwon SH, Kang HB, Kim MJ, Cha JH, Kim YJ, Jun WJ, Lee JM. Epigallocatechin-3-gallate, a histone acetyltransferase inhibitor, inhibits EBV-induced B lymphocyte transformation via suppression of RelA acetylation. *Cancer Research*. 2009;69(2):583–592.
201. Lepage C, Leger DY, Bertrand J, Martin F, Beneytout JL, Liagre B. Diosgenin induces death receptor-5 through activation of p38 pathway and promotes TRAIL-induced apoptosis in colon cancer cells. *Cancer Letters*. 2011;301(2):193–202.
202. Raju J, Bird RP. Diosgenin, a naturally occurring steroid saponin suppresses 3-hydroxy-3-methylglutaryl CoA reductase expression and induces apoptosis in HCT-116 human colon carcinoma cells. *Cancer Letters*. 2007;255(2):194–204.
203. Raju J, Patlolla JM, Swamy MV, Rao CV. Diosgenin, a steroid saponin of *Trigonella foenum graecum* (Fenugreek), inhibits azoxymethane-induced aberrant crypt foci formation in F344 rats and induces apoptosis in HT-29 human colon cancer cells. *Cancer Epidemiology, Biomarkers & Prevention*. 2004;13(8):1392–1398.

204. Wang SL, Cai B, Cui CB, Liu HW, Wu CF, Yao XS. Diosgenin- 3-O-alpha-Lrhamnopyranosyl-(1 – > 4)-beta-D-glucopyranoside obtained as a new anticancer agent from *Dioscorea futschauensis* induces apoptosis on human colon carcinoma HCT-15 cells via mitochondria-controlled apoptotic pathway. *Journal of Asian Natural Products Research*. 2004;6(2):115–125.
205. Ma YS, Weng SW, Lin MW, Lu CC, Chiang JH, Yang JS, et al. Antitumor effects of emodin on LS1034 human colon cancer cells in vitro and in vivo: Roles of apoptotic cell death and LS1034 tumor xenografts model. *Food and Chemical Toxicology*. 2012;50(5):1271–1278.
206. Suboj P, Babykutty S, Valiyaparambil Gopi DR, Nair RS, Srinivas P, Gopala S. Aloe emodin inhibits colon cancer cell migration/angiogenesis by downregulating MMP-2/9, RhoB and VEGF via reduced DNA binding activity of NF-kappaB. *European Journal of Pharmaceutical Sciences*. 2012;45(5):581–591.
207. Han YM, Lee SK, Jeong DG, Ryu SE, Han DC, Kim DK, et al. Emodin inhibits migration and invasion of DLD-1 (PRL-3) cells via inhibition of PRL-3 phosphatase activity. *Bioorganic & Medicinal Chemistry Letters*. 2012;22(1):323–326.
208. El-Shemy HA, Aboul-Soud MA, Nassr-Allah AA, Aboul-Enein KM, Kabash A, Yagi A. Antitumor properties and modulation of antioxidant enzymes' activity by aloe vera leaf active principles isolated via supercritical carbon dioxide extraction. *Current Medicinal Chemistry*. 2010;17(2):129–138.
209. Lu Y, Zhang J, Qian J. The effect of emodin on VEGF receptors in human colon cancer cells. *Cancer Biotherapy and Radiopharmaceuticals*. 2008;23(2):222–228.
210. Patlolla JM, Raju J, Swamy MV, Rao CV. Beta-escin inhibits colonic aberrant crypt foci formation in rats and regulates the cell cycle growth by inducing p21(waf1/cip1) in colon cancer cells. *Cancer Biotherapy and Radiopharmaceuticals*. 2006;5(6):1459–1466.
211. Kumar S, Deshmukh R. Embelin as a potential drug molecule: A review. *Journal of Pharmacognosy and Natural Products* 2017;3:144.
212. Dai Y, Jiao H, Teng G, Wang W, Zhang R, Wang Y, Hebbard L, George J, Qiao L. Embelin reduces colitis-associated tumorigenesis through limiting IL-6/STAT3 signaling. *Molecular Cancer Therapeutics*. 2014;1206–1216.
213. Yousef AI, El-Masry OS, Abdel Mohsen MA. Impact of cellular genetic make-up on colorectal cancer cell lines response to ellagic acid: Implications of small interfering RNA. *Asian Pacific Journal of Cancer Prevention*. 2016;17(2):743–748.
214. Huang J, Chen Z, Ren C, Wang D, Yuan S, Wu Q, He B. Antiproliferation effect of evodiamine in human colon cancer cells is associated with IGF-1/HIF-1α downregulation. *Oncology Reports*. 2015;34:3203–3211.
215. Jaganathan SK, Mazumdar A, Mondhe D, Mandal M. Apoptotic effect of eugenol in human colon cancer cell lines. *Cell Biology International*. 2011;35(6):607–615.
216. Yu SH, Yang PM, Peng CW, Yu YC, Chiu SJ. Securin depletion sensitizes human colon cancer cells to fisetin-induced apoptosis. *Cancer Letters*. 2011;300(1):96–104.
217. Do Lim Y, Park JH. Induction of p53 contributes to apoptosis of HCT-116 human colon cancer cells induced by the dietary compound fisetin. *American Journal of Physiology-Gastrointestinal and Liver Physiology*. 2009;296(5):G1060–G1068.
218. Suh Y, Afaq F, Johnson JJ, Mukhtar H. A plant flavonoid fisetin induces apoptosis in colon cancer cells by inhibition of COX2 and Wnt/EGFR/NF-kappaB-signaling pathways. *Carcinogenesis*. 2009;30(2):300–307.
219. Lu X, Jung J, Cho HJ, Lim DY, Lee HS, Chun HS, et al. Fisetin inhibits the activities of cyclin-dependent kinases leading to cell cycle arrest in HT-29 human colon cancer cells. *Journal of Nutrition*. 2005;135(12):2884–2890.
220. Kumar N, Pruthi V. Potential applications of ferulic acid from natural sources. *Biotechnology Reports*. 2014;4:86–93.

221. Hudson EA, Dinh PA, Kokubun T, Simmonds MS, Gescher A. Characterization of potentially chemopreventive phenols in extracts of brown rice that inhibit the growth of human breast and colon cancer cells. *Cancer Epidemiology, Biomarkers and Prevention*. 2009:1163–1170.
222. Hosokawa M, Kudo M, Maeda H, Kohno H, Tanaka T, Miyashita K. Fucoxanthin induces apoptosis and enhances the antiproliferative effect of the PPAR gamma ligand, troglitazone, on colon cancer cells. *Biochimica et Biophysica Acta*. 2004;1675:113–119.
223. Ambrosini G, Seelman SL, Qin LX, Schwartz GK. The cyclin dependent kinase inhibitor flavopiridol potentiates the effects of topoisomerase I poisons by suppressing Rad51 expression in a p53-dependent manner. *Cancer Research*. 2008;68(7):2312–2320.
224. Nawrocki ST, Carew JS, Douglas L, Cleveland JL, Humphreys R, Houghton JA. Histone deacetylase inhibitors enhance lexatumumab-induced apoptosis via a p21Cip1-dependent decrease in survivin levels. *Cancer Research*. 2007;67(14):6987–6994.
225. Jung C, Motwani M, Kortmansky J, Sirotnak FM, She Y, Gonen M, et al. The cyclin-dependent kinase inhibitor flavopiridol potentiates gamma-irradiation-induced apoptosis in colon and gastric cancer cells. *Clinical Cancer Research*. 2003;9(16 Pt 1):6052–6061.
226. Motwani M, Jung C, Sirotnak FM, She Y, Shah MA, Gonen M, et al. Augmentation of apoptosis and tumor regression by flavopiridol in the presence of CPT-11 in Hct116 colon cancer monolayers and xenografts. *Clinical Cancer Research*. 2001;7(12):4209–4219.
227. Smith V, Raynaud F, Workman P, Kelland LR. Characterization of a human colorectal carcinoma cell line with acquired resistance to flavopiridol. *Molecular Pharmacology*. 2001;60(5):885–893.
228. Kahn ME, Senderowicz A, Sausville EA, Barrett KE. Possible mechanisms of diarrheal side effects associated with the use of a novel chemotherapeutic agent, flavopiridol. *Clinical Cancer Research*. 2001;7(2):343–349.
229. Prasad S, Ravindran J, Sung B, Pandey MK, Aggarwal BB. Garcinol potentiates TRAIL induced apoptosis through modulation of death receptors and antiapoptotic proteins. *Molecular Cancer Therapeutics*. 2010;9(4):856–868.
230. Hong J, Kwon SJ, Sang S, Ju J, Zhou JN, Ho CT, et al. Effects of garcinol and its derivatives on intestinal cell growth: Inhibitory effects and autoxidation-dependent growth-stimulatory effects. *Free Radical Biology and Medicine*. 2007;42(8):1211–1221.
231. Liao CH, Sang S, Ho CT, Lin JK. Garcinol modulates tyrosine phosphorylation of FAK and subsequently induces apoptosis through down-regulation of Src, ERK, and Akt survival signaling in human colon cancer cells. *Journal of Cellular Biochemistry*. 2005;96(1):155–169.
232. Qin J, Chen JX, Zhu Z, Teng JA. Genistein inhibits human colorectal cancer growth and suppresses MiR-95, Akt and SGK1. *Cellular Physiology and Biochemistry*. 2015;35:2069–2077.
233. Ha TK, Kim ME, Yoon JH, Bae SJ, Yeom J, Lee JS. Galangin induces human colon cancer cell death via the mitochondrial dysfunction and caspase-dependent pathway. *Experimental Biology and Medicine*. 2013;238(9):1047–1054.
234. Wen C, Huang L, Chen J, Lin M, Li W, Lu B, Rutnam ZJ, Iwamoto A, Wang Z, Yang X, Liu H. Gambogic acid inhibits growth, induces apoptosis, and overcomes drug resistance in human colorectal cancer cells. *International Journal of Oncology*. 2015;47(5):1663–1671.
235. Bode AM, Ma WY, Surh YJ, Dong Z. Inhibition of epidermal growth factor-induced cell transformation and activator protein 1 activation by [6]-gingerol. *Cancer Research*. 2001;61(3):850–853.

236. Kim EC, Min JK, Kim TY, Lee SJ, Yang HO, Han S, Kim YM, Kwon YG. [6]-Gingerol, a pungent ingredient of ginger, inhibits angiogenesis in vitro and in vivo. *Biochemical and Biophysical Research Communications*. 2005;335(2):300–308.
237. Kim JK, Kim Y, Na KM, Surh YJ, Kim TY. [6]-Gingerol prevents UVB-induced ROS production and COX-2 expression in vitro and in vivo. *Free Radical Research*. 2007;41(5):603–614.
238. Yan F, Cao XX, Jiang HX, Zhao XL, Wang JY, Lin YH, Liu QL, Zhang C, Jiang B, Guo F. A novel water-soluble gossypol derivative increases chemotherapeutic sensitivity and promotes growth inhibition in colon cancer. *Journal of Medicinal Chemistry*. 2010;53(15):5502–5510.
239. Sung B, Ravindran J, Prasad S, Pandey MK, Aggarwal BB. Gossypol induces death receptor-5 through activation of ROS-ERK-chop pathway and sensitizes colon cancer cells to trail. *Journal of Biological Chemistry*. 2010:jbc-M110.
240. Wang X, Wang J, Wong SC, Chow LS, Nicholls JM, Wong YC, Liu Y, Kwong DL, Sham JS, Tsao SW. Cytotoxic effect of gossypol on colon carcinoma cells. *Life Sciences*. 2000;67(22):2663–2671.
241. Zhang M, Liu H, Guo R, Ling Y, Wu X, Li B, Roller PP, Wang S, Yang D. Molecular mechanism of gossypol-induced cell growth inhibition and cell death of HT-29 human colon carcinoma cells. *Biochemical Pharmacology*. 2003;66(1):93–103.
242. An MJ, Cheon JH, Kim SW, Kim ES, Kim TI, Kim WH. Guggulsterone induces apoptosis in colon cancer cells and inhibits tumor growth in murine colorectal cancer xenografts. *Cancer Letters*. 2009;279(1):93–100.
243. Kim ES, Hong SY, Lee HK, Kim SW, An MJ, Kim TI, Lee KR, Kim WH, Cheon JH. Guggulsterone inhibits angiogenesis by blocking STAT3 and VEGF expression in colon cancer cells. *Oncology Reports*. 2008;20(6):1321–1327.
244. Aranganathan S, Nalini N. Antiproliferative efficacy of hesperetin (citrus flavanoid) in 1, 2-dimethylhydrazine-induced colon cancer. *Phytotherapy Research*. 2013;2(7):999–1005.
245. Arora S, Srivastava SK, Bhardwaj A, Singh AP, Piazza GA, Owen LB, Singh S. Honokiol inhibits IL-8 production and exerts anti-tumor effects in colon cancer cells: Therapeutic and preventive implications. 2012;1626.
246. Yoshida T, Maoka T, Das SK, Kanazawa K, Horinaka M, Wakada M, Satomi Y, Nishino H, Sakai T. Halocynthiaxanthin and peridinin sensitize colon cancer cell lines to tumor necrosis factor–related apoptosis-inducing ligand. *Molecular Cancer Research*. 2007;5(6):615–625.
247. Shi J, Shen HM. Critical role of Bid and Bax in indirubin-3′-monoxime-induced apoptosis in human cancer cells. *Biochemical Pharmacology*. 2008;75(9):1729–1742.
248. Weng JR, Tsai CH, Kulp SK, Chen CS. Indole-3-carbinol as a chemopreventive and anti-cancer agent. *Cancer Letters*. 2008;262(2):153–163.
249. Li C, Yang X, Chen C, Cai S, Hu J. Isorhamnetin suppresses colon cancer cell growth through the PI3K-Akt-mTOR pathway. *Molecular Medicine Reports*. 2014;9(3):935–940.
250. Booth C, Hargreaves DF, Hadfield JA, McGown AT, Potten CS. Isoflavones inhibit intestinal epithelial cell proliferation and induce apoptosis in vitro. *British Journal of Cancer*. 1999;80(10):1550.
251. Lewandowska U, Szewczyk K, Owczarek K, Hrabec Z, Podsędek A, Koziołkiewicz M, Hrabec E. Flavanols from Japanese quince (*Chaenomeles japonica*) fruit inhibit human prostate and breast cancer cell line invasiveness and cause favorable changes in Bax/Bcl-2 mRNA ratio. *Nutrition and Cancer*. 2013;65(2):273–285.
252. Cho HJ, Park JH. Kaempferol induces cell cycle arrest in HT-29 human colon cancer cells. *Journal of Cancer Prevention*. 2013;18(3):257.

253. Lee HS, Cho HJ, Yu R, Lee KW, Chun HS, Park JH. Mechanisms underlying apoptosis inducing effects of Kaempferol in HT-29 human colon cancer cells. *International Journal of Molecular Sciences*. 2014;15(2):2722–2737.
254. Ji CF, Ji YB. Laminarin-induced apoptosis in human colon cancer LoVo cells. *Oncology Letters*. 2014;7(5):1728–1732.
255. Wang LM, Xie KP, Huo HN, Shang F, Zou W, Xie MJ. Luteolin inhibits proliferation induced by IGF-1 pathway dependent ERα in human breast cancer MCF-7 cells. *Asian Pacific Journal of Cancer Prevention*. 2012;13(4):1431–1437.
256. Lim DY, Jeong Y, Tyner AL, Park JH. Induction of cell cycle arrest and apoptosis in HT-29 human colon cancer cells by the dietary compound luteolin. *American Journal of Physiology-Gastrointestinal and Liver Physiology*. 2007;292(1):G66–G75.
257. Pandurangan AK, Esa NM. Luteolin, a bioflavonoid inhibits colorectal cancer through modulation of multiple signaling pathways: A review. *Asian Pacific Journal of Cancer Prevention*. 2014;15(14):5501–5508.
258. Babykutty S, Kumar MS, Nair MS, Srinivas P, Gopala S. Nimbolide retards tumor cell migration, invasion, and angiogenesis by downregulating MMP-2/9 expression via inhibiting ERK1/2 and reducing DNA-binding activity of NF-κB in colon cancer cells. *Molecular Carcinogenesis*. 2012;51(6):475–490.
259. Gupta SC, Reuter S, Phromnoi K, Park B, Hema PS, Nair M, Aggarwal BB. Nimbolide sensitizes human colon cancer cells to TRAIL through reactive oxygen species- and ERK-dependent up-regulation of death receptors, p53, and Bax. *The Journal of Biological Chemistry*. 2016;291(32):16925.
260. Roy MK, Kobori M, Takenaka M, Nakahara K, Shinmoto H, Tsushida T. Inhibition of colon cancer (HT-29) cell proliferation by a triterpenoid isolated from *Azadirachta indica* is accompanied by cell cycle arrest and up-regulation of p21. *Planta Medica*. 2006;72(10):917–923.
261. Yang ZR, Liu M, Peng XL, Lei XF, Zhang JX, Dong WG. Noscapine induces mitochondria-mediated apoptosis in human colon cancer cells in vivo and in vitro. *Biochemical and Biophysical Research Communications*. 2012;421(3):627–633.
262. Aneja R, Ghaleb AM, Zhou J, Yang VW, Joshi HC. p53 and p21 determine the sensitivity of noscapine-induced apoptosis in colon cancer cells. *Cancer Research*. 2007;67(8):3862–3870.
263. Sithara T, Arun KB, Syama HP, Reshmitha TR, Nisha P. Morin inhibits proliferation of SW480 colorectal cancer cells by inducing apoptosis mediated by reactive oxygen species formation and uncoupling of warburg effect. *Frontiers in Pharmacology*. 2017;8:640.
264. Reyes-Zurita FJ, Rufino-Palomares EE, Lupiáñez JA, Cascante M. Maslinic acid, a natural triterpene from *Olea europaea* L., induces apoptosis in HT29 human colon-cancer cells via the mitochondrial apoptotic pathway. *Cancer Letters*. 2009;273(1):44–54.
265. Kim ME, Ha TK, Yoon JH, Lee JS. Myricetin induces cell death of human colon cancer cells via BAX/BCL2-dependent pathway. *Anticancer Research*. 2014;34(2):701–706.
266. Lin SY, Liu JD, Chang HC, Yeh SD, Lin CH, Lee WS. Magnolol suppresses proliferation of cultured human colon and liver cancer cells by inhibiting DNA synthesis and activating apoptosis. *Journal of Cellular Biochemistry*. 2002;84(3):532–544.
267. Song HM, Park GH, Eo HJ, Jeong JB. Naringenin-mediated ATF3 expression contributes to apoptosis in human colon cancer. *Biomolecules & Therapeutics*. 2016;24(2):140.
268. Yang ZR, Liu M, Peng XL, Lei XF, Zhang JX, Dong WG. Noscapine induces mitochondria-mediated apoptosis in human colon cancer cells in vivo and in vitro. *Biochemical and Biophysical Research Communications*. 2012;421(3):627–633.

269. Carrera-González MP, Ramírez-Expósito MJ, Mayas MD, Martínez-Martos JM. Protective role of oleuropein and its metabolite hydroxytyrosol on cancer. *Trends in Food Science & Technology*. 2013;31(2):92–99.
270. Cockbain AJ, Toogood GJ, Hull MA. Omega-3 polyunsaturated fatty acids for the treatment and prevention of colorectal cancer. *Gut*. 2012;61(1):135–149.
271. Graf E, Eaton JW. Suppression of colonic cancer by dietary phytic acid. *Nutrition and Cancer*. 1993;19(1):11–19.
272. Sethi G, Ahn KS, Sung B, Aggarwal BB. Pinitol targets nuclear factor-κB activation pathway leading to inhibition of gene products associated with proliferation, apoptosis, invasion, and angiogenesis. *Molecular Cancer Therapeutics*. 2008;7(6):1604–1614.
273. Venkatachalam S, Boobathi L, Balasubramanian MP. D-Pinitol prevents rat colon carcinogenesis induced by azoxymethane through free radical formation induced cell damage and affects enzymes and antioxidants. *Research Journal of Pharmacy and Technology*. 2014;7(8):3.
274. Nutakul W, Sobers HS, Qiu P, Dong P, Decker EA, McClements DJ, Xiao H. Inhibitory effects of resveratrol and pterostilbene on human colon cancer cells: A side-by-side comparison. *Journal of Agricultural and Food Chemistry*. 2011;59(20):10964–10970.
275. Chiou YS, Tsai ML, Nagabhushanam K, Wang YJ, Wu CH, Ho CT, Pan MH. Pterostilbene is more potent than resveratrol in preventing azoxymethane (AOM)-induced colon tumorigenesis via activation of the NF-E2-related factor 2 (Nrf2)-mediated antioxidant signaling pathway. *Journal of Agricultural and Food Chemistry*. 2011;59(6):2725–2733.
276. Zhang H, Jia R, Wang C, Hu T, Wang F. Piceatannol promotes apoptosis via up-regulation of microRNA-129 expression in colorectal cancer cell lines. *Biochemical and Biophysical Research Communications*. 2014;452(3):775–781.
277. Belanger JT. Perillyl alcohol: Applications in oncology. *Alternative Medicine Review: A Journal of Clinical Therapeutic*. 1998;3(6):448–457.
278. Yaffe PB, Power Coombs MR, Doucette CD, Walsh M, Hoskin DW. Piperine, an alkaloid from black pepper, inhibits growth of human colon cancer cells via G1 arrest and apoptosis triggered by endoplasmic reticulum stress. *Molecular Carcinogenesis*. 2015;54(10):1070–1085.
279. Eldhose B, Gunawan MI, Rahman M, Latha MS, Notario V. Plumbagin reduces human colon cancer cell survival by inducing cell cycle arrest and mitochondria-mediated apoptosis. *International Journal of Oncology*. 2014;45(5):1913–1920.
280. Gossé F, Guyot S, Roussi S, Lobstein A, Fischer B, Seiler N, Raul F. Chemopreventive properties of apple procyanidins on human colon cancer-derived metastatic SW620 cells and in a rat model of colon carcinogenesis. *Carcinogenesis*. 2005;26(7):1291–1295.
281. Zhang XA, Zhang S, Yin Q, Zhang J. Quercetin induces human colon cancer cells apoptosis by inhibiting the nuclear factor-kappa B Pathway. *Pharmacognosy Magazine*. 2015;11(42):404.
282. Schuetz EG, Beck WT, Schuetz JD. Modulators and substrates of P-glycoprotein and cytochrome P4503A coordinately up-regulate these proteins in human colon carcinoma cells. *Molecular Pharmacology*. 1996;49(2):311–318.
283. Gwak J, Song T, Song JY, Yun YS, Choi IW, Jeong Y, et al. Isoreserpine promotes beta-catenin degradation via Siah-1 upregulation in HCT116 colon cancer cells. *Biochemical and Biophysical Research Communications*. 2009;387(3):444–449.
284. Khanal P, Kang BS, Yun HJ, Cho HG, Makarieva TN, Choi HS. Aglycon of rhizochalin from the Rhizochalina incrustata induces apoptosis via activation of AMP-activated protein kinase in HT-29 colon cancer cells. *Biological and Pharmaceutical Bulletin*. 2011;34(10):1553–1558.

285. Santandreu FM, Valle A, Oliver J, Roca P. Resveratrol potentiates the cytotoxic oxidative stress induced by chemotherapy in human colon cancer cells. *Cellular Physiology and Biochemistry*. 2011;28(2):219–228.
286. Radhakrishnan S, Reddivari L, Sclafani R, Das UN, Vanamala J. Resveratrol potentiates grape seed extract induced human colon cancer cell apoptosis. *Frontiers in Bioscience*(*Elite Ed*). 2011;3:1509–1523.
287. Carter LG, D'Orazio JA, Pearson KJ. Resveratrol and cancer: A focus on in vivo evidence. *Endocrine-Related Cancer*. 2014:ERC-13.
288. Tili E, Michaille JJ, Alder H, Volinia S, Delmas D, Latruffe N, et al. Resveratrol modulates the levels of microRNAs targeting genes encoding tumor-suppressors and effectors of TGFbeta signaling pathway in SW480 cells. *Biochemical Pharmacology*. 2010;80(12):2057–2065.
289. Vanamala J, Reddivari L, Radhakrishnan S, Tarver C. Resveratrol suppresses IGF-1 induced human colon cancer cell proliferation and elevates apoptosis via suppression of IGF-1R/Wnt and activation of p53 signaling pathways. *BMC Cancer*. 2011;10:238.
290. Radhakrishnan S, Reddivari L, Sclafani R, Das UN, Vanamala J. Resveratrol potentiates grape seed extract induced human colon cancer cell apoptosis. *Frontiers in Bioscience* (*Elite Ed*). 2011;3:1509–1523.
291. Cosan D, Soyocak A, Basaran A, Degirmenci I, Gunes HV. The effects of resveratrol and tannic acid on apoptosis in colon adenocarcinoma cell line. *Saudi Medical Journal*. 2009;30(2):191–195.
292. Kim MY, Trudel LJ, Wogan GN. Apoptosis induced by capsaicin and resveratrol in colon carcinoma cells requires nitric oxide production and caspase activation. *Anticancer Research*. 2009;29(10):3733–3740.
293. Wu H, Liang X, Fang Y, Qin X, Zhang Y, Liu J. Resveratrol inhibits hypoxia-induced metastasis potential enhancement by restricting hypoxia-induced factor-1 alpha expression in colon carcinoma cells. *Biomedicine & Pharmacotherapy*. 2008;62(9):613–621.
294. Tili E, Michaille JJ, Alder H, Volinia S, Delmas D, Latruffe N, et al. Resveratrol modulates the levels of microRNAs targeting genes encoding tumor-suppressors and effectors of TGFbeta signaling pathway in SW480 cells. *Biochemical Pharmacology*. 2010;80(12):2057–2065.
295. Um HJ, Bae JH, Park JW, Suh H, Jeong NY, Yoo YH, et al. Differential effects of resveratrol and novel resveratrol derivative, HS-1793, on endoplasmic reticulum stress-mediated apoptosis and Akt inactivation. *International Journal of Oncology*. 2010;36(4):1007–1013.
296. Majumdar AP, Banerjee S, Nautiyal J, Patel BB, Patel V, Du J, et al. Curcumin synergizes with resveratrol to inhibit colon cancer. *Nutrition and Cancer*. 2009;61(4):544–553.
297. Perdew GH, Hollingshead BD, DiNatale BC, Morales JL, Labrecque MP, Takhar MK, Tam KJ, Beischlag TV. Estrogen receptor expression is required for low-dose resveratrol-mediated repression of aryl hydrocarbon receptor activity. *Journal of Pharmacology and Experimental Therapeutics*. 2010;335(2):273–283.
298. Hope C, Planutis K, Planutiene M, Moyer MP, Johal KS, Woo J, et al. Low concentrations of resveratrol inhibit Wnt signal throughput in colon-derived cells: Implications for colon cancer prevention. *Molecular Nutrition & Food Research*. 2008;52(Suppl 1):S52–S61.
299. Zykova TA, Zhu F, Zhai X, Ma WY, Ermakova SP, Lee KW, et al. Resveratrol directly targets COX-2 to inhibit carcinogenesis. *Molecular Carcinogenesis*. 2008;47(10):797–805.
300. Scheckel KA, Degner SC, Romagnolo DF. Rosmarinic acid antagonizes activator protein-1–dependent activation of cyclooxygenase-2 expression in human cancer and nonmalignant cell lines. *The Journal of Nutrition*. 2008;138(11):2098–2105.

301. Arulselvan P, Wen CC, Lan CW, Chen YH, Wei WC, Yang NS. Dietary administration of scallion extract effectively inhibits colorectal tumor growth: Cellular and molecular mechanisms in mice. *PLoS One*. 2012;7(9):e44658.
302. Tanabe H, Kuribayashi K, Tsuji N, Tanaka M, Kobayashi D, Watanabe N. Sesamin induces autophagy in colon cancer cells by reducing tyrosine phosphorylation of EphA1 and EphB2. *International Journal of Oncology*. 2011;39(1):33–40.
303. Ayella A, Lim S, Jiang Y, Iwamoto T, Lin D, Tomich J, Wang W. Cytostatic inhibition of cancer cell growth by lignan secoisolariciresinol diglucoside. *Nutrition Research*. 2010;30(11):762–769.
304. El-Najjar N, Dakdouki S, Darwiche N, El-Sabban M, Saliba NA, Gali- Muhtasib H. Anti-colon cancer effects of Salograviolide A isolated from Centaurea ainetensis. *Oncology Reports*. 2008;19:897–904.
305. Lee JS, Jung WK, Jeong MH, Yoon TR, Kim HK. Sanguinarine induces apoptosis of HT-29 human colon cancer cells via the regulation of Bax/Bcl-2 ratio and caspase-9-dependent pathway. *International Journal of Toxicology*. 2012;31(1):70–77.
306. Wang JY, Chang CC, Chiang CC, Chen WM, Hung SC. Silibinin suppresses the maintenance of colorectal cancer stem-like cells by inhibiting PP2A/AKT/mTOR pathways. *Journal of Cellular Biochemistry*. 2012;113(5):1733–1743.
307. Kauntz H, Bousserouel S, Gosse F, Raul F. The flavonolignan silibinin potentiates TRAIL-induced apoptosis in human colon adenocarcinoma and in derived TRAIL-resistant metastatic cells. *Apoptosis*. 17(8):797–809.
308. Velmurugan B, Gangar SC, Kaur M, Tyagi A, Deep G, Agarwal R. Silibinin exerts sustained growth suppressive effect against human colon carcinoma SW480 xenograft by targeting multiple signaling molecules. *Pharmaceutical Research*. 2010;27(10):2085–2097.
309. Yang SH, Lin JK, Huang CJ, Chen WS, Li SY, Chiu JH. Silibinin inhibits angiogenesis via Flt-1, but not KDR, receptor Upregulation. *Journal of Surgical Research*. 2005;128(1):140–146.
310. Hogan FS, Krishnegowda NK, Mikhailova M, Kahlenberg MS. Flavonoid, silibinin, inhibits proliferation and promotes cell-cycle arrest of human colon cancer. *Journal of Surgical Research*. 2007;143(1):58–65.
311. Ganesan P, Noda K, Manabe Y, Ohkubo T, Tanaka Y, Maoka T, et al. Siphonaxanthin, a marine carotenoid from green algae, effectively induces apoptosis in human leukemia (HL-60) cells. *Biochimica et Biophysica Acta*. 2011;1810:497–503.
312. Ganesan P, Matsubara K, Ohkubo T, Tanaka Y, Noda K, Sugawara T, et al. Anti-angiogenic effect of siphonaxanthin from green alga, *Codium fragile*. *Phytomedicine*. 2010;17:1140–1144.
313. Martin SL, Kala R, Tollefsbol TO. Mechanisms for inhibition of colon cancer cells by sulforaphane through epigenetic modulation and hTERT down-regulation. *Current Cancer Drug Targets*. 2018;18(1):97–106.
314. Johnson SM, Wang X, Evers BM. Triptolide inhibits proliferation and migration of colon cancer cells by inhibition of cell cycle regulators and cytokine receptors. *Journal of Surgical Research*. 2011;168(2):197–205.
315. Oliveira AR, Beyer G, Chugh R, Skube SJ, Majumder K, Banerjee S, Sangwan V, Li L, Dawra RK, Subramanian S, Saluja AK. Triptolide abrogates growth of colon cancer and induces cell cycle arrest by inhibiting transcriptional activation of E2F. *Laboratory Investigation*. 2015;95(6):648.
316. Yang Z, Xiao H, Jin H, Koo PT, Tsang DJ, Yang CS. Synergistic actions of atorvastatin with gamma-tocotrienol and celecoxib against human colon cancer HT29 and HCT116 cells. *International Journal of Cancer*. 2010;126(4):852–863.

317. Kannappan R, Ravindran J, Prasad S, Sung B, Yadav VR, Reuter S, et al. Gamma-tocotrienol promotes TRAIL-induced apoptosis through reactive oxygen species/extracellular signal-regulated kinase/p53-mediated upregulation of death receptors. *Molecular Cancer Therapeutics*. 2010;9(8):2196–2207.
318. Agarwal MK, Agarwal ML, Athar M, Gupta S. Tocotrienol-rich fraction of palm oil activates p53, modulates Bax/Bcl2 ratio and induces apoptosis independent of cell cycle association. *Cell Cycle*. 2004;3(2):205–211.
319. Zhang JS, Li DM, He N, Liu YH, Wang CH, Jiang SQ, et al. A paraptosis-like cell death induced by delta-tocotrienol in human colon carcinoma SW620 cells is associated with the suppression of the Wnt signaling pathway. *Toxicology*. 2011;285(1–2):8–17.
320. Xu WL, Liu JR, Liu HK, Qi GY, Sun XR, Sun WG, et al. Inhibition of proliferation and induction of apoptosis by gamma-tocotrienol in human colon carcinoma HT-29 cells. *Nutrition*. 2009;25(5):555–566.
321. Gosslau A, En Jao DL, Huang MT, Ho CT, Evans D, Rawson NE, et al. Effects of the black tea polyphenol theaflavin-2 on apoptotic and inflammatory pathways in vitro and in vivo. *Molecular Nutrition & Food Research*. 2011;55(2):198–208.
322. Attoub S, Sperandio O, Raza H, Arafat K, Al-Salam S, Al Sultan MA, Al Safi M, Takahashi T, Adem A. Thymoquinone as an anticancer agent: Evidence from inhibition of cancer cells viability and invasion in vitro and tumor growth in vivo. *Fundamental & Clinical Pharmacology*. 2013;27(5):557–569.
323. Gali-Muhtasib H, Kuester D, Mawrin C, Bajbouj K, Diestel A, Ocker M, et al. Thymoquinone triggers inactivation of the stress response pathway sensor CHEK1 and contributes to apoptosis in colorectal cancer cells. *Cancer Research*. 2008;68(14):5609–5618.
324. Gali-Muhtasib H, Ocker M, Kuester D, Krueger S, El-Hajj Z, Diestel A, et al. Thymoquinone reduces mouse colon tumor cell invasion and inhibits tumor growth in murine colon cancer models. *Journal of Cellular and Molecular Medicine*. 2008;12(1):330–342.
325. Prasad S, Yadav VR, Kannappan R, Aggarwal BB. Ursolic acid, a pentacyclin triterpene, potentiates TRAIL-induced apoptosis through p53-independent up-regulation of death receptors: evidence for the role of reactive oxygen species and JNK. *Journal of Biological Chemistry*. 2011;286(7):5546–5557.
326. Zhang P, Cheng Y, Duan RD. Ursolic acid inhibits acid sphingomyelinase in intestinal cells. *Phytotherapy Research*. 2013;27(2):173–178.
327. Shan JZ, Xuan YY, Zheng S, Dong Q, Zhang SZ. Ursolic acid inhibits proliferation and induces apoptosis of HT-29 colon cancer cells by inhibiting the EGFR/MAPK pathway. *Journal of Zhejiang University Science B*. 2009;10(9):668–674.
328. Shan JZ, Xuan YY, Ruan SQ, Sun M. Proliferation-inhibiting and apoptosis-inducing effects of ursolic acid and oleanolic acid on multi-drug resistance cancer cells in vitro. *Chinese Journal of Integrative Medicine*. 2011;17(8):607–611.
329. Prasad S, Yadav VR, Sung B, Reuter S, Kannappan R, Deorukhkar A, et al. Ursolic Acid inhibits growth and metastasis of human colorectal cancer in an orthotopic nude mouse model by targeting multiple cell signaling pathways: Chemosensitization with capecitabine. *Clinical Cancer Research*. 2012;18(18):4942–4953.
330. Ho K, Yazan LS, Ismail N, Ismail M. Apoptosis and cell cycle arrest of human colorectal cancer cell line HT-29 induced by vanillin. *Cancer Epidemiology*. 2009;33(2):155–160.
331. Mulabagal V, Subbaraju GV, Rao CV, Sivaramakrishna C, Dewitt DL, Holmes D, et al. Withanolide sulfoxide from Aswagandha roots inhibits nuclear transcription factor-kappa-B, cyclooxygenase and tumor cell proliferation. *Phytotherapy Research*. 2009;23(7):987–992.

332. Lee SH, Kim HJ, Lee JS, Lee IS, Kang BY. Inhibition of topoisomerase I activity and efflux drug transporters' expression by xanthohumol. from hops. *Archives of Pharmacal Research*. 2007;30(11):1435–1439.
333. Wang Y, Chen Y, Wang J, Chen J, Aggarwal BB, Pang X, et al. Xanthohumol, a prenylated chalcone derived from hops, suppresses cancer cell invasion through inhibiting the expression of CXCR4 chemokine receptor. *Current Molecular Medicine*. 2012;12(2):153–162.
334. Pan L, Becker H, Gerhauser C. Xanthohumol induces apoptosis in cultured 40–16 human colon cancer cells by activation of the death receptor- and mitochondrial pathway. *Molecular Nutrition & Food Research*. 2005;49(9):837–843.
335. Grudzinski W, Piet M, Luchowski R, Reszczynska E, Welc R, Paduch R, Gruszecki WI. Different molecular organization of two carotenoids, lutein and zeaxanthin, in human colon epithelial cells and colon adenocarcinoma cells. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*. 2018;188:57–63.
336. Yodkeeree S, Sung B, Limtrakul P, Aggarwal BB. Zerumbone enhances TRAIL-induced apoptosis through the induction of death receptors in human colon cancer cells: Evidence for an essential role of reactive oxygen species. *Cancer Research*. 2009;69(16):6581–6589.
337. Murakami A, Miyamoto M, Ohigashi H. Zerumbone, an anti-inflammatory phytochemical, induces expression of proinflammatory cytokine genes in human colon adenocarcinoma cell lines. *Biofactors*. 2004;21(1–4):95–101.

5 Nutraceuticals' Role in Proliferation and Prevention of Breast Cancer

Sadaf Aslam and Beata Casanas

CONTENTS

5.1 INTRODUCTION

Several epidemiological and preclinical studies have shown the role of healthy foods and nutrients in maintaining the overall health and functioning of our body. Healthy foods are known for providing key biomolecules that participate in various physiological processes and reduce the risk of many chronic diseases. There was no specific definition for nutraceuticals, before 1989, when Dr. Stephen Felice

for the first time defined nutraceuticals as foods or food products apart from basic nutrition that might have a role in preventing and treating diseases. The term nutraceuticals is used sometimes interchangeably with food supplements, functional foods, vitamins, micronutrients, herbal products, and so on. Nutraceuticals are medicinal foods that play a vital role in boosting immunity and helping in the prevention and cure of some diseases. Many epidemiological, in vivo, and in vitro studies have investigated the efficacy and safety of nutraceuticals. The understanding of the potential mechanisms of action of active substances found in nutraceuticals is the challenge to be considered as a preventive and therapeutic tool in treating and managing certain chronic diseases. Recently, there has been a global interest in investigating the true role of nutraceuticals and their efficacy in the prevention and progression of breast cancer, along with their synergistic role with chemotherapy and radiation. Despite scientific evidence that cancer patients can benefit from any specific nutraceutical, there is still physician's resistance on its application and inexplicable controversies on its overall efficacy and associated risks. It is not clear, what type of nutrients and vitamin supplements would work best in the prediagnostic stage and after the diagnosis of breast cancer. In this chapter, the role of food and nutrients in the prevention and management of breast cancer will be discussed with the hope of allaying physician's reluctance.

5.2 EPIDEMIOLOGY

Breast cancer is the most common cancer and a leading cause of cancer-related deaths in women. According to a report by the World Health Organization in 2018, around 2 million new cases and half million deaths related to breast cancer are registered annually [1]. It is estimated that every year approximately 252,710 new cases of invasive breast cancer and 63,960 new cases of noninvasive breast cancer in women are diagnosed in the United States, and more than 40,000 women die of cancer [2]. Breast cancer is not that common among men; however, it is estimated that more than 2470 men will be diagnosed with breast cancer and approximately 460 will die each year [2]. Breast cancer patients undergo intensive surgery, chemotherapy, hormonal therapy, and radiation. The quality of life is compromised with all the above mentioned treatment strategies. It is not surprising to see a huge number of people seeking help through nutraceuticals as an alternative or as adjunctive therapy. These patients see a wide array of physicians or healthcare providers for their treatment and follow-up along with getting the guidance on the management of the side effects and complications of chemotherapy and radiation. The patients expect that healthcare providers will provide them some evidence-based guidance on the use of nutraceutical.

More recently, nutritional research has specifically investigated the effects of weight, diet, and healthy lifestyle in reducing the risk of breast cancer, improving survival, reducing comorbidities, and maintaining patients' overall health. Most of the time, primary care physicians provide long-term care for breast cancer survivors and possibly can also implement nutritional strategies that can help in chemoprevention.

5.3 CATEGORIZATION OF BREAST CANCER

Before the details of the nutrients and dietary supplements are discussed in this chapter, it would be important to elaborate on the types of breast cancer, as each type has both modifiable and nonmodifiable risk factors that contribute toward individual disease manifestation. The majority of all breast cancer types carry nonspecific characteristics based on the exogenous and endogenous factors such as oxidizing agents present in food, air, and water, reproductive factors, use of oral contraceptives, hormone replacement therapy, diabetes, and obesity [3]. The familial breast cancer subtype related to gene BRCA1 and BRCA2 mutations account for only 5%–10% [3].

Breast cancer is considered a very heterogeneous disease based on their individual response to different treatments and ultimate prognosis. Before 1990, three receptor proteins (estrogen receptor, progesterone receptor, and human epidermal growth factor 2 (HER2)), tumor size, and number of involved lymph nodes predicted the prognosis and response to treatment [4]. Although more categories were proposed later such as expression-based categories, luminal A type, luminal B type, HER2-positive, and basal-type cancers, the traditional receptor-based categories are still used in most oncology clinics [4]. Basal-type cancer, also known as triple-negative breast cancer, does not express biomarkers such as estrogen and progesterone receptors or HER2 genes and poses challenging treatment strategies because of its nonresponsiveness to endocrine therapy or other targeted chemotherapeutic agents.

5.4 PATHOPHYSIOLOGY OF BREAST CANCER

Breast cancer develops when cells start losing their differentiation and there is no growth control over the tumor cells. Like many other cancers, several factors such as hormones, genes, growth factors, and environmental toxins play a role in the development of cancerous cells. Family history of ovarian and breast cancer, gene mutations, late menopause, and early menstruation, or prolonged use of oral contraceptives are also factors specifically linked to breast cancer in women. Experimental studies have shown a linkage between estrogen exposure, DNA damage, and genetic mutations. There are several signaling mechanisms of growth factors and markers that interact between cells, and any defect or interruption in the signaling mechanism can also lead to the formation of cancerous cells. It is estimated that 75% of all BCs have an expression of estrogen and progesterone receptors, while 20% have an overexpression of HER2 receptors [5]. All these receptors coexist, and there is a crosstalk between these receptors through nuclear and non-nuclear pathways, which, in turn, activates the RAS-MAPK and P13k/Akt pathways, leading to the proliferation and progression of cancer cells [6]. Genetic predisposition to the genes such as BRCA1, BRCA2, and P53 in some people has also been linked to breast cancer. Other factors such as defective immune system can also predispose to breast cancer when damaged DNA and cancer cells are not destroyed by a weak immune system.

5.5 MECHANISM OF ACTION OF NUTRACEUTICALS IN CHEMOPREVENTION FOR BREAST CANCER

For an effective prevention of cancer and cancer-related deaths, it is imperative to keep a balance between positive and negative effects of nutraceuticals and to sustain the genetic make-up of our cells. It is now quite well-established through epidemiological studies that by modifying risk factors through natural diet, supplements, and lifestyle changes, we can prevent many types of cancers.

Several in vivo and in vitro studies have been published looking into the possible mechanisms of action of nutraceuticals in the prevention, progression, and metastasis of breast cancer (Table 5.2). However, due to the variegated structural differences and doses used in these compounds, some studies have varying conclusions. More recently, many nutraceuticals have been studied in clinical and epidemiological studies and their role is better defined in terms of their targeting underlying molecular mechanisms. A number of different pathways involved in carcinogenesis such as suppression of tumor cell proliferation, apoptosis, and angiogenesis have been studied in depth and currently provide sufficient evidence for the beneficial effects of nutraceuticals. Additionally, nutraceuticals may have a positive role in the processes of cell signaling pathways, regulation of cell cycles, reduction in oxidative stress and inflammation. Carotenoids, flavonoids, organosulfur compounds, and polyphenols have been studied for their role in preventing and slowing down the carcinogenesis. Polyphenols are found in a variety of plant-based foods, the seeds and skins of fruits, and many leafy vegetables (Figure 5.1).

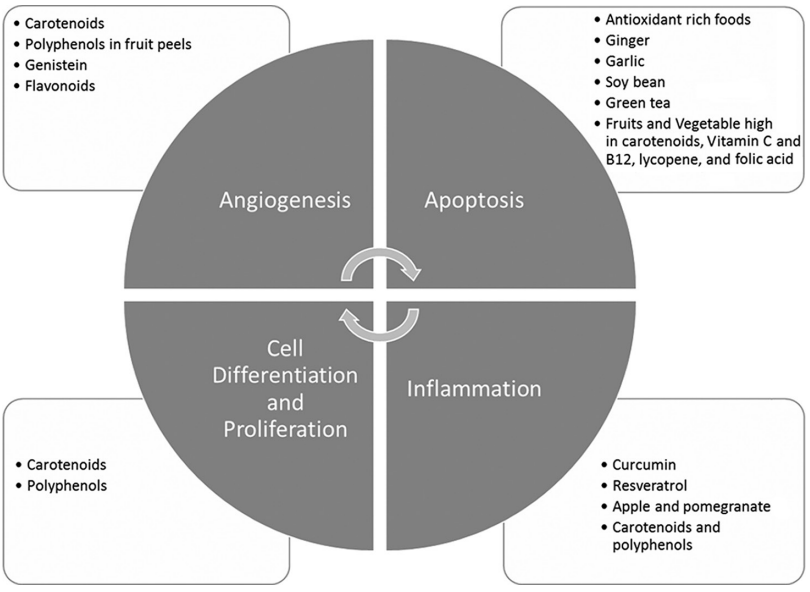


FIGURE 5.1 Effect of nutraceuticals on different pathways.

5.6 APOPTOSIS AND ITS ROLE IN BREAST CANCER

Apoptosis remains the most vital part of normal and abnormal cells. A defect in apoptosis is considered to be the main cause of cancer. The literature is full of studies investigating the reason for defective apoptosis that can be due to defect in the apoptotic pathway, such as enhanced mutation of genes, inactivation of death receptors, and so on. Nutraceuticals of plant origin that are mostly part of our diet and nutrition have shown to have tremendous anticancer properties as studied in many in vitro experiments (Table 5.2). Foods such as soy, ginger, garlic, green tea, and spices curcumin, cinnamon, among others have shown encouraging results due to their effect on prompting apoptotic activity for cancerous cells as well.

5.7 ROLE OF ANTIOXIDANTS IN BREAST CANCER PREVENTION, POSTDIAGNOSIS, AND PROGNOSIS

Antioxidants such as vitamin A, α- and β-carotene, lycopene, vitamin C, and vitamin E have shown their neutralizing effect by trapping the free radicals or oxygen reactive species and preventing the cellular damage [7]. When the concentration of free radicals increases within the cell and is not neutralized by antioxidants and enzymes present in our body or as exogenous dietary antioxidants, this situation can lead to the damage of DNA and cell membranes. Damaged cells then can proliferate and initiate carcinogenesis. In case of breast cancer, there is a link between damage to the DNA and cell membrane and proliferation of cancer cells. A large number of studies have looked into the benefits and harms of using antioxidants postdiagnosis for progression, survival, and recurrence; however, the results have been inconsistent. This is most likely due to the heterogeneity of the population, age, exposure to toxins, comorbid conditions, combinations, types and doses of the supplements, and duration of treatment before and after diagnosis. For example, improved breast cancer survival was observed in a meta-analysis of cohort studies where patients used vitamin C supplementation after diagnosis [8]. Similarly, a large cohort study data analysis by Greenlee et al. showed that although vitamin C was associated with decreased mortality and recurrence, in postdiagnosis cancer patients who used combination carotenoids had an increased risk of death, but there was no increase in the risk of recurrence [7].

The use of supplements, specially antioxidants such as vitamins A, C, and E, has been criticized for causing interference in the effect of chemotherapy or radiation therapy and has always posed a question for the treating physicians and people practicing alternative therapies. It is not clear if antioxidants actually protect only normal tissue and, therefore, decrease the toxicity of the cancer therapies or if equally protect the cancer cell. If it can be shown with evidence that antioxidants can protect normal tissues from chemotherapy-induced damage but does so without decreasing the efficacy of the chemotherapy, then its use might play a vital role in chemoprevention. One study using the data from a large-cohort study concluded that postmenopausal women with breast cancer have poor prognosis with concurrent use of antioxidants and suggested to avoid the use of antioxidants during their treatment phase with chemotherapy [9].

However, vitamin C is the most commonly used dietary supplement known to influence cancer cell through its antioxidant properties and neutralization of free radicals in breast cancer patients. Several studies including in vitro, observational, and clinical trials suggest that vitamin C during chemotherapy and radiation therapy may protect cancer cells as well as protect the normal cells. On the other hand, results from some observational studies suggest that vitamin C intake and survival postdiagnosis can reduce the risk of mortality and improve survival [7,10]. Harris et al. studied the association between vitamin C and mortality in breast cancer patients based on the factors related to reactive oxygen species such as obesity, age, and history of smoking. The group observed that vitamin C had a stronger inverse relationship with mortality in breast cancer patients who were 65 years and older (Table 5.1) [10]. Vitamin C has been shown to demonstrate cytotoxicity at higher doses without exerting its negative effect on normal cells. A recent study published in 2019 concluded that higher doses of vitamin C combined with chemotherapeutic agents can be harmful to cancer cells and can have therapeutic advantages. According to the study, high dose of vitamin C >10 mM significantly reduced the cell viability of specifically MCF-7 cells (human breast adenocarcinoma cell lines) and almost in all other breast cancer cell lines and also the same effect was seen when high dose of vitamin C was combined with tamoxifen [11].

5.8 ROLE OF SOY PRODUCTS

For centuries soy products have been used for potential health benefits. Although most of the soy products have been used by people with chronic diseases such as diabetes, hypertension, and heart diseases; however, its benefits are also linked to breast cancer survival. The evidence for its true benefit on breast cancer is still conflicting. Soy products are popular and considered a healthier option than meats. People have shown some concerns due to its hormonal mimetic estrogenic properties. Natural soy foods that are plant derivatives are full of fibers and essential minerals and nutrients.

Soy contains isoflavinoids, which are considered to be similar to estrogen. Several epidemiological studies have been conducted and showed an association between soy and risk of developing hormone-sensitive breast cancer. On the contrary, some argue its antiestrogenic properties as well. Current research, although not consistent, does not support avoiding soy foods as it has other benefits that can lower the cancer risk and recurrence. There are a few studies that have examined the relationship of isoflavinoids on the outcomes of soy before and after the diagnosis of cancer [12,13]. The question then is: if women who are diagnosed with BC should take soy or isoflavinoids or more specifically only women who receive hormonal therapy such a tamoxifen. Several studies conducted in Asian countries provide evidence on the benefit of using isoflavinoids in lowering the mortality and recurrence. The evidence provided by studies conducted in Western countries involving population such as Caucasians, Latinos, and African Americans are still unclear (Table 5.1). In one study, Zang et al. observed that high intake of isoflavones is associated with decrease in all-cause mortality in women who did not receive hormonal therapy for the estrogen receptor negative tumors [14]. According to the study, only postdiagnosis time period showed inverse relationship with soy intake.

5.9 ROLE OF FOLIC ACID AND VITAMIN B12

In a study conducted on folic acid intake and breast cancer risk in BRCA mutation carrier suggested a protective role of moderate intake of folic acid and vitamin B12 in BRCA-associated breast cancer [15]. Women with daily dietary folate intake between 153 and 400 μg showed a significant reduction in breast cancer risk compared with those showing daily intake of <153 μg [16]. The study also suggested a preventive effect of folate on breast cancer risk in people with higher alcohol consumption. The dose and timings of folate intake are vital to its preventative effects, and more clinical studies are needed.

5.10 ROLE OF VITAMIN D IN BREAST CANCER

Vitamin D can be taken in many forms including natural foods such as dairy and supplements or through sunlight exposure where 7-deoxycholcalciferol is converted to vitamin D. Vitamin D is then converted to 25(OH) cholecalciferol, which is found in the circulation and is considered the best indicator for vitamin D status. The inactive form 25(OH) cholecalciferol is converted to an active form as 1-25 di (OH) vitamin D. This active form binds to the vitamin D receptors of several tissues including breast tissue. Vitamin D is known for its anticancer properties through its effects on regulation of cell differentiation, proliferation, and apoptosis. Vitamin D exists in circulation as 25(OH) D form, and to convert it to its active form 1-25 (OH) D, 1 αhydroxylase enzyme is needed. Like many other tissues, breast tissues also have 1-α-hydroxylase and converts inactive form of vitamin D to active form. Since calcium and vitamin D both have been studied for their regulatory role in estrogen-related cell proliferation, it is observed that the intake of both nutrients might have different effect on pre- and postmenopausal women diagnosed with breast cancer. In a prospective cohort study conducted by Lin et al., it was shown that in premenopausal women, high intake of vitamin D and calcium was associated with a lower risk of breast cancer, more so in more aggressive breast tumors. Additionally, no association of vitamin D and calcium with postmenopausal breast cancer was observed [17]. In a randomized controlled trial, it was shown that another endogenous estrogen receptor modulator, 27 hydroxy cholesterol (HC), has agonistic properties on ER^+ breast cancer. It was suggested that vitamin D supplementation can reduce 27 HC, as its inhibition is regulated by vitamin D [18]. Additionally, de novo vitamin D can be associated with lower mortality in the postdiagnosis state and is considered as a potential inexpensive and nontoxic source to improve patient survival [19]. So, in a nutshell, it can be concluded that vitamin D supplements and vitamin D can be used to suppress 27 HC-mediated ER^+ breast cancer in high-risk patients and have preventive effect on ER^+ breast cancer.

Vitamin D has also been studied for its effect on breast density of premenopausal women. Breast density being the strongest indicator for cancer risk because it masks mammography findings and is estimated to be four to six times higher in women with high density [20]. In a double-blinded randomized controlled trial, Brisson et al. studied the effect of vitamin D_3 in the doses of 1000, 2000, and 3000 IU/day for one year and found no reduction in breast density in premenopausal women [20].

5.11 CAROTENOIDS IN BREAST CANCER PREVENTION

Carotenoids are considered as micronutrients in our food. The bright orange pigments of carrots, lutein, lycopene, and some others all belong to the carotenoid family. Most of the carotenoids are present in fruits and vegetables readily available as part of our diet. Carotenoids act mostly due to their important antioxidants properties. By neutralizing oxidative processes that can damage DNA and interfere with the normal functioning of cells, carotenoids have been found to prevent cancer and its progression. Carotenoids have been linked to block cancer progression and reduce proliferation of estrogen receptor positive ER^+ and negative ER^- breast cancers. One study conducted at Harvard University (Nurses Health Study) has pooled data from eight prospective cohort studies including 3055 breast cancer cases with matched controls and concluded that higher total carotenoids and high concentration of some specific carotenoids such as α- and β-carotene and lycopene had statistically lower risk of breast cancer, and more so in ER^- breast cancer [21]. This study also looked into breast cancer recurrence and mortality and found an inverse association with carotenoid concentrations in the blood. In this large study, the relative risk for β-carotene from very highest to lowest concentrations was found to be 0.32 (confidence interval [CI] 95% $P < 0.001$), suggesting that women with higher levels of β-carotene were at reduced risk of developing breast cancer [21]. These findings are similar to many other studies concluding that the increased consumption of fruits and vegetables rich in carotenoids along with other healthy lifestyles is beneficial in the prevention and progression of breast cancer. However, one cannot confirm these associations very strong as carotenoids found in fruits and vegetables exists with other nutrients as well such vitamins and minerals that may have a protective role in breast cancer prevention and progression.

5.12 OTHER NUTRACEUTICALS LINKED TO BREAST CANCER

High intake of fruits and vegetables has shown a possible benefit in the reduction of breast cancer risk. Cruciferous vegetables such a broccoli, cabbage, cauliflower, and Brussel sprouts contain high content of glucosinolates, and when eaten as raw vegetables, or chewed, an enzyme called myrosinase is released that converts glucosinolates into isothiocyanates [22]. This compound is known for its chemoprotective activity in cancer including breast cancer. The isothiocyanates are of different types and act in different ways; for example, benzyl isothiocyanate induced inhibition is associated with apoptotic cell death. The underlying mechanism of isothiocyanates seems to be mainly through the downregulation of ER and their signaling as well as apoptosis and cell cycle arrest, thus preventing the spread of cancer cells.

Organosulfur compounds found in many plant-derived foods including cruciferous vegetables are also considered beneficial, as they protect important biomolecules from oxidative damage. In vitro studies have also shown their antiproliferative activity on various cancer cell lines including breast cancer cell lines (Table 5.2).

5.12.1 Garlic

Garlic belongs to the Allium class of plants with bulbs and includes other vegetables as well such as onions, scallions, and chives. Garlic is very commonly used in Mediterranean and Asian diets mostly for flavoring. Garlic is considered beneficial due to its high sulfur content; however, it has other beneficial contents such as flavonoids, selenium, and arginine. Garlic has antibacterial properties and has shown to inhibit the activation of cancer-forming substances and enhance DNA repair, reduce cell proliferation, or induce cell death [23].

The National Cancer Institute suggests garlic as one of several vegetables with potential anticancer properties and does not recommend the use of other supplements for cancer treatment. The exact amount of garlic that can have protective effect is hard to determine. The active compound present in garlic may lose their effectiveness with time, handling, and processing. The doses and effectiveness of garlic either in raw form or garlic powder tablets have not been established. There are different sources of evidence for generally recommended doses; for example, in adults approximately 4 g (found in 1–4 cloves) of raw garlic per day, or one tablet of 300 mg dried garlic powder two to three times per day, and approximately 7.2 g of dried garlic extract have been used as an anti-oxidant and anti-carcinogenic [24].

5.12.2 Curcumin in Breast Cancer

Curcumin is one of the most extensively studied natural products that has been in use for centuries in ancient medicine for its various health benefits. It has been known to exert many pharmacological effects via processes such as antiproliferation, anti-inflammation, cell death, and anti-angiogenesis as well as acting as an antioxidant. Curcumin extracted from a plant *Curcuma longa* has shown inhibitory effect on the proliferation of tumor cells in culture, growth of human tumor cells in xeno-transplant animal models, and the same effect was observed when used in combination with chemotherapeutic agents or radiation in animal and rodent models [25].

A known tumor suppressor gene p53 is considered to be involved in many metabolic processes such as in inducing apoptosis and arrest in cell cycle and repairing DNA damage. Curcumin upregulates p53 expression followed by an increase in p21, which causes arrest at G0, G1, and G2/M phases of the cell cycle and upregulation of Bax expression eventually inducing apoptosis [26]. More recently, another mechanism known as oncogene induces senescence (OIS) has been gaining attention. The OIS is another tumor suppressing defense mechanism that may be compromised during cancer cell proliferation. The process of OIS was also observed in a breast cancer cell line, where curcumin was shown to inhibit phosphorylation of Akt within the MAPK/PI3K pathway [27].

5.12.3 Capsaicin

Capsaicin found in red chili pepper is also a well-known spice that has shown anti-inflammatory and antiproliferative activity in breast cancer cells. The suppressive

activity of capsaicin has been observed in several in vivo and in vitro studies. One study conducted on rats showed the suppressive activity of capsaicin against mammary carcinoma that was induced by N-nitrosomethylurea (NMU). Rats treated with NMU and protected with capsaicin improved the histopathological changes in mammary tissues [28].

5.13 SYNERGISTIC EFFECTS OF NUTRACEUTICALS WITH CHEMOTHERAPY AND RADIATION

Some nutraceuticals have shown their synergistic effect by reducing the side effects and enhancing the therapeutic effects by acting on different cell signaling pathways, chemosensitization, enhancing apoptosis, and inhibition of cell proliferation. For example, a combination of a bioactive compound in soy called genistein and doxorubicin has shown synergistic effects on breast cancer cells by increasing the accumulation of doxorubicin to exert its anticancer effect along with suppressing the expression of HER2 [29].

5.14 CONCLUSIONS AND FUTURE PERSPECTIVES

Chemoprevention and management through nutraceuticals has become an acceptable strategy specially in the prevention of breast cancer. The intake of certain foods and supplements has shown inverse correlation with the risk of breast cancer in several observational and experimental studies. Additionally, several nutraceuticals have shown synergistic activity with chemo- and radiotherapy. However, review of some studies suggests to possibly avoid use of certain supplements specially soy and antioxidants postdiagnosis in postmenopausal women undergoing therapy.

Some of the most well-known and studied nutraceuticals are carotenoids, citrus fruits, soy foods, vegetables, certain herbs, and spices. Their role in chemoprevention and treatment has been studied extensively while understanding their mechanism of action through different pathways and their role in the inhibition of proliferation, metastasis, and angiogenesis in inducing apoptosis and cell cycle arrest. It should be noted that pharmacokinetics, bioavailability, and efficacy studies are not that simple to conduct. Although we have valid data from in vivo and in vitro studies, more clinical studies are needed to further completely understand their role. We need to establish optimal conditions, personalized treatment regimens, and patient stratification based on genotyping and phenotyping. The cost-effectiveness should also be considered while providing chemoprevention. Additionally, if more bioactive compounds can be isolated from dietary and natural products to study and understand their mechanism of action, efficacy, toxicity, and adverse effects; these compounds could become the next established potential sources for the prevention and treatment of not just breast cancer but all other cancers. More comprehensive and organized approach is needed for future studies, and breast cancer patients should make an informed decision regarding the use of nutraceuticals specially in postdiagnosis state.

TABLE 5.1
Observational Studies on the Role of Nutraceuticals from 2013 to 2019

Study Type/Sample	Intervention	Outcome	Results	References
Swedish Mammography Cohort, Postdiagnosis, Food Frequency Questionnaire (FFQ) N = 717	Vitamin C versus no vitamin C supplement (1000 mg)	Total mortality N = 228	HR = 0.81 (95% CI 0.53–1.26) after adjustment for age, menopausal status, BMI, and stage	Harris et al. [10]
Swedish Mammography Cohort Prediagnosis, FFQ N = 3405	Vitamin C intake via food (highest quartile vs lowest)	Total mortality (1055)	HR = 0.84 (95% CI 0.71–1.00)	Harris et al. [10]
Meta-analysis of epidemiological studies N = 3789 cases versus 4705 controls	Intake of citrus fruits	Risk of breast cancer	OR = 0.90 (95% CI 0.85–0.96)	Song et al. [30]
Shanghai Womens Health Cohort study N = 70,578	Soy food intake	Risk of breast cancer	Overall HR = 0.78 (95% CI 0.63–0.97) Premenopausal women HR = 0.46 (95% CI 0.29–0.74) ER^+/PR^+ Postmenopausal women HR = 0.72 (95% CI 0.53–0.96)	Baglia et al. [12]
Chinese-American (CA) and Non-Hispanic White (NHW) breast cancer survivors Cross-sectional study N = 192 CA and 173 NHW	Soy and cruciferous vegetables, no intake to 431 and 865 g/day	Breast cancer treatment related symptoms	Menopausal symptoms, OR= 0.51 (95% CI 0.25, 1.03) Fatigue OR = 0.43 (95% CI 0.22, 0.84)	Nomura et al. [13]
Meta-analysis of epidemiological studies N = 22 studies 10,566 in the experimental group and 12,635 in the control group	Vegetables and fruits versus high-fat diet	Breast cancer risk	Vegetables OR = 0.77 (95% CI 0.62–0.96) Fruits OR = 0.68 (95% CI 0.49–0.93) Soy foods, OR = 0.68 (95% CI 0.50–0.93) High fat OR = 1.15 (95% CI 1.01–1.30)	Wu et al. [31]

(*Continued*)

TABLE 5.1 (*Continued*)
Observational Studies on the Role of Nutraceuticals from 2013 to 2019

Study Type/Sample	Intervention	Outcome	Results	References
Case–control study N = 285 BC cases and 297 matched controls	Allium compound in onions and garlic	Breast cancer risk	OR = 0.41 (95% CI 0.20–0.83)	Pourzand et al. [32]
Case–control Study Canada N = 129 BC cases and 271 controls	Folic acid supplement	Breast cancer risk in BRCA mutation carrier	OR = 0.49 (95% CI 0.25–0.79)	Kim et al. [15]
Prospective Cohort Study Age >50 years N = 3608 BC	Soy supplement vs no soy supplement	Breast cancer prognosis	HR = 0.78 (95% CI 0.60—0.99) in ER^+ HR = 2.01 (95% CI 1.4–2.86) in ER^-	Toullaud et al. [33]
Prospective Cohort Study data from MARIE study Postmenopausal nonmetastatic N = 2223	Antioxidant supplement pre diagnosis and postdiagnosis	BC prognosis	HR = 1.64 (95% CI 1.01–2.66)	Jung et al. [9]
Cohort study National Cancer registry Ireland N = 2581 metastatic BC	Postdiagnosis vitamin D intake with prescription	Prognosis/mortality	HR 0.51 (95% CI 0.34–0.74) $p < 0.001$	Madden et al. [19]
Meta-analysis N = 12,265 BC patients	Vitamin B12 supplements	BC risk	RR = 0.85 (95% CI 0.76—0.95)	Yu et al. [34]

(*Continued*)

TABLE 5.1 (*Continued*)
Observational Studies on the Role of Nutraceuticals from 2013 to 2019

Study Type/Sample	Intervention	Outcome	Results	References
Prospective Cohort NutriNet-Santé cohort N = 27,853 N = 462 breast cancer	Vitamin B supplements (thiamin, riboflavin, niacin, pantothenic acid, pyridoxine, folate, and cobalamin) Diet and total	BC risk	Dietary HR = 0.74 (95% CI 0.55–0.99), supplemental (HR = 0.61 (95% CI 0.38–0.98), and total (HR = 0.67 (95% CI 0.50–0.91)	Egnell et al. [35]
Prospective Cohort Study the Breast Cancer Quality of Care (BQUAL) study N = 685 non-metastatic invasive BC	Users vs nonusers Vitamins, minerals, herbs, or other natural products	Initiation of chemotherapy	OR = 0.16 (95% CI, 0.03–0.51; and OR per unit = 0.64 (95% CI, 0.46–0.87)	Greenlee et al. [36]
European Prospective Investigation into Cancer and Nutrition (EPIC) N = 11,782 Pre- and postmenopausal women	Phenol intake (lignans, flavonoids, phenolic acid)	BC survival (all-cause mortality)	Post menopausal HR = 0.72 (95% CI 0.53–0.98) HR = 1.63 (95% CI 1.03–2.57) Quartile 4 versus quartile 1	Kyro et al. [37]

Abbreviations: CI, confidence interval; HR, hazard ratio.

TABLE 5.2
In Vivo and In Vitro Studies 2016–2019

Study Type/Model/Cell Lines	Intervention/Active Compound	Mechanism of Action and Effect	References
In vitro MCF-7-C3 and T47D breast cancer cells	Soy/genistein	• Apoptosis and growth inhibition via downregulation of cancerous inhibitors of protein phosphates (CIP2A)	Zhao et al. [38]
In Vitro TNBC cell line MDA-MB-231	Soy/genistein	• Activation of DNA damage response • Inhibition of TNBC cell growth by regulating the cell cycle and DNA damage response at phosphor proteomic level	Fang et al. [39]
In Vitro Non-neoplastic breast epithelial cell lines MCF-10A and MCF-10F	Resveratrol analogues	• Attenuation of oxidative DNA damage • Activation of Nrf signaling pathway	Chaterjee et al. [40]
In Vitro T47 D breast cancer cells	α-Mangostin	• Apoptosis induction • Modulation of HER2/P13K/Akt and MAPK signaling pathway	Kritsanawong et al. [41]
In Vitro MDA-MB-231 triple-negative breast cancer cells	Citrus sphaerocarpa fruit polysaccharides	• Inhibition of angiogenesis • Inhibition of breast cancer cell migration	Park et al. [42]
In Vivo 4T1 cancer tumors in mice	Pectin in apples	Inhibition of progression of cancer cells through over-expression of P53 and apoptosis	Delphi et al. [43]
In Vitro MCF-7 cells	Annurca apple polyphenol extract	• Pro-oxidant • Antiproliferation • Proapoptotic activity	D' Angelo et al. [44]
In Vivo NMU-induced breast cancer in rats	Saffron carotenoids	• Prevention of tumor volume and incidence both at the initiation and promotion stages	Sajjadi et al. [45]
In Vivo N-nitrosomethylurea group (NMU)	Capsaicin	• Enhances defense mechanism against NMU during carcinogenesis • Chemosupressor against NMU	El Kott et al. [28]
In Vitro T47D breast cancer cell lines	Curcumin treatment for 48 hours	• Prevention of metastasis • Induction of apoptotic cell death by modulating Bcl-2	Coker-Gurkan et al. [46]

Observational, in vitro, and in vivo studies on nutraceuticals effects and possible mechanism on breast cancer risk prevention and progression are given in Tables 5.1 and 5.2.

REFERENCES

1. Organization, W.H., *Cancer Facts*. 2018.
2. Cancer, F.N.B. *Facts about Breast Cancer in the United States*. 2019 [cited February 2019]; Available from: https://www.nationalbreastcancer.org/breast-cancer-facts.
3. Rieder, V. et al., Effect of lifestyle and reproductive factors on the onset of breast cancer in female BRCA 1 and 2 mutation carriers. *Mol Genet Genomic Med*, 2016. **4**(2): pp. 172–177.
4. Narod, S.A., Ten types of breast cancer? *Lancet*, 2012. **380**(9849): pp. 1212–1213.
5. Schettini, F. et al., Hormone receptor/human epidermal growth factor receptor 2-positive breast cancer: Where we are now and where we are going. *Cancer Treat Rev*, 2016. **46**: pp. 20–26.
6. Spector, N.L. and K.L. Blackwell, Understanding the mechanisms behind trastuzumab therapy for human epidermal growth factor receptor 2–positive breast cancer. *J Clin Oncol*, 2009. **27**(34): pp. 5838–5847.
7. Greenlee, H. et al., Antioxidant supplement use after breast cancer diagnosis and mortality in the Life After Cancer Epidemiology (LACE) cohort. *Cancer*, 2012. **118**(8): pp. 2048–2058.
8. Harris, H.R., N. Orsini, and A. Wolk, Vitamin C and survival among women with breast cancer: A meta-analysis. *Eur J Cancer*, 2014. **50**(7): pp. 1223–1231.
9. Jung, A.Y. et al., Antioxidant supplementation and breast cancer prognosis in postmenopausal women undergoing chemotherapy and radiation therapy. *Am J Clin Nutr*, 2019. **109**(1): pp. 69–78.
10. Harris, H.R., L. Bergkvist, and A. Wolk, Vitamin C intake and breast cancer mortality in a cohort of Swedish women. *Br J Cancer*, 2013. **109**(1): pp. 257–264.
11. Lee, S.J. et al., Effect of high-dose Vitamin C combined with anti-cancer treatment on breast cancer cells. *Anticancer Res*, 2019. **39**(2): pp. 751–758.
12. Baglia, M.L. et al., The association of soy food consumption with the risk of subtype of breast cancers defined by hormone receptor and HER2 status. *Int J Cancer*, 2016. **139**(4): pp. 742–748.
13. Nomura, S.J.O. et al., Dietary intake of soy and cruciferous vegetables and treatment-related symptoms in Chinese-American and non-hispanic white breast cancer survivors. *Breast Cancer Res Treat*, 2018. **168**(2): pp. 467–479.
14. Zhang, F.F. et al., Dietary isoflavone intake and all-cause mortality in breast cancer survivors: The breast cancer family registry. *Cancer*, 2017. **123**(11): pp. 2070–2079.
15. Kim, S.J. et al., Folic acid supplement use and breast cancer risk in BRCA1 and BRCA2 mutation carriers: A case-control study. *Breast Cancer Res Treat*, 2019. **174**(3): pp. 741–748.
16. Chen, P. et al., Higher dietary folate intake reduces the breast cancer risk: A systematic review and meta-analysis. *Br J Cancer*, 2014. **110**(9): pp. 2327–2338.
17. Lin, J. et al., Intakes of calcium and Vitamin D and breast cancer risk in women. *Arch Intern Med*, 2007. **167**(10): pp. 1050–1059.
18. Going, C.C. et al., Vitamin D supplementation decreases serum 27-hydroxycholesterol in a pilot breast cancer trial. *Breast Cancer Res Treat*, 2018. **167**(3): pp. 797–802.
19. Madden, J.M. et al., De novo vitamin D supplement use post-diagnosis is associated with breast cancer survival. *Breast Cancer Res Treat*, 2018. **172**(1): pp. 179–190.

20. Brisson, J. et al., A randomized double-blind placebo-controlled trial of the effect of Vitamin D3 supplementation on breast density in premenopausal women. *Cancer Epidemiol Biomarkers Prev*, 2017. **26**(8): pp. 1233–1241.
21. Eliassen, A.H. et al., Circulating carotenoids and risk of breast cancer: Pooled analysis of eight prospective studies. *J Natl Cancer Inst*, 2012. **104**(24): pp. 1905–16.
22. Higdon, J.V. et al., Cruciferous vegetables and human cancer risk: Epidemiologic evidence and mechanistic basis. *Pharmacol Res*, 2007. **55**(3): pp. 224–236.
23. Milner, J.A., Mechanisms by which garlic and allyl sulfur compounds suppress carcinogen bioactivation. Garlic and carcinogenesis. *Adv Exp Med Biol*, 2001. **492**: pp. 69–81.
24. Tattelman, E., Health effects of garlic. *Am Fam Physician*, 2005. **72**(1): pp. 103–106.
25. Kunnumakkara, A.B., P. Anand, and B.B. Aggarwal, Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. *Cancer Lett*, 2008. **269**(2): pp. 199–225.
26. Choudhuri, T. et al., Curcumin induces apoptosis in human breast cancer cells through p53-dependent Bax induction. *FEBS Lett*, 2002. **512**(1–3): pp. 334–340.
27. Squires, M.S. et al., Relevance of mitogen activated protein kinase (MAPK) and phosphotidylinositol-3-kinase/protein kinase B (PI3K/PKB) pathways to induction of apoptosis by curcumin in breast cells. *Biochem Pharmacol*, 2003. **65**(3): pp. 361–376.
28. El-Kott, A.F. and M.M. Bin-Meferij, Suppressive effects of capsaicin against N-nitrosomethylurea-induced mammary tumorigenesis in rats. *Biomed Pharmacother*, 2018. **98**: pp. 673–679.
29. Kaushik, S. et al., Genistein synergizes centchroman action in human breast cancer cells. *Indian J Pharmacol*, 2016. **48**(6): pp. 637–642.
30. Song, J.K. and J.M. Bae, Citrus fruit intake and breast cancer risk: A quantitative systematic review. *J Breast Cancer*, 2013. **16**(1): pp. 72–6.
31. Wu, Y.C. et al., Meta-analysis of studies on breast cancer risk and diet in Chinese women. *Int J Clin Exp Med*, 2015. **8**(1): pp. 73–85.
32. Pourzand, A. et al., Associations between dietary allium vegetables and risk of breast cancer: A hospital-based matched case-control study. *J Breast Cancer*, 2016. **19**(3): pp. 292–300.
33. Touillaud, M. et al., Use of dietary supplements containing soy isoflavones and breast cancer risk among women aged >50 y: A prospective study. *Am J Clin Nutr*, 2019. **109**(3): pp. 597–605.
34. Yu, L., Y. Tan, and L. Zhu, Dietary Vitamin B2 intake and breast cancer risk: A systematic review and meta-analysis. *Arch Gynecol Obstet*, 2017. **295**(3): pp. 721–729.
35. Egnell, M. et al., B-Vitamin intake from diet and supplements and breast cancer risk in middle-aged women: Results from the prospective NutriNet-Sante cohort. *Nutrients*, 2017. **9**(5): p. 488.
36. Greenlee, H. et al., Association between complementary and alternative medicine use and breast cancer chemotherapy initiation: The Breast Cancer Quality of Care (BQUAL) study. *JAMA Oncol*, 2016. **2**(9): pp. 1170–1176.
37. Kyro, C. et al., Pre-diagnostic polyphenol intake and breast cancer survival: The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. *Breast Cancer Res Treat*, 2015. **154**(2): pp. 389–401.
38. Zhao, Q. et al., Genistein targets the cancerous inhibitor of PP2A to induce growth inhibition and apoptosis in breast cancer cells. *Int J Oncol*, 2016. **49**(3): pp. 1203–1210.
39. Fang, Y. et al., Quantitative phosphoproteomics reveals genistein as a modulator of cell cycle and DNA damage response pathways in triple-negative breast cancer cells. *Int J Oncol*, 2016. **48**(3): pp. 1016–1028.
40. Chatterjee, A. et al., Antioxidant activities of novel resveratrol analogs in breast cancer. *J Biochem Mol Toxicol*, 2018. **32**(1): e21925. First Published: September 28, 2017.

41. Kritsanawong, S. et al., Antiproliferative and apoptosis induction of alpha-mangostin in T47D breast cancer cells. *Int J Oncol*, 2016. **48**(5): pp. 2155–2165.
42. Park, J.Y. et al., Polysaccharides from Korean Citrus hallabong peels inhibit angiogenesis and breast cancer cell migration. *Int J Biol Macromol*, 2016. **85**: pp. 522–529.
43. Delphi, L. and H. Sepehri, Apple pectin: A natural source for cancer suppression in 4T1 breast cancer cells in vitro and express p53 in mouse bearing 4T1 cancer tumors, in vivo. *Biomed Pharmacother*, 2016. **84**: pp. 637–644.
44. D'Angelo, S. et al., Pro-oxidant and pro-apoptotic activity of polyphenol extract from Annurca apple and its underlying mechanisms in human breast cancer cells. *Int J Oncol*, 2017. **51**(3): pp. 939–948.
45. Sajjadi, M. and Z. Bathaie, Comparative study on the preventive effect of saffron carotenoids, crocin and crocetin, in NMU-induced breast cancer in rats. *Cell J*, 2017. **19**(1): pp. 94–101.
46. Coker-Gurkan, A. et al., Curcumin prevented human autocrine growth hormone (GH) signaling mediated NF-kappaB activation and miR-183-96-182 cluster stimulated epithelial mesenchymal transition in T47D breast cancer cells. *Mol Biol Rep*, 2019. **46**(1): pp. 355–369.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

6 Nutraceutical's Role in Proliferation and Prevention of Gynecological Cancers

Aaishwarya B. Deshmukh, Jayvadan K. Patel, and Bharat Mishra

CONTENTS

Cancer is a disordered condition between cell proliferation and cell death. Factors have been identified that are involved in the process of invasion and metastasis of tumors and cause resistance to treatment. A huge effort has been made in the past 20 years to provide the data to design more effective, individualized, and target-oriented advance treatment strategies. Regardless of the development of various new treatment regimes, cancer still causes a large number of deaths in the United States, according to the American Cancer Society [1]. It is now concluded by various studies that lifestyle is a major factor behind 90%–95% of all cancers, whereas faulty genes are involved in 5%–10%. A number of research studies have shown that inclusion of foods rich in fruits and vegetables decreased the occurrence of cancer. As per the studies, nutrition could prevent a large number of cancer deaths and a great likelihood of certain cancers could be avoided by dietary modifications [2]. The roles of dietary agents and lifestyle have already been studied for various cancers such as colorectal, skin, prostate, breast, ovarian, cervixal, vaginal, lung, and gastrointestinal tract [4].

It is concluded by studies that occurrence of cancer can be controlled by improving diet, quitting tobacco use, regular exercise, and maintaining body weight. Pharmaceutical companies and various research centers have been working to develop multitargeted therapies. Various nutraceuticals have properties to act as multitargets. In addition, they are cost-effective, safe, and readily available [3]. There are some nutraceuticals that are in clinical trials, but various other nutraceuticals have got approved for clinical use [4].

6.1 GYNECOLOGICAL MALIGNANCIES

Gynecologic cancer is an uncontrolled cell growth and distribution of abnormal cells that spreads from the reproductive organs. There are various kinds of gynecological cancers, which include cervical cancer, cancer of the cervix, ovarian cancer, gestational trophoblastic disease (GTD), primary peritoneal cancer, fallopian tube cancer, uterine/endometrial cancer, vaginal cancer, and vulvar cancer, that are the cause of not only mortality in cancer but also morbidity all over the world. The fallopian tube cancer, choriocarcinomas, vaginal cancer, and vulvar cancer are quite rare, but relatively common cancers are ovarian cancer, cervical cancer, and endometrial cancer. The third very common cancer in women around the world is cervical cancer, the first two are breast and colorectal cancers; overall, it is the seventh most common cancer. Less-developed regions of the world reported greater than 85% of the total cases of cervical cancer globally and 13% of all cancers in women [5]. Regular screenings and self-examinations can detect these cancers in their early stages, which improves the chances of successful treatment and complete cure [6].

6.2 CERVICAL CANCER

Adenocarcinoma and squamous cell carcinoma (SCC) are the two main histological types of cervical cancers present. The large number of cervical cancer cases are associated with HPV types (the human papillomavirus types 16, 18, 31, 33, 35, and more); worldwide, the persistent infections with HPV16 and 18 cause about 70% of total cervical cancers [6]. Other carcinogenic exposures to the cervix are exposure to

diethylstilbestrol, use of oral contraceptives combined with estrogen and progestogen, HIV1 infection, and tobacco smoking. In general, the cervical cancer can be controlled through early detection, supported by Pap test or an HPV test. Cervical cancer can also be prevented by HPV vaccines. Current line of treatment for cervical cancer is Papanicolaou test (PAP test) and it is used to detect potentially precancerous and cancerous processes in the cervix. In late stages, chemotherapy for, for example, cisplatin and topotecan, radical trachelectomy, and/or radiation therapy as radioactive implants are used. In addition, pelvic exenteration is also done, where the urinary bladder, urethra, rectum, and anus are removed, if radiation therapy leaves cancer in pelvic [7].

