

EXPLORING MEDICINAL PLANTS



TRADITIONAL HERBAL THERAPY FOR THE HUMAN IMMUNE SYSTEM

Edited by
Azamal Husen



CRC Press
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Traditional Herbal
Therapy for the Human
Immune System

Exploring Medicinal Plants

Series Editor

Azamal Husen

Wolaita Sodo University, Ethiopia

Medicinal plants render a rich source of bioactive compounds used in drug formulation and development; they play a key role in traditional or indigenous health systems. As the demand for herbal medicines increases worldwide, supply is declining as most of the harvest is derived from naturally growing vegetation. Considering global interests and covering several important aspects associated with medicinal plants, the Exploring Medicinal Plants series comprises volumes valuable to academia, practitioners, and researchers interested in medicinal plants. Topics provide information on a range of subjects including diversity, conservation, propagation, cultivation, physiology, molecular biology, growth response under extreme environment, handling, storage, bioactive compounds, secondary metabolites, extraction, therapeutics, mode of action, and healthcare practices.

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Traditional Herbal Therapy for the Human Immune System

Edited by
Azamal Husen
Wolaita Sodo University, Wolaita, Ethiopia



CRC Press

Taylor & Francis Group

Boca Raton London New York

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

First edition published 2022

by CRC Press

6000 Broken Sound Parkway NW, Suite 300, Boca Raton, FL 33487-2742

and by CRC Press

2 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN

© 2022 selection and editorial matter, Azamal Husen; individual chapters, the contributors

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ISBN: 9780367685256 (hbk)

ISBN: 9781032109121 (pbk)

ISBN: 9781003137955 (ebk)

DOI: 10.1201/9781003137955

Typeset in Times

by Deanta Global Publishing Services, Chennai, India

Dedication



Abu Ali Ibn Sina (980–1037 AD)

(A great physician, astronomer, thinker, and writer of the Islamic Golden Age, and the father of early modern medicine)



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Contents

Preface.....	ix
About the Editor.....	xi
Contributors	xiii
Disclaimer.....	xvii

Chapter 1 Plant-based Potential Nutraceuticals for Improving the Human Immune System.....	1
---	---

Azamal Husen and Muhammad Iqbal

Chapter 2 Antibacterial Properties of Medicinal Plants: Recent Trends, Progress, and Challenges	13
---	----

*Limenew Abate, Archana Bachheti, Rakesh Kumar Bachheti,
and Azamal Husen*

Chapter 3 Antiviral Activity of Medicinal Plants: Current Understanding, Prospects, and Challenges	55
--	----

Venkatesh V P, Nivya V, Vani V, Baskaran V, and Madan Kumar P

Chapter 4 Conventional Medicinal Plants: Boosting the Immune System in Humans.....	75
--	----

*Antul Kumar, Anuj Choudhary, Harmanjot Kaur,
Asish Kumar Padhy, and Sahil Mehta*

Chapter 5 Medicinal Plants for Strong Immune System and Traditional Skin Therapy in South Africa: An Overview	123
---	-----

Learnmore Kambizi and Callistus Bvenura

Chapter 6 Traditional African Medicinal Plants for a Strong Immune System.....	173
---	-----

Anywar Godwin

Chapter 7 Traditional Brazilian Medicinal Plants for a Strong Immune System.....	199
--	-----

*José Crisólogo de Sales Silva,
Solma Lúcia Souto Maior de Araújo Baltar,
and Maria Lusía de Moraes Belo Bezerra*

Chapter 8	Traditional Himalayan Plants: Nature's Gift for Maintaining a Strong Immune System	211
	<i>Antul Kumar, Anuj Choudhary, Harmanjot Kaur, Atul Arya, Baljinder Singh, and Sahil Mehta</i>	
Chapter 9	Traditional South Indian Herbal Plants for a Strong Immune System.....	245
	<i>Mani Divya and Sekar Vijayakumar</i>	
Chapter 10	Sacred Medicinal Plants and their Use by Indigenous People for Strengthening the Immune System.....	255
	<i>Jamal Akhtar and Fouzia Bashir</i>	
Chapter 11	Molecular Features of Potential Herbal Products in Enhancing Human Immune System.....	301
	<i>Chandrabose Selvaraj, Chandrabose Yogeswari, and Sanjeev Kumar Singh</i>	
Chapter 12	Specific Plant Nutrients and Vitamins that Fortify Human Immune System.....	363
	<i>Kirubel Teshome Tadele and Gebeyanesh Worku Zerssa</i>	
Chapter 13	Role of Specific Spices in Fortifying the Human Immune System.....	397
	<i>Yashdeep Srivastava, Swati Upadhyay, Mohd Ahmad, Deepak Kumar Verma, and Vinod Kumar Mishra</i>	
Chapter 14	Specific Fruits and Berries for a Strong Human Immune System	411
	<i>Rakesh Kumar</i>	
Chapter 15	Natural Immunity Boosters and Anticancer Medicinal Plants.....	431
	<i>Swati Agarwal, Sonu Kumari, and Amrendra Kumar</i>	
Chapter 16	Potential of Medicinal Plants as Immunity Booster against COVID-19.....	455
	<i>Saumya Pandey</i>	
Index		475

Preface

The goal of this book is to provide a review, as thorough and up-to-date as possible, of the state-of-the-art herbal therapy for strong human immune systems and research-based information on medicinal plants used for this purpose. A large number of people around the world suffer from daily inconvenience and unpleasantness of a deficient immune system. Tiredness, frequent colds, infections, allergies, mood swings, and premature ageing are all common manifestations of a weakened immunity. The human immune system is an invisible bodyguard, fighting off invasion and working tirelessly around the clock to keep the human body fit and healthy. The immune system is responsible for responding when anyone is exposed to viruses, bacteria, or other microbes, has a cut or a broken bone, or when cells begin to change in an abnormal way, as in the early stages of cancer. The immune system also plays the vital role of differentiating the live materials belonging to the body from those coming from outside, and quickly eliminating the foreign proteins from bacteria, virus, or other microbes. It is also responsible for inflammation, the natural process that occurs in response to injury and is incredibly important to initiate healing, although too much of it can be detrimental and is linked to heart disease, diabetes, cancer, and many other illnesses.

In this connection, medicinal plants and their products are able to affect the immune system and act as immunomodulators. Numerous medicinal plants are popularly used in folk medicine to increase resistance of the body; they strengthen the human immune defence and improve body reactions against infectious agents or exogenous injuries, suppressing the abnormal immune response occurring in immune disorders. Many herbs, shrubs, climbers, or trees, such as *Allium fistulosum*, *Allium sativum*, *Aloe vera*, *Andrographis paniculata*, *Calendula officinalis*, *Camellia sinensis*, *Catharanthus roseus*, *Cinnamomum camphora*, *Curcuma longa*, *Echinacea purpurea*, *Echinacea angustifolia*, *Elettaria cardamomum*, *Emblica officinalis*, *Eucalyptus* spp., *Glycyrrhiza glabra*, *Hypericum perforatum*, *Mentha piperita*, *Nigella sativa*, *Origanum vulgare*, *Ocimum sanctum*, *Ocimum basilicum*, *Panax ginseng*, *Salvia officinalis*, *Sambucus nigra*, *Taraxacum officinale*, *Thymus vulgaris*, *Withania somnifera*, *Zingiber officinale*, etc., have shown success in strengthening immunity against the H1N1 virus, influenza, hepatitis and swine flu-virus, among others. These plants and their products have some specific properties to reduce stress and anxiety, absorb odours and mould, eliminate headaches, improve mood and brain function, enhance blood and oxygen circulation, increase energy levels, boost healing processes, maintain blood pressure, act as a source of vitamins and improve a number of bodily functions. Moreover, these plants have acted as an antiviral and antibacterial agent; and boosted the immune system against cancer, HIV, and COVID-19. This book addresses these issues and many more. In the future, medicinal plant-based products are likely to be in higher demand to facilitate and strengthen the human immune system against infections, allergies, and related ailments. Taken together, this book aims to cover both the indigenous and scientific

knowledge about medicinal plants, and the protective and therapeutic potential and mode of action of plant-based drinks, supplements, nutraceuticals, synergy foods, superfoods, and other products. I hope that this book will be a useful resource to stimulate further research interest in plant-derived medications and will inspire students, industrialists, and policy makers.

With great pleasure, I extend my sincere thanks to all contributors for their timely response, and the excellent, up-to-date contributions. I am extremely thankful to Ms. Randy Brehm, Dr Julia Tanner, and all associates at Taylor & Francis Group, LLC/ CRC Press for their sustained cooperation. I shall be happy receiving comments and criticism, if any, from subject experts and general readers of this book.

Azamal Husen
Wolaita, Ethiopia

About the Editor



Professor Azamal Husen (BSc from Shri Murli Manohar Town Post Graduate College, Ballia, UP, MSc from Hamdard University, New Delhi, and PhD from Forest Research Institute, Dehra Dun, India) is a Foreign Delegate at Wolaita Sodo University, Wolaita, Ethiopia. He has served the University of Gondar, Ethiopia, as a Full Professor of Biology, and also worked as the Coordinator of the MSc Program and as the Head, Department of Biology. He was a Visiting Faculty of the Forest Research Institute, and the

Doon College of Agriculture and Forest at Dehra Dun, India. He has more than 20 years' experience of teaching, research, and administration.

Dr Husen specializes in biogenic nanomaterial fabrication and their application, plant responses to nanomaterials, plant production and adaptation to harsh environments at the physiological, biochemical, and molecular levels, herbal medicine, and clonal propagation and improvement of tree species. He has conducted several research projects sponsored by various funding agencies, including the World Bank, the Indian Council of Agriculture Research (ICAR), the Indian Council of Forest Research Education (ICFRE); and the Japan Bank for International Cooperation (JBIC).

He has published over 150 research papers, review articles and book chapters, edited books of international repute, presented papers in several conferences, and produced over a dozen manuals and monographs. Dr Husen received four fellowships from India and a recognition award from the University of Gondar, Ethiopia, for excellent teaching, research, and community service. An active organizer of seminars/conferences and an efficient evaluator of research projects and book proposals, Dr Husen has been on the Editorial board and the panel of reviewers of several reputed journals published by Elsevier, Frontiers Media SA, Taylor & Francis, Springer Nature, RSC, Oxford University Press, Sciendo, The Royal Society, CSIRO, PLOS, and John Wiley & Sons. He is on the advisory board of Cambridge Scholars Publishing, UK. He is a Fellow of the Plantae group of the American Society of Plant Biologists, and a Member of the International Society of Root Research, Asian Council of Science Editors, ISDS, and INPST. In addition, he is Editor-in-Chief of the American Journal of Plant Physiology; and a Series Editor of 'Exploring Medicinal Plants', published by Taylor & Francis Group, USA.



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Contributors

Limenew Abate

Department of Industrial Chemistry
College of Applied Sciences
Addis Ababa Science and Technology
University
Addis Ababa, Ethiopia

Swati Agarwal

Department of Bioscience and
Biotechnology
Banasthali University
P.O. Banasthali Vidyapith
Rajasthan, India

Mohd Ahmad

S.R. Institute of Management and
Technology
Lucknow, India

Jamal Akhtar

Central Council for Research in Unani
Medicine
Institutional Area
New Delhi, India

Atul Arya

Medicinal Plant Research Laboratory
Department of Botany
Ramjas College
University of Delhi
Delhi, India

Archana Bachheti

Department of Environment Science
Graphic Era University, Dehra Dun
Uttarakhand, India

Rakesh Kumar Bachheti

Centre of Excellence in Nanotechnology
Addis Ababa Science and Technology
University
Addis Ababa, Ethiopia

**Solma Lúcia Souto Maior
de Araújo Baltar**

Department of Biological Sciences
Campus Arapiraca
Federal University of Alagoas
Brazil

Fouzia Bashir

Central Council for Research in Unani
Medicine
Institutional Area
New Delhi, India

Maria Lusía de Moraes Belo Bezerra

Department of Biological Sciences
Campus Arapiraca
Federal University of Alagoas
Brazil

Callistus Bvenura

Cape Peninsula University of
Technology
Horticultural Sciences Department
Cape Town, South Africa

Anuj Choudhary

Department of Botany
Punjab Agricultural University
Ludhiana, India

Mani Divya

Biomaterials and Biotechnology in
Animal Health Lab
Nanobiosciences and
Nanopharmacology Division
Department of Animal Health and
Management
Alagappa University
Karaikudi, India

Anywar Godwin

Department of Plant Sciences
Microbiology & Biotechnology
Makerere University
Kampala, Uganda

Azamal Husen

Wolaita Sodo University
Wolaita, Ethiopia

Muhammad Iqbal

Department of Botany
Faculty of Science
Hamdard University
New Delhi, India

Learnmore Kambizi

Cape Peninsula University of
Technology
Horticultural Sciences Department
Cape Town, South Africa

Harmanjot Kaur

Department of Botany
Punjab Agricultural University
Ludhiana, India

Amrendra Kumar

Division of Livestock Production
Indian Council of Agricultural
Research
Research Complex for North Eastern
Hill Region
Meghalaya, India

Antul Kumar

Department of Botany
Punjab Agricultural University
Ludhiana, India

Deepak Kumar Verma

Centre for Health Research and
Innovation (CHRI)
Lucknow, India

Madan Kumar P

Department of Biochemistry
CSIR-Central Food Technological
Research Institute
Mysore, India

and

Academy of Scientific and Innovative
Research (AcSIR)
Ghaziabad, India

Rakesh Kumar

Vijay Singh Pathik Government Post
Graduate College
Kairana, India

Sahil Mehta

International Centre for Genetic
Engineering and Biotechnology
Aruna Asaf Ali Marg
New Delhi, India

Vinod Kumar Mishra

S.R. Institute of Management and
Technology
Lucknow, India

Sanjeev Kumar Singh

Department of Bioinformatics
Alagappa University
Karaikudi, India

Sonu Kumari

Department of Bioscience and
Biotechnology
Banasthali University
P.O. Banasthali Vidyapith Rajasthan
Rajasthan, India

Asish Kumar Padhy

National Institute of Plant Genome
Research
Aruna Asaf Ali Marg
New Delhi, India

Saumya Pandey

School of Agriculture
Uttaranchal University
Uttarakhand, India

Chandrabose Selvaraj

Department of Bioinformatics
Alagappa University
Karaikudi, India

José Crisólogo de Sales Silva

Department of Animal Science
Campus Santana do Ipanema
State University of Alagoas
Brazil

Baljinder Singh

National Institute of Plant Genome
Research
Aruna Asaf Ali Marg
New Delhi, India

Yashdeep Srivastava

S.R. Institute of Management and
Technology
Lucknow, India

Kirubel Teshome Tadele

Chemistry Department
Natural Sciences College
Jimma University
Jimma, Ethiopia

Swati Upadhyay

S.R. Institute of Management and
Technology
Lucknow, India

Sekar Vijayakumar

Marine College
Shandong University
Weihai, P.R. China

Vani V

Department of Biochemistry
CSIR-Central Food Technological
Research Institute
Mysore, India

and

Academy of Scientific and Innovative
Research (AcSIR)
Ghaziabad, India

Venkatesh V P

Department of Biochemistry
CSIR-Central Food Technological
Research Institute
Mysore, India

and

Academy of Scientific and Innovative
Research (AcSIR)
Ghaziabad, India

Nivya V

Department of Biochemistry
CSIR-Central Food Technological
Research Institute
Mysore, India

and

Academy of Scientific and Innovative
Research (AcSIR)
Ghaziabad, India

Baskaran V

Department of Biochemistry
CSIR-Central Food Technological
Research Institute
Mysore, India

and

Academy of Scientific and Innovative
Research (AcSIR)
Ghaziabad, India

Chandrabose Yogeswari

Vetri Siddha Medical College
Hospital & Research Institute
Madurai, India

Gebeyanesh Worku Zerssa

Natural Resource Management
Department
College of Agriculture and Veterinary
Medicine
Jimma University
Jimma, Ethiopia

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The author and the publishers of this work have checked the sources and believe that the given information presented is genuine. This is only a reference book, not intending to offer any nutritional or medical advice. The information on the role and uses of medicinal plants does not constitute any recommendation. The author and publishers are not responsible if any reader uses these plants for a nutritional or therapeutic purpose.



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1 Plant-based Potential Nutraceuticals for Improving the Human Immune System

Azamal Husen and Muhammad Iqbal

CONTENTS

1.1 Introduction	1
1.2 Immunomodulatory Phytochemicals and Associated Responses	4
1.3 Synergistic Effect of Herbal and Other Plant Products	5
1.4 Conclusion	8
References	8

1.1 INTRODUCTION

Our immune system uses our body's own defence mechanisms to guard against damage, disease, and infections. Composed of various tissues, cells, and proteins, the immune system is a highly complex and multifaceted system, forming an intricate network of cells and proteins that moves throughout the human body *via* the lymph stream and blood stream. A healthy immune system is able to distinguish between body cells (self) and foreign materials (non-self), eliminating the latter. It can also recognize and destroy abnormal cells derived from host tissues. In an autoimmune reaction, however, antibodies and immune cells target the body's own healthy tissues by mistake, signalling the body to attack them (Terrie, 2017). Undernourishment or deficiency of zinc, selenium, iron, copper, or vitamins A, C, E, B₆, or B₉ (folic acid) significantly influence immune system responses. On the other hand, overeating and being overweight or obese may also hamper the immune response. Moreover, chronic stress, lack of sleep, specific medical conditions, prolonged use of corticosteroids or immunosuppressive agents, or immune-mediated diseases damage our immune system (Terrie, 2017). Immunity decreases and morbidity increases with increasing age due to deficiencies of vitamins C, D, E, B₆, B₉, and elements such as zinc, and/or selenium. (Ritz et al., 2009). Use of vitamin D supplements strengthens the physical barrier against viruses, stimulates production of antimicrobial peptides,

and attenuates formation of inflammatory cytokines, whereas selenium improves the function of cytotoxic effector cells and helps in maintaining T-cell functions and the production of T-cell-dependent antibodies. Vitamin C enhances production of antiviral cytokines and free radicals, thus reducing the virus yield, and also inhibits excessive inflammatory responses and/or hyperactivation of immune cells (Bae and Kim, 2020). Use of nutraceuticals supports restoration of the immune system, particularly in the elderly.

Immunomodulators influence the immune system efficiently. These agents strengthen the immune defences, improve the body’s reaction against microbial infections and/or injuries, and suppress irregular immune responses. Nutraceuticals (chemicals from food with health benefits in excess of their nutritional value) are bio-active compounds naturally present in foods, dietary supplements, and plant products/extracts, which have acknowledged potential health applications (Figure 1.1). They play a vital role in maintaining a healthy body by providing necessary supplements required for various metabolic processes in order to regulate bodily functions.

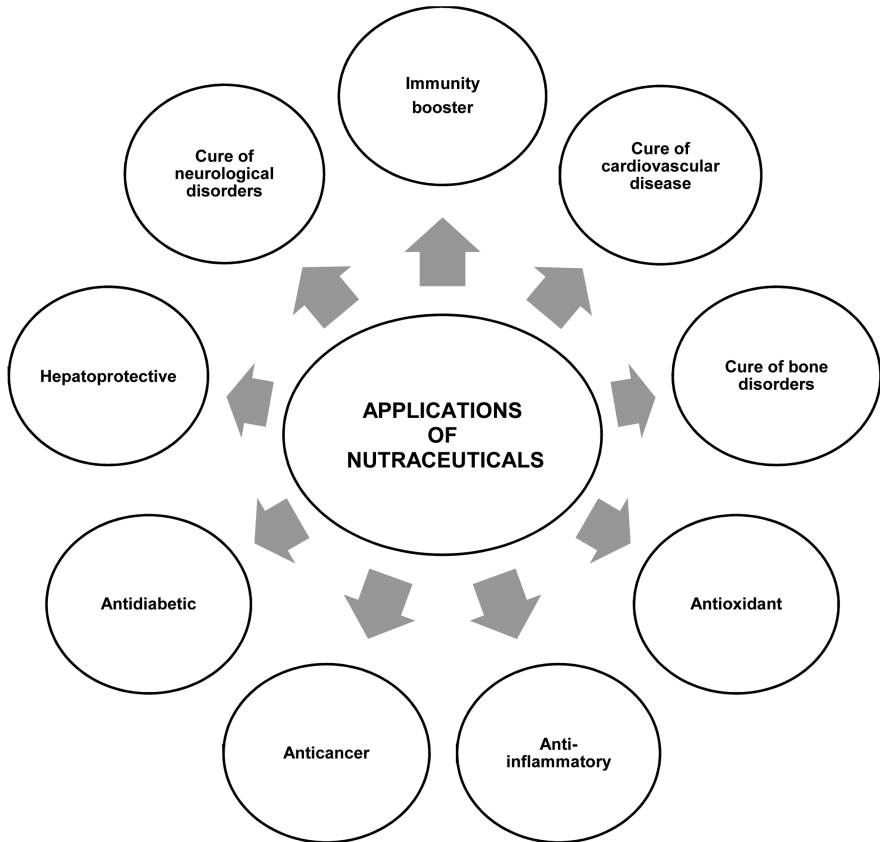


FIGURE 1.1 Various potential applications of nutraceuticals.

Herbs or herbal products may not act as precisely as antibiotics but have proven to be antibacterial (even antiviral) by boosting our body's own defence mechanisms (Nasri et al., 2014; Chanda et al., 2019). Nutraceuticals obtained from plants act as the probable immunomodulating agents in such products. Phytochemicals (flavonoids, folate, polyamines, alkaloids, terpenoids, etc.) and other, essential nutrients (mainly carbohydrates, proteins, fatty acids, minerals, and vitamins) play an important role in maintaining a balance between health and disease (Parveen et al., 2020b). Thus, nutrition is a crucial factor in modulating immune homeostasis. Protein–energy malnutrition or even subclinical deficiencies of a single micronutrient may impair immune responses (Bhaskaram, 2001). Calder et al. (2020) elucidated the significance of optimal nutritional status to resist against viral infections, asserting the roles of vitamins (such as A, B₆, B₁₂, C, D, E, and folate), trace elements (such as zinc, iron, selenium, magnesium, and copper) and the omega-3 fatty acids (such as eicosapentaenoic acid and docosahexaenoic acid) in supporting the immune system. Vitamins A and D have a potential benefit, especially in vitamin-deficient populations, while the micronutrients selenium and zinc give favourable immunomodulatory effects during viral respiratory infections, and many nutraceuticals and probiotics facilitate immune functions (Jayawardena et al., 2020). While proposing nutritional strategies to reduce damage to lungs from coronavirus and other infections, Wu and Zha (2020) asserted that the most promising, fact-acting treatments are herbal formulations, which probably address lung, heart, liver, and kidney functions simultaneously. Rathaur et al. (2020) and Parveen et al. (2020a, 2020b) have described the usefulness of single and compound herbal drugs used in the Ayurvedic and Unani systems of Indian medicine, respectively.

Various food components have the ability to modulate cellular processes and stimulate the immune system. For instance, peppermint (*Mentha × piperita*) and oils obtained from this plant are used as antispasmodic, aromatic, and antiseptic agents and are used for treating cancers, colds, cramps, indigestion, nausea, sore throat, and toothaches (Briggs, 1993). Yellow turmeric powder, a product of *Curcuma longa*, is very active against a range of bacteria, fungi, and viruses, as well as parasites (Moghadamtousi et al., 2014; Prasad and Tyagi, 2015). *Panax ginseng* (Asian ginseng) is used as a tonic, is known to promote immunity (Kang and Min, 2012), and has protective effects for the treatment of neurological disorders (Ong et al., 2015). *Astragalus membranaceus* (commonly known as Mongolian milkvetch) is rich in polysaccharides, flavonoids, and saponins (Auyeung et al., 2016), and exhibits powerful immunity-enhancing, antioxidant, hepatoprotective, antidiabetic, and anticancer activities (Zhao et al., 1990; Auyeung et al., 2016; Wu et al., 2017). The most common and widely used herbal plants, such *Allium sativum* (garlic), *Allium cepa* (onion), and *Zingiber officinale* (ginger), are the basis of all healing herbal products, and can be categorized as food and spice, as well as medicine. In many remote areas, various plants and their products are used as ethnomedicines for treatment of all physical ailments of the local populations (Anis and Iqbal, 1994; Anis et al., 2000; Beigh et al., 2014). We intend to briefly discuss in this chapter some plant-based nutraceuticals and their role in improving the human immune system to ensure and maintain a high quality of life.

1.2 IMMUNOMODULATORY PHYTOCHEMICALS AND ASSOCIATED RESPONSES

Phytochemicals, mainly alkaloids, phenolics, glycoproteins and saponins, can exhibit anti-inflammatory and immunomodulatory features. Additionally, terpenoids, polysaccharides, fatty acids, minerals, vitamins, etc. also play an important role as immunomodulatory agents and help in disease prevention. Polysaccharides from plants have shown low toxicity in comparison with immunomodulatory bacterial polysaccharides and many synthetic compounds (Albuquerque et al., 2020). Therefore, they are the ideal alternative agents to achieve immunomodulation. Since ancient times, it has been recognized that plants, plant parts, or their products and extracts are the sources of medicinally active compounds (Figure 1.2). For instance, alkaloids from plants are utilized as antimalarial agents (quinine), anticancer agents (vinblastine, vincristine, and taxol), and to regulate blood circulation, especially in the brain (vincamine). The terpenoid steroidal saponins obtained from plants, including *Solanum aethiopicum* (Ethiopian eggplant), *Capsicum annuum* (capsicum peppers), *Panax ginseng* (ginseng), and *Yucca schidigera* (Mojave yucca) (Hussain et al., 2015), have shown hypoglycaemic, antioxidant, antifungal, neurotrophic, neuroprotective, and viricidal effects. Such saponins are also involved in the reduction of low-density lipoprotein (LDL)-cholesterol and serum cholesterol levels, inhibition of cancer cell proliferation, and fortification of the cell-mediated immune system (Ding et al., 2019). Reports have also suggested that carotenoids, another class of terpenoids, significantly decrease the risk of prostate, lung, and breast cancers (Mills et al., 1989; Ziegler et al., 1996; Zhang et al., 1997) and provide protection against eye diseases (Yeum et al., 1995).