6.3 UTERINE CANCER

Postmenopausal women get affected more often with endometrial cancer. The histological subtypes of endometrial cancer are of epithelial origin, which are further categorized as Type I, adenocarcinomas of endometrioid type, or Type II, adenocarcinomas of nonendometrioid type. Type I endometrial cancer is typically hormone sensitive and common in women exposed to estrogens unopposed by progesterone. Type II endometrial cancer generally originates from atrophic endometrial tissues, with poor differentiation. It is not linked with estrogen or progestogen stimulation and shows high chances of metastasis [8]. Estrogen and estrogen–progestogen hormone replacement therapy is one of the major causes of uterine cancer [9]. Current line of treatment for uterine cancer is surgery, radio- and chemotherapy, which can be used separately or in combination. In surgery, salpingoophorectomy, laparoscopic surgery, supracervical hysterectomy, total, and radical hysterectomy can be implicated. The commonly used chemotherapeutic drugs in uterine cancers are carboplatin, cisplatin, doxorubicin, and paclitaxel [8].

6.4 OVARIAN CANCER

According to the American Cancer Society, ovarian cancers are the cause for more deaths among all gynecological cancers. Ovarian cancers are classified as per the cell types they originate from: about 90% from epithelial cells, 5% from stromal cells, and less than 5% from germ cell. Estrogen by hormone replacement therapy and smoking tobacco are one of the major causes for epithelial ovarian cancer. Estrogen by hormone replacement therapy and smoking tobacco are one of the major causes for epithelial ovarian cancer, especially in individuals who are carrier of mutant BRCA1/BRCA2 genes [9]. Current line of treatment for ovarian cancer is treatment by using surgery and targeted therapy. Radiotherapy is not much significant, while chemotherapy consists of paclitaxel combined with carboplatin, bleomycin, cisplatin, etoposide, bevacizumab, docetaxel, liposomal doxorubicin, gemcitabine, and topotecan [10].

6.5 VAGINAL, VULVAR, AND FALLOPIAN TUBE CANCER

Some rare gynecological cancers are vaginal and vulvar cancers. Ninety percent of vaginal and greater than 50% of vulvar cancers are linked to HPV infection, similar to cervical cancer. HPV vaccines can be useful for preventing vaginal and vulvar

cancers. Clear cell adenocarcinoma caused by diethylstilbestrol in the vagina of in utero exposed women [11]. Prior or simultaneous gynecological cancers can be the risk factor for women who have been pre exposed to pelvic irradiation [9,12]. Current line of treatment to manage the vulvar cancer is radical vulvectomy. Other procedures available for vaginal cancers surgery are radical hysterectomy, upper vaginectomy, and pelvic lymphadenectomy [13]. For vaginal and vulvar cancers, the most used chemotherapeutic agents are cisplatin, paclitaxel, and 5-fluorouracil (5-FU). In the first trimester of pregnancy, while organogenesis progresses, these agents cause miscarriage or structural abnormalities in fetus [14]. The use of brachytherapy (by using radioactive implants) is suggested in primary vaginal cancers to avoid radiotherapy during pregnancy because of the risk of detrimental effects [7,15]. In case of fallopian tube cancer too, surgery is the first line of effective treatment with the removal of uterus and ovaries, fallopian tubes, adjacent lymph nodes, and surrounding tissues. The use of radiotherapy is rare; however, chemotherapy can begin with carboplatin and paclitaxel [7].

6.5.1 Hydatidiform Mole

It is a growth of an abnormal fertilized egg or an overgrowth of tissue from the placenta; common in young age, the symptoms of hydatidiform mole (HDFM) are feeling pregnant, severe nausea, vomiting, vaginal bleeding, sepsis, shock, and preeclampsia, or eclampsia are the symptoms in HDFM. It may metastasize to other parts of the body. Current line of treatment is surgery, hysterectomy, and chemotherapy with methotrexate and/or dactinomycin, etoposide, methotrexate, cyclophosphamide, actinomycin-D, vincristine, and oral contraceptives [10].

6.5.2 Physiological Mechanism of Gynecological Cancers

There are various ways of defining the proliferation of gynecological cancers: the hypothalamic decapeptide luteinizing hormone-releasing hormone (LHRH) plays a key role in the control of mammalian reproduction by stimulating the synthesis and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Probably the physiology of LHRH contributes to a number malignant tumor such as breast cancer, ovary, endometrium, and prostate cancer [16,17]. In addition, specific binding sites with high affinity for LHRH and the mRNA expression for the pituitary LHRH receptor have been reported in breast, endometrial, and ovarian cancer cell lines, which is confirmed by the biopsy specimens [18,19]. Analogues of LHRH, whether agonistic and antagonistic, inhibit the multiplication of breast, endometrial, ovarian cancer cell lines, which express LHRH receptors. The LHRH receptor interacts with the MAP kinase pathway and causes the reduction in cancer cell proliferation. In addition, LHRH sensitizes the nuclear factor κB and prevents the apoptosis in the cancer cells [17].

6.5.3 Nutraceuticals

One of the definition of A nutraceutical is “any nontoxic food component that has scientifically proven health benefits, including disease treatment or prevention” [20]. Stephen DeFelice, who was the founder of Foundation for Innovation in Medicine (FIM),

New Jersey, USA, had originally coined the term "nutraceuticals" in the 1989 [21]. The term refers to the bioactive components that may be found in normal foods, enriched foods, and dietary supplements and has since been used to describe a wide variety of nonpharmaceutical compounds that may have an impact on health and disease states, general well-being, and performance. Nutraceuticals are commonly used synonymously for designer foods, health foods, fortified foods, medifoods, vita foods, pharma foods, functional foods, and dietary supplements. The term is vaguely explained and utilized by users, producers, and even healthcare personnel to refer to variety of compounds, including substances from natural sources, dietary supplements, plant extracts, phytonutrients, vitamins and minerals, and even (modified) whole foods [22].

6.5.4 Classification

Although there are several systems for classification of nutraceuticals, they are mostly classified on the basis of their natural source such as plants, animals, minerals, or microbial sources, as per chemical composition or the pharmacological aspects of the products. The nutraceuticals can be obtained from various natural food sources and can be classified as probiotics, dietary fiber, polyunsaturated fatty acids, prebiotics, antioxidant, polyphenols, vitamins, and spices [23]. On the basis of chemical constituents, nutrachemicals can be categorized as **nutrients**, including vitamins, minerals, amino acids, and fatty acids, which have established nutritional functions; **herbals**, concentrates or extracts obtained from herbs or botanical products; and **dietary supplements**, substances obtained from other sources having specific functions such as nutrition for sports, fortified conventional foods, supplements for weight loss, and meal replacements, for example, pyruvate, chondroitin sulfate, and steroid hormone precursors [24].

A large number of nutraceuticals ingredients have been identified. Some very important nutraceuticals ingredients include are quercetin, silibinin, allicin, butein, resveratrol, catechin gallate, capsaicin zerumbone, fisetin, epigallocatechin gallate (EGCG), sulforaphane, berberine, curcumin, gambogic acid, plumbagin, apigenin, caffeic acid, sanguinarine, flavopiridol, taxol, genistein, γ-tocotrienol, and celastrol. These have shown positive effects in relation to the specific processes involved in tumor formation, survival, proliferation, invasion, angiogenesis, and metastasis of cancer tumors.

Chronic inflammation is one of the components for tumor growth, and NF-κB is a chief inflammatory transcription factor known to play a key role in tumor cell development; therefore, it is important to know that how a nutraceutical can sensitize NF-κB and can thus affect tumor growth [4]. Dietary supplements are products that tend to complete the daily nutritional requirement and do not cure a disease, whereas nutraceuticals have more pronounced outcomes of either preventing or treating a disease [24,25]. The dietary phytochemicals intervene with cell multiplication and regulation by involving in multiple communication pathways involved in tumor initiation, growth, and propagation [25,26]. The significance of polyphenols in the treatment of different types of cancers are already established [27]. Green tea polyphenols and curcumin are the most frequently studied dietary compounds in human and animal cervical cancer cells [6–28].

6.5.5 Nutraceuticals in Cancer Prevention

Soy protein intake is inversely associated with breast cancer recurrence and mortality [29]. Similarly, in mice models, soy milk treated with various bacterial strains inhibited the ER-positive MCF-7 breast cancer [30]. Another compound found in plant cell membranes is phytosterols, which increase the antioxidant enzyme activity and inhibit carcinogen, ROS, and proinflammatory cytokine production, so they are antiangiogenic [31]. Phytosterols are proapototic by increasing caspase-3 and mitogen-activated protein kinase enzymes, decreasing prostaglandin series 2, Bcl2, phosphotidyl inositol-3-phosphate kinase, and protein kinase B [31]. **Berries** such as raspberries and strawberries containing polyphenols are antiestrogenic and modulate breast cancer development pathways from adolescence through late menopause, including growth factor receptor (GFR) activation [32]. Another set of agents such as apigenin- and luteolin-rich celery heart, parsley, and thyme; quercetin-rich apple and onion; EGCG and ellagic acid-rich green tea; ellagic acid-rich freeze-dried organic berry; genestein-rich soybean; curcumin-rich turmeric; and oridonin-rich *Rabdosia rubescens* would be recommended as part of an ovarian cancer prevention diet [33]. A diet high in carotenoids, fiber, lignans as coffee, carrots, cucumbers, and strawberries, poultry, and stigmasterol are known to be chemoprotective for ovarian cancer [34]. In agreement with this result, researchers have analyzed that a diet rich in vegetable, fruit, nut, fish, and unsaturated fats; moderate alcohol; and diet with low amount of meat, dairy, cereals, and potatoes can reduce endometrial cancer risk [35]. Green Tea, is studied as a complimenting ingredient for preventing side effects due to chemotherapy in breast cancer, fibrosarcoma, gastric cancer, glioblastoma, head and neck cancers, neuroblastoma, and prostate cancer. It is reported that it inhibits VEGF, NF-κβ, c-fos, and cyclinD1 promoter activity, Bax, and stabilizes p53 due to polyphenols present in the green tea. The combination of EGCG 200 mg, epigallocatechin 37 mg, and epicatechin 31 mg, as an oral capsule and/or vaginal ointment, achieves a mean 69% clearance of HPV-related cervical lesions [36]. Kaemferol, a flavanol polyphenol, is chemopreventive for ovarian cancer through COX-2 and IL-4 inhibition, Src kinase suppression, and NF-κβ downregulation [37]. Oleanolic acid, a pentacyclic triterpene found in apples, dates, etc., has shown in vitro antiproliferative potential against breast cancer and melanoma cell lines as MCF-7, MDA-MB-231, and Hs578T by increasing AMPK expression, upregulating p53 and p21WAFI/CIP1 expression, while downregulating ERα expression, inhibiting mTORC1, mTORC2, regulatory-associated protein of mTOR (RAPTOR), rapamycin-insensitive companion of mTOR (RICTOR), and mTOR/ FRAP1 [38]. Oleanolic acid also inhibits MDA-MB-231 cell invasion and migration by decreasing breast tumor kinase (Brk), paxillin, and Ras-related C3 botulinum toxin substrate 1 phosphorylation [38]. Curcumin is a cervical cancer chemopreventive for 25% of women. Vaginal capsules and vaginal cream have been tried with 81.3%–87.7% HPV clearance rates, respectively. The cruciferous indole I3C and its metabolite DIM promoted beneficial estrogen metabolism, in turn protecting against estrogen-enhanced breast, cervical, and endometrial cancers [39,40].

6.6 REGULATION AND MECHANISM OF INFLAMMATORY PATHWAYS AND NUTRACEUTICALS

The tumor initiation and progression is proved to be associated with inflammation. Much support has emerged, pointing that proinflammatory transcription factor, nuclear factor-kappa B (NF-κB) is one of the very important connections between inflammation and cancer.

NF-κB as a nuclear factor was found to bind to the enhancer element of the immunoglobulin kappa light chain of activated B cells (hence abbreviated NF-κB) [41]. The five members of NF-κB group of proteins identified are RelB, p65 (RelA), NF-κB1 (p105/p50), NF-κB2 (p100/p52), and c-Rel [42–45]. The expression of genes involved in the various processes of transformation and development of tumor cells is regulated by the transcription factor NF-κB by various proinflammatory stimuli such as TNF-α, lipopolysaccharide, IL-1b, and oxidative stress, which induce expression of multiple genes encoding proinflammatory cytokines, growth and angiogenic factors, chemokines adhesion molecules, such as ICAM-1 and e-selectin VCAM-1, and inducible enzymes like iNOS and COX-2 [46]. The apprehension that the c-rel, which is a cellular homologue of the oncogene v-rel, encodes for a NF-κB subunit and binds to the same DNA binding domain has given the first proof of link between NF-κB and cancer [47]. In addition, the detection of active NF-κB in cancer tissues of the patients, including those with lymphoma and leukemia and cancers of breast, prostate, pancreas, oral cavity, colon, liver, and ovary support the link between NF-κB and cancer [48]. All these point to the relevance or importance of NF-κB pathway in cancer, and so this pathway has been manifested as a favored target for therapeutic development.

6.6.1 NF-κB in Ovarian Cancer Initiation and Progression

The various inflammatory processes such as repeated ovulation, endometriosis, and pelvis infections are associated with carcinogenesis in the ovary. NF-κB is the molecular link between inflammation and cancer [49]. Various important processes involved in the tumor growth and proliferation like activation of the genes involved in the progression of cell cycle and antiapoptotic genes [50], secretion of growth-enhancing factors such as interleukin (IL) 6 and tumor necrosis factor (TNF) α [49], and enhanced production of IL-8 and VEGF, which promotes a proangiogenic environment [51], are controlled by the NF-κB group of proteins. Inhibition of NF-κB activates the growth of ovarian cancer cell line derived from a papillary serous carcinoma, and inhibition in endometrial tissue results in an increased growth rate of ovarian tumors [52].

6.6.2 NF-κB Signaling Network in Cervical Cancer

There is a link between various types of human papillomavirus (HPV) and cervical cancer. The inhibitory activity for the replication of the virus triggered by the immune system is terminated by the downregulation of NF-κB by the virus, which, in turn, leads to a state of persistent HPV infection. In solid tumors, mutations in the NF-κB

gene are not a common phenomenon, but elevated NF-κB signaling is visualized as a result of mutations of active signaling molecules such as EGFR, RAS, HER2, and PGF. The stimulation of transcription of genes regulating proliferation like c-myc and cyclin D1 genes involved in metastasis and VEGF-dependent angiogenesis can be induced by NF-κB. A link between the NF-κB signaling pathway and mutagenic characteristic of cervical cancer is provided by the fact that NF-κB sensitization can also result in the expression of cytidine deaminase (AID) and the APOBEC proteins ((“apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like”) is a family of evolutionarily conserved cytidine deaminases) [53]. A tumor-activating role for NF-κB in cervical cancer is suggested, as there is a downregulation in the antiproliferative functions of the NF-κB pathway during cervical cancer progression and shows protumorigenic effects [53].

6.6.3 NF-κB Regulate the Proliferation of Endometrial Cancer Cells

The role of NF-κB in this cancer is almost the same as that in ovarian and cervical cancers, as it also regulates the endometrial cancer cell proliferations [54].

6.6.4 NF-κB Signaling Pathway

During the resting state, NF-κB remains in the cytoplasm as a heterotrimer consisting of 2 subunits p50 and p65 and an inhibitory subunit IκBα. The IκBα protein undergoes a process of phosphorylation, then ubiquitination, and degradation, thereby releasing p50 and p65 subunits, which are then moved to the nucleus and the transcription process is initiated as they recognize and bind to specific DNA sequences present in the promoter region of various genes. NF-κB communication pathway includes the involvement of a number of proteins [4].

6.6.5 Anticancer Activity by NF-κB Inhibitors

An interruption in the NF-κB activation pathway results in anticancer activity and more than 700 compounds having the potential to reduce this NF-κB pathway are reported, which includes, small DNA/RNA, peptides, antioxidants, microbial and viral proteins, engineered and active polypeptides, and small molecules [55]. During the past two decades, there have been many research studies showing that nutraceuticals exert their antimalignant activity by inhibiting the NF-κB signaling pathway [4].

6.6.6 Nutraceuticals as NF-κB Inhibitor

Curcumin is found to be a potent inducer of apoptosis in cancer cells by inhibiting the NF-κB activation. Through the downregulation of NF-κB-inducing kinase and IκB kinase (IKK), curcumin acts by inhibiting IκB degradation. By suppression of the IκBα phosphorylation and subsequent degradation, curcumin also represses the TNF-α-induced nuclear translocation and DNA binding of NF-κB in a human myeloid leukemia cell line [56]. In humans, many myeloma cells and melanoma cells in murine, it is reported that curcumin has shown the

decrease in IκBα phosphorylation through oppression of IKK activity, which is involved in its proapoptotic, antiproliferative, and antimetastatic activities. Guggulsterone, which is obtained from the *Commiphora mukul* tree, exerts the anticancer activity by suppressing the activation of NF-κB through the suppression of IκB kinase-dependent IκBα degradation [57]. A phytoalexin, resveratrol, present in grapes has been reported to possess anticancer activity and shown to induce apoptosis in tumor cell lines and suppress constitutive NF-κB in human breast cancer MCF-7 cells. The preponderance of evidence has shown chemoprotective and chemopreventive effects of capsaicin, from the pepper, Caffeic acid phenethyl ester, which is obtained from propolis, sanguinarine, a quaternary ammonium salt from plants like bloodroot (*Sanguinaria canadensis*), Mexican prickly poppy, *Argemone mexicana*, *Chelidonium majus*, and *Macleaya cordata*, and emodin, an active ingredient in the root and rhizome of *Rheum palmatum* (Polygonaceae) and aloe vera, by blocking the degradation of IκBα, which may happen in response to various factors like TNF, interleukin (IL)-1, phorbol ester, or okadaic acid stimulation [4,58].

Another nutraceutical, gallic acid, which is obtained from gallnuts, green tea, oak bark, and sumac, was recently explained to possess antihistone acetyltransferase activity by downregulating NF-κB activation by possessing the antihistone acetyltransferase activity [59]. Thus, nutraceuticals evince their anticancer effect by blocking some steps in this signaling pathway like the suppression of IκB kinase activity, nuclear translocation of p65, phosphorylation of IκBα, acetylation of p65, and p65 DNA binding [4].

6.7 REGULATION OF TUMOR CELL DEVELOPMENT BY NUTRACEUTICALS

The human body is furnished with several mechanisms, whereby it eliminates unnecessary, injured, misplaced, and aged cells from the body and maintains the homeostasis. Caspases, proapoptotic factors, cytochrome c, antiapoptotic Bcl-2 (B cell lymphoma) family proteins, and Apaf (apoptotic protease activating factor)-1 are the array of proteins involved in the pathway. Activation of caspases, induction of proapoptotic proteins, and downregulation of antiapoptotic proteins are some of the most common ways by which nutraceuticals hinder the survival of tumor cells. Through a casp-3-dependent increase in apoptosis, acetoxychavicol acetate derived from *Alpinia galanga* belonging to the Zingiberaceae family decreased the viability of cancer cells in breast-tumor-derived MCF-7 and MDA-MB-231 cells [60]. The gambogic acid, a xanthonoid that is derived from the brownish or orange resin from *Garcinia hanburyi*, produces its effect through upregulation of p53 and downregulation of Bcl-2 and thus inducing apoptosis in MCF-7 cancer cells [61]. Through upregulation of death receptors (DRs), some nutraceuticals have been shown to induce apoptosis. In human breast cancer cells, celastrol, the root extract of *Tripterygium wilfordii* and *Celastrus regelii*, through the downregulation of cell survival proteins and upregulation of death receptors 4 and 5, potentiates TRAIL-induced apoptosis [4,62].

Majority of nutraceuticals with antioxidant activity inhibit NF-κB-regulated anti-apoptotic proteins target by inhibiting NF-κB activation. Garcinol causes apoptosis in human breast carcinoma, MDA-MB-231 and MCF-7, cells through the activation of caspase and NF-κB-regulated genes down regulation [63]. γ-Tocotrienol, acetoxychavicol acetate, evodiamine, thymoquinone, noscapine have shown inhibiting plumbagin-induced apoptosis with related inactivation of DNA binding activity of NF-κB and Bcl-2 in breast tumor cells [64]. Isodeoxyelephantopin, anacardic acid, indirubin, coronarin D, β-escin, and withanolides, are some of the most popular among nutraceuticals reported to have antioxidant activities for cancer treatment [4].

The cancer cells have abilities to produce their own development signals and resist inhibitory signals to promote their growth, and nutraceuticals have shown to regulate the tumor cell proliferation by manipulating this ability of cancer cells [65]. Cell growth is mainly restricted by cell cycle regulators like cyclins and cyclin-dependent kinases (CDKs). CDK becomes active only when cyclin binds with it, whereas p21 and p27 act as CDK inhibitors (CKIs) preventing CDK activity and preventing cell cycle progression. The transition of G1 to S phase and cell cycle succession at the G1 phase is controlled and blocked in response to DNA damage by the well-characterized tumor suppressor p53 [65]. Most of the nutraceuticals inhibit the transition of malignant cells from the G1 to S phase by acting through the tumor suppressors p53 or Rb. Acetyl-keto-beta-boswellic acid was shown to inhibit cellular proliferation in colon cancer by affecting the cell cycle at the G1 phase by decreasing the expression of cyclin D1, cyclin E, CDK-2, CDK-4, and pRb and increasing the expression of p21. In breast cancer cells, a derivative of rotenone, deguelin, evinced an antiproliferative effect by blocking cells at the S phase [66]. Through the decrease in free E2F-1 and pRb, an increase in Rb and arrest of cell cycle in the G1 phase, sulforaphane, a compound obtained from cruciferous vegetables such as broccoli and cabbages, was shown to suppress the proliferation of cells in epithelial ovarian cancer. There are few nutraceuticals that regulate the proliferation of tumor cells by targeting one or more steps in the activation of NF-κB. Another study demonstrated that the antiproliferative activity of curcumin was associated with a decrease in cyclin-D1 and CDK-4 expression in breast tumor cell lines BT-483 and MDA-MB-231 [4].

6.8 NUTRACEUTICALS IN REGULATION OF CANCER CELL INVASION

Cancer cell invasion and metastasis are interconnected processes. Nutraceuticals are natural bioactive products and have shown to suppress cancer cell invasion and metastasis by targeting many molecules. S-Allylcysteine and S-allylmercaptocysteine, obtained from garlic, have been shown to suppress the growth and ability to invade invasive prostate cancer cells, which are androgen-independent, by the reinstatement of E-cadherin expression. Acting through the HER2/HER3/PI3K/AKT pathway, apigenin, a flavone class, shows its importance in inhibiting the adhesion and motility of transformed cells in breast carcinoma [4,67].

Recent studies showed that a polyphenolic compound (Butein) obtained from the bark of the stem of cashews inhibited migration and invasion of the cancer cells through various signaling pathways like NF-κB and ERK-1/ERK-2 in tumor of bladder [4].

The chemokine receptor CXCR4, with its unique ligand, CXCL12 (CXC chemokine ligand 12), performs an important function in the metastasis of breast tumor cells. Antimetastatic ability of MCF-7 and MDA-MB-231 breast cancer cells shown by 3,3′-diindolylmethane through lowering CXCR4 and CXCL12 levels. C-erbB-2 is a chief molecule for metastasis in breast cancer. The overexpression of c-erbB-2 results in increased MMP secretion and is correlated with its metastatic potential in breast tumor cells [4]. The secretion of MMP-9 and MMP-2 in the breast carcinoma cells was found to be inhibited by flavopiridol and connected with major downregulation of c-erbB-2 and inhibition of cell invasion [4]. Ganoderic acids isolated from *Ganoderma lucidum* inhibit the invasion of breast tumor cells by suppressing AP-1 and NF-κB activity and thereby inhibiting u-PA secretion [4]. Genistein suppresses the secretion of urokinase plasminogen activator (u-PA) from tumor cells inhibited by suppressing the transcriptional activity of NF-κB and AP-1 and thus prevents the cell adhesion by vitronectin (VTN, which promotes the cell adhesion by binding to the integrin alfa-V beta 3) and cell migration of invasive breast tumor cells [4]. Sanguinarine, by decreasing the activity of MMP-2 and MMP-9, suppressed the invasive behavior of MDA-MB-231 human breast cancer cells. A Southeast Asian ginger sesquiterpene, zerumbone downregulates the expression of the chemokine receptor on HER2-overexpressing breast tumor cells in a time- and dose-dependent manner [4].

The major events involved in the angiogenic surge of tumor growth include the discharge of angiogenic factors, the binding of the released factors to receptors on ECs, activation of EC, proteases-mediated degradation of the basement membrane, and migration and proliferation of ECs, and are finally or dered into a new arrangement of blood vessels [4]. Vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factors (FGFs), epidermal growth factor (EGF), ephrins, angiopoietins, endothelins, integrins, cadherins, and notch are the major signaling mediators involved [4]. By affecting various steps in the signaling pathway, many nutraceuticals have shown to exhibit angiogenesis-modulating properties. Antiangiogenesis efficacy of alliin, a constituent of fresh garlic, was demonstrated in a chick chorioallantoic membrane (CAM) model through its ability to suppress FGF-2-mediated human endothelial cell (EC) tube formation and angiogenesis. An active compound obtained from *Gamboge hanburyi*, gambogic acid inhibited angiogenesis in human umbilical vein endothelial cells (HUVECs) and human prostate cancer cells (PC3) by suppressing activation of VEGF receptor 2 and downstream kinases such as FAK, c-Src, and AKT [68]. Resveratrol has been shown to have the potential to suppress the formation of new blood vessels in animals. Through suppression of phosphorylation of MAPK in ECs, it can directly inhibit capillary endothelial cell growth and block angiogenic responses mediated through VEGF and FGF receptors [4]. Rosmarinic acid (RA) is a water-soluble polyphenolic compound with antioxidant and anti-inflammatory properties. Antiangiogenic potential of RA is associated with its ability to decrease the ROS level within the cell, reduce H_2O_2-dependent VEGF expression, and reduce IL-8 release of ECs [4]. Sanguinarine exhibited antiangiogenic activity through downregulation of VEGF-induced AKT activation and in doing so it suppresses the proliferative effect of VEGF on ECs [4].

6.9 NUTRACEUTICALS: ADVERSE EFFECTS

Integrative medicine synergism raises conventional cancer treatment efficacy. However, nutraceuticals can also negatively affect conventional cancer treatment. For instance, antioxidant harm has been substantiated for smokers receiving radiotherapy. Lung and prostate cancer risk is significantly raised by vitamin E and high dose of β-carotene. Genistein can be proestrogenic in breast cancer, so it should be avoided by breast cancer patients. The antiestrogens anastrazole, exemestane, letrozole, and tamoxifen were used by 38% of Scottish breast cancer patients along with chamomile, echinacea, garlic, ginseng, grapefruit, pomegranate, or peppermint, all of which affect cytochrome P450 (CYP450) [69]. Ellagic acid is a CYP450 inhibitor capable of reducing anastrazole, exemestane, letrozole, imatinib, and irinotecan levels, while increasing tamoxifen levels. Cell repair, including poly ADP-ribose polymerase 1 (PARP-1)-mediated cell repair and signaling pathways, can be negatively affected by nutraceuticals. Some studies found that integrative medicine use was significantly associated with increased vaginal dryness, fewer hot flushes, and more uncategorized adverse effects. Minor adverse effects associated with polyphenols are abdominal pain, diarrhea, fatigue, insomnia, and nausea. Adverse effects can be dose and comorbidity dependent [40].

6.10 ROLE OF NUTRACEUTICALS IN PREVENTING THE ADVERSITY OF CANCER TREATMENT IN MAJOR GYNECOLOGICAL CANCERS

Nutraceuticals and phytochemicals play a role in preventing and limiting the adverse sequelae of chemotherapy and radiotherapy, without reducing the chemotherapeutic and radiotherapy effectiveness [40].

The compounds acting as potential inhibitors of breast cancer include derivatives of allium, β-carotene, and other carotenoids, dried green coffee, catechin, dithiolthiones, curcumin, coumarin glucosinolates and indoles, isolavones, d-Limonene, glycirrhizic acid, kahweol palmitate, lignans, orange oil, protease inhibitors/Bowman–Birk inhibitor (BBI), selenium/organoselenium compounds, and rosemary extract [70]. Green tea bromelain, curcumin, coenzyme Q10, intravenous artesunate and melatonin, ascorbic acid, vitamin D3, mistletoe injections, Trametes versicolor mushroom, and Wobenzyme TM digestive enzymes are some of the agents used in the treatment of advanced breast cancer, but the factor that limits the use is that it is a costly affair [71]. In murine studies using BITC (benzyl isothiocyanate) has shown that by p53-LKB1 and p73-LKB1 (LKB1 is a mediator of p53 and p73 death pathways) pathway activation, which enhances p53 signaling, BITC could inhibit MCF7, a breast cancer cell line, and HBL-100, an epithelial cell line from human milk. In breast cancer cells, it was demonstrated that BITC increases p53, Erk, and cyclic adenine monophosphate-response element-binding protein (CREB) phosphorylation, whereas it decreases phosphorylation of Akt [71].

Caffeic acid phenethyl ester from propolis has strong cytotoxicity against Hs578T and MDA-MB-231 breast tumor cells [71]. Caffeic acid phenethyl ester by NF-κβ inhibition induces caspase-3 dependent apoptosis, prevents cell proliferation, and

also increases the Bcl-2:Bax ratio. Curcumin and sulforaphane also exhibit antiproliferation action on breast cancer cells by modulating HDACs. Moderate cytotoxic effect was shown by triterpenoids obtained from bitter gourd to MDA-MB-231 and MCF-7 breast tumor cells. Triterpenoids of bitter gourd have number of mechanisms including caspase-dependent apoptosis, downregulation of Akt-NF-κB signaling, activation of protein kinase by p38 mitogen, and upregulation of p-53, generation of ROS and increased cytoprotective autophagy, and decreased expression of histone deacetylases (HDACs) protein. In some other cases, they act by modulation of apoptotic peroxisome proliferator-activated receptor (PPAR) γ-targeted gene products [71,72].

In murine studies, inhibition of triple-negative breast cancer (TNBC) cell lines HCC1806 and HCC1937 was brought about by a synthetic analogue of oridonin (obtained from *Rabdosia rubescens*), CYD-6-28. CYD-6-28 induces cleavage of p21, Erk, PARP, caspase-3, -7, -8, and arrest of cell cycle at G2/M-phase and causes apoptosis mediated by death receptor 5 (DR5). CYD-6-28 is also shown to have the potential to inhibit Akt, cyclin D1, FLIPL, STAT3, and XIAP. *Phaleria macrocarpa* (Scheff.), one of the Indonesian traditional medicine, has lavonoid, lavonol, saponin, phenol, and terpenoid as its derivatives. Methanol extracts of *P. macrocarpa* have strong cytotoxic effect, which is comparable to standard gallic acid. Gallic acid is proven to be cytotoxic to the transformed cell lines of breast, cervix, esophageal, colon, brain, and gastric cancers. Through induction of ROS, the ethanolic extract obtained from mango seed may be apoptotic to the MCF-7 cells. Lavone, chloroform-extracted luteolin from *Eclipta alba* (Bhringraj), showed selective activation of intrinsic apoptosis, caspase-9 inhibition, sensitization of heat shock protein 60 (Hsp60), a proapoptotic molecular chaperone, and downregulation of antiapoptotic protein XIAP in MDA-MB-231 and MCF-7 cells [71].

6.10.1 Cervical Cancer

In U14 cervical carcinoma cells in mice exposed to betulinic acid as a food supplement have shown antitumor activity. Ethanolic extract of Conium maculatum (hemlock) inhibits the proliferation of cells within 48 hours by arresting the cell cycle at sub-G stage. Methanol extracts and ethyl acetate of M. pajang kernel and chloroform and crude petroleum ether extracts of the stem bark, respectively, have produced strong cytotoxic activity against the HeLa cervical carcinoma cell line [72]. Oridonin has the potential to inhibit the P13K-Akt pathway in HeLa cell line. Emodin and curcumin have the ability to downregulate P-Smad3, Smad4, and TGF-β receptor II, which, in turn, suppress the migration and invasion induced by TGF of cell lines in HeLa and SiHa cervical cancers [71]. Curcumin and emodin suppresses the CyclinD1, p15, p16, p21, p27, CDK6, and Pin1 expression by upregulating the Bax:Bcl-2 ratio, thereby suppressing the Wnt/β-catenin in HeLa cells. SiHa cells were chosen for TGF-β resistance, as they lack remarkable growth inhibition when treated with TGF-β [71].

The phenolic compound naringin changes GM3 ganglioside, thereby affecting the signaling of EGFR and resulting in the inhibition of HeLa [71]. Taxifolin from Siberian larch is shown to possess a synergistic effect when used with a diterpenoid

lactone, andrographolide, against HeLa cells by diminishing protective autophagy induced by andrographolide, whereas it increases the mitochondrial outer-membrane permeability and also caspase-dependent and -independent cell death. Various studies have shown that Withaferin A, from *Withania somnifera*, given in vivo to athymic nude mice models (a murine strain bearing spontaneous deletion in the Foxn1 gene that causes deteriorated or absent thymus), reduced CaSki–HPV type 16 and 18 positive cervical tumor cell lines effectively [71].

6.10.2 Ovarian Cancer

There are different types of ovarian cancer based on the type of cell from which they originate, among which epithelial ovarian cancer (EOC) is the most common and also the most lethal of all gynecological malignancies. The methanol extract obtained from an original Indonesian plant *P. macrocarpa* has shown excellent cytotoxic effect against SKOV-3 cells in ovarian cancer. Withaferin A is a steroidal lactone derived from *Acnistus arborescens*, *Withania somnifera*, and other members of Solanaceae family. It has the potential to downregulate Notch1 and total and phosphorylated Akt, Cdc25C, and bcl-2 proteins, thereby inducing early cell death by apoptosis and cell cycle arrest at G2/M phase. Thus, it inhibits adenocarcinoma cell lines CaOV3 and SKOV3 of the ovary [11,73].

6.11 SUMMARY AND FUTURISTIC VIEWPOINT

Tumor generation is a process that involves multiple steps that are controlled by various cell communication pathways and becomes the target or site of action for many anticancer agents. Nutraceuticals have the advantages of being inexpensive, safe, and readily available and also have multiple targets for their action and has already reached from the counter to the bedside in the treatment of many cancers.

However, sufficient consideration must be taken into account to explain the following important points. First, there are various agents that can inhibit and potentiate tumor generation, which depends upon the cell type, stimulus, and NF-κB subunit involved it, and induce apoptosis under special circumstances [4]. Second, even most of the studies have suggested that nutraceuticals have the ability to selectively destroy the cancer cells; some studies have stated that they can also kill normal cells. Third, preclinical conditions, either in vitro or in vivo have only been conducted to determine the efficacy of most nutraceuticals. Whether they have beneficial effects on humans remains a mystery. So far, the success has been restricted to a few molecules and to the treatment of few cancers. Fourth, better information on the pathways involved in mediating the progression of tumor in various conditions is necessary as resistance to chemoprevention is emerging. Fifth, in some instances, pathological changes are associated with the disruption of a particular pathway, as resveratrol's antiangiogenic trait affects both pathological angiogenesis and physiological angiogenesis. Sixth, in many cases, it is possible that the effects shown in the experimental settings might be due to an intermediate formed during the process and not the nutraceutical itself. Finally, the poor bioavailability and low potency of these nutraceuticals create further difficulties to the scientists [4].

Further studies need to be done to determine if the whole plant, the naturally derived phytochemical component, semisynthetic phytochemical, or the completely synthetic one, has the most efficiency as a nutraceutical. Similarly, the dosage form and the route of administration show a lot of variation in effectiveness. The oral bioavailability of nutraceuticals is limited due to the effect of many factors, such as hydrophobicity of the herbal ingredients and high dose levels. Improving the bioavailability of such nutraceutical formulations is a challenge and warrants research in this area [71]. Nanoencapsulated EGCG shows more efficacy than nonencapsulated EGCG. Berberine and curcumin are most effective in the encapsulated form, while kaempferol significantly losses its efficacy when encapsulated. There are trials of withaferin A for the treatment of adenocarcinoma of the ovary, and successful in vitro SKOV3 and CaOV3 ovarian cell line studies are in progress [71]. In order to assess the efficacy and tolerability of *M. pajang*, *C. maculatum*, tangeretin, EGCG, curcumin, oleanolic acid, resveratrol, withaferin A, melatonin enterolactone, tripterine, kaempferol, and 5-AcTMF, further trials and studies should be carried out against cancers of breast, colon, blood, myeloma, and NSCLC, A549, A375, HeLa, WRL68, and HepG2 cell lines. Some of the promising antimetastatic drug candidates like γ-linolenic acid, silibinin, ganoderic acids, *Ganoderma lucidum* polysaccharides cordycepin from *Cordyceps millitaris*, Yangzheng Xiaoji, DME25, and EPA are in various phases of clinical trial [71].

Developing synthetic analogues of nutraceuticals can bring some solution to tackle the issues relating to low potency and poor bioavailability. For example, the potency of synthetic curcumin analogue EF24 was 10-fold greater than that of natural curcumin [4]. In this context, it is pretty clear that we need even better information and understanding of nutraceuticals for their efficacious use in cancer prevention [4].

REFERENCES

1. The American Cancer Society; cancer facts and statistics. https://www.cancer.org/research/cancer-facts-statistics.html.
2. Doll, R., Peto, R. The causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today. *Journal of the National Cancer Institute*. 1981; 66, 1191–1308.
3. Anand, P., Sundaram, C., Jhurani, S., Kunnumakkara, A.B., Aggarwal, B.B. Curcumin and cancer: An "old-age" disease with an "age-old" solution. *Cancer Letters*. 2008; 267, 133–164.
4. Gupta, S.C., Kim, J.H., Prasad, S., Aggarwal, B.B. Regulation of survival, proliferation, invasion, angiogenesis, and metastasis of tumor cells through modulation of inflammatory pathways by nutraceuticals. *Cancer Metastasis Reviews*. 2010; 29:405–434.
5. Ferlay, J., Shin, H.R., Bray, F., Forman, D., Mathers, C., Parkin, D.M. Cancer incidence and mortality worldwide: IARC Cancer Base No. 10. *International Agency for Research on Cancer*. GLOBOCAN 2008 v1.2.2010. http://globocan.iarc.fr/.
6. Weiderpass, E., Labrèche, F. Malignant tumors of the female reproductive system safety and health at work. *Occupational Cancers*. 2012; 3:166–180. doi:10.5491/SHAW.2012.3.3.166.
7. Islam, M.T. Treatment strategies of cancers in female reproductive system. *EC Orthopaedics*. 2017; 7: 135–139.
8. Hendrickson, M., Ross, J., Eifel, P., Martinez, A., Kempson, R. Uterine papillary serous carcinoma: A highly malignant form of endometrial adenocarcinoma. *American Journal of Surgical Pathology*. 1982; 6:93–108.

9. Sonoda, S. Molecular biology of gynecological cancer (Review). *Oncology Letters*. 2016; 11:16–22.
10. Xie, B. et al. Benzyl Isothiocyanate potentiates p53 signaling and antitumor effects against breast cancer through activation of p53-LKB1 and P73-LKB1 axes. *Scientific Reports*. 2017; 7:40070.
11. Herbst, A.L., Ulfelder, H., Poskanzer, D.C. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. *New England Journal of Medicine*. 1971; 284:878–881.
12. Tavassoli, F.A., Devilee, P. International Agency for Research on Cancer (IARC). *IARC WHO Classification of Tumours Series, vol. 4. Pathology and Genetics of Tumours of the Breast and Femal Genital Organs*. Lyon, France: IARC; 2003. 432p.
13. Matsuo, K. et al. Feto-maternal outcome of pregnancy complicated by vulvar cancer a systematic review of literature. *European Journal of Obstetrics and Gynecology and Reproductive Biology*. 2014; 179:216–223.
14. Gwyn, K. Children exposed to chemotherapy in utero. *Journal of the National Cancer Institute. Monographs*. 2005; 34:69–71.
15. Woodard, T.L., Bolcun-Filas, E. Prolonging reproductive life after cancer: The need for fertoprotective therapies. *Trends Cancer*. 2016; 2.5:222–223.
16. Emons, G., Schally, A.V. The use of luteinizing hormone–releasing hormone agonists and antagonists in gynecological cancers. *Human Reproduction*. 1994; 9:1364–1379.
17. Grundker, C., Gunthert, A.R., Westphalen, S., Emons, G. Biology of the gonadotropin-releasing hormone system in gynecological cancers. *European Journal of Endocrinology*. 2002; 146:1–14.
18. Srkalovic, G., Schally, A.V., Wittliff, J.L., Day, T.G. Jr, Jenison, E.L. Presence and characteristics of receptors for [D-Trp6] luteinizing hormone releasing hormone and epidermal growth factor in human ovarian cancer. *International Journal of Oncology*. 1998; 12: 489–498.
19. Fekete, M., Wittliff, J.L., Schally, A.V. Characteristics and distribution of receptors for [D-Trp6]-luteinizing-hormone–releasing hormone, somatostatin, epidermal growth factor and sex steroids in 500 biopsy samples of human breast cancer. *Journal of Clinical Laboratory Analysis*. 1989; 3:137–147.
20. Kalra, E.K. Nutraceutical—Definition and introduction. *AAPS PharmSci*. 2003; 5(3):Article 25.
21. DeFelice, S.T. The nutraceutical revolution: Its impact on food industry R&D. *Trends in Food Science & Technology*. 1995; 6:59–61.
22. Schmitt, J., Ferro, A. Nutraceuticals: Is there good science behind the hype? *British Journal of Clinical Pharmacology*. 2013; 75:3,585–587.
23. Kalia, A.N. *Textbook of Industrial Pharmacognocy*. New Delhi, India: CBS Publisher and Distributor; 2005. pp. 204–208.
24. Chauhan, B., Kumar, G., Kalam, N., Ansar, S.H. Current concepts and prospects of herbal nutraceutical: A review. *Journal of Advanced Pharmaceutical Technology & Research*. 2013; 41.
25. Lee, K.W., Bode, A.M., Dong, Z. Molecular targets of phytochemicals for cancer prevention. *Nature Reviews Cancer*. 2011; 11:211–218.
26. Loeb, L.A., Harris, C.C. Advances in chemical carcinogenesis: A historical review and prospective. *Cancer Research*. 2008; 68:6863–6872.
27. Del Rio, D., Rodriguez-Mateos, A., Spencer, J.P., Tognolini, M., Broges, G., Crozier, A. Dietary (poly)phenolics in human health: Structures, bioavailability, and evidence of protective effects against chronic diseases. *Antioxidants & Redox Signaling*. 2013; 18:1818–1892.

28. Moga, M., Dimienescu, O.G., Arvatescu, C.A., Mironescu, A., Dracea, L., Ples, L. The role of natural polyphenols in the prevention and treatment of cervical cancer—An overview. *Molecules*. 2016; 21(8):1055.
29. Bahadoran, Z., Karimi, Z., Houshiar-rad, A., Mirzayi, H.R., Rashidkhani, B. Dietary phytochemical index and the risk of breast cancer: A case control study in a population of Iranian women. *Asian Pacific Journal of Cancer Prevention*. 2013; 14: 2747–2751.
30. Takagi, A., Kano, M., Kaga, C. Possibility of breast cancer prevention: Use of soy isoflavones and fermented soy beverage produced using probiotics. *International Journal of Molecular Sciences*. 2015; 16:10907–10920.
31. Woyengo, T.A., Ramprasath, V.R., Jones, P.J.H. Anticancer effects of phytosterols. *European Journal of Clinical Nutrition*. 2009; 63:813–820.
32. Aiyer, H.S., Warri, A.M., Woode, D.R., Hilakivi-Clarke, L., Clarke, R. Influence of berry-polyphenols on receptor signaling and cell-death pathways: Implications for breast cancer prevention. *Journal of Agricultural and Food Chemistry*. 2012; 60:5693–5708.
33. Chen, S.S., Michael, A., Butler-Manuel, S. Advances in the treatment of ovarian cancer—A potential role of anti-inflammatory phytochemicals. *Discovery Medicine*. 2012; 13:7–17.
34. McCann, S.E., Freudenheim, J.L., Marshall, J.R., Graham, S. Risk of human ovarian cancer is related to dietary intake of selected nutrient, phytochemicals and food groups. *The Journal of Nutrition*. 2003; 133:1937–1942.
35. Filomeno, M., Bosetti, C., Bidoli, E., Levi, F., Serraino D, Montella, M., La Vecchia, C., Tavani, A. Mediterranean diet and risk of endometrial cancer: A pooled analysis of three Italian case-control studies. *British Journal of Cancer*. 2015; 112:1816–1821.
36. Moga, M.A., Dimienescu, O.G., Arvatescu, C.A., Mironescu, A., Dracea, L., Ples, L. The role of natural polyphenols in the prevention and treatment of cervical cancer—An overview. *Molecules*. 2016; 21:E1055.
37. Wang, Z. et al. Broad targeting of angiogenesis for cancer prevention and therapy. *Seminars in Cancer Biology*. 2015; 35:S224–S243.
38. Sayeed, M.A. et al. Use of potential dietary phytochemicals to target miRNA: Promising option for breast cancer prevention and treatment? *Journal of Functional Foods*. 2017; 28:177–193.
39. Acharya, A., Das, I., Singh, S., Saha, T. Chemopreventive properties of indole-3-carbinol, diindolylmethane and other constituents of cardamom against carcinogensis. *Recent Patents on Food, Nutrition and Agriculture*. 2010; 2:166–177.
40. Nwanodi, O.B. Nutraceuticals: Chemoradiation sensitizers and adverse effect resolvers. *Herbal Medicine*. 2017; 3:2.
41. Sen, R., Baltimore, D., Inducibility of kappa immunoglobulin enhancer-binding protein Nf-kappa B by a posttranslational mechanism. *Cell*. 1986; 47(6):921–928.
42. Baldwin Jr., A.S., Series introduction: The transcription factor NF-kappaB and human disease. *The Journal of Clinical Investigation*. 2001; 107(1):3–6.
43. Barnes, P.J., Karin, M. Nuclear factor-kappaB: A pivotal transcription factor in chronic inflammatory diseases. *New England Journal of Medicine*. 1997; 336(15):1066–1071.
44. Perkins, N.D.NF- kappa B: Tumor promoter or suppressor? *Trends in Cell Biology*. 2004; 14(2):64–79.
45. Tilborghs, S., Corthouts, J., Verhoevena, Y., Arias, D., Rolfoa, C., Trinha, X.B., van Dama, P.A. The role of nuclear factor-kappa B signaling in human cervical cancer. *Critical Reviews in Oncology/Hematology*. 2017; 120:141–150.
46. Kalvin, Q.T., Tin, A.S., Firestone, G.L. Artemisinin triggers a G1 cell cycle arrest of human Ishikawa endometrial cancer cells and inhibits cyclin dependent kinase-4 promoter activity and expression by disrupting NF-kB transcriptional signaling. *Anticancer Drugs*. 2014; 25(3):270–281.

47. Kabrun, N., Enrietto, P.J. The Rel family of proteins in oncogenesis and differentiation. *Seminars in Cancer Biology*. 1994; 5:103–112.
48. Aggarwal, B.B., Gehlot, P. Inflammation and cancer: How friendly is the relationship for cancer patients? *Current Opinion in Pharmacology*. 2009; 9:351–369.
49. Karin, M. Nuclear factor-kappaB in cancer development and progression. *Nature*. 2006; 441:431–436.
50. Joyce, D., Albanese, C., Steer, J., Fu, M., Bouzahzah, B., Pestell, R.G. NF-kappaB and cell-cycle regulation: The cyclin connection. *Cytokine Growth Factor Reviews*. 2001; 12:73–90.
51. Alvero, A.B. Recent insights into the role of NF-κB in ovarian carcinogenesis. *Genome Medicine*. 2010; 2:56.
52. Xiao, X. et al. Inhibition of nuclear factor-kappa B enhances the tumor growth of ovarian cancer cell line derived from a low-grade papillary serous carcinoma in p53-independent pathway. *BMC Cancer*. 2016; 16:582.
53. Tilborghs, S. et al. The role of nuclear factor-kappa B signaling in human cervical cancer. *Critical Reviews in Oncology/Hematology*. 2017; 120:141–150.
54. Saegusa, M., Hashimura, M., Kuwata, T. Pin1 acts as a modulator of cell proliferation through alteration in NF-kappaB but not beta-catenin/TCF4 signalling in a subset of endometrial carcinoma cells. *The Journal of Pathology*. 2010; 222:410–420.
55. Gupta, S.C., Sundaram, C., Reuter, S., Aggarwal, B.B. Inhibiting NF-kappaB activation by small molecules as a therapeutic strategy. *Biochimica et Biophysica Acta*. 2010; 1799:775–787.
56. Singh, S., Aggarwal, B.B. Activation of transcription factor NF-kappa B is suppressed by curcumin (diferuloyl- methane) [corrected]. *The Journal of Biological Chemistry*. 1995; 270:24995–25000.
57. Shishodia, S., Aggarwal, B.B. Guggulsterone inhibits NF-kappaB and IkappaBalpha kinase activation, suppresses expression of anti-apoptotic gene products, and enhances apoptosis. *The Journal of Biological Chemistry*. 2004; 279:47148–47158.
58. Chaturvedi, M.M., Kumar, A., Darnay, B.G., Chainy, G.B., Agarwal, S., Aggarwal, B.B. Sanguinarine (pseudo-chelerythrine) is a potent inhibitor of NF-kappaB activation, IkappaBalpha phosphorylation, and degradation. *The Journal of Biological Chemistry*. 1997; 272:30129–30134.
59. Choi, K.C. et al. Gallic acid suppresses lipopolysaccharide- induced nuclear factor-kappaB signaling by preventing RelA acetylation in A549 lung cancer cells. *Molecular Cancer Research*. 2009; 7:2011–2021.
60. Campbell, C.T., Prince, M., Landry, G.M., Kha, V., Kleiner, H. EPro-apoptotic effects of 1′-acetoxychavicol acetate in human breast carcinoma cells. *Toxicology Letters*. 2007; 173:151–160.
61. Gu, H. et al. Gambogic acid reduced bcl-2 expression via p53 in human breast MCF-7 cancer cells. *Journal of Cancer Research and Clinical Oncology*. 2009; 135:1777–1782.
62. Sung, B., Park, B., Yadav, V.R., Aggarwal, B.B. Celastrol, a triterpene, enhances TRAIL-induced apoptosis through the down-regulation of cell survival proteins and up- regulation of death receptors. *The Journal of Biological Chemistry*. 2010; 285:11498–11507.
63. Ahmad, A. et al. Apoptosis-inducing effect of garcinol is mediated by NF-kappaB signaling in breast cancer cells. *Journal of Cellular Biochemistry*. 2010; 109:1134–1141.
64. Sung, B., Ahn, K.S., Aggarwal, B.B. Noscapine, a benzylisoquinoline alkaloid, sensitizes leukemic cells to chemotherapeutic agents and cytokines by modulating the NF-kappaB signaling pathway. *Cancer Research*. 2010; 70:3259–3268.
65. Kuerbitz, S.J., Plunkett, B.S., Walsh, W.V., Kastan, M.B. Wild-type p53 is a cell cycle checkpoint determinant following irradiation. *Proceedings of the National Academy of Sciences of the United States of America*. 1992; 89:7491–7495.

66. Murillo, G., Peng, X., Torres, K.E., Mehta, R.G. Deguelin inhibits growth of breast cancer cells by modulating the expression of key members of the Wnt signaling pathway. *Cancer Prevention Research* (Philadelphia, PA). 2009; 2:942–950.
67. Way, T.D., Lin, J.K. Role of HER2/HER3 coreceptor in breast carcinogenesis. *Future Oncology*. 2005; 1:841–849.
68. Yi, T. et al. Gambogic acid inhibits angiogenesis and prostate tumor growth by suppressing vascular endothelial growth factor receptor 2 signaling. *Cancer Research*. 2008; 68:1843–1850.
69. McLay, J.S., Stewart, D., George, J., Rore, C., Heys, S.D. Complementary and alternative medicines use by Scottish women with breast cancer. What, why and the potential for drug interactions? *European Journal of Clinical Pharmacology*. 2012; 68:811–819.
70. Zarogoulidis, P. et al. Use of proteins as biomarkers and their role in carcinogenesis. *Journal of Cancer*. 2015; 6:9–18.
71. Nwanodi, O.B. Nutraceuticals: Curative integrative cancer treatment. *Alternative and Integrative Medicine*. 2017; 6:240.
72. Bai, L.Y., Chiu, C.F. A triterpenoid from wild bitter gourd inhibits breast cancer cells. *Scientific Reports*. 2016; 6:22419.
73. Zhang, X., Samadi, A.K., Roby, K.F., Timmermann, B., Cohen, M.S. Inhibition of cell growth and induction of apoptosis in ovarian carcinoma cell lines CaOV3 and SKOV3 by natural withanolide Withaferin A. *Gynecologic Oncology*.2012; 124:606–612.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

7 Mechanism and Role of Probiotics in Suppressing Bowel Cancer

Aaishwarya B. Deshmukh,
Jayvadan K. Patel, and Bharat Mishra

CONTENTS

7.1 INTRODUCTION

Probiotics are the "live microorganisms" and, of course, nondigestible food ingredient. They are given in sufficient quantities to achieve health benefit by selectively exciting the growth and activity of restricted bacterial varieties already present in the intestines [1]. They were initially employed to recover the health of animals and humans by intonation of the intestinal microbiota [2]. Currently, lactobacilli and bifidobacteria strains are used to reduce the risk and treat gastrointestinal (GI) infections [3]. Apart from its role in protection of gut, probiotics also exercise other health benefits like improvement in lactose intolerance, escalation of humoral immune responses, recovery of postmenopausal symptoms by biotransformation of isoflavones, bioactive peptides conversions, and dropping serum cholesterol concentrations [4,5]. Prebiotics on other hand are the types of dietary fiber which are neither hydrolyzed nor absorbed in the GI tract. They selectively induce the population of single or more potentially advantageous intestinal bacteria known as probiotics by providing *food* and creating an environment suitable for probiotics to flourish [6]. Some other synbiotics, which consist of combination of probiotics and prebiotics, are also used.

7.1.1 The Intestinal Microbiota

The location of colonization of GI microbiota is accountable for changes in the quantity and quality of microbes. There are numerous varieties of commensal bacteria residing in intestine. Only 30% of the total microorganisms can be characterized by using microscopic observation. With advancement in methods, utilization of molecular tools has indicated that the widely held dominant bacteria found in fecal microbiota of a person are highly unambiguous to that particular individual. As far as the concentration of microbes is concerned, stomach and small intestine contain only few species, whereas colon has a multifaceted and active microbial ecosystem containing major bacteria up to 10^{12} CFU·g^{-1}, with small intestine having 10^4 to 10^7 CFU·g^{-1}, while stomach only has 10 at 10^2 CFU·g^{-1}. Thus, if the total number of intestinal bacteria are considered, they would be 10 times the number of bacterial cells in the human body. rRNA sequencing studies have discovered 40,000 strains of intestinal bacteria, both cultivable and noncultivable [7]. The intestinal microbiota genome are estimated to contain 100 times more genes than the whole human genome [8]. Thus, intestine displays a symbiotic connection in maintaining homeostasis by modifying metabolism, growth, and immunity.

The chief function of the microbiota of intestine is to use energy from the food before it is lost through excretion. Some food stuffs like polysaccharides, which are unable to get absorbed in the colon, are metabolized by microorganisms, leading to the formation of propionate and butyrate, which are short-chain fatty acids (SCFA), whose formation is dependent on the availability of various substrates responsible for fermentation [9]. SCFA maintains an epithelial layer, which obtains almost 70% of its butyrate through oxidation, which is a trophic factor for integral tissues. On the brighter side, it has also been observed that butyrate lessens the bowel cancer hazard by inhibiting the genotoxic activity of nitrosamines and hydrogen peroxide. It has also been postulated to tempt apoptosis, differentiation, and cell cycle that may

retard bowel cancer. SCFA also attenuates the expression of different types of cytokines and deactivates nuclear factor NF-κB. Apart from this, the other role of microbiota is to digest inadequately digested nutrients, alter bile acids, and supplement food [10]. The microbiota, particularly nonpathogenic commensal microbes, warrant the effectiveness of GI motility, growth, and development of intestine, development of immunity, and strengthening of the mucus barrier. Scientists have executed advancement in characterization of GI microbiota that may add to the expansion of inflammatory bowel diseases as well as bowel cancer. Lately, many intestinal simulators have been developed for studying the intestinal microbial ecosystem and its interactions [11]. There are abundant lines of evidence that have shown an association between several common disorders as well as chronic diseases like cancer and change in gut microbiota. Thus, using the beneficial bacteria in the form of probiotics can resume an equilibrium in disease treatment and prevention [12], with inflection of deranged native microbiota forming the foundation of probiotic therapy [13]. Probiotic consumption leads to an enhancement of the intestinal well-being by regulating the microbiota, improving body's defense mechanisms, creating and augmenting the nutrient bioavailability, reducing signs of lactose intolerance, and dropping the danger of additional ailments (Figure 7.1) [14].

Treatment strategies that work on bacterial substitution are gaining importance because of the fact that there is a swift appearance of pathogenic microbial strains with antibiotic resistance and the side effects of antibiotic treatment on the defensive microbial flora, which increases the jeopardy of infection in the form of opportunistic infections [15]. Novel probiotic with disease-specific role can be developed with advanced understanding about different aspects of intestinal microbiota, immune

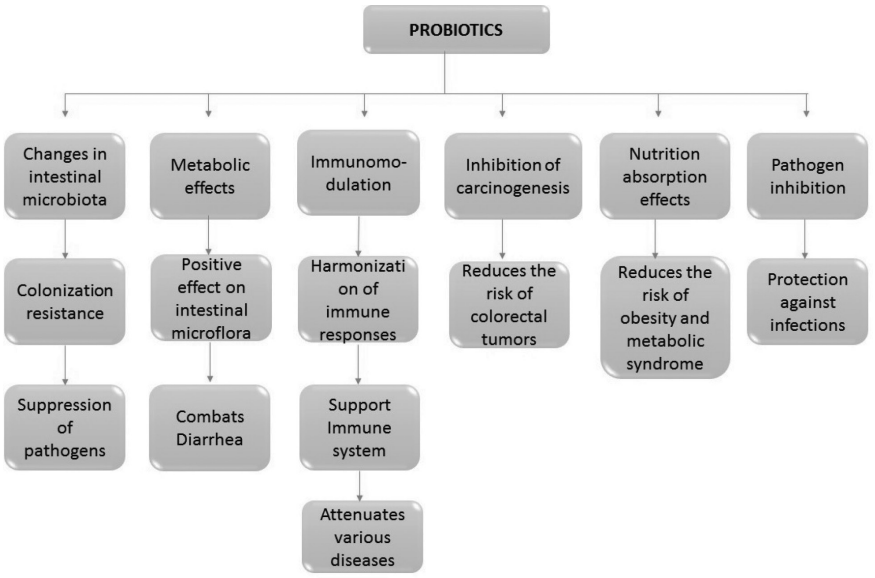


FIGURE 7.1 Health attributes of probiotics.

system, and genotypic traits and would facilitate the understanding of when can probiotics be used and how they may affect specific pathological states. However, a probiotic to be used in individuals should go through clinical trials preceded by preclinical studies for the authentication of appropriateness, well-being, and beneficial effects on human via expansion of functional foods [14]. The anticancer properties of probiotic bacteria have lately become the focus of research. The fundamental mechanisms of their anticancer effects include, but are not limited to, repression of microbial intensification involved in the manufacture of different carcinogenic and mutagenic substances, modification of metabolism of carcinogenic substances, and fortification of DNA from oxide damage and immune system regulation of body [16]. Compelling evidence has shown that the use of probiotics leads to change in the expression of different genes participating in cell death and apoptosis, invasion and metastasis, cancer stem cell maintenance, and cell cycle control. Supplementary studies have also postulated modulatory effects of probiotics on the cancer-related signaling pathways in a cell-type-specific manner. Cell line studies have assessed their antiproliferative effects in many studies [17–19]. A study has shown that conventional fermented milk product inhibits the in vitro proliferation of MCF-7 breast tumor cells but had no effect on normal mammary epithelial cells, which entails that probiotic prompts the responses specifically detected in tumor cells. The mechanisms by which probiotics decreases the invasion and metastasis, considered as important hallmark of malignant cells, have been studied in cancer cells through cell line studies, animal models, and human studies. Diverse and complex genetic or epigenetic aberrations as well as extrinsic signals relayed from malignant cell microenvironment are responsible for these observed invasion and metastasis in cancer [20].

7.1.2 Bowel Cancer or Colorectal Cancer (CRC)

Bowel cancer or CRC represents malignancy of the GI tract. Diet has an essential function in the pathophysiological mechanism of bowel cancer, as research on migrants has demonstrated that differences in dietary habits and lifestyle are responsible for the occurrence of bowel cancer rather than racial factors. Ample evidence supports the notion that a disproportionate intestinal microflora is responsible for the link between diet and bowel cancer. The "normal" gut microflora are the microbes that colonize the GI tract at birth and have physiological, morphological, and genetic features that allow it to reproduce in scrupulous circumstances at definite spots and coexist with additional microorganisms and slow down the development of pathogenic microbes. There is a marked association between the type of diet and risk factors associated with bowel cancer, which is observed from various epidemiological studies. Red meat and animal fat are also connected to amplified risk of colorectal cancer initiation and progression, while fruits and vegetables shield against bowel cancer [21].

Colorectal cancer characterizes the foremost community health problem. Chemotherapy and radiotherapy are adjuvant strategies for the treatment of colorectal tumor; however, they differ in their success rates in terms of reappearance and survival after disease. Moreover, they may present few adverse effects like an amplified fear of infections, hair loss, gastric problems, and so on. Diet

intercession and utilization of supplements that occur in nature and are biologically active in nature are being widely studied as preventive steps to protect from the risks of colonic carcinogenesis with mechanisms postulated as a decline in the action of numerous carcinogenic bacteria and their desmutagenic and anticarcinogenic activities. Prebiotic is also associated with enhanced bowel function and distal colon metabolism, as well as abridged risk of colorectal cancer. In a study of rats treated with carcinogens showed lower tumor numbers when rats were fed cereal bran, the postulated mechanism of which was found to be the formation of short-chain fatty acids (SCFA), particularly butyrate, by means of the fermentation of gut flora prebiotics [22]. The development of bowel cancer is influenced by multiple factors like the genotypic and phenotypic makeup of the body, environmental factors (lifestyle, dietary habits), and various exogenous stimuli [23]. Microbial population in the intestine is one of the essential determinants of the general well-being of humans. Any modification deemed favorable to the composition of microbiota or a change in its metabolic activity might embody an approach in health improvement and thus reduce the risk of bowel cancer development. Use of probiotics can be useful in fulfilling these criteria. The anticancer effects of probiotics in preclinical studies as well as in vitro research studies are abundant; nevertheless in clinical trials protective role of probiotics in the initial phases have been postulated. There is a requirement to determine the long-term effects of probiotics in the incidences of bowel cancer and changes in incidences of thereof. However, challenges for development of probiotics as therapy includes selection of the suitable microbes, control in food intake, the monitoring of dosing frequency and timings as well as monitoring biomarkers during clinical studies [24]. Additional studies are required for better understanding of bowel cancer development.

7.1.3 Essential Properties for Effective and Successful Probiotics

1. It should survive at the active location.
2. It should have capacity of proliferation and colonization at this definite position for maximum activity.
3. It should have the ability to withstand the immunogenic system.
4. It should be nonpathogenic, nonallergic, or nonmutagenic/carcinogenic.
5. It should have short jeopardy of inducing or is linked with the origin of disease and regarded as safe.
6. It should have survival and growth in in vivo settings of the preferred site of administration with human origin.
7. It should endure low pH values and lofty concentrations of both conjugated and deconjugated bile acids.
8. It should be scientifically attuned with the processes of food manufacturing.
9. It must exhibit the distinguishing sensory attributes of the conventional food stuff.

Although the precise mechanism by which microbial species play principal part in these beneficial properties is still not known, it is now an established fact that these indigenous microbes are highly host specific, location specific, and multifaceted in

TABLE 7.1
Probiotic Strains Used in Various Commercial Products Available in Market

Sr. No.	Strain Employed	Source
1	*Lactobacillus acidophilus* NCFM	Rhodia Inc. (Madison, WI)
2	*L. acidophilus* DDS-1	Nebraska Cultures, Inc.
3	*L. acidophilus* SBT-2062	Snow Brand Milk Products Co. Ltd. (Tokyo, Japan)
4	*L. acidophilus* LA-1	Chr. Hansen. Inc. (Milwaukee, WI)
5	*Lactobacillus casei* Shirota	Yakult (Tokyo, Japan)
6	*L. johnsonii* La 1	Nestle (Lausanne, Switzerland)
7	*Lactobacillus rhamnosus* GG	Valio Dairy (Helsinki, Finland)
8	*L. rhamnosus* GR-1	Urex Biotech (Ontario, Canada)
9	*L. rhamnosus* 271	Probi AB (Lund, Sweden)
10	*L. rhamnosus* LB21	Essum AB (Umea, Sweden)
11	*Bifidobacterium lactis* Bb-12	Ghr. Hansen Inc. (Milwaukee, WI)
12	*Bifidobacterium longum* BB536	Morinaga Milk industry Co. Ltd. (Zama-city, Japan)
13	*L. paracasei* CRL 431	Chr. Hansen. Inc. (Milwaukee, WI)

Source: Nagpal, R. et al., *FEMS Microbiol. Lett*., 334, 1–15, 2012.

composition. Numerous probiotics are available commercially (Table 7.1). Some of the benefits of probiotics in human health are their role in cancer and their anticancer properties.

7.1.3.1 Anticarcinogenic Properties

In 1984, Goldin and Gorbach showed that few food and antibiotics lowered the production of intestinal carcinogens and lessened the chemically induced tumors [25], which was in continuation with their previous research of 1980 when they found that *L. acidophilus* in food lessens the frequency of chemically induced intestinal cancer in rats through intestinal microbial communities with a potential mechanism of the inhibition of colon bacteria specific enzymes, which converted procarcinogens molecules to more proximal carcinogens [26,27]. Same caution could be extended by examining the probiotics for their capacity in inhibiting the development of organisms usually found in the flora. Some probiotic bacterial strains bind to aflatoxin B1 (AFB1) and neutralize it in vivo, sinking the bioabsorption of the toxin from the GI tract and leading to genetic alteration in the expression of p53 tumor suppressor gene

and ras protooncogenes, and thus protecting from hepatitis B virus. In yet another study, probiotic *Bifidobacterium longum*, when given along with diet to rats, showed potential anticancer action on mucosal cells of the intestine by inhibiting the level of expression of ras-p21 and cell proliferation [28].

The gene expression concerned with the immunologic and inflammatory responses were affected by the up- and downregulation of 334 and 92 genes, correspondingly determined by Lactobacillus GG administration. The genes that were found by different studies were nitric oxide synthase 1, transforming growth factor β, cytokines, tumor necrosis factor family members, and defensin α-1. Other mechanism affected were apoptotic cell death, growth and differentiation in cells, cell–cell signaling involving intracellular adhesion molecules and integrins as endogenous stimulators, cell adhesion such as cadherins and signal transduction mechanisms, and transcriptional changes [29].

Normal gut flora manipulates carcinogenesis by synthesizing various enzymes that convert precarcinogens into active carcinogens. The enzymes exhibiting the action are nitroreductase, glycosidase, azoreductase, B-glucuronidase, among others. Several studies have shown that decreased fecal content of these enzymes and secondary bile salts and reduced absorption of injurious mutagenic substances contribute toward bowel cancer by the use of probiotics [30]. One such study showed that *Lactobacillus acidophilus* and *L. casei* supplementation facilitated a decline in the intensity of the aforementioned enzymes, while in mice same effects were exerted by Lactobacillus GG administration. Many hypotheses have been postulated on the molecular mechanism of inhibiting colon cancer, like augmenting the immunological responses in host, varying the metabolic activity of the colon flora populations, binding and debasing carcinogenic materials, forming antimutagenic substances, and shifting the physiochemical settings of bowel [26,27].

7.1.3.2 Defensive Functions of Probiotics on Bowel Cancer

Compelling research reported that 20% of germ-free animals showed chemically induced bowel cancer compared with 93% of their complementary with a normal intestinal microbial flora, indicating that broad inhabitants of intestinal bacteria are linked to the commencement of cancer through formation of carcinogenic molecules, co-carcinogens, or pro-carcinogenic substances. Reddy et al. [31], using azoxymethane-induced aberrant crypt foci in rats, found that a stimulated growth of bifidobacteria leads to the attenuation of colon cancer attributed to the pH-lowering effect, which leads to attenuation of aberrant crypt foci and crypt diversity that repressed development of *E. coli* and clostridia. Moreover, postulations also suggested inflection of enzymes of bacteria such as β-glucuronidase, which alters pro-carcinogenics to contiguous carcinogenic substances, which decreased the growth of such pathogenic microorganisms.

Probiotics such as *Bifidobacterium* have also shown to produce metabolites influencing the mixed-function P450s enzymes and consequently the translation of azoxymethane from contiguous to definitive carcinogen and thus lessen the danger of bowel cancer. These studies suggest that probiotics repress colon cancer via different mechanisms. Previous studies on binding properties of probiotics have suggested that mutagens bind to the cell wall of probiotics. Many studies have shown protective

effects of probiotics by altering the differentiation process of tumor cells as well. Baricault et al. [32] studied the outcome of fermented milks on bowel cancer using a cultured human colon cancer cell line (HT-29), where milk was fermented with individual strains of *Lactobacillus helveticus*, *Bifidobacterium*, *L. acidophilus*, or a mix of *Streptococcus thermophilus* and *L. delbrueckii* subsp. *Bulgaricus*; subsequently, HT-29 cells were added into the fermented milk to find that 10%–50% of the HT-29 cells showed a decrease in growth by increasing dipeptidyl peptides, explicit marker for HT-29 cell differentiation, suggesting that cancer cells enter a differentiation process, leading to their lower growth.

The effect of *B. longum* on carcinogenesis in male weanling F344 rats for 40 weeks was studied by Singh et al. [33], which confirmed that administration of lyophilized cultures of *B. longum* in the diet led to repression of colon tumor occurrence and tumor multiplicity and attenuated tumor degree. Further analysis on transitional biomarkers discovered that the intake of *B. longum* inhibited azoxymethane-induced cell proliferation by reducing the activity of ornithine decarboxylase (ODC), which has been implicated in the synthesis of polyamines, which leads to cell proliferation, segregation, and macromolecular production. The augmented ODC activity were linked to mounting colon adenomas and carcinomas, suggesting a hyperproliferative state of the colonic mucosa, which was reduced by *B. longum* [34].

7.2 MECHANISMS OF PROBIOTICS

Although much research has been done, the precise mechanisms of how probiotics induce prevention bowel cancer are unclear. The mechanism may include (Figure 7.2)

1. amendment of the normal gut flora;
2. carcinogenic substances suppression;
3. antagonism with putrefactive and pathogenic microbial population;
4. enhancement in immunogenic reactions;
5. control of apoptosis- and cell-differentiation-induced antiproliferative effects;

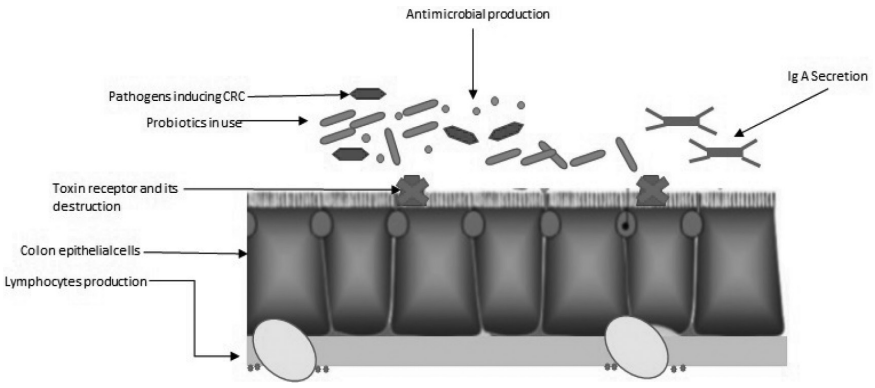


FIGURE 7.2 Probiotics-induced CRC protection.

6. fermentation of food that remain undigested; and
7. attenuation of tyrosine kinase signaling pathways.

Moreover, the co-administration of probiotics with prebiotics, known as synbiotics, can boost the efficacy of the aforementioned anticarcinogenic mechanisms. A postulated mechanism is the acidification of pH that is indistinct, inherent, and elementary through which many probiotics execute their metabolic activities [35].

7.2.1 Inactivation of Cancerogenic Compounds

Heterocyclic aromatic amines (HCA) are produced during the processing of meat at elevated temperature [36]. A meta-analysis of 15 prospective research studies has shown that the comparative threat of developing bowel cancer is 1.28 in subjects consuming large quantities of red meat compared with consuming lesser quantities [37]. Many commensal bacteria and LAB bind or metabolize a number of carcinogens, including HCA and N-nitroso compounds, which correlates well with diminution in mutagenicity due to exposure of HCA to the bacterial strains [38]. Thus, binding or degradation of HCA by probiotics may be the foremost mechanism in eradicating carcinogenic substances from human body.

Another study by Sreekumar and Hosono [39] verified that a significant decrease in the bioavailability of Trp-P-2 was observed in GI tract as well as many tissues in mice when *L. acidophilus* NCFB1748 and *B. longum* BB536 supplements were provided orally. The genotoxicity of Trp-P-1 was decreased by cell fractions of *L. acidophilus* and *Bifidobacterium* spp. The antimutagenic effect of *Lactobacillus plantarum* KLAB21 is mediated by three extracellular glycoproteins. Study by Challa et al. [40] demonstrated that the rats fed with *B. longum* and lactulose significantly increased the activity of intestinal glutathione-S-transferase, the phase II enzymes implicated in the detoxification of noxious metabolites and carcinogenic molecules, and inhibited azoxymethane (AOM)-induced colonic aberrant crypt foci (ACF), which are precarcinogenic markers. However, probiotic capability to attach or metabolize toxic compounds relies on the pH and additional physicochemical conditions.

7.2.2 Putrefactive and Pathogenic Microbiota Interaction

Putrefactive gut microbiota, namely, *Bacteroides* spp. and *Clostridium* spp., are associated with bowel cancer, whereas several LABs have shown tumor-averting attributes. Rafter et al. [41] studied the effect of synbiotic amalgamation of particular oligofructose-enriched inulin with probiotics on fecal flora of polyp and bowel cancer patients and found that it caused amplification in the number of *Bifidobacterium* in both groups and *Lactobacillus* in polyp patients, while *Clostridium perfringens* numbers declined significantly in polyp patients. Probiotics utilization causes change in GI microflora, with a major diminution in fecal putrefactive microbes, like coliforms, as well as an increase in LAB [42,43] interceded by binding to enterocytes and decreasing pH. Hence, probiotics compete with pathogenic intestinal microbiota and counteract bowel cancer development in individuals.

7.2.3 Enhancement of the Immune Response

Body's immune system controls tumor promotion and progression by interacting with numerous essentials of the immunogenic system like antigen-presenting cells (APCs), T cells, B cells, and natural killer cells. Based on earlier studies, hypothesis has drawn additional investigations on the anticancer and immune regulatory action of probiotics LcS in different experimental models. Favorable effects in both humans and animals have been exhibited by oral administration of LcS. Moreover, antitumor action in human bladder cancer cells is also observed in clinical trials. It also suppresses chemically induced carcinogenesis in rodents. Intrapleural administration of LcS into tumor-bearing mice has shown to induce the production of cytokines like interferon-g (IFNγ), interleukin-b (IL-1b), and tumor necrosis factor-a (TNF-α), leading to the inhibition of tumor growth and an amplified survival. LCs too revealed a hard-hitting anticancer effect in mice induced with 3-methylcholanthrene (MC) carcinogenesis. A promising mechanism of antitumor property is the propagation and activation of natural killer cells that play decisive role in immune scrutiny against tumor development [44]. In addition, LcS also stimulates type 1 helper T cells, activates the cellular immune system, and thus restrains the occurrence of tumors and IgE production in mice. Lately, LcS has been shown to produce interleukin-12 (IL-12) and inhibit interleukin-6 production in the intestinal mucosa and thus suppress murine tumorigenesis [45]. These findings advocate the use of probiotics in bowel cancer prevention by modification of the host's cellular immune system.

7.2.4 Regulation of Cell Death and Differentiation

Apoptosis plays a vital role in the regulation of cell numbers and is defined as genetically determined cell death. A condensed ability to cause apoptosis accompanied by modification in the control processes of cell proliferation is an essential pathogenetic episode in numerous types of cancer, and molecules acting on the apoptotic process through the regulation of cell survival and death have vast chemopreventive and therapeutic prospects. There is compelling evidence that probiotics regulate cell proliferation and apoptosis. TNF-induced NF-κB activation was suppressed by *Lactobacillus reuteri* in a dose- and time-dependent manner [46]. Study shows that *L. reuteri* promotes apoptosis of activated immune cells by inhibiting IkBa ubiquitination and augmenting proapoptotic mitogen-activated protein kinase signaling, which, in turn, regulates cell proliferation. COX-2 expression is augmented in colorectal cancer, which protects intestinal epithelial cells from apoptosis and was observed to be suppressed in Colo320 and SW480 intestinal epithelial cells when probiotic mixture VSL#3 was employed. Baricault et al. [47] studied the outcome of milk fermented with bacterial populations in colon cancer cell line (HT-29) of human. The results showed that just *L. acidophilus* was ineffective on cell growth and differentiation, while the other bacterial strains induced a decrement in the rate of HT-29 cell growth significantly but variably, thus producing a 10%–50% decline in the cell number in steady state. Parallel to this, explicit actions of dipeptidyl peptidase IV and enzymes, namely, alkaline phosphatase, sucrase, aminopeptidase N, and so on, were amplified in a significant manner, thus suggesting initiation of differentiation process in these cells. Besides, inhibition of propagation of HT-29 cells without cytotoxic effect

was observed in combinations of *Bifidobacterium breve* R0070, *Lactobacillus lactis* R1058, and oligoalternan [48]. Study by Singh et al. [49] confirmed that the use of lyophilized cultures of *B. longumin* in food resulted in major inhibition of colon cancer prevalence and abridged the tumor volume in rats. Intermediate biomarker analysis uncovered and showed that the intake of *B. longum* reduced ornithine decarboxylase (ODC) activity and inhibited AOM-induced cell proliferation.

7.2.5 Fermentation of Undigested Food

Another mechanism whereby probiotics influence bowel cancer risk is the microbial, that is, bacterial alteration of food components in lumen of intestine and production of cancer-preventive agents. Short-chain fatty acid (SCFA) as well as gas is generated by bacterial fermentation of indigestible carbohydrates. Fecal material eliminates the formed gas, while SCFA, primarily acetate, propionate, and butyrate, correspond to intestinal mucosal nutrients and growth signals by reducing the concentration of secondary bile salts [50]. Convincing study shows that butyrate improves cellular differentiation and diminishes proliferation in bowel cancer cell lines. A specific strain (MDT-1) of the ruminal bacterium *Butyrivibrio fibrisolvens* creates elevated quantity of butyrate and has been evaluated for use as a probiotic to prevent bowel cancer [51] in a mouse model. The result shows that administration of MDT-1 reduces the amount of ACF and the percentage of mice with enlarged ACF fraction. Nonetheless, synbiotics are more active in escalating the production of SCFA probiotics alone, and therefore protection against bowel cancer onset. Furthermore, probiotics also produce collection of fatty acids known as conjugated linoleic acids (CLAs), which can be considered as set of isomers of linoleic acid, which exerts abundant health benefits, such as anti-inflammatory and anticarcinogenic effects besides SCFA [52]. In rodent studies, reduction in the incidence of colonic tumors has been observed by CLA. All these studies support the notion that fermentation of indigestible food by supplemental probiotics can be a strategy for preventing bowel cancer; however, advanced investigations are required.

7.2.6 Attenuation of Tyrosine Kinase Signaling Pathway

Signaling pathways may be defined as biochemical events of cell communication with extracellular setting. These signaling mechanisms play significant part in carcinogenesis. *Saccharomyces boulardii* (Sb) has been shown to act by intonation of the host signaling pathways that regulate inflammatory reactions in intestinal mucosa. More definitely, Sb is found to downregulate MAPK signaling pathways [53], which comprise of downstream pathway of various growth factor receptors like that of epidermal growth factor receptor (EGFR), central in cancer development [54].

7.2.7 Cancer-Immunity Cycle

Diverse components and mechanism such as T cells, NK cells, macrophages, and B cells are engaged in exhibiting antitumor activity [55]. Specific cells known as

dendritic cells perceive the antigen of cancer cells, leading to the activation of effector T cells in the lymph node, which are further transported and infiltrated in cancer. Once the entry of T cells occurs in tumor cells, cancer cells are further recognized and necrosis of cancer cells is done. Dendritic cells further arrest antigen from the killed cancer cell, which, in turn, prompts the cycle again, and this cycle is said to be regulated by probiotics.

7.2.8 Probiotics and Immunotherapy

Immunotherapy has been postulated in the development of anticancer approach by using and modifying patients' immune system. Current research mainly emphasizes the prospective of inhibitors targeting cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed death 1 (PD-1), which are few checkpoint proteins that reduce T-cell activation [56].

7.2.9 Modulation of Inflammatory Response

Many in vitro studies have shown probiotics exhibiting anti-inflammatory effect and thus exerting anticancer activity. The results of these studies suggest a correlation between these two activities. Compelling evidence shows that chronic inflammation is a well-known risk factor for the occurrence of cancer, the simplest example being [57–59] colon cancer, which is actually associated with inflammatory bowel disease (IBD). Studies have shown that *Lactobacillus rhamnosus* GG prevents bowel tumor by attenuating proinflammatory NF-κB pathway [60].

7.2.10 Modulation of T Helper17 Cell Population and Activity

Th17 cells are a crucial aspect of inflammatory and anti-inflammatory responses, and the modulation of these helper cells can in turn modify the cell population as well as activity. Preclinical study in mice has shown that a mixture of probiotics decreased proinflammatory cytokines, namely, IL-17. They also decreased the frequency of Th17 cells and its conscription in cancer. It was also found out that IL-17 favors angiogenesis [61], thus any diminution of Th17 and IL-17 concentrations in turn could attenuate cancer development. Few other studies have also shown that probiotics use augmented IL-10 level, which is an anti-inflammatory molecule, thus leading to the conclusion that Th17-mediated responses are quite well balanced. There is also an increase in the levels of an antiangiogenesis cytokine known as IL-22, which is also associated with Th17 cells.

7.2.11 Modulation of Interferon-γ Level

An increase in the levels of interferon-γ (IFNγ), which is a cytokine involved in inflammatory response, is associated with anticancer actions in experimental mice treated with probiotics. IFNγ has involvement in cancer-immunity cycle like upregulation of major histocompatibility complex class I molecules, Th1 polarization, and T-cell infiltration, leading to anticancer responses [62]. IFNγ also differentiates

T cells into cytotoxic T lymphocytes [63]. IFNγ represses the propagation of tumor cells, thus accepting the data that increase in its concentration is associated with inhibition of tumor development. It has also been observed that IFNγ increases the survival rate, thus playing a key role in shielding against tumor.

7.3 RELEVANCE OF PROBIOTICS USES IN BOWEL CANCER AND RELATED COMPLICATION TREATMENTS

7.3.1 As a Supplement to Advanced Bowel Cancer Treatments

Along with conventional therapy like surgery and chemotherapy, probiotics can be used in combination to improve the chemotherapy-induced secondary effects. In studies, it surely suggests improved intestinal environment and a valuable caution for gaining scientific beneficial effects in patients who are immune-compromised. Results from clinical studies also illustrate that development in the integrity of mucosal barrier of gut and decrement in infectious complications in patients undergoing surgeries are also observed with the use of probiotics [64].

7.3.2 Probiotics Use in Patients Treated with Chemotherapy

The capacity of 5-fluorouracil (5-FU) to induce apoptosis was found to be enhanced by LAB in few studies. In yet another study, *L. rhamnosus* GG supplementation abridged numerous detrimental effects of 5-fluorouracil like frequent diarrhea and abdominal distress. Moreover, patients receiving combination of *L. rhamnosus* GG with 5-fluorouracil and 5-FU-based therapeutic strategies required fewer clinical care and smaller quantity of chemotherapy doses and did not suffer from severe abdominal pain in addition to diarrhea as compared to patients who were not given probiotics [65].

7.3.3 Probiotics in Treatment of Complications Related to Surgery

Supplementation with feasible probiotics prior to surgery can recover bacterial dysbiosis. In a study, hosts with surgically removed colonic polyps were given *L. casei* Shirota to suppress the reappearance of bowel cancer [66]. Preoperative administration of probiotics reduced infection after abdominal surgery, which is determined as a cause of morbidity in patients. In yet another study, patients who were treated with a combination of probiotics containing *L. acidophilus* La-11 *B. longum* BL-88 and *L. plantarum* CGMCC No. 1258 on a daily basis before and after their operation had superior improvement in peristalsis, lower incidence of diarrhea, and condensed infection-related complications [67]. Similarly, research conducted by Zhang and colleagues ascertained that employing viable *Bifidobacterium* preoperatively alleviated the immune status and prediction of patients undergoing bowel cancer resection and reduced postoperative septic complications [68]. Moreover, probiotic mixtures also sustained barrier function of intestine, which prohibited cancer reappearance.

7.3.4 Effects on Inflammation

In a study conducted by Gianotti and colleagues, mixture of *L. johnsonii* La1 and *B. longum* BB536 formulation resulted in amplified expression of naïve and memory lymphocyte subsets and less expression of dendritic phenotypes in subjects who underwent elective colorectal resection for cancer [69]. Oral administration of *Lactobacillus johnsonii* La1, both pre- and postoperatively, remained in the mucosa of colon and decreased the number of pathogenic bacteria in the feces (enterobacteria and enterococci). Probiotics avert tumor recurrence in addition to developing their eminence of life; they also alleviate a lot of unwanted complications associated with bowel cancer treatments. Thus, specific probiotic strains when administered in diverse methods like various blends at different times and doses did bring clinical benefits to patients. However, additional investigations are required to progress probiotic formulations for enhanced efficacy [70].

7.4 CONCLUSION

Probiotics have the ability to reduce the risk of bowel cancer by amending the intestinal microbiota and immune system by species-strain-dependent mechanisms. Conversely, the data obtained from various experiments documented in literature has shown high degree of disagreements regarding the observed actions and effects in various types of cancers. Auxiliary studies are required to characterize and standardize few variables before elucidating the mechanism of probiotics-induced protective effects on bowel cancer. With rigorous research in the field of microbiology and benefits of microbiota in alleviating various diseases, it is anticipated that with advancement and interaction of various fields like nutrition, genetic engineering, pharmacogenomics, and food science and technology, commercial products will be available in near future that will have the potential to reduce the risk of cancer and thus would be used as adjuvant therapy in the treatment of cancer.

REFERENCES

1. FAO/WHO. Guidelines for the evaluation of probiotics in food. Joint FAO/WHO Working Group Report on Drafting Guidelines for the Evaluation of Probiotics in Food London, Ontario, Canada, 2002.
2. Fuller R. Probiotics in man and animals. *J Appl Bacteriol*. 1989; 66: 65–378.
3. Salminen SJ, Gueimonde M, Isolauri E. Probiotics that modify disease risk. *J Nutr.* 2005; 135: 1294–1298.
4. Liong MT. Probiotics: A critical review of their potential role as antihypertensives, immunemodulators, hypocholesterolemics, and perimenopausal treatments. *Nutr Rev.* 2007; 65: 316–328.
5. Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: Introducing the concept of prebiotics. *J Nutr.* 1995; 125: 1401–1412.
6. Collins MD, Gibson GR. Probiotics, prebiotics and synbiotics: Approaches for modulating the microbial ecology of the gut. *Am J Clin Nutr.* 1999; 69: 1052S–1057S.
7. Frank DN, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proc Natl Acad Sci USA*. 2007; 104: 13780–13785.

8. Tsai F, Coyle WJ. The microbiome and obesity: Is obesity linked to our gut flora? *Curr Gastroenterol Rep*. 2009; 11: 307–313.
9. Pryde SE, Duncan SH, Hold GL. The microbiology of butyrate formation in the human colon. *FEMS Microbiol Lett*. 2002; 17: 133–139.
10. Jones BV, Begley M, Hill C, Gahan CG, Marchesi JR. Functional and comparative metagenomic analysis of bile salt hydrolase activity in the human gut microbiome. *Proc Natl Acad Sci USA*. 2008; 105: 13580–13585.
11. Possemiers S, Verthé K, Uyttendaele S, Verstraete W. PCR-DGGE-based quantification of stability of the microbial community in a simulator of the human intestinal microbial ecosystem. *Fems Microbiol Ecol*. 2004; 49: 495–507.
12. Motevaseli E, Dianatpour A, Ghafouri-Fard S. The role of probiotics in cancer treatment: Emphasis on their *in vivo* and *in vitro* anti-metastatic effects. *IJMCM*. 2017; 6(2): 66–76.
13. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*. 2006; 444: 1027–1031.
14. Nagpal R, Kumar A, Kumar M, Behare PV, Jain S, Yadav H. Probiotics, their health benefits and applications for developing healthier foods: A review. *FEMS Microbiol Lett*. 2012; 334: 1–15.
15. Forestier C, De Champs C, Vatoux C, Joly B. Probiotic activities of Lactobacillus caseirhamnosus: In-vitro adherence to intestinal cells and antimicrobial properties. *Res Microbiol*. 2001; 152: 167–173.
16. Abedin-Do A, Taherian-Esfahani Z, Ghafouri-Fard S, Motevaseli E. Immunomodulatory effects of *Lactobacillus* strains: Emphasis on their effects on cancer cells. *Immunotherapy*. 2015; 7: 1307–1329.
17. Tiptiri-Kourpeti A, Spyridopoulou K, Santarmaki V, Aindelis G, Tompoulidou E, Lamprianidou EE et al. *Lactobacillus casei* exerts anti-proliferative effects accompanied by apoptotic cell death and up-regulation of TRAIL in colon carcinoma cells. *PloS One*. 2016; 11: e0147960.
18. Sadeghi-Aliabadi H, Mohammadi F, Fazeli H, Mirlohi M. Effects of *Lactobacillus plantarum* A7 with probiotic potential on colon cancer and normal cells proliferation in comparison with a commercial strain. *Iran J Basic Med Sci*. 2014; 17: 815–819.
19. Choi SS, Kim Y, Han KS, You S, Oh S, Kim SH. Effects of *Lactobacillus* strains on cancer cell proliferation and oxidative stress in vitro. *Lett Appl Microbiol*. 2006; 42: 452–458.
20. Jiang WG, Sanders AJ, Katoh M, Ungefroren H, Gieseler F, Prince M. Tissue invasion and metastasis: Molecular, biological and clinical perspectives. *Semin Cancer Biol*. 2015; 35 Suppl: S244–S275.
21. Uccello M, Malaguarnera G, Basile F, D'agata V, Malaguarnera M, Bertino G et al. Potential role of probiotics on colorectal cancer prevention. *BMC Surgery*. 2012; 12(Suppl 1):S35.
22. Min-TzeLiong. Roles of probiotics and prebiotics in colon cancer prevention: Postulated mechanisms and in-vivo evidence. *Int J Mol Sci*. 2008; 9: 854–863.
23. Lyra A, Lahtinen S, Ouwehand AC. Gastrointestinal benefits of probiotics—clinical evidence. In Salminen S, von Wright A, Lahtinen S, Ouwehand A, eds. *Lactic Acid Bacteria: Microbiological and Functional Aspects*. 4th ed. Boca Raton, FL: CRC Press, 2012. p. 509–523.
24. Zhu Y, Luo TM, Jobin C, Young, HA. Gut microbiota and probiotics in colon tumorigenesis. *Cancer Lett*. 2011; 309: 119–127.
25. Goldin BR, Gorbach SL. The effect of milk and lactobacillus feeding on human intestinal bacterial enzyme activity. *Am J Clin Nutr*. 1984; 39: 756–761.
26. Kumar M, Verma V, Nagpal R, Kumar A, Behare PV, Singh B, Aggarwal PK. Anticarcinogenic effect of probiotic fermented milk and chlorophyllin on aflatoxin-B1 induced liver carcinogenesis in rats. *Br J Nutr*. 2011; 107: 1006–1016.

27. Kumar M, Verma V, Nagpal R, Kumar A, Gautam SK, Behare PV et al. Effect of probiotic fermented milk and chlorophyll in on gene expressions and genotoxicity during AFB1-induced hepatocellular carcinoma. *Gene*. 2011; 490: 54–59.
28. Reddy BS. Prevention of colon cancer by pre- and probiotics: Evidence from laboratory studies. *Br J Nutr.* 1998; 80: S219–S223.
29. Caro DS, Tao H, Grillo A, Elia C, Gasbarrini G, Sepulveda AR, Gasbarrini A. Effects of *Lactobacillus* GG on genes expression pattern in small bowel mucosa. *Dig Liver Dis*. 2005; 37: 320–332.
30. Pedrosa MC, Golner BB, Gold in BR, Barakat S, Dallal GE, Russell RM. Survival of yogurt-containing organisms and *Lactobacillus gasseri* (ADH) and their effect on bacterialenzyme activity in the gastrointestinal tract of healthy and hypochlorhydric elderly subjects. *Am J Clin Nutr.* 1995; 61: 353–359.
31. Reddy BS, Hamid R, Rao CV. Effect of dietary oligofructose and inulin on colonicpreneoplastic aberrant crypt foci inhibition. *Carcinogenesis*. 1997; 18: 1371–1374.
32. Baricault L, Denariaz G, Houri JJ, Bouley C, Sapin C, Trugnan G. Use of HT-29, a cultured human colon cancer cell line, to study the effect of fermented milks on colon cancer cell growth and differentiation. *Carcinogenesis*. 1995; 16: 245–252.
33. Singh J, Rivenson A, Tomita M, Shimamura S, Ishibashi N, Reddy BS. *Bifidobacterium longum*, a lactic acid-producing intestinal bacterium inhibits colon cancer and modulates the intermediate biomarkers of colon carcinogenesis. *Carcinogenesis*. 1997; 18: 833–841.
34. Min-Tze Liong. Roles of probiotics and prebiotics in colon cancer prevention: Postulated mechanisms and *in-vivo* Evidence. *Int J Mol Sci*. 2008; 9: 854–863.
35. Nowak A, Libudzisz Z. Ability of probiotic *Lactobacillus casei* DN 114001 to bind or/and metabolise heterocyclic aromatic amines *in vitro. Eur J Nutr.* 2009; 48: 419–427.
36. Turesky RJ. Formation and biochemistry of carcinogenic heterocyclic aromatic amines in cooked meats. *Toxicol Lett*. 2007; 168: 219–227.
37. Larsson SC, Wolk A. Meat consumption and risk of colorectal cancer: A meta-analysis of prospective studies. *Int J Cancer.* 2006; 119: 2657–2664.
38. Kumar M, Kumar A, Nagpal R, Mohania D, Behare P, Verma V et al. Cancer-preventing attributes of probiotics: An update. *Int J Food Sci Nutr.* 2010; 61: 473–496.
39. Sreekumar O, Hosono A. The antimutagenic properties of a polysaccharide produced by *Bifidobacterium longum* and its cultured milk against some heterocyclic amines. *Can J Microbiol*. 1998; 44: 1029–1036.
40. Challa A, Rao DR, Chawan CB, Shackelford L. *Bifidobacterium longum* and lactulose suppress azoxymethane-induced colonic aberrant crypt foci inrats. *Carcinogenesis*. 1997; 18: 517–521.
41. Rafter J, Bennett M, Caderni G, Clune Y, Hughes R, Karlsson PC et al. Dietary synbiotics reduce cancer risk factors in polypectomized and colon cancer patients. *Am J Clin Nutr.* 2007; 85: 488–496.
42. O'Mahony L, Feeney M, O'Halloran S, Murphy L, Kiely B, Fitzgibbon J et al. Probiotic impact on microbial flora, inflammation and tumour development in IL-10 knockout mice. *Aliment Pharmacol Ther.* 2001; 15: 1219–1225.
43. Berretta M, Lleshi A, Fisichella R, Berretta S, Basile F, Li Volti G et al. The role of nutrition in the development of esophageal cancer: What do we know? *Front Biosci* (*EliteEd*). 2012; 4: 351–357.
44. Takagi A, Matsuzaki T, Sato M, Nomoto K, Morotomi M, Yokokura T. Enhancement of natural killer cytotoxicity delayed murine carcinogenesis by a probiotic microorganism. *Carcinogenesis*. 2001; 22: 599–605.
45. Takagi A, Ikemura H, Matsuzaki T, Sato M, Nomoto K, Morotomi M et al. Relationship between the *in vitro* response of dendritic cells to *Lactobacillus* and prevention of tumorigenesis in the mouse. *J Gastroenterol*. 2008; 43: 661–669.

46. Iyer C, Kosters A, Sethi G, Kunnumakkara AB, Aggarwal BB, Versalovic J. Probiotic *Lactobacillus reuteri* promotes TNF-induced apoptosis inhuman myeloid leukemia-derived cells by modulation of NF-kappa B and MAPK signalling. *Cell Microbiol*. 2008; 10: 1442–1452.
47. Baricault L, Denariaz G, Houri JJ, Bouley C, Sapin C, Trugnan G. Use of HT-29, a cultured human colon cancer cell line, to study the effect offermented milks on colon cancer cell growth and differentiation. *Carcinogenesis*. 1995; 16: 245–252.
48. Grimoud J, Durand H, de Souza S, Monsan P, Ouarné F, Theodorou V, Roques C. In vitro screening of probiotics and synbiotics according to anti-inflammatory and anti-proliferative effects. *Int J Food Microbiol*. 2010; 144: 42–50.
49. Singh J, Rivenson A, Tomita M, Shimamura S, Ishibashi N, Reddy BS. Bifidobacterium longum, a lactic acid-producing intestinal bacterium inhibits colon cancer and modulates the intermediate biomarkers of colon carcinogenesis. *Carcinogenesis*. 1997; 18: 833–841.
50. Mai V. Dietary modification of the intestinal microbiota. *Nutr Rev* 2004; 62: 235–242.
51. Ohkawara S, Furuya H, Nagashima K, Asanuma N, Hino T. Oral administration of *Butyrivibrio fibrisolvens*, a butyrate-producing bacterium decreases the formation of aberrant crypt foci in the colon and rectum of mice. *J Nutr.* 2005; 135: 2878–2883.
52. Evans NP, Misyak SA, Schmelz EM, Guri AJ, Hontecillas R, Bassaganya-Riera J. Conjugated linoleic acid ameliorates inflammation-induced colorectal cancer in mice through activation of PPAR gamma. *J Nutr.* 2010; 140: 515–521.
53. Czerucka D, Dahan S, Mograbi B, Rossi B, Rampal P. *Saccharomyces boulardii* preserves the barrier function and modulates the signal transduction pathway induced in enteropathogenic *Escherichia coli* infected T84 cells. *Infect Immun*. 2000; 68: 5998–6004.
54. Hynes NE, MacDonald G. ErbB receptors and signaling pathways in cancer. *Curr Opin Cell Biol*. 2009; 21: 177–184.
55. Liu Y, Zeng G. Cancer and innate immune system interactions: Translational potentials for cancer immunotherapy. *J Immunother.* 2012; 35: 299–308.
56. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer.* 2012; 12: 252–264.
57. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature*. 2008; 454: 436–444.
58. Kundu JK, Surh Y-J. Inflammation: Gearing the journey to cancer. *Mutat Res* 2008; 659: 15–30.
59. Perwez Hussain S, Harris CC. Inflammation and cancer: An ancient link with novel potentials. *Int J Cancer.* 2007; 121: 2373–2380.
60. Blasingame C, Billups L, Graham T, Henry J, Carter B. Modulation of colorectal cancer by the probiotic organism *Lactobacillus reuteri*. *PAWJ*. 2016; 3(2): 1–14.
61. Bailey SR, Nelson MH, Himes RA, Li Z, Mehrotra S, Paulos CM. Th17 cells in cancer: The ultimate identity crisis. *Front Immunol*. 2014; 5: 276.
62. Mandai M, Hamanishi J, Abiko K, Matsumura N, Baba T, Konishi I. Dual faces of IFNγ in cancer progression: A role of PD-L1 induction in the determination of pro- and antitumor immunity. *Clin Cancer Res*. 2016; 22(10): 2329–2334.
63. Chen DS, Mellman I. Oncology meets immunology: The cancer-immunity cycle. *Immunity*. 2014; 39: 1–10.
64. Liu Z, Qin H, Yang Z, Xia Y, Liu W, Yang J et al. Randomised clinical trial: The effects of perioperative probiotic treatment on barrier function and postoperative infectious complications in colorectal cancer surgery—A double-blind study. *Aliment Pharmacol Ther.* 2011; 33: 50–63.
65. Sterlund P, Ruotsalainen T, Korpela R, Saxelin M, Ollus A, Valta P et al. Lactobacillus supplementation for diarrhoea related to chemotherapy of colorectal cancer: A randomised study. *Br J Cancer.* 2007; 97: 1028–1034.

66. Nanno M, Kato I, Kobayashi T, Shida K. Biological effects of probiotics: What impact does *Lactobacillus casei* Shirota have on us? *Int J Immunopathol Pharmacol*. 2011; 24 (Suppl) 45S–50S.
67. Liu Z, Qin H, Yang Z, Xia Y, Liu W, Yang J et al. Randomised clinical trial: The effects of perioperative probiotic treatment on barrier function and postoperative infectious complications in colorectal cancer surgery—A double-blind study. *Aliment Pharmacol Ther.* 2011; 33: 50–63.
68. Zhang JW, Du P, Chen DW, Cui L, Ying CM. Effect of viable Bifidobacterium supplement on the immune status and inflammatory response in patients undergoing resection for colorectal cancer. *Zhonghua wei chang wai ke za zhi= Chinese Journal of Gastrointestinal Surgery*, 2010; 13(1): 40–43.
69. Gianotti L, Morelli L, Galbiati F, Rocchetti S, Coppola S, Beneduce A et al. A randomized double-blind trial on perioperative administration of probiotics in colorectal cancer patients. *World J Gastroenterol*. 2010; 16: 167–175.
70. Kahouli I, Tomaro-Duchesneau C, Prakash S. Probiotics in colorectal cancer (CRC) with emphasis on mechanisms of action and current perspectives. *J Med Microbiol*. 2013; 62: 1107–1123.

8 Effect of Nutraceuticals on Gut Microbiota—What Is the Deal in Cancer?

Andréa Burgess, Asra Sami, and Sheeba Varghese Gupta

CONTENTS

8.1 INTRODUCTION

The human gut hosts an array of bacteria that conduct many immune and metabolic functions. The co-evolution to the immune system and microbes of the gut is the topic of interest for cancer and nutraceutical research. The environmental and biological factors that impact gut diversity can also lead to the development of intestinal dysbiosis. The incorporation of nutraceuticals like polyunsaturated fatty acids, phytochemicals, and probiotics into the host diet can aid in the prevention of cancer and the reduction of cancer treatment related symptoms.

8.2 GUT DIVERSITY FROM INFANCY TO LATE ADULTHOOD

8.2.1 Infant Microbiota

The developing microbiota of the human gut up until the age of 2 exhibits relatively low diversity, low stability, and more vigor compared to adult microbiota (O'Toole & Claesson 2010). Researchers have explored the budding gut composition of early infants as a means of understanding how changes in microbial population might lead to intestinal dybiosis and the development of certain health conditions. Utilizing culture-dependent and culture-independent methods, researchers have established a general pattern for the colonization of the infant gut with earliest microbes being facultative anaerobes, succeeded by strict anaerobes (Laforest-Lapointe & Arrieta 2017). Other literature has noted a "predominance of enterobacteria and enterococci followed by bifidobacteria, Bacteroides spp., clostridia and anaerobic streptococci" (O'Toole & Claesson 2010) in the settlement of early-life microbiota.

8.2.2 Infant Gut Variations

Variations in the colonization and stabilization of the bacterial phyla of the infant gut is influenced by multiple factors such as prematurity, feeding patterns, mode of delivery, exposure to antibodies and unsanitary surroundings. For example, the introduction of baby formula or breast feeding into an infant diet can increase the

Bifidobacterium and *Lactobacillus* population in the gut (Penders et al., 2006). Infants raised in unsanitary environments can stimulate an earlier colonization by members of Enterobacteriaceae.

In contrast, the exposure to antibody treatments for bacterial infections or due to residing in the Newborn Intensive Care Unit (NICU) may lead to decreased colonization or eradication of vital microbes. Similarity, babies delivered through C-sections may experience later colonization by the *E. coli* species and members of the *Bifidobacterium* genus and Bacteroidetes phylum (Avrelija & Walter 2010). Moreover, infants that were born before the 37th week of pregnancy were also noted to have an increased colonization by *Clostridium difficile* bacteria (Penders et al., 2006).

8.2.3 Prognostic Effects of Infant Gut

While the diversity of the infant microbiota can initially resemble the composition of the birth mother's microbiota due to vertical transmission of bacteria from mother to infant, the overall anatomy of the gut is individualized. The factors previously discussed are influence the emerging microbiota and additionally contribute to variations in population. The importance of analyzing this early-life environment lies in the ability to identify microbial indicators for disorders and to implement preemptive measures.

In the case of obesity, large cohort studies have linked individuals with larger amounts of body fat as positively associated with colorectal cancers and gastric cancers (Ma et al., 2013). A reduction of Clostridiales bacteria, a butyrate-maker, was observed in the gut microbiota of patients with type 2 diabetes, while other studies showed an increase in *E. coli* and Proteobacteria (Gallagher & LeRoith 2015). Earlier intervention and the use of microbial indictors in the emerging gut microbe may prevent the further development of disorders like obesity.

8.2.4 Adult Microbiota

After infancy, the gut microbiota increases in diversity and stability wherein it is inhabited by an estimated 1000 varying species of microbes (The Human Microbiome Project et al., 2012). Previous studies have utilized a sequence analysis of 16S rDNA collected from fecal biota to note that the majority of gut bacteria are members of the Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria phyla. In contrast, Fusobacteria, Cyanobacteria, and Verrucomicrobia phyla were less present in the samples (Eckburg et al., 2005). The stability of the gut microbiota in adults indicates that an equilibrium in population may have a role in the preservation of a healthy state and immune system.

8.2.5 Adult Gut Variations

A few of the factors that prompt alterations in the adult gut composition are chronic inflammation, pregnancy, and geographical location. In a subset of patients with chronic inflammation of the gastrointestinal tract such as Crohn's

disease (CD) and ulcerative colitis (UC), there was a noted decrease in the population of Firmicutes and Bacteroidetes bacteria in the gut. Additionally, increase in the population of proteobacteria was reported in CD and UC (Manichanh et al., 2006). Sokol and cohorts confirmed the preceding results with also a noted decrease in the *Faecalibacterium prausnitzii* levels in a subset of CD patients (Sokol et al., 2008).

Chronic inflammation plays a role in the development of certain cancers because it impedes the effectiveness of the immune system by altering the composition of the gut. The gut microbiota and intestinal immune system has co-evolved and contributes to the development of innate and adaptive immune homeostasis (Wu & Wu 2012).

Hormonal changes that occur during a normal pregnancy such as reduced insulin sensitivity, altered metabolic inflammation, and increased adiposity can alter the gut microbiota. Studies have indicated that a reduction in general population richness can be observed along with a contrasting increase in Proteobacteria and Actinobacteria (Koren et al., 2012). Additionally, the insulin resistance and chronic asymptomatic gut inflammation characterizes a well-known pathway to the development of both gestational diabetes and gestational hypertension.

Interestingly, many studies into the diversity of the gut microbiota across locations have highlighted changes in the pathways involved in vitamin biosynthesis and carbohydrate metabolism. Yatsunenko and researchers have observed a decrease in the ability of the microbes of gut to use glycans in young South Americans as they mature and transition from diet rich in milk to maize and other plant-based polysaccharides. In contrast, the numbers of genes that utilize glycans increase as North Americans they mature into diets rich in absorbed sugars and remain into adulthood (Yatsunenko et al., 2012).

8.2.6 Late Adulthood Microbiota

After young adulthood, aging fosters a variant of biological and physiological changes to the gut microbiota. The composition of the elderly gut microbiota (>65 years) in comparison to younger adults is unstable and has lower microbial diversity. The senior gut microbiota reverts similarly back to the precarious composition of infancy. Likewise, Mariat and cohorts have established that the Firmicutes: Bacteroidetes ratios for infants, young adults, and senior adults were 0.4, 10.9, and 0.6, respectively (O'Toole & Claesson 2010).

Additionally, a decrease in the number of microbes from the major phyla Bacteroidetes, Firmicutes, and Actinobacteria was observed in the elderly gut microbiota. Inversely, an increase in species numbers within Enterobacteriaceae, staphylococci, streptococci, *Candida albicans*, and clostridia was displayed (D'Argenio & Salvatore 2015). Older adults are faced with reduced physiological functions and amplified use of health services that can influence the preservation of a healthy microbiota.

8.2.7 Late Adulthood Variations

The bioavailability of nutrients is reduced in older adults due to factors of aging such as a decreased peristaltic activity, mastication strength, and dentition. This effects their diet through limiting the absorption of nutrients needed for healthy microbial growth. Nutraceuticals derived from phytochemicals are active compounds found in plants and have protective effects against the development of diseases. Ouwehand and colleagues have researched how the ingestion of probiotic oat-based drinks modify the number of *Bifidobacterium* species in elderly guts, which mediated inflammatory responses of the immune systems (O'Toole & Claesson 2010). Largely, the altered efficiency of the senior gut to access and process beneficial intestinal nutraceuticals and other nutrients is connected to their ability facilitate healthy immune responses with age.

Fortifying cognitive, emotional, and physical health is essential with overall wellness, and life changes such as retirement or living an assistance facility can encourage a more sedentary condition. Moreover, health services usage surges with age and the extended exposure to clinical settings or antibiotic medications can further reduce the lowered diversity of elderly gut microbiome. Cultural and metabolic analysis of fecal biota in elderly patients displayed further decline in the species of the *Bacteroides–Prevotella*, *Bifidobacteria* genus, *Desulfovibrio* spp., some clostridia, and *F. prausnitzii* (O'Toole & Claesson 2010). The members of these groups are a major component of the gastrointestinal tract and the eradication of the population may lead to intestinal dysbiosis (Table 8.1).

TABLE 8.1
Dominant Phyla of Gut Microbiota by Age

	Bacterial Phyla (most to least represented)[a]	Influential Factors
Infancy (up to 2–3 years)	• Actinobacteria • Proteobacteria • Firmicutes • Bacteroidetes	• Prematurity • Feeding patterns • Mode of delivery • Antibodies exposure • Unsanitary surroundings
Adulthood	• Firmicutes • Bacteroidetes • Actinobacteria • Proteobacteria	• Chronic inflammation • Pregnancy • Geographical location
Late Adulthood (>65 years)	• Firmicutes • Actinobacteria • Bacteroidetes • Proteobacteria	• Lowered physiological functions • Lowered nutrients intake • Increased clinical visits

[a] *Source:* D'Argenio, V. and Salvatore, F., *Clin. Chim. Acta*, 451, 97–102, 2015.

8.3 THE EFFECT OF GUT FLORA ON CANCER TREATMENTS

In carcinogenesis, dysfunction of cell growth and suppression of the apoptotic pathway are both required for cancer formation. The host immune system and gut flora have the largest surface area of interaction in the human body and evolutionally developed a symbiotic relationship. An imbalance in the relationship such as alterations in the physiological ranges (pH, ions concentrations, etc.), diversity of gut microbiota, diet, surgical intervention, and use of antibiotics can have direct and indirect effects on the responsiveness of the immune system (Pouncey et al., 2018). In particular, research has demonstrated using numerous animal models and in clinical trials that the gut microbiota plays an essential role in suppressing anticancer responses and the toxicity of cancer treatments.

During gut dysbiosis, the number of *Proeobacteria*, *Lentisphaerae*, *Bacteroides*, and *Parabacteroides* species in the gut decrease (Rea et al., 2018). This reduction impacts the gut's ability to directly metabolize chemotherapeutic medication and produce secondary toxic metabolites (Pouncey et al., 2018). Garcia-Gonzalez and colleagues used a *Caenorhabditis elegans* (*C. elegans*) worm model to investigate how the administration of different bacterial strains would influence chemotherapeutic medication potency. The worms fed with *E. coli* were "two orders of magnitude more sensitive to the sterilizing effect" of 5-fluoro-2′-deoxyuridine (FUDR) in comparison to worms fed with *Comamonas* bacteria. It was determined that the RNA metabolism capabilities of inoculated bacteria was essential for the observed enhanced cytotoxic effects (Garcia-Gonzalez et al., 2017).

Moreover, a lack of comprehension regarding microbiota metabolism can have lethal consequences. In Japan, the co-administration of the antiviral sorivudine and fluoropyrimidine drugs resulted in the suppression of 5-fluorouracil (5-FU) catabolism. It was later determined that an inhibitor for catabolic 5-FU enzymes was created by the gut flora rather than host enzymes and caused 16 deaths over a 40-day period (Nakayama et al., 1997). In further research, the toxic levels of 5-FU were overturned with the administration of antibiotics to reduce gut microbiota prior to use of sorivudine (Pouncey et al., 2018).

Recent studies have highlighted methods under which the immune response can be modified through the gut microbiota. Review of these studies have established a pattern of germ-free and antibiotic-treated animal models displaying suppressed immune response and reduced treatment success. The effects were reversed with the use of gut preservation methods such as supplements of different bacterial strains, transmucosal translocation of specific bacteria, and fecal transfers with healthy gut microbes.

One way cancer evades the immune system is by targeting the T-cell pathway. Vétizou and coworkers investigated how mice with healthy gut microbiota could control the growth of MCA205 sarcomas by blocking cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) with the application of Ipilimumab, a monoclonal antibody. In germ-free and antibiotic-treated mice, the disruption of gut flora resulted in the tumors not responding to the CTLA-4 obstruction. The antisarcoma effects of the CTLA-4 blockade depended on certain Bacteroides species, that is, *B. thetaiotaomicron* or *B. fragilis*. Inoculation of *B. fragilis* sugars via immunization

and adoptive transfer of *B. fragilis*-specific T cells in germ-free and antibiotic-treated mice produced antitumor effects (Vetizou et al., 2015).

Another advance to preserving the integrity of the gut flora rests on its protective capabilities against the cellular damage caused by cancer therapy. The mucosal barrier and innate immune system (cellular/chemical) regulates inflammation and promotes healing. The gut flora interacts with the innate immune system through Toll-like receptors, a group of proteins that broadly detect the presence of antigens. A study showed that antibiotic-treated mice were more vulnerable to small bowel injury when administered anticancer methotrexate medication. The damage to the small bowel was abrogated with the supplement of Toll-like receptor 2 ligand (Pouncey et al., 2018).

8.4 COMMON INTESTINAL NUTRACEUTICALS AND THEIR BENEFITS

8.4.1 Polyunsaturated Fatty Acids

The effect of polyunsaturated fatty acids, abbreviated PUFAs, on intestinal health has been studied. The PUFAs are able to interact with the microbiota in the intestine to enhance or inhibit their properties. In one study, the effect of PUFA was tested on various *Lactobacillus* strains. The results showed that the concentration of the PUFA strongly affected the influence on the *Lactobacillus* strains. A too high concentration would lead to the inhibition of growth and mucus adhesion, whereas a low concentration would lead to an enhancement of growth and adhesion to mucus (Laparra & Sanz 2010). Lactobacillus is a probiotic, which are microorganisms that are often used as supplements providing health benefits. Lactobacillus has been found to provide intestinal benefit, including potentially preventing colon cancer and treating ulcerative colitis, so the promotion of its growth and adhesion could be extremely beneficial (Hirayama & Rafter 1999; Kechagia et al., 2013; Hage et al., 2017).

8.4.1.1 Omega-3 Acids

Common PUFAs are omega-3 acids like eicosapentaenoic acid (EPA), docosahexanoic acid (DHA), and docosapentaenoic acid (DPA), and these can be used as supplements due to their health benefits (Costantini et al., 2017). In a case study exploring the impact of omega-3 acids on gut microbiota diversity and abundance, an omega-3 diet was introduced to a 45-year-old healthy and physically active male. The gut microbiota was examined before and after the 2-week long diet. There was significant change in the levels of certain bacterium, including *F. prausnitzii* and *Blautia*, indicating that the diet can affect gut microbiota abundance (Noriega et al., 2016). Furthermore, starch that normally would not be broken down was simplified to short-chain fatty acids (SCFAs) due to the changes in certain bacterium. SCFAs have anti-inflammatory properties, making it capable of reducing intestinal inflammation (Noriega et al., 2016). Bacteria that produces butyrate was also increased as a result of the omega-3 diet. Butyrate also has anti-inflammatory properties among other properties useful to preserving bodily health, like the ability to regulate the expression of certain genes (Noriega et al., 2016).

Other benefits of omega-3 acids include the ability to inhibit the NF-κB pathway, which is responsible for causing expression of inflammatory genes (Liu et al., 2014; Myles 2014). Mediators produced by EPA and DHA are also capable of reducing inflammation (Myles 2014). In these ways, omega-3 acids can act as anti-inflammatory agents, reducing inflammation of the intestine. A study involving rats showed that a combination of EPA and DHA supplements could prevent the destruction of the intestinal mucosa after an ischemia and reperfusion injury (Wang et al., 2012).

8.4.2 Phytochemicals

Phytochemicals, extracted from plants or other biological organisms, can act as nutraceuticals and provide benefit for the intestine. Some phytochemicals have anti-inflammatory and anticancer properties. Curcumin, piperine, and gingerol are all extracted from spices and food additives and are present in many food recipes. Curcumin is extracted from turmeric, a very commonly used spice in India that has also been a fundamental part of India's traditional medicine practices for many years (Higdon 2018a). Piperine is a constituent of black pepper, known as the King of Spices due to its widespread use. Black pepper was also a component of ancient medicine in both China and India (Gorgani et al., 2016). Other extracts of spices and additives of interest in both culinary and medicinal worlds are gingerol, a primary component of ginger, catechins, which are extracted from tea leaves, and resveratrol, extracted from grapes and red wine (Zhang et al., 2004; Zheng et al., 2016; Higdon 2018b).

8.4.2.1 Curcumin

One phytochemical that has been the focus of abundant research in recent years is curcumin. Curcumin is a polyphenol extracted from turmeric that has been found to combat cancer in many ways. In colorectal cancer, research has shown that curcumin has the ability to regulate gene expression and induce the apoptosis of cancer cells (Li et al., 2015). In addition, curcumin can limit inflammation through the inhibition of NF-κB and COX-2 expressions (Li et al., 2015) (Figure 8.1).

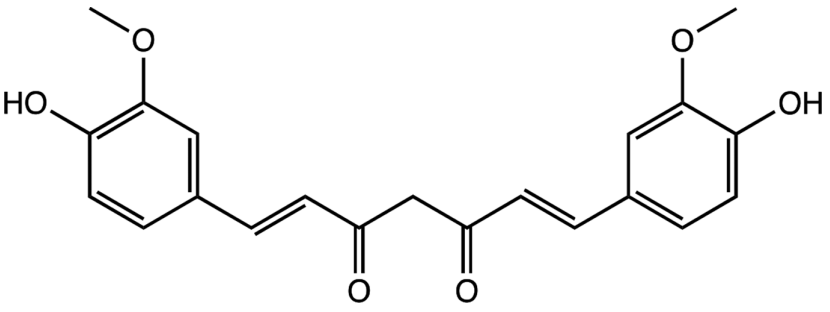


FIGURE 8.1 Structure of curcumin.

8.4.2.2 Piperine

Another phytochemical that can have a positive impact on intestinal health is piperine, which is extracted from black pepper. Piperine can cause apoptosis of colon cancer cells. The mechanism by which this occurs is likely cell cycle arrest at the G1 phase (Yaffe et al., 2014). In addition to its potential as an anticancer agent, piperine has an effect on inflammatory bowel disease (IBD). Piperine is able to reduce inflammation by regulating gene expression and inhibiting NF-κB. TNF-α, a cytokine involved in promoting inflammation in mucosal cells, is decreased with the addition of piperine (Gupta et al., 2015) (Figure 8.2).

8.4.2.3 Gingerol

The phytochemical extracted from ginger known as 6-gingerol contains properties that can be beneficial in combating colorectal cancer. It was found to induce apoptosis in colon cancer cells while avoiding healthy colon cells, which is a useful trait that could prevent unnecessary complications in treatment (Zheng et al., 2016). A study on the small intestine of a rat indicated that the application of gingerol was able to lessen the amount and amplitude of contractions, making it useful for alleviating vomiting (Chatturong et al., 2018) (Figure 8.3).

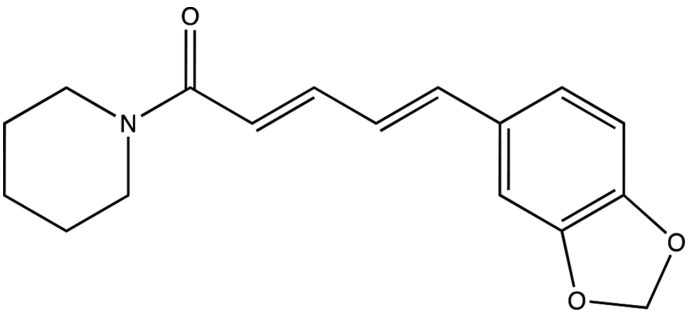


FIGURE 8.2 Structure of piperine.

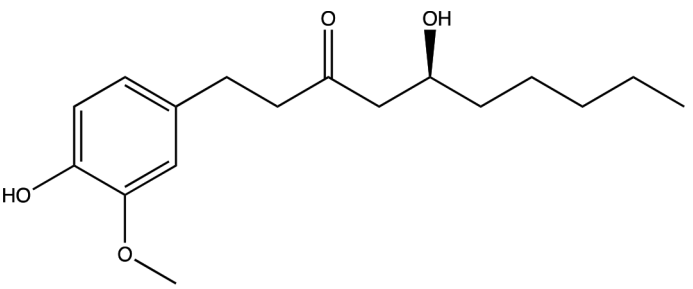


FIGURE 8.3 Structure of 6-gingerol.

8.4.2.4 Catechins

Catechins are flavonoids present in green tea. Some common catechins are epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG), and epigallocatechin gallate (EGCG) (Zhang et al., 2004). Both oxidative stress and inflammation contribute to IBD. Catechins have been found to both scavenge free radicals and regulate protein synthesis in order to reduce oxidative stress (Fan et al., 2017). Epicatechin has been found to increase levels of glutathione (GSH), which has antioxidant properties, in animals with colitis. Epicatechin was also found to be beneficial to lesions of colitis (Vasconcelos et al., 2012) (Figure 8.4).

8.4.2.5 Resveratrol

Resveratrol is a polyphenol commonly extracted from foods including berries, grapes, red wine, and peanuts (Higdon 2018b). A study testing the effect of resveratrol on inflammation in vitro showed that resveratrol can also reduce inflammation through the inhibition of NF-κB (Nunes et al., 2017) (Figure 8.5).

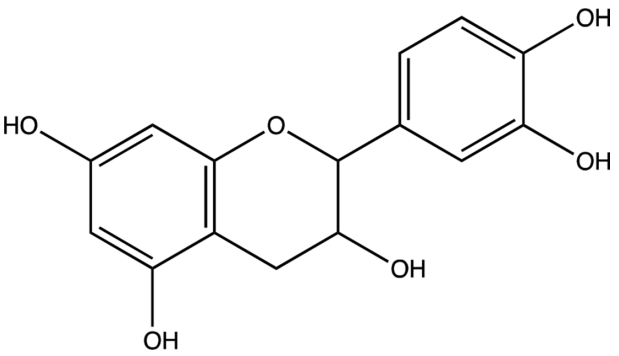


FIGURE 8.4 Structure of epicatechin (EC).

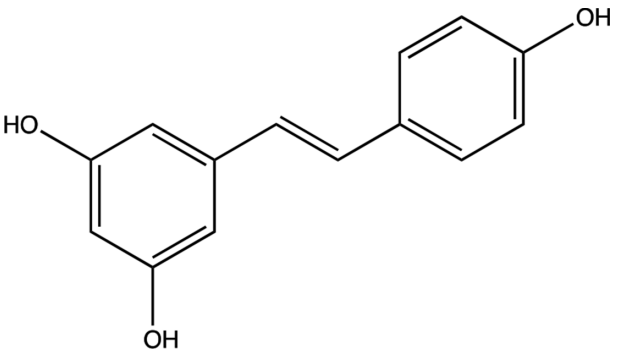


FIGURE 8.5 Structure of resveratrol.

8.4.2.6 Other

Saponins and quercetin are other phytochemicals that have been linked to colorectal cancer prevention (Li et al., 2015).

8.4.3 Probiotics

Probiotics, or live microorganisms with properties that benefit health, are sometimes considered nutraceuticals, as they can be taken as supplements. The microbiota present in the intestine are very important to the health of the human body, so the addition of probiotics can provide further benefit or treat problems caused by deficiencies (Catinean et al., 2018). Some probiotics currently being explored for their beneficial properties in intestinal health are strains of *Lactobacillus*, strains of *Bifidobacterium*, and *F. prausnitzii*.

8.4.3.1 *Lactobacilli* Strains

Common probiotics include the *Lactobacilli* strains. One proven intestinal benefit of *Lactobacillus* was seen in a study of infants with Rotavirus. The frequency of diarrhea and vomiting both decreased as a result of the probiotic treatment with *Lactobacillus* (Park et al., 2017).

8.4.3.2 *Bifidobacterium* Strains

Another very common probiotic of benefit to the intestine are *Bifidobacterium* strains. These strains have been found to benefit IBD, IBS, and diarrhea, having a positive impact on intestinal health (Tojo et al., 2014). *Bifidobacterium* are already present in the gut, and the increase of this microorganism can provide additional benefit. It has been found to contain properties that prevent colorectal cancer as well (O' Callaghan & Sinderen 2016).

8.4.3.3 *Faecalibacterium prausnitzii*

F. prausnitzii makes up 3%–5% of fecal bacteria, making it a large group compared to other bacterium and important to the health of the entire body. One important benefit of this bacteria is its anti-inflammatory properties, making it able to reduce intestinal inflammation, which can in turn help alleviate conditions such as inflammatory bowel disease (Liu et al., 2017). The way in which *F. prausnitzii* affects inflammation is through the inhibition of the NF-κB pathway *in vitro*, which is responsible for controlling the expression of many inflammatory genes (Breyner et al., 2017). *F. prausnitzii* still requires additional research studies to become a more common probiotic, but studies so far indicate that there is potential (Martín et al., 2017).

8.5 THE EFFECT OF NUTRACEUTICALS ON GUT-RELATED CANCERS

Nutraceuticals are alternative therapeutic agents to control the progression of cancer by promoting normal cells function, regulating tumor suppressor genes and bolstering the immune system (Kuppusamy et al., 2014). Traditional synthetic cancer

medications are effective but present with many adverse side effects. The benefits of nutraceuticals usage consist of their capability to improve overall health and present with less side effects (Catinean et al., 2018).

The six dominants phyla in the healthy adult gut are Firmicutes and Bacteroidetes (90%), Proteobacteria, Actinobacteria, Fusobacteria, and Verrucomicrobia (Eckburg et al., 2005). The gut bacterial formation of short-chain fatty acids (SCFAs) and catabolism of amino acids are vital energy sources for cell and metabolic signaling. The Bacteroidetes phylum produces acetate and propionate, while the Firmicutes families create butyrate. Acetate, propionate, and butyrate have significant roles in maintaining hepatic lipids and glucose homeostasis such controlling the effects of peroxisome proliferator-activated receptors (PPAR) (Catinean et al., 2018).

Naturally isolated Flavonoids metabolites like Luteolin have been clinically proven to be effective colon cancer agents. Numerous in vitro studies have recorded that luteolin promotes apoptosis in several cell lines. Demidenko and researchers have shown that luteolin inhibited the HT-29 cell cycle by obstructing cell growth at the G1/S and G2/M phase (Lim et al., 2007). In addition, luteolin inhibits antiapoptotic proteins and controls the activity of CDC2 (CDK1) kinase and cyclin B1 proteins. The CDC2 kinase and cyclin B1 proteins are responsible for starting the G2/M phases in luteolin-treated colon cancer cell lines (Kuppusamy et al., 2014). In short, modest dosage of Luteolin increased the apoptosis of colon cancer cells. This pattern continues with the Flavonoid fisetin that regulates the expression of Bcl-2 metabolites, increased the proapoptotic Bak protein and stimulated caspase-3 in colon cancer cells (Suh et al., 2009).

The suppression of tumor growths by eugenol, a phenylpropanoid derived from cloves and aromatic spices, was noted in the studies of human cancer lines and in the MNNG rat model of gastric cancer. The administration of eugenol had typical nutraceutical anti-inflammatory and growth inhibitory effects. It was achieved by the suppression of the nuclear factor kappa beta (NF-κβ) and the downregulation of MMPs, VEGF, TIMP-2, and RECK expressions (Wargovich et al., 2010). Currently, there is no research that indicates that clove or eugenol can alienate traditional cancer treatments, but review of its VEGF downregulating effects should be further evaluated since it is a *systemic* growth factor. One means of decreasing possible adverse side effects of the phytotherapy would be to administer the eugenol at a lower dose along with a natural VEGF inhibitor (Wargovich et al., 2010).

Green tea polyphenols metabolites like Epigallocatechin gallate (EGCG) have the capability to inhibit aspects of neovascularization and angiogenesis essential to the metastasis of cancers (Wargovich et al., 2010). This was elucidated by its ability to interfere with the Akt and ERK 1 and 2 signaling system for growth factors like VEGF (Wargovich et al., 2010). Park and cohorts recorded that in the presence of low doses of hydrogen peroxide (H_2O_2), EGCG-induced apoptosis in colon cancer cells by activating AMP-activated kinase (AMPK) and inhibiting cyclooxygenase-2 (COX-2) (Park et al., 2009). Currently, there no data that suggest that green tea polyphenols can interfere with common cancer therapies, but there are findings that tea

polyphenols can assist in the responsiveness of chemoresistant cells to therapeutics by associated targeting of the same cellular processes of the desired chemotherapeutic drugs (Wargovich et al., 2010).

8.6 THE APPLICATION OF NUTRACEUTICALS AND CANCER PREVENTION

8.6.1 Curcumin

The effect of curcumin on colorectal cancer cells HCT116 and HT29 was studied in one experiment. The results showed that curcumin not only induced apoptosis but also limited glucose uptake and the production of ATP, successfully reducing the cancer cells' ability to grow. This potentially occurred due to the inhibition of the expression of enzymes involved in the promotion of glycolysis (Wang et al., 2015). There are many ways in which curcumin can target and kill cancer cells. Some of the way apoptosis can be induced involve curcumin's interaction with caspases, death receptors, the p53/p21 pathway, the regulation of other transcription factors, and the regulation of the cell cycle (Ravindran et al., 2009).

8.6.2 Piperine

Piperine, extracted from black pepper, contains anticancer properties. In a study involving rectal cancer cells, piperine effectively stopped the growth of the cells by interrupting the cell cycle and inducing apoptosis (Yaffe et al., 2013). Similarly, in an additional study on colon cancer cell lines, piperine inhibited the growth of HT-29, Caco-2, SW480, and HCT-116 cells. This was most likely due to piperine causing cell cycle arrest and apoptosis through caspase activation (Yaffe et al., 2014).

8.6.3 Gingerol and Ginger

Gingerol has been successful in reducing cancer cell viability. A study of colon cancer cells showed that as the concentration of 6-gingerol increased, the viability of the cell was reduced. Moreover, cell cycle arrest at the G2/M phase occurred (Lin et al., 2012). According to the results of a clinical study in humans with colon cancer, the ginger administered orally could potentially inhibit COX and LOX enzymes, thus inhibiting cancer cell proliferation; however, further experiments and studies are necessary (Zick et al., 2011).

8.6.4 Epigallocatechin Gallate (EGCG)

Catechins, extracted from tea, have been found to inhibit colon cancer cell growth in many studies. One study included epigallocatechin gallate (EGCG) and an HT-29 human colon cancer cell line. The results indicated that EGCG inhibited the cancer cell proliferation through the inhibition of COX-2. The expression of COX-2 is

involved in proliferation, so the inhibition of COX-2 reduces cancer cell proliferation (Park et al., 2009). EGCG can reduce cell proliferation and TROP2. TROP2 is involved in regulating cell growth of colorectal cancer cells (Sukhthankar et al., 2010).

8.6.5 Resveratrol

Resveratrol, another common nutraceutical, can prevent the growth of colorectal cancer. Apart from inducing apoptosis of the cancer cells and reducing cancer cell proliferation, resveratrol has been found to increase m*iR-34c,* which is a tumor suppressor (Yang et al., 2015).

8.6.6 Soy Saponins

Soy saponins are phytochemicals that have an inhibitory impact on human colon cancer cells. With the application of soy saponin on colon cancer cells, there was a reduction in the percentage of cells that survived over time due to autophagic cell death and less cancer cell proliferation in the presence of the saponin (Tsai et al., 2010). Another saponin of interest to colon cancer prevention is astragalus saponin. Astragalus saponin was found to induce apoptosis of human colon cancer cells (Wang et al., 2014).

8.6.7 Quercetin

Another nutraceutical and phytochemical that prevents cancer growth is quercetin due to its ability to cause apoptosis. In one study, quercetin was able to inhibit NF-κB, thus reducing the proliferation of colon cancer cells and inducing apoptosis (Zhang et al., 2015).

8.6.8 *Bifidobacterium*

Probiotics like *Bifidobacterium* strains are also able to prevent colorectal cancer. A study involving rats showed that *B. longum* and *B. breve*, two strains of *Bifidobacterium*, prevented carcinogenic damage on DNA (Pool-Zobel et al., 1996; O'Callaghan & Sinderen 2016).

8.6.9 Other

Oftentimes, the combination of multiple nutraceuticals can also prove beneficial especially in the prevention of cancer. For example, one study tested the effect of curcumin and catechins on multiple types of cancer cells, including HCT 15 and HCT 116. The results of this showed that the combined impact of curcumin and catechin was actually more effective than either of those nutraceuticals would be if administered singularly (Manikandan et al., 2011).

8.7 THE REDUCTION OF CANCER-RELATED SYMPTOMS AND NUTRACEUTICALS

Along with the research conducted to explore nutraceuticals as chemopreventive agents, there are also studies combining nutraceuticals with cancer treatment like chemotherapy to see whether or not the symptoms can be lessened or removed all together. Chemotherapeutic drugs generally used in the treatment of colorectal cancer and approved by the Food and Drug Administration (FDA) include 5-FU (fluorouracil), capecitabine (Xeloda), irinotecan (Camptosar), and oxaliplatin (Eloxatin) ("Drugs Approved for Colon and Rectal Cancer," 2018; "Chemotherapy for Colorectal Cancer," 2018). Unfortunately, there are many side effects of these cancer treatments, like hair loss, nausea, vomiting, diarrhea, and hand–foot syndrome ("Chemotherapy for Colorectal Cancer," 2018).

Apart from the side effects of treatments, there are many symptoms experienced by people who have cancer. Some common signs include unusual weight loss, fever, blood loss that leads to fatigue, and pain. Colorectal in particular can cause pain in the back, diarrhea, or bloody stool ("Signs and Symptoms of Cancer," 2014).

In one study, curcumin c3 was administered in mice with MAC16 colon cancer cells. The mice in the study were afflicted with cachexia, which is muscle degradation, a common symptom of cancer. The mice with curcumin gained weight, whereas the control group began to lose weight. Upon further exploration, it was discovered that the cause of the weight gain was partially due to an increase of the size of muscle fibers. This indicates that cachexia was prevented by the curcumin through the regulation of gene expression (Siddiqui et al., 2009).

Other nutraceuticals with potential in preventing cachexia are the catechin epigallocatechin-3-gallate (EGCG) and resveratrol. The mechanism by which cachexia is prevented is most likely through the regulation of NF-κB. A study involving EGCG concluded that the cachexia was inhibited through the regulation of ubiquitin-proteasome proteolysis, which is controlled by NF-κB (Wang et al., 2011). Similarly, resveratrol was given to mice with colon-26 adenocarcinoma cells were given resveratrol orally, and they were able to resist cachexia because NF-κB inhibition blocked the expression of ubiquitin ligase MuRF1 (Shadfar et al., 2011).

The effect of ginger on nausea and vomiting due to chemotherapy has been tested, but the results remain relatively vague. Although some studies have seen positive results indicating ginger-reduced nausea in comparison to patients not taking ginger, more research may be required in order to provide a more certain conclusion (Ernst & Pittler 2000). A study conducted in 2012 indicated that ginger supplementation did reduce nausea caused by chemotherapy significantly, so there is potential for ginger to lessen the symptoms associated with cancer (Ryan et al., 2011) (Table 8.2).

TABLE 8.2
List of Drugs Approved by the Food and Drug Administration (FDA) for Colon and Rectal Cancer[a]

Drugs for Colon Cancer	Drugs for Rectal Cancer
• Avastin (Bevacizumab)	• Avastin (Bevacizumab)
• Bevacizumab	• Bevacizumab
• Camptosar (Irinotecan Hydrochloride)	• Camptosar (Irinotecan Hydrochloride)
• Capecitabine	• Capecitabine
• Cetuximab	• Cetuximab
• Cyramza (Ramucirumab)	• Cyramza (Ramucirumab)
• Eloxatin (Oxaliplatin)	• Eloxatin (Oxaliplatin)
• Erbitux (Cetuximab)	• Erbitux (Cetuximab)
• 5-FU (Fluorouracil Injection)	• 5-FU (Fluorouracil Injection)
• Fluorouracil Injection	• Fusilev (Leucovorin Calcium)
• Fusilev (Leucovorin Calcium)	• Fluorouracil Injection
• Ipilimumab	• Ipilimumab
• Irinotecan Hydrochloride	• Irinotecan Hydrochloride
• Keytruda (Pembrolizumab)	• Keytruda (Pembrolizumab)
• Leucovorin Calcium	• Leucovorin Calcium
• Lonsurf (Trifluridine and Tipiracil Hydrochloride)	• Lonsurf (Trifluridine and Tipiracil Hydrochloride)
• Nivolumab	• Nivolumab
• Opdivo (Nivolumab)	• Opdivo (Nivolumab)
• Oxaliplatin	• Oxaliplatin
• Panitumumab	• Panitumumab
• Pembrolizumab	• Pembrolizumab
• Ramucirumab	• Ramucirumab
• Regorafenib	• Regorafenib
• Stivarga (Regorafenib)	• Stivarga (Regorafenib)
• Trifluridine and Tipiracil Hydrochloride	• Trifluridine and Tipiracil Hydrochloride
• Vectibix (Panitumumab)	• Vectibix (Panitumumab)
• Xeloda (Capecitabine)	• Xeloda (Capecitabine)
• Yervoy (Ipilimumab)	• Yervoy (Ipilimumab)
• Zaltrap (Ziv-Aflibercept)	• Zaltrap (Ziv-Aflibercept)
• Ziv-Aflibercept	• Ziv-Aflibercept

[a] *Source:* "Drugs Approved for Colon and Rectal Cancer" from https://www.cancer.gov/about-cancer/treatment/drugs/colorectal. August 15, 2018; "Chemotherapy for Colorectal Cancer" from https://www.cancer.org/cancer/colon-rectal-cancer/treating/chemotherapy.html. February 21, 2018.

8.8 FUTURE DIRECTION OF GUT-RELATED CANCER AND NUTRACEUTICAL RESEARCH

The future of cancer and nutraceutical lies in the personalization of chemotherapy treatments through the promotion of gut preservation. Pre-and postadministration of nutraceuticals and specific bacterial stains can ameliorate the damaging effects on

gut flora and increase the toxicity of medication. The symbiotic relationship between the host immune system and gut microbiota presents an opportunity for alleviating debilitating symptoms like GI mucositis, constipation, diarrhea, and nausea/vomiting.

Additionally, replenishing the immune system and gut diversity assists in preventing opportunistic infections that challenge patient recovery and therapy. Recently, the employment of fecal transplants has displayed promising results in basic research and clinical trials in improving bacterial recolonization and bolstering drug therapy (Rea et al., 2018). Another aspect of nutraceutical research relies on the development of proper dosage protocols to reduce the overconsumption of vitamins and mineral, which can lead to serious conditions like hypervitaminosis or nephrolithiasis. In short, current focus on the localized and systemic effects of the gut microbiota may lead to changes in the process of chemotherapeutic drug administration and further the clinical application of nutraceuticals.

REFERENCES

Breyner, N. M. et al. (2017). Microbial anti-inflammatory molecule (MAM) from *Faecalibacterium prausnitzii* Shows a protective effect on DNBS and DSS-induced colitis model in mice through inhibition of NF-κB pathway. *Front Microbiol* **8**(114). doi:10.3389/fmicb.2017.00114.

"Chemotherapy for Colorectal Cancer" from https://www.cancer.org/cancer/colon-rectal-cancer/treating/chemotherapy.html. February 21, 2018.

"Drugs Approved for Colon and Rectal Cancer" from https://www.cancer.gov/about-cancer/treatment/drugs/colorectal. August 15, 2018.

"Signs and Symptoms of Cancer" from https://www.cancer.org/cancer/cancer-basics/signs-and-symptoms-of-cancer.html. August 11, 2014.

Avrelija, C. and C. Walter (2010). "Antimicrobial agents deriving from indigenous plants." *Recent Pat Food Nutr Agric* **2**(1): 83–92.

Catinean, A. et al. (2018). "An overview on the interplay between nutraceuticals and gut microbiota." *Peer J* **6**: e4465.

Chatturong, U., Kajsongkram, T., Tunsophon, S., Chanasong, R., Chootip, K. (2018). Ginger Extract and [6]-Gingerol Inhibit Contraction of Rat Entire Small Intestine. *J Evid Based Integr Med*. 2018;23:2515690X18774273. doi:10.1177/2515690X18774273.

Costantini, L. et al. (2017). "Impact of omega-3 fatty acids on the gut microbiota." *Int J Mol Sci* **18**(12): 2645.

D'Argenio, V. and F. Salvatore (2015). "The role of the gut microbiome in the healthy adult status." *Clin Chim Acta* **451**(Pt A): 97–102.

Eckburg, P. B. et al. (2005). "Diversity of the human intestinal microbial flora." *Science* **308**(5728): 1635–1638.

El Hage, R. et al. (2017). "Emerging trends in 'Smart Probiotics': Functional consideration for the development of novel health and industrial applications." *Front Microbiol* **8**: 1889.

Ernst, E. and M. H. Pittler (2000). Efficacy of ginger for nausea and vomiting: A systematic review of randomized clinical trials. *Br J Anaesth* **84**(3): 367–371.

Fan, F. Y. et al. (2017). "Catechins and their therapeutic benefits to inflammatory bowel disease." *Molecules* **22**(3): 484.

Gallagher, E. J. and D. LeRoith (2015). Obesity and diabetes: The increased risk of cancer and cancer-related mortality." *Physiol Rev* **95**(3): 727–748.

Garcia-Gonzalez, A. P. et al. (2017). "Bacterial metabolism affects the *C. elegans* response to cancer chemotherapeutics." *Cell* **169**(3): 431–441.

Gorgani, L. et al. (2017). "Piperine-the bioactive compound of black pepper: From isolation to medicinal formulations." *Compr Rev Food Sci Food Saf* **16**(1): 124–140.

Gupta, R. A. et al. (2015). "Effect of piperine on inhibition of FFA induced TLR4 mediated inflammation and amelioration of acetic acid induced ulcerative colitis in mice." *J Ethnopharmacol* **164**: 239–246.

Higdon, J. (2005a). "Curcumin." from https://lpi.oregonstate.edu/mic/dietary-factors/phytochemicals/curcumin#introduction.

Higdon, J. (2005b). "Resveratrol." from https://lpi.oregonstate.edu/mic/dietary-factors/phytochemicals/resveratrol.

Hirayama, K. and J. Rafter (1999). "The role of lactic acid bacteria in colon cancer prevention: Mechanistic considerations." *Antonie Van Leeuwenhoek* **76**(1–4): 391–394.

Kechagia, M. et al. (2013). "Health benefits of probiotics: A review." *ISRN Nutr* **2013**: 481651.

Koren, O. et al. (2012). "Host remodeling of the gut microbiome and metabolic changes during pregnancy." *Cell* **150**(3): 470–480.

Kuppusamy, P. et al. (2014). "Nutraceuticals as potential therapeutic agents for colon cancer: A review." *Acta Pharm Sin B* **4**(3): 173–181.

Laforest-Lapointe, I. and M. C. Arrieta (2017). "Patterns of early-life gut microbial colonization during human immune development: An ecological perspective." *Front Immunol* **8**: 788.

Laparra, J. M., Sanz, Y. (2010). "Bifidobacteria inhibit the inflammatory response induced by gliadins in intestinal epithelial cells via modifications of toxic peptide generation during digestion." *J Cell Biochem* **109**(4): 801–807. doi:10.1002/jcb.22459.

Li, Y. H. et al. (2015). "Role of phytochemicals in colorectal cancer prevention." *World J Gastroenterol* **21**(31): 9262–9272.

Lim, D. Y. et al. (2007). "Induction of cell cycle arrest and apoptosis in HT-29 human colon cancer cells by the dietary compound luteolin." *Am J Physiol Gastrointest Liver Physiol* **292**(1): G66–G75.

Lin, C., C. Lin and G. J. Tsay (2012). 6-Gingerol inhibits growth of colon cancer cell LoVo via induction of G2/M arrest. *Evid-Based Complementary Altern Med* 2012: 1–7. doi:10.1155/2012/326096.

Liu, T. et al. (2017). "NF-kappaB signaling in inflammation." *Signal Transduct Target Ther* **2**: 17023.

Ma, Y. et al. (2013). "Obesity and risk of colorectal cancer: A systematic review of prospective studies." *PLoS One* **8**(1): e53916.

Manichanh, C. et al. (2006). "Reduced diversity of faecal microbiota in Crohn's disease revealed by a metagenomic approach." *Gut* **55**(2): 205–211.

Manikandan, R. et al. (2012). "Synergistic anticancer activity of curcumin and catechin: An in vitro study using human cancer cell lines." *Microsc Res Tech* **75**(2): 112–116.

Martín, R. et al. (2017). Functional characterization of novel *Faecalibacterium prausnitzii* strains isolated from healthy volunteers: A step forward in the use of *F. prausnitzii* as a next-generation probiotic. *Front Microbiol* **8**: 1226. doi:10.3389/fmicb.2017.01226.

Myles, I. A. (2014). "Fast food fever: Reviewing the impacts of the Western diet on immunity." *Nutr J* **13**: 61.

Nakayama, H. et al. (1997). "Intestinal anaerobic bacteria hydrolyse sorivudine, producing the high blood concentration of 5-(E)-(2-bromovinyl)uracil that increases the level and toxicity of 5-fluorouracil." *Pharmacogenetics* **7**(1): 35–43.

Noriega, B. S. et al. (2016). "Understanding the impact of omega-3 rich diet on the gut microbiota." *Case Rep Med* **2016**: 3089303.

Nunes, S. et al. (2018). "Resveratrol and inflammatory bowel disease: The evidence so far." *Nutr Res Rev* **31**(1): 85–97.

O'Callaghan, A. and D. van Sinderen (2016). "Bifidobacteria and their role as members of the human gut microbiota." *Front Microbiol* **7**: 925.

O'Toole, P. W. and M. J. Claesson (2010). "Gut microbiota: Changes throughout the lifespan from infancy to elderly." *Int Dairy J* **20**(4): 281–291.

Park, I. J. et al. (2009). "Green tea catechin controls apoptosis in colon cancer cells by attenuation of H2O2-stimulated COX-2 expression via the AMPK signaling pathway at low-dose H2O2." *Ann N Y Acad Sci* **1171**: 538–544.

Park, M. S., Kwon, B., Ku, S., Ji, G. E. (2017). "The efficacy of *Bifidobacterium longum* BORI and *Lactobacillus acidophilus* AD031 probiotic treatment in infants with rotavirus infection." *Nutrients*. **9**(8): 887. Published 2017 Aug 16. doi:10.3390/nu9080887.

Penders, J. et al. (2006). "Factors influencing the composition of the intestinal microbiota in early infancy." *Pediatrics* **118**(2): 511–521.

Pool-Zobel, B. L. et al. (1996). "Lactobacillus- and bifidobacterium-mediated antigenotoxicity in the colon of rats." *Nutr Cancer* **26**(3): 365–380.

Pouncey, A. L. et al. (2018). "Gut microbiota, chemotherapy and the host: The influence of the gut microbiota on cancer treatment." *Ecancermedicalscience* **12**: 868.

Ravindran, J. et al. (2009). "Curcumin and cancer cells: How many ways can curry kill tumor cells selectively?" *AAPS J* **11**(3): 495–510.

Rea, D. et al. (2018). "Microbiota effects on cancer: From risks to therapies." *Oncotarget* **9**(25): 17915–17927.

Ryan, J. L. et al. (2012). "Ginger (*Zingiber officinale*) reduces acute chemotherapy-induced nausea: A URCC CCOP study of 576 patients." *Support Care Cancer* **20**(7): 1479–1489.

Siddiqui, R., Hassan, S., Harvey, K., Rasool, T., Das, T., Mukerji, P., and DeMichele, S. (2009). Attenuation of proteolysis and muscle wasting by curcumin c3 complex in MAC16 colon tumour-bearing mice. *Br J Nutr* **102**(7): 967–975. doi:10.1017/S0007114509345250.

Shadfar, S. et al. (2011). "Oral resveratrol therapy inhibits cancer-induced skeletal muscle and cardiac atrophy in vivo." *Nutr Cancer* **63**(5): 749–762.

Sokol, H. et al. (2008). "*Faecalibacterium prausnitzii* is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients." *Proc Natl Acad Sci USA* **105**(43): 16731–16736.

Suh, Y. et al. (2009). "A plant flavonoid fisetin induces apoptosis in colon cancer cells by inhibition of COX2 and Wnt/EGFR/NF-kappaB-signaling pathways." *Carcinogenesis* **30**(2): 300–307.

Sukhthankar, M. et al. (2010). "(-)-Epigallocatechin-3-gallate (EGCG) post-transcriptionally and post-translationally suppresses the cell proliferative protein TROP2 in human colorectal cancer cells." *Anticancer Res* **30**(7): 2497–2503.

The Human Microbiome Project Consortium. (2012). "Structure, function and diversity of the healthy human microbiome." *Nature* **486**: 207.

Tojo, R. et al. "Intestinal microbiota in health and disease: Role of bifidobacteria in gut homeostasis." *World J Gastroenterol* **20**(41): 15163–15176. doi:10.3748/wjg.v20.i41.15163.

Tsai, C. Y. et al. (2010). "Effect of soy saponin on the growth of human colon cancer cells." *World J Gastroenterol* **16**(27): 3371–3376.

Vasconcelos, P. C. et al. (2012). "Epicatechin used in the treatment of intestinal inflammatory disease: An analysis by experimental models." *Evid Based Complement Alternat Med* **2012**: 508902.

Vetizou, M. et al. (2015). "Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota." *Science* **350**(6264): 1079–1084.

Wang, H. et al. (2011). "Epigallocatechin-3-gallate effectively attenuates skeletal muscle atrophy caused by cancer cachexia." *Cancer Lett* **305**(1): 40–49.

Wang, K. et al. (2015). "Curcumin inhibits aerobic glycolysis and induces mitochondrial-mediated apoptosis through hexokinase II in human colorectal cancer cells in vitro." *Anticancer Drugs* **26**(1): 15–24.

Wang, X. et al. (2012). "N-3 PUFAs attenuate ischemia/reperfusion induced intestinal barrier injury by activating I-FABP-PPARgamma pathway." *Clin Nutr* **31**(6): 951–957.

Wang, Y. et al. (2014). "Astragalus saponins modulates colon cancer development by regulating calpain-mediated glucose-regulated protein expression." *BMC Complement Altern Med* **14**: 401.

Wargovich, M. J. et al. (2010). "Nutraceutical use in late-stage cancer." *Cancer Metastasis Rev* **29**(3): 503–510.

Wu, H. J. and E. Wu (2012). "The role of gut microbiota in immune homeostasis and autoimmunity." *Gut Microbes* **3**(1): 4–14.

Yaffe, P. B. et al. (2013). "Piperine impairs cell cycle progression and causes reactive oxygen species-dependent apoptosis in rectal cancer cells." *Exp Mol Pathol* **94**(1): 109–114.

Yaffe, P. B. et al. (2015). "Piperine, an alkaloid from black pepper, inhibits growth of human colon cancer cells via G1 arrest and apoptosis triggered by endoplasmic reticulum stress." *Mol Carcinog* **54**(10): 1070–1085.

Yang, S. et al. (2015). "Resveratrol elicits anti-colorectal cancer effect by activating miR-34c-KITLG in vitro and in vivo." *BMC Cancer* **15**: 969.

Yatsunenko, T. et al. (2012). "Human gut microbiome viewed across age and geography." *Nature* **486**(7402): 222–227.

Zhang, L. et al. (2004). "Investigation of intestinal absorption and disposition of green tea catechins by Caco-2 monolayer model." *Int J Pharm* **287**(1–2): 1–12.

Zhang, X. A. et al. (2015). "Quercetin induces human colon cancer cells apoptosis by inhibiting the nuclear factor-kappa B Pathway." *Pharmacogn Mag* **11**(42): 404–409.

Zheng, J. et al. (2016). "Spices for prevention and treatment of cancers." *Nutrients* **8**(8): 495. Published 2016 Aug 12. doi:10.3390/nu8080495.

Zick, S. M. et al. (2011). Phase II study of the effects of ginger root extract on eicosanoids in colon mucosa in people at normal risk for colorectal cancer. *Cancer Prev Res* **4**(11): 1929–1937. doi:10.1158/1940–6207.capr-11–0224.

9 Nutrigenomics and Nutrigenetics in Cancer Prevention

Komal Parmar and Jayvadan K. Patel

CONTENTS

9.1 INTRODUCTION

As an undeniably predominant malady and the main cause of death in recent times, malignancy is a noteworthy risk to human well-being. Cancer occurrence is anticipated to increase later on and an efficacious preventive methodology is required to confront this challenge. Although cancer examination has rendered us with a superior comprehension of growth science, we still confront various difficulties in disease treatment and counteractive action. Current treatments are to a great extent constrained to medical procedure, radiation treatment, and chemotherapy, which remain unacceptable. Specifically, there are numerous issues with such therapies such as low response rate, poor specificity, drug resistance, and serious side effects. Cancer is at a very basic level a genetic malady in which alteration of the DNA of single cell occurs. These changes in the DNA might be

responsible for several changes including physical, chemical, or biological ones. The phase of advancement is the second phase of carcinogenesis. The started cell is converted into a cancerous cell via moderate and gradual process. The third phase is of progression in which numerous malignant cells grow uncontrollably (Pitot et al. 2004). Although the connection between diet and cancer is still not definitive, research studies suggest that diet may alter the risk and improve the consequences of cancer. According to the epidemiological information, a vast portion of human malignancies are connected with lifestyle and food habits (Elsamanoudy et al. 2016). There are various environmental factors that can prove harmful. Endogenous reactions such as oxidation and exogenous reactions like smoke, UV light, aflatoxin, and high dose of radiations may cause malignancies (Setlow 2001).

9.2 NUTRIGENOMICS

The observation that eating habits impact health, a relationship between supplement and illness has been built up. This relationship between food and disease is presently being explored through present day epidemiological examinations. In recent years, the cellular events interceding the beginning of carcinogenesis, despite their change by dietary factors, has yielded critical data in comprehension of this abnormal condition (Anderle et al. 2004). Several food components can regulate gene expression patterns resulting into abnormalities. It is possible that because of modification in the nourishment propensities and lifestyle, individuals are becoming more inclined to diet-related chronic sickness and abnormalities. In this context, nutrigenomics, a relatively new science, focuses on exploring the role of dietary nutrients in gene expression and the interaction between genes and bioactive food components. This will in turn provide important information about dietary components having beneficial or negative effects on health (German 2005, Miggiano and Sanctis 2006). In the development of nutraceuticals, effects of functional food on human health have been precisely termed as nutrigenomics or nutrigenetics. Nutrigenomics represents the analysis of consequence of nutrient ingestion on whole genome (genetic material in cells), proteome (set of protein expressed by genome), and metabolome (set of metabolites) (Sharma and Dwivedi 2017). It adverts to the use of genomic standards in dietary research and empowers us to figure relationship between particular dietary supplements and hereditary elements. The interactions between dietary supplements and genetic material influence digestion, absorption, and excretion of bioactive dietary components, and in addition, impact their site of action (Figure 9.1). This science considers nutrients as dietary signals that are detected by cellular sensor systems, which regulate gene expressions and metabolite production (Robert et al. 2001). This understanding will promote health and reduce the risk of growing maladies (Fujii et al. 2010).

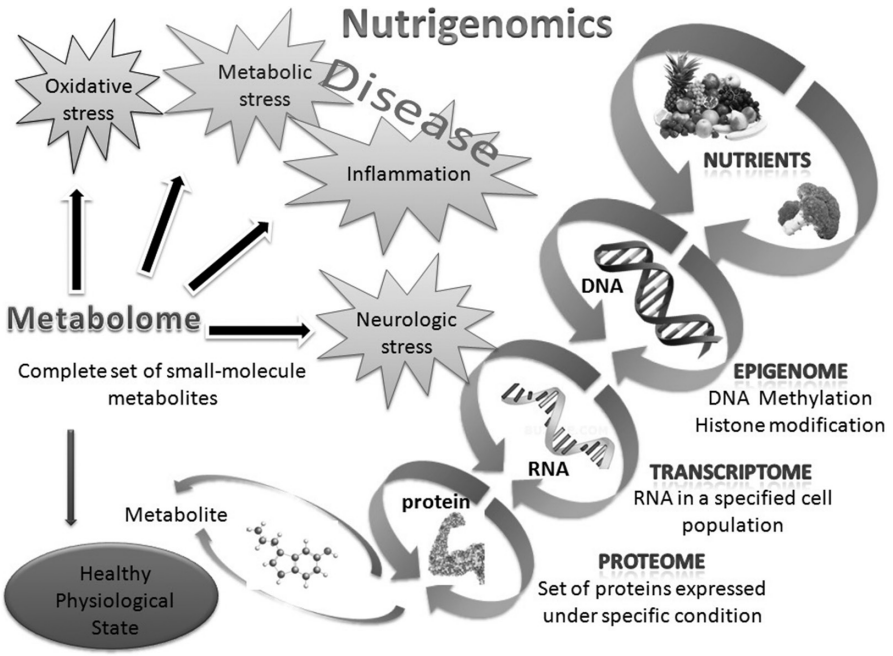


FIGURE 9.1 Relation between nutrigenomics and disease.

9.3 NUTRIGENETICS

In contrast, nutrigenetics studies the genetic variation in an individual in as a result of interaction between diet and disease. These individual differences might be attributed to single nucleotide polymorphisms rather than whole gene (Ardekani and Jabbari 2009). In view of various investigations on populace contrasts in single-nucleotide polymorphisms, it is found that genetic attributes play a significant part in adjudicating an individual's risk of developing of specific ailment (Grody 2003). Further, it is proposed that nutrigenetics is associated with dealing with the system through which genetic variability characterizes the chance of individual to illness, supplement day to day prerequisites, cell metabolic reaction, and response to bioactive supplement or nutritional treatment. Nutrient requirements vary with individual on basis of genetic variations among the population. In addition, different response of genetic variation of different individuals might be observed even with the same nutrient. A well-known example of gene–nutrient interaction is represented by methylene tetra hydrofolate reductase gene (MTHFR). This gene is involved in the metabolism of folic acid and thereby maintains the level of homocysteine amino acid in the blood. MTHFR is responsible for the conversion of 5,10 methylene tetrahydrofolate

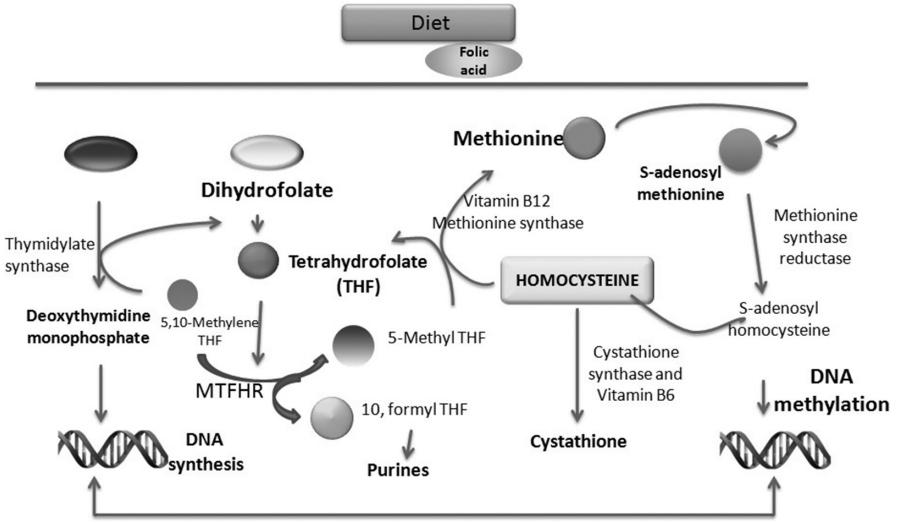


FIGURE 9.2 Importance of folic acid in DNA methylation and DNA synthesis.

to 5-methylene tetrahydrofolate. This step is required for the further conversion of homocysteine to methionine (Figure 9.2). It is observed that the deficiency of folic acid in the diet is associated with elevated levels of homocysteine in blood, which is attributed to specific MTHFR gene single-nucleotide polymorphism (Sharma and Dwivedi 2017). This condition is further associated with inflammation, heart disease, birth defects, and having a debilitated capacity to detoxify. Homocysteine concentrations are affected by nutritional inadequacies, particularly of folic acid, vitamin B12, and vitamin B6 (Patrick et al. 2004, Selhub 2006, 2008). Several investigations have demonstrated that diet has an essential effect on the risk of building up of specific ailments, and genetic sensitivity has been assumed to be part of this (Chang et al. 2016, Little et al. 2017, Osman et al. 2018, Ordovas and Shen 2008). Figure 9.3 describes the difference between nutrigenomics and nutrigenetics.

One example of diet-related genetic variation and disease associated with it fits with a case study on the occurrence of hepatocellular carcinoma in the population of Sudan. Results reported a strong relationship between the risk of developing hepatocellular carcinoma and the intake of peanut butter contaminated with aflatoxins in the Sudanese population. The association of disease and peanut intake was found to be limited to people with glutathione-S-transferase M1 null genotype (Omer et al. 2001).

With the burgeoning information of the human genome sequence, the HapMap project and the classifying genetic variations in human, specialists in the field of nutrigenetics can recognize particular polymorphisms associated with the risk of disease or sensitivity to diet (Sachidanandam et al. 2001, Fareed and Afzal 2013). Recently, a high determination recombination guide of human genome has given and expanded the data on the genetic order of polymorphic markers and the single-nucleotide polymorphism guide of the human genome (Telenti et al. 2016, Kong et al. 2004).