Many plants, such as vegetables (broccoli, green bell pepper, kale, onion, spinach, and tomato), fruits and herbs, mainly *Citrus grandis*, *Hypericum perforatum*, and *Sophora japonica*, are a rich source of flavonoids (a subclass of plant phenolics). Flavonoids play a defensive role in coronary heart diseases, and exhibit antiviral, anti-allergenic, anti-cholinesterase, anticancer, and antioxidant activities (Ren et al. 2003; Ullah et al. 2020). Quercetin, a plant flavonol from the flavonoid group of

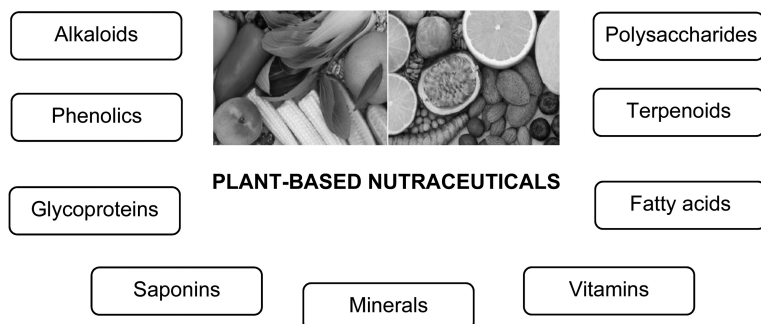


FIGURE 1.2 Major plant-based nutraceuticals.

polyphenols, is an effective antioxidant, and plays a significant role against cardiovascular disease (Finotti and Di Majo, 2003), diabetes, and HIV (Li et al., 2000). Likewise, tannins (water-soluble polyphenol derivatives), which are naturally synthesized and accumulated in various plant parts, are a secondary metabolic product exhibiting numerous useful healthy properties, showing anti-inflammatory, antimicrobial, antileishmanial, immunomodulatory, analgesic, anti-lymphocytic, neuroprotective, antidiarrhoeal, and antihypertensive activities (Uritu et al., 2018). Garlic is rich in sulphur compounds, which stimulate the immune system and decrease atherogenesis, platelet stickiness, and cancer (Arreola et al., 2015; Shang et al., 2019). Sulphoraphane (an antioxidant and stimulator of natural detoxifying enzymes, abundantly found in *Brassica oleracea* var *italica* (broccoli), is an effective phase 2 enzyme inducer, and produces D-glucarolactone, which is an important breast cancer inhibitor (Ghazanfari et al., 2002). Some common plant-based nutraceuticals and their roles in stimulating the immune system are listed in Table 1.1.

1.3 SYNERGISTIC EFFECT OF HERBAL AND OTHER PLANT PRODUCTS

Many nutraceuticals act together synergistically, exhibiting superior performances when co-delivered (Leena et al., 2020). For instance, the interactive herbal combination, known as Triphala (“three fruits”), is prepared by mixing *Terminalia bellirica*, *Terminalia chebula*, and *Emblica officinalis* together for use as a nutritive tonic. This herbal preparation, based on synergy, benefits almost all organs/systems of the human body, most specifically skin, liver, eyes, and the digestive and respiratory systems. It is therapeutically useful in terms of immunomodulation, and as an antibacterial and antimutagenic product (Belapurkar et al., 2014; Peterson et al., 2017). Phytochemicals from tomatoes (*Solanum lycopersicum*) and olive oil from *Olea europaea* also have synergistic effect, as tomatoes contain carotenoids (principally lycopene), which are fat-soluble and their absorption into the bloodstream is higher in a lipid medium, such as olive oil. Lycopene, with its powerful antioxidant nature, minimizes the risk of cardiovascular diseases by improving the serum lipid profile in a high-fat diet. Lycopene bioavailability increases between five- and six-fold following cooking of tomatoes, compared with eating them raw (Fielding et al., 2005; Ahuja et al., 2006; Story et al., 2010). Black grapes are rich in catechins, polyphenol antioxidants that can reduce the risk of obesity, cardiovascular disorders, cancer, and neurological problems. In combination with onion, consumption of black grapes causes a synergistic anti-proliferative effect, compared with consuming onions or grapes alone. The combination inhibits blood clots, improves blood circulation, and boosts cardiovascular health (Wang et al., 2013). Foods like green tea and black pepper also work in a synergistic way, with black pepper increasing the bioavailability of epigallocatechin-3-gallate (EGCG), a useful component of green tea. Piperine, a major alkaloid present in black pepper, inhibits the glucouronidation of EGCG, thereby lowering the transit rate of EGCG in the gastrointestinal (GI) tract and thus increasing its residence time, which ensures maximum absorption. The high catechin content of green tea improves immunotolerance, thereby reducing the possibility of

TABLE 1.1
Examples of Plants Commonly Used as Nutraceuticals, Their Important Phytochemical Constituents, and Their Immune System Functions

Plant Name	Family	Phytochemical Constituents	Immune System Functions
<i>Acacia catechu</i> Willd.	Fabaceae	Flavonoids, phenolic acids, catechins	Immunoaugment and anti-inflammatory activity
<i>Aloe vera</i> (L.) Burman	Asphodelaceae	Acemannan, dithydrocoumarins	Immunostimulant
<i>Andrographis paniculata</i> (Burm. f.) Nees	Acanthaceae	Diterpene lactones (andrographolide)	Immunomodulant/immunosuppressor
<i>Artocarpus tonkinensis</i> A. Chev. ex Gagnep	Moraceae	Auronol glycosides (maeospin 4- <i>O</i> -glucoside and alphonin-4- <i>O</i> -glucoside)	Inhibits humoral and cellular adaptive immunity/immunosuppressor
<i>Astragalus membranaceus</i> (Fisch.) Bge.	Fabaceae	Polysaccharides	Stimulate cellular immunity/immunostimulant
<i>Boswellia serrata</i> Roxb. ex Colebr.	Bursaceae	Boswellic acid	Anti-anaphylactic and mast cell stabilization/immunosuppressor
<i>Camellia sinensis</i> (L.) Kuntze	Theaceae	Polysaccharides	Immunomodulant/immunostimulant
<i>Centella asiatica</i> (L.) Urban	Apiaceae	Madecassoside	Regulates the abnormal humoral and cellular immunity/immunosuppressor
<i>Curcuma longa</i> L.	Zingiberaceae	Curcuminoids	Anti-inflammatory and immunosuppressive activity/immunosuppressor
<i>Echinacea purpurea</i> (L.) Moench	Asteraceae	Alkylamides, glycoproteins, polysaccharides	Anti-inflammatory, immunomodulator and antiviral
<i>Glycyrrhiza glabra</i> L.	Fabaceae	Triterpene saponins (glycyrrhizin)	Anti-inflammatory activity/immunostimulant
<i>Hypoxis rooperi</i> T. Moore	Hypoxidaceae	Phenolic glucosides (hypoxoside)	Immunoaugment and anti-inflammatory activity
<i>Ocimum sanctum</i> L.	Lamiaceae	Monoterpenes (eugenol and methyl eugenol), sesquiterpenes (β -caryophyllene)	Immunostimulant
<i>Panax ginseng</i> C.A. Meyer	Araliaceae	Ginsenosides and panaxosides	Immunostimulant
<i>Syzygium aromaticum</i> (L.) Merr. and L.M. Perry	Myrtaceae	Monoterpenes (eugenol), sesquiterpenes (β -caryophyllene)	Immunostimulant
<i>Tinospora cordifolia</i> (Thunb.) Miers	Menispermaceae	Arabinogalactan	Immunostimulant
<i>Withania somnifera</i> (L.) Dunal	Solanaceae	Steroidal lactones (withaferin A)	Immunostimulant
<i>Zingiber officinalis</i> Roscoe	Zingiberaceae	Phenolics (gingerols)	Immunostimulant

cancer incidence, cardiovascular disease, and elevated cholesterol (Lambert et al., 2004). Similarly, lemon juice, consumed with green tea, enhances the absorption of EGCG ten-fold, as compared with the absorption when green tea is taken alone (Tewari et al., 2000). Furthermore, ascorbic acid (vitamin C), present at high concentrations in lemon, acts synergistically with catechins to stimulate the absorption and utilization of the antioxidant components of green tea five-fold, in comparison with green tea taken alone (Majchrzak et al., 2004; Intra and Kuo, 2007). All these combinations of nutraceuticals boost our immune system in one way or another and enable our body to fight against diseases and disorders.

Honey and garlic each have remarkable antibacterial properties, stimulating the immune system and exhibiting antibacterial activity, while acting synergistically to reduce bacterial growth, an effect which is further enhanced by the presence of phenolics and fatty acids (Natarajan et al., 2019). The combination of honey and garlic is also well known for lowering blood cholesterol and triglyceride levels and providing relief of cardiovascular problems (Shoba et al., 1998). Garlic increases the production of gastric juices and helps in increasing iron absorption (Shoba et al., 1998). Chen et al. (2005) reported that the flavonoids from almond skin acted synergistically with vitamins C and E to protect LDL-cholesterol oxidation. Similarly, a combination of green leafy vegetables and lemon is effective at increasing haemoglobin concentration in iron-deficient anaemic patients, as vitamin C accelerates the dietary absorption of non-haem iron (Hallberg et al., 1989). Furthermore, Fernandez and Marette (2017) suggested that bananas energize growth of beneficial bacteria in yoghurt, with the combination increasing immunity and regulating digestion. Inulins, prebiotic polysaccharides in a number of plants, are present in bananas, promoting the growth of probiotic (good) bacteria in yoghurt, which improves immunity and help in regulating our digestion. This banana–yoghurt combination also increases the level of calcium in our body. Studies on the interaction between turmeric and fish revealed that curcumin, the active component in turmeric, acts synergistically with the polyunsaturated fatty acids (PUFA), docosahexaenoic acid or eicosapentaenoic acid, in fish, decreasing the production of inflammatory eicosanoids and reactive oxygen species (ROS) to relieve oxidative stress (Saw et al., 2010). Piperine, the hot and active component of black pepper, increases the bioavailability of curcumin 1000-fold when added to turmeric or turmeric-based foods (Shoba et al., 1998). Piperine inhibits the metabolic breakdown of curcumin compounds in the gut and liver, thus promoting the bioavailability of curcumin compounds in the body.

In-vitro and *in-vivo* animal studies have shown that ginger (*Z. officinale*) has excellent anti-inflammatory, antioxidant, anti-platelet, hypotensive, and hypolipidaemic effects. Human trials with low ginger doses have demonstrated significant anti-platelet activity (Nicoll and Henein, 2007), although some recent studies have emphasized the need for more clinical trials (Marx et al., 2015). Evidence from animal studies suggests that ginger may help prevent ischaemia–reperfusion injury (IRI) in the heart. Hasanvand et al. (2019) have reported that the use of ginger reduced chest pain during coronary angioplasty, but its effect on the release of biochemical markers of myocardial damage was unclear. Pharmaceutical industries dealing in herb-based Ayurvedic and Unani medicines have developed several combinations

of garlic juice, ginger juice, lemon juice, honey, and apple cider vinegar for managing cardiovascular ailments and maintaining the overall physical and physiological health of the patient. Lipikyure, from Ekyure Herbals in India, is one such preparation with markedly positive results in lowering cholesterol and triglyceride levels, reducing body weight, improving blood circulation, and preventing cardiovascular disorders (e-Kyure, 2021). In addition, Lipikyure also strengthens the digestive system, lowers blood sugar, and ensures skin health due to the inclusion of apple cider vinegar as one of its components.

Recently, Jampilek and Kralova (2020) have suggested a special kind of food supplemented with various types of nanoparticles (nanonutraceuticals) for greater stability, bioavailability, and efficacy. However, it is important to make sure that all these combinations are safe, and do not have any adverse side-effects.

1.4 CONCLUSION

Nutraceuticals are foods based on plants and/or their products/extracts that have an established positive effect on human health. Plants are rich in bioactive constituents (phenolics, alkaloids, terpenoids, folates, polyamines, etc.) and other, essential nutrients (carbohydrates, proteins, fatty acids, minerals, and vitamins), which play a significant role in maintaining the balance between health and disease. Upgrading food products with nutraceuticals is highly desirable to reload the missing vitamins and other health-promoting substances in foodstuffs. Furthermore, the concept of food component synergy is beneficial as an immunity booster for disease control and other health benefits. However, due to limited information, more intensive research on this subject is both highly desirable and of vital importance. Additionally, the concept and practice of using synergistic food combinations for specific health benefits also require thorough investigation.

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2 Antibacterial Properties of Medicinal Plants

Recent Trends, Progress, and Challenges

*Limenew Abate, Archana Bachheti,
Rakesh Kumar Bachheti, and Azamal Husen*

CONTENTS

2.1	Introduction	14
2.2	Common Bacterial Diseases and Their Pathogenesis	16
2.3	Origin-based Classification of Medicinal Plants for Treatment of Bacterial Diseases, and Their Important Phytoconstituents	17
2.3.1	African Medicinal Plants.....	17
2.3.2	Medicinal Plants From the Americas	18
2.3.3	Chinese Medicinal Plants	19
2.3.4	Indian Medicinal Plants.....	19
2.3.5	European Medicinal Plants.....	20
2.4	Recent Progress in Bacterial Activities of Medicinal Plants.....	28
2.4.1	Medicinal Plants for Treating Bacterial Pneumonia	28
2.4.2	Medicinal Plants for Treating Cholera	28
2.4.3	Medicinal Plants for Treating Diphtheria.....	29
2.4.4	Medicinal Plants for Treating Gonorrhoea.....	29
2.4.5	Medicinal Plants for Treating Lyme Disease	30
2.4.6	Medicinal Plants for Treating Bacterial Meningitis	30
2.4.7	Medicinal Plants for Treating Syphilis.....	30
2.4.8	Medicinal Plants for Treating Tetanus.....	31
2.4.9	Medicinal Plants for Treating Tuberculosis.....	31
2.4.10	Medicinal Plants for Treating Typhoid.....	32
2.5	Significance of Antibacterial Drugs from Natural Sources	32
2.6	Mechanism and Mode of Action of Plant-based Antibacterial Drugs	33
2.7	Medicinal Plant-based Antibacterial Chemicals	37
2.8	Plant-based Nanoparticles for Antibacterial Activity.....	39
2.9	Conclusion and Future Perspective.....	40
	References.....	41

2.1 INTRODUCTION

There are various types of disease-causing microorganisms in nature which can cause infectious diseases in human beings. The main cause of morbidity and mortality is still microbial contagious diseases and microbial disease remains a dominant threat to the world (Cos et al. 2006). According to the World Health Organization (WHO, 2014), microbial infections are responsible for approximately half of the deaths each year, occurring mostly in developing and tropical countries worldwide (Fankam et al. 2011). The occurrence of drug-resistant bacterial pathogens leaves many bacterial infectious disease cases untreated and causes a major health problem in the world, resulting in morbidity and morbidity due to such failures of treatment (Levy and Marshall 2004; Ghosh and Haldar 2015). Inappropriate use of antibiotics is the main cause for the development of multidrug-resistant (MDR) pathogens (Bologa et al. 2013). The occurrence of MDR bacteria throughout the world results in ineffective treatment (Djeussi et al. 2013). This has an overwhelming effect on patients suffering from MDR bacterial infections, with the increased treatment cost also making it difficult to afford, as well as causing long-lasting illness and even death (World Health Organization 2014). Some infectious diseases, such as cholera, diphtheria, gonorrhoea, meningitis, syphilis, tetanus, and tuberculosis, cause large numbers of deaths annually, especially in developing countries, as a result of antibiotic resistance problems (Wang et al. 2008). Some research has indicated that, by 2050, the annual number of deaths annually due to MDR bacteria will increase to ten million each year, at a cost of one hundred trillion dollars (Anand et al. 2019). Reports on the significance of drug-resistant bacteria causing untreatable infections showed that the requirement for the development of new antibacterial therapies is more pressing than ever (Cushnie et al. 2014). To alleviate this problem, the use of natural active ingredients obtained from medicinal plants is one of the alternatives (Dhama et al. 2014). Recently, the interest in and awareness of medicinal plants as an alternative source of bioactive compounds against drug-resistant microorganisms have been growing (Uche-Okerefor et al. 2019). For instance, the bioactive compound berberine, extracted from *Berberis vulgaris*, is active against bacteria and protozoa, and piperine, isolated from *Piper nigrum*, is active against some fungi and bacteria, such as *Lactobacillus* spp., *Micrococcus* spp., *Escherichia coli*, and *Enterococcus faecalis*. Moreover, some infectious diseases caused by bacteria, fungi, and viruses can be treated by using tannins isolated from *Rhamnus purshiana* (Khameneh et al. 2019) (Figure 2.1). Bioactive compounds isolated from *Dorstenia* spp., such as amentoflavone and prenyl flavones, showed marked antibacterial activities against *Bacillus cereus* with minimum inhibitory concentration (MIC) values of 3 and 2.4 µg/ml, respectively (Kuate et al. 2007; Mbaveng et al. 2008) and, from flower extracts of *Retama raetam*, bioactive flavonoids called licoflavones also showed antibacterial activities against *E. coli*, with a MIC value of 7.81 µg/ml via the formation of complexes with soluble and extracellular proteins (Edziri et al. 2012). The alkaloids isolated by ethanol extraction of *Datura stramonium* tissue showed *in vitro*-antibacterial activities against some bacterial species, such as *Klebsiella pneumoniae*, *Proteus mirabilis*, *Staphylococcus aureus*, *E. coli*, and *Pseudomonas aeruginosa*, using the agar well diffusion method. The *Datura*

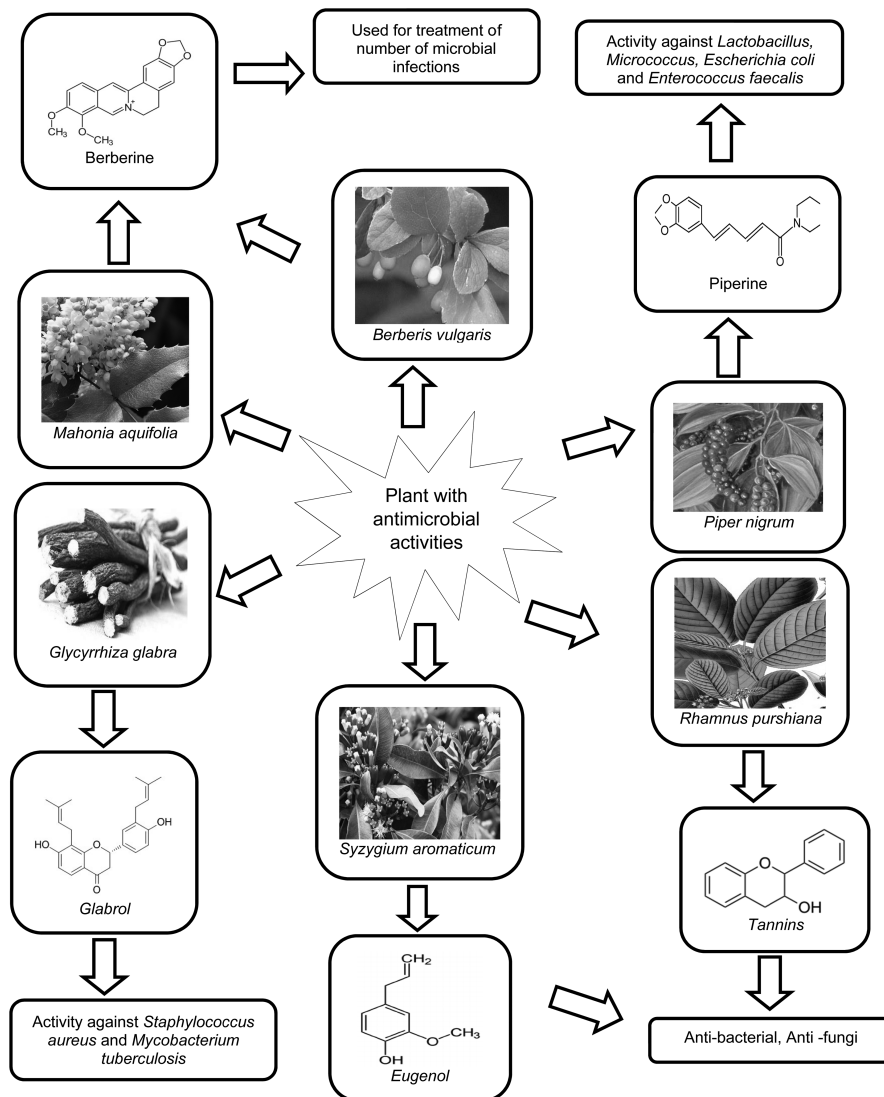


FIGURE 2.1 Antimicrobial activity of some plants and their extracts.

extract showed greater antibacterial effect than that achieved by standard antibiotics (Altameme et al. 2015). Adukwu et al. (2016) indicated that the components of essential oils (EOs) obtained from *Cymbopogon citratus* reduced the growth of *S. aureus* and *Acinetobacter baumannii*. According to Lahmar et al. (2017), synergistic antibacterial activity was achieved by mixing antibiotics and different EO components derived from *Thryptomene calycina*, *Clausena anisata*, *Callitris glaucophylla*, *Melaleuca alternifolia*, and *Eucalyptus* spp. The results showed a marked inhibitory

effect against *Alcaligenes faecalis*, *E. coli*, *Salmonella typhimurium*, *S. aureus* and *Ps. aeruginosa*. Nanoparticles synthesized from plant have been used for antibacterial activities, especially MDR bacteria (Alavi and Rai 2019). Nowadays, because of the presence and growing impact of antibiotic-resistant bacteria and the failure of conventional chemotherapy to treat infectious disease, the burden of bacterial infectious diseases is increasing. The behaviour of only a few phytochemicals from medicinal plants has been studied and the possible modes of action are not fully understood. The aim of this chapter is to provide up-to-date information on the use of medicinal plants as antibacterial agents and the challenges associated with this approach.

2.2 COMMON BACTERIAL DISEASES AND THEIR PATHOGENESIS

Bacteria are single-celled microbes (Bilombele 2019), coming in different sizes and shapes, and being very diverse (Yang et al. 2016). Bacteria can exist in any environment, such as in or on our bodies, in water, or in soil (Seiler and Berendonk 2012). Worldwide, they are the main cause of human morbidity and mortality. The inappropriate and excessive use of antibacterial and antibiotic drugs has caused the emergence of resistance in bacterial populations, which results in increases in the risks of health problems, such as the inability to treat illnesses caused by antibiotic-resistant bacteria (Asadi et al. 2019). Some examples of bacterial diseases include Legionnaires' pneumonia, bacterial vaginosis, gonorrhoea, chlamydia, syphilis, anthrax, tetanus, botulism, cholera, Lyme disease, bacterial meningitis, pneumococcal pneumonia, whooping cough, tuberculosis, listeriosis, etc. (Centers for Disease Control and Prevention 1997).

Different types of disease are associated with, if not definitively caused by, bacteria. For instance, Lyme disease and its complications by the tick-borne bacterium *Borrelia burgdorferi* (Diuk-Wasser et al. 2012), atherosclerosis is associated with *Chlamydia pneumoniae* (Watson and Alp 2008), Sudden Infant Death Syndrome (SIDS) with *Clostridium perfringens* (Deixler 2009), and bloodstream infections with *Klebsiella pneumonia* (Trecarichi et al. 2016). Additionally, *Parachlamydia acanthamoebae* in the human lung acts as an agent of pneumonia causing inflammation of the air sacs (Casson et al. 2008).

Another bacterial disease is cholera, caused by consuming drinking water or eating food contaminated with the bacterium *Vibrio cholerae*. It is an acute diarrhoeal infection, which induces disease exclusively in humans (Moore et al. 2014). Pelvic inflammatory disease (PID) is another bacterial disease that commonly occurs in females aged under 24 years of age. It is caused by bacterial vaginosis and results in infection and inflammation of the female genital tract, which can result in ectopic pregnancy, infertility, and serious reproductive morbidity (Kamwendo et al. 2000; Taylor et al. 2013). The common sexually transmitted disease (STD) gonorrhoea is caused by the bacterium *Neisseria gonorrhoeae*. This disease is transmitted from one person to another person *via* contact with contaminated clothes or bedsheets, or by sexual intercourse (Torpy et al. 2013). Some other common bacterial diseases are listed in Table 2.1.

TABLE 2.1**Common Diseases Caused by or Associated with Different Bacterial Species**

Bacterium	Disease	Reference
<i>Bartonella henselae</i>	Cat-scratch fever	Florin et al. (2008)
<i>Borrelia burgdorferi</i>	Lyme disease and its complications	Diuk-Wasser et al. (2012)
<i>Campylobacter jejuni</i>	Gastroenteritis	Sails et al. (2003)
<i>Chlamydia pneumoniae</i>	Atherosclerosis	Watson and Alp (2008)
<i>Clostridium perfringens</i>	Sudden Infant Death Syndrome (SIDS)	Deixler (2009)
<i>Clostridium difficile</i>	Antibiotic-induced diarrhoea and pseudomembranous colitis	Wilcox (2003)
<i>Corynebacterium amycolatum</i>	Hospital-acquired endocarditis	Knox and Holmes (2002)
<i>Escherichia coli</i>	Haemorrhagic colitis and haemolytic uraemic syndrome	Ameer et al. (2020)
<i>Ehrlichia chaffeensis</i>	Human ehrlichiosis	Mogg et al. (2020)
<i>Helicobacter pylori</i>	Duodenal and gastric ulcers	Ahmed and Belayneh (2019)
<i>Klebsiella pneumoniae</i>	Blood stream infections	Treacarichi et al. (2016)
<i>Legionella pneumophila</i>	Legionnaires' pneumonia	Edelstein et al. (2020)
<i>Enterococcus faecalis</i>	Nosocomial infections	Noskin et al. (1995)
<i>Listeria monocytogenes</i>	Listeriosis	Todd and Notermans (2011)
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	Nosocomial and community-associated infections	Alvarez et al. (2010)
<i>Salmonella enterica</i>	Salmonellosis	Dallap Schaer et al. (2010)
<i>Staphylococcus aureus</i>	Toxic shock syndrome	Tang et al. (2006)
<i>Streptococcus pyogenes</i>	Necrotizing and streptococcal toxic shock syndrome	Tang et al. (2006)
<i>Vibrio cholerae</i>	Epidemic cholera	Moore et al. (2014)
<i>Vibrio vulnificus</i>	Wound infection, septicaemia, and gastrointestinal disease	Tacket et al. (1984)

2.3 ORIGIN-BASED CLASSIFICATION OF MEDICINAL PLANTS FOR TREATMENT OF BACTERIAL DISEASES, AND THEIR IMPORTANT PHYTOCONSTITUENTS

2.3.1 AFRICAN MEDICINAL PLANTS

Approximately 80% of people in Africa cannot afford conventional drugs for treatment of bacterial infections. Nowadays, considerable attention is paid to finding new antibacterial drugs from local medicinal plants (Sieber et al. 2020). In South Africa, the bioactive compounds from *Teucrium trifidum*, like phenolic compounds such as tannins and flavonoids, showed antibacterial activity against *Bacillus subtilis*, *Streptococcus pyogenes*, *K. pneumoniae*, *P. aeruginosa*, *B. cereus*, *S. aureus*

and *V. cholerae* (Mazhangara et al. 2020). In Ethiopia, the antibacterial activity of *Jasminum floribundum*, *Euphorbia hirta*, *Euphorbia abyssinica*, *Sarcophy tepiriei* or *Commiphora myrrha* extracts are used in traditional treatment of infections of common human wounds by *E. coli*, *Ps. aeruginosa*, *S. aureus*, *S. pyogenes*, *P. mirabilis*, and *K. pneumoniae*. The results confirmed that the extracts exhibited growth inhibition zones on bacterial plates ranging from (mean \pm standard deviation) 10 ± 2 mm to 24.9 ± 0.9 mm in diameter (Mahammed et al. 2020). Phytochemicals such as glycosides (6.29 mg/g), flavonoids (6.51 mg/g), tannin (9.14 mg/g), saponins (10.54 mg/g), terpenoids (19.72 mg/g), and alkaloids (30.63 mg/g) were isolated from *Dacryodes edulis* leaf extracts, which showed antibacterial activities (Hassan-Olajokun et al. 2020). The polyphenols derived from four medicinal plants from Burkina Faso, namely *Sida acuta*, *Pterocarpus erinaceus*, *Khaya senegalensis*, and *Combretum micranthum*, were tested for their antibacterial activities against pathogenic bacteria such as *Klebsiella ozenae*, *S. aureus*, *Salmonella paratyphi*, and *Shigella dysenteriae*. The results showed antibacterial activities with MIC values in the range of 20–2000 mg/ml (Karou et al. 2005). Phytochemicals that were extracted in Kenya from *Centella asiatica*, such as terpenoids, flavonoids, tannins, saponins, cardiac glycosides, and alkaloids, showed antibacterial properties. For instance, flavonoids like catechins inhibited the growth of *Streptococcus mutans* and *V. cholerae* (Tapas et al., 2008), whereas quercetin caused growth reduction of *S. aureus* (Zwenger and Basu 2008). Alkaloids extracted from *Aspidosperma ramiflovum* were found to be significantly inhibitory toward *E. faecalis* and *S. aureus* (Tanaka et al. 2006), whereas those from *Sida acuta* showed antibacterial activity against *E. coli*, *E. faecalis*, *B. cereus*, *S. dysenteriae*, and *S. aureus* (Oyekunle et al. 2006). Tannins from extracts also showed inhibition against *Bacillus subtilis* and *S. aureus* (Kumar and Pandey 2013). Saponins from *Sorghum bicolor* were reported to be active against *S. aureus* (Anantharaman et al. 2010). In Nigeria, extracts of some plants, like *Acanthus montanus*, *Carica papaya*, *Acalypha fimbriata*, *Bauhinia variegata*, *Azadirachta indica*, and *Berlinia grandiflora*, have been used to treat syphilis (Abd El-Ghani 2016).

2.3.2 MEDICINAL PLANTS FROM THE AMERICAS

In the Americas, 20% of deaths annually are due to infectious diseases caused by bacteria. Approximately 2,600 species of vascular plants have been used as traditional medicines by people from North and South America (Mahady 2005). In Belize in central America, methanol, chloroform or hexane extracts of herbal plants were tested for the treatment of skin infections. Extracts of bark of *Bursera simaruba*, leaves and bark of *Syngonium podophyllum* and *Aristolochia trilobata*, leaves of *Hamelia patens*, and bark of *Guazuma ulmifolia* were tested against the bacteria *E. faecalis*, *S. aureus* and *Ps. aeruginosa* (Campoprese et al. 2003). In New York state in the USA, the Haudenosaunee peoples used the medicinal plants *Solidago canadensis*, *Hieracium pilosella*, *Ipomoea pandurata*, and *Achillea millefolium* for the treatment of diseases caused by different bacterial species. The result of a study showed that aqueous leaf extracts were strong enough to inhibit some species of bacteria,

such as *E. coli* and *S. typhimurium*, with predicted MIC values in the range of 1 µg/ml to 10 µg/ml. However, the value was 100–1000 µg/ml against *Lactococcus lactis* and *S. aureus* (Frey and Meyers 2010). Medicinal herbs in North America, such as *Allium sativum*, *Hyptis suaveolens*, *Syzygium aromaticum*, *Artemisia absinthium*, *Murraya koenigii*, *Datura metel*, *Lippia alba*, and *Chrysopogon zizanioides*, were used to treat Lyme disease and other tick-borne infections (Yarnell 2016).

2.3.3 CHINESE MEDICINAL PLANTS

Currently, the uses of Chinese herbal medicinal plants is receiving great attention. These herbal medicines are used in traditional Chinese medicine (TCM) to treat different infectious bacterial diseases (Wang et al. 2018). In Northwest Yunnan, China, some traditional medicinal plants, such as *Potentilla fulgens*, *Geranium strictipes*, *Elsholtzia blanda*, and *Elsholtzia rugulosa*, exhibited inhibition of *S. aureus* (Zuoa et al. 2008). McMurray et al. (2020) described the antibacterial activities of some Chinese medicinal plants, such as *Iris domestica*, *Anemone chinensis*, *Smilax glabra*, and *Agrimonia pilosa*, against *E. coli* and *L. monocytogenes*. The results showed MIC values in the range between 7.81 and 125 mg/l, compared with ampicillin. However, ampicillin MIC range was between 0.25 and 8 mg/l. Ginsenosides, bioactive compounds extracted from *Panax ginseng*, a common plant important in traditional Chinese medicine, also show a good antibacterial effect against *L. monocytogenes*, *Ps. aeruginosa*, and *Helicobacter pylori* (Kim et al. 2017), while flavonol glycosides extracted from another Chinese medicinal plant, *Ginkgo biloba*, indicated antibacterial activities against *E. coli* and *C. perfringens* (Lee and Kim 2002). Twelve A-type proanthocyanidins, isolated from *Ephedra sinica* using ethanol as the solvent, exhibited high bacterial inhibition (MIC values in the range 0.00515–1.38 mmol/l) against bacterial species, such as *S. aureus* and *Ps. aeruginosa* (Zang et al. 2013). Phenolic compounds isolated from the TCM plant *E. sinica* also showed considerable antibacterial activity against Gram-positive (*S. aureus*) and Gram-negative bacteria (*Ps. aeruginosa*) (Khan et al. 2017). Janovska et al. (2003) examined the antibacterial activities of ethanolic extracts of *Tussilago farfara*, *Salvia officinalis*, and *Chelidonium majus*, which are all TCM plants, the extracts showing very high activity against the bacteria *B. cereus*, *E. coli*, *S. aureus*, and *Ps. aeruginosa*, and the fungus *Candida albicans*.

2.3.4 INDIAN MEDICINAL PLANTS

The antibacterial activities of some Indian medicinal plants have been investigated. For instance, extracts of the plants *Woodfordia fruticosa*, *Mesua ferrea*, and *Manilkara hexandra* exhibited significant antibacterial activity against several *Staphylococcus* species (Hasan et al. 2013). Bioactive chemicals, like flavonoids, steroids, saponins, and/or tannins, from leaf extracts of *Cassia auriculata* exhibited strong antibacterial activities against five bacterial species, namely *P. mirabilis*, *S. aureus*, *P. aeruginosa*, *K. pneumoniae* and *E. coli* (Murugan et al. 2013). Shihabudeen et al. (2010) reported the antimicrobial effects of methanol extracts of *C. auriculata*

or *Eugenia jambolana*, containing phytochemicals, such as steroids, saponins, tannins, phenols, glycosides, coumarins, and flavonoids. The results revealed the greatest toxicity against the bacteria *E. coli*, *Staphylococcus epidermidis*, *Ps. aeruginosa*, *K. pneumoniae*, and *S. aureus*, and the fungi *C. albicans* and *Aspergillus niger*, using the disc diffusion method. South Indian traditional medicinal plants, like *Adhatoda vasica*, *Aegle marmelos*, *Ocimum gratissimum*, and *Ocimum sanctum*, were examined for their antibacterial activities against *K. pneumoniae*, *S. paratyphi*, *S. typhi*, *S. aureus*, and *E. coli*. The methanolic extract of some of those plants, such as *O. sanctum* and *O. gratissimum*, indicated antibacterial effects, with maximum zone of inhibition diameters of 25.5 mm and 30.0 mm diameter, respectively, against *S. typhi* (Prasannabalaji et al. 2012).

Swain and Rautray (2021) examined the antibacterial activities of regularly consumed Indian medicinal plants. The greatest antibacterial activities were observed in methanol extracts of turmeric (*Curcuma longa*) tested against *Ps. aeruginosa*, *K. pneumoniae*, and *S. aureus*, whereas some inhibition zone was observed in response to extracts of ginger (*Zingiber officinale*) against the same bacteria. Some Indian plants that had not previously been shown to be medicinal plants, such as *Pterygota alata*, *Murraya paniculata*, *Holigarna caustica*, *Acacia pennata*, *Elaeocarpus serratus*, *Bischofia javanica*, *Trema orientalis*, *Syzygium praecox*, *Smilax zeylanica*, and *Cinnamomum glaucescens*, have been used to control the formation of *S. aureus* biofilms (Panda et al. 2020).

2.3.5 EUROPEAN MEDICINAL PLANTS

Different plants have been studied in European countries for treatment of bacterial diseases (Toth et al. 2011). In a review of well-known medicinal plants in Italy used between 1850s to 1950s to treat bacterial skin diseases, some bioactive compounds, such as phenolics extracted from the root of *Beta vulgaris*, sulphides from the essential oil of garlic cloves (*A. sativum*), and alkaloids from the methanolic extract of the leaves of lettuce (*Lactuca sativa*) were used to treat skin infections caused by bacteria such as *E. coli*, *S. typhimurium* and *Providencia stuartii* (Mazzei et al. 2020). Aqueous and alcoholic extracts of aerial parts of *Achillea millefolium*, which grows in Europe, showed antibacterial activity against *E. faecalis*, *Micrococcus luteus*, *Salmonella enterica*, *S. aureus*, *Shigella flexneri*, and *Ps. aeruginosa*, although the aqueous extract exhibited low inhibition against *M. luteus* and *Ps. aeruginosa*. The greatest inhibitory effect of the alcoholic extract was against *M. luteus*, *S. aureus*, and *Ps. aeruginosa* (Hasson 2011). In another study, which was carried out on medicinal plants grown in the warmer part of southern Europe, the aqueous, chloroform or ethanolic extracts of *Tribulus terrestris* showed a marked inhibition of bacterial growth (Al-Bayati and Al-Mola 2008). The fruit of the plant had significant antibacterial activity towards *Bacillus subtilis*, *Corynebacterium diphtheriae*, and *S. aureus*, with effective MIC values of 0.15, 0.31, and 0.62 mg/ml, respectively (Al-Bayati and Al-Mola, 2008). In Poland, aqueous extracts of members of the Rosaceae family, such as *Rosa canina*, *Fragaria vesca*, *Rubus fruticosus*, *Rubus idaeus*, and *Agrimonia eupatoria*, have been widely used to neutralize the cholera toxin (Komiazyk et al. 2019) (Table 2.2).

TABLE 2.2
Ethnobotanical Data on the Medicinal Plants Identified as Active Against Various Bacterial Diseases

Bacteria	Antibacterial Plant	Antibacterial Active Compound(s)	Plant Parts	Extraction Solvent/ Analytical Method	Mechanism of Action	References
<i>Bacillus subtilis</i>	<i>Dracocephalum foetidum</i>	Limonene, <i>n</i> -menthol, and 8-dien-10-al	Aerial part	Hydrodistillation	Initiates changes in integrity or permeability of the cell membrane	Lee et al. (2007)
<i>Bacillus subtilis</i>	<i>Aloe secundiflora</i>	Quercetin 3, 3', 4'-trimethyl ether	Aerial part	Methanol and acetone	Inhibits the activities of β -galactosidase and phosphatase, elevates extracellular, reduces the activities of GrYB protein and ATPase activity	Ahmadu et al. (2011)
<i>Corynebacterium ulcerans</i>	<i>Pachygrapsus crassipes</i>	Quercetin-3- <i>O</i> -rutinoside	Leaf	Aqueous	Inhibit ATPase activity, GrYB protein, elevates extracellular phosphatase and β -galactosidase activities	Bello et al. (2011)
<i>Campylobacter jejuni</i> and <i>Escherichia coli</i>	<i>Allium sativum</i>	Ajoene	Bulb		Sulphydryl-dependent enzyme inhibitor	Rehman and Mairaj (2013)
<i>Escherichia coli</i>	<i>Ipomoea muricata</i>	Chanolavine	Seed	Fast centrifugal partition chromatography	Efflux pump inhibitor	Dwivedi et al. (2019)
<i>Escherichia coli</i>	<i>Diplotaxis harra</i>	Sulphoraphane	Needles	Water	Protein and DNA synthesis inhibitor, ATP synthase inhibitor, and destruction of bacterial membrane	Wu et al. (2012)

(Continued)

TABLE 2.2 (CONTINUED)
Ethnobotanical Data on the Medicinal Plants Identified as Active Against Various Bacterial Diseases

Bacteria	Antibacterial Plant	Antibacterial Compound(s)	Plant Parts	Extraction Solvent/ Analytical Method	Mechanism of Action	References
<i>Enterococcus faecalis</i>	<i>Polymnia fruticosa</i>	Naringenin	—	—	β -Ketoacyl acyl carrier protein synthase (KAS) III	Jeong et al. (2009)
<i>Escherichia coli</i>	<i>Citrus aurantifolia</i>	Flavonoid	Fruits	Methanol	Complex with bacterial cell walls and ability to complex with soluble and extracellular proteins	Lee et al. (2014)
<i>Escherichia coli</i>	<i>Panacratium illyricum</i>	Berberine	Bulbs	Methanol	Inhibition of DNA and protein, as well as cell division	Zorić et al. (2017); Boberek et al. (2010)
<i>Haemophilus influenzae</i>	<i>Achillea clavennae</i>	Geranyl acetate, linalool, camphor, myrcene, β -caryophyllene, and 1,8-cineole	Leaves and flowers	GC-MS analysis	Initiate changes in integrity or permeability of the cell membrane	Skocibusic et al. (2004)
<i>Klebsiella pneumoniae</i>	<i>Achillea clavennae</i>	Geranyl acetate, linalool, camphor, myrcene, β -caryophyllene, and 1,8-cineole	Leaves and flowers	GC-MS analysis	Initiate changes in the integrity or permeability of the cell membrane	Skocibusic et al. (2004)
<i>Listeria monocytogenes</i>	<i>Cyperus longus</i>	B-Himachalene, α -humulene, and γ -himachalene	Aerial parts	GC-MS analysis	Initiate changes in the integrity or permeability of the cell membrane	Ait-Ouazzou et al. (2012)

(Continued)

TABLE 2.2 (CONTINUED)
Ethnobotanical Data on the Medicinal Plants Identified as Active Against Various Bacterial Diseases

Bacteria	Antibacterial Plant	Antibacterial Compound(s)	Plant Parts	Extraction Solvent/ Analytical Method	Mechanism of Action	References
<i>Mycobacterium smegmatis</i>	—	Formononetin	—	—	Efflux pump inhibitor	Lechner et al. (2008)
<i>Mycobacterium smegmatis</i> , Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) and <i>Candida albicans</i>	<i>Scutellaria baicalensis</i> , <i>Scutellaria lateriflora</i> , <i>Thymus vulgaris</i>	Baicalein	Root	Methanol	Efflux pump inhibitor	Lechner et al. (2008); Chan et al. (2011)
<i>Mycobacterium tuberculosis</i>	<i>Terminalia chebula</i>	Chebulinic acid	—	Water	DNA gyrase	Patel et al. (2015)
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) and <i>Staphylococcus aureus</i>	<i>Piper nigrum</i> and <i>Piper longum</i>	Piperine	—	Distilled water	Efflux pump inhibitor	Khameneh et al. (2015b)
<i>Micrococcus luteus</i>	<i>Dracocephalum foetidum</i>	Limonene, <i>n</i> -menthol, and 8-dien-10-al	Leaves	Hydrodistillation	Changes the integrity or permeability of the cell membrane	Lee et al. (2007)
MRSA and <i>Candida albicans</i>	<i>Alpinia calcarata</i>	Kaempferol	Rhizomes	Soxhlet extraction with ethyl acetate and methanol	Efflux pump inhibitor	Randhawa et al. (2016); Shao et al. (2016)

(Continued)

TABLE 2.2 (CONTINUED)
Ethnobotanical Data on the Medicinal Plants Identified as Active Against Various Bacterial Diseases

Bacteria	Antibacterial Plant	Antibacterial Compound(s)	Plant Parts	Extraction Solvent/ Analytical Method	Mechanism of Action	References
<i>Mycobacterium smegmatis</i> and <i>Campylobacter jejuni</i>	—	Resveratrol	Seed	Aqueous methanol	Efflux pump inhibitor	Klancnik et al. (2017)
<i>Neisseria gonorrhoeae</i>	<i>Pavetta crassipes</i>	Quercetin-3-O-rutinoside	Leaf	Aqueous	Complexes with bacterial cell walls, inhibits ability to complex with soluble proteins and extracellular proteins	Bello et al. (2011)
<i>Pseudomonas aeruginosa</i>	<i>Strachium sparganophora</i>	β -caryophyllene, germacrene D, humulene, caryophyllene oxide, and 1,8-cineole	Aerial parts, stem, and leaf	Hydrodistillation	Changes the integrity or permeability of the cell membrane	Anyanwu and Okoye (2017)
<i>Pseudomonas aeruginosa</i>	<i>Pavetta crassipes</i>	Quercetin-3-O-rutinoside	Leaf	Aqueous	Complexes with bacterial cell walls and affects ability to complex with soluble proteins and extracellular proteins	Bello et al. (2011)
<i>Pseudomonas aeruginosa</i>	<i>Achillea clavennae</i>	Camphor, myrcene, cineole, β -caryophyllene, linalool, and geranyl acetate	Leaves and flowers	GC-MS	Changes the integrity or permeability of the cell membrane	Skocibusic et al. (2004)

(Continued)

TABLE 2.2 (CONTINUED)
Ethnobotanical Data on the Medicinal Plants Identified as Active Against Various Bacterial Diseases

Bacteria	Antibacterial Plant	Antibacterial Compound(s)	Plant Parts	Extraction Solvent/ Analytical Method	Mechanism of Action	References
<i>Pseudomonas aeruginosa</i>	<i>Holarrhena antidysenterica</i>	Conessine		Dimethyl sulphoxide (DMSO) and diatrizoic acid (DTA)	Efflux pump inhibitor	Siriyoung et al. (2017)
<i>Pseudomonas aeruginosa</i>	<i>Cyperus longus</i>	B-Himachalene, α -humulene, and γ -himachalene	Aerial parts		Changes the integrity or permeability of the cell membrane	Ait-Ouazzou et al. (2012)
<i>Salmonella enterica</i>	<i>Cyperus longus</i>	β -Himachalene, α -humulene, and γ -himachalene	Aerial parts	GC-MS	Changes the integrity or permeability of the cell membrane	Ait-Ouazzou et al. (2012)
<i>Salmonella typhimurium</i>	<i>Cuminum cyminum</i>	Cuminaldehyde, β -pinene, γ -terpinene, and terpin-7-al	Leaves	GC-MS	Changes the integrity or permeability of the cell membrane	Bisht et al. (2014)
<i>Salmonella typhimurium</i>	<i>Strachium sparganophora</i>	β -caryophyllene, germacrene D, humulene, caryophyllene oxide, and 1,8-cineole	Aerial, stem, leaf	Hydrodistillation	Changes the integrity or permeability of the cell membrane	Anyanwu and Okoye (2017)
<i>Staphylococcus aureus</i>	<i>Artemisia annua</i>	Chrysoplenol-D	Leaves	Chromatography	Efflux pump inhibitor	Stermitz et al. (2003)
<i>Staphylococcus aureus</i>	<i>Artemisia frigida</i>	1,8-cineole, methyl chavicol, and camphor	Aerial parts	GC-MS	Changes the integrity or permeability of the cell membrane	Lopes-Lutz et al. (2008)
<i>Staphylococcus aureus</i>	<i>Cedrus deodara</i>	3- <i>p-trans</i> -coumaroyl-2-hydroxyquinic acid	—	—	Damage to the cytoplasmic membrane	Wu et al. (2016)

(Continued)

TABLE 2.2 (CONTINUED)
Ethnobotanical Data on the Medicinal Plants Identified as Active Against Various Bacterial Diseases

Bacteria	Antibacterial Plant	Antibacterial Active Compound(s)	Plant Parts	Extraction Solvent/ Analytical Method	Mechanism of Action	References
<i>Staphylococcus aureus</i>	<i>Cymbopogon citratus</i>	Limonene, <i>n</i> -menthol, 8-dien-10-al	Leaves	Hydrodistillation	Changes the integrity or permeability of the cell membrane	Lee et al. (2007)
<i>Staphylococcus aureus</i>	<i>Cyperus longus</i>	β -Himachalene, α -humulene, γ -himachalene	Aerial parts	GC-MS	Changes the integrity or permeability of the cell membrane	Ait-Onazzou et al. (2012)
<i>Staphylococcus aureus</i>	<i>Maytenus buchananii</i>	Epicatechin, kaempferol, epigallocatechin, quercetin-3- <i>O</i> - β -D-glucopyranoside, quercetin-3- <i>O</i> - α -L-arabinopyranoside, and quercetin	Leaves	Methanol	Ability to complex with bacterial cell walls and soluble proteins and to complex, disrupt membranes of bacteria	Tebou et al. (2017)
<i>Staphylococcus aureus</i>	<i>Momordica charantia</i>	<i>Cis</i> -dihydrocarvol, <i>trans</i> nerolidol, and germaerene D	Seed	GC-MS	Changes the integrity or permeability of the cell membrane	Braca et al. (2008)
<i>Staphylococcus aureus</i>	<i>Persea lingue</i>	Kaempferol rhamnoside	Leaves	Ethanol	Efflux pump inhibitor	Holler et al. (2012)
<i>Staphylococcus epidermidis</i>	<i>Artemisia frigida</i>	1,8 cineole, methyl chavicol, and camphor	Aerial parts	GC-MS	Changes to integrity or permeability of the cell membrane	Lopes-Lutz et al. (2008)
<i>Staphylococcus epidermidis</i>	<i>Eugenia caryophyllata</i>	Thymol, eugenol, carvacrol, and cinnamaldehyde	Flower buds	GC-MS	Changes the integrity or permeability of the cell membrane	Santos et al. (2015)

(Continued)

TABLE 2.2 (CONTINUED)
Ethnobotanical Data on the Medicinal Plants Identified as Active Against Various Bacterial Diseases

Bacteria	Antibacterial Plant	Antibacterial Active Compound(s)	Plant Parts	Extraction Solvent/ Analytical Method	Mechanism of Action	References
<i>Staphylococcus epidermidis</i>	<i>Eremanthus erythropappus</i>	Viridiflorol, <i>p</i> -cymene, germacrene D, and γ -terpinene (<i>Z</i>)-caryophyllene	Leaves	GC-MS	Changes the integrity or permeability of the cell membrane	Chaieb et al. (2007)
<i>Staphylococcus epidermidis</i>	<i>Plectranthus amboinicus</i>	<i>P</i> -cymene (<i>Z</i>)-caryophyllene, germacrene D, viridiflorol, and γ -terpinene	Leave	GC-MS	Changes the integrity or permeability of the cell membrane	Arumugam et al. (2016)
<i>Streptococcus</i> sp. and <i>Micrococcus</i> sp	<i>Rauwolfia serpentina</i>	Reserpine	Root	Methanol	Efflux pump inhibitor	Sridevi et al. (2017)
<i>Vibrio cholerae</i>	<i>Graptophyllum granditosum</i>	Chrysoeriol-7- <i>O</i> - β -D-xyloside, luteolin-7- <i>O</i> - β -D-apiofuranosyl, β -D-xylopyranoside, chrysoeriol-7- <i>O</i> - α -L-rhamnopyranosyl-glucopyranoside, and isorhamnetin-3- <i>O</i> - α -L-rhamnopyranosyl	Aerial parts	<i>n</i> -Butanol	High capacity for disruption of plasma membrane and disruption of the permeability barrier of bacterial membrane structures	Tagousop et al. (2018)
<i>Vibrio parahaemolyticus</i>	<i>Eleutherine bulbosa</i>	Fatty acid esters, isoquinolines, naphthalenes, phenolics, and E- (7-hydroxy-1,2-dimethoxy xanthone)	Bulb	Ethanol	Inhibition of cell division, targeting RNA polymerase, and DNA intercalation	Munaeni et al. (2019)

2.4 RECENT PROGRESS IN BACTERIAL ACTIVITIES OF MEDICINAL PLANTS

2.4.1 MEDICINAL PLANTS FOR TREATING BACTERIAL PNEUMONIA

Bacterial pneumonia is an infectious disease characterized by lung inflammation. It is not a single disease but can be caused by many species of bacteria, such as *Streptococcus pneumoniae*, *S. aureus*, *P. aeruginosa*, *Moraxella catarrhalis*, *K. pneumoniae* and *Haemophilus influenzae* (Brooks, 2020; Cock and Van Vuuren 2020). Different medicinal plants and parts which have been used for the treatment of bacterial pneumonia include the root of *Abutilon angulatum*, *Combretum platypetalum*, *Rhynchosia caribaea*, and *Terminalia sericea*, leaves of *Acacia eriloba*, *Dodonaea viscosa*, and *Trichilia emetica*, essential oils from the wood of *Cinnamomum camphora*, tubers of *Pelargonium sidoides*, branches of *Rhamnus prinoides*, the bark of *Urtica urens*, twigs of *Dodonaea viscosa*, and whole plants of *Oncosiphon suffruticosum* (Cock and Van Vuuren 2020). Bioactive compounds isolated from peel waste of *Opuntia ficus-indica* fruits, like isorhamnetin, isorhamnetin 3-*O*-glucoside, quercetin 5,4'-dimethyl ether, and flavonols, were shown to be the most potent active fractions against pneumonia pathogens (Elkadya et al. 2020). In the Himalayan region, the plant families most commonly used for the treatment of pneumonia are the Fabaceae, Bignoniaceae, and Asteraceae, of which *Justicia adhatoda*, *Punica granatum*, and *Curcuma longa* exhibited the greatest inhibitory potential (Adnana et al. 2019).