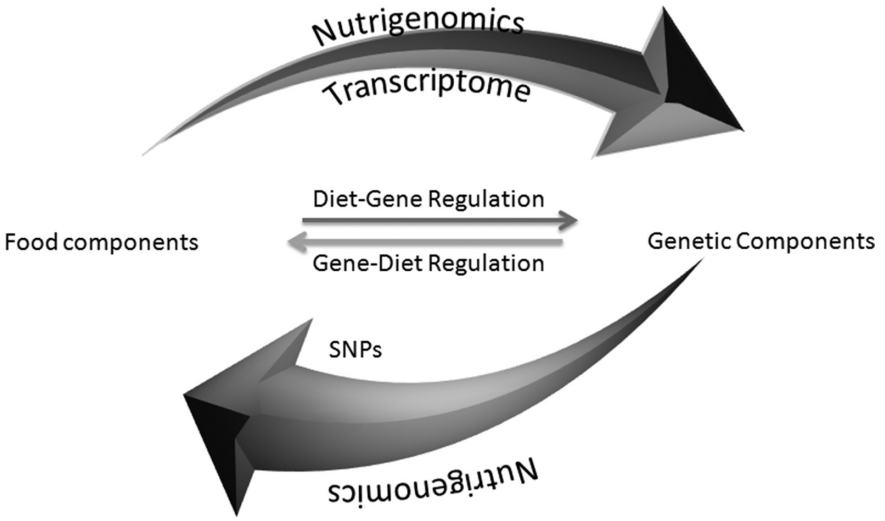


FIGURE 9.3 Distinction between nutrigenomics and nutrigenetics.

The essential components of nutritional genomics are as follows. First, diet is supposed to be the fundamental inclining factor for various diseases in some individuals. For example, saturated-fat-containing food causes cardiovascular disease and sugar-based food cause diabetes. Second component suggests that diet components influence genetic variation and consequently human genome. For example, diet contains several precursors like folate and other B vitamins for the synthesis of S-adenosylmethionine (SAM), which is a universal donor of methyl groups with an essential role in the regulation of various genes. The reduced availability of methyl donor will result in hypomethylation of DNA, affecting the regulation of gene expression. Third component demonstrates the possibility of influence of genetic variation, which can further help explain the balance between health and diet (Arkadianos et al. 2007). Fourth component includes information about the fact that the genes that are dependent on dietary constituents for their regulation may have a role in triggering, development, and progression of chronic illness.

Therefore, general objective of this "omic" science includes how genes interact with the dietary supplements. It explains how DNA and genetic code impact our requirement for particular supplements in particular amounts for sustaining better health. Keeping genetic makeup of the individual and some etiological view points of chronic diseases; It is useful to decide the customized amount of calories that involves person nourishing necessities in view of genetic makeup of the individual and also clears up some etiological point of view of chronic diseases. As given in Table 9.1, during a lifetime, nutrition can change the physiologic and pathologic processes through epigenetic mechanisms that are important for genetic expression. Epigenetics can be defined as somatible heritable states of the genetic expression due to changes in the chromatin structure without alteration in the DNA sequence, including DNA methylation, histone modifications, and chromatin remodeling.

TABLE 9.1
Epigenetic Role of Some Dietary Components in Various Physiologic and Pathologic Processes

Physiologic or Pathologic Process	Nutrition/Diet	Epigenetic Mechanism
Embryogenesis	Folate deficiency	DNA methylation (Chang et al. 2011)
	Choline deficiency	DNA methylation (Zeisel 2009)
	Protein restriction	DNA methylation (Jia et al. 2013)
	Alcohol exposure	DNA methylation, histone modification (Ungerer et al. 2013)
Stem cell	Butyrate formation from dietary plant fiber	Histone acetylation (Mu et al. 2013)
	Retinoic acid intake	Chromosomal transcription (Gudas and Wagner 2011, Nguyen et al. 2016)
Obesity	High-fat diet	DNA methylation (Zwamborn et al. 2017)
	Curcumin intake	Histone acetylation (Shao et al. 2012)
Inflammation	Resveratrol intake	Modification of Interleukin-6 pathway (Larrosa et al. 2009)
	Methyl-deficient diet	TNF pathway, p38, cPLA2, and COX-2 (Chen et al. 2011)
Neurocognition	Choline intake	DNA hypomethylation (Nyaradi et al. 2013)
	Vitamin B12 intake	DNA hypomethylation (Nyaradi et al. 2013)

9.4 DIET–DISEASE INTERACTION

A substantial variation in absorption, metabolism, and elimination of dietary constituents prevails among individuals, which results in different concentrations of dietary constituents in blood or tissue. Reason for such variable and complicated body processes is poorly known till date. These variable responses in individuals make an important area for extensive research ahead. Impact of dietary responses and mediation on phenotypes, for example, body weight, blood pressure, and blood cholesterol levels, indicates substantial interpersonal deviations (Ordovas 2008, Ordovas et al. 2007). Other factors that can influence dietary responses include smoking, genetic difference, age, gender, physical activity, and many more. The objective of nutritional research in genetics is to identify individuals who can be profited from particular nutritional interference and identify the respective alternatives.

9.5 NUTRIGENOMICS–NUTRIGENETICS IN CANCER MANAGEMENT

The World Cancer Research Fund and the American Institute of Cancer Research (WCRF/AICR) have recently updated their 1997 summary in their second expert report that there is an association between food, nutrition, physical activity, and

prevention of cancer. Further, the report suggests that cancer incidence can be avoided by modification in diet and physical activity (Wiseman 2008). Out of the total cases of human cancers, about 5% originate from mutational events, while remaining 95% originate from occasional events resulting from exposure to environmental and dietary factors. The evidence suggests that of all cancer-related deaths, almost 25%–30% are due to tobacco, 30%–35% due to dietary factor, 15%–20% are due to infections, and the remaining are linked to radiations, stress, physical activity, environmental pollutants, and other factors (Anand et al. 2008). In addition, investigations have demonstrated several bioactive food components including phytochemicals found in plants (Manson et al. 2007), zoochemical found in animals and fish like conjugated linoleic acid (Bhattacharya et al. 2006) and omega-3 fatty acids (Simopoulos 2006), respectively, fungochemicals found in mushrooms (Chen et al. 2006), and bacteriochemicals formed from microbial fermentation (Wollowski et al. 2001) probably alter sensitivity to malignancy. In fact, many nutrients are involved in various pathways of cancer considering apoptosis, cell differentiation, inflammation, DNA change, and carcinogen metabolism (Davis and Milner 2007).

Epigenetic changes that mediate changes in genetic expression without changing the DNA sequence include DNA methylation and histone modification. Such changes accumulate with increase in age, which increases the sensitivity toward cancer development in body. Use of bioactive compounds may prove as potential tool for treatment/prevention of cancer. Nuclear receptors are group of transcription factors that function as sensors to dietary constituents and thereby mediate the response to dietary factors (Romagnolo et al. 2014). Nutrient–gene interactions influencing cancer process are modulated by genetic mutations, epigenetic modifications, interactions with dietary constituents, and heterogeneity of cells in tumor. Therefore, in order to find out how nutrigenomics and nutrigenetics will help in preventing cancer disease, knowledge of gene polymorphisms, gene targets that regulate cell and tissue pathways, and strategies to control clinical heterogeneity are important.

The International Agency for Research on Cancer (2015) stated that consumption of red and processed meat is carcinogenic to humans and increases mortality. Investigations have reported a correlation between colon cancer and consumption of red meat, animal protein, and total fat. Major theories found experimentally behind the association are (1) high-fat or -protein diet could promote carcinogenesis, (2) mutagenic and carcinogenic heterocyclic amines and polycyclic aromatic hydrocarbons are formed on heating meat at high temperature, (3) carcinogenic N-nitroso compounds are formed in food and in cell by nitrosation of nitrites/nitrates, and (4) heme group iron of myoglobin present in red meat can be carcinogenic because of its property to proliferate through lipoperoxidation (Santarelli et al. 2008, Ferguson 2010). It may also function as a catalyst to nitrosoamine formation and generate free radicals that may further damage the DNA (Kushi et al. 2012).

Phase II enzymes are involved in glucuronidation, sulfation, acetylation, and methylation processes. It has been demonstrated that the actions of phase II enzymes are interceded by the antioxidant reaction component, which is situated in the promoter locale of particular genes. Food nutrients can likewise incite numerous enzymes through actuation of signal transduction pathways. Food nutrients can thereby

modulate signal pathways including mitogen-activated protein kinase, protein kinase C, and phophatidylinositol 3-kinase that link multiple cellular processes to cancer (Lee and Surh 2005).

Dietary bioactive constituents found in fruits and vegetables can counteract carcinogenesis by blocking the metabolic actuation by enhancing detoxification process. Several investigations have concluded that plant food constituents can modulate detoxification enzymes. Examples include but are not limited to flavanoids, such as quercetin, kaempferol, and genistein (Moon et al. 2006, Miron et al. 2017); phenols, for example, vanillic acid, coumaric acid, and curcumin (Link et al. 2013, Altay et al. 2017); isothiocyanates (Grundemann and Huber 2018); and others that induce apoptosis and inhibit cell proliferation.

9.6 POLYPHENOLS

Polyphenols are essential micronutrients found abundantly in our diet, and the ground for their role in the prevention of cancer is egressing. Found in fruits and vegetables, wine, tea, extra virgin olive oil, chocolate, and other cocoa products, they form major antioxidants of our diet. Generally, food contains complex mixture of polyphenols, which comprise mostly flavones, isoflavones, flavanols, catechins, and phenolic acids (Pandey and Rizvi 2009). Clove is the richest dietary source of polyphenols, with 15188 mg per 100 g of fresh fruit (Perez-Jimenez et al. 2010). Rao and Pagidas (2010) evaluated the effect of tea polyphenol on human ovarian cancer. Reports suggested epigallocatechin-3-gallate, a tea polyphenol present in green tea, is found to be an antiproliferative and proapoptotic agent in the human ovarian cancer via DNA damage. Further, Huang et al. (2016) reported the effects of tea polyphenols on the ovarian cancer cells. The authors find that tea polyphenols induced apoptosis and inhibited proliferation and invasion of ovarian cancer cells by regulating the gene expression of cyclin D, MMP2, Bax, and Bcl-2. Hong et al. (2009) demonstrated that pomegranate polyphenols reduced tumor cell growth in prostate cancer. The bioactive components also induced apoptosis in both androgen-dependent and -independent cancer cells. Further, Thomas et al. (2014) carried out a double-blind randomized trial to evaluate the effect of polyphenol-rich whole food supplement on prostate-specific antigen (PSA) progression in patients with prostate cancer. A blend of pomegranate, broccoli, green tea, and turmeric was used for the study. They reported a significant short-term and favorable effect on the rising PSA in patients. Thangapazham et al. (2007) reported an investigation suggesting the effectiveness of green tea polyphenols and its constituent epigallocatechin gallate in tumor regression in breast cancer. Results suggested a downregulation of the gene expression of cyclin D, cyclin E, CDK 4, CDK 1, and PCNA in the treated investigated group. Various types of polyphenols and their dietary sources are summarized in Table 9.2.

TABLE 9.2
Polyphenols for Cancer Prevention/Therapy

Polyphenol	Dietary Source	Cancer and Mechanism
Quercetin	Fruits and green leafy vegetables	Lymphocytic leukemia; Downregulates Mcl-1 mRNA (an antiapoptotic protein) (Spagnuolo et al. 2012)
Xanthohumol	Beer	Cervical cancer; downregulation of XIAP, upregulation of p53 proteins, and S phase cell cycle arrest (Yong and Abd Malek 2015), nonsmall cell lung cancer; accumulation of cells in sub-G1 and -S phase (Yong et al. 2015)
Epigallocatechin-3-gallate	Green tea	Lung cancer; suppress MMP-2 expression via JNK signaling (Deng and Lin 2011); gastric cancer; multiple signal transduction pathways (Tanaka et al. 2011), colon cancer; suppressing kinase pathways (Cerezo-Guisado et al. 2015)
Naringenin	Citrus fruits	Gastric cancer; Down regulation of AKT pathway (Bao et al. 2016), lung cancer; TRAIL-induced apoptosis (Jin et al. 2011), colon cancer; apoptosis through p38-dependent ATF3 activation (Song et al. 2016), liver cancer; multiple signal transduction pathways (Yen et al. 2015)
Hesperitin	Fruits and vegetables	Gastric cancer; mitochondrial pathway (Zhang et al. 2015), breast cancer; ASK1/JNK pathway (Palit et al. 2015), cervical cancer; mitochondrial pathways and cell cycle arrest (Alshatwi et al. 2013)
Apigenin	Fruits, vegetables, tea	Prostate cancer; epithelial mesenchymal transition (Zhu et al. 2015), lung cancer; mitochondria-dependent pathways (Lu et al. 2011), gastric cancer; mitochondria signal pathway (Chen et al. 2014), colorectal cancer; decreasing phosphorylation of Akt (Chunhua et al. 2013)
Luteolin	Fruits, vegetables, spices	Lung cancer; multiple pathways (Choi et al. 2016)
Kaempferol	Fruits and vegetables	Gastric cancer; Bax expression (Song et al. 2015), Liver cancer; CDK1/cyclin B expression and the AMPK and AKT signaling pathways (Huang et al. 2013)
Geinstein	Soy products	Small cell lung cancer; downregulating FoxM1 (Tian et al. 2014), colorectal cancer; inhibiting phosphorylation of Akt (Qin et al. 2016)
Ellagic acid	Fruits	Breast cancer; TGF-β/Smads pathway (Chen et al. 2015a), colorectal cancer; multiple pathways (Yousef et al. 2016)
Ferulic acid	Cereals	Prostate cancer; cell cycle arrest and apoptosis (Eroğlu et al. 2015)
Resveratrol	Fruits, red wine	Gastric cancer; G1 phase arrest (Yang et al. 2013), gastric cancer; apoptosis via reactive oxygen species (Wang et al. 2012), colorectal cancer; MDR1 expression inhibition (Wang et al. 2015), cervical cancer; apoptosis and autophagy (García-Zepeda et al. 2013)

9.7 VITAMINS AND OTHER MICRONUTRIENTS

Some natural antioxidants found in diet are observed to have important role in prevention of cancer. Such antioxidant vitamins, including vitamins A, E, and C, show these prophylactic effects. Studies have suggested that interactions between dietary vitamins and other micronutrients on genetic polymorphisms lead to cancer. Carotenoids are found in dietary fruits and vegetables such as carrots, sweet potato, and cantaloupe. β-Carotene, lutein, lycopene, zeaxanthin, and β-cryptoxanthin are the examples that are studied extensively for the cancer preventive investigations. Gong et al. (2018) investigated the association of carotenoid lutein and the reduced risk of breast cancer. Results demonstrated significant reduction in breast cancer cell growth by lutein. The probable mechanism found was cell cycle arrest and caspase-independent cell death. Additionally, it was found that the p53 signaling pathway was activated and HSP60 levels were increased with lutein treatment, which might have contributed to the growth inhibition of tumor cells. Another such work by Rafi et al. (2015) described the association of lutein and modulation of prostate cancer cells. The findings suggested that lutein was capable of regulating the expression of growth and survival-associated genes in prostate cancer cells.

Lycopene found in tomatoes and other red vegetables and fruits is studied to influence cancer growth by the investigators. Palozza and coworkers (2010) demonstrated the beneficial role of lycopene in cancer. Results indicated an antitumor activity of lycopene due to reduction in Ras-dependent activation of nuclear factor kappa B (NF-κB). Also, the inhibition of mevalonate pathway had a key role in the growth inhibitory action of lycopene.

Bi et al. (2013) studied the effect of zeaxanthin, a carotenoid found in egg yolk, corn, and other vegetables and fruits, on human uveal melanoma cells. Western blot analysis performed suggested the inhibition of expressions of antiapoptotic proteins (Bcl-2 and Bcl-xL) by zeaxanthin. Also, proapoptotic proteins (Bak and Bax) were activated by the nutrient resulting in the apoptosis of melanoma cells.

A meta-analysis was carried out by Zhang et al. (2016) to determine the association between dietary intake of vitamin A and pancreatic cancer risk. After exclusive literature search, total 11 study reports were taken as material for further assessment. Results demonstrated that higher category of dietary intake of vitamin A was associated with reduced pancreatic cancer risk. In another similar type of study, researchers carried out meta-analysis to demonstrate the association of dietary vitamin A and β-carotene intake with reduced risk of lung cancer (Yu et al. 2015). Results from the 19 studies suggested that these micronutrients could reduce the risk of lung cancer. Effect of dietary intake of vitamin E on lung cancer was evaluated by Chen et al. (2015b) from the meta-analysis. Ten articles reporting 11 studies were evaluated for the investigation. Overall, the analysis indicated that the higher dietary intake of vitamin E might reduce the risk of lung cancer. Bai et al. (2015) attempted to investigate the association of vitamin C intake and risk of prostate cancer. Meta-analysis involving 103,658 subjects was carried out. From the results, an inverse dose–response linear relationship was obtained between vitamin C intake and risk of prostate cancer. In another dose–response meta-analysis, an association between

dietary vitamin C intake and risk of esophageal cancer was demonstrated (Bo et al. 2016). From 15 articles including 20 studies, it was found that a higher dietary vitamin C was inversely related with the risk of esophageal cancer.

9.8 SUMMARY

Dietary nutrients are likely to be associated with the reduced risk of cancer in humans. Genetic polymorphisms influenced by some dietary deficiency may lead to cancer development. Thus, nutrigenomics and nutrigenetics may provide us a deep insight into the association between dietary nutrients and cancer risk. However, as the field of molecular nutrition is expanding, a greater and better understanding of how dietary constituents can be utilized for the cancer treatment or prevention should be achieved through more in vivo research work.

REFERENCES

Alshatwi AA, Ramesh E, Periasamy VS, Subash-Babu P. The apoptotic effect of hesperetin on human cervical cancer cells is mediated through cell cycle arrest, death receptor, and mitochondrial pathways. *Fundam Clin Pharmacol*. 2013; 27(6): 581–592.

Altay A, Kartal DI, Sadi G, Guray T, Yaprak AE. Modulation of mRNA expression and activities of xenobiotic metabolizing enzymes, CYP1A1, CYP1A2, CYP2E1, GPx and GSTP1 by the Salicornia freitagii extract in HT-29 human colon cancer cells. *Arch Biol Sci*. 2017; 69(3): 439–448.

Anand P, Kunnumakara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, Sung B, Aggarwal BB. Cancer is a preventable disease that requires major lifestyle changes. *Pharm Res.* 2008; 25(9): 2097–2116.

Anderle P, Farmer P, Berger A, Roberts MA. Nutrigenomic approach to understanding the mechanisms by which dietary long-chain fatty acids induce gene signals and control mechanisms involved in carcinogenesis. *Nutrition*. 2004; 20: 103–108.

Ardekani AM, Jabbari S. Nutrigenomics and Cancer. *Avicenna J Med Biotechnol*. 2009; 1(1): 9–17.

Arkadianos I, Valdes AM, Marinos E, Florou A, Gill RD, Grimaldi KA. Improved weight management using genetic information to personalize a calorie controlled diet. *Nutr J*. 2007; 6: 29. doi:10.1186/1475-2891-6-29.

Bai XY, Qu X, Jiang X, Xu Z, Yang Y, Su Q, Wang M, Wu H. Association between dietary vitamin C intake and risk of prostate cancer: A meta-analysis involving 103,658 subjects. *J Cancer.* 2015; 6(9): 913–921.

Bao L, Liu F, Guo HB, Li Y, Tan BB, Zhang WX, Peng YH. Naringenin inhibits proliferation, migration, and invasion as well as induces apoptosis of gastric cancer SGC7901 cell line by downregulation of AKT pathway. *Tumour Biol*. 2016; 37(8): 11365–11374.

Bhattacharya A, Banu J, Rahman M, Causey J, Fernandes G. Biological effects of conjugated linoleic acids in health and disease. *J Nutr Biochem*. 2006; 17(12): 789–810.

Bi M-C, Rosen R, Zha R-Y, McCormick SA, Song E, Hu D-N. Zeaxanthin induces apoptosis in human uveal melanoma cells through Bcl-2 family proteins and intrinsic apoptosis pathway. Evidence-based complementary and alternative medicine: eCAM. 2013; 2013: 205082. doi:10.1155/2013/205082.

Bo Y, Lu Y, Zhao Y, Zhao E, Yuan L, Lu W, Cui L, Lu Q. Association between dietary vitamin C intake and risk of esophageal cancer: A dose-response meta-analysis. *Int J Cancer.* 2016; 138(8): 1843–1850.

Cerezo-Guisado MI, Zur R, Lorenzo MJ, Risco A, Martín-Serrano MA, Alvarez-Barrientos A, Cuenda A, Centeno F. Implication of Akt, ERK1/2 and alternative p38MAPK signalling pathways in human colon cancer cell apoptosis induced by green tea EGCG. *Food Chem Toxicol*. 2015; 84: 125–132.

Chang H, Zhang T, Zhang Z, Bao R, Fu C, Wang Z, Bao Y, Li Y, Wu L, Zheng X, Wu J. Tissue-specific distribution of aberrant DNA methylation associated with maternal low-folate status in human neural tube defects. *J Nutr Biochem*. 2011; 22(12): 1172–1177.

Chang TJ, Wang WC, Hsiung CA, He CT, Lin MW, Sheu WH, Chang YC, Quertermous T, Chen I, Rotter J, Chuang LM. SAPPHIRe Study Group. Genetic variation in the human SORBS1 gene is associated with blood pressure regulation and age at onset of hypertension: A SAPPHIRe Cohort Study. *Medicine* (*Baltimore*). 2016; 95(10): e2970. doi:10.1097/MD.0000000000002970.

Chen HS, Bai MH, Zhang T, Li GD, Liu M. Ellagic acid induces cell cycle arrest and apoptosis through TGF-β/Smad3 signaling pathway in human breast cancer MCF-7 cells. *Int J Oncol*. 2015a; 46(4): 1730–1738.

Chen G, Wang J, Hong X, Chai Z, Li Q. Dietary vitamin E intake could reduce the risk of lung cancer: Evidence from a meta-analysis. *Int J Clin Exp Med*. 2015b; 8(4): 6631–6637.

Chen J, Chen J, Li Z, Liu C, Yin L. The apoptotic effect of apigenin on human gastric carcinoma cells through mitochondrial signal pathway. *Tumour Biol*. 2014; 35(8): 7719–7726.

Chen M, Peyrin-Biroulet L, George A, et al. Methyl deficient diet aggravates experimental colitis in rats. *J Cell Mol Med*. 2011; 15(11): 2486–2497.

Chen S, Oh SR, Phung S, et al. Anti-aromatase activity of phytochemicals in white button mushrooms (*Agaricus bisporus*). *Cancer Res*. 2006; 66: 12026–12034.

Choi HJ, Choi HJ, Chung TW, Ha KT. Luteolin inhibits recruitment of monocytes and migration of Lewis lung carcinoma cells by suppressing chemokine (C-C motif) ligand 2 expression in tumor-associated macrophage. *Biochem Biophys Res Commun*. 2016; 470(1): 101–106.

Chunhua L, Donglan L, Xiuqiong F et al. Apigenin up-regulates transgelin and inhibits invasion and migration of colorectal cancer through decreased phosphorylation of AKT. *J Nutr Biochem*. 2013; 24(10): 1766–1775.

Davis CD, Milner JA. Molecular targets for nutritional preemption of cancer. *Curr Cancer Drug Targets*. 2007; 7(5): 410–415.

Deng YT, Lin JK. EGCG inhibits the invasion of highly invasive CL1-5 lung cancer cells through suppressing MMP-2 expression via JNK signaling and induces G2/M arrest. *J Agric Food Chem*. 2011; 59(24): 13318–13327.

Elsamanoudy AZ, Neamat-Allah MAM, Mohammad FAZ, Hassanien M, Nada HA. The role of nutrition related genes and nutrigenetics in understanding the pathogenesis of cancer. *J Microsc Ultrastruct*. 2016; 4(3): 115–122.

Eroğlu C, Seçme M, Bağcı G, Dodurga Y. Assessment of the anticancer mechanism of ferulic acid via cell cycle and apoptotic pathways in human prostate cancer cell lines. *Tumour Biol*. 2015; 36(12): 9437–9446.

Fareed M, Afzal M. Single nucleotide polymorphism in genome-wide association of human population: A tool for broad spectrum service. *Egypt J Med Hum Genet*. 2013; 14(2): 123–134.

Ferguson LR. Meat and cancer. *Meat Sci*. 2010; 84(2): 308–313.

Fujii TMM, Medeiros R, Yamada R. Nutrigenomics and nutrigenetics: Important concepts for the nutrition science. *J Brazilian Soc Food Nutr*. 2010; 35(1): 149–166.

García-Zepeda SP, García-Villa E, Díaz-Chávez J, Hernández-Pando R, Gariglio P. Resveratrol induces cell death in cervical cancer cells through apoptosis and autophagy. *Eur J Cancer Prev*. 2013; 22(6): 577–584.

German JB. Genetic dietetics: Nutrigenomics and the future of dietetics practice. *J Am Diet Assoc*. 2005; 105(4): 530–531.

Gong X, Smith JR, Swanson HM, Rubin LP. Carotenoid lutein selectively inhibits breast cancer cell growth and potentiates the effect of chemotherapeutic agents through ROS-mediated mechanisms. *Molecules*. 2018; 23(4). pii: E905.

Grody WW. Molecular genetic risk screening. *Annu Rev Med*. 2003; 54: 473–490.

Grundemann C, Huber R. Chemoprevention with isothiocyanates—From bench to bedside. *Cancer Lett*. 2018; 414: 26–33.

Gudas LJ, Wagner JA. Retinoids regulate stem cell differentiation. *J Cell Physiol*. 2011; 226(2): 322–330.

Hong MY, Seeram NP, Heber D. Pomegranate polyphenols downregulate expression of androgen synthesizing genes in human prostate cancer cells overexpressing the androgen receptor. *J Nutr Biochem*. 2008; 19(12): 848–855.

Huang Q, Du T, Qu QX. Tea polyphenol decreased growth and invasion in human ovarian cancer cells. *Int J Inflam*. 2016, 14(3): 206–211.

Huang WW, Tsai SC, Peng SF, Lin MW, Chiang JH, Chiu YJ, Fushiya S, Tseng MT, Yang JS. Kaempferol induces autophagy through AMPK and AKT signaling molecules and causes G2/M arrest via downregulation of CDK1/cyclin B in SK-HEP-1 human hepatic cancer cells. *Int J Oncol*. 2013; 42(6): 2069–2077.

International Agency for Research on Cancer. Press release No 240: IARC Monographs evaluate consumption of red meat and processed meat. *Lyon: IARC*; 2015.

Jia Y, Li R, Cong R, Yang X, Sun Q, Parvizi N, Zhao R. Maternal low-protein diet affects epigenetic regulation of hepatic mitochondrial DNA transcription in a sex-specific manner in newborn piglets associated with GR binding to its promoter. *PLoS One*. 2013; 8(5): e63855. doi:10.1371/journal.pone.0063855.

Jin CY, Park C, Hwang HJ, Kim GY, Choi BT, Kim WJ, Choi YH. Naringenin up-regulates the expression of death receptor 5 and enhances TRAIL-induced apoptosis in human lung cancer A549 cells. *Mol Nutr Food Res*. 2011; 55(2): 300–309.

Kong X, Murphy K, Raj T, He C, White PS, Matise TC. A combined linkage-physical map of the human genome. *Am J Hum Genet*. 2004; 75(6): 1143–1148.

Kushi LH, Doyle C, McCullough M, Rock CL, Demark-Wahnefried W, Bandera EV, Gapstur S, Patel AV, Andrews K, Gansler T; American cancer society 2010 nutrition and physical activity guidelines advisory committee. American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: Reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin*. 2012; 62(1): 30–67.

Larrosa M, Yañéz-Gascón MJ, Selma MV, González-Sarrías A, Toti S, Cerón JJ, Tomás-Barberán F, Dolara P, Espín JC. Effect of a low dose of dietary resveratrol on colon microbiota, inflammation and tissue damage in a DSS-induced colitis rat model. *J Agric Food Chem*. 2009; 57(6): 2211–2220.

Lee JS, Surh YJ. Nrf2 as a novel molecular target for chemoprevention. *Cancer Lett*. 2005; 224(2): 171–184.

Link A, Balaguer F, Shen Y, Lozano JJ, Leung HC, Boland CR, Goel A. Curcumin modulates DNA methylation in colorectal cancer cells. *PLoS One*. 2013; 8(2): e57709. doi:10.1371/journal.pone.0057709.

Little J, Barakat-Haddad C, Martino R, Pringsheim T, Tremlett H, McKay KA, van Lieshout P, Walsh SJ, Gomes J, Krewski D. Genetic variation associated with the occurrence and progression of neurological disorders. *Neurotoxicology*. 2017; 61: 243–264.

Lu HF, Chie YJ, Yang MS et al. Apigenin induces apoptosis in human lung cancer H460 cells through caspase- and mitochondria-dependent pathways. *Hum Exp Toxicol*. 2011; 30(8): 1053–1061.

Manson MM, Foreman BE, Howells LM, Moiseeva EP. Determining the efficacy of dietary phytochemicals in cancer prevention. *Biochem Soc Trans*. 2007; 35(5): 1358–1363.

Miggiano GA, De Sanctis R. Nutritional genomics: Toward a personalized diet US National Library of Medicine, National institutes of health. *Clin Ter.* 2006; 157(4): 355–361.

Miron A, Aprotosoaie AC, Trifan A, Xiao J. Flavonoids as modulators of metabolic enzymes and drug transporters. *Ann N Y Acad Sci*. 2017; 1398(1): 152–167.

Moon YJ, Wang X, Morris ME. Dietary flavonoids: Effects on xenobiotic and carcinogen metabolism. *Toxicol In Vitro*. 2006; 20(2): 187–210.

Mu D, Gao Z, Guo H, Zhou G, Sun B. Sodium butyrate induces growth inhibition and apoptosis in human prostate cancer DU145 cells by up-regulation of the expression of annexin A1. *PLoS One*. 2013; 8(9): e74922. doi:10.1371/journal.pone.0074922.

Nguyen PH, Giraud J, Staedel C et al. All-trans retinoic acid targets gastric cancer stem cells and inhibits patient-derived gastric carcinoma tumor growth. *Oncogene*. 2016; 35(43): 5619–5628.

Nyaradi A, Li J, Hickling S, Foster J, Oddy WH. The role of nutrition in children's neurocognitive development, from pregnancy through childhood. *Front Hum Neurosci*. 2013; 7: 97. doi:10.3389/fnhum.2013.00097.

Omer RE, Verhoef L, Van't Veer P, Idris MO, Kadaru AM, Kampman E, Bunschoten A, Kok FJ. Peanut butter intake, GSTM1 genotype and hepatocellular carcinoma: A case-control study in Sudan. *Cancer Causes Control*. 2001; 12(1): 23–32.

Ordovas JM, Shen J. Gene-environment interactions and susceptibility to metabolic syndrome and other chronic diseases. *J Periodontol*. 2008; 79(8 Suppl): 1508–1513.

Ordovas JM. Genotype-phenotype associations: Modulation by diet and obesity. *Obesity* (*Silver Spring*); 2008; 16 Suppl 3: S40–S46.

Ordovas JM, Kaput J, Corella D. Nutrition in the genomics era: Cardiovascular disease risk and the Mediterranean diet. *Mol Nutr Food Res*. 2007; 51(10): 1293–1299.

Osman W, Tay GK, Alsafar H. Multiple genetic variations confer risks for obesity and type 2 diabetes mellitus in Arab descendants from UAE. *Int J Obes* (*Lond*). 2018. doi:10.1038/s41366-018-0057-6.

Palit S, Kar S, Sharma G, Das PK. Hesperetin induces apoptosis in breast carcinoma by triggering accumulation of ROS and activation of ASK1/JNK pathway. *J Cell Physiol*. 2015; 230(8): 1729–1739.

Palozza P, Colangelo M, Simone R, Catalano A, Boninsegna A, Lanza P, Monego G, Ranelletti FO. Lycopene induces cell growth inhibition by altering mevalonate pathway and Ras signaling in cancer cell lines. *Carcinogenesis*. 2010; 31(10): 1813–1821.

Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. *Oxid Med Cell Longev.*. 2009; 2(5): 270–278.

Patrick TE, Powers RW, Daftary AR, Ness RB, Roberts JM. Homocysteine and folic acid are inversely related in black women with preeclampsia. *Hypertension*. 2004; 43(6): 1279–1282.

Perez-Jimenez J, Neveu V, Vos F, Scalbert A. Identification of the 100 richest dietary sources of polyphenols: An application of the Phenol-Explorer database. *Eur J Clin Nutr.* 2010; 64: S112–S120.

Pitot HC, Goldsworthy T, Moran S. The natural history of carcinogenesis: Implications of experimental carcinogenesis in the genesis of human cancer. *J Supramol Struct Cell Biochem*. 2004; 17: 133–146.

Qin J, Teng J, Zhu Z, Chen J, Huang WJ. Genistein induces activation of the mitochondrial apoptosis pathway by inhibiting phosphorylation of Akt in colorectal cancer cells. *Pharm Biol*. 2016; 54(1): 74–79.

Rafi MM, Kanakasabai S, Gokarn SV, Krueger EG, Bright JJ. Dietary lutein modulates growth and survival genes in prostate cancer cells. *J Med Food*. 2015; 18(2): 173–181.

Rao SD, Pagidas K. Epigallocatechin-3-gallate, a natural polyphenol, inhibits cell proliferation and induces apoptosis in human ovarian cancer cells. *Anticancer Res*. 2010; 30(7): 2519–2523.

Roberts MA, Mutch DM, German JB. Genomics: Food and nutrition. *Curr Opin Biotechnol*. 2001; 12(5): 516–522.

Romagnolo DF, Zempleni J, Selmin OI. Nuclear receptors and epigenetic regulation: Opportunities for nutritional targeting and disease prevention. *Adv Nutr*. 2014; 5(4): 373–385.

Sachidanandam R, Weissman D, Schmidt SC et al. International SNP map working group. A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. *Nature*. 2001; 409(6822): 928–933.

Santarelli RL, Pierre F, Corpet DE. Processed meat and colorectal cancer: A review of epidemiologic and experimental evidence. *Nutr Cancer*. 2008; 60(2): 131–144.

Selhub J. Public health significance of elevated homocysteine. *Food Nutr Bull*. 2008; 29(2 Suppl): S116–S125.

Selhub J. The many facets of hyperhomocysteinemia: Studies from the Framingham cohorts. *J Nutr*. 2006; 136 (6 Suppl): 1726S–1730S.

Setlow RB. Human cancer: Etiologic agents/dose responses/DNA repair/cellular and animal models. *Mutat Res*. 2001; 477(1–2): 1–6.

Shao W, Yu Z, Chiang Y, Yang Y, Chai T, Foltz W, Lu H, Fantus IG, Jin T. Curcumin prevents high fat diet induced insulin resistance and obesity via attenuating lipogenesis in liver and inflammatory pathway in adipocytes. *PLoS One*. 2012; 7(1): e28784. doi:10.1371/journal.pone.0028784.

Sharma P, Dwivedi S. Nutrigenomics and nutrigenetics: New insight in disease prevention and cure. *Indian J Clin Biochem*. 2017; 32(4): 371–373.

Simopoulos AP. Evolutionary aspects of diet, the omega-6/omega-3 ratio and genetic variation: Nutritional implications for chronic diseases. *Biomed Pharmacother*. 2006; 60: 502–527.

Song H, Bao J, Wei Y, Chen Y, Mao X, Li J, Yang Z, Xue Y. Kaempferol inhibits gastric cancer tumor growth: An *in vitro* and *in vivo* study. *Oncol Rep*. 2015; 33(2): 868–874.

Song HM, Park GH, Eo HJ, Jeong JB. Naringenin-mediated ATF3 expression contributes to apoptosis in human colon cancer. *Biomol Ther* (*Seoul*). 2016; 24(2): 140–146.

Spagnuolo C, Russo M, Bilotto S, Tedesco I, Laratta B, Russo GL. Dietary polyphenols in cancer prevention: The example of the flavonoid quercetin in leukemia. *Ann N Y Acad Sci*. 2012; 1259: 95–103.

Tanaka T, Ishii T, Mizuno D, Mori T, Yamaji R, Nakamura Y, Kumazawa S, Nakayama T, Akagawa M. (–)-Epigallocatechin-3-gallate suppresses growth of AZ521 human gastric cancer cells by targeting the DEAD-box RNA helicase p68. *Free Radic Biol Med*. 2011; 50(10): 1324–1335.

Telenti A, Pierce LC, Biggs WH et al. Deep sequencing of 10,000 human genomes. *Proc Natl Acad Sci U S A*. 2016; 113(42): 11901–11906.

Thangapazham RL, Singh AK, Sharma A, Warren J, Gaddipati JP, Maheshwari RK. Green tea polyphenols and its constituent epigallocatechin gallate inhibits proliferation of human breast cancer cells *in vitro* and *in vivo*. *Cancer Lett*. 2007; 245(1–2): 232–241.

Thomas R, Williams M, Sharma H, Chaudry A, Bellamy P. A double-blind, placebo-controlled randomised trial evaluating the effect of a polyphenol-rich whole food supplement on PSA progression in men with prostate cancer—the UK NCRN Pomi-T study. *Prostate Cancer P D*. 2014; 17: 180–186.

Tian T, Li J, Li B, Wang Y, Li M, Ma D, Wang X. Genistein exhibits anti-cancer effects via down-regulating FoxM1 in H446 small-cell lung cancer cells. *Tumour Biol*. 2014; 35(5): 4137–4145.

Ungerer M, Knezovich J, Ramsay M. In utero alcohol exposure, epigenetic changes, and their consequences. *Alcohol Res*. 2013; 35(1): 37–46.

Wang Z, Li W, Meng X, Jia B. Resveratrol induces gastric cancer cell apoptosis via reactive oxygen species, but independent of sirtuin1. *Clin Exp Pharmacol Physiol*. 2012; 39(3): 227–232.

Wang Z, Zhang L, Ni Z, Sun J, Gao H, Cheng Z, Xu J, Yin P. Resveratrol induces AMPK-dependent MDR1 inhibition in colorectal cancer HCT116/L-OHP cells by preventing activation of NF-κB signaling and suppressing cAMP-responsive element transcriptional activity. *Tumour Biol*. 2015; 36(12): 9499–9510.

Wiseman M. The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: A global perspective. *Proc Nutr Soc*. 2008; 67(3): 253–256.

Wollowski I, Rechkemmer G, Pool-Zobel BL. Protective role of probiotics and prebiotics in colon cancer. *Am J Clin Nutr* 2001; 73: 451S–455S.

Yang Q, Wang B, Zang W, Wang X, Liu Z, Li W, Jia J. Resveratrol inhibits the growth of gastric cancer by inducing G1 phase arrest and senescence in a Sirt1-dependent manner. *PLoS One*. 2013; 8(11): e70627.

Yen HR, Liu CJ, Yeh CC. Naringenin suppresses TPA-induced tumor invasion by suppressing multiple signal transduction pathways in human hepatocellular carcinoma cells. *Chem Biol Interact*. 2015; 235: 1–9.

Yong WK, Abd Malek SN. Xanthohumol induces growth inhibition and apoptosis in ca ski human cervical cancer cells. *Evid Based Complement Alternat Med*. 2015; 2015: 921306.

Yong WK, Ho YF, Malek SN. Xanthohumol induces apoptosis and S phase cell cycle arrest in A549 non-small cell lung cancer cells. *Pharmacogn Mag*. 2015; 11(Suppl 2): S275–S283.

Yousef AI, El-Masry OS, Abdel Mohsen MA. Impact of cellular genetic make-up on colorectal cancer cell lines response to ellagic acid: Implications of small interfering RNA. *Asian Pac J Cancer Prev*. 2016; 17(2): 743–748.

Yu N, Su X, Wang Z, Dai B, Kang J. Association of dietary vitamin A and β-carotene intake with the risk of lung cancer: A meta-analysis of 19 publications. *Nutrients*. 2015; 7(11): 9309–9324.

Zeisel SH. Epigenetic mechanisms for nutrition determinants of later health outcomes. *Am J Clin Nutr*. 2009; 89(5): 1488S–1493S.

Zhang J, Wu D, Vikash, Song J, Wang J, Yi J, Dong W. Hesperetin induces the apoptosis of gastric cancer cells via activating mitochondrial pathway by increasing reactive oxygen species. *Dig Dis Sci*. 2015; 60(10): 2985–2995.

Zhang T, Chen H, Qin S, et al. The association between dietary vitamin A intake and pancreatic cancer risk: A meta-analysis of 11 studies. *Bioscience Rep*. 2016; 36(6): e00414. doi:10.1042/BSR20160341.

Zhu Y, Wu J, Li S et al. Apigenin inhibits migration and invasion via modulation of epithelial mesenchymal transition in prostate cancer. *Mol Med Rep*. 2015; 11(2): 1004–1008.

Zwamborn RAJ, Slieker RC, Mulder PCA, et al. Prolonged high-fat diet induces gradual and fat depot-specific DNA methylation changes in adult mice. *Sci Rep*. 2017; 7: 43261. doi:10.1038/srep43261.

10 Novel Drug Delivery Systems for Nutraceuticals with Anticancer Properties

Priyanka Bhatt, Imran Vhora, and Rohan Lalani

CONTENTS

10.1 INTRODUCTION

Cancer is one of the deadliest diseases and a major cause of death worldwide. Cancer is characterized by uncontrolled growth of immature and abnormal cells followed by development of new blood vessels and finally tumor. According to statistics given by International Agency for Research on Cancer (IARC), 17.0 million new cancer cases were reported and 9.5 million deaths because of cancer were noted worldwide in 2018 [1]. The worldwide burden of cancer by 2040 is expected to reach 27.5 million new cases and 16.3 million deaths. Cancer is a multifactorial disease and genetic and lifestyle factors play an important role in the development of cancer. Certain lifestyle factors such as unhealthy diet, poor nutrition, physical inactiveness, smoking, excess alcohol intake, and obesity are crucial factors. According to research, one-third of cancer incidents can be prevented by controlling these factors [2,3].

Besides changing the listed factors as a key procedure for preventing cancer, another idea is regular intake of nutraceuticals to decrease the risk of development of cancer. Nutraceutical is amalgamation of two different words, "nutrition" and "pharmaceutical." Stephen L. DeFelice defined nutraceuticals as "any substance that is a food or a part of the food and provides medical or health benefits, including the prevention and treatment of disease" [4].

At present, nutraceuticals are highly researched for their application in prevention and treatment of various types of cancers. The pleiotropic effects, anticancer potential, and other beneficial properties such as antioxidant, anti-inflammatory, and relatively low toxicity are key factors that attract researchers around the globe to work on them with the hope to find a potential strategy of cancer therapy [5].

Figure 10.1 describes major examples of nutraceutical agents that are currently in research for cancer therapy. Dietary fibers, vitamins, minerals, carotenoids, fatty acid, prebiotic, probiotic, and phenolics are key examples of nutraceutical compounds for cancer therapy. They differ from each other structurally as well as functionally, and their mechanisms of action are also not same. There are mainly three

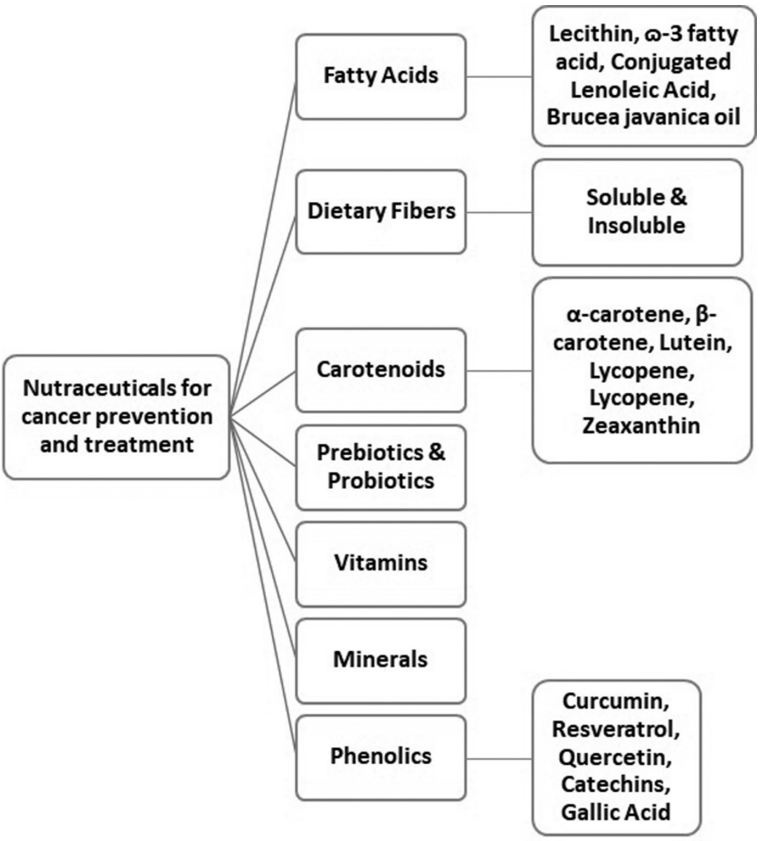


FIGURE 10.1 Nutraceuticals for prevention and treatment of cancer.

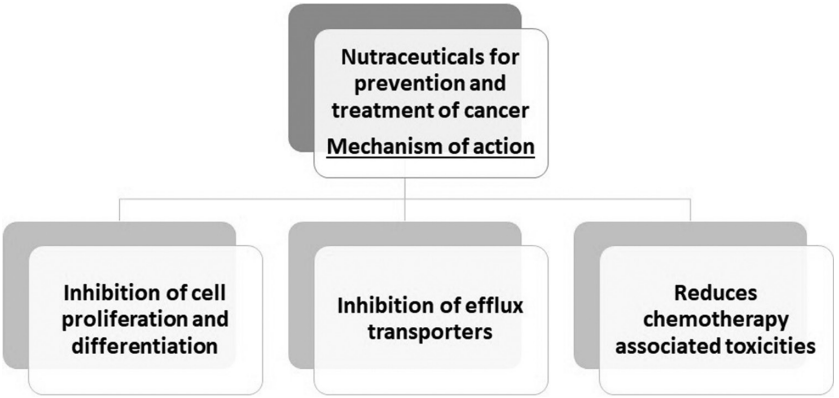


FIGURE 10.2 Most common three mechanism of actions of nutraceuticals for prevention and treatment of cancer.

mechanisms through which they exert their action (Figure 10.2): first is by inhibiting differentiation and proliferation of cells either by interfering in mitosis, DNA differentiation, or other molecular pathway; second is by decreasing multidrug resistance by the inhibiting effect of efflux transporters such as P-glycoprotein, breast cancer resistance protein, and multidrug resistance protein; and third is by reducing chemotherapeutic drugs-related toxicities [6].

For example, a study was conducted in order to investigate the relationship between pancreatic cancer risk and dietary carotenoids. The study revealed that the consumption of lycopene (a major component of tomatoes) through tomato-based products with high levels of lycopene causes 31% reduction in the risk of pancreatic cancer among men [7]. Many nutraceuticals have been studied for their application in prevention and treatment of cancer globally; however, the inherent challenges of nutraceutical compounds such as low aqueous solubility and poor bioavailability hinder their further applications [8].

Thus, there is an unmet need to develop a delivery system to improve the solubility and bioavailability profiles of nutraceutical agents and deliver them at the right place in the required concentration for successful eradication of cancer. Various approaches are being used by researchers worldwide to improve solubility and hence bioavailability of drugs. The examples of these approaches are sustained release of drug from the matrix, formation of soluble complex by loading insoluble drug (e.g., cyclodextrin complex), designing soluble prodrugs that lead to biotransformations in the GIT, loading of insoluble drug in various lipids as well as polymeric nanoparticles, dispersing insoluble drug in micelles and emulsions, and use of co-solvents. To characterize the main limiting factors such as solubility and oral bioavailability of nutraceuticals, a novel classification system has been recently introduced called the nutraceutical biopharmaceutical classification scheme (NuBACS), which is comparable to the biopharmaceutical classification system (BCS) [9]. Thus, nanocarrier-based delivery platform has emerged to overcome the pharmaceutical and pharmacological challenges of a nutraceutical compound and has been shown to

FIGURE 10.3 Major advantages of novel nanocarrier drug delivery systems for nutraceuticals delivery.

be a successful vehicle for cancer therapy in preclinical and clinical studies [10]. Their nanoscale size, high surface-to-volume ratio, favorable physicochemical characteristics, ease of surface modification, and targeting leads to applications of nutraceutical formulations to the highest level for cancer therapy. Figure 10.3 describes major advantages of novel drug delivery systems for nutraceutical applications in cancer therapy. By modifying the delivery system, a formulation scientist can also regulate and modulate pharmacokinetic as well as pharmacodynamic profiles of the nutraceutical agent encapsulated formulations. In this chapter, various kinds of drug delivery systems and nanocarriers have been discussed in following sections in context of their application in nutraceutical delivery for cancer therapy with their in vitro, in vivo, and clinical outcomes.

10.2 NUTRACEUTICALS AND THEIR ROLE IN CANCER THERAPY

Cancer, one of the leading causes of death globally, is a multifactorial disease in which genetic mutations of cells lead to their abnormal growth. The uncontrolled growth of cells and lack of apoptotic pathways stimulate the formation of new blood vessel, followed by formation of group of immature cells with tiny newly developed blood vessels called malignant tumor. Various factors such as physical and metabolic

activity, diet or food habits, environmental factors, daily habits, and overall health of a person play an important role in cancer development and its progression. It has been researched that approximately 35% of cancer-related mortalities are because of diet and 70% of cancer-related mortalities are dependent on the site of cancer [11]. While treating cancer, stage of cancer is also important, as early stage cancers can be cured, while the rate of treatment of later stage cancers is low. The traditional approach for cancer therapy involves surgery, radiotherapy, and chemotherapy either alone or in combination. The currently available chemotherapeutic agents give relief from symptoms and are capable of eradicating tumor; however, problems in early stage diagnosis, relapse or recurrence, multidrug resistance, and nonspecific action of chemotherapeutic drugs are major challenges that limit the current therapy [12]. Thus, there is an unmet need to have a potential anticancer agent and their delivery system that can deliver the correct quantity of drug to the correct site at the right time to eradicate cancer.

Nutraceutical comes from nutrition and pharmaceutical, which can be defined as "any substance that is a food or a part of a food and provides medical or health benefits, including the prevention and treatment of diseases" [13]. Thus, nutraceutical is an umbrella that covers a wide range of dietary supplements, phytochemicals, functional food, and medicinal food [14]. On the other hand, phytochemical, to be more precise, is a term that deals with compounds derived from plants that have potential therapeutic activities for instance anti-inflammatory, anticancer, and antioxidant [15]. In the past also nutraceuticals have been proved to treat many of the disease and have a significant biomedical application with a variety of therapeutic properties. These therapeutic properties are associated with the presence of several chemical constituents such as flavonoids, polyphenols, carotenoids, isothiocyanates, organosulfur compounds, indoles, phenolic acids, chlorophyll, and monoterpenes.

Currently, tremendous research is going on to evaluate the effect of nutraceutical active constituents and their formulations for the prevention and treatment of cancer along with overall improvement of patient's health. Chemoprevention refers to the intake of a natural remedy to decrease the incidence and mortality of cancer. This is an upcoming area of research specifically in oncology that emphasizes on preventing the development of cancer using natural constituents, which play a crucial role in inhibiting the relapse or recurrence and metastasis in cancer. Several nutraceuticals are being used alone or in combination or with traditional chemotherapy for synergic anticancer effects. Various studies have proved that nutraceuticals have potential effects in prevention as well as treatment of cancer and play an important role in inhibiting cancer stage progression, metastasis, angiogenesis, and carcinogenic process by regulating molecular pathways involved without added toxicities. There are various mechanisms by which nutraceuticals suppress carcinogenesis such as such as regulating transcription of DNA, blocking activation of transcription nuclear factor kappa B, controlling DNA-damaging factors, inhibiting inflammation, stimulating apoptosis, antioxidation properties, activating detoxifying enzymes, and so on. Curcumin, quercetin, resveratrol, green tea, propolis, silymarin, genistein vitamin D3, capsaicin, and so on are such agents that have showed potential anticancer effects in research and clinic. By understanding the mechanism of the anticancer effects of these naturally available herbal drugs will offer valuable information for

their probable applications in chemoprevention and treatment. In the following sections, the mechanism of anticancer activity of some of the nutraceutical drugs are discussed, with special emphasis on their delivery systems for prevention and treatment of cancer.

10.3 NOVEL DRUG DELIVERY SYSTEMS FOR NUTRACEUTICAL DELIVERY IN CANCER

Almost four of the 10 newly identified chemical entities possessing potent anticancer property are hydrophobic in nature, and the poor aqueous solubility of such agents is the key limitation for their successful use as anticancer agents in cancer therapy [16]. The traditional formulation approaches to deal with insolubility of these drugs are minimizing the particle size, use of co-solvent, modification in pH, and use of surfactants. Taxol, a commercially available formulation of paclitaxel drug for the treatment of various categories of cancer, is an example of a surfactant (Cremophor EL) that has been used to improve the solubility of drug for intravenous administration. However, Cremophor EL itself is toxic and exerts vehicle-associated toxicity such as acute hypersensitivity reactions and neurotoxicity [17]. Additionally, these traditional delivery vehicles do not direct specific delivery of anticancer drug, and the nonspecific distribution of drug leads to treatment-associated toxicities and reduced efficiency of the therapy. Although having an effective anticancer potential and successful results, they are not utilized for efficacious cancer therapy owing to pharmacokinetic challenges mostly after oral administration [18]. The nanodrug delivery systems have been developed as an encouraging strategy to improve the solubility and bioavailability of such compounds and hence overcome pharmacokinetic limitations. Various formulations and approaches have been studied so far to evaluate their effectiveness in drug delivery applications and as ideal therapy for cancer. The examples of these nanocarrier systems are polymeric nanoparticles, lipidic nanoparticles, micelles, nanoemulsions, dendrimers, hydrogel, and so on. Figure 10.3 describes major advantages of nanocarrier systems for drug delivery applications.

These nanodrug delivery systems exhibit "Enhanced Permeation and Retention" (EPR) effect through passive targeting [19]. On the other hand, surface of these nanocarrier systems can also be modified for active targeting [20]. Through passive targeting because of the leaky nature of blood vessels in tumor tissues and endothelial cells, these nanosized drug delivery carriers can efficiently infiltrate into malignant tumors. Moreover, the poor lymphatic drainage of tumors will lead to enhanced retention of the drug in the tumor environment, which is called the EPR effect though which a nanocarrier can improve the effectiveness of the therapy by enhancing permeation and retention of an anticancer drug in cancer cells. Besides passive targeting, the nanocarrier systems also are able to exhibit active targeting of anticancer drug by specifically targeting the cells of interest. The surface of nanocarriers can be modified and targeting ligands such as antibodies, aptamers, folic acid, and peptides can be attached to recognize their specific protein or receptor overexpressed on cancer cells and thus lead to site-specific drug delivery.

10.3.1 Polymeric Nanoparticles

Polymeric nanoparticles have been developed using certain polymers that are nontoxic, biodegradable, and biocompatible in nature and can demonstrate a controlled release of nutraceutical drug loaded into the nanoparticle. They can be targeted to deliver drug to the specific cell type by modifying their surface properties and by attaching a specific ligand against specific protein present on the cell type of interest. These solid colloidal nanocarrier system have size of less than 200 nm preferably in order to escape the uptake by reticuloendothelial system upon intravenous injection and to exert EPR effect. Examples of polymers that have been explored for nutraceutical delivery are poly (D, L-lactic acid) (PLA), poly (D, L-lactic-co-glycolic acid) (PLGA), poly(ethylene glycol) (PEG), poly (Ɛ-thylene glyc) (PCL), and their copolymers diblocked or multiblocked with d-a-tocopheryl polyethylene glycol 1000 succinate (TPGS), etc. [21,22]. Besides these polymers, certain polysaccharides such as alginate, chitosan, pectin, etc., have also been explored for nutraceutical delivery applications [23]. Besides their nontoxic and biodegradable nature, they have been shown to improve the oral bioavailability of certain nutraceuticals too. For example, chitosan nanoparticles can follow a paracellular pathway to cross tight junctions and thus control the role of P-glycoprotein. Advantages of polymeric nanoparticles are controlled and stimuli-sensitive release (e.g., pH, enzymes) of nutraceutical, ease of surface modification for targeted applications, and their biocompatible nature. Certain targeting ligands can be decorated on the surface of the nanoparticles such as antibodies, antibody fragment, peptides, aptamers, folic acid, and so on to target specific protein present on the cancer cells for target-specific delivery of drugs and nutraceuticals. Additionally, certain polymers, for instance hyaluronic acid and chondroitin sulfate, have inherent property to target CD44 overexpressing cancer cells [24].

10.3.2 Lipidic Nanocarrier

Another colloidal carrier that consist of solid or liquid lipids such as glyceryl monostearate, stearic acid, tristearin, cholesterol, and so on are lipidic nanoparticles. These nanocarriers have the ability to bypass P-glycoprotein by traveling through a paracellular route across the tight junctions and are could be up taken by microfold cell. Liposomes, solid lipid nanoparticles, lipid nanoconstructs, nanoemulsions, and self-emulsifying nanoemulsions are major examples of lipidic nanocarrier systems that have been researched so far for their applications in cancer therapy in regards to pharmaceutical and nutraceutical drugs. Of these, liposomes have been widely explored as commercially available lipidic nanocarriers for cancer therapy. Liposomes are self-assembling bilayer vesicular systems that consist of one or more lipid bilayers and an aqueous core. Hydrophobic drug can be encapsulated in the lipidic layer; however, hydrophilic agents can be entrapped into the aqueous core separately or simultaneously [25,26]. Naturally available phospholipids and cholesterol as the key building blocks for liposomes makes them nontoxic, biocompatible, and biodegradable. The surface of the liposomes can be modified by PEGylation that can improve the systemic circulation of liposomes upon intravenous injection

by avoiding reticuloendothelial system and phagocytosis. The surface can be decorated with targeting ligands such as peptides [27], antibodies [28], aptamers, folic acid, transferrin, and so on to specifically target certain protein or receptor overexpressed in cancer cells. Hence, it can deliver a drug to the specific site by reducing the nonspecific distribution of the drug to improve the effectiveness of the therapy and reduce the side effects.

Solid lipid nanoparticles and lipid nanoconstructs are colloidal lipidic nanoparticles that are around 200 nm in size preferably and can load hydrophobic as well as hydrophilic drugs. They have advantages to improve solubility and permeability of anticancer nutraceutical drug for cancer therapy.

Nanoemulsions are a heterogeneous mixture of two or more immiscible liquids in which one phase is dispersed in a second immiscible/partially miscible phase [29]. The approach has been used widely for poorly soluble drugs to improve their solubility. Certain advantages of this system include small globule size, thermodynamic stability, improved solubility, improved bioavailability, and the use of GRAS excipients to reduce vehicle-related toxicities.

10.3.3 Micelles and Dendrimers

Certain polymers are amphiphilic in nature and, beyond a certain concentration, tend to self-aggregate to form a micellar system [30]. While loading the anticancer nutraceuticals in micelles, the hydrophilic blocks of the polymer accommodate at the interface between the inner lipid-loving sphere, which is made up of the hydrophobic tail of the polymer, recognized as an external medium, and the core of the micellar system [31].

Dendrimers vary from conventional polymers in a sense that they are three-dimensional, well-organized nanoscopic macromolecules with higher molecular weight of mostly between 5000 and 500,000 g/mol, retain low polydispersity index, and are highly branched [32]. Till today, certain dendrimer carriers have been synthesized and explored for the anticancer drug delivery of nutraceuticals and examples are polyamidoamine, poly-L-lysine, poly propylene imine, melamine, poly (etherhydroxylamine), polyglycerol, and poly (esteramine). They have the ability to cross cellular barriers via both transcellular and paracellular pathways having diameters in a range from 1.1 nm for the first generation to 12.4 nm for the tenth generation. Further, the solubility of poorly soluble nutraceuticals can also be improved by encapsulating them into dendrimers [6].

10.3.4 Hydrogel

Hydrogels are another drug delivery carrier system in which polymers cross-link with each other to form a hydrophilic polymeric network and can be applied to provide sustained delivery of nutraceuticals at a particular site. Although they have high affinity for water, hydrogels do not easily dissolve in water because of their physical entanglements of covalent cross-linking or noncovalent attractions [33]. These hydrogels can also be thermoreversible, meaning that they will be in the liquid phase at certain temperature, for example in refrigerated conditions

or at room temperature, but become a gel at body temperature to deliver a drug in a sustained manner. They can also be modified for targeted applications to specific site.

10.4 NANOFORMULATIONS OF NUTRACEUTICALS UNDER IN VITRO AND PRECLINICAL EVALUATION

Nanotechnology-based formulations could provide beneficial outcomes for nutraceuticals such as enhancement of solubility, improvement of bioavailability, and protection of stability of micronutrients and bioactive during processing and storage [34]. Mostly, nutraceuticals have been tried through oral route in their raw forms such as crude extracts or powdered/liquid forms due to convenience. However, as nutraceuticals, similar to most pharmaceuticals, bear the physicochemical properties such as low water solubility, hydrophobicity, and variable physiological properties, that is, variability in absorption due to the accessibility of the active molecules in the food matrices, interaction with GIT components, metabolism, and epithelial permeability. Nanoformulations can help improve the oral bioavailability of nutraceuticals by increasing the gastrointestinal membrane permeability, reducing the degradation in GIT, and reducing the first-pass metabolism. Moreover, this can also open the possibility for the use of these nutraceuticals through other routes of administration as well as providing additional benefits of enhanced tumor accumulation through the EPR effect and targeting.

Several nanoparticulate-based formulation strategies have been devised for different nutraceuticals of anticancer potential. A detailed account of such strategies is included in Table 10.1 with their in vitro studies and preclinical evaluation. Most of the delivery systems have been directed toward the enhancement of oral bioavailability, while others are aimed at providing parenteral administration of nutraceuticals. Some strategies that have novelty, but have been explored in vitro only, are discussed below.

Liposomes have been explored for oral as well as nonoral delivery of nutraceuticals. Cationic liposomes of curcumin using cationic cholesterol derivative have been developed, which has shown higher cellular uptake and hence 2–8 times higher in vitro cytotoxicity against free curcumin in a variety of cell lines (HeLa, A549, HepG2, K562, and 1301) [35]. DDAB-based cationic liposomes of curcumin showed higher cytotoxicity than free curcumin in HeLa and SiHa cervical cancer cells in vitro [36]. However, the authors also noticed the higher toxicity of nonloaded DDAB liposomes. Recently, curcumin has been encapsulated in liposomes using the HP-βCD complex of curcumin [37]. Formulation showed effectiveness against in vivo breast cancer models of mesenchymal as well as epithelial origin. Studies with PEG-, mPEG-, and carboxymethyl dextran (CMD)-coated curcumin liposomes have been developed, and it was observed that the CMD coating improved in vitro cellular uptake and cytotoxicity of curcumin liposomes against HeLa cells in comparison to noncoated and PEG/mPEG-coated liposomes [38].

Gambogic acid-loaded PLGA nanoparticles were coated with RBC membrane to obtain biomimetic nanoparticles for delivery to cancer cells for intravenous

TABLE 10.1
Preclinical Studies of Novel Formulations of Anticancer Nutraceuticals

Nutraceutical	Nanocarrier	Biological Evaluation	Remarks	References
Oral Nanoformulations of Nutraceuticals				
Lycopene	Nanostructured lipid carrier (NLC)	In vitro cytotoxicity and ex vivo permeation	Improved ex vivo permeation in vitro anti-cancer activity against breast cancer cells	[39]
	oligomerized (-)-epigallocatechin-3-O-gallate (OEGCG)-chitosan nanoparticles	In vivo PK study in mice	It was observed that formulation contributed improvement in antiglioma effects	[40]
	Niosomes	In vitro cell line studies (HeLa and MCF-7) In vivo PK study in rats	Enhanced cytotoxicity against marketed microencapsulated formulation of lycopene (Lycored) Threefold higher relative bioavailability compared to Lycored	[41]
γ-Tocotrienol	SLN	In situ rat intestinal perfusion study and in vivo bioavailability	SLN showed 10-fold higher intestinal perfusion compared to mixed micelles (MM) In vivo study showed threefold higher bioavailability from SLN over MM	[42]
	Self-emulsifying drug delivery system (SEDDS)	In vitro permeability and uptake studies In vivo oral PK studies in fed rats	Improved solubilization and passive permeability uptake of SEDDS compared to Tocovid (marketed product) and mixed micelles Twofold higher oral bioavailability from SMEDDS at 10, 25, and 50 mg/kg doses, but not at 1 and 2.5 mg/kg doses where no significant change was observed compared to Tocovid	[43]

(*Continued*)

TABLE 10.1 (*Continued*)
Preclinical Studies of Novel Formulations of Anticancer Nutraceuticals

Nutraceutical	Nanocarrier	Biological Evaluation	Remarks	References
Curcumin	Casein micelles	In vitro cytotoxicity	Cytotoxicity similar to free curcumin against cervical cancer cells	[44]
	Sodium caseinate micelles	In vitro cytotoxicity	Improved cytotoxicity due to improved dispersibility	[45]
	Curcumin nanoparticles (2–40 nm) (nanocurcumin) by wet milling	In vitro antimicrobial activity	Water solubility and antimicrobial properties were greatly improved by nanosizing 2–40 nm particles showed higher antimicrobial properties against 500–800 nm size	[46]
	Curcumin nanoparticles (34.0–359.4 nm) by wet milling	In vitro cytotoxicity	Improved anticancer activity against prostate cancer cell line	[47]
	Theracurmin	In vitro cell line studies (human prostate and bladder cancer cell lines)	Theracurmin effectively induced cell apoptosis in cancer cell lines	[48]
	Theracurmin	In vivo PK study in rats	40-fold higher AUC with theracurmin than with curcumin powder	[49]
	Meriva—Curcumin phytosome, curcumin-phospholipid complex	In vivo PK study in rats	Meriva showed fivefold increase in AUC and Cmax against unformulated curcumin	[50]
	Meriva®	In vivo tumor xenograft study in Balb/c mice (triple negative breast cancer-4T1)	Meriva alone did not reduce the tumor load in mice significantly; however, significant reduction in lung metastasis was observed	[51]

(*Continued*)

TABLE 10.1 (*Continued*)
Preclinical Studies of Novel Formulations of Anticancer Nutraceuticals

Nutraceutical	Nanocarrier	Biological Evaluation	Remarks	References
Curcumin and piperine	Cubosomes and Eudragit nanoparticles	In vivo PK and tissue distribution study in NIH mice	Cubosomes showed extensive increase in AUC compared to Eudragit nanoparticles and suspension of curcumin + piperine Cubosomes showed improved distribution of curcumin in heart, liver, kidney, spleen, and lungs	[52]
Curcumin and resveratrol	Mixture of individually prepared liposomal formulations of curcumin and resveratrol	In vitro cell line studies (PTEN-CaP8 cancer cells) In vivo PK study in mice In vivo efficacy studies in PTEN knockout mice	Higher cytotoxicity and apoptosis by combination Significantly decreased prostatic adenocarcinoma in vivo by combination	[53]
Capsaicin	Nanoemulsion with alginate coating and chitosan coating (double layered nanoemulsions)	—	Improved zeta potential with the coatings improve the stability of nanoemulsion	[54]
β-Carotene	Electrospun Zein prolamine micro- and nanofibers	—	Improved stability of antioxidant from light and storage	[55]
Gallic acid	Electrospun zein fibers	—	Retained antioxidant activity of gallic acid	[56]
	Gold nanoparticles coated with gallic acid	In vitro cell line study (C33A cervical cancer cells, HPV infected CaSki) or HeLa, and normal Vero kidney cells)	Cell cytotoxicity was reduced for nanoparticles compared to free gallic acid; however, coating reduced the toxicity of gallic acid to normal cells	

(*Continued*)

TABLE 10.1 (*Continued*)
Preclinical Studies of Novel Formulations of Anticancer Nutraceuticals

Nutraceutical	Nanocarrier	Biological Evaluation	Remarks	References
Resveratrol	PLGA nanoparticles	In vivo PK, biodistribution, and single-pass intestinal perfusion studies	Improved absorption and AUC (10.6-fold rise against free resveratrol) after oral administration NPs overcame the enterohepatic circulation	[57]
	NLC and solid lipid nanoparticles (SLN)	—	Improved association with SLN upon contact with simulated GI fluids	[58]
	Eudragit RL 100 nanoparticles	Rat PK studies	NPs sustained drug release and improved the PK parameters significantly compared to free drug and marketed formulation	
Quercetin	DSPE-PEG2000 nanomicelles	In vitro cytotoxicity (A549) permeability (Caco-2) studies In vivo xenograft studies	Nanomicelles showed improved cytotoxicity and improved permeability Xenograft study showed improved efficacy compared to quercetin ethanol suspension	[59]
	Soluplus-poloxamer F127 polymeric micelles	In vivo PK study in beagle dogs	Micelles enhanced oral absorption of quercetin with 2.19-fold increase in t1/2 and relative oral bioavailability 286% that of free quercetin	[60]
Parenteral Nanoformulations of Nutraceuticals				
Curcumin	Nanosuspension IV delivery	In vitro cell line studies (HepG2) In vivo PK study in rats	Higher cytotoxicity than curcumin solution t1/2 and AUC0-t of Cur-NS were enhanced by 11.0-fold and 4.2-fold increase in t1/2 and AUC compared to curcumin solution	[61]

(*Continued*)

TABLE 10.1 (*Continued*)
Preclinical Studies of Novel Formulations of Anticancer Nutraceuticals

Nutraceutical	Nanocarrier	Biological Evaluation	Remarks	References
	Nanosuspension IV delivery	In vitro cell line study (HCT-8 human colon carcinoma), Hela (human cervix carcinoma), HepG2 (human hepatocellular carcinoma), 4T1 (murine mammary carcinoma), and H22 (murine hepatocarcinoma) In vivo PK study in rats In vivo efficacy and biodistribution study in H22 tumor-bearing mice	Improved cytotoxicity compared to parent curcumin in several types of cell lines In vivo PK and biodistribution study showed enhanced t1/2 by 35.95-fold and AUC by 4.5-fold with 18.9-fold higher MRT compared to curcumin solution Improved tumor accumulation and tumor growth inhibition compared to parent curcumin	[62]
	Cholesterol (Ch)-conjugated poly(D, L-lactide) (PLA)-mPEG polymeric micelles IP delivery	In vitro cell line studies (murine melanoma (B16F10) and human breast cancer (MDA-MB-231) cells) In vivo B16F10 melanoma xenograft studies in C57BL/6 mice	Higher drug-loading compared to PLA-mPEG micelles Higher cytotoxicity compared to free curcumin with hemocompatibility 1.8-fold higher tumor growth reduction compared to free curcumin	[63]
	mPEG-PLA micelles IV delivery	In vitro cell line studies (C6 and U251 glioma cells) In vivo C6 glioma xenograft model studies	Enhanced cytotoxicity compared to free curcumin More effective tumor growth suppression in vivo	[40]

(*Continued*)

TABLE 10.1 (*Continued*)
Preclinical Studies of Novel Formulations of Anticancer Nutraceuticals

Nutraceutical	Nanocarrier	Biological Evaluation	Remarks	References
	Liposomes IV delivery	In vitro cell line studies (LL/2 lung cancer cells) In vivo LL/2 xenograft model in mice	Enhanced cytotoxicity in vitro Enhanced in vivo inhibition of tumor growth inhibition Reduced angiogenesis	[64]
	Liposomes of curcumin with/without oxaliplatin solution IV delivery	In vitro cell line studies (LoVo and Colo205 colorectal cancer cells) In vivo LoVo and Colo205 xenograft studies in nude mice	Comparable to greater tumor growth inhibition and apoptotic activity of liposomal curcumin with oxaliplatin in vitro and in vivo	[65]
	Magnetic nanoparticle Intratumoral injection and IP injection	In vitro cell line studies (HPAF-II and Panc-1 pancreatic cancer cells) Tumor HPAF-II xenograft studies in nude mice (tumor distribution and efficacy)	Nanoparticles led to enhanced uptake in cancer cells and effectiveness in vitro Enhanced tumor accumulation upon intratumoral injection compared to IP injection IP administration of nanoparticles showed sustained blood levels compared to curcumin-Pluronic F127	[66]
	Inulin-D-α-tocopherol succinate (INVITE) nanomicelles IV delivery	In vitro cell line studies (HEK 293) In vivo PK study in Balb/c mice	Nanomicelles showed improved cellular uptake and controlled release Nanomicelles improved blood residence of curcumin up to 6 h compared to naked curcumin, which was rapidly cleared from bloodstream	[67]
Curcumin + doxorubicin	Coloaded PEG-PCL micelles IV administration	In vitro cell line studies (LL/2 lung carcinoma cells) In vivo LL/2 xenograft studies in C57 mice (efficacy study)	Synergistic effectiveness of curcumin and doxorubicin was achieved by coloaded micelles in vitro and in vivo	[90]

(*Continued*)

TABLE 10.1 (*Continued*)
Preclinical Studies of Novel Formulations of Anticancer Nutraceuticals

Nutraceutical	Nanocarrier	Biological Evaluation	Remarks	References
Ursolic acid (UA)	Folate-chitosan nanoparticles IP administration	In vitro: cellular uptake, cytotoxicity In vivo: MCF-7 breast cancer xenograft model in mice	Improved uptake in MCF-7 cells by folate mediated endocytosis Induced overproduction of ROS and destruction of mitochondrial membrane potential inducing apoptosis compared to free UA Significantly reduced the tumor burden in xenograft model compared to free drug	[68]
	Caroxymethyl cellulose-UA conjugate nanoparticles (with or without hydroxycamptothecin, CMC-UA NPs or CMC-UA-HCPT NPs) IV administration	In vitro cell line In vivo PK and 4T1 mouse breast cancer xenograft studies	Nanoparticles showed improved cytotoxicity compared free UA CMC-UA-HCPT NPs showed enhanced cytotoxicity compared to individual drugs and individual NPs CMC-UA and CMC-UA-HCPT NPs increased t1/2 of UA from 1 to 4.5 h and 7.3 h, respectively CMC-UA nanoparticles loaded with HCPT Both nanoparticles reduced tumor burden significantly with reduced side effects	[69]
	PLGA NPs IP administration	In vitro cell line studies In vivo CaSki, SiHa, and HeLa cell xenograft studies	A battery of cell line studies showed improved apoptosis and cytotoxicity by nanoparticles Significant tumor volume reduction in all three xenograft models ($p < 0.001$)	[70]
	PLGA nanoparticles IV administration	In vitro cell line studies In vivo PK study in rats and biodistribution study in B16F10 melanoma cells bearing mice	Slower blood clearance of NPs with higher uptake in tumor region compared to free drug	[71]

(*Continued*)

TABLE 10.1 (*Continued*)
Preclinical Studies of Novel Formulations of Anticancer Nutraceuticals

Nutraceutical	Nanocarrier	Biological Evaluation	Remarks	References
Quercetin	MPEG-polycaprolactone polymeric nanomicelles IV administration	In vitro cell line study in colon cancer cell line (Ct26) In vivo CT26 xenograft study	Improved cytotoxicity in vitro by nanomicelles Micelles provided longer t1/2 and bioavailability Nanomicelles led to significant low tumor growth compared to free quercetin	[72]
	MPEG-polycaprolactone polymeric nanomicelles IV administration	In vitro cell line study (A2780S ovarian cancer cell lines) In vivo A2780S ovarian tumors xenograft study in mice	Improved cytotoxicity in vitro in ovarian cancer cells Induced cancer cell apoptosis and inhibited angiogenesis	[73]
	mPEG-PLA micelles Peritumoral injection	In vitro cell line study: MDA-MB-231 breast cancer cells In vivo MDA-MB-231 xenograft model	Sustained release for 10 days Reduced tumor growth significantly as compared to free quercetin	[74]
Gambogic acid (GA)	RBC membrane-coated PLGA nanoparticles IV administration	In vitro cell line studies (SW480, MKN45, and AGS gastrointestinal cancer cell lines) In vivo SW480 xenograft studies for efficacy and biocompatibility	Improved cell uptake and cytotoxicity compared to free GA Improved tumor growth inhibition compared to free GA with no signs of toxicity in heart, lung, liver, kidney, and spleen	[82]
	PEG-PCL nanoparticles Peritumoral injection	In vitro cell line studies (MKN-45 gastric cancer cell lines) In vivo MKN-45 xenograft study in nude Balb/c mice (in vivo bioimaging and efficacy study)	Superior cytotoxicity and antitumor activity compared to free GA due to improved tumoral accumulation of nanoparticles	[75]

(*Continued*)

TABLE 10.1 (*Continued*)
Preclinical Studies of Novel Formulations of Anticancer Nutraceuticals

Nutraceutical	Nanocarrier	Biological Evaluation	Remarks	References
	Nanoparticles of telodendrimer composed of linear PEG-blocking-dendritic oligomer of cholic acid (CA) and vitamin E (VE) IV administration	In vitro cell line study (HT-29 and HCT116 and MCF-7 MX100) In vivo HT29 xenograft study in mice (tumor distribution and efficacy studies)	Similar cytotoxicity against colon cancer cells as free drug Preferential distribution of dendrimers in tumor Increased efficacy in compared to drug—Cremophor EL formulation at equivalent doses	[76]
Gambogic acid + all-trans retinoic acid (ATRA)	Hyaluronic-ATRA (HRA) conjugate based nanoparticles IV administration	In vitro cell line study (MCF-7) In vivo MCF-7 breast cancer xenograft study (biodistribution and efficacy)	Improved cytotoxicity in MCF-7 cells HRA nanoparticles showed improved tumor accumulation in tumor tissue and higher efficacy	[77]
Celatrol	PEG-PCL nanoparticles IP administration	In vitro cell line study (SO-Rb 50) In vivo SO-Rb 50 retinoblastoma xenograft study	Improved cytotoxicity in vitro Improved tumor growth inhibition by nanoparticles	[78]
Berberine	Silver nanoparticles (AgNPs) IV administration	In vitro cell line studies (HBL-100 normal mammary cells; MCF-7 and MDA-MB-231 breast cancer cells) In vivo MCF-7 xenograft studies in nude mice (efficacy and histocompatibility)	In vitro cancer cytotoxicity was higher for berberine loaded AgNPs compared to individual berberine and AgNPs with low toxicity to normal mammary cells MCF-7 cells showed highest sensitivity followed by MDA-MB-231 cells	[79]

(*Continued*)

TABLE 10.1 (*Continued*)
Preclinical Studies of Novel Formulations of Anticancer Nutraceuticals

Nutraceutical	Nanocarrier	Biological Evaluation	Remarks	References
Emodin	TPGS-based liposomes Transferrin-TPGS-based liposomes IV administration	In vitro cell line studies (L1210 and K562, MV4-11 leukemia cells) In vivo PK and biodistribution study in mice	TPGS-based liposomes enhanced cytotoxicity of emodin in leukemia cells TPGS-based liposomes showed 1.7-fold and 0.91-fold higher AUC in blood than free emodin and DSPE-PEG-based liposomes TPGS-based liposomes also showed higher AUC in lung and kidney as compared to DSPE-PEG-based liposomes	[80]
Emodin+heparin	PLGA-TPGS nanoparticles of emodin combined with PGLA-TPGS nanoparticles of heparin IP administration	In vitro cell line studies (HepG2 and HCa-F hepatic cancer cells) In vivo diethylnitrosamine and CCl_4-induced liver cancer studies (efficacy)	In vivo liver targeting was observed with nanoparticles Synergistic cytotoxicity against hepatic cancer cells as well as in vivo tumors	[81]

administration [82]. The system showed improved cytotoxicity as well as in vivo antitumor efficacy along with demonstrating biocompatibility. N-Octyl-N-arginine-chitosan (OACS) was synthesized to develop micelles of gambogic acid for the enhancement of oral bioavailability [83]. In situ intestinal perfusion studies in rat intestinal segments (jejunum, ileum, and colon) showed improved perfusion of gambogic acid.

Nutraceutical-coated metal nanoparticles have been explored for their anticancer potential. Gallic acid coated on gold nanoparticles has been studied for their anticancer potential. Gallic acid coating on gold nanoparticles helped to reduce cytotoxic effects on cervical cancer cells as well as on normal cells. However, free gallic acid was found to be more cytotoxic to the normal cells [84]. However, another study showed that gallic acid gold nanoparticles enhanced the effectiveness of gallic acid on M213 and M214 cholangiocarcinoma cells [85]. These nanoparticles have also shown their in vitro potential against triple negative breast cancer cells (MDA-MB-231) by reducing the effective concentration by 100 times for inhibiting EGF-induced MMP-9 expression [86]. Similar studies with resveratrol-coated gold nanoparticles showed a decreased metastatic potential in breast cancer cells in vitro (MDA-MB-231) [87]. This gives the potential for exploring these strategies with other nutraceuticals and to further study these strategies in vivo.

Magnetic nanoparticles have recently got attention for the delivery of anticancer nutraceuticals. Gambogic acid loaded magnetic Fe_3O_4 nanoparticles have been shown to obstruct the proliferation and migration of Panc-1 pancreatic cancer cells [88]. Magnetic nanoparticles of curcumin showed enhanced effectiveness as well as magnetic targeting in vitro in MDA-Mb-231 cells [89].