2.4.2 MEDICINAL PLANTS FOR TREATING CHOLERA

Cholera is an infectious bacterial disease of the intestine. The disease is caused by the bacterium *V. cholerae* (Sousaa et al. 2020). In developing countries, it is an acute, diarrhoeal illness, although it is rare in the developed world. The distribution of the disease globally shows that it still occurs in Africa, South America, and Eastern Asia, with the incidence increasing since 2005 (Mandal et al. 2011). The WHO has encouraged the investigation of medicinal plants as alternative strategies for the control of various diarrhoeal diseases, including cholera (Laloo and Hemalatha 2011). Flavonoids extracted from the leaves of *Maytenus buchananii* using methanol showed a potential anticholera chemotherapeutic agent (Tebou et al. 2017). Kayira and Nakanoa (2020) showed that cholera can be treated using methanol extracts of *Syzygium aromaticum*, *Corymbia citriodora*, *Glycyrrhiza glabra*, *Salvia rosmarinus*, *Salvia officinalis*, or *Thymus praecox*. Their results indicated significant activity against *V. cholerae* with diameters of inhibitory zone of between 11.3 mm and 25 mm. The antibacterial activity was in the order *S. aromaticum* > *S. officinalis* > *T. praecox* > *C. citriodora* > *G. glabra*. Jose et al. (2017) also showed that methanolic extracts obtained from the plants *Holarrhena antidysenterica*, *Camellia sinensis*, *Elephantopus scaber*, or *Centella asiatica* exhibited promising antibiofilm activity against *V. cholerae*. In some studies, aqueous extracts of members of the Rosaceae family, such as *Rosa canina*, *Fragaria vesca*, *Rubus fruticosus*, *Rubus*

idaeus, and *Agrimonia eupatoria*, have been widely used to neutralize the cholera toxin (Komiazyk et al. 2019).

2.4.3 MEDICINAL PLANTS FOR TREATING DIPHTHERIA

Diphtheria is another bacterial infectious disease that can result in mortality. Among infected people, 5–10 % of cases result in death. The mortality rate in people with ages of 40 years old and above and 5 years old and below is approximately 20% (Holy et al. 2017). In developed countries, because of advances in medical treatment, outbreaks of diphtheria are rare, although they are more common in continents like Africa and South America (Truelove et al. 2019). The disease is caused by the bacterium *Corynebacterium diphtheriae* (Dover et al. 2004). Parts of different plant species, such as leaves of *Carissa edulis*, *Artemisia afra*, *Dodonaea viscosa*, *Eucalyptus globulus*, *Carpobrotus edulis*, *Ficus carica*, *Mentha longifolia*, and *Olea europea*, the sap of *Astridia velutina*, the roots of *Carissa edulis*, *Ficus carica*, *Mentha longifolia*, twigs of *Dodonaea viscosa*, stems of *Mentha longifolia*, and fruit of *Vitis vinifera*, have been used to prevent diphtheria (Cock and Van Vuuren 2020).

2.4.4 MEDICINAL PLANTS FOR TREATING GONORRHOEA

Gonorrhoea is the second most common sexually transmitted infectious disease (Chinsembu 2016), and is caused by the bacterium *Neisseria gonorrhoeae* (Rice et al. 2017). In the work of Silva et al. (2020), some traditional medicinal plants, such as *Prunus serotina* (bark), *Rhodiola rosea* (root), *Terminalia macroptera* (root and leaves), *Senna podocarpa* (root), *Guiera senegalensis* (leaves), and *Bersama engleriana* (bark) were shown to be the most active in preventing gonorrhoea infection. In different countries, medicinal plants *Adenia gummifera*, *Agave sisalana*, *Anredera cordifolia*, *Jacaranda mimosifolia*, *Lantana camara*, *Opuntia stricta*, *Senna didymobotrya*, and *Solanum mauritianum* in South Africa (Maema and Potgieter 2019), *Abelmoschus moschatus*, *Abroma augustum*, *Acacia farnesiana*, *Acalypha hispida*, *Aegle marmelos*, *Alternanthera sessilis*, *Arachis hypogaea*, *Asparagus racemosus*, *Benincasa hispida*, *Boerhavia diffusa*, *Caesalpinia bonducella*, and *Calophyllum inophyllum* in Bangladesh (Rahmatullah et al. 2011), and *Centella asiatica*, *Curculigo orchioides*, *Gloriosa superba*, *Grewia subinaequalis*, *Ocimum gratissimum*, *Petalium murex*, *Phyllanthus fraternus*, *Pouzolzia zeylanica*, *Premna arborea*, and *Scoparia dulcis* in India (Das et al. 2013) have been used for gonorrhoea treatment. In Tanzania, for treatment of the disease, a decoction made from roots of *Achyranthes aspera* is given to a patient, whereas, in the Philippines, a decoction of the whole plant of *Centella coriacea* and or roots of *Amaranthus spinosus* is given. In addition, *Centella asiatica* is very important for treatment of gonorrhoea in the folk medicine of South Africa. The plant *Grewia asiatica* is also used in the Himalayan traditional medicinal system of India to treat gonorrhoea (Hossan et al. 2010).

2.4.5 MEDICINAL PLANTS FOR TREATING LYME DISEASE

Lyme disease is a well-known tick-borne bacterial disease in humans. In the United States, about 300,000 new cases of Lyme disease occur each year (Alinia-Ahandani et al. 2020). In most cases of Lyme disease, a bacterium, such as *Borrelia burgdorferi*, *Borrelia afzelii*, or *Borrelia garinii*, are responsible (Aguero-Rosenfeld et al. 2005). Essential oils from several common herbs and medicinal plants show strong activity against the bacterium that causes Lyme disease (Feng et al. 2018). Essential oils from cloves of *Allium sativum*, berries of *Pimenta officinalis*, seed of *Cuminum cyminum*, resin of *Commiphora myrrha*, flowers of *Hedychium spicatum*, wood of *Amyris balsamifera*, leaves of *Eucalyptus citriodora* or *Thymus vulgaris*, and fruit of *Litsea cubeba* have shown potent activities against *Borrelia burgdorferi* (Feng et al. 2018). In some studies, medicinal herbs such as *Hyptis suaveolens*, *Lippia alba*, *Allium sativum*, *Syzygium aromaticum*, *Artemisia absinthium*, *Murraya koenigii*, *Datura metel*, and *Chrysopogon zizanioides* have been used to treat Lyme disease and other tick-borne infections (Yarnell 2016).

2.4.6 MEDICINAL PLANTS FOR TREATING BACTERIAL MENINGITIS

Meningitis is an acute inflammation of the protective membranes covering the brain and neural structure. The inflammation can be caused by infection with bacteria, viruses, or other microorganisms (Priya et al. 2019). Tijani et al. (2019) studied the potential medicinal values of *Allium sativum* on bacterial meningitis pathogens such as *K. pneumoniae*, *E. coli*, *S. pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*. Their results showed that the plant extracts reduced bacterial growth, with MIC values in the range 0.04–1.56 mg/ml. In the work of Akpo et al. (2020), the antibacterial activity of *Alchornea cordifolia* and *Moringa oleifera* against four meningitis-causing bacteria, namely *E. coli*, *Micrococcus* spp., *B. subtilis*, and *S. aureus* were examined. The results indicated that an aqueous extract of *A. cordifolia* inhibited all the bacteria tested, with a range of zones of inhibition from 7.0 mm to 17.5 mm in diameter, whereas the ethanolic extract of *M. oleifera* inhibited *S. aureus* and *B. subtilis*, with zones of inhibition in the range of 3.0–9.0 mm diameter.

2.4.7 MEDICINAL PLANTS FOR TREATING SYPHILIS

Syphilis is a common disease caused by the bacterium *Treponema pallidum*. The disease can be transmitted *via* sexual activities or by contact with an infected person (Santacroce et al. 2020). The disease can be treated using different medicinal plants, such as *Streblus asper* (leaves, roots, and stems) or *Plumbago indica* (leaves and stems). A tincture of the roots of *Plumbago indica* is also used to treat secondary syphilis in India (Hossan et al. 2010). In Nigeria, parts of traditional medicinal plants, such as leaves of *Acanthus montanus*, *Carica papaya*, *Acalypha fimbriata*, *Bauhinia variegata*, or *Azadirachta indica*, the root of *Bauhinia variegata* or *Berlinia grandiflora*, the bark of *B. variegata*, *B. grandiflora*, and *A. indica*, seed of *Carica papaya* or *A. indica*, the stem of *B. grandiflora* or *A. indica*, fruits of *Carica papaya*, and the

whole plant of *Ambrosia maritima*, *Centaurea perrottetii*, or *Adenia venenata*, have been used to treat syphilis (Abd El-Ghani 2016). In Jharkhand state in India, some of the traditional medicinal plants used for the treatment of syphilis are *Cynodon dactylon* (whole plant), *Benincasa hispida* (fruit), *Benincasa hispida*, and *Fumaria parviflora* (aerial parts) (Pandey et al. 2020). An ethnomedicinal survey of plants used by Abagusii traditional healers of Southwest Kenya indicated that the root of *Agave americana* and *Tabernaemontana stapfiana*, whole plants of *Achyranthes aspera*, leaves of *Cassia didymobotrya*, and stems of *Cassia floribunda* are used for treatment of syphilis (Charles and Bonareri 2020).

2.4.8 MEDICINAL PLANTS FOR TREATING TETANUS

Tetanus is a serious, life-threatening infectious disease caused by a bacterial toxin that affects the nervous system, leading to painful muscle contractions; if not diagnosed and treated at an early stage, it can result in death (Lakonawa et al. 2020). In the developing world, tetanus has a high mortality rate but, in the developed world, the disease is rare (Cook et al. 2001). Indian medicinal plants, such as *Lantana camara*, are used to treat tetanus infections, possibly due to the presence of phytochemicals like saponins, flavonoids, alkaloids, tannins, anthocyanins, flavones, isoflavones, coumarins, lignans, catechins, carotenoids, carbohydrates, proteins, glycosides, and steroids in the plant extract (Poddar et al. 2020). *Hymenocardia acida* extract is used to treat tetanus in Benin (Novotna et al. 2020) and *Aristolochia esperanzae*, *Copaifera langsdorffii*, *Capsicum frutescens*, and *Nicotiana tabacum* are also used for treatment of the disease in Brazil (Ribeiro et al. 2017).

2.4.9 MEDICINAL PLANTS FOR TREATING TUBERCULOSIS

Tuberculosis (TB) is one of the most serious infectious bacterial diseases of the respiratory system, caused by the bacterium *Mycobacterium tuberculosis* (Floyd et al. 2018). It is one of the top ten diseases in terms of number of deaths caused. Nowadays, it is very difficult to control the disease, with the evolution of drug-resistant bacteria making ineffective the use of medications previously used to control the bacterium. This has resulted in an urgent search for new medicines from local traditional medicinal plants (Tabuti et al. 2010). Flowers, leaves, roots, and the whole plant of *Taraxacum officinale* can be used to treat TB. Furthermore, bark extracts of *Cryptocarya latifolia*, *Acacia xanthophloea*, *Berchemia discolor*, *Bridelia micrantha*, *Cassia petersiana*, and *Cassine papillosa*, and leaf extracts of *Artemisia afra*, *Bauhinia petersiana*, *Chaetachme aristata*, *Clerodendrum glabrum*, *Combretum molle*, and *Conyza scabrada* have been used to treat TB (Cock and van Vuuren 2020). *Acalypha indica* has proved to be important in treatment against *M. tuberculosis*. Various phytochemicals, like gallic acid, myricetin, quercetin, piperine, vasicine, curcumin, and ascorbic acid, obtained from *A. indica* have been shown to exhibit antibacterial activities (Adnana et al. 2019). In addition, aqueous extracts of pure gel from *Aloe vera* leaves, cloves of *Allium sativum*, bulbs of *Allium cepa*, *Adhatoda vasica*, and *Acalypha indica* were examined *in vitro* for their potential activity

against multidrug-resistant *M. tuberculosis*. Extracts of all five species exhibited anti-tuberculosis activity with inhibition of 95, 32, 37, 72, and 32%, respectively (Gupta et al. 2010).

2.4.10 MEDICINAL PLANTS FOR TREATING TYPHOID

Typhoid is an infectious disease of concern throughout developing countries around the world (Khadka et al. 2020). It is a systemic infection caused by the bacterium *Salmonella enterica* ssp. *enterica* serotype *typhi*, by ingestion of contaminated water or food (Iroha et al. 2010). Different solvent extracts of the bark of *Azadirachta indica*, leaves of *Crinum purpurascens*, *Bidens pilosa*, *Carica papaya*, *Cymbopogon citratus*, *Mangifera indica*, *Momordica charantia*, and *Psidium guajava*, and fruit of *Aegel marmelous*, *Punica granatum*, *Myristica fragrans*, and *Solanum lycopersicum* have been used to treat typhoid (Syarif et al. 2020). Traditional medicine practitioners have described that the root of *Vitex doniana*, the leaf of *Cassia tora*, the bark of *Alstonia boonei*, and the leaf of *Stachytarpheta jamaicensis* and *Carica papaya* are also beneficial for effective treatment against typhoid fever (Abbas and Ain, 2020). Roger et al. (2015) described *Bidens pilosa* antibacterial activity as being effective against *Salmonella*. *B. pilosa* contains many phytochemicals, such as porphyrins, flavonols, chalcones, phenols, acetylenic hydrocarbons, aliphatic carboxylic acids, saturated carbohydrates, tannins, triterpenoids, steroids, alkaloids, phenyl-acetylenes, and flavonoids. According to Iroha et al. (2010), typhoid can also be prevented by using medicinal plant extracts such as both crude cold and hot water extracts and ethanol extracts of *Carica papaya* (leaf), *Stachytarpheta jamaicensis* (leaf), *Alstonia boonei* (bark), *Cassia tora* (leaf), and *Vitex doniana* (root). More frequently used medicinal plants to treat typhoid and the associated fever are *Aconitum gammiei*, *Neopicrorhiza scrophulariiflora*, *Abelmoschus manihot*, *Mussaenda frondosa*, *Asparagus racemosus*, *Rubus ellipticus*, *Iris domestica*, *Begonia picta*, and *Achyranthes bidentata* (Khadka et al., 2020).

2.5 SIGNIFICANCE OF ANTIBACTERIAL DRUGS FROM NATURAL SOURCES

Antibacterial drugs may be naturally derived from living organisms, such as plants, actinomycetes, and fungi, and prepared semi-synthetically or synthetically in the laboratory. Natural antibacterial drugs exhibit some remarkable properties, such as the low possibility of the evolution of bacterial resistance, long-lasting antibacterial effects, low cost, high solubility in the bodily fluids, nontoxicity to the human body, and long shelf life (Moellering 1981). Over the past ten years, the development of antimicrobial resistance (AMR), which started after the widespread use of antibiotics, has focused attention on the sustainability of current modern medical practices in the global arena (Moloney 2016). Each year, approximately 8,000 people die from antibiotic-resistant infections; synthetic antibiotics or drugs could make a significant contribution to reducing these deaths. Because of increasing resistance to man-made antibiotics, there is a vital need to change the focus to naturally occurring

plant-derived antibacterial products because their vast chemical diversity not only possesses a potent therapeutic effect but also makes the microbes unable to adapt to them to achieve resistance (Naqvi et al. 2019). Natural occurring antibacterial drugs will be used to supplement the body's natural ability to fight off bacterial infections in the future. Unlike pharmaceutical antibiotics, with a single, specific point of action, plant-derived antibacterial drugs have multiple points of action, so that drug resistance does not develop in the target bacteria (Naqvi et al. 2019). Also, they will not kill beneficial bacterial species that exist in our gut microbiome to help break down the food we eat (Corrêa et al. 2020), to benefit our immune system and to improve other aspects of our physiological and mental health. The effectiveness of traditional medicines is becoming widely accepted because of their fewer side effects, better cultural acceptability, and greater compatibility with the human body (Mustafa et al. 2017).

2.6 MECHANISM AND MODE OF ACTION OF PLANT-BASED ANTIBACTERIAL DRUGS

In many countries, synthetic antibacterial drugs have been widely used, but the importance of plant-derived drugs is increasingly attracting the attention of many researchers (Khameneh et al. 2015). In nature, plants are rich in phytochemicals. These plant-derived chemical compounds have advantages for controlling bacteria through their antibacterial properties (Barbieri et al. 2017). Some of the bioactive compounds in plants used as antibacterials are glucosinolates, lignans, tannins, essential oils, terpenoids, flavonoids, alkaloids, phenolics, quinines, and other secondary metabolites (Chandra et al. 2017). Plant-based constituents may affect bacterial cells in many ways (Figure 2.2), such as inhibiting bacterial enzymes involved in the synthesis of essential structural bacterial components or in the production of cellular energy, or by increasing the permeability of the cell, resulting in the loss of cellular constituents (Kotzekidou et al. 2008), interrupting the communication between normal cells, inducing the coagulation of cytoplasmic constituents, affecting RNA/DNA function, interrupting cell component synthesis, disrupting the structure and function of membranes, and interfering with intermediary metabolism (Radulovic et al. 2013), plus synergistic effects (Wagner and Ulrich-Merzenich 2009).

In general, the mode of action of antibacterial phytochemicals is considered to involve the coagulation of cell components, disturbance of active transport mechanisms and electron flow, and disruption of the proton motive force and the cytoplasmic membrane function (Kotzekidou et al. 2008). Phytochemicals affect the stability and structure of the phospholipid bilayer of the membrane, increasing its permeability to ions as a result of damage or disturbed membrane integrity. The effect also alters the electrochemical potential of membranes and membrane-associated enzyme activities. Some phytochemicals can also affect the transfer of protons across the membrane of the cell by interrupting the synthesis of ATP, inhibiting anabolism/catabolism and respiration, and decreasing active transport (Radulovi et al. 2013).

Different phytochemicals vary in their mechanism of action (Omojate Godstime et al. 2014). For instance, flavonoids have the following modes of action against

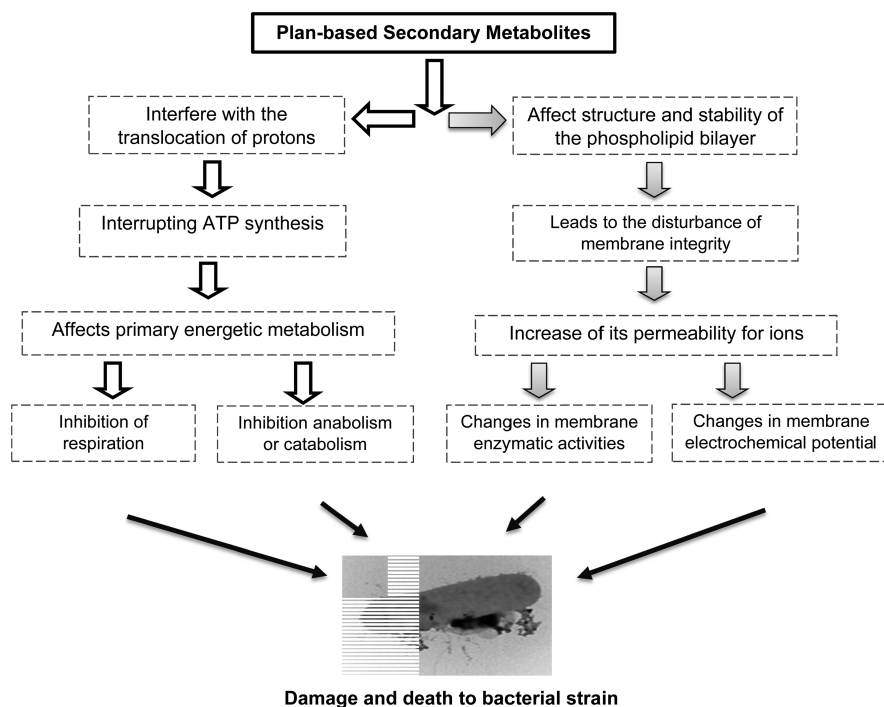


FIGURE 2.2 Possible mode of action of plant-based metabolic products on bacterial cell growth, damage, or death.

bacteria: attenuation of pathogenicity, change in membrane permeability, inhibition of nucleic acid synthesis, reduction in cell attachment and biofilm formation, inhibition of energy metabolism, and change in the function of the cytoplasmic membrane (Farhadi et al. 2019). Flavonoids like epigallocatechin, myricetin, and robinetin (Figure 2.3) exhibit antibacterial activities against *Proteus vulgaris* due to inhibition of DNA synthesis, by the formation of hydrogen bonds between the B-ring of flavonoids and nucleic acid bases, preventing the synthesis of bacterial DNA (Mori et al. 1987; Cushnie and Lamb, 2005). Sophoraflavanone G and naringenin (Figure 3) exhibit considerable antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and streptococci. A change of membrane fluidity in the region of hydrophobic and hydrophilic may be attributed to flavonoids, decreasing the fluidity of the inner and outer components of membranes (Cushnie and Lamb 2005). Anthraquinones from *Cassia italica* showed antibacterial activities against *Burkholderia pseudomallei*, *P aeruginosa*, *Corynebacterium pseudodiphthericum*, and *Bacillus anthracis* because of their ability to make a complex between the bacterial cell wall and extracellular soluble proteins (Al-AISheikh et al. 2020). Quercetin flavonoids, derived from the skin of yellow onion, reduced the effect on antibiotic-resistant *Helicobacter pylori* by obstructing the DNA supercoils from achieving DNA scission by forming the gyrase DNA-quercetin cleavable

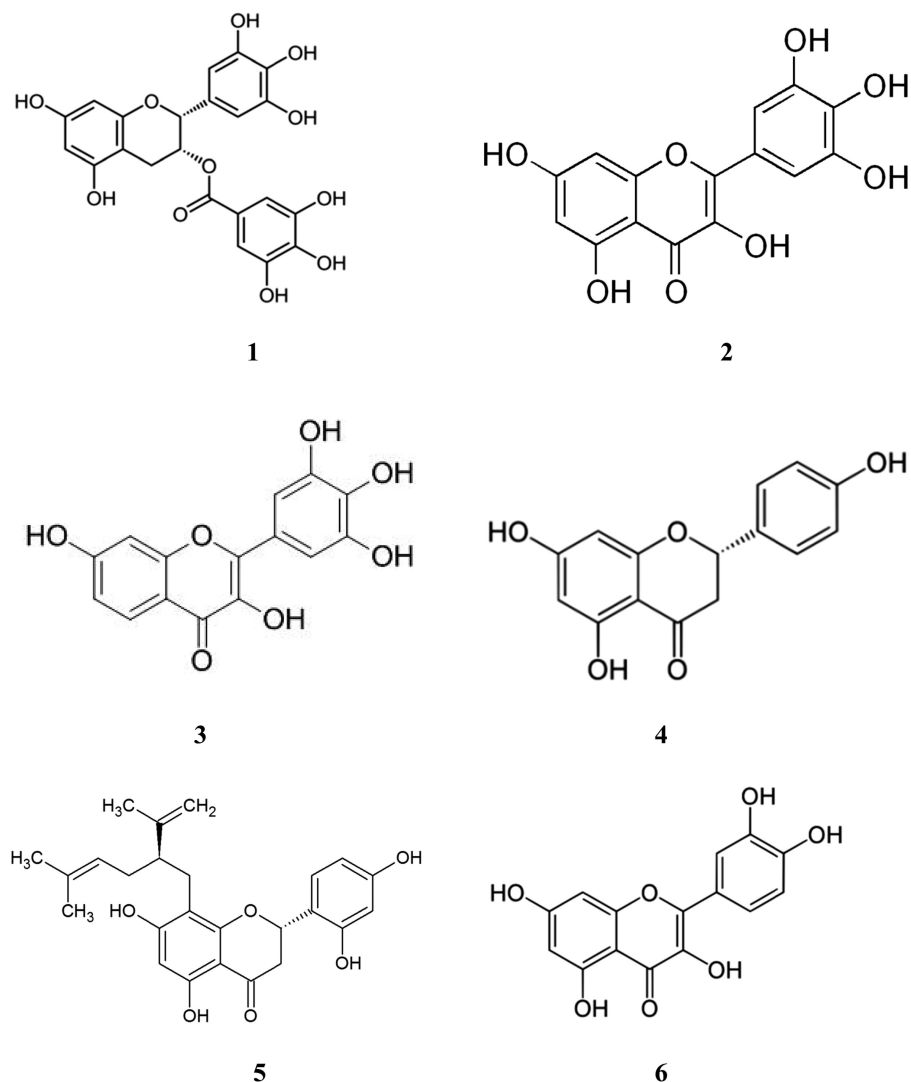


FIGURE 2.3 Structures of epigallocatechin (1), myricetin (2), robinetin (3), naringenin (4), sophoraflavanone G (5), and quercetin (6).

complex. Other flavonoids, such as kaempferol, daidzein, and apigenin, act to reduce the growth of some bacteria, like *Vibrio harveyi*, *E. coli*, and *B. subtilis*, by imposing drastic effects on bacterial RNA and DNA synthesis (Naqvi et al. 2019).