Newer approaches include co-delivery of anticancer nutraceuticals with other nutraceuticals or pharmaceuticals for enhanced effectiveness against cancer cells. A lot of research has been directed at chemosensitization and chemoenhancement of nutraceuticals to anticancer pharmaceuticals. Wang et al. developed mPEG-PCL micelles co-loaded with curcumin and doxorubicin for systemic therapy [90]. In vivo studies on the LL/2 lung carcinoma xenograft model in mice demonstrated that the co-loaded micelle formulation enhanced the efficacy compared to micelles of individual drugs or free drugs, demonstrating the synergistic effects between curcumin and doxorubicin as well as effectiveness of delivery system, which provided sustained levels of drugs in blood. Moreover, co-delivery can improve the bioavailability of the anticancer nutraceuticals. Recently, electron spray method has been developed for preparation of curcumin-loaded zein nanoparticles coated with piperine-embedded chitosan layer in order to get advantages of piperine's pGP inhibitory activity and chitosan's absorption enhancement activity [91]. The nanoparticles have shown increased in vitro cytotoxicity against SH-SY5Y neuroblastoma cells. In another study, PLGA nanoparticles were co-loaded with rapamycin (pGP substrate) and piperine to enhance the oral absorption and enhance its effectiveness [92]. In another study, triptolide-loaded and celastrol-loaded silk fibroin nanoparticles were prepared [93]. Both nanoparticles showed—two- to threefold more potent cytotoxicity against MIA PaCa-2 and PANC-1 pancreatic cancer cell

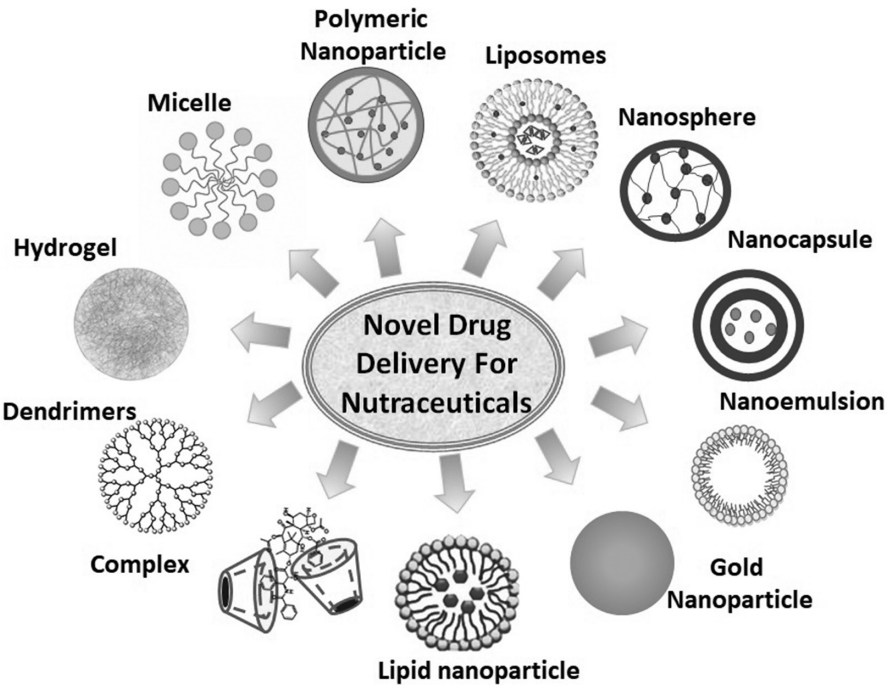


FIGURE 10.4 Novel drug delivery systems for nutraceutical delivery in cancer.

lines. Moreover, combination of both nanoparticles showed synergistic activity. Figure 10.4 is a graphical representation of various nanocarrier systems explored for the delivery of anticancer nutraceutical drugs for cancer therapy.

10.5 CLINICAL TRIALS AND MARKETED FORMULATIONS WITH NANOPARTICULATE SYSTEMS OF ANTICANCER NUTRACEUTICALS

Despite a lot of research going on for the development of nanoformulations of nutraceuticals and their in vitro and preclinical evaluation, only few have made to the clinical trials. In those too, there are very few clinical trials for cancer. Nanoparticulate formulations of nutraceuticals with anticancer potential are detailed in Table 10.2.

Only nanoformulations that have made it to clinical trials are curcumin formulations, Theracurmin, and Meriva. Theracurmin (Theravalues Corporation, Tokyo, Japan) is a submicron particulate system of curcumin that disperses in water, improving the dispersibility and stability. Human PK study with Theracurmin showed 27 times higher bioavailability compared to pristine curcumin powder. When compared to other marketed products, it showed equivalent or higher absorption at 1/30th dose of conventional products. Moreover, Theracurmin was proved to be safe for humans by a battery of oral toxicity studies—acute

TABLE 10.2
Clinical Trials of Novel Formulations of Nutraceuticals of Anticancer Use

Formulation (Drug)	Study Type	Compared to	Remarks	References
Theracurmin (curcumin)	Human PK study (double-blind three-way cross-over study in healthy volunteers)	Marketed products (BCM-95 and Meriva)	AUC0-24 showed 11.0- and 4.6-fold higher for Theracurmin against BCM-95 and Meriva	[94]
	Dose escalation and PK study in healthy volunteers	Dose escalation study of Theracurmin	Dose-dependent increase in AUC was observed Compared with other clinical trials with curcumin, theracurmin reported very high AUC at low doses	[95]
	PK study in healthy volunteers	Curcumin powder	27-fold higher AUC than curcumin powder	[61]
Meriva (Curcumin)	Human PK study in healthy volunteers	Unformulated curcumin	~29-fold (27-fold for the low dosage, 31-fold for the high dose) increase in total curcuminoid levels in blood by Meriva (with 20-fold higher absorption of monomolecular curcumin and 50–60 fold higher for demethoxycurcumin and bisdemethoxycurcumin)	[96]
Lyc-*O*-Mato®/ Lycored® softules (Lycopene)	Human PK study in healthy volunteers	Raw tomato/ spaghetti sauce	Dose-dependent increase in bioavailability from lycomato and spaghetti sauce	[97,98]
	Phase II study in prostate cancer patients before radial prostactomy	Placebo	Reduced growth of prostate cancer with reduction in PSA levels in 18% patients though no firm conclusions were reported	[99]
	Phase II study in hormone refractory prostate cancer	Placebo	Complete response in 1 (5%) patient, partial response in 6 (30%) patients with 10 (50%) patient showed stable disease and 3 (15%) patients showed progression No toxicity or drug intolerance was observed	[100]

toxicity study (2000 mg/kg), 2-week subacute toxicity study (1000 mg/kg/day), and 3 months repeated dose toxicity study (100 mg/kg/day) and negative mutagenicity test.

Other drug molecules that have shown beneficial outcomes in clinical trials include resveratrol and gambogic acid. Multiple clinical trials have been carried out on micronized resveratrol [101], and it has been demonstrated that micronization enhanced the oral bioavailability by 3.6-fold as compared to non-micronized resveratrol. This in turn, improved the therapeutic effects in hepatic malignant tissues [102] and in Phase II study of multiple myeloma in combination with bortezomib [103]. This opens the possibility for nanosizing of the resveratrol as well as other nutraceuticals with lower oral bioavailability. Gambogic acid solution for IV injection is in clinical trials in China for solid tumors and hematological malignancies. In Phase I tolerability study with gambogic acid solution, liver dysfunction and pain were the dose-limiting toxicities [104]. In Phase II efficacy studies on patients with advanced solid tumor who were not receiving any treatment or were not sensitive to previous conventional chemotherapy, gambogic acid solution showed improved disease control rates compared to control arm [105]. Lyc-O-Mato (lycopene soft gel capsules by Lycored Natural Products Industries, Israel) is lycopene in which the particle size is controlled below 3 μ to enhance the bioavailability [106]. It has shown enhanced bioavailability in clinical trials compared to raw tomato [97,98] and has demonstrated reduced prostate cancer growth in clinical trials [99]. So, efforts can be directed toward nanoformulations of these molecules to improve the bioavailability and overcome toxicities.

There are a lot of other marketed formulations containing nutraceuticals. These formulations have been used for their nutraceutical properties but bear potential for clinical anticancer evaluation. George Weston Foods, Australia, uses the nanocapsulation of tuna fish oil (omega-3 fatty acids) to mask the taste and odor so that they can be impregnated in bread. The nanocapsules break down only in stomach so that the bad taste can be avoided. Nanocapsules has also been used for the protection and controlled release of live probiotics. Calcium alginate nanocapsules can be used for the encapsulation of live lactobacillus and bifidobacterial species in the freeze-dried yogurt while providing better viability and survival [107]. BASF patented its spray-drying process of producing cold-water-dispersible powders of carotenoids, which produce nanoparticulate dispersion of the carotenoids for improving its coloring agent and bioavailability (US5968251) [108]. BioGeode nanocochelates have been developed by BioDelivery Sciences International. These nanocochelates <50 nm in size are prepared by crystallization of soy phospholipids and calcium around an oil nanodroplets comprising micronutrients. Micronutrients such as omega-fatty acids and antioxidants are easily destroyed during manufacturing process and storage; however, crystalline nature of these nanocochelates provide stability and protection to the micronutrients during such processing. These nanoformulation strategies have the potential for incorporation in food products for their oral delivery.

Moreover, similar to the biopharmaceutical classification system (BCS) of pharmaceuticals, efforts have been made to develop a similar classification system for nutraceuticals (nutraceuticals bioavailability classification system—NuBACS) considering the major factors affecting their biological fate including bioaccessibility (B*), absorption

(A*), and transformation (T*) in the gastrointestinal tract (GIT) [9]. Such a classification system helps in the classification of nutraceuticals and hence identifying the nutraceuticals that can be further enhanced by modifying their formulation strategy. Moreover, combining the use of NuBACS and using nanoformulations for externally fortifying food product with nutraceuticals with low oral bioavailability could provide new alternatives for the oral delivery of anticancer nutraceuticals through food products.

A lot of formulation strategies with proven benefits have been developed starting from simple micellar formulations to lipidic, polymeric, and metal nanoparticles. Additionally, complex formulation and delivery strategies have also been developed for overcoming challenges with nutraceuticals, that is, nanoparticles co-loaded with multiple nutraceuticals or nutraceuticals with pharmaceuticals or co-delivery strategy by using nanoparticulate-based nutraceuticals with other drugs. These strategies work by enhancing the bioavailability of agents or by chemoenhancement or chemosensitization. Targeting strategies could also help enhance the effectiveness of these drug delivery systems. Although a lot of attention has been given to anticancer nutraceuticals and plenty of research is directed toward the development of nanoparticulate drug delivery systems of nutraceuticals, the studies are limited to their in vitro and preclinical evaluation only. Newer strategies and newer concepts described earlier can help overcome the challenges and provide beneficial therapeutic option to cancer patients. Hence, more efforts are needed to clinically translate the developed strategies. This would help bring these nutraceuticals in market to provide benefit of improved quality of life at reduced costs to patients.

10.6 CONCLUSION AND FUTURE INSIGHTS

In last few years, research has provided confirmation of the versatile applications of nutraceuticals and their potential use as anticancer agents for prevention and treatment of cancer. Although in vitro and in vivo studies undoubtedly proved that nutraceuticals hold anticancer activity in accordance with other health benefits, the clinical use of these agents is limited and still under investigation. The idea of applications of nanodrug delivery system as a delivery vehicle for nutraceuticals for cancer therapy has emerged as a crucial approach to prevent the unwanted side effects of chemotherapeutics and improve the effectiveness of cancer therapy. The utilization of nanocarriers based on nanodrug delivery system has facilitated researchers to overcome poor aqueous solubility, poor bioavailability, poor pharmacokinetic, and toxicity-related issues of anticancer nutraceutical drugs. Further, these nanoformulations have exhibited passive as well as active targeting of nutraceutical drug for cancer treatment. Recently, amalgamation of chemotherapeutic and nutraceuticals using nanodrug delivery systems has gained much interest for the prevention and treatment of cancer because of certain advantages such as synergistic effects, controlled release, site-specific targeting, and improved pharmacokinetic and reduced toxicities to the normal healthy cells. It is expected that ongoing research and efforts in the application of nutraceuticals in cancer therapy and the role of nanocarriers in nutraceutical delivery for cancer as well as combination approaches of chemotherapeutics and nutraceutical encapsulated nanocarrier will lead to development of new alternative therapy for cancer.

REFERENCES

1. society Ac. Global Cancer Facts & Figures 2018 [05/08/2018]. Available from: https://www.cancer.org/research/cancer-facts-statistics/global.html.
2. Huang P, Yang LL, Wang CY, Chen JP, Wang SS, Wang SJ et al. Preparation and characterization of folate targeting magnetic nanomedicine loaded with gambogenic acid. *Journal of Nanoscience and Nanotechnology*. 2015;15(7):4774–4783.
3. Gonzalez-Vallinas M, Gonzalez-Castejon M, Rodriguez-Casado A, Ramirez de Molina A. Dietary phytochemicals in cancer prevention and therapy: A complementary approach with promising perspectives. *Nutrition Reviews*. 2013;71(9):585–599.
4. DeFelice SL. The nutraceutical revolution: Its impact on food industry R&D. *Trends in Food Science & Technology*. 1995;6(2):59–61.
5. Nair HB, Sung B, Yadav VR, Kannappan R, Chaturvedi MM, Aggarwal BB. Delivery of antiinflammatory nutraceuticals by nanoparticles for the prevention and treatment of cancer. *Biochemical Pharmacology*. 2010;80(12):1833–1843.
6. Saneja A, Khare V, Alam N, Dubey RD, Gupta PN. Advances in P-glycoprotein-based approaches for delivering anticancer drugs: Pharmacokinetic perspective and clinical relevance. *Expert Opinion on Drug Delivery*. 2014;11(1):121–138.
7. Nkondjock A, Ghadirian P, Johnson KC, Krewski D. Dietary intake of lycopene is associated with reduced pancreatic cancer risk. *The Journal of Nutrition*. 2005;135(3):592–597.
8. Li Y, Go VL, Sarkar FH. The role of nutraceuticals in pancreatic cancer prevention and therapy: Targeting cellular signaling, MicroRNAs, and epigenome. *Pancreas*. 2015;44(1):1–10.
9. McClements DJ, Li F, Xiao H. The nutraceutical bioavailability classification scheme: Classifying nutraceuticals according to factors limiting their oral bioavailability. *Annual Review of Food Science and Technology*. 2015;6:299–327.
10. Din FU, Aman W, Ullah I, Qureshi OS, Mustapha O, Shafique S et al. Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. *International Journal of Nanomedicine*. 2017;12:7291–7309.
11. Wiseman M. The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: A global perspective. *The Proceedings of the Nutrition Society*. 2008;67(3):253–256.
12. Bhatt P, Vhora I, Patil S, Amrutiya J, Bhattacharya C, Misra A et al. Role of antibodies in diagnosis and treatment of ovarian cancer: Basic approach and clinical status. *Journal of Controlled Release*. 2016;226:148–67.
13. DeFelice SL. FIM, Rationale and Proposed Guidelines for the Nutraceutical Research and Education Act NREA, Foundation for Innovation in Medicine. 2002.
14. Go VLW, Harris DM, Srihari P. 2012. Global overview of the role of nutraceuticals in cancer. In: Sarkar F. (eds) *Nutraceuticals and Cancer*. Springer, Dordrecht.
15. McGuire S. US Department of Agriculture and US Department of Health and Human Services, Dietary Guidelines for Americans, 2010. *Advances in Nutrition International Review Journal*. 2011;2:293–294.
16. Yadollahi R, Vasilev K, Simovic S. Nanosuspension technologies for delivery of poorly soluble drugs. *Journal of Nanomaterials*. 2015;2015:13.
17. Nehate C, Jain S, Saneja A, Khare V, Alam N, Dubey RD et al. Paclitaxel formulations: Challenges and novel delivery options. *Current Drug Delivery*. 2014;11(6):666–686.
18. Tandel H, Bhatt P, Jain K, Shahiwala A, Misra A. 2018. In-vitro and in-vivo tools in emerging drug delivery scenario: Challenges and updates. In: Misra ASaA, editor. *In-Vitro and In-Vivo Tools in Drug Delivery Research for Optimum Clinical Outcomes*. CRC Press, Boca Raton, FL.

19. Yewale C, Baradia D, Patil S, Bhatt P, Amrutiya J, Gandhi R et al. Docetaxel loaded immunonanoparticles delivery in EGFR overexpressed breast carcinoma cells. *Journal of Drug Delivery Science and Technology*. 2018;45:334–345.
20. Vhora I, Patil S, Bhatt P, Gandhi R, Baradia D, Misra A. Receptor-targeted drug delivery: Current perspective and challenges. *Therapeutic Delivery*. 2014;5(9):1007–1024.
21. Kumari A, Yadav SK, Yadav SC. Biodegradable polymeric nanoparticles based drug delivery systems. *Colloids and Surfaces B, Biointerfaces*. 2010;75(1):1–18.
22. Patel J, Amrutiya J, Bhatt P, Javia A, Jain M, Misra A. Targeted delivery of monoclonal antibody conjugated docetaxel loaded PLGA nanoparticles into EGFR overexpressed lung tumour cells. *Journal of Microencapsulation*. 2018;35(2):204–217.
23. Arora D, Sharma N, Sharma V, Abrol V, Shankar R, Jaglan S. An update on polysaccharide-based nanomaterials for antimicrobial applications. *Applied Microbiology and Biotechnology*. 2016;100(6):2603–2615.
24. Lo Y-L, Sung K-H, Chiu C-C, Wang L-F. Chemically conjugating polyethylenimine with chondroitin sulfate to promote CD44-mediated endocytosis for gene delivery. *Molecular Pharmaceutics*. 2013;10(2):664–676.
25. Perche F, Torchilin VP. Recent trends in multifunctional liposomal nanocarriers for enhanced tumor targeting. *Journal of Drug Delivery*. 2013;2013:32.
26. Bhatt P, Lalani R, Vhora I, Patil S, Amrutiya J, Misra A et al. Liposomes encapsulating native and cyclodextrin enclosed paclitaxel: Enhanced loading efficiency and its pharmacokinetic evaluation. *International Journal of Pharmaceutics*. 2018;536(1):95–107.
27. Lalani RA, Bhatt P, Rathi M, Misra A. Abstract 2063: Improved sensitivity and in vitro efficacy of RGD grafted PEGylated gemcitabine liposomes in RRM1 siRNA pretreated cancer cells. *Cancer Research*. 2016;76(14 Supplement):2063.
28. Bhatt P, Lalani R, Mashru R, Misra A. Abstract 2065: Anti-FSHR antibody Fab' fragment conjugated immunoliposomes loaded with cyclodextrin-paclitaxel complex for improved in vitro efficacy on ovarian cancer cells. *Cancer Research*. 2016;76(14 Supplement):2065.
29. Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nature Biotechnology*. 2015;33(9):941–951.
30. Talelli M, Barz M, Rijcken CJF, Kiessling F, Hennink WE, Lammers T. Core-crosslinked polymeric micelles: Principles, preparation, biomedical applications and clinical translation. *Nano Today*. 2015;10(1):93–117.
31. Saneja A, Nehate C, Alam N, Gupta PN. 2016. Recent advances in chitosan-based nanomedicines for cancer chemotherapy. In: Dutta PK, editor. *Chitin and Chitosan for Regenerative Medicine*. New Delhi, India: Springer. pp. 229–259.
32. Madaan K, Kumar S, Poonia N, Lather V, Pandita D. Dendrimers in drug delivery and targeting: Drug-dendrimer interactions and toxicity issues. *Journal of Pharmacy & Bioallied Sciences*. 2014;6(3):139–150.
33. Hoare TR, Kohane DS. Hydrogels in drug delivery: Progress and challenges. *Polymer*. 2008;49(8):1993–2007.
34. Chen H, Weiss J, Shahidi F. Nanotechnology in nutraceuticals and functional foods. *Food Technology*. 2006;6(3):30–36.
35. Apiratikul N, Penglong T, Suksen K, Svasti S, Chairoungdua A, Yingyongnarongkula B. In vitro delivery of curcumin with cholesterol-based cationic liposomes. *Bioorganicheskaia Khimiia*. 2013;39(4):497–503.
36. Saengkrit N, Saesoo S, Srinuanchai W, Phunpee S, Ruktanonchai UR. Influence of curcumin-loaded cationic liposome on anticancer activity for cervical cancer therapy. *Colloids and Surfaces B, Biointerfaces*. 2014;114:349–356.
37. Dhule SS, Penfornis P, Frazier T, Walker R, Feldman J, Tan G et al. Curcumin-loaded gamma-cyclodextrin liposomal nanoparticles as delivery vehicles for osteosarcoma. *Nanomedicine: Nanotechnology, Biology, and Medicine*. 2012;8(4):440–451.

38. Huang Q, Zhang L, Sun X, Zeng K, Li J, Liu Y-N. Coating of carboxymethyl dextran on liposomal curcumin to improve the anticancer activity. *RSC Advances*. 2014;4(103):59211–59217.
39. Singh A, Neupane YR, Panda BP, Kohli K. Lipid Based nanoformulation of lycopene improves oral delivery: Formulation optimization, ex vivo assessment and its efficacy against breast cancer. *Journal of Microencapsulation*. 2017;34(4):416–429.
40. Zheng S, Gao X, Liu X, Yu T, Zheng T, Wang Y et al. Biodegradable micelles enhance the antiglioma activity of curcumin in vitro and in vivo. *International Journal of Nanomedicine*. 2016;11:2721–2736.
41. Sharma P, Saxena P, Jaswanth A, Chalamaiah M, Tekade KR, Balasubramaniam A. Novel encapsulation of lycopene in niosomes and assessment of its anticancer activity. *Journal of Bioequivalence & Bioavailability*. 2016;8:224–232.
42. Abuasal BS, Lucas C, Peyton B, Alayoubi A, Nazzal S, Sylvester PW et al. Enhancement of intestinal permeability utilizing solid lipid nanoparticles increases gamma-tocotrienol oral bioavailability. *Lipids*. 2012;47(5):461–469.
43. Alqahtani S, Alayoubi A, Nazzal S, Sylvester PW, Kaddoumi A. Enhanced solubility and oral bioavailability of gamma-tocotrienol using a self-emulsifying drug delivery system (SEDDS). *Lipids*. 2014;49(8):819–829.
44. Sahu A, Kasoju N, Bora U. Fluorescence study of the curcumin−casein micelle complexation and its application as a drug nanocarrier to cancer cells. *Biomacromolecules*. 2008;9(10):2905–2912.
45. Pan K, Zhong Q, Baek SJ. Enhanced dispersibility and bioactivity of curcumin by encapsulation in casein nanocapsules. *Journal of Agricultural and Food Chemistry*. 2013;61(25):6036–6043.
46. Bhawana, BRK, Buttar HS, Jain VK, Jain N. Curcumin nanoparticles: Preparation, characterization, and antimicrobial study. *Journal of Agricultural and Food Chemistry*. 2011;59(5):2056–2061.
47. Adahoun MaA, Al-Akhras M-AH, Jaafar MS, Bououdina M. Enhanced anti-cancer and antimicrobial activities of curcumin nanoparticles. *Artificial Cells, Nanomedicine, and Biotechnology*. 2017;45(1):98–107.
48. Kang M, Ho JN, Kook HR, Lee S, Oh JJ, Hong SK et al. Theracurmin(R) efficiently inhibits the growth of human prostate and bladder cancer cells via induction of apoptotic cell death and cell cycle arrest. *Oncology Reports*. 2016;35(3):1463–1472.
49. Sasaki H, Sunagawa Y, Takahashi K, Imaizumi A, Fukuda H, Hashimoto T et al. Innovative preparation of curcumin for improved oral bioavailability. *Biological & Pharmaceutical Bulletin*. 2011;34(5):660–665.
50. Marczylo TH, Verschoyle RD, Cooke DN, Morazzoni P, Steward WP, Gescher AJ. Comparison of systemic availability of curcumin with that of curcumin formulated with phosphatidylcholine. *Cancer Chemotherapy and Pharmacology*. 2007;60(2):171–177.
51. Chandra D, Jahangir A, Cornelis F, Rombauts K, Meheus L, Jorcyk CL et al. Cryoablation and meriva have strong therapeutic effect on triple-negative breast cancer. *OncoImmunology*. 2016;5(1):e1049802.
52. Tu YS, Fu JW, Sun DM, Zhang JJ, Yao N, Huang DE et al. Preparation, characterisation and evaluation of curcumin with piperine-loaded cubosome nanoparticles. *Journal of Microencapsulation*. 2014;31(6):551–559.
53. Narayanan NK, Nargi D, Randolph C, Narayanan BA. Liposome encapsulation of curcumin and resveratrol in combination reduces prostate cancer incidence in PTEN knockout mice. *International Journal of Cancer*. 2009;125(1):1–8.
54. Choi A-J, Kim C-J, Cho Y-J, Hwang J-K, Kim C-T. Characterization of capsaicin-loaded nanoemulsions stabilized with alginate and chitosan by self-assembly. *Food and Bioprocess Technology*. 2011;4(6):1119–1126.

55. Fernandez A, Torres-Giner S, Lagaron JM. Novel route to stabilization of bioactive antioxidants by encapsulation in electrospun fibers of zein prolamine. *Food Hydrocolloids*. 2009;23(5):1427–1432.
56. Neo YP, Ray S, Jin J, Gizdavic-Nikolaidis M, Nieuwoudt MK, Liu D et al. Encapsulation of food grade antioxidant in natural biopolymer by electrospinning technique: A physicochemical study based on zein–gallic acid system. *Food Chemistry*. 2013;136(2):1013–1021.
57. Singh G, Pai RS. Optimized PLGA nanoparticle platform for orally dosed trans-resveratrol with enhanced bioavailability potential. *Expert Opinion on Drug Delivery*. 2014 ;11(5):647–659.
58. Neves AR, Lucio M, Martins S, Lima JL, Reis S. Novel resveratrol nanodelivery systems based on lipid nanoparticles to enhance its oral bioavailability. *International Journal of Nanomedicine*. 2013;8:177–187.
59. Tan B-J, Liu Y, Chang K-L, Lim BKW, Chiu GNC. Perorally active nanomicellar formulation of quercetin in the treatment of lung cancer. *International Journal of Nanomedicine*. 2012;7:651–661.
60. Dian L, Yu E, Chen X, Wen X, Zhang Z, Qin L et al. Enhancing oral bioavailability of quercetin using novel soluplus polymeric micelles. *Nanoscale Research Letters*. 2014;9:684.
61. Li X, Yuan H, Zhang C, Chen W, Cheng W, Chen X et al. Preparation and in-vitro/in-vivo evaluation of curcumin nanosuspension with solubility enhancement. *The Journal of Pharmacy and Pharmacology*. 2016;68(8):980–988.
62. Hong J, Liu Y, Xiao Y, Yang X, Su W, Zhang M et al. High drug payload curcumin nanosuspensions stabilized by mPEG-DSPE and SPC: In vitro and in vivo evaluation. *Drug Delivery*. 2017;24(1):109–120.
63. Kumari P, Muddineti OS, Rompicharla SV, Ghanta P, BBN AK, Ghosh B et al. Cholesterol-conjugated poly(D, L-lactide)-based micelles as a nanocarrier system for effective delivery of curcumin in cancer therapy. *Drug Delivery*. 2017;24(1):209–223.
64. Wang LQ, Shi HS, Wang YS. Liposomal curcumin inhibits tumor growth and angiogenesis in Lewis lung cancer. *Sichuan da xue xue bao Yi xue ban = Journal of Sichuan University Medical science edition*. 2013;44(1):46–48, 75.
65. Li L, Ahmed B, Mehta K, Kurzrock R. Liposomal curcumin with and without oxaliplatin: Effects on cell growth, apoptosis, and angiogenesis in colorectal cancer. *Molecular Cancer Therapeutics*. 2007;6(4):1276–1282.
66. Yallapu MM, Ebeling MC, Khan S, Sundram V, Chauhan N, Gupta BK et al. Novel curcumin loaded magnetic nanoparticles for pancreatic cancer treatment. *Molecular Cancer Therapeutics*. 2013;12(8):1471–1480.
67. Tripodo G, Pasut G, Trapani A, Mero A, Lasorsa FM, Chlapanidas T et al. Inulin-d-α-tocopherol succinate (INVITE) nanomicelles as a platform for effective intravenous administration of curcumin. *Biomacromolecules*. 2015;16(2):550–557.
68. Jin H, Pi J, Yang F, Jiang J, Wang X, Bai H et al. Folate-Chitosan nanoparticles loaded with ursolic acid confer anti-breast cancer activities in vitro and in vivo. *Scientific Reports*. 2016;6:30782.
69. Liu Y-X, Liu K-F, Li C-X, Wang L-Y, Liu J, He J et al. Self-assembled nanoparticles based on a carboxymethylcellulose–ursolic acid conjugate for anticancer combination therapy. *RSC Advances*. 2017;7(58):36256–36268.
70. Wang S, Meng X, Dong Y. Ursolic acid nanoparticles inhibit cervical cancer growth in vitro and in vivo via apoptosis induction. *International Journal of Oncology*. 2017;50(4):1330–1340.

71. Baishya R, Nayak DK, Kumar D, Sinha S, Gupta A, Ganguly S et al. Ursolic acid loaded PLGA nanoparticles: In vitro and in vivo Evaluation to explore tumor targeting ability on B16F10 melanoma cell lines. *Pharmaceutical Research*. 2016;33(11):2691–2703.
72. Xu G, Shi H, Ren L, Gou H, Gong D, Gao X et al. Enhancing the anti-colon cancer activity of quercetin by self-assembled micelles. *International Journal of Nanomedicine*. 2015;10:2051–2063.
73. Gao X, Wang B, Wei X, Men K, Zheng F, Zhou Y et al. Anticancer effect and mechanism of polymer micelle-encapsulated quercetin on ovarian cancer. *Nanoscale*. 2012;4(22):7021–7030.
74. Sharma G, Park J, Sharma AR, Jung JS, Kim H, Chakraborty C et al. Methoxy poly(ethylene glycol)-poly(lactide) nanoparticles encapsulating quercetin act as an effective anticancer agent by inducing apoptosis in breast cancer. *Pharmaceutical Research*. 2015;32(2):723–735.
75. Zhang D, Zou Z, Ren W, Qian H, Cheng Q, Ji L et al. Gambogic acid-loaded PEG–PCL nanoparticles act as an effective antitumor agent against gastric cancer. *Pharmaceutical Development and Technology*. 2018;23(1):33–40.
76. Huang W, Wang X, Shi C, Guo D, Xu G, Wang L et al. Fine-tuning vitamin E-containing telodendrimers for efficient delivery of gambogic acid in colon cancer treatment. *Molecular Pharmaceutics*. 2015;12(4):1216–1229.
77. Yao J, Li Y, Sun X, Dahmani FZ, Liu H, Zhou J. Nanoparticle delivery and combination therapy of gambogic acid and all-trans retinoic acid. *International Journal of Nanomedicine*. 2014;9:3313–3324.
78. Li Z, Wu X, Li J, Yao L, Sun L, Shi Y et al. Antitumor activity of celastrol nanoparticles in a xenograft retinoblastoma tumor model. *International Journal of Nanomedicine*. 2012;7:2389–2398.
79. Bhanumathi R, Vimala K, Shanthi K, Thangaraj R, Kannan S. Bioformulation of silver nanoparticles as berberine carrier cum anticancer agent against breast cancer. *New Journal of Chemistry*. 2017;41(23):14466–14477.
80. Wang T, Yin X, Lu Y, Shan W, Xiong S. Formulation, antileukemia mechanism, pharmacokinetics, and biodistribution of a novel liposomal emodin. *International Journal of Nanomedicine*. 2012;7:2325–2337.
81. Liu H, Xu H, Zhang C, Gao M, Gao X, Ma C et al. Emodin-loaded PLGA-TPGS nanoparticles combined with heparin sodium-loaded PLGA-TPGS nanoparticles to enhance chemotherapeutic efficacy against liver cancer. *Pharmaceutical Research*. 2016;33(11):2828–2843.
82. Zhang Z, Qian H, Yang M, Li R, Hu J, Li L et al. Gambogic acid-loaded biomimetic nanoparticles in colorectal cancer treatment. *International Journal of Nanomedicine*. 2017;12:1593–1605.
83. Yu F, He C, Waddad AY, Munyendo WLL, Lv H, Zhou J et al. N-octyl-N-arginine-chitosan (OACS) micelles for gambogic acid oral delivery: Preparation, characterization and its study on in situ intestinal perfusion. *Drug Development and Industrial Pharmacy*. 2014;40(6):774–782.
84. Daduang J, Palasap A, Daduang S, Boonsiri P, Suwannalert P, Limpaiboon T. Gallic acid enhancement of gold nanoparticle anticancer activity in cervical cancer cells. *Asian Pacific Journal of Cancer Prevention: APJCP*. 2015;16(1):169–174.
85. Rattanata N, Daduang S, Wongwattanakul M, Leelayuwat C, Limpaiboon T, Lekphrom R et al. Gold nanoparticles enhance the anticancer activity of gallic acid against cholangiocarcinoma cell lines. *Asian Pacific Journal of Cancer Prevention: APJCP*. 2015;16(16):7143–7147.

86. Chen YJ, Lee YC, Huang CH, Chang LS. Gallic acid-capped gold nanoparticles inhibit EGF-induced MMP-9 expression through suppression of p300 stabilization and NFkappaB/c-Jun activation in breast cancer MDA-MB-231 cells. *Toxicology and Applied Pharmacology*. 2016;310:98–107.
87. Park SY, Chae SY, Park JO, Lee KJ, Park G. Gold-conjugated resveratrol nanoparticles attenuate the invasion and MMP-9 and COX-2 expression in breast cancer cells. *Oncology Reports*. 2016;35(6):3248–3256.
88. Wang C, Zhang H, Chen Y, Shi F, Chen B. Gambogic acid-loaded magnetic Fe(3)O(4) nanoparticles inhibit Panc-1 pancreatic cancer cell proliferation and migration by inactivating transcription factor ETS1. *International Journal of Nanomedicine*. 2012;7:781–787.
89. Yallapu MM, Othman SF, Curtis ET, Bauer NA, Chauhan N, Kumar D et al. Curcumin-loaded magnetic nanoparticles for breast cancer therapeutics and imaging applications. *International Journal of Nanomedicine*. 2012;7:1761–1779.
90. Wang BL, Shen YM, Zhang QW, Li YL, Luo M, Liu Z et al. Codelivery of curcumin and doxorubicin by MPEG-PCL results in improved efficacy of systemically administered chemotherapy in mice with lung cancer. *International Journal of Nanomedicine*. 2013;8:3521–3531.
91. Baspinar Y, Üstündas M, Bayraktar O, Sezgin C. Curcumin and piperine loaded zein-chitosan nanoparticles: Development and in-vitro characterisation. *Saudi Pharmaceutical Journal: SPJ*. 2018;26(3):323–334.
92. Katiyar SS, Muntimadugu E, Rafeeqi TA, Domb AJ, Khan W. Co-delivery of rapamycin- and piperine-loaded polymeric nanoparticles for breast cancer treatment. *Drug Delivery*. 2016;23(7):2608–2616.
93. Ding B, Wahid MA, Wang Z, Xie C, Thakkar A, Prabhu S et al. Triptolide and celastrol loaded silk fibroin nanoparticles show synergistic effect against human pancreatic cancer cells. *Nanoscale*. 2017;9(32):11739–11753.
94. Sunagawa Y, Hirano S, Katanasaka Y, Miyazaki Y, Funamoto M, Okamura N et al. Colloidal submicron-particle curcumin exhibits high absorption efficiency-a double-blind, 3-way crossover study. *Journal of Nutritional Science and Vitaminology*. 2015;61(1):37–44.
95. Kanai M, Imaizumi A, Otsuka Y, Sasaki H, Hashiguchi M, Tsujiko K et al. Dose-escalation and pharmacokinetic study of nanoparticle curcumin, a potential anticancer agent with improved bioavailability, in healthy human volunteers. *Cancer Chemotherapy and Pharmacology*. 2012;69(1):65–70.
96. Cuomo J, Appendino G, Dern AS, Schneider E, McKinnon TP, Brown MJ et al. Comparative absorption of a standardized curcuminoid mixture and its lecithin formulation. *Journal of Natural Products*. 2011;74(4):664–669.
97. Bohm V, Bitsch R. Intestinal absorption of lycopene from different matrices and interactions to other carotenoids, the lipid status, and the antioxidant capacity of human plasma. *European Journal of Nutrition*. 1999;38(3):118–125.
98. Rao AV, Agarwal S. Bioavailability and in vivo antioxidant properties of lycopene from tomato products and their possible role in the prevention of cancer. *Nutrition and Cancer*. 1998;31(3):199–203.
99. Kucuk O, Sarkar FH, Sakr W, Djuric Z, Pollak MN, Khachik F et al. Phase II randomized clinical trial of lycopene supplementation before radical prostatectomy. *Cancer Epidemiology, Biomarkers & Prevention: A publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology*. 2001;10(8):861–868.
100. Ansari MS, Gupta NP. Lycopene: A novel drug therapy in hormone refractory metastatic prostate cancer. *Urologic Oncology*. 2004;22(5):415–420.

101. Tome-Carneiro J, Larrosa M, Gonzalez-Sarrias A, Tomas-Barberan FA, Garcia-Conesa MT, Espin JC. Resveratrol and clinical trials: The crossroad from in vitro studies to human evidence. *Current Pharmaceutical Design*. 2013;19(34):6064–6093.
102. Howells LM, Berry DP, Elliott PJ, Jacobson EW, Hoffmann E, Hegarty B et al. Phase I randomized, double-blind pilot study of micronized resveratrol (SRT501) in patients with hepatic metastases—Safety, pharmacokinetics, and pharmacodynamics. *Cancer Prevention Research*. 2011;4(9):1419.
103. Popat R, Plesner T, Davies F, Cook G, Cook M, Elliott P et al. A phase 2 study of SRT501 (resveratrol) with bortezomib for patients with relapsed and or refractory multiple myeloma. *British Journal of Haematology*. 2013;160(5):714–717.
104. Zhou Z, Wan J. Phase I human tolerability trial of gambogic acid. *Chinese Journal of New Drugs*. 2007;1:679–682.
105. Chi Y, Zhan XK, Yu H, Xie GR, Wang ZZ, Xiao W et al. An open-labeled, randomized, multicenter phase IIa study of gambogic acid injection for advanced malignant tumors. *Chinese Medical Journal*. 2013;126(9):1642–1646.
106. http://www.lycored.com/innovations/ [Internet].
107. Kailasapathy K, Rybka SL. Acidophilus and bifidobacterium spp.-their therapeutic potential and survival in yogurt. *Australian Journal of Dairy Technology*. 1997;52(1):28.
108. Auweter H, Bohn H, Haberkorn H, Horn D, Luddecke E, Rauschenberger V. Inventors; BASF, assignee. Production of carotenoid preparations in the form of coldwater-dispersible powders, and the use of the novel carotenoid preparations. 1997, US1999.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

11 Delivery Strategies and Formulation Approaches of Anticancer Nutraceuticals

Sunita Dahiya and Rajiv Dahiya

CONTENTS

11.1 PREAMBLE

The term "nutraceutical" was coined in 1989 by Stephen L. Defelice, who established "The Foundation for Innovation in Medicine" in 1976 [1]. There is no internationally recognized universal definition; however, nutraceuticals are known as oral dietary components naturally found in foods and believed to have medical or health benefits or "food or part of a food, such as a dietary supplement, that has a medical or health benefit, including the prevention and treatment of disease." Numerous classes of compounds found in natural and processed foods are claimed to have beneficial effects on human health and wellness, and are known as nutraceuticals, for example, vitamins, carotenoids, flavonoids, curcuminoids, polyunsaturated fatty acids, proteins, peptides, dietary fibers, oligosaccharides, and minerals [2,3]. Nutraceuticals have enormous chances for growth and expansion in terms of health benefits [4], as they are biologically active molecules found in foods that may not be essential for maintaining normal human functions, but may enhance human health and well-being by inhibiting certain diseases or improving human performance [3,5]. Various classes of nutraceuticals are found in both natural and processed foods including carotenoids, flavonoids, curcuminoids, phytosterols, dietary fibers, phenolics, and certain fatty acids [6]; some of these have anticancer potential and may be incorporated into functional or medical foods for preventing or treating certain types of cancers. Nutraceuticals vary considerably in their chemical structures, physiochemical properties, and biological properties such as molar mass, structure, polarity, charge, and functional groups, which influence their chemical reactivity, physical state, solubility characteristics, and biological fate and functions [7]. Some nutraceuticals are naturally present in whole foods, such as fruits, vegetables, and cereals, and are therefore often consumed in this form, whereas other nutraceuticals are isolated from their natural states and converted into additives that can be incorporated into functional foods, dietary supplements, or pharmaceuticals. The delivery of nutraceuticals using foods may decrease the risk of certain types of chronic diseases, including cancer [8]. Recently, nutraceuticals have gained much attention in the area of cancer research because of their multiple beneficial effects and relatively nontoxic behavior [9].

11.2 ANTICANCER NUTRACEUTICALS

11.2.1 Nutraceuticals' Chemopreventive and Chemotherapeutic Role against Cancer Development: Molecular Targets and Anticancer Mechanisms

Nutraceutical-rich bioactive dietary components have the ability to prevent cancer [10]. Many herbal nutraceuticals possess antimutagenic and anticarcinogenic properties; for example, carotenoids have antioxidant activities, lycopene are effective in cancer, and ginseng is an anti-inflammatory molecule that prevents chronic inflammation of cancer. These constituents are oxygen quenchers and decrease oxidative stress. Also, nutraceuticals control DNA-damaging factors in the cells and prevents DNA transcription in tumors [11]. Chemopreventive components in fruits and vegetables have potential anticarcinogenic and antimutagenic activities. β-Carotene from yellow and orange fruits has anticancer activity. Cruciferous vegetables lower the chances of colorectal and lung cancer. They block the enzymes that promote tumor growth. Sulfur compounds in garlic boost immune system, reduce atherosclerosis and platelet aggregation [12], and have the ability to alter metastatic spread of cancer [13]. Some nutraceuticals are naturally present in whole foods, such as fruits, vegetables, and cereals, and therefore often consumed in this form. Conversely, other nutraceuticals are isolated from their natural states and converted into additives that can be incorporated into functional foods, dietary supplements, or pharmaceuticals. There are a number of factors that currently limit the utilization of many types of anticancer nutraceuticals in functional foods. First, many nutraceuticals cannot easily be incorporated into foods because they have poor-solubility characteristics, or they cause undesirable changes in appearance, texture, or flavor of foods. Second, many nutraceuticals are chemically or biochemically unstable and therefore lose their bioactivity because they are degraded within food products or the human body. Third, many nutraceuticals have low bioavailability and therefore only a small fraction of them are actually absorbed and utilized by the body. Fourth, for some nutraceuticals, the optimum dose has not been established; therefore, it is unclear how much to deliver in the bioactive form, for example, the anticancer efficacy of resveratrol actually decreases as the dose increases [14]. Anticancer nutraceuticals mediate their positive health benefits directly by affecting specific molecular targets such as genes or indirectly as stabilized conjugates affecting metabolic pathways [15]. Many genes play significant roles in the cell cycle pathway, and some of these are mutated in cancer cells [16,17]. Most studies attempted to explain the mechanistic pathways that are regulated by nutraceuticals to bring about changes in the tumor environment and serve as alternative approaches for cancer prevention and therapy to alter the fate of a cell. For a cancerous cell to survive, it should be able to proliferate, obtain energy, and establish angiogenic pathways in a tumor mass. Mutation of genes that affect these pathways can serve as a suitable tool to decrease tumor mass and also allows for tumor regression. Initial *in vitro* studies found that phytochemicals may help the tumorigenic actions of carcinogens by blocking their mutagenic activity and suppressing cell proliferation [18]. Chemoprevention can be defined as the use of natural or synthetic chemicals to reverse, suppress, or prevent

the process of carcinogenesis. Solid cancers in early stage are generally detected as intraepithelial neoplasia or carcinoma *in situ*, which corresponds to the promotion and progression stages. Therefore, "anti-promotion" and "anti-progression" agents may be of particular clinical interest. Dietary bioactive substances, even in very low concentrations, may have a great impact on the regulation of gene expression. Continuing research on the effects of nutraceuticals on gene expression should provide a better knowledge of the mechanisms of prevention of diseases, such as obesity, diabetes, atherosclerosis, hypertension, and cancer, through dietary manipulations. Studies investigated that phytochemicals protect against lipid peroxidation and modulate innate and inflammatory responses [19]. These effects of plant extracts in combination with their lack of toxicity make them potentially efficient agents in the fight against cancer. However, each compound's mechanism of action and its effectiveness in a specific type of cancer must be studied in order to apply the correct compound to the appropriate clinical situation. The term "nutritional genomics" was coined to describe the research at the interface of plant biochemistry, genomics, and human nutrition [20]. A few studies on the action of selected nutraceuticals on the activity have paved a path to further investigate these molecules in a great detail using various genetic diseased animal models [21]. Besides the active role of nutraceuticals and functional foods in the control of cancer progress, there is also a great need to develop food supplements as the add-on therapy to provide better quality of life for cancer patients [22]. In fact, some cancer patients show cachexia, which may be defined as significant alterations in their carbohydrate, protein, and fat metabolism, resulting in bad quality of life, reduced response to therapy, and shortened survival span. Nutritional modulation may be beneficial in the treatment of cancer patients to reverse these metabolic alterations. Nutritional intervention can be a powerful tool for controlling malignant disease and reducing the toxicity associated with chemotherapy and radiation therapy [23]. Moreover, nutraceuticals can significantly increase natural killer cells function and tumor necrosis factor [TNFα] in patients with late stage cancer [24]. Various phytochemicals have shown different mechanisms of action at different cellular levels, most of which emerged as a versatile source of antioxidants affecting the signaling pathway related to redox-mediated transcription factors. Besides, they directly modulate the endocrine system, immunological cascade, and enzymes related to inflammation. Nutraceuticals have been found to exert a wide range of cellular effects. The possible mechanisms of action of anticancer nutraceuticals include induction of cell cycle arrest and apoptosis in cancerous cells, detoxification of highly reactive molecules, activation of the host immune system, and sensitization of malignant cells to cytotoxic agents [25]. Some of them have shown direct effect on DNA repair and cleavage process. Figure 11.1 depicts the possible pathways and mechanisms by which anticancer nutraceuticals demonstrate their chemopreventive and chemotherapeutic roles.

11.2.2 Nutraceuticals' Use in Cancer Patient

Cancer remains a worldwide health problem and despite much advances in medical field. A number of plant extracts are used for treating and preventing cancer. One-third of all cancer deaths are preventable by lifestyle changes including appropriate

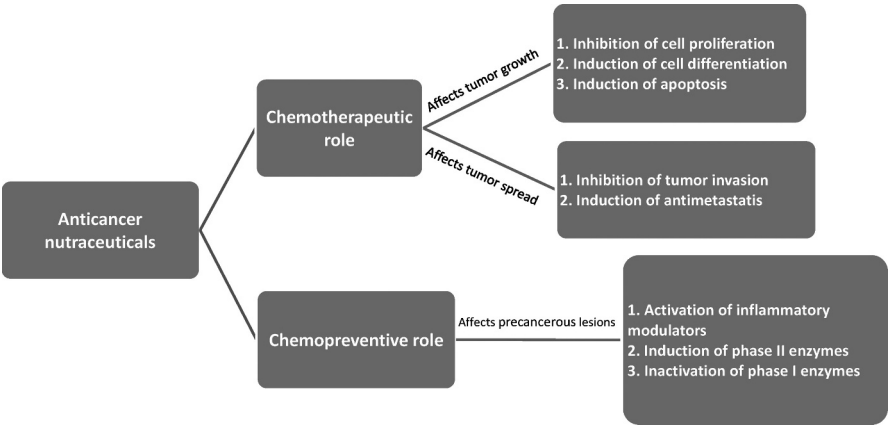


FIGURE 11.1 Nutraceuticals action pathways for chemoprevention and chemotherapeutics.

nutrition [26]. Previous report suggests that plant extracts have long history of use and many nutraceuticals, and many alkaloids such as vinca alkaloids (vincristine and vinblastine) and taxol, are derived from plants. Curcumin, resveratrol, tea polyphenols, sulforaphane, anthocyanins, genistein, quercetin, and lycopene exhibit proven anticancer activities against various forms of cancer [27]. One of the important advantages of utilizing nutraceuticals to prevent and treat cancer is that they generally exhibit little or no adverse effects frequently associated with pharmaceutical agents after long-term administration. There is evidence that foods, relatively low in simple carbohydrates with moderate amounts of high-quality protein, fiber, and fat (especially fats of the omega-3 fatty acid series) are beneficial for cancer patients [28]. In addition, nutraceuticals may also be helpful in reducing toxicity associated with chemotherapy and radiation therapy and may lead to better life conditions by reducing cancer cachexia [29]. It has been reported that nutritional modulation may be beneficial in the treatment of cancer patients [30].

11.2.3 Major Anticancer Nutraceuticals

11.2.3.1 Resveratrol

Resveratrol is a natural phenol produced by many fruits and plants such as grapes, blueberries, raspberries, and peanuts with antiproliferative activity due to its role as a plant antibiotic. It is believed to possess multiple bioactivities including anticancer, anticarcinogenesis, and anti-inflammatory effects [31]. In vivo studies have shown protective effects of resveratrol against several types of cancers, such as breast, skin, gastric, colon, prostate, and pancreatic, by interfering with multiple stages of carcinogenesis [32]. Clinical trials have established the safety and potential anticancer effects of resveratrol as both a single agent and a constituent of foods [33]. A phase I pilot study conducted in colorectal cancer patients (women with high risk for developing breast cancer) to determine the anticancer effects of freeze-dried

grape powder containing a low dose of resveratrol in combination with other bioactive components suggested that dietary intake of the dry grape powder inhibited the Wnt signaling pathway in the colon, demonstrating the suppression of carcinogenesis [34]. Despite several clinical trials, pharmacokinetics studies of resveratrol have shown poor bioavailability (only 1%) due to extensive glucuronidation and sulfation as well as metabolism by gut bacterial enzymes [35].

11.2.3.2 Quercetin

Flavonoids are a large group of polyphenolic secondary metabolites of fruits, vegetables, and other plants with a broad spectrum of bioactivities, including inhibitory effects on a wide range of human cancers [36]. Epidemiological evidence suggests a positive correlation between flavonoids-rich diets and low risk of colon, breast, and prostate cancers. Flavonoids can be categorized into flavones, flavonols, flavanones, flavanols, anthocyanins, and isoflavones based on their structures. Flavonoids can target multiple signaling pathways during carcinogenesis to inhibit cancer cell proliferation, suppress tumor angiogenesis, and induce apoptosis in cancer cells [37]. Quercetin displays a poor oral bioavailability due to its low absorption and a microencapsulation approach has been shown to enhance the effects of quercetin in reducing the oxidative damage and attenuating inflammation in a mouse colitis model due to increased absorption [38]. Quercetin acts by inducing cell apoptosis through multiple mechanisms. In vivo studies of quercetin have demonstrated that oral administration can prevent induced carcinogenesis, particularly in the colon and can also inhibit melanoma growth, invasion, and metastatic potential [39].

11.2.3.3 Curcumin

Curcumin is a polyphenol found in turmeric (*Curcuma longa*, family Zingiberaceae) [40]. One study reported that curcumin inhibits gastric carcinoma cell growth and induces apoptosis by suppressing the Wnt/b-catenin signaling pathway [41]. Several phase I and phase II clinical trials have been conducted and demonstrated the safety and anticancer effects of curcumin in patients with different malignancies including myeloma, pancreatic, and colorectal cancer [25]. Various edible delivery systems have been developed to improve the low bioavailability and bioactivities of curcumin, including liposomes, phospholipid complexes, organogel-based nanoemulsions, chitosan-based nanoparticles, and self-emulsifying drug delivery systems [42]. For example, polylactide co-glycolide nanocapsulated curcumin suppressed cell proliferation, induced cancer cell apoptosis, and improved pathological structures in a hepatocellular carcinoma model, whereas identical concentration of free curcumin was found to be ineffective [43]. In another study, liquid micellar formulations of curcumin showed a 185-fold enhancement in bioavailability within 24 hours without increased toxicity in healthy subjects compared to powdered curcuminoids [44].

11.2.3.4 Vinca Alkaloids

Vinca alkaloids were originally isolated in 1950s by Canadian scientists Robert Noble and Charles Thomas Beer from the Madagascar periwinkle plant, *Catharanthus roseus* (formerly known as *Vinca rosea*) of the Apocynaceae family [45]. Accordingly,

a phytochemical study led to the separation and the identification of Vinblastine, the prototype of vinca alkaloid, which is able to cause myelosuppression in xenograft mouse models of leukemia [46–48]. This breakthrough opened the door toward a new therapeutic approach against cancer. Thus, the Food and Drug Administration (FDA) approved vinca alkaloids as pharmaceutical strategy against different tumor types such as leukemia, Hodgkin's lymphoma, lung cancer, and breast cancer [49]. Five vinca alkaloids currently in clinical use are the natural vinca alkaloids vinblastine and vincristine that were approved by FDA in 1961 and 1963, respectively, the semisynthetic derivative vindesine that are in clinical use only in few countries, vinorelbine that was approved by FDA in 1994, [50] and vinflunine, a bis-fluorinated derivative. In the search for novel approaches, the drug delivery systems of vinca alkaloids were developed and successfully introduced in the market for better cancer treatment and management [51]. Particularly, therapeutics based on microspheres, nanoparticles, and liposomes offered a novel life to vinca alkaloids, and many of them have been investigated as drug delivery platforms [52–56].

11.2.3.5 Epigallocatechin-3-gallate

Epigallocatechin-3-gallate (EGCG) is a type of catechin found in green tea that exhibits a variety of activities such as anti-inflammatory, antidiabetes, antiobesity, and antitumor. The antitumor effects of EGCG including carcinogen activity, tumorigenesis, proliferation, and angiogenesis, and induced cell death were reviewed [57]. These effects are associated with the modulation of reactive oxygen species [ROS] production, which is mainly responsible for its anticancer effects despite its dual function of antioxidant and pro-oxidant potential. The EGCG-mediated inhibition of the nuclear factor (κB) signaling is also associated with the inhibition of migration, angiogenesis, and cell viability. Further, activation of mitogen-activated protein kinases activity upregulates the anticancer effect of EGCG on migration, invasion, and apoptosis. Additionally, EGCG causes the upregulation of apoptosis by inducing epigenetic modification through inhibition of DNA methyltransferase activity and regulation of acetylation on histone. Although EGCG promotes strong anticancer effects by multiple mechanisms, further studies are needed to define the use of EGCG in clinical treatment [58].

11.2.3.6 Sulforaphane

Sulforaphane is an isothiocyanate mainly found in cruciferous vegetables, especially abundant in broccoli and broccoli sprouts. Cell culture and animal studies have shown that sulforaphane is a potent chemopreventive agent against various types of cancers, and the molecular targets of sulforaphane vary with cancer type and stage. The major anticancer mechanism by which sulforaphane protects normal cells from carcinogenesis is the Nrf2-mediated induction of phase II antioxidant and detoxifying enzymes [59]. These enzyme systems enhance cell defense against oxidative damage, and facilitate the removal of carcinogens. Sulforaphane also exerts anticancer activities through various mechanisms of action that are involved in regulating cell proliferation, differentiation, apoptosis, and cell cycle progression [60]. To date, only a few clinical trials have been conducted on sulforaphane in cancer patients or high-risk populations. In a phase II study, patients who had recurrent prostate cancer

were given 200 μmoles/day of sulforaphane-rich extracts for a maximum period of 20 weeks. The results indicated no large decline by ≥50% in prostate-specific antigen (PSA); however, 7 out of 20 patients experienced moderate PSA decline by <50%. Moreover, the on-treatment PSA doubling time [PSADT] was significantly lengthened compared to the pretreatment PSADT [61]. In another study using melanoma mouse model, sulforaphane-loaded albumin microspheres demonstrated a significantly stronger suppression of tumor growth as compared to nonencapsulated sulforaphane, without showing any adverse effects [62].

11.3 BIOAVAILABILITY ENHANCEMENT OF ANTICANCER NUTRACEUTICALS

The potential benefits of many of the nutraceuticals are not optimally realized because of their relatively low and/or variable oral bioavailability that may be the result of various physicochemical and/or physiological processes: restricted liberation from the food matrix, low solubility in gastrointestinal fluids [63,64], formation of insoluble complexes with other components in the gastrointestinal tract (GIT) [65], low permeability across the mucus layer or epithelium cells [66–68], and/or molecular transformations in the GIT [69,70]. Also, it was evidenced that both the composition and structure of the food matrix can influence the bioavailability of co-ingested nutraceuticals and depends on the nature of the food matrix co-ingested with them [64,71–73]. The dependence of oral bioavailability on the food matrix properties means that foods can be specifically designed to improve the nutraceutical biological activity [74,75]. For example, functional foods or excipient foods can be designed to increase the oral bioavailability of nutraceuticals present within them or co-ingested with them, respectively [75]. Designing food matrices that overcome the challenges associated with the oral bioavailability of certain nutraceuticals requires understanding the key factors potentially limiting their uptake in a biologically active form. Also, the use of mucolytics and permeation enhancers, encapsulation and nanosized formulation, and optimization of delivery systems are among the widely used methods for bioavailability enhancement of nutraceuticals.

11.3.1 Nutraceutical Bioavailability Classification Scheme

McClements and coworkers proposed a new classification scheme known as nutraceutical bioavailability classification scheme (NuBACS) to characterize the main factors limiting the oral availability of nutraceuticals in food matrices [14]. This system is related to the Biopharmaceutical Classification Scheme (BCS) commonly used to classify the factors limiting the bioavailability of pharmaceuticals based on their solubility and permeability. NuBACS categorizes the factors limiting the bioavailability of nutraceuticals into three major classes based on their bioaccessibility, absorption, and transformation within the GIT. Within these three major classes, there are subclasses related to the specific physicochemical or physiological mechanisms that influence the bioavailability. Knowledge of the precise reason that limits the bioavailability of a particular nutraceutical is useful for

Nutraceutical Bioavailability Classification Scheme (NuBACS)	
Major classes	**Subclasses**
B* (Bioaccessability)	L: liberation S: solubilization I: interactions
A* (Absorption)	ML: mucus layer TJ: tight junction transport BP: bilayer permeability AT: active transporters ET: efflux transporters
T* (Transformation)	C: chemical degradation M: metabolism

FIGURE 11.2 Nutraceutical Bioavailability Classification Scheme.

designing effective delivery systems or food matrices to improve its bioavailability. Figure 11.2 represents the NuBAC scheme [14], which characterizes bioactive food components according to their bioaccessibility, absorption, and transformation characteristics.

11.3.2 Factors Limiting the Bioavailability of Nutraceuticals Based on NuBAC

11.3.2.1 Bioaccessibility

The bioaccessibility (B^*) of an anticancer nutraceutical represents the fraction of the total amount of orally consumed nutraceuticals that is in a form that can be readily absorbed by the GIT. The bioaccessibility may be affected by three main factors in the GIT: liberation, solubility, and interactions [7,14]. A bioactive substance with a relatively high overall bioaccessibility [>75%] can be classified as $B*(+)$, while the one with a low overall bioaccessibility may be classified as $B*(-)_L$, $B*(-)_S$, or $B(-)_I*$ depending on whether its bioaccessibility is limited primarily by liberation (L), solubilization (S), or interactions (I). If more than one of these limiting mechanisms strongly influences bioaccessibility, then the number of subscripts used to designate the limiting factors can be increased, for example, $B*[-]_{L,S}$ for a substance limited by both liberation and solubilization.

11.3.2.2 Absorption

After an anticancer nutraceutical is released from any structures containing it and then solubilized within the gastrointestinal fluids, it has to be transported through the GIT contents and then be absorbed by the epithelial cells lining the GIT [76]. The absorption of nutraceuticals is affected by numerous physicochemical and physiological factors. This group of factors is related to the absorption of the nutraceutical from the gastrointestinal fluids, that is, the fraction that travels through the mucus layer, across the epithelium cells, and into the systemic circulation. The absorption class can be divided into several subclasses according to the specific factors limiting

the bioavailability. The absorption of a nutraceutical by the epithelium cells lining the GIT may be limited by one or more factors, depending on its molecular and physicochemical characteristics. For example, it may be classified as $A*[-]_{ML}$, $A*[-]_{BP}$, $A*[-]_{TJ}$, $A*[-]_{AT}$, or $A*[-]_{ET}$ if its absorption is limited by the mucus layer transport (ML), bilayer permeability (BP), tight junctions (TJ), active transporters (AT), or efflux transporters (ET), respectively. Nutraceuticals whose absorption is limited by more than one physicochemical phenomena can be categorized by multiple subscripts, for example, $A*[-]_{BP, TJ}$ for a nutraceutical that is limited by both poor bilayer permeability and low tight junction transport. A nutraceutical with a relatively high absorption [>75%] by epithelium cells can be classified as $A*[+]$ [14].

11.3.2.3 Transformation

The bioavailability of many nutraceuticals is limited because they are transformed into an inactive form within the GIT. These molecular transformations can be divided into two subclasses according to their origin. The bioavailability and bioactivity of anticancer nutraceuticals is a result of their precise chemical structures and molecular conformation. Changes in the structure or conformation of these nutraceuticals due to chemical or biochemical reactions within the GIT fluids may therefore alter their bioefficacy. A nutraceutical may therefore be classified as $T*[-]_{C}$, $T*[-]_{M}$, or $T*[-]_{CM}$ if its bioaccessibility is limited by chemical degradation (C), metabolism (M), or both (CM), respectively. If a nutraceutical is relatively stable to molecular transformations within the GIT (>75% remaining in a bioactive form), then it can be designated as $T*[+]$. If a detailed study is carried out to identify all the major factors influencing the oral bioavailability of a nutraceutical, then it is possible to develop a quantitative expression to define the overall bioavailability (*BA*) [74,77]:

$$BA = B^* \times A^* \times T^*$$

11.3.3 Nutraceuticals' Bioavailability Enhancement Methods

11.3.3.1 Delivery Systems' Optimization

The process of fortification, incorporation, or addition of nutraceuticals into food, beverage or an existing product is complex, as it affects the composition, physicochemical, and sensory properties of the original food and beverage formulation and consequently the taste, texture, and shelf life may be compromised. Also, the type, format, and solubility of the nutraceutical ingredient influence the design of the formulation and processing used for its production and thus influence the desired characteristics of the food. Often, the direct incorporation of nutraceuticals into foods is not possible, as many nutraceuticals are susceptible to degradation and may interact with other components in the food, resulting in the loss of bioactivity of the nutraceutical ingredient and reduction in the quality of the food product. Therefore, the successful incorporation of nutraceuticals into foods requires that they are protected by a well-designed delivery system that is specifically designed for the target food application. To improve nutraceuticals' dispersibility, stability, food compatibility,

and bioavailability, the specifically designed colloidal delivery system is an efficient option. This is because bioavailability depends on the delivery systems' composition, size, and interfacial properties, which can be optimized to develop effective delivery systems [7]. Different approaches could be used such as particle size reduction of the delivery system, incorporation of specific ingredients in the delivery systems' formulation known to increase the absorption of encapsulated nutraceuticals, or co-ingestion of nutraceuticals and excipient foods. Delivery system technologies used successfully for various nutraceuticals with their characteristics and applications are described in Table 11.1.

11.3.3.2 Permeation Enhancers and Mucolytic Agents

Permeation enhancers can increase the oral bioavailability assuming that the nutraceutical can also survive liver-first-pass metabolism. The medium chain fatty acid sodium caprate is well established as a food additive and is a component of an antibiotic suppository once marketed in Sweden and Japan [78]. These enhancers are often used for peptide oral delivery with candidates including insulin, glucagon-like peptide 1 (GLP-1) analogues, and octreotide. The technology of Enteris Biopharma, New Jersey, USA, is completed Phase II with an acyl carnitine, a peptidase inhibitor (citric acid), and parathyroid hormone [79]. The technology of Chiasma [Jerusalem, Israel] completed Phase III for oral octreotide, and it comprised caprylic acid as an enhancer in a water-in-oil system [80]. Merrion Pharmaceuticals, Ireland, used a gastrointestinal permeation enhancement technology [GIPET™] in matrix tablets, which completed an oral Phase I study with GLP-1 [81]. The technology of Oramed (Jerusalem, Israel) reached Phase IIb for oral insulin, and it comprises a EDTA as an enhancer and soybean trypsin inhibitor [82]. Medium-chain fatty acid based enhancers act by reorganizing the proteins at the epithelial tight junction and by mild detergent fluidizing effect on the plasma membrane [83,84]. This allowed poorly permeable molecules to either transiently permeate across tight junctions, or be entrapped in mixed micelles with capacity to cross lipid bilayers. Permeation enhancers generally cause a reduction of transepithelial electrical resistance using *in vitro* and *ex vivo* intestinal epithelial models. This reduction suggested an opening of tight junctions or perturbation of the epithelia with significant increase in apparent permeability of (14C)-mannitol, a marker for paracellular transport and FD-4 across isolated intestinal mucosa. Examples of permeation enhancers including cocoglucosides, chitosan derivatives, bromelain, EDTA, oleic acid, alkyl maltosides, medium-chain fatty acids, and sucrose esters are commonly used in food processing with GRAS status or are of food origin [85,86]. Mucus diffusion enhancers such as *N*-acetylcysteine (NAC), bromelain, and papain hold potential for nutraceuticals affected by the inability to penetrate the small intestinal mucus layer. NAC is an antioxidant nutritional supplement and also used as a mucolytic agent by breaking disulfide bonds [87]. Papain is a mucolytic protease found in papaya; when decorated on nanoparticles, it improved the permeation and reduced the mucus viscosity *in vitro* [88]. Bromelain, a pineapple stem mucolytic enzyme, was formulated on the surface of nanoparticles and compared against papain for *in vitro* mucus permeation resulting in enhanced penetration in the rank order of bromelain>papain>conventional nanoparticles [89]. Papain-decorated nanoparticles were also shown to penetrate into deeper mucus

TABLE 11.1
Delivery System Technologies Used Successfully for Various Nutraceuticals

Technology	Characteristics	Application	Company
Ubisol-Aqua™	It is family of neutral, nonionic carriers for hydrophobic compound to be solubilized forming a noncovalently bound complex with Ubisol-Aqua™, with both hydrophobic and hydrophilic subsections. This self-assembly possesses micellar arrays with a hydrophobic interior and a hydrophilic exterior shell and when mixed with water and can solubilize the resultant stable complex, which is soluble in both water and lipid	Coenzyme Q10, vitamin A acetate, vitamin A palmitate, vitamin B pentapalmitate, squalene, fish oil, betacarotene, etc.	Zymes LLC, USA
NovaSOL®	It creates liquid carrier solutions as "solubilisates" that transport the active raw materials in the smallest stable capsules as "product micelles," forming 100% water-soluble micelle	Carrier system for hydrophobic substances for a higher and faster intestinal and dermal resorption and penetration of active ingredients in the fields of functional food, cosmetics, pharmaceuticals, and biotechnology, can be used for aqua feed supplement with better binders	Aquanova, Germany
Nano-sized Self-assembled Structured Liquids (NSSL) technology	The chemical structures formed using this technology are micelles. When adding the nutraceutical to the system, the micelles expand to form the fortifying nanovehicles	Hydrophobic or hydrophilic nutraceutical	Nutralease, Israel
Bioral® (Nanocochleate Delivery System)	It encapsulates and protects a drug without chemically bonding to it and may facilitate oral dosing of drugs that typically need to be given by intravenous administration. Alternating layers of lipids spiraling around the molecule protect it from acidic or enzymatic degradation in the stomach, as well as from degradation during manufacturing and storage	Drug delivery to fishes through in-feed formulations	BioDelivery Sciences International (BDSI), USA

layers when delivered by oral gavage in a rat model, with higher retention within the jejunum [90]. This is of particular interest, as the jejunum is the main target for nutraceutical bioactive absorption. When an intestinal PE, tetradecyl maltoside (TDM), was tested on Caco-2- and mucus-producing HT29-MTX-E12 monolayers, it was shown that the NAC pretreatment of E12 monolayers resulted in comparable apparent permeability [Papp] values of salmon calcitonin across Caco-2 and E12 [91]. The application of mucolytic agents also holds promise for lipophilic nutraceuticals, which interact with glycoproteins and lipids in the mucus [92]. This interaction reduces the likelihood of epithelial permeation as mucus is continuously turned over and would result in the bioactive being washed away. Mucolytics reduce this risk by enhancing mucus penetration and are often investigated in the context of airway mucus in cystic fibrosis, where NAC is used at high concentrations. A synthetic thiol-carbohydrate [methyl 6-thio-6-deoxy-α-D-galactopyranoside] was found to be a more potent mucolytic [93]. Co-administration of lipophilic nutraceuticals and mucolytics in the context of an enteric-coated oral dosage form may therefore control the release in the small intestine, improve mucus penetration, and improve absorption.

11.3.3.3 Nanoformulations and Polymer Conjugates

The advent of nanotechnology for pharmaceutical applications has opened a new avenue for enhancement of stability, solubility, and/or permeability of problematic nutraceuticals. An effective approach to improve the oral bioavailability of nutraceuticals is to use the delivery systems at the nanoscale due to the increase of the surface-to-volume ratio by reducing the particle size to nano range [94]. In this context, the nanometric systems in the absence or presence of carriers have been attempted. In the absence of a carrier, nanonization of the bioactive, according to the Noyes–Whitney equation, improves its wettability and dissolution rate. In presence of a carrier, nanocapsules, micelles, and nanoparticles can be prepared using biopolymers, particularly those of food origin to formulate nutraceuticals. This class of polymers is encountered by our bodies in dietary intake; as a result, they are generally recognized as safe materials [95]. In addition, they are available in relatively large amounts and at low cost, and many of them can be extracted by eco-friendly methods. Moreover, some of the biopolymers are not only biodegradable and biocompatible but also biofunctional, providing additional beneficial effects in the prophylaxis or the treatment of cancer [96]. Significant advantages of nanoformulations are given in Figure 11.3. Researchers also focus on the development of simple reproducible eco-friendly synthetic pathways that avoid the use of organic solvents or catalysis. The use of nanodelivery systems could facilitate the entry of the nutraceutical through biological barriers while avoiding the metabolic modifications that lead to low absorption [73]. Poor oral bioavailability of nutraceuticals lowers their efficacy as disease-preventing agents [67,74,75,97]. An effective way to improve the oral bioavailability of nutraceuticals is to utilize nanotechnology to encapsulate nutraceuticals in engineered nanoparticles-based delivery systems [97–99]. Numerous engineered nanoparticles have been fabricated and tested for their potential use as delivery systems for nutraceuticals with the purpose of enhancing their health benefits through encapsulation, protection, and/or controlled release

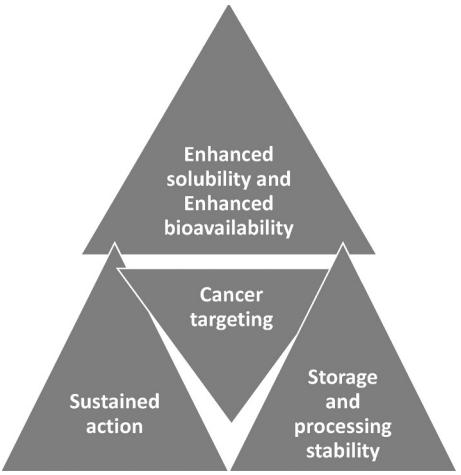


FIGURE 11.3 Advantages of anticancer nutraceuticals' nanoformulations.

of nutraceuticals [74,75,97,100–102]. Engineered nanoparticles can be categorized as lipid-based or nonlipid-based depending on the presence or absence of lipids as the major components of the delivery systems (Table 11.1). Further, comprehensive descriptions of the manufacture and characteristics of different type of engineered nanoparticles suitable for food applications with 100% foodgrade materials, such as edible lipids, proteins, carbohydrates, and surfactants, have increased the challenges in creating effective delivery systems and have been extensively attempted and reviewed [75,97,102].

Biodegradable FDA-approved polymers, for example, polyesters are favored by formulators to develop nutraceutical-loaded nanoparticles. Polymer-based nanoparticles modulate the release of encapsulated bioactives, protect them from degradation, alter their biodistribution, and shift their transport across biological membranes from a passive diffusion process to an endocytosis one [103–106]. Additionally, targeting moiety can be fixed to nanoparticles surface [107–110]. The targeted and/or endocytic uptake of nanoparticles maximizes their intracellular delivery, which is strictly needed to exert, for example, an anticancer effect [111–114]. Subcellular organelle targeting like mitochondrial targeting in the case of coenzyme Q10 have been achieved by targeting the lipophilic triphenylphosphonium cation either chemically conjugated to the nanocarrier or the coenzyme Q10 [115], or resveratrol molecule [116]. Conjugating resveratrol to the membrane-permeable lipophilic triphenylphosphonium cation provided transient protection against metabolic conjugation, accumulated into mitochondria, and was cytotoxic for fast-growing but not for slower-growing cells [116]. Such mitochondrial targeting of antioxidant nutraceuticals furnished a powerful tool to mediate mitochondrial and cellular redox processes of pathophysiological consequences [117]. The approach in which a bioactive is chemically linked to a polymer is known as "Polymer Conjugates," which can modulate the physicochemical, pharmacokinetic, and therapeutic properties of the therapeutic agent. The water-soluble anticancer curcumin polyconjugates showed altered

biodistribution and improved anticancer efficacy, as they combine the dual advantage of enhanced aqueous solubility and polymer-mediated drug internalization [118].

11.3.3.4 Food and Food Matrix Design

Recently, foods have been designed not only to improve their composition and structure to enhance their quality attributes, such as appearance, texture, mouthfeel, and taste, but also to improve their nutritional profiles by reducing the levels of macronutrients believed to have adverse health impacts such as saturated fats, digestible carbohydrates, and salt or to enrich them with food components that are believed to bring beneficial health effects such as vitamins, minerals, dietary fibers, or nutraceuticals [119]. Due to increasing interests of the pharmaceutical and food industries in the development of products to prevent or treat human diseases, the pharmaceutical industry is developing drug preparations to combat chronic or acute diseases, whereas the food industry is developing food and beverage products whose purpose is to promote human health and well-being through diet. This emerged as a considerable overlap in the development of food-based approaches to improve the bioavailability of lipophilic bioactive agents, such as nutraceuticals and pharmaceuticals. These approaches are based on the design of the composition or structure of food matrices to increase bioavailability and have led to new classes of foods: functional foods and excipient foods (Figure 11.4). Functional food is fabricated from generally recognized as safe (GRAS) food ingredients and typically contains one or more food-grade bioactive agents ["nutraceuticals"] dispersed within a food matrix. The examples include milks fortified with vitamin D, yogurts fortified with probiotics, spreads fortified with phytosterols, and breakfast cereals fortified with omega-3 fatty acids, vitamins, and minerals. Excipient food may not have any bioactivity itself, and therefore can be consumed with a conventional pharmaceutical dosage form such as capsule, pill or syrup, a dietary supplement or nutraceutical-rich food including fruits, vegetables, nuts, seeds, grains, meat, fish, and some processed foods. Different kinds of excipient foods can be designed for different types of bioactive agents or delivery matrices. Some excipient foods could be developed to increase the bioavailability of nutraceuticals. For example, the bioaccessibility of carotenoids in a salad may be increased by consuming it with a specifically designed

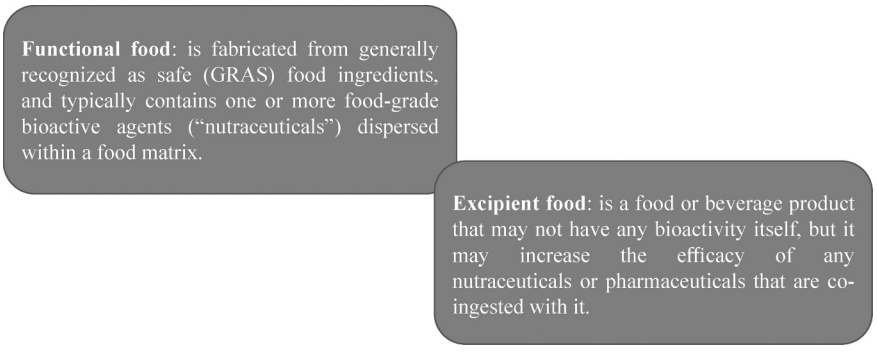


FIGURE 11.4 Functional and excipient food.

salad dressing. This dressing may contain various food components that increase the bioavailability of the nutraceuticals in the salad: lipids that increase intestinal solubility; antioxidants that inhibit chemical transformations; enzyme inhibitors that retard metabolism; permeation enhancers that increase absorption; and efflux inhibitors. Previous studies have shown that the bioavailability of oil-soluble vitamins and carotenoids in salads can be increased by consuming them with dressings containing some fat, which supports the concept of excipient foods. Details of excipient food ingredients such as lipids, carbohydrates, proteins, minerals, surfactants, chelating agents, and phytochemicals are reviewed [75].

11.4 DELIVERY STRATEGIES AND FORMULATION APPROACHES OF ANTICANCER NUTRACEUTICALS

Nanoformulations of nutraceuticals provide many advantages over conventional formulations and consequently allow their clinical use for protection and treatment of different tumors. The examples of advantages include increased stability during storage and inside the body, optimized aqueous/lipid solubility, which improves the overall bioavailability, sustained release of the active ingredients, improved therapeutic efficiency, and selective targeting toward tumors [120]. Many different nanoformulations are available, which differ in preparation techniques, particle size, structure, morphology, pharmacodynamics, and therapeutic properties. In this section, some of the major nanoformulations used for delivery of anticancer nutraceuticals are discussed.

11.4.1 Liposomes and Nanoliposomes

Liposomes are lipid bilayer structures composed of phospholipids, which have hydrophilic heads and hydrophobic fatty acid tails with hydrophobic and hydrophilic parts of the same molecule, which rearrange spontaneously to keep the hydrophobic parts away from contact with the aqueous environment, forming distinct water-soluble and lipid compartments. Liposomes consist of single or multiple concentric layers; each one of them consists of a double layer of lipids, which encapsulate at their core part of the surrounding microenvironment to deliver hydrophilic, hydrophobic, or amphiphilic drugs. Some major advantages of liposomes include biocompatibility, biodegradability, simple preparation methods, and simple targeting toward reticulo endothelial system as an inherent property of most lipids used in the liposome preparation [121]. The term nanoliposome has been introduced to exclusively refer to nanometric size of liposomes [122]. Liposomes and nanoliposomes have the same chemical, structural, and thermodynamic properties, the smaller size of nanoliposomes could produce larger interfacial area of encapsulated compounds with biological tissues providing higher potential to increase the bioavailability of encapsulated compounds [122]. Specifically, for solid tumor treatment, nanoliposomes can accumulate more in tumors because of the enhanced permeation and retention effect [122,123]. Nanoliposome production requires higher energy input in the aqueous solution [124], and the commonly used methods for nanoliposome synthesis include sonication, extrusion, freeze-thawing, ether injection, and microfluidization, among which sonication and extrusion are widely used at the laboratory scale [124,125].

11.4.2 Nanoemulsions

Nanoemulsions are colloidal systems in which heterogeneous lipid phases are dispersed as droplets in aqueous phases or the reverse, and are required to be stabilized by the use of surfactants. The usual droplet size of nanoemulsions lies in the range of 20–200 nm. Nanoemulsions are normally directed in vivo toward the lymph. The lipid nanodroplets formed after absorption of the emulsion are subject to phagocytosis by macrophages followed by accumulation in the liver, kidney, and spleen; thus, they are beneficial when targeting these sites [126]. Nanoemulsion is a better option to incorporate poorly soluble nutraceuticals into food matrix, although their systemic bioavailability is influenced by their poor solubility in water or oil. The properties such as solubility, partition coefficient, lipophilicity, and so on decide the route of administration, transport, and target sites of the incorporated nutraceutical. Entrapment of such bioactives into nanoemulsions can prove advantageous, as the small particle size of nanoemulsions will increase their surface area, thereby resulting in enhanced digestion rates, rapid diffusion across mucus membrane, and increased epithelium cell permeability [42,127]. Additionally, nanoemulsions may protect the chemically labile bioactives from oxidation, thereby resulting in increased shelf life and reduced degradation in the GIT [128,129]. A large number of reports on entrapment of bioactives into nanoemulsions are available, and recent trends have shown the use of food-grade nanoemulsions [130].

11.4.3 Polymeric Nanoparticles

Formulation of polymeric nanoparticles is one of the several innovative delivery systems made from natural, biodegradable, and biocompatible polymers and represents an option for controlled and targeted drug delivery [131,132]. These nanoparticles are polymeric colloidal systems with a usual particle size range of 10–500 nm, while still protecting drugs efficiently. These are the most versatile delivery systems with the possibility to attach different targeting moieties to their surface or introduce desired structural modifications. Due to colloidal system network, polymeric nanoparticles work as vectors to control drug release, targeting it toward specific locations. Compared with conventional formulations, polymeric nanoparticles can increase the solubility of constituents, reduce the therapeutic dose, and improve the absorption of the active components. Polymeric nanoparticles offer advantages when used in blood because they are stable, nontoxic, nonthrombogenic, nonimmunogenic, noninflammatory, do not activate neutrophils, and avoid the reticuloendothelial system. Sometimes, polymeric nanoparticles are used to reach specific tissues, or work as a cell surface [120,133]. They can be formulated as nanospheres made only from a polymeric structure with the pharmaceutically active substances dispersed in their matrix, whereby the active constituent is retained or adsorbed, or as nanocapsules with the active ingredients loaded into their core, whereby the active constituent can be adsorbed to the polymeric membrane and/or dissolved in the oily core. Although there is increasing search for new types of polymers, some of the polymers are already used extensively for polymeric nanoparticles, including poly-L-lactic acid (PLA) and copolymers with glycolic acid (PLGA) [120,133].

Various studies of polymeric nanoparticles have solved some formulation problems, such as the hydrophobic properties of some constituents, such as curcumin. A mixture containing curcumin-loaded polymeric nanoparticles, using aggregated structures, have been synthesized containing randomly cross-linked copolymers of N-isopropylacrylamide, N-vinyl-2-pyrrolidone, and poly(ethylene glycol) monoacrylate [134]. In one more study, curcumin was encapsulated in PLGA nanospheres, using a solid/oil/water emulsion solvent evaporation method. When evaluated for activity against prostate cancer, a 35% reduction was observed when curcumin was encapsulated [135]. To evaluate the antioxidant effects of pure quercetin and quercetin incorporated in nanoparticles, a nanoprecipitation technique was developed using Eudragit E and polyvinyl alcohol (PVA), alongside the flavonoid quercetin. The system was prepared using a 1:10:10 weight ratio of quercetin to Eudragit E to PVA because the yield was better, and the encapsulation efficiency was greater than 99%. Relative to di(phenyl)-(2,4,6-trinitrophenyl) iminoazanium (DPPH) scavenging, antisuperoxide formation, superoxide anion scavenging, and antilipid peroxidation activities, this developed encapsulated queceton formulation was more effective than pure quercetin [136]. Further, camptothecin, a natural plant alkaloid extracted from *Camptotheca acuminata* decne, has been demonstrated to be a potent anticancer drug, targeting intracellular topoisomerase. However, due to its low water solubility and unstable lactone ring, clinical use is not viable. Min and coworkers developed hydrophobically modified glycol chitosan nanoparticles of camptothecin as a delivery system that demonstrated strong antitumoral activity, attributed to prolonged blood circulation, and high accumulation in tumors, as confirmed by near-infrared study [137]. Polymeric nanoparticles' production method varies depending on their intended application and payload. Natural materials are preferred in its preparation because they generally have more advantages, such as the ability to deliver more than one active constituent using the same carrier, increase residence time in the body, provide a sustained release system, and reduce side effects [138].

11.4.4 Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

Solid lipid nanoparticles (SLNs) are colloidal carrier systems, developed in the early 1990s, that combine the advantages of other colloidal systems such as emulsions, liposomes, and polymeric nanoparticles for drug delivery, while or minimizing some of their drawbacks. SLNs have higher physicochemical stability and offer better protection against degradation of labile drugs [139,140]. SLNs are colloidal particles containing highly purified triglycerides, composed mainly of lipids that are solid at room temperature. These structures are produced from solid lipids, or mixtures thereof, and stabilized by surfactants. The matrix of the lipid particle is solid; it can protect drug molecules against chemical degradation. However, when the system is produced, crystallization occurs, resulting in low encapsulation efficiency and drug release [139]. Adding a liquid lipid (oil) to an oil/water emulsion containing a solid lipid, or mixture of solid lipids, promotes the formation of SLNs [140]. Due to their small size (50–1,000 nm) and biocompatibility,

SLNs may be used in the pharmaceutical field for various routes of administration, such as oral, parenteral, and percutaneous. NLCs are the second-generation system that improves the encapsulation efficiency of actives and minimizes the expulsion of active particles during encapsulation. The NLCs consist of a mixture of lipid and solid phases that form a disorganized liquid lipid matrix to accommodate active ingredient. Lipids used in the solid phase are stearic acid, glyceryl dilaurate, hydrine, glyceryl monostearate, and cetyl alcohol, while the liquid phase includes oleic acid, glyceryl monodicaprylate, and caprylic/capric acid. Approximately 5% of the drug can be incorporated initially in the in NLCs to achieve about 3%–4% loading efficiency, whereas typical encapsulation efficiency is approximately 70%. It is feasible to employ various routes to administer these formulations including oral, pulmonary, intravenous, and dermal. SLNs and NLCs can be produced by methods such as high-pressure homogenization, emulsification–sonication, microemulsion, and solvent emulsification–evaporation techniques. Quercetin, a poorly water soluble flavonoid was more effective when incorporated in NLCs. However, quercetin was incorporated using the emulsification-solidification method at low temperatures in case of SLNs. When the desired amounts of quercetin, glyceryl monostearate, and soy lecithin were mixed with the solvent (chloroform and acetone in 1:1 ratio *v/v*), the resulting SLNs were spherical, with an average size of 155.3 ± 22.1 nm, falling into the nanoscale range [20–500 nm]. This formulation exhibited controlled release in vitro with the fivefold enhanced bioavailability and enhanced intestinal absorption compared to free quercetin [141]. In another study, quercetin was incorporated into NLCs employing glyceryl monostearate, stearic acid, and soy lecithin using the emulsion evaporation–solidification method at low temperatures to evaluate the formulation's potential as a topical delivery system providing the evidence that NLCs have a targeting capability, a prolonged release, and a great potential for dermal delivery [142].

11.5 COMBINATION NUTRACEUTICAL TREATMENT

Combinatorial approaches can be of the various types such as a phytonutrient and an effective drug, two or more phytonutrients, a synthetic phytonutrient and an effective drug, or a synthetic phytonutrient and a natural nutrient during the prevention or treatment of diseases or medical conditions. Synergistic effects of many combinations of nutraceuticals and/or drugs belonging to different or the same chemical class of compounds have been investigated for their antitumorigenic activities, and the overall results have been reviewed [12]. A synergistic therapeutic effect is defined as a stronger effect by the combination of two or more compounds compared to individual compounds. Basically, chemotherapeutic or chemopreventive combinational approaches have been used to reduce drug toxicity, to delay the development of cancer cells, and to reach a greater effect than with one active agent alone. Although the nutraceuticals may act both independently or in combination as anticancer agents. The additive and synergistic effects of nutraceuticals may be attributed to their potent antioxidant and anticancer activities, as well as the benefit of a diet rich in fruits and vegetables is attributed to the complex mixture of nutraceuticals present in whole foods. This hypothesis partially explains why a single antioxidant cannot replace the

combination of natural nutraceuticals in achieving health benefits. Limited knowledge is available regarding any interaction between/among nutraceuticals in suppressing neoplastic development. Some of the combinatorial effects of nutraceuticals against neoplastic development are described in Table 11.2. Literature reports detailed review of combination mechanisms of nutraceutical or nutraceuticals with drugs [32,143].

TABLE 11.2
Nutraceuticals' Combinations for Enhanced Anticancer Effect

Type of Cancer	Combination of Nutraceuticals With or Without Drugs	Main Food Source
Oral cancer	Tomato + garlic	Tomato, garlic
	Curcumin + EGCG	Turmeric, Green tea
Breast cancer	Apple extract + Q3G	Apples
	Capsaicin + genistein	Chilli peppers, soybeans
	EGCG + tamoxifen*	Green tea
	Honokiol + adriamycin*	Magnolia plant bark
Lung cancer	Luteolin + EGCG	Green vegetables such as artichoke, celery, broccoli, cauliflower, green pepper, cabbage, and spinach
	PPE + atorvastatin*	Green tea
Skin cancer	PFE + DAS	Pomegranate fruit extract and garlic constituent
Colorectal cancer	Curcumin + green tea	Turmeric, green tea
	EGCG + sulindac*	Green tea
	EGCG + EC	Green tea
	Curcumin + celecoxib*	Turmeric
Ovarian cancer	I3C + resveratrol	I3C in broccoli, cabbage, and cauliflower
	ITC + cisplatin*	Resvaretrol in peanuts, pistachios, grapes, red and white wine, blueberries, and cranberries
		ITC in cruciferous vegetables such as cabbage, broccoli, Brussels sprouts, watercress, and cauliflower
Prostate cancer	PEITC + curcumin	Cruciferous vegetables, turmeric
	Genestein + resveratrol	Soybean, broccoli, cabbage, and cauliflower
	Black tea + green tea	Black tea, green tea
	EGCG + genestein + quercetin	Green tea, soybean, leafy vegetables, broccoli, red onions, peppers, apples, grapes, black tea, green tea, red wine, and some fruit juices
	Sylibin + doxorubicin*	Sylibin is a supplement prepared from seed extract of milk thistle
	Sylibin + mitoxantrone*	

* Drug/pharmaceutical agent, PEITC, phenylethylisoathiocyanate; EGCG, epigallocatechin-3-gallate; Q3G-quercetin-3-glycoside; PFE, standard green tea polyphenol preparation; PPE, polyphenol E; PFE, pomegranate fruit extract; DAS, diallyl sulfide; EC, epicatechin; I3C, indole-3-carbinol; ITC, indole-3-ethyl isothiocyanate.

11.6 CHALLENGES IN ANTICANCER NUTRACEUTICALS' DELIVERY

Due to various reasons, the successful incorporation of nutraceuticals into foods requires to be protected by a specifically designed delivery system for achieving the target application. Also, since the incorporation of nutraceutical impacts the taste and aroma of the final product, the requirement to deliver an effective dosage of nutraceuticals for a specific health benefit is a major challenge. Other challenges include the prevention of undesirable interactions of the nutraceutical with the environment and components of the food matrix, avoiding the degradation of the nutraceutical when it is incorporated under conditions used for food processing, stabilization of the nutraceutical during the shelf life of the finished product, and assurance that the food containing the nutraceutical provides the intended health benefit after ingestion. Further, many bioactives are unstable after isolations from their natural food sources, necessitating encapsulation of the nutraceutical to produce more stable ingredient formats prior to be used in the manufacture of formulated functional foods, and the development of an encapsulation system for an unstable nutraceutical ingredient cannot be considered suitable for the end food application and desired health outcome. There are also many challenges to be considered for achieving desired nutraceuticals bioavailability. This is because the bioavailability of a nutraceutical after ingestion depends on its absorption and in part on the changes that occur to it and the surrounding food matrix during passage through the GIT. Also, the chemopreventive or therapeutic action is affected by nutraceuticals' pharmacokinetic properties, that is, absorption, distribution, metabolism, and excretion. The chemical structure of a compound influences its rate and level of absorption and the nature of the derivatives or metabolites circulating in the plasma. The absorption affects bioavailability, as it has consequences on how much of the nutraceutical or its active metabolites end up in the circulatory system, become available at the site of action, and are distributed into tissues and organs following absorption. However, the rate of the delivery of a nutraceutical can have a significant effect on the health outcome even when the same dose is provided in different food matrices. In some cases, there could be benefits for some nutraceuticals that escape absorption in the small intestine and make their way to the colon [144]. The chemical structure of some bioactives such as polyphenols and their interactions with the food matrix and gut microflora as they transit through the gastrointestinal tract can affect bioavailability [145]. Although the in vivo physiological environment is more complex than in vitro conditions, in most of the cases, evaluations of delivery systems to improve the bioavailability and efficacy of nutraceuticals are based on in vitro chemical or cell line models. This accounts for the lack of correlation between in vitro and in vivo bioavailability when different delivery systems are used. Researchers must take care when considering the relevance of various in vitro models to in vivo conditions [146]. Delivery systems can provide an effective means to enhance the oral bioavailability and bioefficacy of nutraceuticals; however, no universal delivery system is available for all nutraceuticals [42]. Unlike pharmaceuticals, which are typically taken in a well-defined dose at a particular time, nutraceuticals are obtained from numerous sources at levels that vary from person to person and from time to time as part of a complex diet. In addition, the beneficial effects of nutraceuticals may arise from taking relatively low levels over

an extended period. Consequently, it is often difficult to carry out clinical studies using humans to prove their efficacy.

11.7 CONCLUDING REMARKS AND FUTURE PROSPECTIVE

There is growing interest in using specific nutraceuticals commonly found in foods as chemopreventative agents. Cell culture and animal studies suggest that ingestion of these nutraceuticals may inhibit certain types of cancers. However, many anticancer nutraceuticals cannot simply be incorporated into foods because of their poor solubility, stability, and bioavailability characteristics; there is a considerable potential to create functional food products designed to overcome these challenges and therefore increase the potential efficacy of anticancer nutraceuticals. These foods may be designed to contain the nutraceuticals themselves as delivery systems, or they may be designed to boost the bioavailability of nutraceuticals in other foods excipient systems. Production of nanoparticles using the environment-friendly processes and their controlled release from food products are quite promising areas of nutraceuticals research. There is increasing awareness about the potential health benefits of nutraceuticals, and the ongoing research advancements in this field reveal that nanoparticle-based delivery systems will have more commercial status in the market in the near future. Also, such enabling nanotechnology-based systems may interest the food product manufacturers to introduce nano-based ingredients into their food products as part of their marketing strategy. However, regardless of the strategy applied, the interaction between the nutraceutical ingredient and the different components of the food matrix during processing needs to be understood as such interactions can influence the bioavailability and bioefficacy of the added nutraceutical ingredient. More work is required to understand the interaction of nutraceuticals with complex food matrices to support the potential health benefits of nutraceuticals added to food to apprehend the complexities of their passage from the gut into the body and to understand how the encapsulant may influence this process.

REFERENCES

1. Aronson JK. Defining "Nutraceuticals": Neither Nutritious Nor Pharmaceutical. *Br J Clin Pharmacol*. 2017;83(1):8–19.
2. McClements DJ, Decker EA, Park Y, Weiss J. Structural Design Principles for Delivery of Bioactive Components in Nutraceuticals and Functional Foods. *Crit Rev Food Sci Nutr*. 2009;49(6):577–606.
3. Wildman REC, Kelley M. Nutraceuticals and functional foods. In: Wildman REC, ed. *Handbook of Nutraceuticals and Functional Foods*. 2nd ed. Boco Raton, FL: CRC Press 2007; pp. 1–22.
4. Saikia D, Deka SC. Cereals: From Staple Food to Nutraceuticals. *Int Food Res J*. 2011;18(1):21–30.
5. Das L, Bhaumik E, Raychaudhuri U, Chakraborty R. Role of Nutraceuticals in Human Health. *J Food Sci Technol*. 2012;49(2):173–183.
6. Wang X, Maher S, Brayden DJ. Restoration of Rat Colonic Epithelium after In Situ Intestinal Instillation of the Absorption Promoter, Sodium Caprate. *Ther Deliv*. 2010;1(1):75–82.

7. McClements DJ. Nanoscale Nutrient Delivery Systems for Food Applications: Improving Bioactive Dispersibility, Stability, and Bioavailability. *J Food Sci*. 2015;80(7):N1602–N1611.
8. Kaur G, Mukundan S, Wani V, Kumar MS. Nutraceuticals in the Management and Prevention of Metabolic Syndrome. *Austin J Pharmacol Ther.* 2015;3(1):1063.
9. Nair HB, Sung B, Yadav VR, Kannappan R, Chaturvedi MM, Aggarwal BB. Delivery of Anti-inflammatory Nutraceuticals by Nanoparticles for the Prevention and Treatment of Cancer. *Biochem Pharmacol*. 2010;80(12):1833–1843.
10. Avrelija C, Walter C. Antimicrobial Agents Deriving from Indigenous Plants. *Recent Pat Food Nutr Agric*. 2010;2(1):83–92.
11. Balsano C, Alisi A. Antioxidant Effects of Natural Bioactive Compounds. *Curr Pharm Des*. 2009;15(26):3063–3073.
12. Saldanha SN, Tollefsbol TO. The Role of Nutraceuticals in Chemoprevention and Chemotherapy and Their Clinical Outcomes. *J Oncol*. 2012;2012:192464.
13. Wargovich MJ, Morris J, Brown V, Ellis J, Logothetis B, Weber R. Nutraceutical Use in Late-stage Cancer. *Cancer Metastasis Rev.* 2010;29(3):503–510.
14. McClements DJ, Li F, Xiao H. The Nutraceutical Bioavailability Classification Scheme: Classifying Nutraceuticals According to Factors Limiting their Oral Bioavailability. *Annu Rev Food Sci Technol*. 2015;6:299–327.
15. Kelloff GJ, Crowell JA, Steele VE et al. Progress in Cancer Chemoprevention: Development of Diet-derived Chemopreventive Agents. *J Nutr*. 2000;130(2S):467S–471S.
16. Hahn WC, Counter CM, Lundberg AS, Beijersbergen RL, Brooks MW, Weinberg RA. Creation of Human Tumour Cells with Defined Genetic Elements. *Nature*. 1999;400(6743):464–468.
17. Hahn WC, Dessain SK, Brooks MW et al. Enumeration of the Simian Virus 40 Early Region Elements Necessary for Human Cell Transformation. *Mol Cell Biol*. 2002;22(7):2111–2123.
18. Surh YJ. Cancer Chemoprevention with Dietary Phytochemicals. *Nat Rev Cancer.* 2003;3(10):768–780.
19. Issa AY, Volate SR, Wargovich MJ. The Role of Phytochemicals in Inhibition of Cancer and Inflammation: New Directions and Perspectives. *J Food Compos Anal*. 2006;19(5):405–419.
20. DellaPenna D. Nutritional Genomics: Manipulating Plant Micronutrients to Improve Human Health. *Science*. 1999;285(5426):375–379.
21. Orzechowski A, Ostaszewski P, Jank M, Berwid SJ. Bioactive Substances of Plant Origin in Food—Impact on Genomics. *Reprod Nutr Dev.* 2002;42(5):461–477.
22. Ogilvie GK. Interventional Nutrition for the Cancer Patient. *Clin Tech Small Anim Pract*. 1998;13(4):224–231.
23. McCullough ML, Giovannucci EL. Diet and Cancer Prevention. *Oncogene*. 2004;23:6349–6364.
24. See D, Mason S, Roshan R. Increased Tumor Necrosis Factor Alpha (TNF-alpha) and Natural Killer Cell (NK) Function using an Integrative Approach in Late Stage Cancers. *Immunol Invest*. 2002;31(2):137–153.
25. Kotecha R, Takami A, Espinoza JL. Dietary Phytochemicals and Cancer Chemoprevention: A Review of the Clinical Evidence. *Oncotarget*. 2016;7(32):52517–52529.
26. Weiderpass E. Lifestyle and Cancer Risk. *J Prev Med Public Health*. 2010;43(6):459–471.
27. Ullah MF, Khan MW. Food as Medicine: Potential Therapeutic Tendencies of Plant Derived Polyphenolic Compounds. *Asian Pac J Cancer Prev.* 2008;9(2):187–195.
28. Tuomisto JT, Tuomisto J, Tainio M et al. Risk-Benefit Analysis of Eating Farmed Salmon. *Science*. 2004;305(5683):476–477.
29. Grimble RF. Nutritional Therapy for Cancer Cachexia. *Gut*. 2003;52(10):1391–1392.

30. Weisburger JH. Antimutagens, Anticarcinogens, and Effective Worldwide Cancer Prevention. *J Environ Pathol Toxicol Oncol*. 1999;18(2):85–93.
31. Singh CK, George J, Ahmad N. Resveratrol-based Combinatorial Strategies for Cancer Management. *Ann NY Acad Sci*. 2013;1290(1):113–121.
32. Shukla Y, George J. Combinatorial Strategies Employing Nutraceuticals for Cancer Development. *Ann NY Acad Sci*. 2011;1229(1):162–175.
33. Singh CK, Ndiaye MA, Ahmad N. Resveratrol and Cancer: Challenges for Clinical Translation. *Biochim Biophys Acta*. 2015;1852(6):1178–1185.
34. Nguyen AV, Martinez M, Stamos MJ et al. Results of a Phase I Pilot Clinical Trial Examining the Effect of Plant-derived Resveratrol and Grape Powder on Wnt Pathway Target Gene Expression in Colonic Mucosa and Colon Cancer. *Cancer Manag Res*. 2009;1:25–37.
35. Scott E, Steward WP, Gescher AJ, Brown K. Resveratrol in Human Cancer Chemoprevention—Choosing the "Right" Dose. *Mol Nutr Food Res*. 2012;56(1):7–13.
36. Tapas AR, Sakarkar DM, Kakde RB. Flavonoids as Nutraceuticals: A Review. *Trop J Pharm Res*. 2008;7(3):1089–1099.
37. Batra P, Sharma AK. Anti-cancer Potential of Flavonoids: Recent Trends and Future Perspectives. *3 Biotech*. 2013;3(6):439–459.
38. Cai X, Fang Z, Dou J, Yu A, Zhai G. Bioavailability of Quercetin: Problems and Promises. *Curr Med Chem*. 2013;20(20):2572–2582.
39. Zhang X, Chen LX, Ouyang L, Cheng Y, Liu B. Plant Natural Compounds: Targeting Pathways of Autophagy as Anti-cancer Therapeutic Agents. *Cell Prolif*. 2012;45(5):466–476.
40. Joe B, Vijaykumar M, Lokesh BR. Biological Properties of Curcumin-Cellular and Molecular Mechanisms of Action. *Crit Rev Food Sci Nutr*. 2004;44(2):97–111.
41. Zheng R, Deng Q, Liu Y, Zhao P. Curcumin Inhibits Gastric Carcinoma Cell Growth and Induces Apoptosis by Suppressing the Wnt/β-Catenin Signaling Pathway BC. *Med Sci Monit*. 2017;23:163–171.
42. Ting Y, Jiang Y, Ho C-T, Huang Q. Common Delivery Systems for Enhancing In Vivo Bioavailability and Biological Efficacy of Nutraceuticals. *J Funct Foods*. 2014;7:112–128.
43. Ghosh D, Choudhury ST, Ghosh S et al. Nanocapsulated Curcumin: Oral Chemopreventive Formulation against Diethylnitrosamine Induced Hepatocellular Carcinoma in Rat. *Chem Biol Interact*. 2012;195(3):206–214.
44. Schiborr C, Kocher A, Behnam D, Jandasek J, Toelstede S, Frank J. The Oral Bioavailability of Curcumin from Micronized Powder and Liquid Micelles is Significantly Increased in Healthy Humans and Differs Between Sexes. *Mol Nutr Food Res*. 2014;58(3):516–527.
45. Nejat N, Valdiani A, Cahill D, Tan Y-H, Maziah M, Abiri R. Ornamental Exterior versus Therapeutic Interior of Madagascar Periwinkle (Catharanthus roseus): The Two Faces of a Versatile Herb. *The Sci World J*. 2015;2015:982412.
46. Johnson IS, Armstrong JG, Gorman M, Burnet JP Jr. The Vinca Alkaloids: A New Class of Oncolytic Agents. *Cancer Res*. 1963;23:1390–1427.
47. Johnson IS. Historical Background of Vinca Alkaloid Research and Areas of Future Interest. *Cancer Chemother Rep*. 1968;52(4):455–461.
48. Gidding CE, Kellie SJ, Kamps WA, de Graaf SS. Vincristine Revisited. *Crit Rev Oncol Hematol*. 1999;29(3):267–287.
49. Lucas DM, Still PC, Perez LB, Grever MR, Kinghorn AD. Potential of Plant-derived Natural Products in the Treatment of Leukemia and Lymphoma. *Curr Drug Targets*. 2010;11(7):812–822.
50. Fahy J. Modifications in the "Upper" Velbenamine Part of the Vinca Alkaloids have Major Implications for Tubulin Interacting Activities. *Curr Pharm Des*. 2001;7(13):1181–1197.

51. Zhang M, Shi X. Folic Acid-modified Dendrimer-DOX Conjugates for Targeting Cancer Chemotherapy. *J Control Release*. 2013;172(1):e55–e56.
52. Marinina J, Shenderova A, Mallery SR, Schwendeman SP. Stabilization of Vinca Alkaloids Encapsulated in Poly(lactide-co-glycolide) Microspheres. *Pharm Res*. 2000;17(6):677–683.
53. Chen B, McClements DJ, Decker EA. Design of Foods with Bioactive Lipids for Improved Health. *Annu Rev Food Sci Technol*. 2013;4:35–56.
54. O'Brien S, Schiller G, Lister J et al. High-dose Vincristine Sulfate Liposome Injection for Advanced, Relapsed, and Refractory Adult Philadelphia Chromosome-negative Acute Lymphoblastic Leukemia. *J Clin Oncol*. 2013;31(6):676–683.
55. Kaplan LD, Deitcher SR, Silverman JA, Morgan G. Phase II Study of Vincristine Sulfate Liposome Injection (Marqibo) and Rituximab for Patients with Relapsed and Refractory Diffuse Large B-Cell Lymphoma or Mantle Cell Lymphoma in Need of Palliative Therapy. *Clin Lymphoma Myeloma Leuk*. 2014;14(1):37–42.
56. Wang Y, Dou L, He H, Zhang Y, Shen Q. Multifunctional Nanoparticles as Nanocarrier for Vincristine Sulfate Delivery to Overcome Tumor Multidrug Resistance. *Mol Pharm*. 2014;11(3):885–894.
57. Min K-j, Kwon TK. Anticancer Effects and Molecular Mechanisms of Epigallocatechin-3-gallate. *Integr Med Res*. 2014;3(1):16–24.
58. Granja A, Pinheiro M, Reis S. Epigallocatechin Gallate Nanodelivery Systems for Cancer Therapy. *Nutrients*. 2016;8(5):E307.
59. Houghton CA, Fassett RG, Coombes JS. Sulforaphane and Other Nutrigenomic Nrf2 Activators: Can the Clinician's Expectation be Matched by the Reality? *Oxid Med Cell Longev*. 2016;2016:7857186.
60. Clarke JD, Dashwood RH, Ho E. Multi-targeted Prevention of Cancer by Sulforaphane. *Cancer Lett*. 2008;269(2):291–304.
61. Alumkal J, Slottke R, Schwartzman J et al. A Phase II Study of Sulforaphane-rich Broccoli Sprout Extracts in Men with Recurrent Prostate Cancer. *Invest New Drugs*. 2015;33(2):480–489.
62. Do DP, Pai SB, Rizvi SA, D'Souza MJ. Development of Sulforaphane-encapsulated Microspheres for Cancer Epigenetic Therapy. *Int J Pharm*. 2010;386(1–2):114–121.
63. Porter CJ, Trevaskis NL, Charman WN. Lipids and Lipid-based Formulations: Optimizing the Oral Delivery of Lipophilic Drugs. *Nat Rev Drug Discov*. 2007;6(3):231–248.
64. Pouton CW, Porter CJ. Formulation of Lipid-based Delivery Systems for Oral Administration: Materials, Methods and Strategies. *Adv Drug Deliv Rev*. 2008;60(6):625–637.
65. Rimbach G, Pallauf J, Moehring J, Kraemer K, Minihane AM. Effect of Dietary Phytate and Microbial Phytase on Mineral and Trace Element Bioavailability:A Literature Review. *Curr Top Nutraceutical Res*. 2008;6(3):131–144.
66. Actis-Goretta L, Leveques A, Rein M et al. Intestinal Absorption, Metabolism, and Excretion of (−)-Epicatechin in Healthy Humans Assessed by using an Intestinal Perfusion Technique. *Am J Clin Nutr*. 2013;98(4):924–933.
67. Fleisher D, Li C, Zhou Y, Pao LH, Karim A. Drug, Meal and Formulation Interactions Influencing Drug Absorption after Oral Administration. Clinical Implications. *Clin Pharmacokinet*. 1999;36(3):233–254.
68. Martinez MN, Amidon GL. A Mechanistic Approach to Understanding the Factors Affecting Drug Absorption: A Review of Fundamentals. *J Clin Pharmacol*. 2002; 42(6):620–643.
69. D'Ambrosio DN, Clugston RD, Blaner WS. Vitamin A Metabolism: An Update. *Nutrients*. 2011;3(1):63–103.
70. Hurst S, Loi CM, Brodfuehrer J, El-Kattan A. Impact of Physiological, Physicochemical and Biopharmaceutical Factors in Absorption and Metabolism Mechanisms on the Drug Oral Bioavailability of Rats and Humans. *Expert Opin Drug Metab Toxicol*. 2007;3(4):469–489.

71. Brown MJ, Ferruzzi MG, Nguyen ML et al. Carotenoid Bioavailability is Higher from Salads Ingested with Full-fat than with Fat-reduced Salad Dressings as Measured with Electro-chemical Detection. *Am J Clin Nutr.* 2004;80(2):396–403.
72. Charman WN, Porter CJ, Mithani S, Dressman JB. Physicochemical and Physiological Mechanisms for the Effects of Food on Drug Absorption: The Role of Lipids and pH. *J Pharm Sci*. 1997;86(3):269–282.
73. Rein MJ, Renouf M, Cruz-Hernandez C, Actis-Goretta L, Thakkar SK, da Silva Pinto M. Bioavailability of Bioactive Food Compounds: A Challenging Journey to Bioefficacy. *Br J Clin Pharmacol*. 2013;75(3):588–602.
74. McClements DJ. Utilizing Food Effects to Overcome Challenges in Delivery of Lipophilic Bioactives: Structural Design of Medical and Functional Foods. *Expert Opin Drug Deliv.* 2013;10(12):1621–1632.
75. McClements DJ, Xiao H. Excipient Foods: Designing Food Matrices that Improve the Oral Bioavailability of Pharmaceuticals and Nutraceuticals. *Food Funct*. 2014;5(7):1320–1333.
76. Gleeson JP, Heade J, Ryan SM, Brayden DJ. Stability, Toxicity and Intestinal Permeation Enhancement of Two Food-derived Antihypertensive Tripeptides, Ile-Pro-Pro and Leu-Lys-Pro. *Peptides.* 2015;71:1–7.
77. Arnott JA, Planey SL. The Influence of Lipophilicity in Drug Discovery and Design. *Expert Opin Drug Discov.* 2012;7(10):863–875.
78. Maher S, Ryan B, Duffy A, Brayden DJ. Formulation Strategies to Improve Oral Peptide Delivery. *Pharm Pat Anal*. 2014;3(3):313–336.
79. Stern W, Mehta N, Carl SM. Oral Delivery of Peptides by Peptelligence Technology. *Drug Dev Deliv.* 2013;13(2):38–42.
80. Tuvia S, Atsmon J, Teichman SL et al. Oral Octreotide Absorption in Human Subjects: Comparable Pharmacokinetics to Parenteral Octreotide and Effective Growth Hormone Suppression. *J Clin Endocrinol Metab.* 2012;97(7):2362–2369.
81. Karsdal MA, Riis BJ, Mehta N et al. Lessons Learned from the Clinical Development of Oral Peptides. *Br J Clin Pharmacol*. 2015;79(5):720–732.
82. Lewis AL, Richard J. Challenges in the Delivery of Peptide Drugs: An Industry Perspective. *Ther Deliv.* 2015;6(2):149–163.
83. Brayden DJ, Gleeson J, Walsh EG. A Head-to-head Multi-parametric High Content Analysis of a Series of Medium Chain Fatty Acid Intestinal Permeation Enhancers in Caco-2 Cells. *Eur J Pharm Biopharm*. 2014;88(3):830–839.
84. Krug SM, Amasheh M, Dittmann I, Christoffel I, Fromm M, Amasheh S. Sodium Caprate as an Enhancer of Macromolecule Permeation Across Tricullular Tight Junctions of Intestinal Cells. *Biomaterials*. 2013;34(1):275–282.
85. Aguirre TA, Rosa M, Guterres SS, Pohlmann AR, Coulter I, Brayden DJ. Investigation of Coco-glucoside as a Novel Intestinal Permeation Enhancer in Rat Models. *Eur J Pharm Biopharm*. 2014;88(3):856–865.
86. Szűts A, Szabó-Révész P. Sucrose Esters as Natural Surfactants in Drug Delivery Systems-A Mini-review. *Int J Pharm*. 2012;433(1–2):1–9.
87. Aldini G, Altomare A, Baron G et al. N-Acetylcysteine as An Antioxidant and Disulphide Breaking Agent: The Reasons Why. *Free Radic Res*. 2018;52(7):751–762.
88. Müller C, Leithner K, Hauptstein S, Hintzen F, Salvenmoser W, Bernkop-Schnürch A. Preparation and Characterization of Mucus-penetrating Papain/poly(acrylic acid) Nanoparticles for Oral Drug Delivery Applications. *J Nanopart Res*. 2013;15:1353.
89. Pereira de Sousa I, Cattoz B, Wilcox MD et al. Nanoparticles Decorated with Proteolytic Enzymes, A Promising Strategy to Overcome the Mucus Barrier. *Eur J Pharm Sci*. 2015;97(Pt A):257–264.

90. Müller C, Perera G, König V, Bernkop-Schnürch A. Development and In Vivo Evaluation of Papain-functionalized Nanoparticles. *Eur J Pharm Biopharm*. 2014;87(1):125–131.
91. Petersen SB, Nielsen LG, Rahbek UL, Guldbrandt M, Brayden DJ. Colonic Absorption of Salmon Calcitonin using Tetradecyl Maltoside (TDM) as a Permeation Enhancer. *Eur J Pharm Sci*. 2013;48(4–5):726–734.
92. Sigurdsson HH, Kirch J, Lehr C-M. Mucus as a Barrier to Lipophilic Drugs. *Int J Pharm*. 2013;453(1):56–64.
93. Yuan S, Hollinger M, Lachowicz-Scroggins ME et al. Oxidation Increases Mucin Polymer Cross-links to Stiffen Airway Mucus Gels. *Sci Transl Med*. 2015;7(276):276ra27.
94. Faridi Esfanjani A, Jafari SM. Biopolymer Nano-particles and Natural Nano-carriers for Nano-encapsulation of Phenolic Compounds. *Colloids Surf B*. 2016;146:532–543.
95. Donald A. Food for Thought. *Nat Mater*. 2004;3(9):579–581.
96. Wimardhani YS, Suniarti DF, Freisleben HJ, Wanandi SI, Siregar NC, Ikeda MA. Chitosan Exerts Anticancer Activity through Induction of Apoptosis and Cell Cycle Arrest in Oral Cancer Cells. *J Oral Sci*. 2014;56(2):119–126.
97. Yao M, Xiao H, McClements DJ. Delivery of Lipophilic Bioactives: Assembly, Disassembly, and Reassembly of Lipid Nanoparticles. *Annu Rev Food Sci Technol*. 2014;5:53–81.
98. Porter CJ, Pouton CW, Cuine JF, Charman WN. Enhancing Intestinal Drug Solubilisation using Lipid-based Delivery Systems. *Adv Drug Deliv Rev*. 2008;60(6):673–691.
99. McClements DJ. Emulsion Design to Improve the Delivery of Functional Lipophilic Components. *Annu Rev Food Sci Technol*. 2010;1:241–269.
100. Sanguansri P, Augustin MA. Nanoscale Materials Development—A Food Industry Perspective. *Trends Food Sci Technol*. 2006;17(10):547–556.
101. Ezhilarasi PN, Karthik P, Chhanwal N, Anandharamakrishnan C. Nanoencapsulation Techniques for Food Bioactive Components: A Review. *Food Bioprocess Technol*. 2013;6(3):628–647.
102. Joye IJ, Davidov-Pardo G, McClements DJ. Nanotechnology for Increased Micronutrient Bioavailability. *Trends Food Sci Technol*. 2014;40(2):168–182.
103. Song XR, Cai Z, Zheng Y et al. Reversion of Multidrug Resistance by Co-encapsulation of Vincristine and Verapamil in PLGA Nanoparticles. *Eur J Pharm Sci*. 2009;37(3–4):300–305.
104. Ravindran J, Nair HB, Sung B, Prasad S, Tekmal RR, Aggarwal BB. Thymoquinone Poly (lactide-co-glycolide) Nanoparticles Exhibit Enhanced Anti-proliferative, Anti-inflammatory, and Chemosensitization Potential. *Biochem Pharmacol*. 2010;79(11):1640–1647.
105. Patil Y, Panyam J. Polymeric Nanoparticles for siRNA Delivery and Gene Silencing. *Int J Pharm*. 2009;367(1–2):195–203.
106. Mundargi RC, Babu VR, Rangaswamy V, Patel P, Aminabhavi TM. Nano/micro Technologies for Delivering Macromolecular Therapeutics using Poly(D,L-lactide-co-glycolide) and its Derivatives. *J Control Release*. 2008;125(3):193–209.
107. Chavanpatil MD, Patil Y, Panyam J. Susceptibility of Nanoparticle-encapsulated Paclitaxel to P-glycoprotein-mediated Drug Efflux. *Int J Pharm*. 2006;320(1–2):150–156.
108. Cegnar M, Kos J, Kristl J. Intracellular Delivery of Cysteine Protease Inhibitor Cystatin by Polymeric Nanoparticles. *J Nanosci Nanotechnol*. 2006;6(9–10):3087–3094.
109. Chan JM, Zhang L, Yuet KP et al. PLGA-lecithin-PEG Core-shell Nanoparticles for Controlled Drug Delivery. *Biomaterials*. 2009;30(8):1627–1634.

110. Acharya S, Dilnawaz F, Sahoo SK. Targeted Epidermal Growth Factor Receptor Nanoparticle Bioconjugates for Breast Cancer Therapy. *Biomaterials*. 2009;30(29):5737–5750.
111. Zaki NM, Tirelli N. Gateways for the Intracellular Access of Nanocarriers: A Review of Receptor-Mediated Endocytosis Mechanisms and of Strategies in Receptor Targeting. *Expert Opin Drug Deliv*. 2010;7(8):895–913.
112. Zaki NM, Tirelli N. Assessment of Nanomaterials Cytotoxicity and Internalization. *Methods Mol Biol*. 2011;695:243–259.
113. Zaki NM, Nasti A, Tirelli N. Nanocarriers for Cytoplasmic Delivery: Cellular Uptake and Intracellular Fate of Chitosan and Hyaluronic Acid-coated Chitosan Nanoparticles in a Phagocytic Cell Model. *Macromol Biosci*. 2011;11(12):1747–1760.
114. Zaki NM. Augmented Cytotoxicity of Hydroxycamptothecin-loaded nanoparticles in lung and colon cancer cells by chemosensitizing pharmaceutical excipients. *Drug Deliv*. 2014;21(4):265–275.
115. Cocheme HM, Kelso GF, James AM et al. Mitochondrial Targeting of Quinones: Therapeutic Implications. *Mitochondrion*. 2007;7(Suppl):S94–S102.
116. Biasutto L, Mattarei A, Marotta E et al. Development of Mitochondria-targeted Derivatives of Resveratrol. *Bioorg Med Chem Lett*. 2008;18(20):5594–5597.
117. Porteous CM, Logan A, Evans C et al. Rapid Uptake of Lipophilic Triphenylphosphonium Cations by Mitochondria In Vivo Following Intravenous Injection: Implications for Mitochondria-specific Therapies and Probes. *Biochim Biophys Acta*. 2010;1800 (9):1009–1017.
118. Safavy A, Raisch KP, Mantena S et al. Design and Development of Water-soluble Curcumin Conjugates as Potential Anticancer Agents. *J Med Chem*. 2007;50(24):6284–6288.
119. McClements DJ. Requirements for food ingredient and nutraceutical delivery systems. In: Garti N, McClements DJ, eds. *Encapsulation Technologies and Delivery Systems for Food Ingredients and Nutraceuticals*. Woodhead Publishing Limited, Oxford, UK 2012; pp. 3–18.
120. Ajazuddin, Saraf S. Applications of Novel Drug Delivery System for Herbal Formulations. *Fitoterapia*. 2010;81(7):680–689.
121. El-Sherbiny I, ElBaz NM, Hefnawy A. Chapter 4. Potential of nanotechnology in nutraceuticals delivery for the prevention and treatment of cancer. In: Grumezescu A, eds. *Nanotechnology in the Agri-Food Industry*. Vol. 4, Elsevier, UK 2016.
122. Mozafari MR, Pardakhty A, Azarmi S, Jazayeri JA, Nokhodchi A, Omri A. Role of Nanocarrier Systems in Cancer Nanotherapy. *J Liposome Res*. 2009; 19(4):310–321.
123. Abreu AS, Castanheira EM, Queiroz MJ, Ferreira PM, Vale-Silva LA, Pinto E. Nanoliposomes for Encapsulation and Delivery of the Potential Antitumoral Methyl 6-Methoxy-3-(4-methoxyphenyl)-1H-indole-2-carboxylate. *Nanoscale Res Lett*. 2011;6(1):482.
124. Mozafari MR, Johnson C, Hatziantoniou S, Demetzos C. Nanoliposomes and Their Applications in Food Nanotechnology. *J Liposome Res*. 2008;18(4):309–327.
125. Mozafari MR. Nanoliposomes: Preparation and Analysis. *Methods Mol Biol*. 2010;605:29–50.
126. Solans C, Izquierdo P, Nolla J, Azemar N, Garcia-Celma MJ. Nano-emulsions. *Curr Opin Colloid Interface Sci*. 2005;10(3–4):102–110.
127. Sivakumar M, Tang SY, Tan KW. Cavitation Technology—A Greener Processing Technique for the Generation of Pharmaceutical Nanoemulsions. *Ultrason Sonochem*. 2014;21(6):2069–2083.

128. Augustin MA, Sanguansri L. Challenges in developing delivery systems for food additives, nutraceuticals and dietary supplements. In: Garti N, McClements DJ, eds. *Encapsulation Technologies and Delivery Systems for Food Ingredients and Nutraceuticals*. Cambridge, UK: Woodhead Publishing 2012; pp. 19–48.
129. Frede K, Henze A, Khalil M, Baldermann S, Schweigert FJ, Rawel H. Stability and Cellular Uptake of Lutein-loaded Emulsions. *J Funct Foods*. 2014;8:118–128.
130. Sun Y, Xia Z, Zheng J, Qiu P, Zhang L, McClements D, Xiao H. Nanoemulsion-based Delivery Systems for Nutraceuticals: Influence of Carrier Oil Type on Bioavailability of Pterostilbene. *FASEB J*. 2015;29(1S):AN249.5.
131. Mainardes RM, Gremião MPD, Evangelista RC. Thermoanalytical Study of Praziquatel-loaded PLGA Nanoparticles. *Braz J Pharm Sci*. 2006;42(4):523–530.
132. Khuda-Bukhsh AR, Bhattacharyya SS, Paul S, Boujedaini N. Polymeric Nanoparticle Encapsulation of a Naturally Occurring Plant Scopoletin and Its Effects on Human Melanoma Cell A375. *Zhong Xi Yi Jie He Xue Bao*. 2010;8(9):853–862.
133. Alexis F, Pridgen E, Molnar LK, Farokhzad OC. Factors Affecting the Clearance and Biodistribution of Polymeric Nanoparticles. *Mol Pharm*. 2008;5(4):505–515.
134. Bisht S, Feldmann G, Soni S et al. Polymeric Nanoparticle-encapsulated Curcumin ("Nanocurcumin"): A Novel Strategy for Human Cancer Therapy. *J Nanobiotechnology*. 2007;5:3.
135. Mukerjee A, Vishwanatha JK. Formulation, Characterization and Evaluation of Curcumin-loaded PLGA Nanospheres for Cancer Therapy. *Anticancer Res*. 2009;29(10):3867–3875.
136. Wu TZ, Yen FL, Lin LT, Tsai TR, Lin CC, Cham TM. Preparation, Physicochemical Characterization, and Antioxidant Effects of Quercetin Nanoparticles. *Int J Pharm*. 2008;346(1–2):160–168.
137. Min KH, Park K, Kim YS et al. Hydrophobically Modified Glycol Chitosan Nanoparticles-encapsulated Camptothecin Enhance the Drug Stability and Tumor Targeting in Cancer Therapy. *J Control Release*. 2008;127(3):208–218.
138. Kumari A, Yadav SK, Yadav SC. Biodegradable Polymeric Nanoparticles Based Drug Delivery System. *Colloids Surf B Biointerfaces*. 2010;75(1):1–18.
139. dos Santos FK, Oyafuso MH, Kiill CP, Daflon-Gremião MP, Chorilli M. Nanotechnology-based Drug Delivery Systems for Treatment of Hyperproliferative Skin Diseases—A Review. *Curr Nanosci*. 2013;9(1):159–167.
140. Pardeike J, Hommoss A, Müller RH. Lipid Nanoparticles (SLN, NLC) in Cosmetic and Pharmaceutical Dermal Products. *Int J Pharm*. 2009;366(1–2):170–184.
141. Li H, Zhao X, Ma Y, Zhai G, Li L, Lou H. Enhancement of Gastrointestinal Absorption of Quercetin by Solid Lipid Nanoparticles. *J Control Release*. 2009;133(3):238–244.
142. Chen-yu G, Chun-fen Y, Qi-lu L et al. Development of a Quercetin-loaded Nanostructured Lipid Carrier Formulation for Topical Delivery. *Int J Pharm*. 2012;430(1–2):292–298.
143. Santini A, Tenore GC, Novellino E. Nutraceuticals: A Paradigm of Proactive Medicine. *Eur J Pharm Sci*. 2017;96:53–61.
144. Faulks RM, Southon S. Assessing the bioavailability of nutraceuticals. In: Garti N, ed. *Delivery and Controlled Release of Bioactives in Foods and Nutraceuticals*. Cambridge, UK: Woodhead Publisher 2008; pp. 3–25.
145. Rubio L, Macia A, Motilva MJ. Impact of Various Factors on Pharmacokinetics of Bioactive Polyphenols: An Overview. *Curr Drug Metab*. 2014;15(1):62–76.
146. Mackie A. Interaction of food ingredient and nutraceutical delivery systems with the human gastrointestinal tract. In: Garti N, McClements DJ, eds. *Encapsulation Technologies and Delivery Systems for Food Ingredients and Nutraceuticals*. Cambridge, UK: Woodhead Publishing 2012; pp. 49–70.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

12 Efficacy, Safety, and Toxicological Aspects of Nutraceuticals

Jayvadan K. Patel and Anita Patel

CONTENTS

12.1 INTRODUCTION

Nutraceutical was first defined by Stephen DeFelice in 1989 "as a foods, food components or nutritional supplements that show specific health or medical benefits counting the prevention and treatment of disease further than essential nutritional functions" (Kalra 2003).

Plant foods have crucial nutrients whose deficiency are associated straightforwardly to explicit pathological situations, for example, deficiency of vitamin C and scurvy, in addition to nonessential ingredients that may possibly be short of nutritional importance but can control manifold cellular processes. Together recognized as nutraceuticals, these foodstuff ingredients contain extensive list of biologically active matters, counting, although not restricted to, carotenoids for instance astaxanthin from salmon and shellfish, catechins from tea and chocolate, isoflavones from soybeans, lutein from soybeans, lycopene from tomatoes, polyunsaturated fatty acids derived from fish as well as plant oils, probiotics, polyphenolic substances such as resveratrol obtained from grapes plus wine, and quercetin obtained from berries as well as leafy vegetables. Several in vitro in addition to animal studies have determined that nutraceuticals can slow down the development of tumor cells (Jang et al. 1997; Espin et al. 2007; Ahmad et al. 2015), and these outcomes recommended a defensive role for nutraceuticals against cancer. However, there is not enough clinical or epidemiological confirmation to sustain these outcomes, and the existing information for human being are either questionable or debatable (Espin et al. 2007; Ahmad et al. 2015).

12.2 TIME SERIES OF NUTRACEUTICALS IN CANCER MANAGEMENT

Till 1990, the notion of nutraceuticals was regarded as natural foodstuffs to give energy as suggested every day requisite in the body for healthiness. Afterward the significance of nutraceuticals was comprehended as helpful in diverse dietetic disorders with increasing utilization of the nutraceuticals as self-prescription in cancer, cardiovascular, and developmental situations in the last decade. Tremendous rising knowledge of nutraceuticals as powerful beneficial supplements with established notion of nutraceutical medicine as the latest branch of "complementary and alternative medicine" (CAM) was demonstrated in new era of twenty-first century. In last nine years, nutraceuticals have been accepted by the national and federal bodies as a promising nutraceutical therapy in most important stream of medical education as well as health. The shift of increasing number of people from medicinal management of cancer toward nonprescription nutraceuticals as self-medication in cancer therapy and avoidance have been established by the healthcare industry. The upward knowledge of nutraceutical advantages and shift of healthcare finances in favor of nutraceuticals conveyed nutraceutical medication in focus of government health plan on efficient exploitation of nutraceuticals in the suppression as well as management of

a variety of chronic disorders. In the last six years, the National Cancer Institute (NCI) and other universal attempts have well-documented information sheets and a number of health documentation on nutraceuticals in managing cancer (Sharma 2009). The most important attempts were committed in study of inhibitory consequence of active nutraceutical constituent(s) on cell propagation, cancer oncogenesis to up-shoot the diminished metastasis, late apoptosis, decreased necrosis, and malignancy growth rate in primary phases. In last two years, the employment of nutraceuticals for management of diseases has been extended further as defensive nutrition supplementation strategy by Center of Disease Control (CDC) under its independent direction. Nevertheless, mechanisms remain unproven and invalidated, although use of nutraceuticals as food supplements in prevention of cancer is admissible (Sharma 2009).

12.3 NUTRACEUTICALS AND CANCER

In developing nations, cancer has come out as a main community health problem. According to the World Cancer Report, the rate of cancer is growing and would be approximately 15 million new cases in 2020 to be precise, an increase of about 50%. Diet and healthy way of life can aid in prevention of cancer (Nasri et al. 2013).

At present, a number of nutraceuticals are available in the market. Table 12.1 shows examples of existing nutraceuticals, their ingredients, sources, and prospective human health advantages explicitly for cancer (Wildman and Kelley 2007; Parasuram 2011).

TABLE 12.1
Nutraceuticals, Their Sources and Potential Human Health

Nutraceuticals (Functional Ingredients)	Source	Potential Health Benefits
Conjugated linoleic acid	Cheese, meat products	Decrease risk of certain cancers
Flavonones	Citrus fruits	Reduce risk of cancer
Flavones	Fruits, vegetables, soya beans	Reduce risk of cancer
Glucosinolates	Cruciferous vegetables, cauliflower	Anticancer-greatest protection against bladder cancer
Insoluble dietary fiber	Whole grain foods, wheat and corn bran, nuts	Reduce the risk of breast or colon cancer
Lignans	Flaxseed, rye, vegetables	Inhibit the development of breast cancer and colon cancer
Lutein	Corn, avocado, egg yolk, spinach	Anticancer (colon cancer)
Lycopene	Tomatoes, watermelon, pink grapefruit, guava, papaya	Reduce the risk of prostate, bladder, cervical, leukemia
Phenolic acids	Berries, legumes	Reduce formation of cancer
Phytoestrogens (Isoflavones like genistein and daidzein)	Soya beans, legumes, linseeds	Reduce risk of prostate, breast, bowel, and other cancers
Saponins	Chickpeas, soya beans	Effective against colon cancer
Soluble dietary fiber (Prebiotics)	Legumes, oats, barley, some fruits	Anticancer
Tocotrienol (Isoprenoids)	Grains, palm oil	Anticancer (breast cancer)

Comprehensive investigation recommends that regular eating of specific fruits and vegetables can lessen the danger of getting particular cancers (Cragg and Newman 2001). The cause looks to be associated with the components in this foodstuff. The predominant data referred to compounds known as chemopreventive agents, that consist of curcumin, genistein, resveratrol, in addition to others, for example capsaicin, ellagic acid, 6-gingerol, and lycopene (Aggarwal et al. 2004; Dorai and Aggarwal 2004). Those compounds have been recommended to subdue proliferation of cancer cell, slow down growth factor signaling pathways, cause apoptosis, and prevent angiogenesis (Dorai and Aggarwal 2004).

12.4 EFFICACY AND SAFETY PROFILE OF SOME CHEMICAL CONSTITUENTS OF NUTRACEUTICALS IN CANCER

12.4.1 Carotenoids

Carotenoids are category of photochemical accountable for various colors of the foodstuffs, which contain antioxidant activities and are effective in preventing cancer. One of the main carotenoids, a lycopene is mostly present in guava, papaya, pink grapefruit, tomatoes, and water melon (Stahl and Sies 2005). Latest curiosity in carotenoids is regarding the effect of lycopene on human health, particularly on various cancers (Willis and Wians 2003). Lycopene is regarded as a strong antioxidant and a single oxygen quencher owing to its unsaturated nature. Lycopene found to be concentrated in the prostate, skin, testes, and adrenal where it protects against cancer (Kruger et al. 2002; Shirzad et al. 2013). The relationship among carotenoids and cancer prevention intensified the significance of fruits and vegetables in human diet. Fruits and vegetables containing lycopene showed cancer-protective result through reduction in oxidative stress and change in the DNA (Shirzad et al. 2013).

β-Carotene mainly presents in green, orange, and yellow leafy fruits and vegetables, for example, broccoli, cantaloupe, carrots, lettuce, oranges, tomatoes, spinach, sweet potatoes, and winter squash. β-Carotene exhibits the greatest antioxidant activity and prevents cancer as well as other ailments. The antioxidant activity of α-carotene is 50%–54% of β-carotene, while ε-carotene has 42%–50% of the antioxidant activity (Stahl and Sies 2005). Encapsulation of carotenoids results in better effectiveness in pharmacological doses; so, it can be employed for the treatment of some types of cancers (Gonnet et al. 2010).

12.4.2 Flavonoids

Flavonoids are familiar photochemicals that are formed by a variety of plants in large amounts. They are subdivided into anthocyanidins, flavan-3-ols, flavones, flavonols, flavanones, and isoflavones. Epidemiological investigations recommend that nutritional ingestion of flavonoids may well lessen the danger of tumors of the breast, colon, lung, pancreas, and prostate (Romagnolo and Selman 2012). Flavonoids demonstrated inhibition of carcinogenesis in vitro; however, ample data point out that they can as well perform in vivo (Caltagirone et al. 2000). Catechin tea can prevent lung tumorigenesis,

as demonstrated in the A/J mice (Yang et al. 2000). Nobiletin, a polymethoxy flavonoid, derived from *Citrus depressa*, suppresses the human fibrosarcoma HT-108 cell's activity of tumor invasion in the Matrigel model by restraining the of expression of matrix metalloproteases (MMPs) along with boosting tissue inhibitors of metalloproteinase (Sato et al. 2002). Quercetin, a natural product flavonoid, present in lots of fruits and vegetables, has revealed antitumor activities. Quercetin at 25 and 50 μM concentrations considerably subdued the development of PC-3 plus DU-145 prostate cancer cell line, where it was not influenced by the formation of colony via weakly hostile LNCaP prostate cancer cell line or the usual BG-9 fibroblast cell line (Nair et al. 2004).

12.4.3 Phytoestrogen

Right now, photochemicals with cancer-preventive characteristics have maximum interest (Shirzad et al. 2009). An extensive variety of phytopharmaceuticals with the stated hormonal activity, identified as "phytoestrogens," is suggested for the avoidance of breast and prostate cancers (Limer and Speirs 2004). Phytoestrogens have a pivotal role in cell cycle arrest, antiangiogenic potential and anti-metastatic potential and in improving of the outcome of radiotherapy. Phytoestrogens notably suppress tumor growth, invasion, and metastasis in rodent cancer models. By regulating the nuclear factor kappa light-chain enhancer of the activated B cells (NF-κB), phytoestrogens were found to be valuable in dropping the resistance to anticancer drugs (Virk-Baker et al. 2010). The use of phytoestrogens in diet has been related with many positive effects, predominantly concerning cancers of breast, colon, endometrium, lung, prostate, rectum, and stomach (Dixon 2004). In different studies, some of active phytoestrogens have exhibited antitumor activity comprises puerarin as of Kudzu vine (*Pueraria lobata*) (Boue et al. 2003), formononetin of clovers, fenugreek in addition to black cohosh (*Actaea racemosa* syn. *Cimicifuga racemosa*) (Piersen 2003).

12.4.4 Soy Isoflavones

Soy isoflavones, nutritional components have an imperative role in lessening the occurrence of breast and prostate cancers. The three major isoflavones in soybeans are daidzein, genistein, and glycitein, and these compounds have been proposed and established to be the most important biologically active anticancer constituents (Zhou et al. 1999; Sarkar and Li 2004). It has been revealed that these soy isoflavones suppress the development of cancer cells during the inflection of genes controlling the cell-cycle progression. Genistein slows down the activation of NF-κB signaling pathway, which is related to the steadiness among cell survival as well as programmed cell death (apoptosis) (Adiakly et al. 2013).

Epidemiological and animal investigations have found that the eating of dietetic soy declines the prevalence of certain tumors, especially those of colon and rectum (Toyomura and Kono 2002; Spector et al. 2003). The mechanism by which soy defends against the growth of colorectal cancer stays indistinct. It has been stated that there is a reduction in the expression of estrogen receptor-β (ER-β) expression in colorectal cancer (Bielecki et al. 2011).

12.4.5 Epigallocatechin Gallate

Epigallocatechin gallate (EGCG) is the uppermost copious catechin-type polyphenol mostly found in green plus white teas and defensive outcomes of EGCG against cancer have been described (Isbrucker et al. 2006). There was not any genotoxic special effects found in vivo or in vitro (Isbrucker et al. 2006), though EGCG is a powerful preventer of DNA methyl transferases (Lee et al. 2005), histone acetyltransferases (Choi et al. 2009), and topoisomerases I and II (Suzuki et al. 2001). These results possibly will be behind a number of the anticancer properties associated with EGCG; however, they as well elevate distresses for carcinogenicity.

12.4.6 Curcumin

Curcumin, a natural pigment, gives the spice turmeric its yellow color. Latest investigations have studied its cancer-fighting ability (Takahashi et al. 2009). Curcumin adapts manifold molecular pathways implicated in the prolonged carcinogenesis process to put forth its chemopreventive effects through some mechanisms: encouraging apoptosis, preventing survival signals, scavenging reactive oxidative species (ROS), and lessening the microenvironment of inflammatory cancer. Curcumin accomplishes the individuality for an idyllic chemopreventive agent by the way of its affordability, easy accessibility, and little toxicity (Park et al. 2013).

In the present day, clinical trials have been carried out using curcumin for the treatment of breast, colon, pancreatic, gastric, hepatocellular, lung, prostate, and skin cancer, as well as multiple myeloma. Such in vivo animal studies investigating curcumin's chemosensitizing as well as radiosensitizing characteristics have positively established the effect of curcumin on the Gemcitabine for pancreatic cancer (Epelbaum et al. 2010). Additional investigations have confirmed comparable effects of curcumin and oxaliplatin on colon cancer (Zhou et al. 2014). In the management of colorectal cancer, the role of curcumin is particularly imperative for the reason that the assumed mechanism of its effectiveness could transform the way to treat malignancies (Fadus et al. 2017). Takahashi et al. (2009) showed that nanosized curcumin capsules may enhance the body's uptake of the element and improve its ability to prevent colon cancer.

12.4.7 Capsaicin

Capsaicin, the pungent constituent of red hot chili peepers, has been shown to have anticancer activities on quite a few cancer cells, including prostate cancer (Torres et al. 2016). Capsaicin has been revealed to change the expression of more than a few genes implicated in angiogenesis, cancer cell survival, growth arrest, and metastasis. In recent times, numerous research associations have established that capsaicin targets manifold signaling pathways and oncogenes in addition to tumor-suppressor genes in different types of cancer models (Clark and Lee 2016).

12.4.8 Saponins

Saponins are photochemical mostly present in alfalfa, clove, potatoes, peas, spinach, soybeans, tomatoes, and a few herbs with names indicative of foaming properties,

for example, soapberry, soapbark, and soapwort. Commercial saponins are isolated mostly from *Yucca schidigera* as well as *Quillaja saponaria*. Saponins are stated to have antimutagenic and antitumor activities and may lessen the danger of human cancers by stopping cancer cells from growing (Li et al. 2003).

12.4.9 Tannins

Tannins, found in blackberries, blueberries, cranberries, grapes, lentils, and tea, is a proven anticarcinogen and employed in alternative medicine to prevent cancer. Tannins hunts injurious free radicals and detoxifies the carcinogens. Tea is, in addition water, the most extensively consumed cocktail globally. Of quite a few forms of this beverage existing, most investigations probing the effectiveness of tea in avoidance of cancer focus on green tea; this attention is rooted in epidemiological confirmations, which suggest that populace who drink more quantities of green tea have a lesser chances of developing different cancers (Jung and Ellis 2001).

12.4.10 Glucosinolates

Glucosinolates and their hydrolysis products, like indoles as well as isothiocyanates, and elevated ingestion of vegetables belonging to cruciferous have been related to minor hazard of colorectal as well as lung cancer. Dithiol thiones, isothiocyanates, and sulforaphane are the biotransformation products of glucosinolates, which obstruct the enzymes that encourage tumor growth, chiefly in breast, colon, esophagus, liver, lung, and stomach (Higdon et al. 2007).

12.4.11 Sulfur Compounds

Sulfur compounds, found in garlic, improve the immune system and diminish atherogenesis and stickiness of platelet as well as cancer. Sulforaphane, a powerful phase 2 enzyme inducer mostly found in broccoli, generates D-glucarolactone, an important preventer of breast cancer. Sulforaphane is an antioxidant along with stimulator of natural detoxifying enzymes and has been described to decrease the danger of breast as well as prostate cancer (Tamadon et al. 2014).

12.4.12 Berberine

Berberine is an isoquinoline flavonoid mostly found in the bark, root, and other parts of plants, characteristically present in traditional Chinese as well as East Asian medicines (Teodoro et al. 2013). Berberine is a dominant anti-neoplastic agent (Sun et al. 2009). Experimentation with a broad group of cell lines and tumors has revealed that berberine has the ability to apprehend growth, carcinogenesis, and metastization in almost all types of cancers (Ortiz et al. 2014). These effects range from radio-sensitization of the modified cells, however not of normal cells, by modulating the levels of anti-apoptotic along with pro-apoptotic proteins (Khan et al. 2010). Per se, berberine has a significant role in fundamental pathway for growth of cancer; for instance, the mitogen-activated protein kinase (MAPK) as well as the NF-κB

pathways (Lin et al. 2004). Interestingly, berberine can also guard normal cells from adverse effects of radiotherapy (Liu et al. 2008).

Berberine attaches to the molecular DNA and quite few other proteins implicated in cancer progressions, such as telomerase, topoisomerase I plus p53 (Ortiz et al. 2014), resulting in DNA strand breakdown, cell cycle capture, and generation of proapoptotic features. Interestingly, these pro-apoptotic properties of berberine come out to be p53-dependent because its elimination obstructs anticancerous effects of berberine (Zhang et al. 2010). Berberine has been stated to induce arrest of cell cycle at both G0/G1, as well as G2 and G2/M stages, depending on the types of cell and dose utilized (Ortiz et al. 2014). Actually, the dissimilarities in berberine being protective and inducing apoptosis may rely on the dose. A similar result is observed in the mitochondrial function, where doses of berberine bring about improved mitochondrial function (Gomes et al. 2012; Teodoro et al. 2013), while high doses induce mitochondrial complex I dysfunction (Diogo et al. 2011), which may in addition clarify some of the anticancerous effects (Pereira et al. 2007). Berberine and its derivatives may well present an influential means of fighting nearly all types of cancers.

12.4.13 Resveratrol

Resveratrol is a stilbenoid phenol formed by a number of plants, predominantly in the skin of berries such as blueberries and raspberries, with significant effects on human fitness (Frémont 2000). Since the late 1990s, resveratrol has been the focus of cancer investigation, as various available works confirmed quasi-incredible alleviation for numerous cancer types, mainly in rodent animal models. Starting from small doses of resveratrol to pharmacologically accessible higher doses, its effects on cancer expansion and propagation were simply amazing (Baur and Sinclair 2006; Baur et al. 2006). By inhibiting COX1, COX2, and other related proteins related to cancer development and reducing the rate of angiogenic and metastization (Tseng et al. 2004), resveratrol could prevent cancers (Khanduja et al. 2004). It can also reduce levels of drug-metabolizing enzymes, reducing the processing of carcinogens via the cells and consequently permitting the body to remove them rather than manage them (Baur and Sinclair 2006). Compared to berberine, resveratrol too hinders cell cycle and induces apoptosis. A decisive set of information on resveratrol and tumor cell lines as well as in vivo tumor models (Aggarwal et al. 2004) undoubtedly depicts that the anticancer activity of resveratrol greatly depends on the downregulation of the cell cycle proteins in addition to the initiation of apoptosis. However, it is still ambiguous whether these activities take place in the course of straight resveratrol action or else due to the sensitization of cancer cells to other proapoptotic effectors (Baur et al. 2006). Resveratrol is also able to change the antioxidant capability of cells either through alteration of the level of antioxidant enzymes or its intrinsic antioxidant effect (Sengottuvelan et al. 2006). Owing to its anticancer properties, resveratrol inhibits the propagation of lymphoid and myeloid cancers, cancers of breast, colon, thyroid, pancreas, prostate, and stomach, head and neck squamous cell carcinoma, ovarian carcinoma, and cervical carcinoma (Aggarwal et al. 2004).

12.4.14 Nexrutine

Concerning the photochemical, substantial attempt has been made to search for naturally arising compounds that may possibly helpful in the management of cancer (Kwon et al. 2007). Nexrutine is a commercially available herbal extract from the *Phellodendron amurense*. Isoquinoline alkaloids, phenolic compounds, and flavone glycosides are active constituents of nexrutine. A latest investigation discovered that nexrutine prevented the proliferation of lung and prostate cancer cells via the modulation of signal pathways mediated by Akt and cAMP response element binding; furthermore, its antiproliferative capabilities are analogous to those of berberine (James et al. 2011). In the mouse prostate model, nexrutine was found to be effectual against the initial stage of prostate tumor growth in addition to tumor succession in transgenic adenocarcinoma. Moreover, a recent study performed of stage II mouse skin tumorigenesis model demonstrated that nexrutine prevented the progress of skin tumorigenesis (Kumar et al. 2012). The similar group supplementary stated an antitumor effect in a tumorigenesis model of rat liver (Alam et al. 2015). In mice, only single dose of nexrutine before the use of 12-*O*-tetradecanoylphorbol 13-acetate (TPA) considerably reduced TPA-induced skin edema, hyperplasia, incorporation of thymidine, and activity of ornithine decarboxylase (Kumar et al. 2012).

12.5 ROLE OF NUTRACEUTICALS IN CANCER CHEMOTHERAPY

Concurrent utilization of nutraceuticals with chemotherapy is common. Cancer patients self-medicate to alleviate the adverse effects of chemotherapy, get a better disease upshot, and recover their health. Conversely, there is limited experimental confirmation on the possible drug–nutraceutical interactions and their resultant consequences on the effectiveness of chemotherapy (Angka and Spagnuolo 2015).

At some point after diagnosis, 60%–80% of the patients suffering from a hematological malignancy consumed an over-the-counter nutritional supplement (i.e., nutraceutical, or food-derived bioactive compound) (Ben-Arye et al. 2010). Although the development of methotrexate involved understanding the negative impact of folic acid on acute lymphoblastic leukemia cell growth and acute lymphoblastic leukemia cell growth and patient survival, there remains limited clinical evidence supporting or refuting nutraceutical use by cancer patients. Thus, given the importance of understanding the role of nutraceuticals in cancer chemotherapy, researchers performed a drug combination screening to identify nutraceuticals that enhanced and hindered the efficacy of cytarabine and daunorubicin, two primary therapeutics used in the treatment of acute myeloid leukemia (Angka and Spagnuolo 2015). A high throughput screening of a nutraceutical library has shown that zinc is able to enhance and echinachea is able to hinder the efficacy of acute myeloid leukemia chemotherapy. Given the high rate of nutraceutical consumption, this information is critical for accurate patient recommendations.

Zinc is an vital trace constituent in humans and supplementation (2 mg/kg/day for 60 days) in children and adolescents with acute leukemia and was effective in relieving chemotherapy-associated side effects (weight loss, malnutrition, nausea, and vomiting) (Consolo et al. 2013). This study demonstrated the safety and physiological

benefit of zinc supplementation but did not evaluate the supplementation effects on chemotherapy efficacy (Angka and Spagnuolo 2015). Through this screening researchers have also demonstrated that echinacea, among the most purchased nutraceuticals, hindered the efficacy of acute myeloid leukemia chemotherapy. Echinacea has been shown to increase the cellular concentration of CYP3A, a potent drug metabolizer, which could decrease the plasma concentrations of anticancer drugs that are CYP3A substrates such as cytarabine (Colburn et al. 2004; Penzak et al. 2010). Therefore, given echinacea's ability to reduce chemotherapy efficacy, cancer patients undergoing chemotherapy should avoid echinacea until further studies can confirm its safety (Angka and Spagnuolo 2015).

12.6 POSSIBLE MECHANISMS OF ACTION OF NUTRACEUTICALS AS CHEMOPREVENTIVE AGENT

The study of natural or synthetic chemicals to reverse, repress, or stop the development of carcinogenesis is known as chemoprevention. In initial stages, solid cancers are in general identified as intraepithelial neoplasia or carcinoma in situ, which resemble the promotion and progression phases. Consequently "anti-promotion" and "anti-progression" components might require meticulous experimental attention. Eventually, these components hinder the development and survival of cells previously devoted for melanoma.

Bioactive substances present in nutritional compounds, even in miniscule concentrations, possibly will have a far better influence than earlier recognized on the gene expression regulation. Understanding the mechanism behind the prevention of diseases like atherosclerosis, cancer, diabetes, hypertension, and obesity through nutritional manipulations has come from ongoing studies on the effects of nutraceuticals on gene expression. A few current studies on the action of selected nutraceuticals on the activity of transcription factors for instance activator protein (AP-1), counting NF-κB, peroxisome proliferator-activated receptor-gamma (PPARgamma), sterol response element binding proteins (SREBPs), and intonation of the expression of antioxidant genes similar to Bcl-2 as ultimate targets in the signal transduction cascade, in addition to gene regulation, have covered a route to additional study these compounds in a splendid detail, by means of a variety of genetically diseased models of animal (Orzechowski et al. 2002; Tripathi et al. 2005).

12.7 GENOMIC AND PROTEOMIC MECHANISMS AND MODELS IN TOXICITY AND SAFETY EVALUATION OF NUTRACEUTICALS

12.7.1 Nutraceuticals in Cell Culture

There is a need to develop method for quick and authentic evaluation of nutraceutical effectiveness and safety. At present, the widespread practices entail testing precise doses of nutraceuticals as well as extracts in most suitable cell cultures plus animal models, for instance mice as well as rats. The medicinal and nutritional values of grapes and its products, for example, wine, have been extensively argued (Nassiri-Asl and Hosseinzadeh 2009; Li and Forstermann 2012). A mixture of polyphenolic

molecules like flavonoid present in grape products is supposed to be responsible for the anticancer activity (Zhou and Raffoul 2012). Therapy of human pancreatic cancer cells by grape seed proanthocynidins considerably declined the viability of cell and induced apoptosis in a dose-dependent as well as time-dependent way and can inhibit migration of human pancreatic cancer cells through deactivating the NF-κB (Prasad and Katiyar 2013). In one more investigation, extracts of diverse varieties of grape were studied for their effect on human colon cancer cells through antioxidant as well as anti-inflammatory effects (Kountouri et al. 2013).

12.7.2 High-Throughput Technologies for Transcriptomic Analyses and Verification

Resveratrol is one of the well-known nutraceuticals that has chemopreventive, antiangiogenic, and anti-inflammatory activity. To study the activity of resveratrol in diverse human cancer cell lines, microarray technique has been widely used. Yang et al. (2003) investigated the alterations of global gene expression at some stage in resveratrol-induced growth suppression along with apoptosis in the human ovarian cancer PA-1 cells. The investigation established over 100 genes that alter their level of expressions considerably, comprising NAD(P)H: quinone oxidoreductase 1 (NQO-1), which is known to be related to the regulation of p53 and offers hints for resveratrol's mechanism of action (Yang et al. 2003). Similarly, human prostate cancer cell line LNCaP was processed with resveratrol; moreover, DNA microarray was employed to examine the temporal transcriptional profile (Jones et al. 2005).

In an additional case, by utilizing RNA microarray, resveratrol's apoptotic effects on the human fibrosarcoma cells (HT1080) were examined. Resveratrol-induced death of the apoptotic cell, considerably diminished HT1080 cells proliferation, and microarray study demonstrated changed apoptosis-associated genes expression (Harati et al. 2015). Such in vitro investigations demonstrated resveratrol's anticancer activity against human cancer cells in addition assisting in vivo trials evaluating the outcome of the natural polyphenol resveratrol.

Polyphenol curcumin, a chemopreventive agent, has been observed to be an important nutraceutical having anticancer effects. Kronski et al. (2014) demonstrated that curcumin in metastatic breast cancer cells modified the expression of miRNA, in particular miR181b. This investigation revealed that miR181b downmodulates the expressions of proinflammatory cytokines CXCL1 and CXCL2, thereby reducing the development of breast and prostate cancer. Taken together, these data show that curprovides promise in the therapeutic campaign for cancer (Kronski et al. 2014).

12.7.3 Application of Proteomic Approaches to Nutrition Research

Remarkably, proteomic examinations established that food supplement containing genistein boosts the GTP cyclohydrolase-I expression, a major protein concerned with the synthesis of nitric oxide in the rat mammary gland in connection with a decrease in the proliferation of cell as well as vulnerability to cancer (Rowell et al. 2005). Nevertheless, the majority of research studies have been carried out in animal models; therefore, restricted proteomics analysis in humans was implicated in

recognizing the molecular goal of nutritional ingredients in human being. For example, proteomic study of butyrate-treated human colon cancer cells (Tan et al. 2002, 2008), recognition of cellular target proteins of genistein action in the endothelial cells of human (Fuchs et al. 2005), and detection of quercetin molecular targets in human colon cancer cells (Wenzel et al. 2004). For identification of novel impending soybean allergens from transgenic plus nontransgenic samples of soy Batista et al. (2007), 2D gel as well as mass spectrometry technique was employed.

The effectiveness and security of nutraceuticals have been evaluated by various examinations, and adverse effects have been stated. This information requires to be coupled with the information obtained from the studies on adverse reaction to facilitate patients as well as physicians to create the best risk–benefit estimation prior to using any nutraceutical product. Perfect and better manage over the security and superiority of nutraceuticals might be attained during good manufacturing practice, regulatory control, in addition to research attempts, over and above by describing of adverse effects (Koh and Woo 2000).

12.8 TOXICITY POTENTIAL OF NUTRACEUTICALS

A great number of populaces accept that nutraceuticals are progressively being utilized as dietary supplements in the management of diseases without side effects. This belief has been raised from the fact that they have been used for a long period without serious toxicities. Even if this is factual for an extensive range of nutraceuticals and they normally contain lesser side effects compared with pharmaceuticals, traditional medication is reasons that if a medicine is effective, it will inexorably comprise side effects (Baradaran 2012). The therapeutic organization believes herbal medicines as drugs, and intrinsically, they must have side effects and so, they need to be prepared with right constituents and use with caution, as well (Nasri et al. 2014).

Most commonly used nutraceuticals are compounds derived from fruits and vegetables. They are often compounds with antioxidant or anti-inflammatory properties that are suggested to provide protection against chronic diseases such as cardiovascular disease, diabetes, cancer, and osteoporosis (Weaver et al. 2012). Widely consumed nutraceuticals include flavonoid plant pigments such as anthocyanins from berries, flavonols from dark chocolate, polyphenols such as resveratrol from red grapes, catechins from tea, and quercetin. There are little data to suggest that these compounds are toxic.

Owing to the plant source of these supplements, they are regarded as harmless for human consumption. Nonetheless, the quantities of the active ingredient eaten show a discrepancy when interpreted as a complete foodstuff, as contrary to a food supplement (Egert and Rimbach 2011; Kyselova 2011). There are scarce investigations that have described the long-standing consequences of food supplements in humans. Higher intake of lipids is linked with a greater risk of cancer, cardiovascular disease, diabetes, and obesity (Hooper et al. 2011; Salas-Salvado et al. 2011). High intake of flavonoid supplements can change the physiological levels of iron, vitamins, and other nutrients (Kyselova 2011). Flavonoids have the ability to interrelate with cytochrome P450 enzymes and consequently change the pharmacodynamics

and pharmacokinetics of a variety of medicines (Cermak 2008; Choi and Kim 2008; Simmen et al. 2010). Several flavonoids, for example genestein, have been related with a greater risk of cancer (Koro et al. 2007; Ramos-Nino et al. 2007; Andres et al. 2011).

Since evidence has emerged regarding health risks following hormone replacement therapy in postmenopausal women, menopausal women have increasingly turned to dietary supplements to treat symptoms such as hot flashes, depression, and bone loss. Latest study suggested that up to 42% of women were using soy foodstuffs; counting isoflavone extracts plus purified isoflavones, for example, genistein (Mazzanti et al. 2009). As these products are concentrated or purified, they have higher levels of plasma in comparison to isoflavones eaten as a portion of soy protein isolate or soy foodstuff, which are complex mixes of bioactive proteins, peptides, and more than one hundred phytochemicals (Fang et al. 2004; Ronis et al. 2016). There have been case reports of endometriosis in women consuming isoflavone supplements (Mahady et al. 2003); also, there is a likelihood of increased risk of estrogen-sensitive cancers in consumers of these products.

Humans eat thousands of varieties of plants and additional nutraceuticals to meet their fundamental dietary requirements; however, very few people have established noteworthy safety examinations. Many remain poorly understood and largely undeveloped, and their wild relatives are threatened with extinction and in need of conservation attention. Stewardship of these precious plant resources will have need of rigorous science combined with an approach that respects and values traditional knowledge systems (Nasri et al. 2014). For that reason, apart from safeguard outlines regarding these nutraceutical supplements in humans, vigilance ought to be practiced in their long-term use.

12.9 POTENTIAL TOXIC CONTAMINATION OF NUTRACEUTICALS

Nutraceuticals are defined by the Dietary Supplement Health and Education Act (DSHEA) as food supplements that might include herbs or else botanical, or a concentrate, constituent, extract, metabolite, or mixture of a few components from other classes (Frankos et al. 2010). At some stage in the production, presence of toxic contamination in nutraceutical can bring about alterations in their trait and safety. The health risk of these products mostly relies on the existence of abnormally elevated amounts of chemical components that might bring about adverse or even fatal effects if consumed (Chan 2003). The DSHEA sets up regulations as well as confines label claims on food supplements in the United States, whereas food supplements are congregated by the Directive 2002/46/EC and herbal therapeutic products are congregated by Directive 2004/27/EC in Europe. Conversely, there is no official legislation controlling the products of nutraceuticals (Gulati and Ottaway 2006; Martínez-Domínguez et al. 2014).

Plant-based nutraceuticals can be gathered arbitrarily from noncultivated and nonenvironmentally affable regions by untaught populace and positioned into the marketplace devoid of any regulation. It clearly indicates that users may be subjected to herbal foodstuffs possibly infected with pesticides, heavy metals, as well as metalloids, mycotoxins, or else radioactive materials or drugs (Figure 12.1). The existence

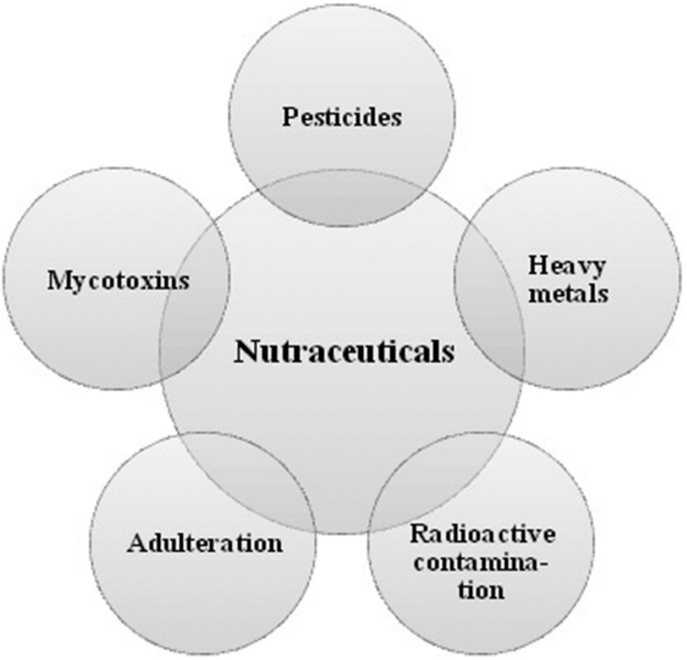


FIGURE 12.1 Major toxic contaminants found in nutraceuticals.

of verboten pesticides or extreme quantities of pesticides plus heavy metals relies on the origin of herbal substances and whether or not they are grown in a polluted region. In addition, chemical pollutants possibly enter from hostile or incorrect storage or chemical treatment at some point in the storage. Sequentially, the occurrence of medicines might be linked to unethical methods of manufacturing. In an ideal world, nutraceutical ingestion must be austerely managed and is relevant to superior understanding of the levels of diverse contaminants (distinctively heavy metals as well as pesticides) in raw materials (Chan 2003; Meena et al. 2010; Harris et al. 2011).

On the basis of a variety of factors, the amount of important as well as trace elements in therapeutic plants differ (Haider et al. 2004). Among these factors are geoclimatic conditions, geochemical uniqueness of the soil, anthropogenic activities, plant types (a few could be capable of electively generating toxic elements), along with the portion of the plant utilized for the preparation of herbal medication. In plants, the level of metals is also affected by the physicochemical characteristics of the soil where plants grow (distinctiveness of soil or else sediments, level of pH, exposure time, range of dispersion, and existence or nonexistence of other essential elements). These characteristics decide the nature of the connection of trace constituents with soil elements and are major elements for the bioavailability of metal elements (Sarma et al. 2011). Whereas plants voluntarily consume trace elements through roots, these composites are capable of rapt via the leaves. Rainwater, atmospheric dirt, plant's defense agents, and fertilizers are supplementary supplies of trace elements for plants (Lozak et al. 2002).

Even if a few trace metals present in foodstuffs take part in the physiological function as indispensable components as well as co-factors, contagion or defilement of nutraceuticals by heavy metals, metalloids, and mineral nutrients is a topic of interest. Even though low quantity of trace elements has health profits, elevated amounts may perhaps pretense health hazards (Bhat et al. 2010). On account of their cumulative belongings, as well as toxic potential, heavy metal concentrations might attain levels possibly conductive of harmful effects on human well-being.

The International Agency for Research on Cancer (IARC) has categorized specific trace elements (As, Sb, Be, Cd, Cr, Co, Pb, Ni, and V) as conceivably carcinogenic to humans owing to their ability to cause damage of DNA. Therefore, it must be distinguished that it is imperative to observe the existence of metal elements in medicinal plants utilized as nutraceuticals to avoid excess exposures of humans (Sarma et al. 2011).

Most extensively used chemicals in the earth are pesticides, and they are also one of the most hazardous contaminations for humans. The application of pesticides in modern cultivation becomes indispensable for a growing demand of quantity and quality in products, particularly to increase crop productivity and minimize any possible loss due to uncontrollable pests. Lot of diverse adverse health effects occur because of exposure to pesticide residues such as asthma, skin rashes, chronic problems including cancer (Zuin and Vilegas 2000; Calvert et al. 2004; Parrón et al. 2011). These pesticides, in addition, demonstrate long-term toxicity, mainly, cancer and endocrine disruption capacity (Mnif et al. 2011).