Alkaloids also have different mechanisms in different classes of alkaloids, such as polyamines, agelasine, quinolone, isoquinoline, and indolizidine alkaloids. A class of phenanthroindolizidine alkaloids, including tylophorinidine and pergularinine (Figure 2.4), operate by inhibiting the enzyme dihydrofolate reductase and

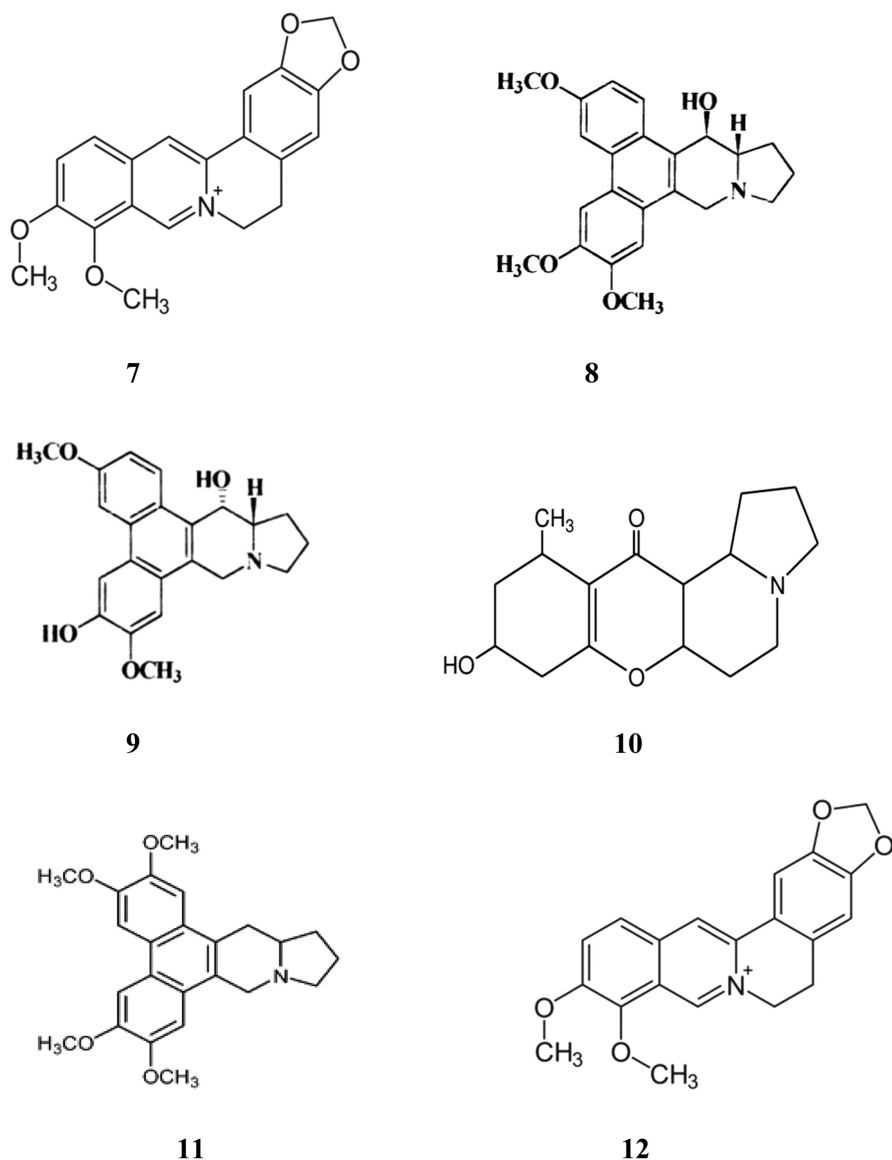


FIGURE 2.4 Structures of the alkaloids berberine (7), pergularinine (8), tylophorinidine (9), indolizidine (10), tylophorinidine (11), and protoberberine (12).

blocking nucleic acid synthesis (Cushnie et al. 2014), whereas a class of isoquinoline alkaloids, including isoquinolines, protoberberine, and benzophenanthridine (Figure 2.4), reduce the growth of bacteria by inhibiting cell division and by perturbing the Z ring at the site of cell division (Cushnie et al. 2014). In another study, berberine (Figure 2.4), which is obtained from plants like *Rhizoma coptidis* and

Cortex phellodendri, showed antibacterial activity against *Streptococcus agalactiae* by increasing the membrane permeability of the bacteria, by intercalating with DNA (Chandra et al. 2017). Antibacterial activity was also exhibited by alkyl methyl quinolone alkaloids against *Helicobacter pylori* through a respiratory inhibitory effect (Tominaga et al. 2002). Moreover, squalamine, a polyamine alkaloid, has the same mode of action as a detergent. It depolarizes Gram-positive bacteria membranes, leading, in Gram-negative bacteria, to the disruption of their outer membranes (Alhanout et al. 2010).

Essential oils in different extracts from various plants have been used by exploiting their antibacterial activities (Akthar et al. 2014). The chemical structure of an essential oil enables it to have antibacterial activity against different bacteria. Essential oils, like thymol, eugenol, and carvacrol, originating from various plants, are highly active against many microorganisms (Saad et al. 2013). The hydroxide group present in essential oils shows strong antibacterial activity (Guimaraes et al. 2019). Ultee et al. (2002) explained that the carvacrol phenolic hydroxyl group was responsible for its antibacterial activities against *Bacillus cereus* by enhancing membrane fluidity and reducing the pH gradient across the cytoplasmic membrane, causing bacterial cell death by the resulting collapse of the proton motive force and depletion of the ATP pool. Essential oils result in bacteria cell death by increasing cell membrane permeability for K^+ and depleting intracellular ATP. A study on the mechanism of antibacterial activity towards *E. coli* by thymol and carvacrol (Figure 2.5) showed the leakage of protons and potassium ions, increased membrane permeability, and the disruption of membrane integrity (Xu et al. 2008). Some essential oil components, like terpenoids and terpenes, exhibit a particular mechanism to kill bacterial cells. The passage of lipophilic compounds through the cell wall and disruption of cytoplasmic membranes are part of the mechanism. Permeabilization is also involved in the mechanism of bacterial cell death by initiating a cascade of reactions as a result of a collapse of proton pumps and depletion of the ATP pool, reduction of the membrane potential, and damage to the cell wall and membrane, resulting in leakage of macromolecules and subsequent cell lysis (Oussalah et al. 2006). Diterpenoid essential oils, like aethiopinone and salvipisone (Figure 2.5), obtained from the roots of *Salvia sclarea*, kill bacterial cells, in combination with betalactam antibiotics, as a result of increased cell surface hydrophobicity or greater cell wall permeability (Walencka et al. 2007).

2.7 MEDICINAL PLANT-BASED ANTIBACTERIAL CHEMICALS

Plant-based antibacterial chemicals, either alone or in combination with antibiotics, can be used to solve the problem of controlling infectious bacterial disease caused by antibiotic resistance. A chemical compound obtained from saffron crocus (*Crocus sativus*) has been studied by Carradori et al. (2016). The result indicated that the plant extracts exhibited antibacterial activity to control multidrug-resistant *S. aureus*. Also, the diverse effects of clinical isolates of MRSA in Kolkata, India were resolved by using ethanolic extract of the stem bark of *Cinnamomum verum* (Mandal et al. 2011). The result concluded that the plant can be used for the preparation of

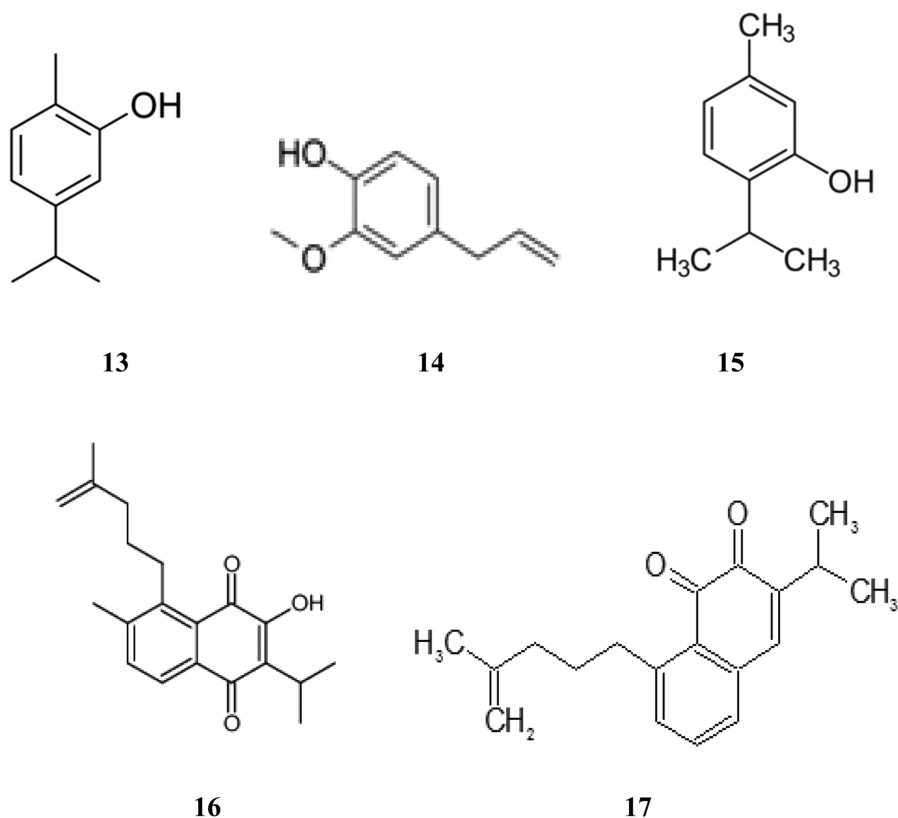


FIGURE 2.5 Structure of the essential oil chemicals carvacrol (13), eugenol (14), thymol (15), salvipisonone (16), and aethiopinone (17).

potential antibacterial agents against MRSA. Pandaa et al. (2020) prepared a novel antibiotic drug from Indian plant extracts, such as those of *Beilschmiedia roxburghiana* and *Mikania micrantha*. The bacterium *Porphyromonas gingivalis* is the keystone pathogen of periodontitis, a chronic inflammatory disease that results in the deterioration of gingival tissues and causes tooth loss (Hajishengallis et al. 2012). Carrol et al. (2020) showed that, to maintain oral hygiene and to prevent tooth loss and deterioration, extracts of some plants, such as *Sassafras albidum*, *Morella cerifera*, *Zanthoxylum armatum*, *Citrus sinensis*, *Juglans regia*, *Carya alba*, and *Vicia faba*, can be used as antibacterial agents. Their results indicated a promising collection of resources of natural products that could be further explored for use for the development of oral hygiene care products and for pharmaceutical development.

The work of Fadhel et al. (2012) investigated, for the first time, the antibacterial effects of leaf extracts of *Eucalyptus cinerea* and *Eucalyptus odorata*, applied on wool or woven cotton fabrics, against *E. coli* and *S. aureus*. The results indicated that the *E. odorata* extract showed good antibacterial activity when applied to a piece of wool fabric. These effects remained without change until the wool was washed ten

times, although loss of antibacterial activity occurred after only three washes of the cotton fibre.

The antibacterial activities of some phytochemicals are very important for food preservation and cosmetics. For instance, the bioactive compounds cinnamaldehyde and eugenol eliminate or reduce bacterial degradation and decrease the incidence of infection of cosmetics and food (Nabavi et al. 2015). Plant-based antibacterial products also showed their importance in cleaning products, such as hand lotions, disinfectants, toothpaste, cleaning cloths, soaps and detergents, and rubbish bags and plastic wrap (Lewis and Elvin-Lewis 2003) (Figure 2.6). The antibacterial properties of extracts of different plant species can also be used for improved oral health against *P. gingivalis*. For example, *Syzygium aromaticum* essential oil (mouthwash) and *Salvadora persica* twigs (toothbrush) are very important for oral hygiene in Africa and the Middle East. Also twigs of *Azadirachta indica* are used as toothbrushes, tongue cleaner, toothache reliever, and oral deodorant in Asia (Carrol et al. 2020). In India, *Zanthoxylum armatum* and *Juglans regia* bark and wood are used as chewing sticks to control *P. gingivalis* bacteria, and, in the Americas, *Sassafras albidum* is also used as a chewing stick (Lewis and Elvin-Lewis 2003).

2.8 PLANT-BASED NANOPARTICLES FOR ANTIBACTERIAL ACTIVITY

The emergence of MDR bacteria and other drug-resistant pathogenic bacteria has become a global health concern because of the inability to treat infectious diseases caused by these bacteria (Tomasz 1994). Treatment of the illness using the available antibiotics is insufficient to arrest the increasing incidence of multidrug-resistant bacteria (Olaitan et al. 2014). Combined with plant-derived antibacterial drugs, the development of nanotechnology offers an alternative means for treating and curing an infectious disease caused by these bacteria (Yuan et al. 2018). Various metal and metal-oxide nanoparticles (NPs) with different morphological features have been synthesized (Siddiqi and Husen 2016, 2017; Siddiqi et al. 2016; 2020). They have shown several uses, including antibacterial activities against a number of Gram-positive and Gram-negative bacteria (Husen et al. 2019; Bachheti et al. 2019; Siddiqi et al. 2019, 2020; Bachheti et al. 2020a, 2020b, 2020c; Husen 2020a, 2020b, 2020c). NPs are designed at the atomic or molecular level, and as extremely small-sized nanospheres. Hence, they can move more freely in the human body in comparison to larger materials. Silver nanoparticles (AgNPs) exhibiting antibacterial activities against Gram-negative and Gram-positive bacteria in combination with different plant extracts were investigated by Mohanta et al. (2020). According to their results, AgNPs prepared by using a leaf extract of *Glochidion lanceolarium* exhibited MIC (IC_{50}) values of 43.94 mg/ml, 68.6 mg/ml, and 44.02 mg/ml against *S. aureus*, *Ps. aeruginosa*, and *E. coli*, respectively, whereas AgNPs prepared from extracts of *Semecarpus anacardium* showed corresponding MIC values of 33.77 mg/ml, 12.9 mg/ml, and 23.49 mg/ml. Moreover, AgNPs synthesized with an extract of *Breynia retusa* also showed significant antibacterial activities towards the test pathogens, with MIC values of 43.94 mg/ml, 12.90 mg/ml, and

64.13 mg/ml for *E. coli*, *Ps. aeruginosa*, and *S. aureus*, respectively. In another study, a preparation of zinc oxide NPs (ZnONPs) with aqueous *Prosopis juliflora* extract was carried out by a straightforward green synthetic approach by Mydeen et al. (2020), according to which the synthesized nanoparticles exhibited significant MIC values against four different bacterial species, namely *E. coli*, *V. cholerae*, *B. subtilis*, and *Rhodococcus rhodochrous*. A study on the green synthesis of chromium oxide (Cr_2O_3) nanoparticles, using *Abutilon indicum* leaf extract as a capping and reducing agent, showed significant antibacterial activities against *B. subtilis*, *S. aureus*, *E. coli*, and *Bordetella bronchiseptica*, using the agar well diffusion assay (Khan et al. 2021). In addition, the preparation of AgNPs, using an extract of *Allium giganteum*, exhibited higher antibacterial activity than AgNPs without the extract towards pathogenic bacteria such as *Ps. aeruginosa*, *E. coli*, *B. subtilis*, and *S. aureus* (Taghavizadeh et al. 2019). Mubarak Ali et al. (2011) examined plant extract-mediated synthesis of AgNPs and AuNPs and their antibacterial properties towards clinically isolated pathogens, such as *E. coli* and *S. aureus*. The results showed very strong antibacterial activities. Cavallo et al. (2021) examined the antibacterial activities of polylactic acid (PLA) and PLA nanocomposite films containing 3 % wt of lipid nanoparticles (LNPs) against *E. coli* and *Micrococcus luteus*. The results indicated that, for either bacterium, PLA/LNPs caused a decrease in the growth of the microorganism, compared with PLA alone. In addition, the LNPs, which were delivered by linen fabrics, using ultrasonic treatment, also exhibited antibacterial characteristics for bacteria, such as *Ps. aeruginosa*, *E. coli*, *K. pneumoniae*, *S. aureus*, *Staphylococcus haemolyticus*, *Micrococcus flavus*, *Bacillus licheniformis*, and *Corynebacterium xerosis* (Zimniewska et al. 2008). The biological synthesis of gold nanoparticles (AuNPs) with essential oils (EOs) from *Nigella sativa* (NsEO-AuNPs) exhibited antibacterial activities against Gram-positive bacteria, like *S. aureus*, and Gram-negative bacteria by reducing the hydrophobicity index by 46% and 78%, respectively (Manju et al. 2016). In an alloy nanoparticle antibacterial study against *S. aureus* and *E. coli* conducted using the agar well diffusion assay, the bactericidal effect of the alloy nanoparticles has been shown to be prominent against *E. coli* with an inhibition zone diameter of 28 mm at a concentration of 150 μl (Vilas et al. 2016).

2.9 CONCLUSION AND FUTURE PERSPECTIVE

Worldwide, especially in developing countries, the occurrence of human illness due to different bacterial pathogens has become a great burden, resulting in huge economic loss and social losses. For many years, the development and mass production of chemically synthesized antibiotics have been very important in improving health by controlling different bacterial pathogens in different parts of the world. The evolution of drug-resistant bacteria due to the overuse and abuse of synthetic antibiotics has increased the burden on people and society to treat bacterial diseases. The presence of MDR bacteria is a global problem with respect to different bacteria infectious diseases, such as pneumonia, cholera, diphtheria, gonorrhoea, meningitis, syphilis, tetanus, tuberculosis, etc. MDR bacteria are continuously challenging the

scientific community, especially in the developing world, and particularly in African countries. The reduction in efficacy of synthetic drugs is aggravating the problem and has forced researchers to look towards plant-derived bioactive antibacterial drugs to alleviate the effects of diseases caused by bacteria, because plant-derived products are safer, have fewer side effects, are cheap, offer new or alternative modes of action, improve the body's natural ability to fight off bacterial disease, and do not select for resistant bacteria. For instance, berberine, which is extracted from *Berberis vulgaris*, is active against bacteria and protozoa, and piperine, isolated from *Piper nigrum*, is active against some bacteria, like *Micrococcus* spp. and *E. coli*. Alkaloids isolated from *Datura stramonium* are active against *E. coli*, *Ps. aeruginosa*, *S. aureus*, *P. mirabilis*, and *K. pneumoniae*. The antibacterial activities of nanoparticles, combined with extracts of medicinal plants, also show great potential for addressing the problem of MDR bacteria. However, only small numbers of combinations of phytochemicals from medicinal plants and nanoparticles have been investigated and the modes of action of different bioactive compounds have still not been widely investigated. Great attention must be paid to evaluating and exploring molecular characterization of the potential bioactive compounds found in plants to identify less toxic and more effective drugs that will benefit the global population.

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3 Antiviral Activity of Medicinal Plants

Current Understanding, Prospects, and Challenges

*Venkatesh V P, Nivya V, Vani V,
Baskaran V, and Madan Kumar P*

CONTENTS

3.1	Introduction	55
3.2	Common Human Viral Diseases and Their Pathogenesis.....	57
3.3	Origin-based Classification of Antiviral Medicinal Plants	58
3.3.1	European Medicinal Plants with Antiviral Activity.....	58
3.3.2	Chinese Medicinal Plants with Antiviral Activity	59
3.3.3	Medicinal Plants from the Americas with Antiviral Activity.....	59
3.3.4	Indian Ayurvedic Plants with Antiviral Activity	60
3.4	Recent Insights on Antiviral Activities of Medicinal Plants.....	61
3.4.1	Medicinal Plants for Treatment of Viral Hepatitis	61
3.4.2	Medicinal Plants for Treatment of HSV	65
3.4.3	Medicinal Plants for Treating Influenza Virus.....	65
3.4.4	Medicinal Plants for Treating SARS-CoV	66
3.5	Significance of Antiviral Drugs from Natural Sources.....	66
3.6	Clinical Rationale for Antiviral Medicinal Plants.....	67
3.7	Challenges and Future Perspectives	67
3.8	Conclusion	68
	References.....	68

3.1 INTRODUCTION

Viruses are extremely small, infectious organisms surrounded by a protein coat, composed of either DNA or RNA as the genetic material, and requiring a host for multiplication (Wasik et al., 2019). Compared with bacteria, fungi, and parasites, viruses are not individual, autonomous organisms and need to replicate within living cells. Therefore, most replication processes require specific cellular host metabolic pathways, making it almost impossible to design a therapy that directly targets the

virion or inhibits it with no associated harmful effects on the injured host cells. Numerous medicinal plants have shown inhibition of the herpes simplex virus (HSV), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), poxvirus, or severe acute respiratory syndrome coronavirus (SARS-CoV) (Chen, 2020). Certain viruses can replicate and contribute to host cell lysis and then further infect and propagate the condition, while others integrate into a host chromosome and stay latent for years. A shortage of specific treatments and the minimal clinical effectiveness of most medications for viral diseases have contributed to a reliance on vaccination as a viral disease prevention treatment. Viral diseases are usually handled with various antiviral drugs, but the development of resistance to such drugs by certain infectious viruses intensifies the situation, with these drugs also often having undesirable effects on patients (Nathanson, 2008).

Viral pathogens continue to evolve new methods of evading the host immune system. These are the challenges that researchers developing antiviral treatments face, since it is challenging to identify specific biochemical properties of viruses that can be selectively targeted. Much information is needed to understand plant anti-virus remedial qualities from the available knowledge of conventional Indian, Chinese, and other ethnic plant-derived medicines that can be evaluated as possible drugs for different viral diseases (Boukhatem and Setzer, 2020). However, improved knowledge of the molecular occurrence of virus infections has ensured that potential antiviral medications can be scanned for particular targets more rationally. Because of the overall burden of virus-related diseases, novel and more efficient antiviral drugs are desperately required. At present, medicinal plants and their bioactive metabolites are of particular importance, which may provide desirable medical options for citizens in developing countries where the bulk of the population cannot afford expensive Western therapeutics (Boukhatem and Setzer, 2020).

The term “antiviral agent/drug” is generally defined as ‘substances, other than attenuated viruses or virus-containing vaccines, or unique antimicrobial antibodies, which offer protective or therapeutic effect to the virus-infected host’. Plants possess tremendous biosynthetic capabilities, synthesizing a rich collection of natural compounds that are commonly employed as promising phytotherapeutics in human viral disease control. Medicinal plants have been directly employed for years as therapeutic agents in various traditional medicine practices. The recent development of sophisticated analytical instruments has rendered medicinal plants an invaluable resource for modern drug exploration (Saklani and Kutty, 2008). Plant-based antiviral medicines offer a stable worldwide market and antiviral medicinal plants tend to be an important source of new medications and lead compounds. Global commerce in the plant-derived antiviral chemicals is a growing market. The worldwide market is estimated to trade in approximately 2000 species of medicinal plants (Ma and Yao, 2020). This chapter intends to report on the antiviral medicinal plants and their metabolites commonly employed as safer alternatives to conventional antiviral drugs, mainly due to their limited side effects and their substantial overall therapeutic effect.

3.2 COMMON HUMAN VIRAL DISEASES AND THEIR PATHOGENESIS

Viruses (sizes in the range 100–1000 nm) cause diseases and spread from one individual to another. They have distinct characteristics which differentiate them from other pathogens. Using the host's own cell machinery, viruses synthesize proteins and nucleic acids to produce new virus particles. Based on the genome type, viruses are broadly classified into two types, namely RNA viruses and DNA viruses. Examples of RNA viruses include dengue virus, while DNA viruses include HSV and poxvirus (Payne, 2017). The most important RNA viruses that cause diseases in humans include influenza, rotavirus, arbovirus, HCV, SARS, Nipah virus, Hendra virus, and Ebola virus (Virgin, 2014).

Although the pathogenesis of each virus is unique, they all share common steps during their life cycle (Nathanson, 2008). The virus's entry into the host depends on its interaction with specific molecules or receptors on the host cell's surface. Virus interaction with the host cell receptor is crucial because it determines the cell or tissue tropism of the viruses and the efficiency of the virus to cause disease (Rossmann et al., 2002; Spear, 2004). Viruses interact with the host cell's different cell surface structures; for example, rhinoviruses bind to ICAM-1 to promote entry, whereas HSV interacts with heparin sulphate to achieve infection. Infection of HIV into a host cell depends on CD4 and CCR5, which allow virus interaction with viral gp120. CD4 is a protein expressed in a subset of T cells within the host and its expression is limited in other cell types, like macrophages. In addition to the binding of gp120 to the CD4 molecule, HIV binding to CCR5/4 is also essential for viral fusion. Some individuals have a non-functional form of CCR5, so are HIV resistant (Vicenzi et al., 2007; Akram et al., 2018). Zoonotic viruses interact with humans only if they have conserved receptors that can be recognized in humans. Also, the zoonotic viruses need to mutate to effectively interact with cell receptors in humans (Rose et al., 2011). SARS-CoV, a zoonotic virus typically seen in bats, infects human cells through their spike proteins, interacting with angiotensin-converting enzyme 2 (ACE2) receptors. Studies show that a mutation in this virus receptor-binding domain leads to its infection of humans (Hamming et al., 2004).