12.10 RESTRAINTS OF NUTRACEUTICALS IN CANCER

The ability of certain herbal supplements to obstruct drug treatment is renowned. Such as, anti-coagulant activities have been recognized for intake of garlic supplements and warfarin interactions have been shown for ginger and gingko (Posadzki et al. 2013). Almost certainly, the most widely known drug–herb interaction is the prospective for St. John's Wort (*Hypericum perforatum*) to cause cytochrome P4503A4, the main cytochrome related to the metabolic activation of definite drugs of cancer (Ranzato et al. 2014).

Antagonism of selective estrogen receptor modifiers such as tamoxifen has been demonstrated for the isoflavones characteristic of soy (Ranzato et al. 2014). Anthranoid-comprising plants like senna (*Cassia senna*) plus cascara (*Rhamnus purshiana*) in addition to soluble fibers like guar gum as well as psyllium are capable of reducing the absorption of certain drugs (Fugh-Berman 2000). Latest investigations have also established that a few antioxidants derived from plant extracts possibly will augment the endurance to chemotherapy if employed in patients having a higher cancer stage (Zhang 2010; Ranzato et al. 2014).

12.11 CONCLUSION AND FUTURE DIRECTIONS

At the moment, nutraceuticals have gained sky-scraping attentions owing to their probable nutritional and safety profiles, excluding therapeutic ability. The victory of nutraceuticals is anchored in the self-prescription and own individual familiarities.

Yet, the amazing benefits of nutraceuticals would not be understood unless critical clinical trials provide proof and particulars of nutraceuticals' defensive therapeutic efficiency. Despite every existing tool, cancer is one of the chief health perils. The majority of existing information on nutraceuticals in cancer comes from epidemiological health and populace data. The reduced cancer incidence due to nutraceuticals seems hype but greater hopes are anticipated with advancements in food science. Pharmaceutical and nutritional companies are attentive to the shift in the development owing to the benefits of these substances. The majority of nutraceuticals have manifold therapeutic advantages. The common community and healthcare professionals ought to be well knowledgeable regarding the fundamental notion of nutraceuticals and their helpfulness and must also be advised regarding the possible adverse events linked to their use due to the prospective contamination. Supervisory body must also acquire actions to diminish these difficulties.

REFERENCES

Adiakly M, Ngollo M, Boiteux JP, Bignon YJ, Guy L, Bernard-Gallon D. Genistein and daidzein: Different molecular effects on prostate cancer. *Anticancer Res*. 2013; 33(1):39–44.

Aggarwal BB, Bhardwaj A, Aggarwal RS, Seeram NP, Shishodia S, Takada Y. Role of resveratrol in prevention and therapy of cancer: Preclinical and clinical studies. *Anticancer Res.* 2004; 24(5A):2783–2840.

Ahmad A, Ginnebaugh KR, Li Y, Padhye SB, Sarkar FH. Molecular targets of naturopathy in cancer research: Bridge to modern medicine. *Nutrients.* 2015; 7:321–334.

Alam S, Yadav RS, Pal A, Purshottam SK, Chaudhari BP, Das M et al. Dietary administration of Nexrutine inhibits rat liver tumorigenesis and induces apoptotic cell death in human hepatocellular carcinoma cells. *Toxicol Rep.* 2015; 2:1–11.

Andres S, Abraham K, Appel KE, Lampen A. Risks and benefits of dietary isoflavones for cancer. *Crit Rev Toxicol.* 2011; 41(6):463–506.

Angka L, Spagnuolo PA. Interactions between nutraceutical supplements and standard acute myeloid leukemia chemotherapeutics. *J Pharm Pharm Sci.* 2015; 18(4):339–343.

Baradaran A. Beyond mineral metabolism, the bright immunomodulatory effect of vitamin D in renal disease. *J Nephropharmacol*. 2012; 1:17–18.

Batista R, Martins I, Jeno P. Ricardo CP, Oliveira MM. A proteomic study to identify soya allergens—The human response to transgenic versus non-transgenic soya samples. *Int Arch Allergy Immunol*. 2007; 144:29–38.

Baur JA, Pearson KJ, Price NL, Jamieson HA, Lerin C, Kalra A et al. Resveratrol improves health and survival of mice on a high-calorie diet. *Nature*. 2006; 444(7117):337–342.

Baur JA, Sinclair DA. Therapeutic potential of resveratrol: The *in vivo* evidence. *Nat Rev Drug Discov*. 2006; 5(6):493–506.

Ben-Arye E, Attias S, Tadmor T, Schiff E. Herbs in hemato-oncological care: An evidence-based review of data on efficacy, safety, and drug interactions. *Leuk Lymphoma*. 2010; 51(8):1414–1423.

Bhat R, Kiran K, Arun AB, Karim AA. Determination of mineral composition and heavy metal content of some nutraceutically valued plant products. *Food Anal Methods*. 2010; 3:181–187.

Bielecki A, Roberts J, Mehta R, Raju J. Estrogen receptor-β mediates the inhibition of DLD-1 human colon adenocarcinoma cells by soy isoflavones. *Nutr Cancer.* 2011; 63:139–150.

Boue SM, Wiese TE, Nehls S, Burow ME, Elliott S, Carter-Wientjes CH et al. Evaluation of the estrogenic effects of legume extracts containing phytoestrogens. *J Agric Food Chem*. 2003; 51(8):2193–2199.

Caltagirone S, Rossi C, Poggi A, Ranelletti FO, Natali PG, Brunetti M et al. Flavonoids apigenin and quercetin inhibit melanoma growth and metastatic potential. *Int J Cancer.* 2000; 87:595–600.

Calvert GM, Plate DK, Das R, Rosales R, Shafey O, Thomsen C et al. Acute occupational pesticide-related illness in the US, 1998–1999: Surveillance findings from the SENSOR-pesticides program. *Am J Ind Med.* 2004; 45 (1):14–23.

Cermak R. Effect of dietary flavonoids on pathways involved in drug metabolism. *Expert Opin Drug Metab Toxicol.* 2008; 4(1):17–35.

Chan K. Some aspects of toxic contaminants in herbal medicines. *Chemosphere.* 2003; 52(9):1361–1371.

Choi EJ, Kim T. Daidzein modulates induction of hepatic CYP1A1, 1B1, and AhR by 7, 12-dimethylbenz[a]anthracene in mice. *Arch Pharm Res.* 2008; 31(9):1115–1119.

Choi KC, Jung MG, Lee YH, Yoon JC, Kwon SH, Kang HB. Epigallocatechin-3-gallate, a histone acetyltransferase inhibitor, inhibits EBV-induced B lymphocyte transformation via suppression of RelA acetylation. *Cancer Res.* 2009; 69:583–592.

Clark R, Lee SH. Anticancer properties of capsaicin against human cancer. *Anticancer Res.* 2016; 36(3):837–843.

Colburn DE, Giles FJ, Oladovich D, Smith JA. In-vitro evaluation of cytochrome P450-mediated drug interactions between cytarabine, idarubicin, itraconazole and caspofungin. *Hematology.* 2004; 9(3):217–221.

Consolo LZ, Melnikov P, Consolo FZ, Nascimento VA, Pontes JC. Zinc supplementation in children and adolescents with acute leukemia. *Eur J Clin Nutr.* 2013; 67(10):1056–2059.

Cragg GM, Newman DJ. Medicinals for the millennia: The historical record. *Ann N Y Acad Sci* 2001; 953:3–25.

Diogo CV, Machado NG, Barbosa IA, Serafim TL, Burgeiro A, Oliveira PJ. Berberine as a promising safe anti-cancer agent—Is there a role for mitochondria? *Curr Drug Targets.* 2011; 12(6):850–859.

Dixon RA. Phytoestrogens. *Annu Rev Plant Biol.* 2004; 55:225–261.

Dorai T, Aggarwal BB. Role of chemo-preventive agents in cancer therapy. *Cancer Lett.* 2004; 215:129–140.

Egert S, Rimbach G. Which sources of flavonoids: Complex diets or dietary supplements? *Adv Nutr.* 2011; 2(1):8–14.

Epelbaum R, Schaffer M, Vizel B, Badmaev V, Bar-Sela G. Curcumin and gemcitabine in patients with advanced pancreatic cancer. *Nutr Cancer.* 2010; 62:1137–1141.

Espin JC, Garcia-Conesa MT, Tomas-Barberan FA. Nutraceuticals: Facts and fiction. *Phytochemistry.* 2007; 68:2986–3008.

Fadus MC, Lau C, Bikhchandani J, Lynch HT. Curcumin: An age-old anti-inflammatory and anti-neoplastic agent. *J Tradit Complement Med.* 2017; 7(3):339–346.

Fang N, Yu S, Badger TM. Comprehensive phytochemical profile of soy protein isolate. *J Agric Food Chem.* 2004; 52:4012–4020.

Frankos VH, Street DA, O'Neill RK. FDA regulation of dietary supplements and requirements regarding adverse event reporting. *Clin Pharmacol Ther.* 2010; 87:239–244.

Frémont L. Biological effects of resveratrol. *Life Sci.* 2000; 66(8):663–673.

Fuchs D, Erhard P, Rimbach G, Daniel H, Wenzel U. Genistein blocks homocysteine-induced alterations in the proteome of human endothelial cells. *Proteomics.* 2005; 5:2808–2818.

Fugh-Berman A. Herb-drug interactions. *Lancet.* 2000; 355:134–138.

Gomes AP, Duarte FV, Nunes P, Hubbard BP, Teodoro JS, Varela AT et al. Berberine protects against high fat diet-induced dysfunction in muscle mitochondria by inducing SIRT1-dependent mitochondrial biogenesis. *Biochim Biophys Acta.* 2012; 1822(2):185–195.

Gonnet M, Lethuaut L, Boury F. New trends in encapsulation of liposoluble vitamins. *J Controlled Rel.* 2010; 146:276–290.

Gulati OP, Ottaway PB. Legislation relating to nutraceuticals in the European Union with a particular focus on botanical-sourced products. *Toxicology.* 2006; 221(1):75–87.

Haider S, Naithani V, Barthwal J, Kakkar P. Heavy metal content in some therapeutically important medicinal plants. *Bull Environ Contam Toxicol*. 2004; 72(1):119–127.

Harati K, Slodnik P, Chromik AM, Goertz O, Hirsch T, Kapalschinski N et al. Resveratrol induces apoptosis and alters gene expression in human fibrosarcoma cells. *Anticancer Res*. 2015; 35:767–774.

Harris ES, Cao S, Littlefield BA, Craycroft JA, Scholten R, Kaptchuk T et al. Heavy metal and pesticide content in commonly prescribed individual raw Chinese herbal medicines. *Sci Total Environ*. 2011; 409(20):4297–4305.

Higdon JV, Delage B, Williams DE, Dashwood RH. Cruciferous vegetables and human cancer risk: Epidemiologic evidence and mechanistic basis. *Pharmacol Res*. 2007; 55:224–236.

Hooper L, Summerbell CD, Thompson R, Sills D, Roberts FG, Moore H et al. Reduced or modified dietary fat for preventing cardiovascular disease. *Cochrane Database Syst Rev*. 2011; 7:Article IDCD002137.

Isbrucker RA, Bausch J, Edwards JA, Wolz E. Safety studies on epigallocatechin gallate (EGCG) preparations. Part 1: genotoxicity. *Food Chem Toxicol*. 2006; 44:626–635.

James MA, Fu H, Liu Y, Chen DR, You M. Dietary administration of berberine or *Phellodendron amurense* extract inhibits cell cycle progression and lung tumorigenesis. *Mol Carcinog.* 2011; 50(1):1–7.

Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CW et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science.* 1997; 275:218–220.

Jones SB, Deprimo SE, Whitfield ML, Brooks JD. Resveratrol-induced gene expression profiles in human prostate cancer cells. *Cancer Epidemiol Biomarkers Prev.* 2005; 14:596–604.

Jung YD, Ellis LM. Inhibition of tumour invasion and angiogenesis by epigallocatechin gallate (EGCG), a major component of green tea. *Int J Exp Pathol* 2001; 82:309–316.

Kalra EK. Nutraceutical—Definition and Introduction. *AAPS PharmSci.* 2003; 5(3):Article 25.

Khan M, Giessrigi B, Vonach C, Madlener S, Prinz S, Herbaceck L et al. Berberine and a Berberis lycium extract inactivate Cdc25A and induce α-tubulin acetylation that correlate with HL-60 cell cycle inhibition and apoptosis. *Mutat Res*. 2010; 683 (1–2):123–130.

Khanduja KL, Bhardwaj A, Kaushik G. Resveratrol inhibits *N*-nitrosodiethylamine-induced ornithine decarboxylase and cyclooxygenase in mice. *J Nutr Sci Vitaminol*. 2004; 50(1):61–65.

Koh HL, Woo SO. Chinese proprietary medicine in Singapore: Regulatory control of toxic heavy metals and undeclared drugs. *Drug Saf.* 2000; 23(5):351–361.

Koro C, Barrett S, Qizilbash N. Cancer risks in thiazolidinedione users compared to other anti-diabetic agents. *Pharmacoepidem Dr S.* 2007; 16(5):485–492.

Kountouri AM, Gioxari A, Karvela E, Kaliora AC, Karvelas M, Karathanos VT. Chemopreventive properties of raisins originating from Greece in colon cancer cells. *Food Funct*. 2013; 4:366–372.

Kronski E, Fiori ME, Barbieri O, Astigiano S, Mirisola V, Killian PH et al. miR181b is induced by the chemopreventive polyphenol curcumin and inhibits breast cancer metastasis via down-regulation of the inflammatory cytokines CXCL1 and-2. *Mol Oncol*. 2014; 8:581–595.

Kruger CL, Murphy M, DeFreitas Z, Pfannkuch F, Heimbach J. An innovative approach to the determination of safety for a dietary ingredient derived from a new source: Case study using a crystalline lutein product. *Food Chem Toxicol*. 2002; 40:1535–1549.

Kumar R, Das M, Ansari KM. Nexrutine(R) inhibits tumorigenesis in mouse skin and induces apoptotic cell death in human squamous carcinoma A431 and human melanoma A375 cells. *Carcinogenesis*. 2012; 33(10):1909–1918.

Kwon KH, Barve A, Yu S, Huang MT, Kong AN. Cancer chemoprevention by phytochemicals: Potential molecular targets, biomarkers and animal models. *Acta Pharmacol Sin*. 2007; 28(9):1409–1421.

Kyselova Z. Toxicological aspects of the use of phenolic compounds in disease prevention. *Interdiscip Toxicol*. 2011; 4(4):173–183.

Lee WJ, Shim JY, Zhu BT. Mechanisms for the inhibition of DNA methyltransferases by tea catechins and bioflavonoids. *Mol Pharmacol*. 2005; 68:1018–1030.

Li H, Forstermann U. Red wine and cardiovascular health. *Circ Res*. 2012; 111:959–961.

Li H, Wang Z, Liu Y. Review in the studies on tannins activity of cancer prevention and anticancer. *Zhong Yao Cai*. 2003; 26:444–448.

Limer JL, Speirs V. Phyto-oestrogens and breast cancer chemoprevention. *Breast Cancer Res*. 2004; 6:119–127.

Lin S, Tsai SC, Lee CC, Wang BW, Liou JY, Shyu KG. Berberine inhibits HIF-1alpha expression via enhanced proteolysis. *Mol Pharmacol*. 2004; 66(3):612–619.

Liu Y, Yu H, Zhang C, Cheng Y, Hu L, Meng X et al. Protective effects of berberine on radiation-induced lung injury via intercellular adhesion molecular-1 and transforming growth factor-beta-1 in patients with lung cancer. *Eur J Cancer*. 2008; 44(16):2425–2432.

Lozak A, Soltyk K, Ostapczuk P, Fijalek Z. Determination of selected trace elements in herbs and their infusions. *Sci Total Environ*. 2002; 289:33–40.

Mahady G, Parrot J, Lee C, Yun G, Dan A. Botanical dietary supplement use in peri- and postmenopausal women. *Menopause*. 2003; 10:65–72.

Martínez-Domínguez G, Plaza-Bolaños P, Romero-González R, Garrido-Frenich A. Analytical approaches for the determination of pesticide residues in nutraceutical products and related matrices by chromatographic techniques coupled to mass spectrometry. *Talanta*. 2014; 118:277–291.

Mazzanti G, Menniti-Ippolito F, Moro PA, Cassetti F, Raschetti R, Cassetti F et al. Hepatotoxicity from green tea: A review of the literature and two unpublished cases. *Eur J Clin Pharmacol*. 2009; 65:331–341.

Meena AK, Bansal P, Kumar S, Rao MM, Garg VK. Estimation of heavy metals in commonly used medicinal plants: A market basket survey. *Environ Monit Assess*. 2010; 170 (1–4):657–660.

Mnif W, Hassine AI, Bouaziz A, Bartegi A, Thomas O, Roig B. Effect of endocrine disruptor pesticides: A review. *Int J Environ Res Public Health*. 2011; 8:2265–2303.

Nair HK, Rao KV, Aalinkeel R, Mahajan S, Chawda R, Schwartz SA. Inhibition of prostate cancer cell colony formation by the flavonoid quercetin correlates with modulation of specific regulatory genes. *Clin Diagn Lab Immunol*. 2004; 11(1):63–69.

Nasri H, Behradmanesh S, Ahmadi A, Rafieian-Kopaei M. Impact of oral vitamin D (cholecalciferol) replacement therapy on blood pressure in type 2 diabetes patients; a randomized, double-blind, placebo controlled clinical trial. *J Nephropathol*. 2014; 3:29–33.

Nasri H, Sahinfard N, Rafieian M, Rafieian S, Shirzad M, Rafieian-kopaei M. Effects of *Allium sativum* on liver enzymes and atherosclerotic risk factors. *J HerbMed Pharmacol*. 2013; 2:23–28.

Nassiri-Asl M, Hosseinzadeh H. Review of the pharmacological effects of *Vitis vinifera* (Grape) and its bioactive compounds. *Phytother Res*. 2009; 23:1197–1204.

Ortiz L, Lombardi P, Tillhon M. Scovassi A. Berberine, an epiphany against cancer. *Molecules*. 2014; 19(8):12349–12367.

Orzechowski AP, Ostaszewski MJ, Berwid SJ. Bioactive substances of plant origin in food—Impact on genomics. *Reprod Nutr Dev*. 2002; 42(5):461–477.

Parasuram RR. Nutraceuticals: An area of tremendous scope. *Int J Res Ayurveda Pharm*. 2011; 2(2):410–415.

Park W, Amin AR, Chen ZG, Shin DM. New perspectives of curcumin in cancer prevention. *Cancer Prev Res*. 2013; 6(5):387–400.

Parrón T, Requena M, Hernández AF, Alarcón R. Environmental exposure to pesticides and cancer risk in multiple human organ systems. *Toxicol Lett*. 2011; 230:157–165.

Penzak SR, Robertson SM, Hunt JD, Chairez C, Malati CY, Alfaro RM et al. Echinacea purpurea significantly induces cytochrome P450 3A activity but does not alter lopinavir-ritonavir exposure in healthy subjects. *Pharmacotherapy*. 2010; 30(8):797–805.

Pereira GC, Branco AF, Matos JA, Pereira SL, Parke D, Perkins EL et al. Mitochondrially targeted effects of berberine [Natural Yellow 18, 5, 6-dihydro-9, 10-dimethoxybenzo (g)-1, 3-benzodioxolo (5, 6-a) quinolizinium] on K1735-M2 mouse melanoma cells: Comparison with direct effects on isolated mitochondrial fractions. *J Pharmacol Exp Ther*. 2007; 323(2):636–649.

Piersen CE. Phytoestrogens in botanical dietary supplements: Implications for cancer. *Integr Cancer Ther*. 2003; 2(2):120–138.

Posadzki P, Watson L, Ernst E. Herb-drug interactions: An overview of systematic reviews. *Br J Clin Pharmacol*. 2013; 75:603–618.

Prasad R, Katiyar SK. Grape seed proanthocyanidins inhibit migration potential of pancreatic cancer cells by promoting mesenchymal-to-epithelial transition and targeting NF-kappaB. *Cancer Lett*. 2013; 334:118–126.

Ramos-Nino ME, MacLean CD, and Littenberg B. Association between cancer prevalence and use of thiazolidinediones: Results from the Vermont diabetes information system. *BMC Med*. 2007; 5:Article 17.

Ranzato E, Martinotti S, Calabrese CM, Calabrese G. Role of nutraceuticals in cancer therapy. *J Food Res*. 2014; 3(4):18–25.

Romagnolo DF, Selmin OI. Flavonoids and cancer prevention: A review of the evidence. *J Nutr Gerontol Geriatr*. 2012; 31(3):206–238.

Ronis MJ, Gomez-Acevedo H, Blackburn ML, Cleves MA, Singhal R, Badger TM. Uterine responses to feeding soy protein isolate and treatment with 17β-estradiol differ in ovariectomized female rats. *Toxicol Appl Pharmacol*. 2016; 297:68–80.

Rowell C, Carpenter DM, Lamartiniere CA. Chemoprevention of breast cancer, proteomic discovery of genistein action in the rat mammary gland. *J Nutr*. 2005; 135:2953S–2959S.

Salas-Salvado J, Martinez-Gonzalez MA, Bullo M, Ros E. The role of diet in the prevention of type 2 diabetes. *Nutr Metab Cardiovasc Dis*. 2011; 21(2):B32–B48.

Sarkar FH, Li Y. The role of isoflavones in cancer chemoprevention. *Front Biosci*. 2004; 9:2714–2724.

Sarma H, Deka S, Deka H, Saikia RR. Accumulation of heavy metals in selected medicinal plants. *Rev Environ Contam Toxicol*. 2011; 214:63–86.

Sato T, Koike L, Miyata Y, Hirata M, Mimaki Y, Sashida Y et al. Inhibition of activator protein-1 binding activity and phosphatidylinositol 3-kinase pathway by nobiletin, a polymethoxy flavonoid, results in augmentation of tissue inhibitor of metalloproteinases-1 production and suppression of production of matrix metalloproteinases-1 and -9 in human fibrosarcoma HT-1080cells. *Cancer Res*. 2002; 62:1025–1029.

Sengottuvelan M, Viswanathan P, Nalini N. Chemopreventive effect of trans-resveratrol—A phytoalexin against colonic aberrant crypt foci and cell proliferation in 1, 2-dimethylhydrazine induced colon carcinogenesis. *Carcinogenesis*. 2006; 27(5):1038–1046.

Sharma R. Nutraceuticals and nutraceutical supplementation criteria in cancer: A literature survey. *Open Nutraceuticals J*. 2009; 2:92–106.

Shirzad H, Kiani M, Shirzad M. Impacts of tomato extract on the mice fibrosarcoma cells. *J HerbMed Pharmacol*. 2013; 2:13–16.

Shirzad H, Shahrani M, Rafieian-Kopaei M. Comparison of morphine and tramadol effects on phagocytic activity of mice peritoneal phagocytes *in vivo*. *Int Immunopharmacol*. 2009; 9:968–970.

Simmen FA, Mercado CP, Zavacki AM, Huang SA, Greenway AD, Kang P et al. Soy protein diet alters expression of hepatic genes regulating fatty acid and thyroid hormone metabolism in the male rat. *J Nutr Biochem*. 2010; 21(11):1106–1113.

Spector D, Anthony M, Alexander D, Arab L. Soy consumption and colorectal cancer. *Nutr Cancer.* 2003; 47:1–12.

Stahl W, Sies H. Bioactivity and protective effects of natural carotenoids. *Biochim Biophys Acta*. 2005; 1740:101–107.

Sun Y, Xun K, Wang Y. Chen X. A systematic review of the anticancer properties of berberine, a natural product from Chinese herbs. *Anticancer Drugs*. 2009; 20 (9):757–769.

Suzuki K, Yahara S, Hashimoto F, Uyeda M. Inhibitory activities of (–)-epigallocatechin-3-*O*-gallate against topoisomerases I and II. *Biol Pharm Bull*. 2001; 24:1088–1090.

Takahashi M, Uechi S, Takara K, Asikin Y, Wada K. Evaluation of an oral carrier system in rats: Bioavailability and antioxidant properties of liposome-encapsulated curcumin. *J Agri Food Chem*. 2009; 57 (19):9141–9146.

Tamadon MR, Baradaran A, Rafieian-Kopaei M. Antioxidant and kidney protection; differential impacts of single and whole natural antioxidants. *J Renal Inj Prev.* 2014; 3:41–42.

Tan HT, Tan S, Lin Q, Lim TK, Hew CL, Chung MC. Quantitative and temporal proteome analysis of butyrate-treated colorectal cancer cells. *Mol Cell Proteomics.* 2008; 7:1174–1185.

Tan S, Seow TK, Liang RC. Koh S, Lee CP, Chung MC et al. Proteome analysis of butyrate-treated human colon cancer cells (HT-29). *Int J Cancer.* 2002; 98:523–531.

Teodoro JS, Duarte FV, Gomes AP. Varela AT, Peixoto FM, Rolo AP et al. Berberine reverts hepatic mitochondrial dysfunction in high-fat fed rats: A possible role for SirT3 activation. *Mitochondrion*. 2013; 13(6):637–646.

Torres AR, Bort A, Morell C, Henche NR, Laviada ID. The pepper's natural ingredient capsaicin induces autophagy blockage in prostate cancer cells. *Oncotarget*. 2016; 7(2):1569–1583.

Toyomura K, Kono S. Soybeans, soy foods, isoflavones and risk of colorectal cancer: A review of experimental and epidemiological data. *Asian Pac J Cancer Prev.* 2002; 3:125–132.

Tripathi YB. Tripathi P, Arjmandi BH. Nutraceuticals and cancer management. *Front Biosci*. 2005; 10:1607–1618.

Tseng SH, Lin SM, Chen JC, Su YH, Huang HY, Chen CK et al. Resveratrol suppresses the angiogenesis and tumor growth of gliomas in rats. *Clin Cancer Res*. 2004; 10(6):2190–2202.

Virk-Baker MK, Nagy TR, Barnes S. Role of phytoestrogens in cancer therapy. *Planta Med*. 2010; 76(11):1132–1142.

Weaver CM, Alekel DL, Ward WE, Ronis MJ. Flavonoid intake and bone health. *J Nutr Gerontol Geriatr.* 2012; 31:239–253.

Wenzel U, Herzog A, Kuntz S, Daniel H. Protein expression profiling identifies molecular targets of quercetin as a major dietary flavonoid in human colon cancer cells. *Proteomics.* 2004; 4:2160–2174.

Wildman REC, Kelley M. Nutraceuticals and functional foods. In: Wildman REC, editor. *Handbook of Nutraceuticals and Functional Foods*. 2nd edition. New York: CRC Press; 2007, pp. 1–9.

Willis MS, Wians FH. The role of nutrition in preventing prostate cancer: A review of the proposed mechanism of action of various dietary substances. *Clin Chim Acta*. 2003; 330:57–83.

Yang CS, Chung JY, Yang GY, Chhabra SK, Lee MJ. Tea and tea polyphenols in cancer prevention. *J Nutr.* 2000; 130:472S–478S.

Yang SH, Kim JS, Oh TJ, Kim MS, Lee SW, Woo SK et al. Genome-scale analysis of resveratrol-induced gene expression profile in human ovarian cancer cells using a cDNA microarray. *Int J Oncol.* 2003; 22:741–750.

Zhang DD. The Nrf2-Keap1-ARE signaling pathway: The regulation and dual function of Nrf2 in cancer. *Antioxid Redox Signal*. 2010; 13:1623–1626.

Zhang X, Gu L, Li J, Shah N, He J, Yang L et al. Degradation of MDM2 by the interaction between berberine and DAXX leads to potent apoptosis in MDM2-overexpressing cancer cells. *Cancer Res.* 2010; 70(23):9895–9904.

Zhou D, Ding N, Du Z, Cui XX, Wang H, Wei XC et al. Curcumin analogues with high activity for inhibiting human prostate cancer cell growth and androgen receptor activation. *Mol Med Rep Mol Med Rep.* 2014; 10:1315–1322.

Zhou JR, Gugger ET, Tanaka T, Guo Y, Blackburn GL, Clinton SK. Soybean phytochemicals inhibit the growth of transplantable human prostate carcinoma and tumor angiogenesis in mice. *J Nutr.* 1999; 129:1628–1635.

Zhou K, Raffoul JJ. Potential anticancer properties of grape antioxidants. *J Oncol*. 2012; 803294.

Zuin VG, Vilegas JHY. Pesticide residues in medicinal plants and phytomedicines. *Phytother Res*. 2000; 14:73–88.

13 Dietary Habits and Susceptibility to Various Cancers

Kimberly Padawer and Yashwant V. Pathak

CONTENTS

13.1 INTRODUCTION

Cancer is ranked one of the leading causes of death in the twenty-first century. In 2018, it is estimated that there will be roughly 18 million new cases of cancer and 10 million cancer deaths. Based on the number of new cases, the most commonly diagnosed forms of cancer around the world (percent of all cases) include lung (12%), breast (12%), colorectal (10%), prostate (7%), stomach (6%), and liver (5%). However, within individual countries, the incidence and mortality due to oncological malignancy varies based on socioeconomic factors. Additionally, incidence of cancer increases with age, with almost a third of cancer diagnoses occurring in adults over the age of 75 years [1,2]. Only about 5% of cancers in the United States occur in individuals below the age of 40 years. Cancer in children and young adults

appear to be more likely due to inherited genetic predisposition, viral infection (HIV, HPV, etc.), exposures to chemotherapy or radiation from treatment of childhood cancer, or exposure to ultraviolet (UV) light from tanning beds or from the sun. These exposures occurring in young individuals play an important role in cancer risk as they age [3].

Cancer risk is due to a combination of both modifiable and nonmodifiable risk factors. Nonmodifiable risk factors include age, race, genetics, and family history, whereas modifiable risk factors include environmental and lifestyle factors such as diet, tobacco use, physical activity, alcohol use, and exposure to carcinogens. It is estimated that roughly half of cancers are potentially preventable with adequate lifestyle modifications taken at an appropriate stage of life. It is important that individuals attempt to minimize potential risk factors and exposures throughout their lifetime in order to prevent malignancy [4]. Due to the importance of modifiable risk factors, adequate public health policies and education can play a significant role in the prevention of cancer. Robust public health interventions have resulted in a decline in various preventable forms of cancer. For example, smoking cessation has shown to reduce lung cancer rates in the United States [4,5].

Nutrition is generally considered an important modifiable risk factor for a multitude of diseases including cardiovascular disease, type 2 diabetes, and cancer. A wholesome diet that includes high intake of fruits, vegetables, and whole grains are recommended to decrease cancer risk [4].

The American Heart Association (AHA) Guidelines recommend the following nutrient composition 20%–35% fat, 45%–65% carbohydrates, and 10%–35% protein for most adults.

Modifiable Risk Factors for Cancer [4]

- Tobacco Smoking
- Physical Activity and Exercise
- Weight, Obesity, and Metabolic Diseases
- Diet and Nutrition
- Alcohol Consumption
- Sun Exposure
- Vaccination (Human papillomavirus, Hepatitis B)

Being physically active decreases the risk of many cancers by reducing body fat, likely by improving immune response, decreasing inflammation, and improving the body's use of insulin. Avoidance of excess caloric intake can prevent obesity-related risk factors.

Individuals come into contact to a wide range of carcinogenic substances throughout their lifetime. Carcinogens can either be naturally occurring or can occur through industrial or manufacturing processes. Oral and lung cancers have been directly linked to carcinogens found in tobacco smoke and chewing tobacco. The rise in the incidence of certain cancers involving the esophagus, colorectal, and stomach are likely due to changes or differences in dietary habits. However, achievable lifestyle

changes like limiting one's calorie consumption, or avoiding foods like red meat, fried foods, or refined sugar can make potentially make a significant difference in risk over the course of a lifetime for certain types of cancers [1,4,5].

13.2 NUTRITION IN CANCER PATIENTS

Nutrition and diet play an essential role in management of individuals with a diagnosis of cancer. Side effects of chemotherapy and radiation treatments can include nausea and mucositis, which often makes receiving adequate nutrition a challenge, especially with patients with head and neck or stomach cancers. Many chemotherapy regimens cause side effects including nausea, vomiting, changes in taste or smell, gastrointestinal side effects, and loss in appetite. Gastrointestinal side effects may alter how the body digests and absorbs nutrients. Weight loss and cachexia occur frequently in patients with late stage cancer. Conversely, weight gain may also occur as a complication of chemotherapy treatment. Cancer patients should attempt to maintain a body mass index (BMI) between 18.5 and 25. Patients with cancer of the head and neck areas often have difficulty swallowing, and may be unable to eat without the assistance of feeding tubes and enteral feeding. In extreme cases, intravenous parenteral nutrition is an option.

Registered dietitians play a central role in the interdisciplinary care of these patients and can make recommendations to assist in changes in nutritional needs in a patient. Adequate nutrition increases the quality of life in these patients and greatly improves patient outcomes. Patients who are unable to receive adequate nutrition from food can benefit from nutrient-fortified beverages and shakes. Doctors may also prescribe medications to improve appetite. Individuals who exercise regularly and have a well-balanced diet have a lower risk of getting cancer, and patients with cancer who exercise generally have a better prognosis and outcome. It is important for those with cancer to maintain good nutrition because cancer survivors are at increased risk of developing secondary cancers and are at higher risk of other metabolic diseases from chemotherapy. Inadequate nutrition and cachexia may also delay healing and prevent continuation of chemotherapy. Individuals treated appropriately for their cancer are now living longer with a diagnosis, and a healthy lifestyle can not only help prevent their cancer from returning but also prevent secondary chronic diseases such as diabetes and kidney disease [3,6,7].

13.3 OBESITY

Calorically dense but often nutritionally poor foods can be obtained inexpensively and conveniently thanks to modern facilities like drive-throughs and meal delivery services. American food service companies cater to consumer demand, which historically has meant that healthier food choices come secondary to palatability. Women and men need an average of 2000 and 2500 calories per day, respectively. A hamburger combo meal from a popular American fast food restaurant, which comes with a large hamburger with toppings (540 calories), medium soda beverage (220 calories), and medium French fries (340 calories) contains 1090 calories for a single meal. An individual who consumes the equivalent of these three times daily

would have a daily surplus of 500 calories, which would result in an average gain of one pound in weight per week [8].

The prevalence of obesity has increased globally with increased availability of food in modern developed countries and predisposition to a sedentary lifestyle. It is a major modifiable risk factor for cardiovascular disease, cancer, and diabetes. It is implicated in about 20% of total cancer-associated mortality. Obese patients also are at higher risk of postoperative infections, poor wound healing, and failure of chemotherapy treatment due to differences in the pharmacokinetics of drugs in overweight individuals. Cancer patients should be educated on how weight loss and positive lifestyle modifications can improve survival because currently most Americans are unaware of the relationship between obesity and cancer. Obese individuals are at a higher risk of certain cancers including gastroenterological, prostate, breast, and gynecological [9]. In addition to direct effects of obesity and cancer, obese individuals suffering from cancer have a poorer cancer prognosis once a diagnosis made [10]. Obese people have a much higher risk of complications and side effects of surgery, resulting in predisposition to mortality after surgery to remove or debulk tumors. Patients are at increased risk of poor wound healing, infection, post-op pneumonia, and other complications specific to each type of surgery [11]. Weight management from healthy eating habits and exercise is a sensible and recommended strategy to prevent cancer and reduce overall burden of the disease. However, studies have shown that the general public have limited awareness of the link between obesity and cancer risk. Overweight patients often misperceive their status and may not know that they are at increased risk of diseases. Healthcare providers should make an effort to educate patients at this risk in order to increase awareness. Patients report higher degrees of success with weight loss when it is discussed with their doctor. However, many healthcare providers may not be properly trained in order to deliver adequate weight management and nutrition counseling [10]. Weight status should be discussed by primary care providers, along with reduction of alcohol use and smoking cessation [9–11].

Obesity is considered to be a proinflammatory state due to increased levels of free fatty acids, interleukins, and other oncogenic cell signaling factors. Increased adipose tissue results in increased levels of active estrogens by expression of aromatase enzymes, which may help drive tumor development. Insulin resistance appears to play a role in cancer progression by activation of oncogenic cellular signaling pathways affecting cellular proliferation and metabolism. Insulin and insulin-like growth factor (IGF) receptors are found to be expressed on malignant cells, and their overactivation can help drive tumor growth. Cancer signal transduction pathways like AKT, Ras, and mitogen-activated protein kinase are downstream targets of these IGF receptors. Additionally, insulin can reduce endogenous sex-hormone binding globulin (SHBG), which effects bioavailability of estrogen [12,13].

13.4 WHOLE GRAINS VERSUS REFINED SUGAR

It is recommended to avoid excess consumption of calories in one's diet and prevent excess body fat. Consumption of simple refined sugars sugary beverages or other foods high in starches or sugars can result in excess caloric intake and are associated

with adverse risk of various cancers. Refined sugars like flour also lack fiber, which has known benefits. Whole-grain wheat, on the other hand, contains multiple healthful bioactive compounds. Bran contains fiber, antioxidants, vitamins, and minerals. The majority of whole-grain fraction is the starchy endosperm component, which, in addition to starches, also contains antioxidants, minerals, and vitamins. Various benefits of whole grains are lost during the refinement process, including loss of fiber. It is recognized that synergy exists in the beneficial components of whole-grain cereals that are lost when individual components are supplemented alone. Whole grains contain many trace elements like zinc and selenium, which are involved in hormone activation and synthesis [14].

13.5 FIBER

The health benefits of a diet containing adequate amounts of fiber are numerous. Adequate fiber intake can help lower the risk of obesity and diabetes by increasing early satiety and preventing spikes in blood sugar. Heart disease, stroke, and other inflammatory-related diseases can be reduced by fiber's effect on lowering blood pressure, cholesterol, and inflammation. Compared to a low-fiber diet, a high-fiber diet does a better job at enhancing satiety, thus helping with weight loss. Some scientists speculate that consuming fibrous whole grain may actually help neutralize some potentially carcinogenic compounds in food [14]. Of note, adequate intake of fiber is important for lower risk of esophageal, gastric, and colorectal cancers. It is recommended that individuals receive enough fiber in their diet by choosing fruits, vegetables, whole grains, and legumes. The majority of Americans do not receive the recommended amount of daily fiber of 14 grams per 1000 calories consumed. In fact, most only receive about half that amount. Fiber is categorized as either being soluble, meaning it absorbs water in the food, which can help slow down the digestive process and help lower spikes in blood sugar. Soluble fiber has also been shown to help reduce LDL cholesterol. Soluble fiber is found in whole grains and fruits and vegetables. Fiber supplements may be used if an individual is unable to get adequate amounts from dietary sources. Soluble fiber supplements are available in the form of methylcellulose, inulin, psyllium, wheat dextrin, among others. Insoluble, or bulk forming fiber, helps maintain regularity and relieve constipation. Insoluble fiber can be found in foods such as nuts, wheat bran, and green leafy vegetables. Insoluble fiber can help deliver antioxidant phenol compounds to the colon where it can prevent colon cancer. Resistant starches, which by definition cannot be broken down by digestion, contain butyrate, which serves as a tumor suppressant. Oligosaccharides like fructans, stachyose, and raffinose also are involved in butyrate production and help stimulate the immune system [15–17].

13.6 ANTIOXIDANTS

Adequate intake of antioxidant vitamins and minerals like carotenoids, α-tocopherol, and vitamin C, either from whole foods or dietary supplements, provide cells protection from oxidative damage. Oxidative damage occurs naturally from cellular metabolism, various enzymatic processes, exercise, radiation, and xenobiotics [18].

This oxidative stress results in damage to cellular components including DNA, lipid membranes, carbohydrates, and proteins. Damage to DNA, if left unrepaired, leads to mutations in genes and may potentially promote cancer phenotypes in cells. Natural antioxidant sources from whole foods like fruits, nuts, legumes, and vegetables help lower the risk of cancer, as well as cardiovascular disease and even all-cause mortality. Receiving sufficient daily requirements of vitamins and minerals is best achieved through the diet; however, alternative sources like vitamin supplements are available. Additionally, a well-balanced diet can ensure that the immune system is strong enough to recognize and eliminate abnormal cancerous cells. Achieving sufficient amounts of nutrition from the diet can prevent cancer from occurring due to their role in metabolic and signaling pathways, which regulate cancer growth [19] (Table 13.1).

Folate (B9), or its synthetic form, folic acid, is a naturally occurring water-soluble vitamin B involved in cellular development and growth. It is an important nutrient needed by the body for many metabolic processes involved in DNA synthesis and maintenance. There are many known associations of folate with various health conditions including cancer, heart disease, dementia, mental health, autism, and birth defects. Deficiencies in folic acid can lead to adverse health effects including neural tube defects, anemia, and certain cancers. Like many vitamins, it appears to be more easily usable by the body when obtained from natural food sources. Foods found to contain the greatest sources of folate include beef liver, leafy green vegetables like spinach, fortified breakfast cereals, and beans. Some countries, including the United States, require that wheat flour is fortified with at least 140 micrograms of folic acid per 100 grams of grain cereal. It is recommended that children receive around 150–300 micrograms (mcg) per day of dietary folate equivalents (DFE), while the average teens and adults obtain 400 mcg per day. Pregnant women should get at least

TABLE 13.1
Important Antioxidants from Food Sources

Antioxidant	Example Food Source	Known Benefit
Vitamin C (ascorbic acid)	Citrus fruits, berries, broccoli, green beans	Immunity, skin health, reduced risk of cancer, cardiovascular disease, and mortality
Vitamin E (α-tocopherol)	Vegetable oils, fresh fruits, vegetables, nuts and seeds	Antiaging, vision, anti-inflammation, reduced risk of stroke, total cancer, all-cause mortality
Carotenoids (β-carotene, lycopene, β-cryptoxanthin)	Carrots, green yellow fruits and vegetables	Eye health, reduced risk of cancer, cardiovascular disease, and mortality
Lutein	Leafy green vegetables	Vision, skin health
Folate	Beef liver, Spinach, Avocado	Reduced risk of cancer, Mental health, fetal development

Source: Lobo, V. et al., *Pharmacogn. Rev*., 4, 118–126, 2010; Aune, D. et al., *Am. J. Clin. Nutr*., 108, 1069–1091, 2018.

600 mcg of folate per day. Women who do not receive adequate folate before and during earlier stages of pregnancy run the risk of giving birth to children with serious birth defects of the brain and spine. Because it is important for pregnant women to receive adequate amounts of folate early on in pregnancy, women and teens who could become pregnant should consume adequate amounts of folate or receive folic acid from prenatal vitamins. Individuals generally require larger amounts of folate as they get older. Folate is available over the counter as a supplement in 1000 mcg (1 milligram) tablets. Patients with nutrient deficiencies such as chronic alcoholics and cancer patients may be prescribed to take folic acid supplements by their doctor. Individuals with a genetic polymorphism in the MTHFR gene are unable to convert active folate and are at increased risk of deficiency. However, it should be noted that folic acid may interact or interfere with certain medications used to treat cancer (methotrexate) or many antiepilepsy drugs like valproate, phenytoin, and carbamazepine. Supplementation may decrease the risk of many forms of cancer; however, higher doses taken in some patients who already have cancer may actually have their cancer progression sped up. However, like many aspects of nutrition and cancer, more studies are needed to further assess the role of folate [20–22].

Foods Highest in Folic Acid

Food	Micrograms (mcg) per Serving	Percent of Daily Requirement (%)
Beef liver (3 ounces)	215	54
Spinach (boiled, ½ cup)	131	33
Breakfast cereals	100	25
Asparagus (4 spears)	89	22
Avocado (raw, ½ cup)	59	15
Rice (½ cup)	54	14
Broccoli (cooked, ½ cup)	52	13
Kidney beans (½ cup)	46	12

Nutrient content available by U.S. Department of Agriculture's National Nutrient Database

Vitamin C, also known as ascorbic acid or ascorbate, is a water-soluble antioxidant with many essential physiological functions. It is a cofactor used by cells in the process of building collagen fibers and aids in the absorption of nonheme iron. This vitamin is important for cellular immunity, with high amounts found in leukocytes. Its carcinogen-neutralizing activity and role in cellular immunity may be why it is a popular area of research in the prevention or treatment of cancer. It is found in various foods including fruits and vegetables. The highest amount of ascorbic acid is found in red and green peppers, oranges, grapefruit, kiwis, and broccoli. Many breakfast cereals in the United States are fortified with vitamin C. Since heat can degrade this vitamin, so it is best consumed from raw fruits and vegetables. Humans are unable to synthesize their own vitamin C and therefore it is an essential dietary requirement. Serum vitamin C is tightly regulated by the body, and excess supplementation is likely to have little benefit. According to the Food and Nutrition Board

at the Institute of Medicine, the recommended daily amount of vitamin C for adults is 90 mg in males and 75 mg in females. Pregnant or lactating women may require up to 120 mg per day. Even though it is water soluble, adults should limit their consumption of vitamin C to 2 grams per day due to the potential for adverse effects. Prolonged excess consumption has been associated with kidney injury due to the breakdown of the vitamin into oxalate leading to the formation of kidney stones, thus should not be used in those with history of kidney disease. A deficiency of vitamin C, also known as scurvy, can lead to bleeding, weakness, anemia, and various other maladies. Scurvy is best known to affect individuals with poor nutrition, and it historically affected malnourished sailors in the eighteenth century or residents of underdeveloped counties. Scurvy can develop in less than a month's time in individuals who lack adequate daily requirements. Smokers require higher daily amounts and are at an increased risk of deficiency, likely due to the increased expenditure of antioxidants from the harmful effects of cigarette smoke. It is a popular dietary supplement available over the counter and advertised for the management or prevention of cold symptoms; however, its efficacy in this use is questionable unless taken before the onset of symptoms [23]. Multiple clinical trials have been performed in cancer patients given intravenous vitamin C either alone or in combination with chemotherapy; however, the results have been mixed or inconclusive. However, it is recommended that individuals with cancer, intestinal malabsorption, or other chronic disease receive adequate amount to prevent deficiency-related complications. Cancer patients should first consult with their oncologist because it and other antioxidants may interfere with chemotherapy [24].

Vitamin E, or α-tocopherol, is a fat-soluble vitamin with antioxidant properties. It is found in vegetable oils, nuts, and seeds. Most adults should consume about 15 mg (about 22 international units, or IUs) of vitamin E daily. Excess supplementation actually appears to be harmful, with consumption greater than 400 IU/day resulting in a significant increase in all-cause mortality. Most Americans, especially individuals on low-fat diets, may be receiving insufficient daily amounts, but deficiency does not appear to display noticeable symptoms like with vitamin C. It has been researched for its potential health benefits for its antioxidant and anti-inflammatory properties. Scientists have looked at how it could be involved in cardiovascular health, prevention of dementia, vision and eye health, and cancer [25]. Major studies investigating the utility of vitamin E in cancer prevention included the HOPE-TOO Trial, Women's Health Study, and the ATBC trial. In the HOPE-TOO trial, which was a randomized double-blinded trial, participants aged ≥55 years were either given 400 IU per day of vitamin E (552 patients) or placebo (586 patients) for an average of 7 years. The authors concluded that supplementation did not prevent cancer or cardiovascular events. There was a decreased incidence of lung cancer, but it did not reach statistical significance [26]. In the Women's Health Study, approximately 40,000 women aged ≥45 years were randomized to receive either 600 IU of natural vitamin E or placebo every other day for an average of 10 years. The authors of this study concluded that vitamin E supplementation does not have a significant role in the prevention of cancers [27]. The ATBC trial was conducted in men, and the patients given 50 mg per day of vitamin E had lower incidence of prostate cancer; however, further studies would be needed to confirm this finding. Current evidence has been insufficient to recommend that vitamin E supplementation can be used to prevent cancers [28].

13.7 ARTIFICIAL SWEETENERS

Artificial sweeteners are preferred by some because of their minimal impact on blood sugar in relation to the fact that their sweetness is much greater than compared to regular table sugar. They are generally considered healthy sugar alternatives for individuals with diabetes. Artificial sweeteners are regulated by the US Food and Drug Administration (FDA) and are "generally recognized as safe." However, they have been frequently scrutinized for a purported increased risk of cancer. One study group in 2006 looked at whether aspartame had the potential to cause cancer in rats. They concluded from the study that aspartame had carcinogenic properties and should not be used as an artificial sweetener. However, FDA challenged their results due to design flaws present in the study and requested the results be retracted. The FDA and other health regulatory agencies have concluded that aspartame is safe based on results of numerous epidemiological studies. In addition to aspartame, the FDA has also concluded that sucralose, acesulfame, and cyclamate do not pose a significant cancer risk [29–31].

Common Artificial Sweeteners [29–31]

Cycalmate	Assugryn, Sucaryl, Banned by FDA in 1970 but still available in certain foreign countries. Blended with saccarin
Aspartame	Equal, NutraSweet, Sugar substitute
Saccharin	Splenda, Sweet'nLow, Sugar substitute
Xylitol	Various commercial food products
	Sugar alcohol. Found in various low sugar foods. May cause GI symptoms. Toxic to dogs
Sorbitol	Chewing gum, candy, toothpaste, mouthwash, laxative effect

13.8 ALCOHOLIC BEVERAGES

There is strong evidence to support the finding that ethanol consumption can predispose an individual to cancer at various locations including esophagus, liver, breast, larynx, and pharynx. It is likely one of, if not the most important modifiable risk factor for cancer. Ethanol is metabolized by the body into acetaldehyde by alcohol dehydrogenase (ADH). Acetaldehyde is a highly toxic substance and it, along with free radicals produced by ethanol metabolism, can damage cellular components like lipids, DNA, and proteins. Chronic exposure can decrease cellular glutathione (GSH) levels. Heavy alcohol consumption in women is related to increased levels of estrogen, which is associated with increased risk of breast cancer. Additionally, various alcoholic beverages may also contain other chemicals introduced via the manufacturing process like nitrosamines. Alcohol can also impair the body's ability to absorb various nutrients due to damage to intestinal mucosa. Chronic alcoholics often suffer from malnutrition from deficiencies in important nutrients such as folate, thiamine, pyridoxine, vitamin A, and calcium. Chronic heavy drinkers have reduced intake of food calories because they receive a greater amount of their daily calories from alcohol consumed. Lean body mass,

which may be protective against cancer, is reduced in alcoholics. The secondary end organ damage to the liver and pancreas caused by excessive alcohol intake can also cause nutritional complications. Limiting consumption of alcohol is recommended by multiple health agencies to reduce the risk of cancer. It is recommended that treatment of alcoholism should include supplementation with vitamins to make up for any deficiency [32–34].

13.9 DIET AND ESOPHAGEAL CANCER

Heartburn is felt as a burning pain in the chest, which often is described in a similar manner as cardiac symptoms. Certain foods can trigger heartburn or acid-reflux including spicy or fatty foods, chocolate, alcohol, caffeine, or peppermint. Esophageal adenocarcinoma is an associated complication of gastroesophageal reflux disease, or GERD, which is when heartburn occurs on a regular basis over at least a 2-week period. In addition to heartburn, regurgitation of food can occur, or even vomiting and difficulty and pain when swallowing [35]. Barrett's esophagus is when abnormal cellular growth (dysplasia) occurs in the lining of the esophagus due to chronic acid reflux from the stomach. Normal esophageal cells lining the lower esophagus are typically squamous epithelial cells. However, in Barrett's esophagus, these squamous cells have differentiated into a more intestinal cell type capable of malignant transformation. Individuals with chronic heartburn symptoms or GERD may want to have an endoscopy in order to test for Barrett's esophagus as directed by a healthcare provider. Endoscopy is a procedure when a small flexible tube is placed down the esophagus in order to view whether tissue is damaged. Additionally, a 24-hour pH study can be performed when endoscopy is inconclusive. However, patients should be made aware of the benefits or risks of the procedure, including cost. If left unmanaged, Barrett's esophagus could potentially lead to esophageal cancer [36].

Antacids can be used in order to neutralize acid from the stomach; however, they should only be taken as needed and are known to interact with certain medications by affecting drug absorption. Other medications such as proton pump inhibitors (PPIs) (e.g., pantoprazole, omeprazole) or histamine 2 receptor antagonists (H2RAs) (e.g., famotidine, ranitidine) may be used to suppress acid production to treat reflux symptoms. PPIs are FDA approved for treating symptomatic GERD and healing erosive esophagitis [37,38]. PPIs are best taken 30 minutes before breakfast and on an empty stomach. Alternatively, acid reflux symptoms can be managed nonpharmacologically with multiple methods including modifications to lifestyle. Weight loss and limiting alcohol should be encouraged. Eating smaller portions but possibly more frequently may help minimize heartburn symptoms. Various activities that trigger or exacerbate heart burn should be avoided including smoking tobacco and consuming spicy or fatty foods and caffeinated or acidic beverages, as previously mentioned. It is advised to avoid lying flat after eating in order to prevent acid reflux. A triangular pillow may be used when lying in bed in order to keep a more elevated position of the head. It is recommended that raising the head of the bed about six to eight inches, or higher than the stomach can prevent reflux [39].

13.10 COLON CANCER, RED MEATS, NITRATES

Consumption of cooked animal meat, including red or processed meats, may be associated with elevated cancer risk due to the fact they contain various chemicals that are known to be carcinogenic. Processed foods are widely available for their convenience to the modern world. Nitrates/nitrites, heme iron, polycyclic aromatic hydrocarbons (PAHs), heterocyclic aromatic amines (HAAs), and N-nitroso compounds are all carcinogenic and are contained in meats [40,41]. Heterocyclic aromatic amines, or HAAs, are chemicals formed via the Maillard reaction when proteins like meats are heated which have been shown to have the property of inducing cancer in animal cells. Creatine, sugars, and amino acids found in meats serve as substrates of this reaction [42,43]. This reaction can occur whenever foods of animal origin are heated, including chicken and fish. The World Cancer Research Fund recommends that individuals limit their weekly intake of red meat to less than 500 grams. Consumption of processed meat should be limited to less than 50 grams weekly. This recommendation is based on strong evidence that frequent consumption of red and/or processed meat increases risk of colorectal cancers. The consumption of red meat was significantly associated with increased rates of breast cancer [40,44].

The food manufacturing process of curing meats such as bacon, hot dogs, and pepperoni is used to prolong shelf-life and give meats a more appealing coloration. These foods are highly popular and consumed to a large degree in the Western world. A diet high in processed meals additionally contains a greater proportion of saturated fats and cholesterol.

Nitrate compounds, which are commonly used as a food additive introduced in the meat curing process, includes nitrate, nitrites, and nitrosamines. They are found in various foods as a preservative. The nitrosamines, such as N-nitrosodimethylamine (NDMA), can increase the risk of developing cancer. Consumption of these compounds are weakly associated with susceptibility of gastric cancer [42].

13.11 MEDITERRANEAN DIET

Epidemiological data may suggest that the "Mediterranean diet," which is a plant-centric diet that may lower the risk of various types of cancers including colorectal, breast, liver, prostate, and gastrointestinal cancer. This diet includes adherence to consumption of olive oil or polyunsaturated fats, legumes, vegetables, and fish. The ratio to monounsaturated to saturated fatty acids is recommended. Researchers are interested in the impact of the Mediterranean diet on cancer risk because individuals located in regions appear to have a lower burden of disease. A meta-analysis concluded that a diet with a high intake of fruits, vegetables, moderation of alcohol, and whole grain could reduce the overall cancer risk, including breast cancer. Risk of colorectal, breast, liver, gastric, gallbladder, head and neck, and biliary cancers were observed. These studies demonstrated that a potential benefit specifically for dairy, fish, and nuts while additional risk of cancer with consumption of meats. Essential polyunsaturated fatty acids include omega-3 and omega-6. Other foods that include monosaturated or polyunsaturated fats include nuts, fish, and vegetable oils. Saturated fats are typically found in red meats and dairy products [43,45].

13.12 KETOGENIC DIET

The ketogenic diet has recently become a new trend for losing weight and it has even been advertised by some as a potential way to help prevent or starve off cancer cells. Its utility as a treatment modality for epilepsy has been extensively demonstrated. It is a low-carbohydrate, high-fat diet in which the body transitions to utilizing fat and ketones as the primary source of ATP production. The fat burning state is referred to as ketosis, which takes 3–4 days after carbohydrates have stopped being consumed. This is partially based on the hypothesis that some cancer cells become more heavily reliant on glucose metabolism as an energy source. The cancer cells cannot then more adapt as readily to lowered glucose availability when an individual is in a ketogenic state. It is common for cancer cells to modulate their metabolism in order to promote growth and survival by increasing the update of glucose and relying heavily on anaerobic metabolism (e.g., glycolysis) despite the fact that oxygen is readily available to the cells. This is known as the Warburg effect, which was discovered in the 1920s when it was observed that tumors were utilizing glucose at a faster rate than surrounding tissue while downregulating oxidative phosphorylation. Even though glycolysis is a generally considered an inefficient means of producing ATP compared to oxidative phosphorylation, it may give cancer cells an advantage when sources of energy are limited within the tumor microenvironment. Additional mechanisms have been proposed to explain how this increased utilization of aerobic glycolysis can allow for increased growth and proliferation.

Early studies performed in mice and other animal models have shown that the ketogenic diet may be able to slow the growth of brain, prostate, and gastric cancer cells. Small human trials have shown some varying degree of success when used in addition to the current standard of care. Randomized controlled trials would need to be performed to in order to determine which cancer genotypes would be likely to respond to this diet in human patients, and where its place in therapy would be located. Additionally, there may be risks involved with the utilization to this diet. For example, a diet that relies heavily on fats for energy may put an individual at increased risk of heart disease. And if the individual in ketosis increases the amount of red meat they consume, then that can actually increase their risk of certain cancers. In order to be successful, the patient would likely need to be consistently adherent with the diet in order for it to be efficacious. Another criticism of the ketogenic diet in use in cancer patients is that it may potentially worsen cachexia in patients. It is strongly recommended that anyone interested in putting themselves into ketosis, especially cancer patients, speak to their doctor or a dietitian before beginning this new diet [46–52].

13.13 MYCOTOXIN AFLATOXIN HAS BEEN FOUND IN CERTAIN FOODS

Aflatoxins are fungus-derived toxins that are food contaminants. Aflatoxin B1 is the most carcinogenic to humans and can be found in food grains and is widespread in Sub-Saharan regions of Africa and Southeastern Asia. It is produced by *Aspergillus* species and can be found as a contamination of stored grain crops in warmer weather conditions. This is more likely to occur in low-income countries with poor sanitary and/or food handling practices.

After being taken up by the liver, the toxin is metabolized by cytochrome P450 enzymes where they form a highly reactive epoxide capable of forming complexes with various cellular components. Reaction to the active form of the toxin with DNA can cause double strand breakage, potentially leading to pro-oncogenic mutations including mutations in the p53 tumor suppressor gene. Individuals are at increased risk of hepatocellular carcinoma if repeatedly exposed to aflatoxin contaminated food. This highlights the importance of proper food handling and storage techniques and the downstream implications to public health and safety [53].

13.14 CONCLUSION

Diet may affect susceptibility specific types of cancers more than others. Studying the influence of diet on cancer may be challenging due to the fact that individuals who have a healthy diet also tend to have a healthier lifestyle as well. Unhealthy dietary patterns seem to be associated with a higher risk of colon and colorectal cancers, particularly in women. Colon cancer risk may be reduced, however, with a diet rich in fiber. Epidemiological evidence supports the hypothesis that unhealthy diet is associated with increased risk of breast, pancreatic, lung, and prostate cancers. Alcohol consumption may increase estrogen concentrations and increase risk of breast cancers. Alcohol should be consumed in quantity of no more than 1 serving or wine or beer per day. A diet rich in antioxidants may help prevent lung cancer by countering the detrimental and inflammatory effects of smoking. An antioxidant-rich diet can potentially help prevent different types of cancers. Differences in body mass index (BMI) and smoking status differ between individuals with healthy dietary patterns versus unhealthy ones. Higher amounts of body fat in obese individuals can be considered a low-grade state of chronic inflammation.

Overall, dietary habits are known to have an important role in the susceptibility of various cancers. Adherence to a healthy diet containing 2–3 cups of fruits and vegetables per day and 13 ounces of meat per week reduced that risk. Avoidance of red and processed meat, sugary beverages and sodas, and refined carbohydrates can also decrease the risk. Not only does the content of foods matter but also the quantity consumed. Cancer has a significant burden on society in terms of cost but also morbidity and mortality. Since it is a modifiable risk factor, individuals, health organizations, and governments can all play a role in helping to mitigate the risk of cancer due to diet. This risk can be minimized by adherence to a healthy diet and supplementing with appropriate nutrients if they are unable to be obtained through foods. Healthcare practitioners and public health officials play an important role in educating the populace in healthy dietary habits to reduce the risk of cancer through both primary and secondary preventions [54].

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394–424.
2. Centers for Disease Control and Prevention (CDC). (2016). National Center for Health Statistics Morbidity. Retrieved from: https://www.cdc.gov/nchs/fastats/cancer.htm.

3. National Cancer Institute. (2018). Adolescents and Young Adults with Cancer. Retrieved from https://www.cancer.gov/types/aya.
4. Stein CJ, Colditz GA. Modifiable risk factors for cancer. *Br J Cancer*. 2004;90(2):299–303.
5. Puckett M, Neri A, Underwood JM, Stewart SL. Nutrition and physical activity strategies for cancer prevention in current national comprehensive cancer control program plans. *J Community Health*. 2016;41(5):1013–1020. doi:10.1007/s10900–016-0184–8.
6. Rock CL, Doyle C, Demark-Wahnefried W et al. Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin*. 2012;62(4):243–274.
7. Ng AK, Travis LB. Second primary cancers: An overview. *Hematol Oncol ClinNorth Am*. 2008;22(2):271–289.
8. Fast Food and Nutrition. (2018). Fast Food Nutrition. Retrieved from https://fastfoodnutrition.org.
9. Ligibel JA, Alfano CM, Courneya KS et al. American society of clinical oncology position statement on obesity and cancer. *J Clin Oncol*. 2014;32(31):3568–3574.
10. Pool AC, Kraschnewski JL, Cover LA, Lehman EB, Stuckey HL, Hwang KO, Pollak KI, Sciamanna CN. The impact of physician weight discussion on weight loss in US adults. *Obes Res Clin Pract*. 2014;8(2):e131–e139.
11. Ri M, Aikou S, Seto Y. Obesity as a surgical risk factor. *Ann Gastroenterol Surg*. 2017;2(1):13–21.
12. Arcidiacono B, Iiritano S, Nocera A, Possidente K, Nevolo MT, Ventura V, Foti D, Chiefari E, Brunetti A. Insulin resistance and cancer risk: An overview of the pathogenetic mechanisms. *Exp Diabetes Res*. 2012;2012:789174.
13. Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. *Nat Rev Cancer*. 2008;8(12):915–928. doi:10.1038/nrc2536.
14. Fardet A. New hypotheses for the health-protective mechanisms of whole-grain cereals: What is beyond fibre? *Nutr Res Rev*. 2010;23(1):65–134.
15. Song M, Garrett WS, Chan AT. Nutrients, foods, and colorectal cancer prevention. *Gastroenterology*. 2015;148(6):1244–60.e16.
16. Anderson JW, Baird P, Davis RH Jr, Ferreri S, Knudtson M, Koraym A, Waters V, Williams CL. Health benefits of dietary fiber. *Nutr Rev*. 2009;67(4):188–205.
17. Wu AH, Tseng CC, Hankin J, Bernstein L. Fiber intake and risk of adenocarcinomas of the esophagus and stomach. *Cancer Causes Control*. 2007;18(7):713–722.
18. Lobo V, Patil A, Phatak A, Chandra N. Free radicals, antioxidants and functional foods: Impact on human health. *Pharmacogn Rev*. 2010;4(8):118–126.
19. Aune D, Keum N, Giovannucci E, Fadnes LT, Boffetta P, Greenwood DC, Tonstad S, Vatten LJ, Riboli E, Norat T. Dietary intake and blood concentrations of antioxidants and the risk of cardiovascular disease, total cancer, and all-cause mortality: A systematic review and dose-response meta-analysis of prospective studies. *Am J Clin Nutr*. 2018;108(5):1069–1091.
20. NIH Office of Dietary Supplements. (2018). Fact Sheet for Health Professionals. Retrieved from: https://ods.od.nih.gov/factsheets/Folate-Consumer/.
21. Pieroth R, Paver S, Day S, Lammersfeld C. Folate and its impact on cancer risk. *Curr Nutr Rep*. 2018;7(3):70–84.
22. Crider KS, Bailey LB, Berry RJ. Folic acid food fortification-its history, effect, concerns, and future directions. *Nutrients*. 2011;3(3):370–384.
23. NIH Office of Dietary Supplements. (2018). Fact Sheet for Health Professionals. Retrieved from: https://ods.od.nih.gov/factsheets/VitaminC-HealthProfessional/.
24. NIH National Cancer Institute. (2018). High-Dose Vitamin C for Health Professionals. Retrieved from: https://www.cancer.gov/about-cancer/treatment/cam/hp/vitamin-c-pdq.
25. NIH Office of Dietary Supplements. (2018). Vitamin E Fact Sheet for Health Professionals. Retrieved from: https://ods.od.nih.gov/factsheets/VitaminE-HealthProfessional/.

26. Lonn E, Bosch J, Yusuf S et al. HOPE and HOPE-TOO Trial Investigators. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: A randomized controlled trial. *JAMA*. 2005;293(11):1338–1347.
27. Lee IM, Cook NR, Gaziano JM, Gordon D, Ridker PM, Manson JE, Hennekens CH, Buring JE. Vitamin E in the primary prevention of cardiovascular disease and cancer: The Women's Health Study: A randomized controlled trial. *JAMA*. 2005;294(1):56–65.
28. Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med*. 1994;330(15):1029–1035.
29. National Cancer Institute. (2018). Artificial Sweeteners and Cancer. Retrieved from: https://www.cancer.gov/about-cancer/causes-prevention/risk/diet/artificial-sweeteners-fact-sheet.
30. Food and Drug Administration. (2018). FDA Statement on European Aspartame Study. Retrieved from: https://www.fda.gov/food/ingredientspackaginglabeling/foodadditivesingredients/ucm208580.htm.
31. Marinovich M, Galli CL, Bosetti C, Gallus S, La Vecchia C. Aspartame, low-calorie sweeteners and disease: Regulatory safety and epidemiological issues. *Food Chem Toxicol*. 2013;60:109–115.
32. McKillop IH, Schrum LW. Alcohol and liver cancer. *Alcohol*. 2005;35(3):195–203.
33. Dumitrescu RG, Shields PG. The etiology of alcohol-induced breast cancer. *Alcohol*. 2005;35(3):213–225.
34. Baena Ruiz R, Salinas Hernández P. Diet and cancer: Risk factors and epidemiological evidence. *Maturitas*. 2014;77(3):202–208.
35. Palladino-Davis AG, Mendez BM, Fisichella PM, Davis CS. Dietary habits and esophageal cancer. *Dis Esophagus*. 2015;28(1):59–67.
36. Rubenstein JH, Scheiman JM, Sadeghi S, Whiteman D, Inadomi JM. Esophageal adenocarcinoma incidence in individuals with gastroesophageal reflux: Synthesis and estimates from population studies. *Am J Gastroenterol*. 2011;106(2):254–260.
37. National Comprehensive Cancer Network. (2018). Esophageal and Esophagogastric Junction Cancers. Retrieved from: http://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf.
38. Prilosec (omeprazole). [package insert] Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2012.
39. Kahrilas P. Patient information: Acid reflux (gastroesophageal reflux disease) in adults (beyond the basics). (2018). Wolters Kluwer Health. Retrieved from: www.uptodate.com/contents/acid-reflux-gastroesophageal-reflux-disease-in-adults-beyond-the-basics.
40. Wiseman M. The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: A global perspective. *Proc Nutr Soc*. 2008;67(3):253–256.
41. Knize MG, Salmon CP, Pais P, Felton JS. Food heating and the formation of heterocyclic aromatic amine and polycyclic aromatic hydrocarbon mutagens/carcinogens. *Adv Exp Med Biol*. 1999;459:179–193.
42. Robbana-Barnat S, Rabache M, Rialland E, Fradin J. Heterocyclic amines: Occurrence and prevention in cooked food. *Environ Health Perspect*. 1996;104(3):280–288.
43. Schwingshackl L, Schwedhelm C, Galbete C, Hoffmann G. Adherence to Mediterranean diet and risk of cancer: An updated systematic review and meta-analysis. *Nutrients*. 2017;9(10):1063–1087.
44. Diallo A, Deschasaux M, Latino-Martel P, Hercberg S, Galan P, Fassier P, Allès B, Guéraud F, Pierre FH, Touvier M. Red and processed meat intake and cancer risk: Results from the prospective NutriNet-Santé cohort study. *Int J Cancer*. 2018;142(2):230–237.
45. Bravi F, Spei ME, Polesel J et al. Mediterranean diet and bladder cancer risk in Italy. *Nutrients*. 2018;10(8):1061–1071.

46. Schwartz KA, Noel M, Nikolai M, Chang HT. Investigating the ketogenic diet as treatment for primary aggressive brain cancer: Challenges and lessons learned. *Front Nutr.* 2018;5:11.
47. Vergati M, Krasniqi E, Monte GD, Riondino S, Vallone D, Guadagni F, Ferroni P, Roselli M. Ketogenic diet and other dietary intervention strategies in the treatment of cancer. *Curr Med Chem*. 2017;24(12):1170–1185.
48. Liberti MV, Locasale JW. The Warburg effect: How does it benefit cancer cells? *Trends Biochem Sci*. 2016;41(3):211–218.
49. Barañano KW, Hartman AL. The ketogenic diet: Uses in epilepsy and other neurologic illnesses. *Curr Treat Options Neurol*. 2008;10(6):410–419.
50. Zhou W, Mukherjee P, Kiebish MA, Markis WT, Mantis JG, Seyfried TN. The calorically restricted ketogenic diet, an effective alternative therapy for malignant brain cancer. *Nutr Metab (Lond)*. 2007;4:5.
51. Freedland SJ, Mavropoulos J, Wang A et al. Carbohydrate restriction, prostate cancer growth, and the insulin-like growth factor axis. *Prostate*. 2008;68(1):11–19.
52. Otto C, Kaemmerer U, Illert B, Muehling B, Pfetzer N, Wittig R, Voelker HU, Thiede A, Coy JF. Growth of human gastric cancer cells in nude mice is delayed by a ketogenic diet supplemented with omega-3 fatty acids and medium-chain triglycerides. *BMC Cancer.* 2008;8:122.
53. Hamid AS, Tesfamariam IG, Zhang Y, Zhang ZG. Aflatoxin B1-induced hepatocellular carcinoma in developing countries: Geographical distribution, mechanism of action and prevention. *Oncol Lett*. 2013;5(4):1087–1092.
54. Grosso G, Bella F, Godos J, Sciacca S, Del Rio D, Ray S, Galvano F, Giovannucci EL. Possible role of diet in cancer: Systematic review and multiple meta-analyses of dietary patterns, lifestyle factors, and cancer risk. *Nutr Rev.* 2017;75(6):405–419.

14 Indian Diet and Cancer Prevention

Vasudha Pritipaul, Asra Sami, and Sheeba Varghese Gupta

CONTENTS

14.1 INTRODUCTION

The use of chemoprophylaxis occurring in natural substances in fruits, vegetables, herbs, and spices is increasing significantly nowadays, as recent research studies suggest that they contain chemicals that may reduce the incidence of cancer [1]. Substances that are potential cancer-preventing compounds are likely to have one or more properties such as the ability to prevent DNA damage, enhance DNA repair, and augment apoptosis of damaged cells. They should also be able to improve immunosurveillance, reduce tumor growth, and prevent metastases [2]. This implies that the consumption of fresh aliments diminishes the risk of carcinogenesis in the body. One particular diet that encompasses fresh vegetables and many spices is the Indian diet, and this diet has the potential to prevent cancer.

The Indian diet is one of the most diverse in the world, stemming from a multitude of cultural and religious backgrounds. Indian cuisine is known to comprise a myriad of spices adding flavor to fresh, natural ingredients [3]. A few common spices used in the dishes prepared are turmeric, black pepper, and amrita bindu. Several research studies have demonstrated the cancer-combating effect of these spices. Turmeric, an ingredient common in Indian curry powder, is the most studied and has been found to suppress and destroy blood cancer cells. Turmeric is also a potent antioxidant and anti-inflammatory agent [4].

Apart from the heavy use of spices in this cuisine, the Indian diet comprises a variety of vegetarian dishes, as vegetarianism is prevalent in Indian communities. A vegetarian diet can be considered to be cancer preventive, as it is high in dietary fiber and phytochemicals and eliminates the intake of potential carcinogens found in red meat. According to a report by the International Agency for research on cancer, red and processed meats are sources of essential carcinogens [5].

The cancer incidences in India are considered to be among the lowest in the world in an analysis by the Institute of Health Metrics and Evaluation, Washington University. Figure 14.1 demonstrates the cancer incidence risk in various regions of the world.

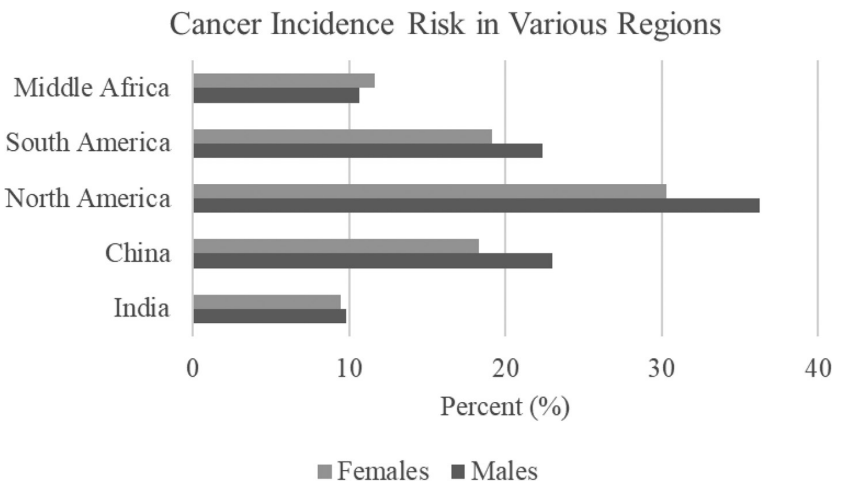


FIGURE 14.1 Cancer incidence among people aged between 0 and 74, all cancers considered.

This chapter's focus is on the common spices used in the Indian diet and their cancer-preventive effects as well as how a vegetarian diet can help reduce the risk of getting cancer.

14.2 VEGETARIANISM IN INDIA

Vegetarianism is a diet that involves little to no consumption of meat, poultry, and fish or meat products. One of the largest vegetarian communities of the globe is India, with 37.71% of the population adopting a vegetarian diet [6]. The four main types of vegetarians, which are prevalent in India are vegans, ovo-lacto-vegetarians, Jain vegetarians, and lacto-vegetarians. Vegans consume no meat or meat products, and their diet consists only of plant-based food products, ovo-lacto-vegetarians' diet includes eggs and milk but excludes any other animal product, and the Jain diet consists of no products harvested under the ground and no meat, but includes dairy products.

Most people in India follow a vegetarian diet because of their religious beliefs. About one-third of Indians are lacto-vegetarians, and this form of vegetarianism was popularized during the rule of Emperor Ashoka of the Maurya Empire. He was a promoter of Buddhism [7]. Vegetarianism is less prevalent amongst Sikhs, Muslims, Christians, Bahais, Parsis, and Jews [8]. Several studies have demonstrated that consumption of meat has been linked to a variety of cancers, while a vegetarian diet can be considered a cancer preventive diet [9].

Figure 14.1 demonstrates the percentage of vegetarians in every state in India. The state of Rajasthan has the highest population of vegetarians with 81.2% of its population consuming no meat, fish, or poultry [10], while the state of Telangana has the fewest consumers of a vegetarian diet with only 1.3% of the population being vegetarian (Figure 14.2) [11].

14.2.1 Vegetarian Proteins as Cancer-Preventive Agents

The main proteins eaten in a vegetarian Indian diet are legumes such as peas, beans, lentils, peanuts, and other podded plants [12]. Pulses contain a wide range of nutrients and non-nutrient bioreactive microconstituents that can be protective against cancers such as resistant starch, which contain protease inhibitors, nonstarch polysaccharides, which contain saponins, oligosaccharides, which contain phytosterols and folates, which are the primary sources of lectins and selenium. These phytochemicals, if consumed in adequate quantities, may help in protecting one from cancer [2]. However, in a recent report from the World Cancer Research Fund and American Institute for Cancer Research, there was a limited suggestive evidence for a protective effect on cancers, but Aune et al (2009) investigated the relationship between legume intake and the risk of cancer and the result suggested that higher the consumption of legumes, the lesser the risk of developing certain types of cancers such as cancers of the digestive tract and this includes oral cavity and pharynx, esophagus, larynx, stomach, and colorectum [12].

14.2.2 Components of Legumes and Their Cancer-Preventive Properties

Dietary fiber is defined as "that part of plant material in the diet which is resistant to enzymatic digestion which includes cellulose, noncellulosic polysaccharides such as

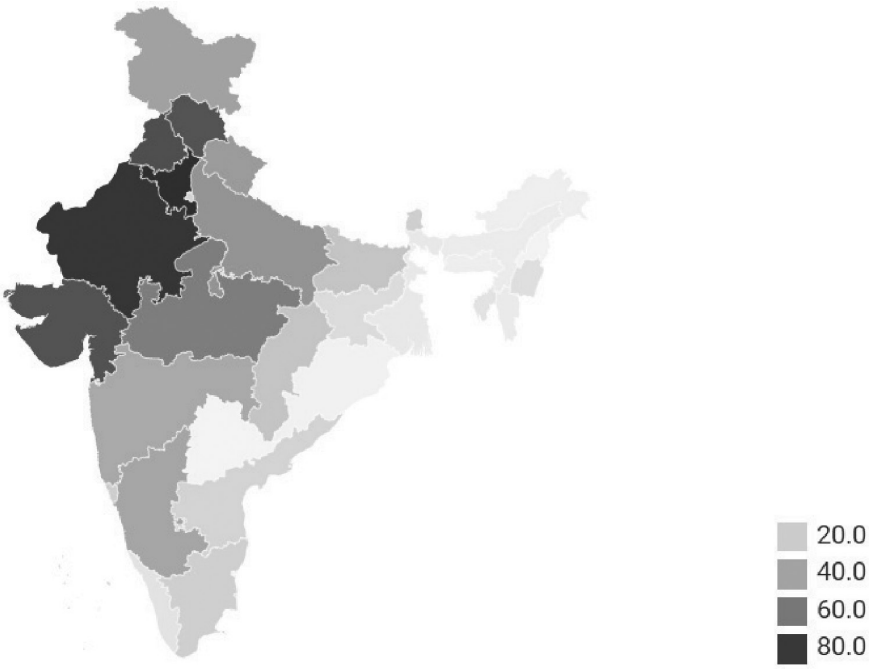


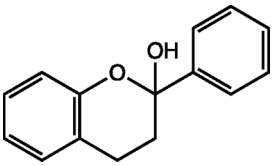
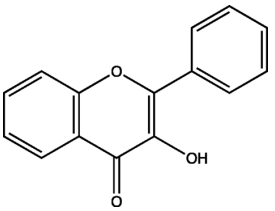
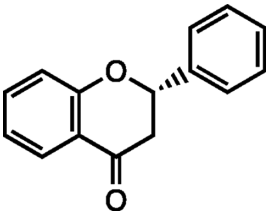
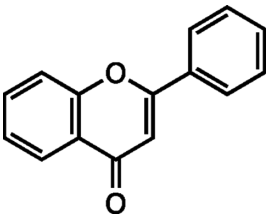
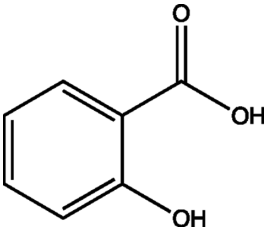
FIGURE 14.2 Percentage of vegetarians in India.

hemicellulose, pectic substances, gums, mucilages, and non-carbohydrate component lignin" [13]. Dietary fibers from pulses play a significant role in breast, colon, and colorectal cancer prevention through various mechanisms [14]. They increase the fecal bulk, which dilutes the number of carcinogens, especially tumor promoters like secondary bile acids [15]. Dietary fibers also increase the viscosity of the food digested, and this decreases the time of proteolytic fermentation and decreases the contact between potential carcinogens and mucosal cells [16]. The dietary pectin is a fiber that produces high amounts of butyrate during fermentation [17]. There is evidence of butyrate as a cancer-protective chemical against colorectal cancer from studies in carcinogen-induced rodent models of this malignancy [18].

Resistant starch from pulses is a complex carbohydrate that is resistant to degradation in the small intestine by α-amylase, an enzyme that digests starch [19]. In vitro studies with human feces suggest that the fermentation of the resistant starch produces butyrate, which, as mentioned above, is cancer protective and also downregulates Bcl2, which acts as an oncogene when it prevents apoptosis [14].

Pulses are rich in phenolic compounds, and many phenolic compounds are known to have anticancer properties. These compounds are important for plants, as they have different functions such as coloring the leaves and the fruits and protecting the plants against predators [20]. Table 14.1 shows the several phenolic acids and how they protect against cancers.

TABLE 14.1
Polyphenols and the Herbs and Spices Where They Are Found

Polyphenols		
Class	**Subclass**	**Examples of Compounds and Herbs and Spices**
Flavonoids	Flavanols 	Catechin • Nutmeg
	Flavonols 	Quercetin • Basil, Coriander, Cumin, Fennel Kaempferol • Basil, Coriander, Cumin, Fennel Isorhamnetin • Dill, Parsley, Tarragon
	Flavanones 	Hesperitin • Peppermint Naringenin • Rosemary Eriodictyol • Peppermint
	Flavones 	Apigenin • Parsley, Thyme Luteolin • Oregano, Parsley, Peppermint, Rosemary
Phenolic Acids	Hydroxybenzoic acid derivatives 	Vanillic acid • Sage Gallic acid • Thyme Salicylic acid • Cumin

14.2.3 Meat Consumption in Indian Diet

Indians have the lowest rate of meat consumption according to a report by the United Nations Food and Agriculture Organization (UNFAO) in 2007. Meat consumption is however increasing, and according to Fiala (2008), if the meat consumption trend remains along the same line, the rates would be higher by 72% in 2030 than the rate of meat consumption recorded in the year 2000 [21]. The current average annual supply of meat per capita, in carcass weight, is below 5 kg in India [22].

Chicken is the meat protein that is the most eaten in India [23]. Meat preference is also related to the cultural criteria the consumer is abiding by or to their religious beliefs. For instance, Hinduism followers do not eat cattle meat and Islam followers do not eat pork [22]. Goat is the next most preferred meat in India and about 95% of the goat meat produced is consumed locally. Fish is popular in coastal areas of the country, and pork is consumed mainly in the northeastern regions [22].

14.2.4 Compounds from Meat Causing Tumors and Cancers

Red meat such as lamb, pork, and beef as well as processed meat such as bacon, chicken nuggets, salted and cured meats, luncheon meats, and hot dogs have been associated with higher risks of developing certain types of cancers as shown in Figure 2.1. Four main cancers have been associated with the intake of meat, and they are colorectal cancer, breast cancer, prostate cancer, and pancreatic cancer. Animal studies and human studies have shown evidence that there are meat carcinogens, such as heterocyclic amines (HCAs) and polycyclic aromatic amines (PAHs), which enmesh that they have a role to play in the pathogenesis of cancer [24].

Heterocyclic amines (HCAs) are potent mutagenic compounds found in cooked meats. These compounds are formed from the reaction of creatine and creatinine, amino acids, and sugar [24]. The higher the temperature used to cook the meat and longer cooking time creates more HCAs in meat. The most mass-abundant HCAs detected in meat are 2-amino-1-methyl-6-phenylimidazo (4,5-b) pyridine (PhIP) and 2-amino-3,8-dimethylimidazo (4,5-f) quinoxaline (MeIQx). These HCAs are also the most readily absorbed in the body [25].

Most HCAs are mutagenic in bacterial mutagenicity assays, and many of them are carcinogenic when administered to laboratory animals such as rodents and nonhuman primates [26,27]. Nineteen HCAs have been identified, and ten of them were tested for carcinogenicity. The results demonstrated that all ten of them induced tumors in rodents at multiple sites [28,29]. The tumors were found mainly in the large intestine in rodent models [30].

HCAs require metabolic activation to act as a mutagen or a carcinogen, and therefore, the cancer risk posed to humans by the intake of HCAs through food may depend on the extent to which the compound has been metabolized.

Polycyclic aromatic amines (PAHs) are formed by incomplete combustion of organic materials. Grilling meat over a direct flame, resulting in fat/meat juices dripping onto the fire, yields to the production of PAHs such as benzo(a)pyrene

(BaP), which adhere to the surface of the food [24]. PAHs have been found mainly in charcoal-broiled, grilled, and smoked meats, and such cooked meats contain the highest levels of BaP, up to 4 ng BaP per gram of cooked meat [31]. PAHs, in order to be excreted, need to be metabolized, and the resulting metabolites can damage DNA. When BaP is given to rodents as part of their diet, tumors of the forestomach, esophagus, and tongue were diagnosed [32].

14.3 SPICES AND ADDITIVES PREVENTING CANCER

In Indian cuisine, the dishes served are known to comprise a plethora of spices. Other than having flavor-enhancement characteristics, spices have been known to have medicinal properties [33]. The definition of a spice according to the FDA is "Aromatic vegetable substances, in the whole, broken, or ground form, whose significant function in food is seasoning rather than nutrition" and the spices "are true to name, and from them no portion of any volatile oil or other flavoring principle has been removed" [34]. From the definition stated, it can be implied that the spices are used in their most pristine forms and therefore all the nutritive values are conserved for a maximum benefit.

Phytochemicals are compounds found in spices, and these compounds are known to have chemoprotective properties. These substances are formed during secondary metabolisms in plants. They are not vital for the plants' tissue growth, storage, or energy production but are important for the viability of the plant in nature. The three main pathways through which the phytochemicals are formed are the shikimate pathway, the cinnamic acid pathway, and the isoprenoid pathway [35]. The shikimate pathway provides three end products, namely, phenylalanine, tryptophan, and tyrosine [36]. Phenylalanine starts the cinnamic acid pathway and produces phenolic acids, coumarins, flavonoids, isoflavonoids, and lignans [35]. Pyruvic acid, formed during early photosynthesis, starts the isoprenoid pathway and this pathway produces terpenes. Table 14.2 show the sources and subfamilies of some phytochemicals and in which spices they can be found [33].

14.3.1 Curcumin

Curcuma Longa, or turmeric, is one of the most commonly used spices in Indian dishes. This yellow-orange spice is a critical ingredient in many Indian dishes, providing a unique flavor and color to the food. In addition to its culinary value, turmeric is known for its perceived health benefits in Ayurveda, traditional medicine in India. It has been used as a treatment to bruises and sprains and as an antiseptic. As this spice has been brought to the attention of modern-day researchers, many began to believe that there may be a link between the prevalence of turmeric in the Indian diet and the low rates of certain cancers. This sparked many experiments and clinical trials.

As the fundamental component of turmeric, curcumin was isolated and studied as part of the effort to pinpoint the source of turmeric's health benefits. Curcumin's ability to target cancer cells and its role as an anti-inflammatory agent reveal the potential advantages of using the ancient spice to limit or prevent cancer.

TABLE 14.2
Terpenes and Examples of Herbs and Spices Containing Terpenes

Terpenes	
Class	**Examples of Compounds and Herbs & Spices**
Monoterpenes	Camphor • Thyme, Sage, Rosemary, Marjoram, Fennel, Coriander, Basil Citral • Thyme, Sage Limonene • Cumin, Thyme, Rosemary, Caraway, Mint, Dill, Celery seed, Sage, Coriander, Fennel, Marjoram Menthol • Peppermint, Basil Perillyl alcohol • Spearmint, Sage
Sesquiterpenes	Humulene • Turmeric, Coriander
Diterpenes	Retinol • Paprika, Red pepper, Chili powder
Triterpenes	Glycyrrhizin • Licorice
Tetraterpenes	Carotenoids • Mustard, Fennel, Cumin, Coriander, Sage

14.3.1.1 Curcumin's Ability to Target Cancer Cells

Since curcumin has been found to target and kill cancer cells, researchers have studied it as a potential alternative to cancer treatments that target both cancer cells and healthy cells. Curcumin can lead to apoptosis, or cell death, through the regulation of gene expression. As apoptosis is an effective way to remove cancer cells, the tendency of curcumin to induce apoptosis is of interest in many studies.

Proteases called caspases are involved in the process of apoptosis. A research study exploring lung cancer revealed that there was an activation of caspase-3 and caspase-9 with the addition of curcumin. The activation of these caspases can subsequently lead to apoptosis and the reduction of cancer cell proliferation [37,38].

Studies involving the function of curcumin in colorectal cancer indicated that the compound is a possible contributor to the low rates of colorectal cancer in India. With curcumin, there was limited growth of the adenocarcinoma cell lines of the human colon. Epidermal growth factor receptor (EGFR) is commonly present in colorectal tumors, but it is reduced with the addition of curcumin through the suppression of gene expression [37,39].

By inducing the expression of death receptors that lead to apoptosis, curcumin can effectively lead to the removal of cancer cells in a manner that is more selective than many current cancer treatment options. The selectivity of curcumin to cancer cells may be due to the lower glutathione levels in cancer cells, the specific

genes expressed by cancer cells, or a generally increased uptake of curcumin by cancer cells [38].

14.3.1.2 Curcumin as an Anti-inflammatory Agent

Inflammation plays a significant role in many cancers by creating an environment more favorable for cancer cells, contributing to their continued survival and reproduction [40]. Anti-inflammatory properties in curcumin have been discovered, perhaps due to the methoxy groups present in the structure of the compound [41].

NF-κB is a transcription factor involved in the regulation of inflammatory genes. This transcription factor is a target of curcumin, and through the inhibition of NF-κB, inflammation can be significantly reduced. This can lead to the subsequent reduction of cancer cell proliferation [37].

Clinical trials have indicated that curcumin is useful in reducing symptoms present in many cancer patients, like cachexia, which involves weakness of the body and the wasting of skeletal muscle. This is most likely because the symptoms reduced by curcumin are caused by or aggravated by inflammation [37].

14.3.1.3 Limitations of Curcumin

However, although the benefits of curcumin seem advantageous, the limitations must also be taken into consideration. Despite considerable research, the unknown effect of curcumin's interaction with the drugs used for cancer treatment prevents it from being commonly used to reduce the symptoms of chemotherapy. Another concern in herbal compounds like curcumin is that they sometimes contain impurities and may have unexpected side effects based on the specificities of individual patients [42].

The bioavailability of curcumin when introduced to patients also must be considered, as only around 1% of orally administered curcumin was found to be bioactive, partly due to its hydrophobic properties. In an effort to increase bioavailability, lipid nanoparticles and other similar techniques are being tested [43].

14.3.2 Black Pepper

Piper nigrum or black pepper is a spice that originated in Kerala, a region in India. Over time, black pepper became accessible to the rest of the world through trade [44]. It remains a staple ingredient in the Indian diet.

Piperine is a constituent of black pepper that has been found to have anticancer functions. Piperine, with its nitrogen and ring structure, is an alkaloid, and many alkaloids contain properties that aid in the formulation of drugs [45]. Through the induction of cancer cell apoptosis, the regulation of specific genes that contribute to cancer growth, and the interruption of the cell cycle of cancer cells, piperine is able to block cancer in many experiments. Piperine also contains antioxidative properties, enabling it to impact cancer growth.

14.3.2.1 Piperine's Anticancer Properties

Similar to curcumin, piperine also induces apoptosis in order to limit the growth and spread of cancer. A study utilizing 4T1 mouse breast cancer cells revealed the

ability of piperine to induce apoptosis by activating caspase-3, a protease commonly involved in cell death [46].

Another anticancer function of piperine is its ability to reduce the expression of the HER2 gene. Abundant expression of HER2 gene is linked to an increase in the continuance of cancer, a resistance to apoptosis, and an increase in cancer cell proliferation. A study indicated that piperine was able to inhibit the expression of HER2 in breast cancer cells [47].

In mice prostate cancer cells, proliferation was reduced significantly, along with the suppression of cancer cell growth at the G_0/G_1 phase of the cell cycle. In this way, piperine was able to lessen the growth of cancer adequately [37].

14.3.2.2 Piperine as an Antioxidant

Oxidative stress can lead to inflammation through the activation of transcription factors such as NF-κB. This, in turn, can aggregate cancer by increasing cancer cell proliferation. Thus, according to research and observational studies, there is a very potent connection between oxidative stress and cancer due to inflammation [48]. According to a study conducted on rats, piperine was able to lessen the oxidative stress caused by an unhealthy diet [49].

14.3.3 Ginger

Zingiber officinale, commonly known as ginger, is a widely used spice in India, present in entrées, desserts, and teas. Beyond its culinary value, ginger has been used for medicinal purposes in Asian culture, primarily to provide relief for those suffering from indigestion [50].

The effect of ginger on many cancer cells, including breast cancer, gastrointestinal cancer, and prostate cancer cells, determines the usefulness of ginger as an anticancer agent. Specifically, the phenolics that make up ginger, such as gingerol and shogaol, have unique properties that act against cancer [37].

14.3.3.1 Ginger's Effect on Cancer Cells

Approximately 23%–25% of ginger is comprised of gingerol, one of the phenolic constituents of ginger. In experiments exploring the impact of ginger on gastrointestinal cancer, 6-gingerol was able to successfully cause apoptosis of the cancer cells involved in gastric cancer through gene regulation. 6-Gingerol was also effective in the inhibition of pancreatic cancer cells by interrupting the cell cycle and the regulation of the expression of certain transcription factors [51].

Besides, the growth of prostate cell lines has been effectively inhibited in an experimental study with the application of ginger extract [52].

14.3.3.2 Ginger and Oxidative Stress

Similar to piperine, ginger can reduce oxidative stress, thus reducing inflammation and the survival of cancer cells. A study of breast cancer patients used the identification of biomarkers commonly associated with oxidative stress in order to reveal whether or not ginger supplements had an impact. The result of this study showed

that ginger supplementation coupled with water-based exercise was able to lessen oxidative stress [53].

14.3.4 Amrita Bindu

Amrita bindu, commonly used in cooking in India, is a collection of various salts, spices, and herbs. This combination is antioxidant-rich, with a multitude of phytochemicals that can provide health benefits in addition to flavor. One of the first spices present in this mixture is black pepper, which is useful in inhibiting cancer and acting as an antioxidant. Other spices in amrita bindu include long pepper (*piper longum*) and ginger (*Zingiber officinale*) [54].

The salts in amrita bindu include rock salt, bangle salt, and black salt, providing a myriad of nutritional values and trace minerals. The main herbal constituents of amrita bindu are *Cyperus rotundus* and *Plumbago zeylanica* [54].

14.3.4.1 Antioxidative Properties

Many of the compounds that make up amrita bindu act as antioxidants. Antioxidants can find and neutralize free radicals, which are reactive chemicals that can cause extensive damage to DNA and cell parts. This cell damage can lead to cancer [55].

The results of a research study indicate that amrita bindu can successfully scavenge free radicals and potentially preserve the number of antioxidant enzymes and vitamins A, C, and E [56].

Although the antioxidants that makeup amrita bindu are able to scavenge free radicals successfully, the results from a multitude of clinical trials have not been able to find a clear link between dietary antioxidant supplementation and cancer prevention [57]. Specific clinical trials involving vitamin E proved that the compound was not effective in preventing cancer [58]. Therefore, it is likely that the prevalence of amrita bindu in the Indian diet does not have a significant impact on the cancer rates.

14.3.5 Black Cumin

Nigella sativa, or black cumin, is used for culinary and medicinal purposes in many countries, including India, Egypt, and countries in the Middle East. The spice has been highly regarded for its medicinal purposes throughout history, but its benefits have only recently been considered as a cure for diseases like cancer in Western medicine [59].

Research studies indicate that the component in black cumin that contains the majority of beneficial properties in healing is thymoquinone (TQ). TQ is a bioactive compound extracted from black cumin oil. It has been found to reduce cancer cell proliferation and work against tumors [37].

14.3.5.1 Black Cumin's Ability to Inhibit Cancer

Black cumin oil is able to inhibit cancer in a few different ways. One of these includes the regulation of gene expression to encourage the apoptosis, or cell death, of cancer cells. By suppressing gene products like IAP1 and IAP2 that are known to reduce

apoptosis, thymoquinone was able to increase apoptosis in the presence of other anticancer drugs [60].

Another way in which cumin is able to act as an anticancer agent is through the promotion of Bax and p53. These proteins are useful in stopping the cell cycle, thus reducing the growth and spread of cancer cells [61]. In a study involving rats, treatments of black cumin extract successfully reduced the size of tumors located in the colon and lessened esophageal and lung cancer. This was most likely due to the inhibition of cell proliferation [62].

Thymoquinone can also impact epithelial to mesenchymal transition (EMT) of cervical cancer cells. EMT is thought to encourage cancer metastasis, and thymoquinone limited the effect of the transcription factors that contribute to EMT [63].

14.3.5.2 Anti-inflammatory Properties of Thymoquinone

Thymoquinone can also reduce inflammation by regulating NF-κB, a transcription factor involved with inflammation. Inflammation can lead to greater cell proliferation among other cancer-promoting processes, hence making the anti-inflammatory properties of thymoquinone relevant when discussing its role as a potential anticancer agent [64].

14.3.5.3 Toxicity of Thymoquinone

An additional property of thymoquinone is its proven lack of side effects when orally administered. A clinical trial administered thymoquinone in breast cancer patients, and the study indicated that thymoquinone was relatively safe to use based on the lack of side effects in the patients [65]. However, administering thymoquinone through injections was proven toxic on rats, indicating the importance of the manner of administration when considering thymoquinone for treatment purposes [66].

14.3.6 Saffron

Crocus sativus L. belongs to the Iridaceae family and is cultivated in mild and dry climates such as Iran, India, and Greece. It is mainly cultivated to harvest the bright red colored stigma from its flowers. The dried red stigma with a small portion of the yellowish style attached is commonly referred to as saffron [67]. Saffron is known as an adaptogen in Ayurvedic Medicine, as it is used to treat several ailments such as diaphoretic, eupeptic, tranquilizer, expectorant, aphrodisiac, abortifacient, emmenagogue, and in the treatment of hepatic disorders, flatulence, spasm, vomiting, dental, and gingival pain, insomnia, depression, seizures, cognitive disorders, lumbago, asthma, cough, bronchitis, colds, fever, cardiovascular disorders, and cancer [68]. The anticarcinogenic activity of saffron was reported in 1990 and research about this topic has increased immensely since then.

The chemical analysis of Saffron shows that contains more than 150 volatile, nonvolatile, and aroma-yielding compounds. This comprises lipophilic and hydrophilic carbohydrates, proteins, amino acids, minerals, vitamins such as riboflavin and thiamine, and pigments including crocin, anthocianin, carotene, lycopene, zigzantin, flavonoids, starch, gums, and other chemical compounds [69]. The compounds that are of interest are crocin and crocetin, as it has been found from in vitro and in vivo that

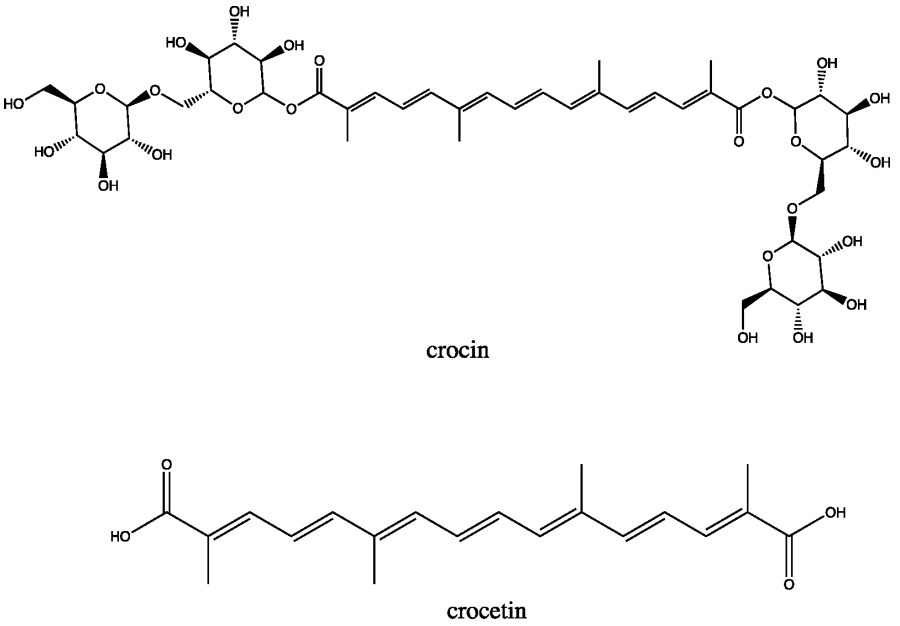


FIGURE 14.3 Molecules of crocetin and crocin.

they can have anticancer properties in breast, lung, pancreatic, and leukemic cells. The in vitro studies have been designed to evaluate and observe how the saffron and its derivatives work against certain types of cancer. Cultured malignant cells were observed and the behavior of its distinct cell surface receptors and intracellular retention were recorded. The cytotoxic effect of the components of saffron was also observed (Figure 14.3).

14.3.6.1 Mechanisms of Crocin and Crocetin against Certain Cancer Types

Crocin and crocetin have the ability to induce several anticarcinogenic mechanisms such as the induction of cytotoxicity, the inhibition of cell proliferation, the induction of apoptosis, the inhibition of DNA, RNA and protein synthesis, among others [69].

Crocin and crocetin have been found to be responsible for the inhibition of growth of human chronic myelogenous leukemia K562 and promyelocytic leukemia HL60 cells [70]. Dimethyl-crocetin and crocin disrupt DNA–protein interactions, thus inhibiting cellular DNA synthesis [71]. Liposomal encapsulation of crocin was used on HeLa cells derived from a cervical epitheloid carcinoma and apoptosis of these cells were observed, therefore implying that the liposomes were cytotoxic to the cancer cells. Crocetin did not have much effect on this HeLa cell line according to a study by Abdullaev [72,73]. Although crocetin does not have an anticarcinogenic effect on cervical cancer cells, Abdullaev (1994) indicated that it is effective in causing apoptosis in certain lung cancer cell lines such as A549 cells.

14.4 CONCLUSION

The Indian diet consists of several cancer-preventive components. However, there are more elements of the Indian diet and lifestyle that need to be assessed in order to get an appropriate picture of how effective the Indian diet in preventing cancer.

REFERENCES

1. Deng, Y. et al., Studies on the pharmacological effects of saffron (*Crocus sativus* L.)—A review. *Zhongguo Zhong Yao Za Zhi*, 2002. **27**(8): pp. 565–568.
2. Mathers, J.C., Pulses and carcinogenesis: Potential for the prevention of colon, breast and other cancers. *Br J Nutr*, 2002. **88**(Suppl 3): pp. S273–S279.
3. Sinha, R. et al., Cancer risk and diet in India. *J Postgrad Med*, 2003. **49**(3): pp. 222–228.
4. Aggarwal, B.B., A. Kumar, and A.C. Bharti, Anticancer potential of curcumin: Preclinical and clinical studies. *Anticancer Res*, 2003. **23**(1A): pp. 363–398.
5. Bouvard, V. et al., Carcinogenicity of consumption of red and processed meat. *Lancet Oncol*, 2015. **16**(16): pp. 1599–1600.
6. Mehta, V., Vegetarian diet: A boon or bane for health? *J Med Res Innovat*, 2018. **2**(1).
7. Thakrar, R., Japanese warm to real curries and more, *Japan Times*. 2007.
8. Yadav Y. and S. Kumar, The food habits of a nation, *The Hindu*. 2012.
9. Lanou, A.J. and B. Svenson, Reduced cancer risk in vegetarians: An analysis of recent reports. *Cancer Manag Res*, 2010. **3**: pp. 1–8.
10. Agrawal, S. et al., Type of vegetarian diet, obesity and diabetes in adult Indian population. *Nutr J*, 2014. **13**: pp. 89–89.
11. Bose, A., Vegetarian India A Myth? Survey Shows Over 70% Indians Eat Non-veg, Telangana Tops List, in Huffpost. 2016.
12. Aune, D. et al., Legume intake and the risk of cancer: A multisite case-control study in Uruguay. *Cancer Causes Control*, 2009. **20**(9): pp. 1605–1015.
13. Dhingra, D. et al., Dietary fibre in foods: A review. *J Food Sci Technol*, 2012. **49**(3): pp. 255–266.
14. Vohra, K., H. Dureja , and V. Garg, An insight of pulses: From food to cancer treatment. *J Pharmacog Nat Prod*, 2016. **1**(1): p. 108.
15. Weisburger, J.H. et al., Protective mechanisms of dietary fibers in nutritional carcinogenesis. *Basic Life Sci*, 1993. **61**: pp. 45–63.
16. Lattimer, J.M. and M.D. Haub, effects of dietary fiber and its components on metabolic health. *Nutrients*, 2010. **2**(12): pp. 1266–1289.
17. Chapkin, R.S. and J.R. Lupton, Colonic cell proliferation and apoptosis in rodent species. Modulation by diet. *Adv Exp Med Biol*, 1999. **470**: pp. 105–118.
18. Zeng, H., D.L. Lazarova, and M. Bordonaro, Mechanisms linking dietary fiber, gut microbiota and colon cancer prevention. *World J Gastrointest Oncol*, 2014. **6**(2): pp. 41–51.
19. Maier, T.V. et al., Impact of dietary resistant starch on the human gut microbiome, metaproteome, and metabolome. *MBio*, 2017. **8**(5): pp. 01343–17.
20. Balasundram, N., K. Sundram, and S. Samman, Phenolic compounds in plants and agri-industrial by-products: Antioxidant activity, occurrence, and potential uses. *Food Chem*, 2006. **99**(1): pp. 191–203.
21. Fiala, N., Meeting the demand: An estimation of potential future greenhouse gas emissions from meat production. *Ecol Econ*, 2008. **67**(3): pp. 412–419.
22. Devi, S.M. et al., An outline of meat consumption in the Indian population—A pilot review. *Korean J Food Sci Anim Resour*, 2014. **34**(4): pp. 507–515.
23. Vasant, P.G. and Z. Zhang-Yue, Rising demand for livestock products in India: nature, patterns and implications. *Aust Agr Rev*, 2010. **18**: p. 114421.

24. Cross, A.J. and R. Sinha, Meat-related mutagens/carcinogens in the etiology of colorectal cancer. *Environ Mol Mutagen*, 2004. **44**(1): pp. 44–55.
25. Lynch, A.M. et al., Intra-and interindividual variability in systemic exposure in humans to 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine, carcinogens present in cooked beef. *Cancer Res*, 1992. **52**(22): pp. 6216–6223.
26. Snyderwine, E.G. et al., Metabolism of the food-derived mutagen/carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) in nonhuman primates. *Carcinogenesis*, 1993. **14**(12): pp. 2517–2522.
27. Ohgaki, H., S. Takayama, and T. Sugimura, Carcinogenicities of heterocyclic amines in cooked food. *Mutat Res*, 1991. **259**(3–4): pp. 399–410.
28. Wakabayashi, K. et al., Food-derived mutagens and carcinogens. *Cancer Res*, 1992. **52**(7 Suppl): pp. 2092s–2098s.
29. Sugimura, T., Overview of carcinogenic heterocyclic amines. *Mutat Res*, 1997. **376**(1–2): pp. 211–219.
30. Shirai, T. et al., Carcinogenicity of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) in rats: Dose-response studies. *Princess Takamatsu Symp*, 1995. **23**: pp. 232–239.
31. Kazerouni, N. et al., Analysis of 200 food items for benzo[a]pyrene and estimation of its intake in an epidemiologic study. *Food Chem Toxicol*, 2001. **39**(5): pp. 423–436.
32. Culp, S.J. et al., A comparison of the tumors induced by coal tar and benzo[a]pyrene in a 2-year bioassay. *Carcinogenesis*, 1998. **19**(1): pp. 117–124.
33. Kaefer, C.M. and J.A. Milner, The role of herbs and spices in cancer prevention. *J Nutr Biochem*, 2008. **19**(6): pp. 347–361.
34. U.S. Food & Drug Administration. Available from: https://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074468.htm.
35. Lampe, J.W., Spicing up a vegetarian diet: Chemopreventive effects of phytochemicals. *Am J Clin Nutr*, 2003. **78**(3 Suppl): pp. 579S–583S.
36. Jallu, S. and T.P. Singh, The shikimate pathway: Review of amino acid sequence, function and three-dimensional structures of the enzymes AU—Mir, Rafia. *Crit Rev Microbiol*, 2015. **41**(2): pp. 172–189.
37. Zheng, J. et al., Spices for prevention and treatment of cancers. *Nutrients*, 2016. **8**(8): p. 495.
38. Ravindran, J., S. Prasad, and B.B. Aggarwal, curcumin and cancer cells: How many ways can curry kill tumor cells selectively? *AAPS J*, 2009. **11**(3): pp. 495–510.
39. Chen, A., J. Xu, and A.C. Johnson, Curcumin inhibits human colon cancer cell growth by suppressing gene expression of epidermal growth factor receptor through reducing the activity of the transcription factor Egr-1. *Oncogene*, 2006. **25**(2): pp. 278–287.
40. Colotta, F. et al., Cancer-related inflammation, the seventh hallmark of cancer: Links to genetic instability. *Carcinogenesis*, 2009. **30**(7): pp. 1073–1081.
41. Yang, H. et al., Structure-activity relationship of curcumin: Role of the methoxy group in anti-inflammatory and anticolitis effects of curcumin. *J Agric Food Chem*, 2017. **65**(22): pp. 4509–4515.
42. Nath, S., Spicy approach to cancer treatment. *J Natl Cancer Inst*, 2011. **103**(24): pp. 1817–1818.
43. Gibson-Moore, H. and A. Spiro, Can turmeric really prevent cancer? *Nutr Bull*, 2017. **42**(2): pp. 141–147.
44. Butler, S. Off the Spice Rack: The Story of Pepper. 2013; Available from: https://www.history.com/news/off-the-spice-rack-the-story-of-pepper.
45. Rather, R.A. and M. Bhagat, Cancer chemoprevention and piperine: Molecular mechanisms and therapeutic opportunities. *Front Cell Dev Biol*, 2018. **6**: p. 10.

46. Lai, L.H. et al., Piperine suppresses tumor growth and metastasis in vitro and in vivo in a 4T1 murine breast cancer model. *Acta Pharmacol Sin*, 2012. **33**(4): pp. 523–530.
47. Do, M.T. et al., Antitumor efficacy of piperine in the treatment of human HER2-overexpressing breast cancer cells. *Food Chem*, 2013. **141**(3): pp. 2591–2599.
48. Reuter, S. et al., Oxidative stress, inflammation, and cancer: How are they linked? *Free Radic Biol Med*, 2010. **49**(11): pp. 1603–1616.
49. Vijayakumar, R.S., D. Surya, and N. Nalini, Antioxidant efficacy of black pepper (*Piper nigrum* L.) and piperine in rats with high fat diet induced oxidative stress. *Redox Rep*, 2004. **9**(2): pp. 105–110.
50. Indian Spices of Ginger in History and Uses. Indian Mirror; Available from: http://www.indianmirror.com/ayurveda/indian-spices/ginger.html.
51. Prasad, S. and A.K. Tyagi, Ginger and its constituents: Role in prevention and treatment of gastrointestinal cancer. *Gastroenterol Res Pract*, 2015. **2015**: p. 142979.
52. Karna, P. et al., Benefits of whole ginger extract in prostate cancer. *Br J Nutr*, 2012. **107**(4): pp. 473–484.
53. Karimi, N. and V.D. Roshan, Change in adiponectin and oxidative stress after modifiable lifestyle interventions in breast cancer cases. *Asian Pac J Cancer Prev*, 2013. **14**(5): pp. 2845–2850.
54. Natarajan, K.S. et al., Antioxidant activity of a salt-spice-herbal mixture against free radical induction. *J Ethnopharmacol*, 2006. **105**(1–2): pp. 76–83.
55. Antioxidants and Cancer Prevention. Available from: https://www.cancer.gov/about-cancer/causes-prevention/risk/diet/antioxidants-fact-sheet.
56. Pal, D., S. Banerjee, and A.K. Ghosh, Dietary-induced cancer prevention: An expanding research arena of emerging diet related to healthcare system. *J Adv Pharm Technol Res*, 2012. **3**(1): pp. 16–24.
57. Bennett, L.L., S. Rojas, and T. Seefeldt, Role of antioxidants in the prevention of cancer. *J Exp Clin Med*, 2012. **4**(4): pp. 215–222.
58. Myung, S.K. et al., Effects of antioxidant supplements on cancer prevention: Meta-analysis of randomized controlled trials. *Ann Oncol*, 2010. **21**(1): pp. 166–179.
59. Khan, M.A. et al., Anticancer activities of *Nigella sativa* (black cumin). *Afr J Tradit Complement Altern Med*, 2011. **8**(5 Suppl): pp. 226–232.
60. Aggarwal, B.B. et al., Potential of spice-derived phytochemicals for cancer prevention. *Planta Med*, 2008. **74**(13): pp. 1560–1569.
61. Majdalawieh, A.F. and M.W. Fayyad, Recent advances on the anti-cancer properties of *Nigella sativa*, a widely used food additive. *J Ayurveda Integr Med*, 2016. **7**(3): pp. 173–180.
62. Salim, E.I., Cancer chemopreventive potential of volatile oil from black cumin seeds, *Nigella sativa* L., in a rat multi-organ carcinogenesis bioassay. *Oncol Lett*, 2010. **1**(5): pp. 913–924.
63. Li, J. et al., Thymoquinone inhibits the migration and invasive characteristics of cervical cancer cells SiHa and CaSki in vitro by targeting epithelial to mesenchymal transition associated transcription factors Twist1 and Zeb1. *Molecules*, 2017. **22**(12): p. 2105.
64. Mostofa, A.G.M. et al., Thymoquinone as a potential adjuvant therapy for cancer treatment: Evidence from preclinical studies. *Front Pharmacol*, 2017. **8**: pp. 295–295.
65. Al Amri A.M. and A.O. Bamosa, Phase I safety and clinical activity study of thymoquinone in patients with advanced refractory malignant disease. *Shiraz E-Med J*, 2009. **10**: p. 4.
66. Abukhader, M.M., The effect of route of administration in thymoquinone toxicity in male and female rats. *Indian J Pharm Sci*, 2012. **74**(3): pp. 195–200.
67. Srivastava, R., et al., *Crocus sativus* L.: A comprehensive review. *Pharmacogn Rev*, 2010. **4**(8): pp. 200–208.

68. Kianbakht, S. and K. Mozaffari, Effects of saffron and its active constituents, crocin and safranal, on prevention of indomethacin induced gastric ulcers in diabetic and non-diabetic rats. *JMPIR*, 2009. **1**(29): pp. 30–38.
69. Samarghandian, S. and A. Borji, Anticarcinogenic effect of saffron (*Crocus sativus* L.) and its ingredients. *Pharmacognosy Res*, 2014. **6**(2): pp. 99–107.
70. Tarantilis, P.A. et al., Inhibition of growth and induction of differentiation of promyelocytic leukemia (HL-60) by carotenoids from *Crocus sativus* L. *Anticancer Res*, 1994. **14**(5a): pp. 1913–1918.
71. Nair, S.C. et al., Effect of saffron on thymocyte proliferation, intracellular glutathione levels and its antitumor activity. *Biofactors*, 1992. **4**(1): pp. 51–54.
72. Abdullaev, F.I., Inhibitory effect of crocetin on intracellular nucleic acid and protein synthesis in malignant cells. *Toxicol Lett*, 1994. **70**(2): pp. 243–251.
73. Escribano, J. et al., Crocin, safranal and picrocrocin from saffron (*Crocus sativus* L.) inhibit the growth of human cancer cells in vitro. *Cancer Lett*, 1996. **100**(1–2): pp. 23–30.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

15 Dietary Isoflavones-Mechanism and Efficacy in Cancer Prevention and Treatment

Richa Dayaramani and Jayvadan K. Patel

CONTENTS

15.1 DIETARY ISOFLAVONES: DEFINITION, CLASSIFICATION, EXAMPLES

Isoflavones are colorless, diphenolic compounds belonging to the category of natural flavonoids with limited taxonomical distribution (only found in legumes) [1]. It is an essential component of the human diet, which reduces the risk of heart disease [2], prostate cancer and breast cancer [3]. In Asian countries, especially those in the East Asian region, the traditional cuisine commonly contains natural isoflavones at high

concentration. It is probably a prime cause that Eastern Asia is less prone to cancer (specifically breast and prostate) and coronary heart diseases than the Western countries. Due to the well-known health benefits, in 1999, the USFDA approved soy protein containing food as a protective agent against coronary heart disorder [4] and as dietary supplements.

Isoflavones are nonsteroidal phenolic bioactive molecules that are structurally similar to the mammalian estrogen, particularly estradiol. Owing to the structural similarity, they competitively bind to the estrogen receptors and also exert mild estrogen-like behavior [5,6]. Along with this activity they are also found to exhibit potent antioxidant property and protect the cells from the free radicals produced during the normal metabolic processes [7,8]. The antioxidant and estrogen-like behavior make isoflavones potential candidates to act against the prostate cancer and breast cancer.

Extensive scientific works and studies prove the health benefits of isoflavones and consider it as a functional food that relieves different chronic disorders. Various studies show that the isoflavones can be useful in chronic heart disorder, prostate cancer, breast cancer, gastrointestinal cancer, menopausal symptoms, osteoporosis, diabetes, obesity, neuronal and cognitive functions, and various microbial infections [9].

15.1.1 Occurrence

Isoflavone is a by-product of phenylpropanoid pathway, which is responsible for flavonoid synthesis [10]. It is the secondary plant metabolite, exclusively found in the members of Leguminosae family such as soybean, red clover (blossom and sprout) (*Trifolium pratense*), and Kudzu root (*Pueraria lobate*) at high concentration [9,11]. Among all these plants, soybean (*Glycine max* L.) is the prime source of isoflavones. Along with this, green beans, cowpea, chickpea, moong beans, alfalfa sprout, peanuts, highly processed food like tofu also contain isoflavones in lesser amounts [12]. Moreover, it is also found in some animal and dairy products like seafood, egg, and meat, but the concentration is very low [13]. Some countries like the UK utilize the Chorleywood bread process to prepare soy isoflavone-rich bread [14]. The composition and content of Isoflavone in various plant species are shown in Table 15.1.

15.1.2 Classification

The phytoestrogens were first discovered in 1926 as plant-based sex hormone and named over two Greek words “phyto,” which stands for plant and “estrogen” depicting the sex hormone [15]. The phytoestrogens can be obtained from 300 different plant species among which most belong to the leguminous family [16]. These are secondary metabolites of plants that mimic the properties of human estrogen. The phytoestrogens are classified into various classes by their chemical structure. The most commonly occurring phytoestrogens are

TABLE 15.1
Isoflavone Composition and Content in Different Plant Species

S. No.	Plant Species	Isoflavone Content	Types of Isoflavones
1.	Soyabean (*Glycine max*)	0.1%–0.5%	Daidzein, Genistein, Glycetein
2.	Red clover (*Trifolium pratense*)	1.5%–2.5%	Daidzein, Genistein, Formononetein, Biochanin A
3.	Kudzu root (*Pueraria lobate*)	0.95 gm/kg Daidzein	Puerarin, Daidzein, Genistein
4.	Chickpea (*Cicer arietinum*)	—	Biochanin A, Genistein
5.	Alfalfa (*Medicago sativa*)	0.5%–3.5%	Formononetin, Coumestrol
6.	Moong bean (*Vigna radiata*)	3.51 mg/kg crude sample	—
7.	Psoralea (*Psoralea corylifolia*)	2 gm/kg dried sample	—

Source: Nikolić, I.M. et al., *Adv. Technol.*, 6, 96–106, 2017.

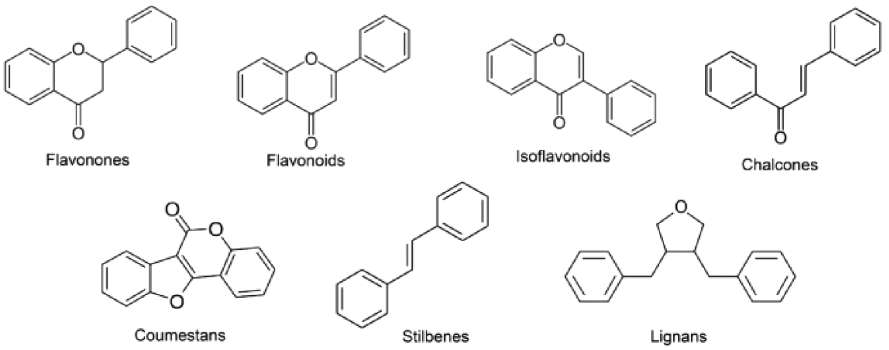


FIGURE 15.1 General structure of some common phytoestrogens. (Adapted form Nikolić, I.M. et al., *Adv. Technol.*, 6, 96–106, 2017.)

flavones, flavonoids, isoflavonoids, chalcones, coumestans, lignans, and stilbenes (Figure 15.1) [17,18]. All of these above compounds are steroidal, while the isoflavones are nonsteroidal in nature. The general classification of phytoestrogens is shown in Figure 15.2.

15.1.2.1 Isoflavones

Chemically, they are heterocyclic compounds having a chemical name as 3-phenyl-4H-chrome-4-one or 4H-1-benzopyran-4-one. They differ from flavones in the location of the phenyl group, which is found attached to the second carbon in the latter. Their molecular formula is $C_{15}H_{10}O_2$ and molecular weight is 222.243 g/mol. The basic structure of isoflavone is shown in Figure 15.3.

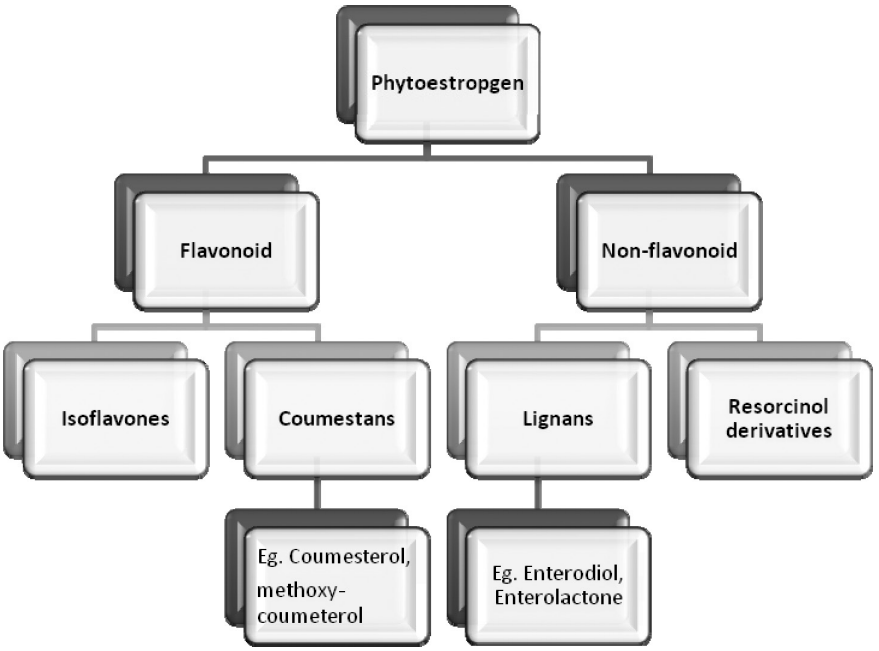


FIGURE 15.2 Classification of phytoestrogen by their chemical structure.

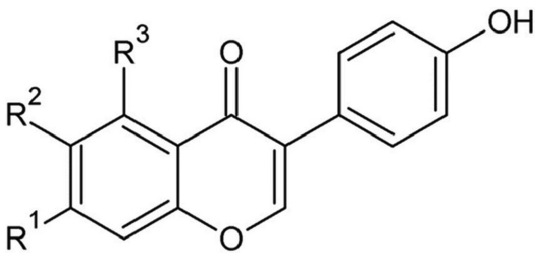


FIGURE 15.3 The basic skeleton of isoflavone.

The isoflavones found in the plants are broadly classified into two categories by glucose conjugation. It occurs in the form of β-glucosides (conjugated to glucose), aglycone form (without glucose residue), and cyclites [15]. These are also present in the form of nonactive glycosides (like genistin, daidzin) and 4-methylated derivative (formononetin and biochanin A). The basic aglycone and glycosides skeleton are shown in Figure 15.4 and Table 15.2, respectively. The sugar/glucose and the hydroxyl group enhance the aqueous solubility of isoflavones, while the isopentyl and methyl groups impart lipophilicity [19]. Daidzein, genistein, glycitein,

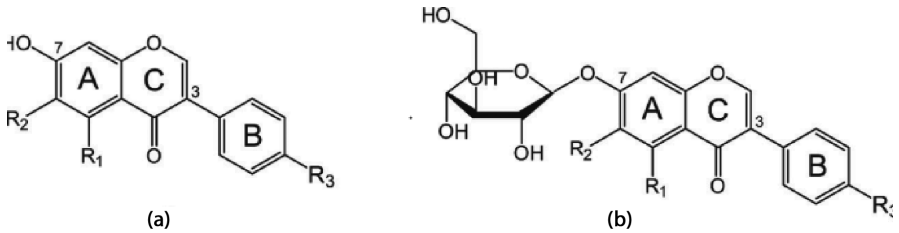


FIGURE 15.4 Basic skeleton of two primary isoflavones (a) aglycones and (b) glycosides. (Adapted form Nikolić, I.M. et al., *Adv. Technol.*, 6, 96–106, 2017.)

TABLE 15.2
Structural Components of Some Common Isoflavones

S.N.	Aglycone	Glycoside	R_1	R_2	R_3
1.	Daidzein	Daidzin (daidzein-7-glucoside)	H	H	OH
2.	Genistein	Genistin (genistein-7-*O*-glucoside)	OH	H	OH
3.	Glycitein	Glycitin (glycitein-7-*O*-glucoside)	H	OCH_3	OH
4.	Formononetin	Ononin (formononetin-7-*O*-glucoside)	H	H	OCH_3
5.	Biochanin A	Sissotrin (biochanin A-7-*O*-glucoside)	OH	H	OCH_3

Source: Nikolić, I.M. et al., *Adv. Technol.*, 6, 96–106, 2017.

formononetin, and biochaninA are some common isoflavones abundant in the natural source (Figure 15.5). On the basis of the structural composition, the isoflavones can be divided into four categories:

1. aglycone
2. 7-*O*-glucoside
3. 6′-*O*-acetyl-7-*O*-glucoside
4. 6′-*O*-malonyl-7-*O*-glucoside

The glycoside, acetyl, and malonyl forms of isoflavones get converted into the corresponding aglycone derivatives by degradation into the acidic or alkaline medium. The transformation of acetyl and malonyl esters into the respective glycoside by hydrolysis and decarboxylation of malonyl glycoside into the aglycone are a most common form of chemical transformation. The formation of aglycone isoflavones takes place by degradation of the glycosidic bond (Figure 15.6) [20].

15.1.3 Metabolism of Isoflavones

Acidic hydrolysis and alkaline hydrolysis are the two primary and most popular ways of the transformation of glycosidic isoflavones into the aglycone isoflavones. The glycosidic hydrolysis could be conducted before, during, and even after the

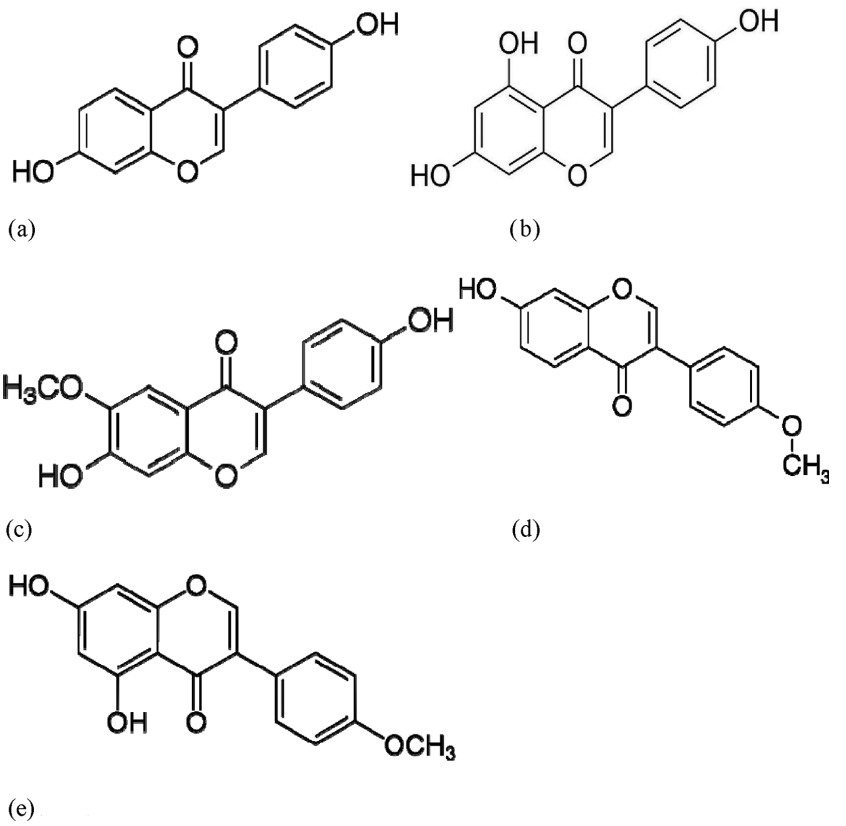


FIGURE 15.5 Chemical structure of some common isoflavones like (a) daidzein, (b) genistein, (c) glycitein, (d) formononetin, and (e) biochanin A.

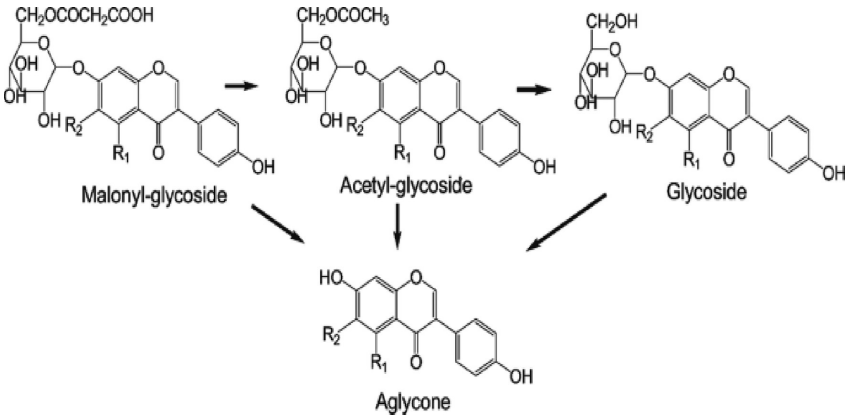


FIGURE 15.6 Schematic representation of decomposition of the glycosidic derivative of isoflavones into the aglycone form. (Adapted form Nikolić, I.M. et al., *Adv. Technol.*, 6, 96–106, 2017.)

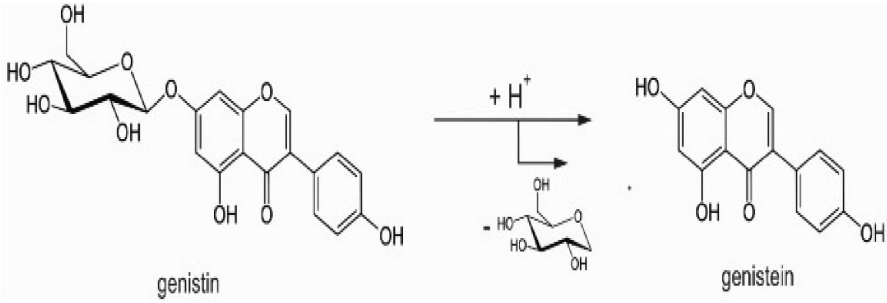


FIGURE 15.7 Schematic representation of acidic hydrolysis of genistin (glycosidicisoflavone) into genistein (aglycon isoflavone) by removal of a glucose molecule from the seventh position. (Adapted form Nikolić, I.M. et al., *Adv. Technol.*, 6, 96–106, 2017.)

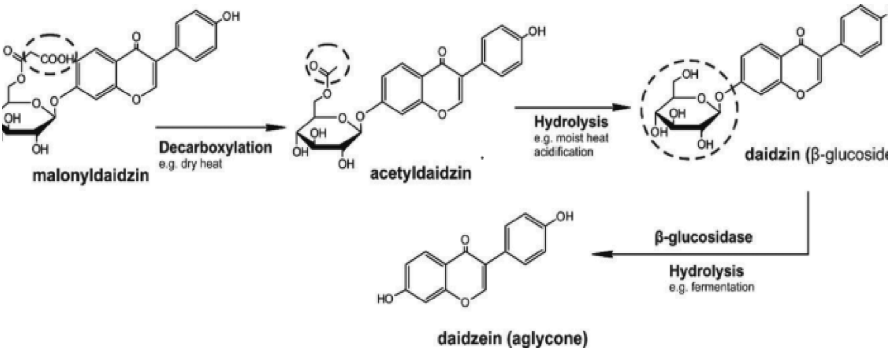


FIGURE 15.8 Schematic representation of malonyl-daidzin into daidzein form via a series of chemical processes including decarboxylation, acidic hydrolysis, and enzymatic hydrolysis, respectively. (Adapted form Nikolić, I.M. et al., *Adv. Technol.*, 6, 96–106, 2017.)

extraction of isoflavones. For example, the use of hydrochloric acid at 80°C temperature results in complete hydrolysis of isoflavones [21]. Acidic hydrolysis of genistin into the genistein form is shown in Figure 15.7. Now, in the past few years, the hydrolysis of glucosidic isoflavone into the desired corresponding aglycone can also be carried out by enzymatic hydrolysis using the β-glucosidase enzyme [22].

If the isoflavones are taken in its natural form via food, the decomposition into the aglycone form takes place after ingestion in the body. The raw glycosidic isoflavone releases the active constituent aglycones like genistein, glycitein, and daidzein by enzymatic degradation with an intestinal β-glucosidase enzyme or by fermentation [23]. The conversion of malonyl-daidzin into the aglycondaidzein is shown in Figure 15.8.

The aglycon form of isoflavones are found to be relatively more stable in the GIT and possess higher estrogenic and antioxidant properties than the glycosidic form. Some of the aglycons like genistein and daidzein decomposed in the GIT into the more effective metabolite equol [20]. The equol binds to both the estrogenic receptors and hence demonstrates higher estrogenic behavior and anti-oxidant property.

The studies have shown that the human body cannot produce equol itself and, hence, it should be consumed externally from the food [16].

15.2 MECHANISM OF VARIOUS ISOFLAVONES IN CANCER PREVENTION

The dietary isoflavones or phytoestrogens are found to be effective in breast cancer, ovarian cancer, prostate cancer, gastric cancer, and many other types of cancers. They are also found to be effective in coronary heart diseases. The isoflavones possess strong antioxidant activity and mimic the behavior of human estrogen, which is supposed to be the possible mechanism of its anticancer activity. According to a study, it was demonstrated that once the isoflavones enter into the body, owing to the estrogen-like structure, they interact with the estrogen receptors and produce estrogenic or antiestrogenic effects. Together with this, they also affect the hormone production and hormone-binding proteins by inhibiting the enzyme activity [24]. On the other hand, its antioxidant property also reduces the tumor formation and protects the cells from the harmful effect of free radicals.

It antagonizes the growth promoting the effect of 17β-estradiol by binding with the estrogen receptor as a ligand. Genistein is one of the most studied and biologically active isoflavones for the treatment of cancer. It has been observed that, after interacting with the estrogenic receptors, it promotes the cell growth at lower concentration and inhibit the cell growth at a higher concentration [25]. The plasma concentration of isoflavones is 100 times higher than the endogenous estrogens after that it is considered as weaker than the endogenous estrogen. The phytoestrogen and endogenous estrogen, both compete for the estrogenic receptors, which sometimes block the estrogenic activity or produce antiestrogenic behavior and thus result in hormonal diseases. The isoflavones particularly bind to the β-estrogen receptor and α-estrogen receptor, which target it to the particular body tissues like thymus and bone in female and vascular and prostate in the male. Thereby, it is found useful in the disease of the relevant area like breast cancer, prostate cancer, and heart diseases.

Various studies reported that the metabolites of isoflavones like equol, *p*-ethylphenol, *o*-DMA, etc., are sometimes more effective than the parent compounds owing to the higher affinity toward the estrogenic receptors [26]. For example, the equol was found to be more effective in tumor lines and have a higher estrogenic effect than its parent compound daidzein. This may be because of equol decreased the expression of the estrogen-responsive *pS2* gene in the MCF7 breast cancer cell line.

15.3 AN ACCOUNT OF THE EFFICACY OF ISOFLAVONES IN CANCER PREVENTION

Nowadays, the natural bioactives, food contents, dietary supplements, and nutrients become more popular among scientists to prevent and treat various pathological conditions including cancer because of their safety and biocompatibility. Research demonstrated that a modification in lifestyle and healthy dietary habits significantly

reduces the risk of cancer and also slowdown and sometimes cure the developing cancers [27]. One of the potential compounds is dietary isoflavones, which are found effective in breast cancer, ovarian cancer, prostate cancer, gastrointestinal tract cancer, and some other cancer owing to its antioxidant and estrogen-like properties. The efficacy of isoflavone in cancer prevention is discussed in the following sections.

15.3.1 Breast Cancer

Breast cancer is the most frequent malignancy and a prime cause of cancer mortality in women throughout the world [28]. The statistics show around 14 million new patients and 8 million casualties each year throughout the globe [29]. A strange fact about breast cancer is that it is not limited to the women but also affect the men and trans genders [30]. Hence, the effective treatment or preventive measures are highly desirable to control the disease and improve the survival. The studies reported a relationship between the dietary and lifestyle habits and risk of the cancer prevalence [31]. Frequent consumption of oily food, animal products, high-calorie content, alcohol, refined sugar, etc., increases the risk of cancer [32], while a healthy lifestyle and some inclusion of some phytochemical in a regular diet may reduce the risk. Phytoconstituent like isoflavone or phytoestrogen possesses effective anticancer activity and acts by interfering with various metabolic pathways, modulating the enzymatic and hormonal functions, modifying the DNA synthesis process and by free radical scavenging [33]. In Asian countries, the incidences of breast cancer are significantly lower than those in the Western countries like the USA and Europe [34,35]. The reason behind that is the daily Asian food is rich in isoflavone content with around 30–50 mg of mean isoflavone intake in the form of soy foods like soy milk, tofu, miso, soybean seed oil, and other products. On the other hand, after recognizing the benefits of soy food or isoflavone in the cancer therapy, the Western countries also started to incorporate soy protein in their food and prepared soy foods like soy protein added meat, bread, and many more [36]. The WHEL (Women Healthy Eating and Living) study reported a significant reduction (31%) in the risk of breast cancer in the group of women provided with a high vegetable, fruits, dietary fibers, and low-fat diet than the others [37].

Among different isoflavones, genistein, daidzein, biochaninA, formononetin, and glycitein are the most effective phytoestrogens in the prevention of breast cancer. The structure of these compounds shows a higher resemblance with the 17-β-estradiol, and thus it binds to the β-estrogen receptors. Depending on the estrogen level in the body the isoflavones act as estrogen receptor agonist (postmenopausal stage) and antagonist (premenopausal stage) [38,39]. It inhibits the tumor formation by modifying the hormonal level and enzymatic activity. Also, the isoflavones interfere with the DNA transduction process and thus inhibit the excessive cell growth. Moreover, the antioxidant potency also reduces cancer cell formation [40]. Genistein mainly inhibits the tyrosine kinase enzyme and encourages the tumor suppressor protein [41]. Some commercial products containing isoflavones are also available in the market, which include red clover extracts for the menopausal symptoms and other health benefits, Promensil® (for bone loss and dyslipidemia), Trinovin® (as men health supplement), and so on [42].

15.3.2 Ovarian Cancer

As per the annual report on cancer statistics "Cancer Facts and Figures 2018" published in American Cancer Society, nearly 22,240 new cases of ovarian cancer were diagnosed in the year 2018 in the USA [43], which is significantly higher than the past data. It is a leading cause of death in women because of the late diagnosis of the disease, which reduces the survival rate. The Reports shows that incidences of ovarian cancer may vary in different geographical regions. Majority of cases are observed in the developed countries, which shows that lifestyle and diet play major role in the control of the disease prevalence [44]. However, the exact role of dietary nutrients in cancer growth and prevention is still not clear [45,46]. A dietary modification trial by Women Health Initiative (WHI) evaluated the effect of diet on the ovarian cancer risk. The trial suggested a low-fat diet after menopausal stage could be helpful in reduction ovarian cancer risk [47]. Isoflavone is one of the phytoconstituent with estrogen-like activity and modifies the hormonal regulation in the body. Hence, it is found to be effective in ovarian cancer, which may be affected by hormonal changes. A meta-analysis shows the protective effect of soy isoflavone in ovarian cancer [48]. On a similar note, approximately 41% of risk reduction in women with regular intake of high amount of soy seed oil was observed by the Italian multicentered case–control study [49]. Control case studies conducted USA, Japan, Korea, China, etc. support the same hypothesis that the isoflavones reduce the risk of ovarian cancer. The Southern Asian region have less disease prevalence because of isoflavone-rich food habits [50]. Chen et al. studied the effect of isoflavone on the in vitro ovarian cancer cell lines. They observed that the soy isoflavone inhibits the cancer cell proliferation by affecting the cytokine synthesis. Specifically, daidzein and genistein bind to the estrogen receptor and modify the cytokine synthesis pathway, thus reducing the ovarian cancer cell line viability [51].

15.3.3 Prostate Cancer

Prostate cancer is a growing disease in men, commonly known as the enlargement of the prostate gland, which further develops into tumor and/or malignancy [9]. It is one of the most common malignancies and the second-leading cause of cancerous death among men. Despite higher disease frequency and increasing risk every year, the exact pathology of the disease is still not clear. The incidences of the disease may vary according to the geographical locations, age, race, and ethnicity [11]. It is more frequent in the American population than Asian men. The difference in the disease frequency is also because of the microbiota of the individual, which convert the genistein and daidzein into equol and other relevant, more effective, metabolites. The microbiota is more abundant in the Asian region than in America and Europe [52]. In addition, environmental, genetic, and epigenetic factors also affect tumor growth. Dietary habits also influence the occurrence of prostate cancer. Various studies throughout the world found that soybean and soy products effective in the prevention of prostate cancer. The soy isoflavones reduce the prostate tumor growth by minimizing the serum PSA (prostate-specific antigen) concentration. The multiple analysis of

randomized clinical trial confirms the efficiency of dietary isoflavones in controlling prostate cancer. A significant reduction in the prostate tumor growth was observed in the group of men with regular intake of soy isoflavones. However, short-term isoflavone intake does not affect the hormonal concentration in serum and does not reduce the disease [53]. The studies demonstrated that the isoflavones pleiotropically affect the cancer cell line and also interfere with the signal transduction pathways of cancer cells, thus inhibiting the cell growth and proliferation [11]. Additionally, the cellular studies indicate that isoflavones genetically regulate the cell cycle and cellular apoptosis. Other possible mechanisms are the apoptosis and the androgen- and estrogen-mediated signaling pathway-related growth arrest of the prostate tumor cells by intake of isoflavone-rich food. Moreover, the antioxidant property, angiogenesis inhibition, DNA repair, and so on are other mechanisms of anticancer efficacy of the isoflavones. The genistein and daidzein reverse the DNA methylation in cancerous cells by interacting with β-estrogen receptor [54].

15.3.4 Gastric Cancer

Gastrointestinal cancer is referred to as a malignant disease of GIT and related organs, which commonly includes stomach cancer, pancreatic cancer, colorectal cancer, esophageal neoplasm, ulcerating antralneoplasia, and so on [55]. Stomach cancer is the second major type of cancer affecting the people worldwide and a leading cause of cancer-related death [56,57]. While the colorectal cancer is considered as the third primary type of cancer in both women and men, a report by the American Chemical Society, "Cancer Facts and Figures 2012," claims increasing incidences of pancreatic cancer, liver cancer, and esophageal adenocarcinoma. These data are supported by a recent report "Global Cancer Statistics 2018," that in 2018, the incidences of colorectal cancer, stomach cancer, and liver cancer increase by 9.2%, 8.2%, and 8.2, respectively [58]. In this sequence, some of the food, nutrients, and dietary supplements drag the attention of scientists and researchers because of their ability to prevent the occurrence, delay the onset, and treat disease condition [59].

It has been reported that the constant intake of N-nitroso compound and salty food may increase the risk of gastric cancer, while the consumption of some vegetables, fruits, isoflavone-rich food material like soy products, peanuts, chickpeas, red clover, alfalfa, and so on prevent gastric cancer [60,61]. Among different types of isoflavones, genistein and daidzein were most effective in the treatment of gastric cancer [62]. In the GIT, the daidzein gets converted into a more biologically active form equol by enzymatic hydrolysis [63]. The dietary isoflavones interfere with various metabolic pathways and thus prevent tumor formation [64]. Owing to the structural similarities with 17β-estradiol, it has an affinity toward the β-estrogenic receptor, which also helps to avoid gastric cancer. Along with this, the anticancer property is also attributed to the anti-inflammatory and antioxidant properties [65].

However, some studies in Asian countries including Korea and Japan, reported adverse effects of isoflavones on gastric cancer, which might be because of the higher

N-nitroso and salt content in some of the soy products [66]. Such results establish controversies among the scientists for the effectiveness of isoflavone in gastric cancer.

15.4 PROSPECTS OF USE OF ISOFLAVONES AS NUTRITIONAL SUPPLEMENTS

Isoflavones, particularly the soy isoflavones, are found beneficial in controlling various chronic diseases primarily the cardiovascular disease, hormonal disorders and cancer (breast cancer, ovarian cancer, prostate cancer, gastric cancer, etc.). In the present global scenario, due to the environmental changes, lifestyle, food habits, genetic factors, and many other reasons, the risk of such incurable diseases is increasing every year. The survival rate is relatively poor because of the late diagnosis; also, after diagnosis, the treatment is very painful and costly. So, it would be better if we have some preventive measures to reduce the risk of disease prevalence. The dietary supplements can be an answer to such a situation, and isoflavones are important nutrients found to control various cancers if taken regularly in the diet. Worldwide, some studies have been conducted to study the effect of dietary isoflavones in the cancer occurrence, and most of the studies found positive effect. While some negative results are also observed on the different side of the globe (Korea, Japan, etc.), possibly due to the geographical and environmental factors, such a contradiction between scientists provides a huge scope of studying the efficacy of isoflavones and confirming its benefits. In addition, a proper investigation of the in vivo behavior, toxicity assessment, and clinical trials are also desirable in the future.

15.5 CHALLENGES IN ISOLATION AND USE OF ISOFLAVONES AS NUTRITIONAL SUPPLEMENTS

The isolation/extraction of isoflavones from the natural sources is a critical and challenging process because the composition of isoflavone may be altered at the time of sample preparation. Previously, the method used commonly for the separation of isoflavone utilizes the reflux alcohol, which causes conversion of glycone to aglycone form. Hence, the latest method employs chilled extraction or extraction at room temperature to avoid the decomposition of bioactives. Thus a proper extraction of isoflavones is necessary to prevent hydrolysis of isoflavones for better efficacy of the nutraceutical ingredients. There is lot of evidence supporting the health benefits of dietary isoflavones, but no proper evidence related to the safety consideration and toxicity profile is available. Some observations suggested harmful effect of multiple and high doses of isoflavones. Also, the proper use of isoflavones in single or combined dose of different derivatives and their benefits are not clear. Genistein, daidzein, glycitein, and biochanin arrest the cell cycle, modify the DNA transduction, and promote cell apoptosis of the tumor cells, but they can also exert cytotoxicity to normal cells. Although USFDA recognizes it as a dietary supplement, it is sometimes found effective at a lower dose and shows adverse effects at higher dose. Such conflicts and dilemma need to be clarified through proper scientific investigations.

REFERENCES

1. H.L. Esch, C. Kleider, A. Scheffler, L. Lehmann, Chapter 34—Isoflavones: Toxicological aspects and efficacy, in: R.C. Gupta (Ed.), *Nutraceuticals*, Academic Press, Boston, MA, 2016, pp. 465–487.
2. F.M. Sacks, A. Lichtenstein, L. Van Horn, W. Harris, P. Kris-Etherton, M. Winston, Soy protein, isoflavones, and cardiovascular health: An American Heart Association Science Advisory for professionals from the Nutrition Committee, *Circulation* 113(7) (2006) 1034–1044.
3. J. Ferlay, I. Soerjomataram, R. Dikshit, S. Eser, C. Mathers, M. Rebelo, D.M. Parkin, D. Forman, F. Bray, Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012, *International Journal of Cancer* 136(5) (2015) E359–E386.
4. C.W. Xiao, Health effects of soy protein and isoflavones in humans, *The Journal of Nutrition* 138(6) (2008) 1244s–1249s.
5. V.R. Preedy (Ed.), *Isoflavones: Chemistry, Analysis, Function and Effects*, Royal Society of Chemistry, Cambridge, UK, 2013.
6. P. Delmonte, J. Perry, J.I. Rader, Determination of isoflavones in dietary supplements containing soy, Red Clover and kudzu: Extraction followed by basic or acid hydrolysis, *Journal of Chromatography A* 1107(1) (2006) 59–69.
7. R.P. Patel, B.J. Boersma, J.H. Crawford, N. Hogg, M. Kirk, B. Kalyanaraman, D.A. Parks, S. Barnes, V. Darley-Usmar, Antioxidant mechanisms of isoflavones in lipid systems: Paradoxical effects of peroxyl radical scavenging, *Free Radical Biology & Medicine* 31(12) (2001) 1570–1581.
8. Antioxidants and cancer prevention: Fact sheet, National Cancer Institute (NCI), 2004.
9. K. Zaheer, M. Humayoun Akhtar, An updated review of dietary isoflavones: Nutrition, processing, bioavailability and impacts on human health, *Critical Reviews in Food Science and Nutrition* 57(6) (2017) 1280–1293.
10. N.C. Veitch, Isoflavonoids of the leguminosae, *Natural Product Reports* 24(2) (2007) 417–464.
11. A.M. Mahmoud, W. Yang, M.C. Bosland, Soy isoflavones and prostate cancer: A review of molecular mechanisms, *The Journal of Steroid Biochemistry and Molecular Biology* 140 (2014) 116–132.
12. J. Kasparovska, M. Pecinkova, K. Dadakova, L. Krizova, S. Hadrova, M. Lexa, J. Lochman, T. Kasparovsky, Effects of isoflavone-enriched feed on the Rumen Microbiota in dairy cows, *PLoS One* 11(4) (2016) e0154642.
13. G.G. Kuhnle, C. Dell'Aquila, S.M. Aspinall, S.A. Runswick, A.A. Mulligan, S.A. Bingham, Phytoestrogen content of foods of animal origin: Dairy products, eggs, meat, fish, and seafood, *Journal of Agricultural and Food Chemistry* 56(21) (2008) 10099–10104.
14. A.A. Mulligan, A.A. Welch, A.A. McTaggart, A. Bhaniani, S.A. Bingham, Intakes and sources of soya foods and isoflavones in a UK population cohort study (EPIC-Norfolk), *European Journal of Clinical Nutrition* 61(2) (2007) 248–254.
15. I.L. Nikolić, I.M. Savić-Gajić, A.D. Tačić, I.M. Savić, Classification and biological activity of phytoestrogens: A review, *Advanced Technologies* 6(2) (2017) 96–106.
16. R.A. Dixon, Phytoestrogens, *Annual Review of Plant Biology* 55(1) (2004) 225–261.
17. Y. Jacquot, C. Rojas, B. Refouvelet, J.F. Robert, G. Leclercq, A. Xicluna, Recent advances in the development of phytoestrogens and derivatives: An update of the promising perspectives in the prevention of postmenopausal diseases, *Mini Reviews in Medicinal Chemistry* 3(5) (2003) 387–400.
18. R.J. Miksicek, Estrogenic flavonoids: Structural requirements for biological activity, *Proceedings of the Society for Experimental Biology and Medicine. Society for Experimental Biology and Medicine* 208(1) (1995) 44–50.

19. A. Crozier, M.N. Clifford, H. Ashihara, *Plant Secondary Metabolites: Occurrence, Structure and Role in the Human Diet*, John Wiley & Sons, New York, 2008.
20. J. Tan, University of Leeds, Dietary Isoflavones: Aglycones and Glycosides, University of Leeds PhD Thesis, UK, 2011.
21. M.K. Piskula, Soy isoflavone conjugation differs in fed and food-deprived rats, *The Journal of Nutrition* 130(7) (2000) 1766–1771.
22. N.T. Pandit, V.B. Patravale, Design and optimization of a novel method for extraction of genistein, *Indian Journal of Pharmaceutical Sciences* 73(2) (2011) 184–192.
23. H. Adlercreutz, Lignans and human health, *Critical Reviews in Clinical Laboratory Sciences* 44(5–6) (2007) 483–525.
24. D.M. Tham, C.D. Gardner, W.L. Haskell, Clinical review 97: Potential health benefits of dietary phytoestrogens: A review of the clinical, epidemiological, and mechanistic evidence, *The Journal of Clinical Endocrinology and Metabolism* 83(7) (1998) 2223–2235.
25. A. Matsumura, A. Ghosh, G.S. Pope, P.D. Darbre, Comparative study of oestrogenic properties of eight phytoestrogens in MCF7 human breast cancer cells, *The Journal of Steroid Biochemistry and Molecular Biology* 94(5) (2005) 431–443.
26. I. Rowland, H. Wiseman, T. Sanders, H. Adlercreutz, E. Bowey, Metabolism of oestrogens and phytoestrogens: Role of the gut microflora, *Biochemical Society Transactions* 27(2) (1999) 304–308.
27. N. Khan, H. Mukhtar, Cancer and metastasis: Prevention and treatment by green tea, *Cancer Metastasis Reviews* 29(3) (2010) 435–445.
28. M. Ghoncheh, Z. Pournamdar, H. Salehiniya, Incidence and mortality and epidemiology of breast cancer in the world, *Asian Pacific Journal of Cancer Prevention: APJCP* 17(S3) (2016) 43–46.
29. L.A. Torre, F. Bray, R.L. Siegel, J. Ferlay, J. Lortet-Tieulent, A. Jemal, Global cancer statistics, 2012, *CA: A Cancer Journal for Clinicians* 65(2) (2015) 87–108.
30. G.R. Brown, Breast cancer in transgender veterans: A ten-case series, *LGBT Health* 2(1) (2015) 77–80.
31. A. Giacosa, R. Barale, L. Bavaresco et al., Cancer prevention in Europe: The Mediterranean diet as a protective choice, *European Journal of Cancer Prevention: The Official Journal of the European Cancer Prevention Organisation (ECP)* 22(1) (2013) 90–95.
32. W.Y. Chen, B. Rosner, S.E. Hankinson, G.A. Colditz, W.C. Willett, Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk, *JAMA* 306(17) (2011) 1884–1890.
33. R.H. Liu, Potential synergy of phytochemicals in cancer prevention: Mechanism of action, *The Journal of Nutrition* 134(12 Suppl) (2004) 3479s–3485s.
34. S.M. Mense, T.K. Hei, R.K. Ganju, H.K. Bhat, Phytoestrogens and breast cancer prevention: Possible mechanisms of action, *Environmental Health Perspectives* 116(4) (2008) 426–433.
35. P.E. Miller, D.C. Snyder, Phytochemicals and cancer risk: A review of the epidemiological evidence, *Nutrition in Clinical Practice: Official Publication of the American Society for Parenteral and Enteral Nutrition* 27(5) (2012) 599–612.
36. J.W. Lampe, D.R. Gustafson, A.M. Hutchins, M.C. Martini, S. Li, K. Wahala, G.A. Grandits, J.D. Potter, J.L. Slavin, Urinary isoflavonoid and lignan excretion on a Western diet: Relation to soy, vegetable, and fruit intake, in *Cancer Epidemiology, Biomarkers & Prevention*, A publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology 8(8) (1999) 699–707.
37. S.R. Bhanot A, Noolvi MN, Natural sources as potential anti-cancer agents: A review, *International Journal of Phytomedicine* 3 (2011) 9–26.

38. H. Fritz, D. Seely, G. Flower et al., Soy, red clover, and isoflavones and breast cancer: A systematic review, *PLoS One* 8(11) (2013) e81968.
39. C.S. Hwang, H.S. Kwak, H.J. Lim, S.H. Lee, Y.S. Kang, T.B. Choe, H.G. Hur, K.O. Han, Isoflavone metabolites and their in vitro dual functions: They can act as an estrogenic agonist or antagonist depending on the estrogen concentration, *The Journal of Steroid Biochemistry and Molecular Biology* 101(4–5) (2006) 246–253.
40. S. Ziaei, R. Halaby, Dietary isoflavones and breast cancer risk, *Medicines* 4(2) (2017) 18.
41. K. Park, K. Choi, H. Kim, K. Kim, M.H. Lee, J.H. Lee, J.C. Kim Rim, Isoflavone-deprived soy peptide suppresses mammary tumorigenesis by inducing apoptosis, *Experimental & Molecular Medicine* 41(6) (2009) 371–381.
42. N.L. Booth, C.E. Piersen, S. Banuvar, S.E. Geller, L.P. Shulman, N.R. Farnsworth, Clinical studies of red clover (Trifolium pratense) dietary supplements in menopause: A literature review, *Menopause* 13(2) (2006) 251–264.
43. American cancer Society facts and Figures, 2018. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2018.html.
44. A.H. Lee, D. Su, M. Pasalich, L. Tang, C.W. Binns, L. Qiu, Soy and isoflavone intake associated with reduced risk of ovarian cancer in southern Chinese women, *Nutrition Research* 34(4) (2014) 302–307.
45. T.E. Crane, B.R. Khulpateea, D.S. Alberts, K. Basen-Engquist, C.A. Thomson, Dietary intake and ovarian cancer risk: A systematic review, in *Cancer Epidemiology, Biomarkers & Prevention*, A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology 23(2) (2014) 255–273.
46. C. Bosetti, A. Altieri, C. La Vecchia, Diet and environmental carcinogenesis in breast/gynaecological cancers, *Current Opinion in Obstetrics & Gynecology* 14(1) (2002) 13–18.
47. R.L. Prentice, C.A. Thomson, B. Caan et al., Low-fat dietary pattern and cancer incidence in the Women's Health initiative dietary modification randomized controlled trial, *Journal of the National Cancer Institute* 99(20) (2007) 1534–1543.
48. S.K. Myung, W. Ju, H.J. Choi, S.C. Kim, Soy intake and risk of endocrine-related gynaecological cancer: A meta-analysis, *BJOG: An International Journal of Obstetrics and Gynaecology* 116(13) (2009) 1697–1705.
49. C. Bosetti, E. Negri, S. Franceschi, R. Talamini, M. Montella, E. Conti, P. Lagiou, F. Parazzini, C. La Vecchia, Olive oil, seed oils and other added fats in relation to ovarian cancer (Italy), *Cancer Causes & Control: CCC* 13(5) (2002) 465–470.
50. A.H. Lee, D. Su, M. Pasalich, L. Tang, C.W. Binns, L. Qiu, Soy and isoflavone intake associated with reduced risk of ovarian cancer in southern Chinese women, *Nutrition Research* 34(4) (2014) 302–307.
51. X. Chen, J.J. Anderson, Isoflavones inhibit proliferation of ovarian cancer cells in vitro via an estrogen receptor-dependent pathway, *Nutrition and Cancer* 41(1–2) (2001) 165–171.
52. H. Akaza, Prostate cancer chemoprevention by soy isoflavones: Role of intestinal bacteria as "second genome," *Cancer Science* 103 (2012) 969–975.
53. N. Miyanaga, H. Akaza, S. Hinotsu et al., Prostate cancer chemoprevention study: An investigative randomized control study using purified isoflavones in men with rising prostate-specific antigen, *Cancer Science* 103(1) (2012) 125–130.
54. M. Adjakly, M. Ngollo, A. Lebert, A. Dagdemir, F. Penault-Llorca, J.P. Boiteux, Y.J. Bignon, L. Guy, D. Bernard-Gallon, Comparative effects of soy phytoestrogens and 17beta-estradiol on DNA methylation of a panel of 24 genes in prostate cancer cell lines, *Nutrition and Cancer* 66(3) (2014) 474–482.
55. M.F. Ullah, S.H. Bhat, E. Husain, F. Abu-Duhier, S.M. Hadi, F.H. Sarkar, A. Ahmad, Pharmacological Intervention through dietary nutraceuticals in gastrointestinal Neoplasia, *Critical Reviews in Food Science and Nutrition* 56(9) (2016) 1501–1518.

56. Y. Yang, J. Liu, X. Li, J.C. Li, PCDH17 gene promoter demethylation and cell cycle arrest by genistein in gastric cancer, *Histology and Histopathology* 27(2) (2012) 217–224.
57. S. Golpour, N. Rafie, S.M. Safavi, M. Miraghajani, Dietary isoflavones and gastric cancer: A brief review of current studies, *Journal of Research in Medical Sciences: The Official Journal of Isfahan University of Medical Sciences* 20(9) (2015) 893–900.
58. J.F. Bray, I. Soerjomataram, R.L. Siegel, L.A. Torre, Ahmedin Jemal Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, *CA: A Cancer Journal for Cinicians* 68(6) (2018) 394–424.
59. H. Vainio, E. Weiderpass, Fruit and vegetables in cancer prevention, *Nutrition and Cancer* 54(1) (2006) 111–142.
60. K.P. Ko, S.K. Park, B. Park et al., Isoflavones from phytoestrogens and gastric cancer risk: A nested case-control study within the Korean Multicenter Cancer Cohort, *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 19(5) (2010) 1292–1300.
61. L.Z. Lin, X.G. He, M. Lindenmaier, J. Yang, M. Cleary, S.X. Qiu, G.A. Cordell, LC-ESI-MS study of the flavonoid glycoside malonates of red clover (Trifolium pratense), *Journal of Agricultural and Food Chemistry* 48(2) (2000) 354–365.
62. Y. Sugiyama, N. Masumori, F. Fukuta et al., Influence of isoflavone intake and equol-producing intestinal flora on prostate cancer risk, *Asian Pacific Journal of Cancer Prevention: APJCP* 14(1) (2013) 1–4.
63. J.P. Yuan, J.H. Wang, X. Liu, Metabolism of dietary soy isoflavones to equol by human intestinal microflora—Implications for health, *Molecular Nutrition & Food Research* 51(7) (2007) 765–781.
64. X.L. Qu, Y. Fang, M. Zhang, Y.Z. Zhang, Phytoestrogen intake and risk of ovarian cancer: A meta-analysis of 10 observational studies, *Asian Pacific Journal of Cancer Prevention: APJCP* 15(21) (2014) 9085–9091.
65. S.S. Kweon, X.O. Shu, Y. Xiang, H. Cai, G. Yang, B.T. Ji, H. Li, Y.T. Gao, W. Zheng, M. Epplein, Intake of specific nonfermented soy foods may be inversely associated with risk of distal gastric cancer in a Chinese population, *The Journal of Nutrition* 143(11) (2013) 1736–1742.
66. O.K. Chun, S.J. Chung, W.O. Song, Urinary isoflavones and their metabolites validate the dietary isoflavone intakes in US adults, *Journal of the American Dietetic Association* 109(2) (2009) 245–254.

Index

Note: Page numbers in italic and bold refer to figures and tables, respectively.

E

F

G

Q

R

S

T

U

V