The target tissue of infection of any virus also depends on other factors, such as proviral factors. Proviral factors are molecules in the host system that help to achieve efficient viral replication. HCV infection provides an example of the importance of virus-specific proviral factors that interact with the host microRNA, miR-122. HCV is a single-stranded RNA virus that infects the liver, resulting in organ failure and liver cancer. The specificity of HCV in causing infection in the liver and its ability to replicate in the hepatocyte depends on the host miR-122. miR-122 is expressed explicitly in the hepatocytes, increasing the levels of HCV RNA in the liver. Lanford et al. (2010) showed that administration of an antagonist specific to miR-122 led to decreased HCV viral load in the liver and a reduction in the incidence of associated diseases.

During a viral infection, the host system also executes several defence mechanisms to prevent the virus from entering and causing infection. One such defence

mechanism is provided by host restriction endonucleases that actively inhibit virus replication. A restriction endonuclease from Rhesus macaque, TRIM-5 α , is known to interact with HIV to prevent its replication and subsequent disease progression (McNab et al., 2011). The host immune system is another factor that prevents the virus from infecting the host. Like the type 1 interferons (IFN) and CD8-positive T cells, the innate immune system prevents the virus from replicating within the host and clears the virus particles from the host. Therefore, for successful infection, replication, and dissemination, within-host infecting viruses should have the ability to invade the host and evade the immune system. Numerous viruses can inhibit the host immune system. For example, the SARS-CoV inhibits the host type 1 IFN through nucleocapsid proteins present on the SARS-CoV (García-Sastre et al., 1998; Lanford et al., 2010).

Once a virus enters a cell, the type of cell or tissue it affects and its impact on the tissue determines the type of disease it causes. Some viruses kill the target host cell after infection, while others do not. Examples of viruses that directly kill the host cell upon infection and replication are the Venezuelan equine encephalitis virus (VEE) and the Sindbis virus. Both these viruses directly infect the neuron, replicating, causing neuron cell death and inhibiting neuron functions (Kimura and Griffin, 2003; Spear, 2004). As mentioned above, some viruses are not cytopathic, where they cause diseases associated with a viral infection. Examples include HBV, which cause acute and chronic inflammation in hepatocytes in infected humans. This is because of the over-expressed target host immune system for clearing the viruses, where the immune system becomes less effective and leads to the viral disease (Chisari et al., 2010). HCV infection induces immune reactions, where complexes of viruses and antibodies precipitate in small blood vessels, leading to inflammation (Mutz et al., 2018).

3.3 ORIGIN-BASED CLASSIFICATION OF ANTIVIRAL MEDICINAL PLANTS

3.3.1 EUROPEAN MEDICINAL PLANTS WITH ANTIVIRAL ACTIVITY

Practically every culture around the world relies on the use of medicinal plants for therapeutic purposes. Numerous medicinal plants are reported to have antiviral activity and are widely used to treat humans and animals suffering from viral diseases. In Europe, research into antiviral agents began after World War II. Two hundred and eighty-eight plant species were screened for their antiviral activity against the influenza A virus by the Boots drug company in Nottingham, England, finding that 12 showed antiviral potential (Chantrill et al., 1952). *Veronica persica*, a plant native to Eurasia, was reported to exhibit antiviral activity against HSV-1 and HSV-2 viral strains in Vero cells (Sharifi-Rad et al., 2018). *Sambucus nigra*, also known as a black elder, is a shrub or small tree native to Europe and North America and is approved by USFDA as Generally Recognized as Safe (GRAS) for use as a flavouring agent. It has been reported to exhibit antiviral activity against influenza viral

infections (Porter and Bode, 2017). *Verbascum thapsus*, native to Europe and North Africa and naturalized in North America, showed antiviral effect against HSV-1 (McCutcheon et al., 1995; Jassim and Naji, 2003).

3.3.2 CHINESE MEDICINAL PLANTS WITH ANTIVIRAL ACTIVITY

Traditional Chinese medicine includes numerous herbal medicines, as well as acupuncture, nutritional therapy, and massage techniques, which are based on more than 2000 years of historical usage. Aqueous extracts of *Morus alba* and *Dryopteris crassirhizoma* exhibited anti-dengue potential with a half-maximal inhibitory concentration (IC₅₀) values of 130 and 221 µg/ml, respectively (Maryam et al., 2020). In a study conducted against RSV, 27 Chinese herbs were among the 44 which exhibited the greatest antiviral activity. Other important Chinese herbal plants that have shown antiviral activity are *Sophora flavescens* and *Scutellaria baicalensis*, containing active ingredients, such as anagyrine, sophoranol, oxymatrine, wogonin, and oroxylin A (Ma et al., 2002). Extracts of *Agrimonia pilosa*, *Pithecellobium clypearia*, and *Punica granatum* from China exhibited inhibitory activity against HSV-1. Extracts of *Blumea laciniata*, *Elephantopus scaber*, *Laggera pterodonta*, *Mussaenda pubescens*, *Schefflera octophylla*, and *Scutellaria indica* showed anti-RSV activity with IC₅₀ values ranging from 12.5 to 32 µg/ml (Li et al., 2004). Plants of the *Aglaia* genus, which typically grow in Southeast Asia, are widely used in traditional Chinese medicine, containing phytochemicals known as flavaglines. Flavaglines exhibit activity against several viral diseases, such as coronavirus, Ebola, dengue, and chikungunya (Nebigil et al., 2020). *Illicium verum*, a medicinal plant from China, exhibited dose-dependent antiviral activity against iridovirus infection (Liu et al., 2020).

3.3.3 MEDICINAL PLANTS FROM THE AMERICAS WITH ANTIVIRAL ACTIVITY

Ethanol extracts of *Heisteria acuminata* and aqueous extracts of *Eupatorium articulatum* displayed antiviral activity against vesicular stomatitis virus (VSV) and HSV-1. Aqueous extracts of *Tagetes pusilla* (native to Venezuela), *Baccharis teindalensis* (Ecuador) and *Eupatorium glutinosum* also prevented VSV replication (Abad et al., 1999). Other plants from South America such as *Limonium brasiliense*, *Psidium guajava*, and *Phyllanthus niruri* were reported to exhibit antiviral activity against HSV-1 with IC₅₀ values of 185, 118, and 60 µg/ml, respectively (Faral-Tello et al., 2012). In another study, the antiviral activity of 100 medicinal plant species from British Columbia, Canada, were screened against seven viruses. Extracts from *Rosa nutkana* (Canada) and *Amelanchier alnifolia* (North America) were found to be potent against coronavirus. Extracts of *Potentilla arguta* root and *Sambucus racemosa* branch tips inhibited infection from the respiratory syncytial virus (RSV) whereas *Ipomopsis aggregata* inhibited infection by parainfluenza virus type 3 infection. Proliferation of rotavirus was prevented by root extract from *Lomatium dissectum* from North America. *Cardamine angulata*, *Lysichiton americanum*, *Polypodium glycyrrhiza*, *Conocephalum conicum* (all native to North America), and

Verbascum thapsus (native to Europe but naturalized in North America) showed antiviral effect against HSV-1 (McCutcheon et al., 1995; Jassim and Naji, 2003).

3.3.4 INDIAN AYURVEDIC PLANTS WITH ANTIVIRAL ACTIVITY

Ayurveda is a product of India's rich tradition of herbal knowledge, with the term meaning "the experience of life". Many medicinal plants are used in Ayurveda to treat viral diseases, and now research has been initiated to develop a scientific validation for the antiviral activity of these medicinal herbs (Kalyani, 2013). Aqueous extracts and freeze-dried powder of *Punica granatum* displayed antiviral activity against HSV infections and demonstrated the highest selectivity index (the ratio between antiviral activity and cytotoxicity) of 14 and 12.5, respectively (Jadhav et al., 2012). Aqueous extract of leaves and stem of *Swertia chirata* showed antiviral activity against HSV, confirmed by the plaque reduction assay and the time kinetics of the HSV-1 antigen expression assays (Verma et al., 2008). Balasubramanian et al. (2007) surveyed the viral white spot syndrome in shrimp and screened 20 medicinal plants for antiviral activity, finding that *Aegle marmelos*, *Cynodon dactylon*, *Lantana camara*, *Momordica charantia*, and *Phyllanthus amarus* exhibited potent activity. A study on the antiviral activity of medicinal plants from southern India found that several, such as *Sphaeranthus indicus*, *Cassia alata*, *Indigofera tinctoria*, *Vitex trifolia*, *Clerodendrum inerme*, *Leucas aspera*, and *Clitoria ternatea*, showed antiviral activity against mouse coronavirus and HSV infections (Vimalanathan et al., 2009). In addition to these plant extracts, many individual active phytochemicals, such as andrographolide from *Andrographis paniculata* and curcumin from turmeric (*Curcuma longa*), have also undergone clinical evaluation studies against viral diseases (Dhawan, 2012). *Embelia ribes*, also known as false black pepper, is used in Ayurveda to promote longevity and to treat diabetic ulcers, etc. An ethyl acetate fraction of fruits of *E. ribes* showed antiviral activity against the influenza virus. Its primary active compound, embelin, exhibited greatest activity when used at the early stages of infection (Hossan et al., 2018). Dried seeds of *Azadirachta indica* possesses many medicinal properties, such as anti-inflammatory, antiviral, antibacterial, anti-hyperglycaemic activities, etc. In a study conducted using Vero cells, a petroleum ether extract of *A. indica* oil (50 µg/ml) showed antiviral effects against poliovirus multiplication, whereas *Baccharis trinervis* exhibited antiviral activity against HSV-1 replication at concentrations of 50–200 µg/ml (Sai Ram et al., 2000). *Arisaema tortuosum* is widely found in India's Himalayas and Western Ghats and has been commonly used in traditional medicine to treat various ailments for many years. A chloroform-soluble fraction of leaves of *A. tortuosum* exhibited anti-HSV type 2 activity. The extract also showed antiviral activity against acyclovir-resistant HSV-2 and HSV-1. It was found that the flavones apigenin and luteolin are the two significant bioactives present in the extract responsible for this antiviral activity (Rittà et al., 2020). Some of the frequently studied medical plants have been shown to contain antiviral compounds, and their details are shown in Figure 3.1 and Table 3.1.

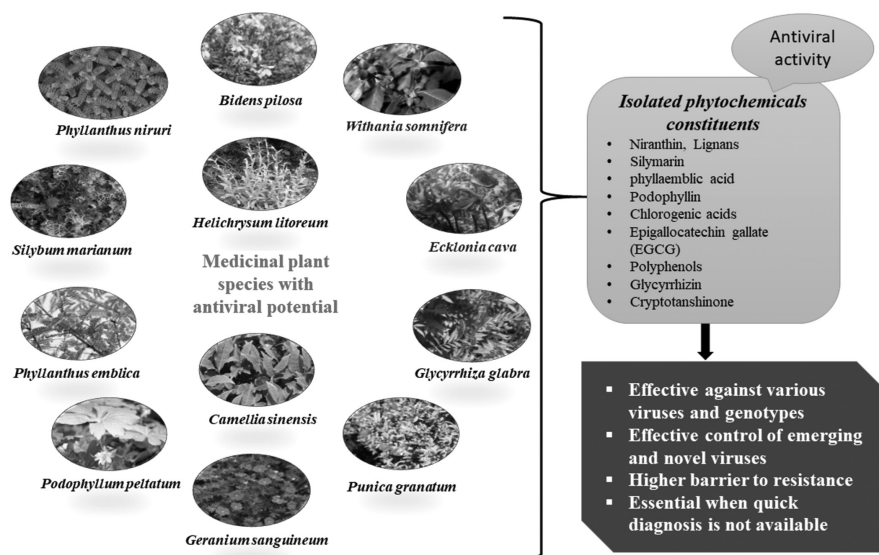


FIGURE 3.1 Plant-based antiviral compounds and their applications.

3.4 RECENT INSIGHTS ON ANTIVIRAL ACTIVITIES OF MEDICINAL PLANTS

3.4.1 MEDICINAL PLANTS FOR TREATMENT OF VIRAL HEPATITIS

The viral liver disease hepatitis is triggered by an inflamed liver and causes various infections, named hepatitis type A, B, C, D, and E. Although susceptibility to these viruses results in acute illness, types B, C, and D are uniquely correlated with a chronic condition. Conventional viral hepatitis medicines are based primarily on plants from the Euphorbiaceae family, particularly the genus *Phyllanthus*. Venkateswaran et al. (1987) showed that active components in the aqueous extract of *Phyllanthus niruri* inhibited replication of HBV and the woodchuck hepatitis virus (WHV). 3-Hydroxy caruillignan C (3-HCL-C), isolated from *Swietenia macrophylla* stems, exhibited potent anti-HCV activity by inhibiting HCV replication (Wu et al., 2012). *Embelia ribes* plant extracts enriched with quercetin inhibited non-structural protein 3 (NS3) which exhibits RNA helicase and serine protease activities, and heat shock proteins, thereby inhibiting HCV (Bachmetov et al., 2012). Wahyuni et al. (2013) conducted a study in Huh7.5 cells using nine strains of HCV (1a to 7a, 1b and 2b) with different genotypes. The ethanol extracts prepared from *Toona sureni* leaves, *Melicope latifolia* leaves, *Ficus fistulosa* leaves, and *Melanolepis multiglandulosa* stem prevented replication of all the nine genotypes of HCV. Niranthin extracted from *P. niruri* showed strong anti-HBV efficacy in both cell lines and animal models. Subsequently, niranthin demonstrated a defensive role against liver

TABLE 3.1
Ethnobotanical Data on Medicinal Plants Used Against Various Viral Diseases

Virus	Antiviral Plant Responsible	Antiviral Compound(s) Responsible	Plant Part(s)	Extract Type	Type of Test Model Studied	Mechanism of Action	References
HBV/HCV	<i>Phyllanthus niruri</i>	Niranthin, lignans	Whole plant	Aqueous	HepG2 cells	Inhibits replication of HBV DNA and expression of HBV antigen	Yong Li et al. (2017)
	<i>Silybum marianum</i>	Silymarin/silibinin	Seeds	Ethanol	HeLa cells	Serum ALT, AST reduction	Wagoner et al. (2010)
	<i>Phyllanthus emblica</i>	Phyllaemblic acid, phyllaemblic acids B and C, phyllaemblicin	Roots	70% ethanol	A549 cells	Inhibition of hepatitis C, HSV-1, and anti-CVB3	Ly et al. (2014)
HSV	<i>Podophyllum peltatum</i>	Podophyllin, deoxypodophyllotoxin	-	Ethanol	Lung fibroblast cells	Inhibition of HSV-1 and HSV-2 replication	Sudo et al. (1998)
	<i>Bidens pilosa</i>	Chlorogenic acid, feruloyl-caffeoylquinic acid	Seeds	Aqueous	Vero and RAW cells	Reduces the infectivity of HSV-1 strain, inhibits HSV-1 replication	Nakama et al. (2012)
	<i>Helichrysum litoreum</i>	6,11-Diacetyl-9,11-dihydroxydrimane	Leaves	Aqueous	Human lung fibroblasts	Reduction of HSV-1 viral replication	Guarino and Sciarrillo (2003)
Influenza virus	<i>Camellia sinensis</i>	EGCG, ECG, EGC	Leaves	Aqueous	MDCK cells	Inhibition of viral RNA synthesis, viral haemagglutinin and neuraminidase	Song et al. (2005)
	<i>Geranium sanguineum</i>	Polyphenols	Roots	Aqueous and alcohol	Mice	Inhibition of viral replication	Serkedjeva et al. (2008)
	<i>Cistus incanus</i>	Polyphenol-rich extract (CYSTUS052)	-	-	A549; MDCK cells	Reduction of influenza A viral replication	Ehrhardt et al. (2007)

(Continued)

TABLE 3.1 (CONTINUED)
Ethnobotanical Data on Medicinal Plants Used Against Various Viral Diseases

Virus	Antiviral Plant Responsible	Antiviral Compound(s) Responsible	Plant Part(s)	Extract Type	Type of Test Model Studied	Mechanism of Action	References
	<i>Punica granatum</i>	Ellagic acid, caffeic acid, luteolin and punicalagin	Fruit	-	MDCK cells	Inhibition of viral replication and viral entry	Haidari et al. (2009)
	<i>Allium fistulosum</i>	Fructans	-	-	Mice	Inhibition of viral replication	Lee et al., (2012)
	<i>Sambucus nigra</i>	-	Berry	Concentrated juice	Mice	Suppression of viral replication in the bronchoalveolar lavage fluids, and increased levels of the IFV-specific neutralizing antibody	Kinoshita et al. (2012)
	Shahakusan	Kampo medicine	Mori Cortex roots, Lycii Cortex roots, <i>Glycyrriza uralensis</i> roots, Oryzae Fructus caryopses	Aqueous	Mice	Immunomodulating activity through action of NK cells	Hokari et al. (2012)
	<i>Rapanea melanophloeos</i> and <i>Pitrosporium viridiflorum</i>	-	-	Methanol, ethanol (100% and 30%), acetone, hot and cold water	MDCK cells	Modification of viral titre loads	Mehrbod et al. (2018)
	<i>Geranium thunbergii</i>	Kaempferitin and geraniin	-	Ethanol	MDCK and A549 cells	Inhibition of neuraminidase	Choi et al. (2019)

(Continued)

TABLE 3.1 (CONTINUED)
Ethnobotanical Data on Medicinal Plants Used Against Various Viral Diseases

Virus	Antiviral Plant Responsible	Antiviral Compound(s) Responsible	Plant Part(s)	Extract Type	Type of Test Model Studied	Mechanism of Action	References
SARS-CoV	<i>Glycyrrhiza glabra</i>	Glycyrrhizin	Roots	Aqueous	Vero cells	Inhibition of SARS-associated virus replication	Cinatl et al. (2003)
	<i>Withania somnifera</i>	Withanoside V, somniferine	Roots	Aqueous	Molecular docking study	Binds to SARS virus	Shree et al. (2020)
	<i>Ecklonia cava</i>	Dieckol	Whole plant	Ethanol	SARS-CoV-3CL (pro) cells	Inhibition of the SARS-CoV 3CL (pro) activity	Park et al. (2013)
	<i>Sabvia miltiorrhiza</i>	Cryptotanshinone	Roots	Hexane	SARS-CoV PLpro	Dose- and time-dependent SARS-CoV inhibition in the slow-binding process of PLpro behaviour	Benarba and Pandiella (2020)

damage induced by HBV in ducklings (Liu et al., 2014). The ethanol fraction of *P. niruri*, enriched with ellagic acid, exerted cytotoxic effects against HepG2/C3A cells infected with HBV (Yong Li et al., 2017).

3.4.2 MEDICINAL PLANTS FOR TREATMENT OF HSV

HSV (both HSV-1 and HSV-2) are human pathogenic viruses that primarily affect adults. After latency has been developed, HSV can reactivate and cause repeated infections in some patients, whereas most people have few, if any, repeat episodes (Yoosook et al., 1989). Podophyllotoxin, a phytochemical extracted from the aqueous extract of *Podophyllum peltatum*, inhibited HSV-1 (Bedows and Hatfield, 1982). *Helichrysum litoreum* plant extracts (1.35 mg fresh weight/ml) exhibited antiviral activity against HSV-1 in human lung fibroblasts (Guarino and Sciarrillo, 2003). Lyu et al. (2005) performed a study to determine the anti-herpetic activities of flavonoids, using Vero cells infected with HSV-1 and HSV-2. Of the 18 flavonoids tested, epicatechin (EC), galangin, epicatechin gallate (ECG), and kaempferol showed potent antiviral activity against HSV-1. Aqueous and ethanolic extracts from *Pelargonium sidoides* demonstrated anti-HSV activity (Schnitzler et al., 2008). *Opuntia streptacantha* blocked virus multiplication and down-regulated extracellular viruses, such as HSV, equine herpes virus, pseudorabies virus, etc. *Bidens pilosa* extract showed potent virucidal activity against HSV-1 and HSV-2 (Marina et al., 2018).

3.4.3 MEDICINAL PLANTS FOR TREATING INFLUENZA VIRUS

Influenza viruses are universal and show marked annual morbidity and mortality worldwide (Cannell et al., 2008). Among the three types of influenza viruses, type A has caused significant health concerns to humans (Hudson, 2009). Song et al. (2005) demonstrated that aqueous extracts of *Camellia sinensis* (green tea) affected influenza A and B virus strains by inhibiting viral RNA synthesis, viral haemagglutinin and neuraminidase. Aqueous and alcoholic extracts of *Geranium sanguineum* aerial roots showed antiviral activities against influenza A virus, mainly by preventing virus multiplication (Serkedjieva et al., 2008). *Cistus incanus* extracts, rich in catechins, achieved its antiviral activity by reducing the replication of the influenza A virus (Ehrhardt et al., 2007). Haidari et al. (2009) showed that polyphenol-rich extracts of pomegranate exerted effects against the influenza virus by preventing virus replication and its entry into the host cell. Fructans isolated from a hot aqueous extract of the leafy part of *Allium fistulosum* inhibited virus replication in a mouse model and exhibited anti-influenza virus activity (Lee et al., 2012). Administration of concentrated elderberry juice (*Sambucus nigra*) to mice infected with influenza virus showed anti-influenza virus activity, with viral replication being suppressed (Kinoshita et al., 2012). Hokari et al. (2012) showed that Shahakusan, a Kampo (Japanese herbal) medicine, exhibited an anti-influenza virus effect in mice through NK cell action by altering immunomodulating activity. Five South African medicinal plants, extracted using methanol, ethanol (100% and 30%), acetone, hot and cold water, were screened for anti-influenza activity using Madin–Darby canine kidney

(MDCK) cells. Among the five plant species tested, *Rapanea melanophloeos* and *Pittosporum viridiflorum* showed strong anti-viral activity (Mehrbood et al., 2018). An ethanolic extract of the traditional Korean herbal preparation Geranii Herba, made from *Geranium* sp., showed higher anti-influenza activity in MDCK by inhibiting neuraminidase than was achieved with oseltamivir, the commercial synthetic anti-viral medication (Choi et al., 2019).

3.4.4 MEDICINAL PLANTS FOR TREATING SARS-CoV

The first coronavirus (SARS-CoV) outbreak was reported in 2002. MERS-CoV, first reported in 2012, has shown that coronaviruses can cross between hosts of different genera and appear as highly pathogenic viruses in humans (Lu et al., 2015). Recently, a very large number of cases of COVID-19 have been witnessed in many countries around the world since 2020. Hispidulin, a flavonoid found in *Salvia officinalis*, *Helichrysum bracteatum*, *Grindelia argentina*, *Crossostephium chinense*, and *Artemisia* spp., exhibits pharmacological activities, such as antioxidant, anti-fungal, anti-inflammatory, antimutagenic, and antiviral activities (Kavvadias et al., 2004). Studies in mice showed that hispidulin (50–150 mg/kg) prevented bromobenzene-induced liver damage and lipid oxidation, thereby acting against viral toxicity (Ferrándiz et al., 1994). Cirsimaritin is a bioflavonoid present in many medicinal plants, including *Cantuarea pseudosinaica*, *Micotea debilis*, *Salvia palaestina*, and *Scorparia centaurea* (Adeem Mahmood and Hamad Alkhatlan, 2020). An *in-silico* study evaluated the efficacy of phytochemicals against SARS-CoV-2 Mpro and ACE2, compared with hydroxychloroquine, showed that hispidulin, quercetin, and cirsimaritin exhibited greater inhibitory ability in terms of virus-binding affinity than did hydroxychloroquine (Shah et al., 2020). Jensenone is a monoterpene found in eucalyptus essential oil (Goodger et al., 2016). The potential of Jensenone as an inhibitor of SARS-CoV-2 Mpro was evaluated using an *in-silico* method, finding that Jensenone had a sizeable binding affinity with low binding energies (Sharma and Kaur, 2020). Glycyrrhizin, a triterpene saponin present in *Glycyrrhiza glabra*, could be a potential candidate for COVID-19 inhibition, based on its potential to bind to ACE2, thereby down-regulating levels of pro-inflammatory cytokines, preventing the accumulation of intracellular reactive oxygen species, inhibiting thrombin accumulation, and activating endogenous interferon (Luo et al., 2020).

3.5 SIGNIFICANCE OF ANTIVIRAL DRUGS FROM NATURAL SOURCES

The identification, supply, and use of effective medications are among the necessities for primary health care quality. Plants have long been an important source of drugs, be it in the context of conventional tissue extracts or as pure active constituents. For decades, the natural origin of medical substances, with many valuable medicines produced from plant sources, pioneered treatments against many important diseases

(Mushtaq et al., 2018). Consequently, it is appropriate for decision makers to include commonly available plants or plant extracts on the national list of medicinal products or to use them to substitute for those prescription preparations that need to be bought and imported. Around 12,000 secondary metabolites have been extracted from medicinal plants, but this amount is estimated to be only a small proportion (<10%) of the total phytochemicals, such as quinine, atropine, galantamine, vinblastine and vincristine, terpenoids, flavonoids, etc., which are a tremendous resource for human health researchers.

3.6 CLINICAL RATIONALE FOR ANTIVIRAL MEDICINAL PLANTS

There are many benefits to using natural medicines. Medicinal plants appear to be more successful for treating long-term health conditions which do not react adequately to conventional medication. Medicinal plants typically have adequate beneficial health effects and can be used more safely over time. For severe and abrupt infections, on the other hand, mainstream medicine usually prevails. New conventional treatments for treating disease and injuries are regarded as being far safer than natural or alternative therapies (Craig, 1999). Herbal medicine is now mostly regarded as an unsubstantiated, flawed topic. Whereas the past history of herbal medicine provides anecdotal evidence from many decades, centuries, or even millennia of use, the systematic research of herbal medicine is still in its adolescence. Although modern-day medical practitioners remain dismissive of herbal medicine, many conventional medicines used in practice today were originally extracted from plant resources.

3.7 CHALLENGES AND FUTURE PERSPECTIVES

Plant-based herbal antiviral drugs are released to the market without any compulsory protection or toxicological review of the impact of the medication. Many countries still lack reliable machinery for governing the activities and quality requirements of herbal medicines. Problems linked to regulatory status, protection, and effectiveness evaluation, quality management, and safety compliance abound, and incomplete or poor awareness of traditional, complementary or alternative medicines is prevalent in many countries (Zhou et al., 2013). The concept of dietary supplement is that of a food which is consumed which is meant to supplement the diet and includes a “dietary” ingredient, in which various vitamins, minerals, herbs, or other botanicals needed by the body can be used as a dietary supplement. No additional toxicity tests are usually needed under the Dietary Supplement Health and Education Act of 1994 (DSHEA) of the United States if the herb was on the market prior to 1994 (Dietary Supplements | FDA, 2020). The other significant problem in many countries is the reality that regulatory knowledge on herbal medicinal goods is often not exchanged amongst regulators and centres of safety testing or pharmacovigilance. No one can refute that the protection and efficacy assessment of herbal medicinal products, as well as the corresponding testing procedures, criteria, and methods, are far more

complicated than those needed for conventional single-chemical pharmaceuticals (Dietary Supplement Fact Sheets, 2020).

There can be hundreds of natural constituents in a single herbal remedy or medicinal plant species, and a herbal medicinal substance blended from several herbal plant species can include many times the number present in a single species. It can be practically impossible to assess the effects, including safety, of individual active constituents, particularly if the herbal product consists of a mixture of two or more herbs. The consistency of the raw materials used in the manufacture of herbal medicinal products primarily determines the consistency of the safety and effectiveness of the preparation. The nature of the source or raw material depends not only on intrinsic (genetic) influences, but also on external factors, such as environmental conditions, farming and medicinal plant collecting practices, like selection of the correct plant and plant part, and cultivation conditions. This combination of several variables makes quality controls on the raw materials of herbal pharmaceutical goods impossible to carry out (Rodrigues and Barnes, 2013). A variety of causes are responsible for harmful effects resulting from the use of herbal medicinal products, including the use of incorrect plant species, adulteration of herbal products, undeclared medicinal products, poisoning, overdose, abuse of herbal medicinal products by health care practitioners or customers, and the use (and subsequent interaction) of herbal medicinal products with other medicinal products. There is a shortage of proper information on the significance of taxonomic botany and documentation in most herbal medicinal products manufacturers, which presents unique challenges in identifying and harvesting herbal plants (Farah et al., 2000; Bhardwaj et al., 2018).

3.8 CONCLUSION

The global disease burden caused by viral infection has encouraged researchers worldwide to develop novel and more effective antiviral drugs. Medicinal plants have provided ample scope for researchers to explore and establish viable alternative treatments for many emerging viral infections. In this chapter, the significance and treatment options of medicinal plants for managing various viral diseases have been discussed. Although the molecular mechanisms behind the antiviral effects of medicinal plants are often well documented, controlled human clinical trials are still warranted. Overall, this chapter should help current and future researchers to find, understand, and assess new molecules from the numerous antiviral medicinal plants available.

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4 Conventional Medicinal Plants

Boosting the Immune System in Humans

Antul Kumar, Anuj Choudhary, Harmanjot Kaur, Asish Kumar Padhy, and Sahil Mehta

CONTENTS

4.1	Introduction	75
4.2	History of Medicinal Systems	76
4.2.1	Ayurvedic Medicinal System (AYMS).....	77
4.2.2	Traditional Chinese Medicinal (TCM) System	77
4.3	Importance of Conventional Medicinal Systems	79
4.4	Immunity-enhancing Plant-derived Drugs	92
4.5	Potential of Local Medicinal Plants as an Immunity Enhancer.....	99
4.5.1	Immunostimulants	99
4.5.2	Immunosuppressants	100
4.5.3	Immuno-adjuvants	100
4.6	Phytochemical Evidence Associated with Traditional Medicinal Systems.....	102
4.6.1	Phytochemistry	102
4.6.1.1	Flavonoids	102
4.6.1.2	Terpenoids.....	103
4.6.1.3	Organosulphur Compounds	104
4.6.2	Pharmacology	104
4.7	Conclusion	113
	References.....	114

4.1 INTRODUCTION

In humans, the immune system is a unique, complex network that helps to deal with various stresses, foreign particles, insults, and illnesses (Anywar et al. 2020). It regulates different pathways and interconnection processes involving microbial recognition, inflammation, microbial clearance, cell/tissue damage, and healing. This homeostatic system entails the well-organized interplays

of different classes of immune cells and their crosstalk with particular tissue microenvironments to sustain immune homeostasis. The immune responses are rapid or slow, depending upon infection halting, infection rate, severity, and the memory of functions. In homeostasis, immunity plays a pivotal role and can be categorized into two types: adaptive immunity or innate immunity (Singh et al. 2016). The acquired or adaptive immune system responses are relatively slow (and are coordinated by B cells and T cells) compared with the innate immunity system, (which includes basophils, dendritic cells, eosinophils, mast cells, macrophages, neutrophils, and invariant natural killer cells). Together, both immune systems help in regulating the activity of cells responsible for the elimination of pathogens and damaged cells, as well as tumour cells (Kumar et al. 2011; Uttpal et al. 2019).

Over the past few decades, paradigm shifts in the medical system have been reported, with changes in interest towards disease prevention. Interest has been boosted to a new level due to the recent catastrophic pandemic situation of COVID-19 (Khanal et al. 2020; Ahmad et al. 2021). In the traditional medicinal system, the disease ailment is based only on primary symptoms and not according to its evaluation or clinical diagnosis, in order to improve the overall quality of life and the maintenance of human health. Based on herbal formulations, various plant parts, ranging from roots, leaves, stems, berries, flowers, buds, twigs, barks, seeds to fruits and whole plants, are used in the treatment of diseases by naturally enhancing the human immune system as a result of supplying vitamins, flavonoids, carotenoids, alkaloids, or other secondary metabolites present in the herbal plant preparation (Archana et al. 2011; Thangadurai et al. 2018; Tuy et al. 2020).

Traditionally, inflammation is considered to be the first symptom and is characterized by pain, swelling, redness, heat, and other functional disturbances. During treatment, medicinal practitioners target such primary symptoms and prescribe herbal formulations (Cundell 2014). Conventional medical research expects that a single chemical compound confers low toxicity, high potency, and selectivity towards targeted cellular diseases. However, understanding the pathways of compounds involved in the immune response is difficult and needs more thorough research (Sultan et al. 2014; Sharma et al. 2017; Singh 2020). Overall, the present chapter highlights the potential of conventional medicinal plants, including members of the same family, major bioactive molecules, and their associated therapeutic role in a strong immune system in humans.

4.2 HISTORY OF MEDICINAL SYSTEMS

Folk or conventional medicine is based on the strategic utilization of basic ingredients of the traditional medicine system, i.e., herbal material and other herbal products that are enriched with bioactive phytochemicals. For example, aspirin was originally obtained from *Filipendula ulmaria* (as the herbal preparation *Spiraea Ulmaria*), which has been recommended for fever and pain swelling since being prescribed by Hippocrates as presented on Egyptian papyri. The medicinal

practical system started in Iraq about 60,000 years ago and about 8,000 years ago in China. The medicinal practitioners used to gain knowledge through their parents/grandparents and recommended the specific herbal medicine formulations (or their products) without any hesitation to the various patients in local communities. Even after so many years of being in use, the conventional medicinal system still requires answers to a variety of questions related to the exact mechanism, functional response, and facts relying on the response of the immune systems, directly or indirectly (Thangadurai et al. 2018).

The concept of immunomodulation has been practiced by the Ayurvedicists for many decades (Sharma et al. 2017). The objective of Ayurvedic practices for immune systems is achieved *via* the implementation of Vajikarana and Rasayana therapy. Disease prevention is acceptable but how they regulate it is unclear and creates an enthusiasm for the endorsement of the traditional medicinal system. The conventional medicinal system is followed by many medicinal systems such as Ayurveda, Chinese, Siddha, Amachis, and Arabic herbal medicines, but the most widely accepted ones are the Ayurvedic and Chinese medicinal systems, which are described in the following sections.

4.2.1 AYURVEDIC MEDICINAL SYSTEM (AYMS)

The Charaka Samhita is considered to be a primary record that is fully devoted to practical and conceptual medicinal health care and longevity systems. AYMS believes that “every plant can be a medicinal plant” and has been deeply explained in the Indian culture. Medicinal practitioners have utilized these extensive collections of herbs, shrubs, climbers, lianas, etc. and have described their roles meticulously (Tripathi et al. 1999; Sharma et al. 2017). Reference to such plants was reported earliest in the publication known as Rig Veda in the Sanskrit literature. Another one is Bhava Prakasha (1550 Before the Common Era, BCE), which lists 470 Indian herbal medicines (IHMs), and is an important textbook on plants/herbs written by Bhava Mishra, which is held in great esteem by medicinal practitioners (Khodadadi et al. 2015; Anywar et al. 2020). Other important textbooks explaining IHMs are Sushruta Samhita (600 BCE), which describes 516 IHMs, Yajurveda (1000–600 BCE), that lists 87 IHMs, and Atharva Veda (4500–2500 BCE), which records 290 IHMs. Currently, 8,000 herbal remedies are confirmed in AYSM and are explained in Materia Medica of Ayurveda (Chulet and Pradhan 2010; Ven et al. 2010; Kumar et al. 2012; Anywar et al. 2020; Figure 4.1).

4.2.2 TRADITIONAL CHINESE MEDICINAL (TCM) SYSTEM

In the 18th century, a book known as Mian Yi Lei Fang or “Formulas for the Immunity from Plague” referred to a Chinese word for “immune” for the first time. For example, the variolation incubation against the smallpox method, in which the patient inhales the powdered vaccine *via* the nostrils with the aid of silver tubes, is of Chinese origin. However, the terminology from the Western world provided an

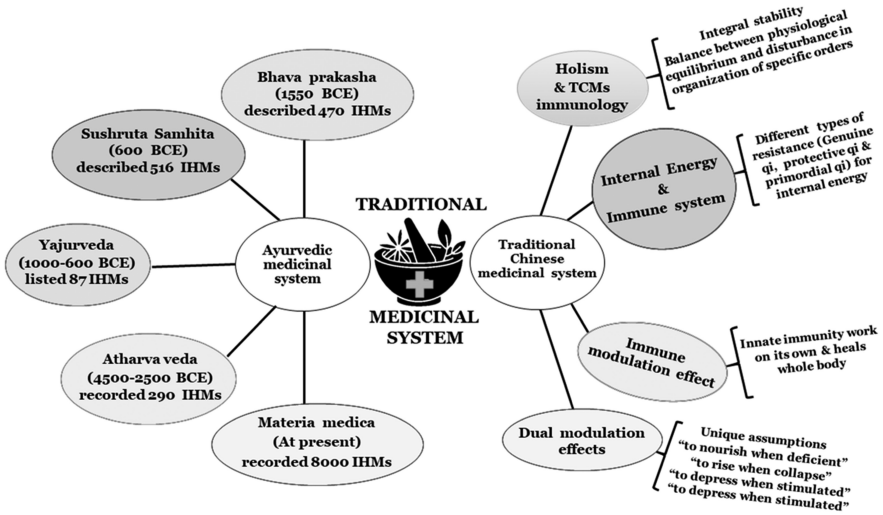


FIGURE 4.1 Contributions of different medicinal systems and their immunoprotective role.

explanation of immunology (Wang and Ren 2002). The TCM has various concepts, which are listed below:

- Holism and TCM immunology. The TCMs are based on holistic approaches and consider that the human body is composed of organic matter. The integral stability, balance between physiological equilibria, and disturbance in the organization of specific orders are the root cause of blockages of the the immune systems. According to Zheng Qi, healthy energy is the vital manifestation of immune functions (Wen et al. 2010).
- Internal energy and the immune system. Different types of resistance, such as genuine qi, protective qi, and primordial qi, are explained by TCMs for internal energy as the natural resistance mechanism of the body against disharmonized energy and diseases (Figure 4.1).
- Immune modulation effect and immune functionality. TCM’s focus on energy flow is known as innate immunity, which works on its own, not to a specific system, but heals the whole body.

According to the yin yang theory, the equilibrium between yin and yang adjusts continuously and is most important to keep the body disease free. The approaches are mainly based on the possession and regulation of holism modulation that re-balance and remove extreme deficiencies. The TCM therapeutic immune system functions in dual states, including excessive hyper-functioning states and deficient or under-functioning states. The rehabilitation of the body occurs from an under-functional state to a Mohan normal state or from a hyper-functioning state to a normal state (Archana and Jatawa 2011; Venkatalakshmi et al. 2016).

This strategy manages to enhance our immune functions and to eliminate internal pathogenic factors with dual modulation effects. TCM has a unique assumption regarding immune functionality and regulatory properties in different actions; “to nourish when deficient”, “to rise when collapsed”, and “to depress when stimulated” (Cundell 2014; Tuy et al. 2020).

4.3 IMPORTANCE OF CONVENTIONAL MEDICINAL SYSTEMS

In modern-day disease management, immunomodulators of plant origin have been established to be the most potent tool, as they promote the non-specific activation of immune responses against pathogens. As a result, it became a scientific concept that has gained much attention in recent years (Thatte et al. 1997; Singh et al. 2016). The Ayurvedic principles (such as Ojas, Vyadhi-ksamatva, and Bala) and modern medicine concepts, including circadian rhythms, neuro-endocrine immune axis, seasonal variations, the influence of exercise, and different physiological states, are much closer to unfolding issues of immune systems (Chulet and Pradhan 2010; Doshi et al. 2013; Pan et al. 2014; Jantan et al. 2015; Utpal et al. 2019). The Vyadhi-ksamatva is regarded as immunity and is highly acceptable in Ayurveda, and also known as Vyadhibala. Charaka has also mentioned Bala as the component that eradicates the pathogens by killing them inside the body. The first action of Bala helps to inhibit, counteract, and overcome the disease-causing factors that cause degradation and cell death, such as anaemia, pulmonary tuberculosis, diabetes mellitus, premature senility, and malignant and other tumours. The second action of Bala relates to both humoral and cellular immunological factors that neutralize or destroy disease-causing agencies which attack the body. Furthermore, in clinical conditions, pathogen entry results in moderate or severe impairment of tissue, distribution in vessels, altered composition, and sometimes certain deficiencies. In addition, mental, physical, severe degenerative and wasting diseases, psychological diseases, starvation, and malnutrition also reduce immune functions (Sharma et al. 2007; Kulkarni et al. 2012).

The combination of four important medicinal plants are explained in Ayurveda, namely Tulsi (*Ocimum sanctum*), Amalaki (*Embllica officinalis*), Ashwagandha (*Withania somnifera*) and Guduchi (*Tinospora cordifolia*), mixed in equal proportions, is taken to elevate humoral and cellular components of the immune system (Reis et al. 2008; Rachh et al. 2014; Table 4.1). This preparation directly enhances the microbiocidal action of the neutrophil cells and increases the levels of globulin components in the circulatory system. Intake of the above medicinal plant preparation with the given composition results in increased levels of lymphocytes, which increase the memory of the T cells along with enhanced cell number and size of the macrophages (phagocytic cells). The preparation is also helpful in improving our immune response and accelerating recovery when used as an adjunct to various immune-related disorders, such as multidrug-resistant tuberculosis, chronic wasting therapy, cancer, and other immunocompromized disorders (Chatterjee and Dass 1996; Tiillu et al. 2020). The concept of Bala for innate immunity, acquired immunity, or immunological capabilities, playing a central role in disease and health, have to be appreciated and understood by Western immunologists. There is a wide range

TABLE 4.1
Comparative List of Conventional Medicinal Plants and Their Constituent Properties

S. No	Plant Species	Common Name	Family	Parts Used	Properties	Traditional Uses	Drug Derivatives	Commonly Used Drugs	References
1	<i>Atropa belladonna</i>	Belladonna	Solanaceae	Leaves and branches	<ul style="list-style-type: none"> • Pain reliever • Muscle relaxer • Anti-inflammatory • Treatment of menstrual problems 	Treatment of headache, ulcers, typhoid, and scarlet fever	Atropine	Atrocealth	Lanculov et al. (2004)
2	<i>Withania somnifera</i>	Ashwagandha	Solanaceae	Flower, root, bark, seeds, and leaves	<ul style="list-style-type: none"> • Antimicrobial • Anti-snake venom treatment • Antitumor • Anti-inflammatory 	Treatment of asthma, diabetes, hypertension, stress, arthritic diseases, and cancer	Withanolides	Ashwagand harita	Gupta and Rana (2007)
3	<i>Andrographis paniculata</i>	Kalmegh	Acanthaceae	Leaf, roots, and aerial part	<ul style="list-style-type: none"> • Antimicrobial • Cytotoxicity • Antiprotozoan • Anti-inflammatory • Antioxidant • Immunostimulant • Antidiabetic • Anti-infective 	Treatment of cancer, diabetes, high blood pressure, flatulence, ulcers, leprosy, skin diseases, colic, bronchitis, influenza, dysentery, dyspepsia, and malaria	Andrographolide	Jaborandi	Biswa et al. (2011)
4	<i>Andrographis paniculata</i>	Kalmegh	Acanthaceae	Leaves, roots, and whole plant	<ul style="list-style-type: none"> • Antimicrobial • Antiprotozoan • Anti-inflammatory • Anti-oxidant, • Immunostimulant, • Antidiabetic • Anti-infective 	Treatment of cancer, high blood pressure, ulcer, leprosy, diabetes, bronchitis, dyspepsia skin diseases, flatulence, colic, influenza, dysentery, and malaria	Andrographolide	Fleximark	Biswa et al. (2011)

(Continued)

TABLE 4.1 (CONTINUED)
Comparative List of Conventional Medicinal Plants and Their Constituent Properties

S. No	Plant Species	Common Name	Family	Parts Used	Properties	Traditional Uses	Drug Derivatives	Commonly Used Drugs	References
5	<i>Berberis aristata</i>	Darhaid	Berberidaceae	Fruits, roots, leaves, stem, and bark	<ul style="list-style-type: none"> • Immunostimulant • Antidiabetic • Antimicrobial • Hepatoprotective • Antidepressant 	Treatment of diarrhoea, jaundice, syphilis, chronic rheumatism, skin diseases, and urinary disorders	Berberine	Daruharida	Sharma et al. (2011)
6	<i>Nycatanthes arbores-trists</i>	Parijat	Oleaceae	Leaves, flowers, seeds, stem, and bark	<ul style="list-style-type: none"> • Hepatoprotective • Antileishmaniasis • Antiviral • Antifungal • Antipyretic • Anthistaminic • Antimalarial • Antibacterial • Anti-inflammatory • Antioxidant activities 	Reduce fever, enlargement of the spleen, malaria, blood dysentery, cough, and gastritis	Artemisinin and quinine	Harshingar	Rani et al. (2011)
7	<i>Ocimum sanctum</i>	Tulsi	Lamiaceae	Leaves, seeds, and root	<ul style="list-style-type: none"> • Analgesic • Anticancer • Antifertility • Antirheumatic • Antistress 	Treatment of bronchitis, malaria, diarrhoea, dysentery, skin disease, arthritis, eye diseases, and insect bites	Monoterpenes and sesquiterpenes	Curill capsule	Vishwabhan et al. (2011)

(Continued)

TABLE 4.1 (CONTINUED)
Comparative List of Conventional Medicinal Plants and Their Constituent Properties

S. No	Plant Species	Common Name	Family	Parts Used	Properties	Traditional Uses	Drug Derivatives	Commonly Used Drugs	References
8	<i>Aegle marmelos</i>	Bael	Rutaceae	Leaves, bark, roots, fruits, and seeds	<ul style="list-style-type: none"> • Antidiarrhoeal • Antimicrobial • Antiviral • Radioprotective • Anticancer • Chemopreventive • Antipyretic • Ulcer healing 	Treatment of asthma, jaundice, fever, and constipation	Dibutyl phthalate	WDPL Bilva	Atul et al. (2012)
9	<i>Acacia catechu</i>	Katha	Fabaceae	Bark, fruits, and gum	<ul style="list-style-type: none"> • Antioxidant • Anti-inflammatory • Free radical scavenging • Tissue-protective effects 	Reduce swelling of the nose, swelling of the colon (colitis), and throat, treat diarrhoea, dysentery, bleeding, osteoarthritis, and cancer.	Catechin, catechol, and catecholamine	Unibest	Verma (2012)
10	<i>Calotropis procer</i>	Aak	Apocynaceae	Root and root bark	<ul style="list-style-type: none"> • Antimicrobial • Anthelmintic • Anti-inflammatory • Analgesic • Antipyretic • Anticancer • Anti-angiogenic • Immunological • Antidiabetic • Gastroprotective, 	Treatment of jaundice, diarrhoea, stomatic, sinus fistula, and skin disease	Cardiac glycosides	Calotropis 1000ch	Khairnar et al. (2012)

(Continued)

TABLE 4.1 (CONTINUED)
Comparative List of Conventional Medicinal Plants and Their Constituent Properties

S. No	Plant Species	Common Name	Family	Parts Used	Properties	Traditional Uses	Drug Derivatives	Commonly Used Drugs	References
11	<i>Trachyspermum ammi</i>	Ajwain	Apiaceae	Whole plant	<ul style="list-style-type: none"> • Stimulant • Antispasmodic • Carminative property 	Acts as carminative, stimulant, antispasmodic, tonic, dyspepsia, and used to treat cholera	Glycosides, saponins, phenolic compounds	Ajwain oil	Jeet et al. (2012)
12	<i>Trigonella foenum-graecum</i>	Methi	Fabaceae	Seed	<ul style="list-style-type: none"> • Anticarcinogenic • Anti-diabetic • Anthelminthic • Anti-ulcer • Hypoglycaemic 	Treatment of diarrhoea, dysentery, cough, liver, and spleen disorder	Trigonelline, iso-orientin, orientin, vitexin, and isovitexin	Indigo foenogreek tincture	Meghwal et al. (2012)
13	<i>Commiphora wightii</i>	Guggul	Burseraceae	Bark, leaves, and flowers	<ul style="list-style-type: none"> • Anti-inflammation • Anti-obesity • Antirheumatism • Gout treatment 	Treatment of rheumatoid arthritis, neurological diseases, hypercholesterolaemia, leprosy, muscle and skin disorders, high blood pressure, and urine problems	Steroidal compounds	Gokshura	Ikram and Chahar (2013)
14	<i>Eclipta alba</i>	Vringraj	Asteraceae	Leaves, seed, and stem	<ul style="list-style-type: none"> • Antihypertoxic • Antimicrobial • Antidiabetic • Anticancer • Analgesic • Anti-venom 	Acts as liver tonic, to treat diabetes, eye health, and promote hair growth	Coumestan steroids	Bhringraj	Bhalerao (2013)

(Continued)

TABLE 4.1 (CONTINUED)
Comparative List of Conventional Medicinal Plants and Their Constituent Properties

S. No	Plant Species	Common Name	Family	Parts Used	Properties	Traditional Uses	Drug Derivatives	Commonly Used Drugs	References
15	<i>Datura metel</i>	Dhatura	Solanaceae	Leaves and flowers	<ul style="list-style-type: none"> • Analgesic • Antiviral • Anti-ulcer • Antistress • Antifungal • Anti-asthmatic 	Treatment of Parkinson's disease, asthma, coughs, tuberculosis, and bronchitis	Withanolides and amides	Schwable Datura metel	Maheshwari et al. (2013)
16	<i>Aloe vera</i>	Gritkumari	Asphodelaceae	Leaf pulp	<ul style="list-style-type: none"> • Anti-inflammatory • Antiaging • Antitumor • Antibacterial • Antiseptic 	Treatment for burns, skin irritations, cuts and insect bites, to relieve itching and skin swellings	Aloin	Clarina	Sahu et al. (2013)
17	<i>Abrus precatorius</i>	Gunja	Fabaceae	Roots, seeds, and leaves	<ul style="list-style-type: none"> • Antioxidative • Immunostimulant • Antimalarial • Anti-allergic • Anticataract 	Treatment of tetanus, to cure fever, cough and cold, and to prevent rabies	Abrol, abrasine	Abrus precatorius	Bhatia et al. (2013)
18	<i>Azadirachta indica</i>	Neem	Meliaceae	Bark, leaves, and fruits	<ul style="list-style-type: none"> • Antibacterial • Antiviral • Antiparasitic • Anti-inflammatory • Anticarcinogenic • Antioxidant • Immune system upregulation • Anti-snake venom activity 	Treatment of fungal infection, to reduce acne and nourish skin	Azadirachtin	Azadirachta indica tablets	Dubey et al. (2014)

(Continued)

TABLE 4.1 (CONTINUED)
Comparative List of Conventional Medicinal Plants and Their Constituent Properties

S. No	Plant Species	Common Name	Family	Parts Used	Properties	Traditional Uses	Drug Derivatives	Commonly Used Drugs	References
19	<i>Curcuma longa</i>	Haldi	Zingiberaceae	Rhizome	<ul style="list-style-type: none"> • Anti-inflammatory • Antioxidant • Antidiabetic • Click here to enter text. • Anti-asthmatic 	Treat wounds infections, bruises, inflamed joints and sprains, treat various other illnesses	Curcuminoid	-	Nasri et al. (2014)
20	<i>Tinospora cordifolia</i>	Giloe	Menispermaceae	Roots, stem, and leaves	<ul style="list-style-type: none"> • Antiperiodic • Antispasmodic • Antimicrobial • Anti-osteoporotic • Anti-inflammatory • Anti-arthritis • Anti-allergic • Antidiabetic 	Treatment of diabetes, high cholesterol, allergic rhinitis, upset stomach, gout, lymphoma and other cancers, rheumatoid arthritis, hepatitis, peptic ulcer disease, fever, gonorrhoea, and syphilis	Tinosporic acid, cordifoliosides	Himalaya Guduchi	Mittal (2014)
21	<i>Terminalia arjuna</i>	Arjuna	Combretaceae	Stem and bark	<ul style="list-style-type: none"> • Antioxidant • Hypotensive • Anti-atherogenic • Anti-inflammatory • Anticarcinogenic • Antimutagenic • Gastro-productive effect 	Treatment of cardiovascular diseases (CVD), ulcers, diabetes, cough, excessive perspiration, asthma, tumour, inflammation, and skin disorders	Triterpenoids	Arjuna	Dwivedi and Chopra (2014)

(Continued)

TABLE 4.1 (CONTINUED)
Comparative List of Conventional Medicinal Plants and Their Constituent Properties

S. No	Plant Species	Common Name	Family	Parts Used	Properties	Traditional Uses	Drug Derivatives	Commonly Used Drugs	References
22	<i>Saraca asoca</i>	Ashoka	Fabaceae	Stem, bark, seeds, and leaves	<ul style="list-style-type: none"> • Anti-oestrogenic • Anti-inflammatory • Anti-implantation • Antioxidant • Antitumor • Anticancer 	Treatment of neurological disorders, snake bites, fever, tumours, poisoning, diarrhoea, worm infestations, burning sensation, excessive menstrual bleeding, and abdominal swelling	Gallic acid	Ashoka powder	Singh et al. (2015)
23	<i>Abutilon indicum</i>	Kanghi	Malvaceae	Leaves, bark, and seeds	<ul style="list-style-type: none"> • Anti-inflammatory • Antiproliferative activity • Anti-arthritic activity • Analgesic and sedative property • Antioxidant • Antimicrobial activity • Hepatoprotective activity 	Reduce toothache, tender gums, also used in treatment of ulcers	Palmitic acid, β -sitosterol, and stigmasterol	Organic pure abutilon indicum powder	Raja and Kailasam (2015)
24	<i>Picrohiza kurroa</i>	Kutaki	Plantaginaceae	Leaf, bark, root, and rhizomes	<ul style="list-style-type: none"> • Immunostimulant • Antioxidant • Anti-inflammatory • Anti-allergic • Hepatoprotective • Choloretic • Anti-asthmatic • Anti-cancerous activity 	Promote liver functioning, to treat dyspepsia, chronic diarrhoea, scorpion sting, and reduce fevers	Picrosides	Kutki	Qureshi et al. (2015)

(Continued)

TABLE 4.1 (CONTINUED)
Comparative List of Conventional Medicinal Plants and Their Constituent Properties

S. No	Plant Species	Common Name	Family	Parts Used	Properties	Traditional Uses	Drug Derivatives	Commonly Used Drugs	References
25	<i>Bryophyllum pinnatum</i>	Ghamari	Crassulaceae	Leaves	<ul style="list-style-type: none"> • Antimicrobial • Anticancer • Antihypertensive • Antidiabetic • Hepatoprotective • Anti-inflammatory 	Treatment of earache, burns, abscesses, ulcer, insect bites, diarrhoea, and lithiasis	5- Methyl 4, 5, 7- trihydroxyl flavone 1 and 4-, 3, 5, 7 tetrahydroxy 5-methyl 5 1-propenamine anthocyanidins 2	SBL Bryophyllum calycinum	Nagaratna et al. (2015)
26	<i>Allium sativum</i>	Lasun	Amaryllidaceae	Bulb	<ul style="list-style-type: none"> • Hepatoprotective • Antioxidant • Anticarcinogenic • Antiprotozal • Diuretic 	Treatment of fevers, dysentery, diabetes, rheumatism, intestinal worms, colic, flatulence, liver disorders, facial paralysis, tuberculosis, high blood pressure, and bronchitis	Allicin	Garlic oleoresin	Alam et al. (2016)
27	<i>Asparagus racemosus</i>	Satavari	Asparagaceae	Roots	<ul style="list-style-type: none"> • Anti-ulcer • Antioxidant • Antidiarrhoeal • Antidiabetic • Immunomodulatory 	Treatment of dyspepsia, constipation, stomach spasms, stomach ulcers, cancer, diarrhoea, bronchitis, tuberculosis, dementia, and diabetes	Shatavarin	Spermon	Hasan et al. (2016)

(Continued)

TABLE 4.1 (CONTINUED)
Comparative List of Conventional Medicinal Plants and Their Constituent Properties

S. No	Plant Species	Common Name	Family	Parts Used	Properties	Traditional Uses	Drug Derivatives	Commonly Used Drugs	References
28	<i>Nardostachys jatamansi</i>	Jatamansi	Caprifoliaceae	Roots	<ul style="list-style-type: none"> • Antifungal • Antioxidant • Antidiabetic • Immunostimulant 	Treatment of hysteria, syncope, epilepsy, and mental weakness	Sesquiterpene	Yuvika jatamansi	Sahu et al. (2016)
29	<i>Allium cepa</i>	Piyaz, onion	Amaryllidaceae	Bulb	<ul style="list-style-type: none"> • Anticholesterol • Anticancer • Antioxidant • Antibiotic • Antimicrobial • Antidiabetic 	Help in scar removal, heal burns and wounds, reduce hair loss, treatment of diabetes, High cholesterol, blood pressure, asthma, whooping cough, sore throat, and bronchitis	SMCS (S-methyl cysteine sulfoxide)	SBL Allium Cepa Dilution 30 CH	Upadhyay et al. (2016)
30	<i>Cuminum cyminum</i>	Zira	Apiaceae	Seed	<ul style="list-style-type: none"> • Antimicrobial • Anti-inflammatory • Insecticidal • Antiplatelet • Diuretic 	Treatment of stomach disorders, diuretic, carminative, stimulant	-	-	Al-Shafi (2016)
31	<i>Croton tiglium</i>	Jamalgotia	Euphorbiaceae	Seeds	<ul style="list-style-type: none"> • Anti-tumour • Anti-inflammatory • Antioxidant • Antidermatophytic 	Acts as purgative, stimulant, to treat bronchitis, asthma, paralysis, sciatica	Cardiac glycosides, phorbol esters, lectins, and cyanogenic glycoside	Croton tig 200	Sinsinwar et al. (2016)

(Continued)

TABLE 4.1 (CONTINUED)
Comparative List of Conventional Medicinal Plants and Their Constituent Properties

S. No	Plant Species	Common Name	Family	Parts Used	Properties	Traditional Uses	Drug Derivatives	Commonly Used Drugs	References
32	<i>Clitoria ternatea</i>	Aparijita	Fabaceae	Flower, roots, and seeds	<ul style="list-style-type: none"> • Immunostimulant • Antipyretic • Anti-inflammatory • Analgesic • Antimicrobial activity 	Treatment of heart disease, depression, gonorrhoea, and other skin diseases	Finotin	-	Chauthan et al. (2017)
33	<i>Catharanthus roseus</i>	Sada bahar	Apocynaceae	Leaf, stem, root, and flower	<ul style="list-style-type: none"> • Antimalarial • Immunostimulant • Anticancer • Antihyperglycaemic • Analgesic 	Help in relieving muscle pain, depression, diabetes, treatment of stomach ache, wasp stings, to heal wounds	Vinblastine, vincristine	Vincristine	Gupta et al. (2017)
34	<i>Bacopa monnieri</i>	Brahmi	Plantaginaceae	Twig, leaf, and flower	<ul style="list-style-type: none"> • Memory enhancing • Anti-inflammatory • Analgesic • Antipyretic • Sedative • Anti-epileptic agent 	Acts as nerve tonic, diuretic, to treat asthma, epilepsy, insanity, and hoarseness	Baccosoids	Mentat	Rai et al. (2017)
35	<i>Zingiber officinale</i>	Adrak	Zingiberaceae	Rhizome	<ul style="list-style-type: none"> • Antioxidant • Anticancer • Antipyretic • Anti-obesity • Gastroprotective • Analgesic • Antimigraine 	To treat heart problems, stomach upset, diarrhoea, headache, and nausea	Gingerol	Organic ginger	Dhanik et al. (2017)

(Continued)

TABLE 4.1 (CONTINUED)
Comparative List of Conventional Medicinal Plants and Their Constituent Properties

S. No	Plant Species	Common Name	Family	Parts Used	Properties	Traditional Uses	Drug Derivatives	Commonly Used Drugs	References
36	<i>Cymbopogon martini</i>	Gandh	Poaceae	Leaves, rhizomes, roots	<ul style="list-style-type: none"> Immunostimulant Antimicrobial Antifungal Antiviral Anthelminthic Antioxidant 	Treatment of scabies, asthma, rheumatism, arthritis, common cold, and reduce hair loss	Geraniol	Cymbopogon martini	Promila (2018)
37	<i>Hyoscyamus niger</i>	Parsikaya	Solanaceae	Roots, leaves, and seeds	<ul style="list-style-type: none"> Immunostimulant Anti-inflammatory Analgesic Antipyretic Antiparkinsonism 	Treatment during rheumatism, asthma, cough, nervous diseases, stomach pain, and toothache	Hyoscyamine	Hyoscyamine oral drops	Al-Shafi (2018)
38	<i>Terminalia chebula</i>	Harida	Combretaceae	Fruit	<ul style="list-style-type: none"> Antibacterial Antifungal Antiviral Antidiabetic Antimutagenic Antioxidant Anti-ulcer Wound healing 	Treatment of dementia, constipation, and diabetes	Chebulagic acid, coriagin, mannitol, ascorbic acid	Haritaki capsules	Kolla and Kulkarni (2018)

(Continued)

TABLE 4.1 (CONTINUED)
Comparative List of Conventional Medicinal Plants and Their Constituent Properties

S. No	Plant Species	Common Name	Family	Parts Used	Properties	Traditional Uses	Drug Derivatives	Commonly Used Drugs	References
39	<i>Jatropha curcas</i>	Arandi	Euphorbiaceae	Leaves, fruit, seed, stem bark, branches, and roots	<ul style="list-style-type: none"> • Anti-inflammatory • Antioxidant • Antimicrobial • Antiviral • Anticancer • Antidiabetic • Anticoagulant • Hepatoprotective • Analgesic 	Treatment of burn spot, chest inflammation, congestion, headache, hypertension, eczema, and galactogogue	Apigenin	Jatropha cur 30	Abobatta (2019)
40	<i>Cinnamomum zeylanicum</i>	Dalchini	Lauraceae	Bark and leaves	<ul style="list-style-type: none"> • Anti-bacterial • Anti-fungal • Antioxidant • Lowering cholesterol level 	Treatment of nausea, vomiting, and diarrhoea.	Cinnamaldehyde	Ceylon cinnamon	Rawat et al. (2019)

of these herbal formulations and their derived drugs available in India, focusing on the nutritional dynamics that help to enhance the ability of the immune system to protect the body from infectious and communicable diseases and to act as a promoter of the treatment of the immunocompromized condition (Gan et al. 2003; Sharma et al. 2007; Archana et al. 2011; Derouiche 2020).

4.4 IMMUNITY-ENHANCING PLANT-DERIVED DRUGS

Plants synthesize a remarkably wide range of secondary metabolites. These secondary metabolites are mainly non-essential for the primary metabolism of plants, but play significant roles in defence by creating a strong immune response to pathogen infections, stress conditions, and environmental effects (Piasecka et al. 2015; Lokhande et al. 2019). The literature has tended to identify the active phytochemicals that are responsible for the therapeutic effects of most immunity-boosting plants, including Greco-Arab herbs (Venditti et al. 2016). They include flavonoids, tannins, terpenoids, steroids, and polysaccharides. Furthermore, the main immunity-enhancing drugs originated from plants are alkaloids, such as sophocarpine, chelerythrine, curcumin, piperine, sinomenine, quercetin, matrine, tetrandrine, berberine, capsaicin, colchicine, leonurine, gelsegine, pseudocoptisine, andrographolide, koumine, rhyngophylline, lycorine and genistein (Table 4.2). These chemicals can also be further categorized into other categories, such as:

- **Essential oil:** Tetramethylpyrazine and Z-ligustilide.
- **Flavonoids:** Dihydroxanthohumol, mallotophilippens C, D, E, licochalcone E, chalcone, butein, and xanthohumol.
- **Flavones:** Apigenin, baicalein, chrysin, oroxylin A, luteolin, nobiletin, and wogonin.
- **Flavonols:** Quercetin, rutin, and kaempferol.
- **Flavanols:** Epigallocatechin-3-gallate.
- **Isoflavones:** Daidzein, puerarin, and genistein.
- **Phloroglucinols:** Arzanol and myrtucommulone.
- **Quinones:** Emodin-8-*O*- β -D glucoside, shikonin, and thymoquinone.
- **Other Apocynins:** Piceatannol, resveratrol, and stilbenes.
- **Terpenoids:** Asiaticoside celastrol, demethylzelastrol, ginsan, oleanolic acid, echinocystic acid, triptolide, 11-keto- β -boswellic acid, 14-deoxyandrographolide, 14-deoxy-11,12-didehydroandrographolide, and madecassoside (Table 4.2) (Cook and Samman 1996; Fernandez et al. 2001; Petronelli et al. 2009).

In all medicinal systems over the centuries, the treatment and prevention of disease, using plant-derived drugs, have been long-term processes but, using the immunity enhancer plants provides a better and more efficient way of achieving these goals than was previously possible in human history. Traditionally, these compounds were considered to be solely responsible for a strong immune system but validation by pre-clinical trials is needed (Kumar et al. 2011). As a result, much research

TABLE 4.2
Phytochemical Compounds, Derived from Medicinal Plants, as Immunity Boosters

S. No	Plant	Phytochemical Compounds	References
1.	<i>Atropa belladonna</i>	Apoatropine, belladonnine, scopolamine, tropine, 6 β -hydroxyhyoscyamine, hyoscyamine and norhyoscyamine,	Lanculov et al. (2004)
2.	<i>Withania somnifera</i>	Anahygrine, anaferine, cysteine, chlorogenic acid, cuscohygrine, pseudotropine, withanine, tropanol, somniferine, withanolides, withanamine, scopoletin, iron and A-Y, β -sitosterol	Gupta and Rana (2007)
3.	<i>Embllica officinalis</i>	Ellagic acid, quercetin, gallic acid, 1-O galloyl-beta-D-glucose, chebulagic acid, 3,6-di-o-galloyl-D-glucose, 1,6-di-O-galloyl beta D-glucose, corilagin, chebulinic acid, isostriatinin and 3-ethylgallic acid	Khan (2009)
4.	<i>Piper longum</i>	Asarine, brachystamide-A, brachystine, brachystamide, fargesin, piperine, cinnamoyl-piperidine, iperonaline, piperlonguminine, piperlongumine, piperderidine, pipericide piperettine, pellitorine, 1-piperoyl piperidine, methyl pregumidiene, piperundecalidine refractomide A, longamide, dehydripiperonaline, tetrahydropiperine, terahydro piperlongumine, piperine, terahydro piperlongumine pulvuatitol, piperidine, trimethoxy piperlongumine and sesamin,	Zaveri et al. (2010)
5.	<i>Centella asiatica</i>	Asiaticoside, asiatic acid, α -pinene, brahmnic acid, brahminoside, <i>trans</i> - β -farnesene, centellose, β -caryophyllene, bicycloelemene, brahmioside, bornyl acetate, campesterol, β -elemene, β -pinene, mesoositol, myrcene, terpenic acetate, γ -terpinene, α -copaene, germacrene-D, sitosterol, glucose, saponin, and stigmasterol,	Singh et al. (2010)
6.	<i>Berberis aristata</i>	Aporphine, oxyberberine, palmatine, pseudopalmatine chloride, pseudoberberine chloride, aromoline, berberine, taxilamine, berbamine, oxyacanthine, proaporphine, protoberberine, 1-O-methyl pakistanine, pakistanine, and karachine,	Sharma et al. (2011)
7.	<i>Nyctanthus arbores-tristis</i>	Acetophenone, <i>p</i> -cymene, <i>p</i> -cymene, cineole, <i>n</i> -dodecanol, eugenol, (E)- β -damascone, methyl anthranilate, <i>p</i> -vinylquaiacol, camphor, nonanal 2-phenylethyl alcohol, α -pinene, nerol, limonene, α -terpineol, methyl salicylate, hexenyl acetate, 1,8-phenylacetaldehyde, hexenyl butanoate, hexenol, linalool, geraniol, <i>m</i> -cymen-8-ol, and (3Z)-hexenyl tiglate,	Rani et al. (2011)

(Continued)

TABLE 4.2 (CONTINUED)
Phytochemical Compounds, Derived from Medicinal Plants, as Immunity Boosters

S. No	Plant	Phytochemical Compounds	References
8.	<i>Ocimum sanctum</i>	Carvacrol, β caryophyllene, β -elemene, germacrene, ursolic acid, eugenol, linalool, oleanolic acid, and rosmarinic acid,	Vishwabhan et al. (2011)
9.	<i>Aristolochia indica</i>	Aristolochene, aristolactam IIa, Aristolindiquinone, aristolide, cephradione, methylaristolate, β -sitosterol- β D-glucoside aristolactam glycoside I, ishwarone, ishwarol, 2-hydroxy-1-methoxy-4H-dibenzo quinolone-4,5-(6H)-dione, stigmastenes II and III, and methylaristolate,	Dey and de (2011)
10.	<i>Andrographis paniculata</i>	Deoxyandrographolide, β -daucosterol, β -sitosterol, oleanolic acid, <i>trans</i> -cinnamic acid, neoandrographolide, isoandrographolide, 7- <i>O</i> -methylwogonin, 5-hydroxy-7,8,2'-trimethoxyflavone, 4-hydroxy-2-methoxycinnamaldehyde, 5-hydroxy-7,8,2',5'-tetramethoxy flavone, 2'-methyl ether, 5-hydroxy7,8,2',3'-tetramethoxyflavone, 5-hydroxy-7,8-dimethoxyflavone and 14-deoxy11,12-didehydroandrographide	Biswa et al. (2011)
11.	<i>Soymida febrifuga</i>	Deoxyandirobin-3- <i>O</i> -rutinoside, lupeol, methyl angolensate, sitosterol and quercetin-3- <i>O</i> -L-rhamnoside	Riazunnisa (2011)
12.	<i>Trachyspermum ammi</i>	Caryophyllene, β -pinene, cadinene, cadinol, <i>p</i> -cymene elemol, elemene, carvacrol, humulene, eudesmol, muurolene, γ -terpinene, muurolol, limonene, myrcene, limonene, and thymol	Jeet et al. (2012)
13.	<i>Trigonella foenum-graecum</i>	Coumarin, nicotinic acid, fenugreekine, scopoletin, phytic acid, trigonelline and saponins,	Meghwal et al. (2012)
14.	<i>Aegle marmelos</i>	Bicyclo heptane-2,3-diol, 2(4H)-benzofuranone, 2,3-dioxabicyclo oct-5-ene, cinnamic acid, 2-propenoic acid, phenol, 2,6-bis(1,1-dimethylethyl)-4-methyl-(BHT), 4-hydroxy-3-methyl-6-(1-methylethyl), 1-dodecanol, 2-cyclohexen-1-one, 2,3-dihydro-3,5-dihydroxy-6-methyl, 2-methyl-5-(1-methylethyl)-(1-phellandrene), myristic acid, 1,3-cyclohexadiene, 2,6,6-trimethyl (2,3-pinanediol), 5,6,7,7A-tetrahydro-6-hydroxy-4,4,7a-trimethyl, 3-(4-hydroxy-3-methoxyphenyl)-, 3,7,11,15-tetramethyl-2-hexadecen-1-ol, 1-methyl-4-(1-methylethyl)-(limonene dioxide 1), methyl ester, marmelosin, 4H-pyran-4-one, psoralen, marmin, luvangeitin, and tannins,	Atul et al. (2012)

(Continued)

TABLE 4.2 (CONTINUED)
Phytochemical Compounds, Derived from Medicinal Plants, as Immunity Boosters

S. No	Plant	Phytochemical Compounds	References
15.	<i>Calotropis procera</i>	Benzoyllineolone, benzoylisoloneolane, cardenolides, triterpenes, calotoxin, calotropagin, calotropin, choline, glycoside- <i>O</i> -pyrocatechuric acid, alkaloids, triterpenoid, syringenin, usechardin, uscharin, uzariganin, and phytosterols	Khairnar et al. (2012)
16.	<i>Commiphora wightii</i>	Steroids, amino acids, carbohydrates, aliphatic esters, diterpenoids, cholesterol and sesamin, E-guggulsterone, Z-guggulsterone, guggulsterol I, guggulsterol II, guggulsterol III	Ikram and Chahar (2013)
17.	<i>Eclipta alba</i>	Demethylweddelactone, a-terthienylmethanol, stigmasterol, demethylweddelactone-7-glucoside, and weddelactone,	Bhalerao (2013)
18.	<i>Datura metel</i>	Adenosine, ilekudinoside C, pterodantriol B, scopolamine, dioscoroside D, thymidine, and disciferitriol	Maheshwari et al. (2013)
19.	<i>Abrus precatorious</i>	Abrine, abrusin, abrol, abraline, arabinose, abrasine, abruslactone, abrusoside A, abruslactone A, abrusoside B, abrusoside C, abrusoside D, Abrusin-2'- <i>O</i> -apioside, abricin, abrusic acid, anthocyanins, amyrin, abrusgenic-acid-methyl-ester, abrusgenic-acid, alanine, choline, coumaroylgalloyl glucodelphinidin, cycloartenol, campesterol, D-monomethyl ether, delphinidin, <i>N,N</i> -dimethyl-tryptophan, kaikasaponin III, hederagenin, hemiphloin, hypaphorine, precatorine polysaccharide, precasine, precool, Protein P phosphorus, pectin, pentosans, precatorine, polygalacturonic acids, pinitol, glycyrrhizin, galactose, sophoradiol-2,2- <i>O</i> -acetate, sophoradiol, methyl ester, montanyl alcohol, serine, quinones, abruquinones, tryptophan, trigonelline, <i>N</i> -gallic-acid, <i>N</i> -dimethyl-tryptophan-metho-cation-methyl-ester, hypaphorine, ursolic acid, isoflavonoids, xylose, and valine.	Sahu et al. (2013)
20.	<i>Aloe vera</i>	Sugars, amino acids, campesterol, choline, folic acid, vitamin B ₁₂ , cholesterol, β -sitosterol, 12 anthraquinones, lignin, saponins, salicylic acids, and lupeol	Dubey et al. (2014)
21.	<i>Azadirachta indica</i>	Ascorbic acid, quercetin, β -sitosterol, nimbol, nimbim, nimbandioli, nimbane, nimbolide, 7-desacetyl-7-benzoylazadiradione, <i>N</i> -hexacosanol 6-desacetylnimbimene, flavonoids, polyphenolic compounds, 7-desacetyl-7-benzoylgedunin, amino acids, and 17-hydroxyazadiradione	

(Continued)

TABLE 4.2 (CONTINUED)
Phytochemical Compounds, Derived from Medicinal Plants, as Immunity Boosters

S. No	Plant	Phytochemical Compounds	References
22.	<i>Curcuma longa</i>	α -turmerone, β -bisabolene, β -turmerone, curlone, <i>ar</i> -curcumene, 1,8-cineole β -caryophyllene, caryophyllene oxide, (<i>E</i>)- β -ocimene, (<i>Z</i>)- β -ocimene, α -santalene, β -sesquiphellandrene, (<i>E</i>)- γ -atlantone, α -zingiberene, β -selinene, β -sesquiphellandrene, santalene, 1,8-cineole, α -phellandrene, <i>ar</i> -turmerone, (<i>Z</i>)- γ -atlantone, (<i>Z</i>)- β -farnesene, α -thujene, (<i>E</i>)- γ -atlantone, humulene oxide, β -myrcene, β -bisabolene, terpinolene, limonene, and zingiberene	Nasri et al. (2014)
23.	<i>Terminalia arjuna</i>	Ajungenin, arjunic acid, arjunone, arjunolone, arjunolic acid, arjun glycosides, luteolin, ellagic acid, oligomeric triterpenoid saponins, zinc, copper calcium and magnesium, gallic acid, phytosterols, flavonoids, proanthocyanidins and tannins,	Dwivedi and Chopra (2014)
24.	<i>Tinospora cordifolia</i>	Cordifolioside A, tinocordiside, formylannonain, <i>N</i> -methyl-2-pyrrolidone, hydroxymustakone, and syringine	Mittal (2014)
25.	<i>Saraca asoca</i>	Clerodane, catechin, duorene alkaloids, noroliveroline, 11'-deoxyprocyanidin B4, oliveroline-f3- <i>N</i> -oxide, epicatechin, procyanidin B-2, leucocyanidin, polyfithine and liriodemine,	Singh et al. (2015)
26.	<i>Picrorhiza kurroa</i>	Apocynin, kutki sterol, D-mannitol and picrosides I and II	Qureshi et al. (2015)
27.	<i>Bryophyllum pinnatum</i>	α -D-Glucopyranoside, octadecanoic acid, benzaldehyde, <i>N</i> -hexadecanoic acid, 3,5-dihydroxy-6- methyl-2,3-dihydro-4H-pyran-4-one, and oleic acid	Nagaratna et al. (2015)
28.	<i>Abutilon indicum</i>	Aldehydes, amino acids, amyirin, caprylic acid, caprylic, eudesmic acid, flavonoids, ferulic acid, fatty acids, ketones, esters <i>g</i> -galactose, terpenes, caffeic acid, palmitic acid, 9, 10-methylene octadec-9-enoic (sterculic) acid, 13-epoxyoleic (vermolic) acid, 8, 9-methylene-heptadec-8-enoic (malvalic) acid, myristic, oleic, linoleic, palmitic, lauric, stearic acids, and sitosterol.	Raja and Kailasam (2015)
29.	<i>Allium sativum</i>	Ajoenes (<i>E</i> -ajoene, <i>Z</i> -ajoene), thiosulphates (allicin), diallyl disulphide (DADS), diallyl trisulphide (DATS), vinylidithiins (2-vinyl-(4H)-1,3-dithiin, 3-vinyl-(4H)-1,2-dithiin)	Alam et al. (2016)
30.	<i>Croton tiglium</i>	Crotonic acid, crotonic resin, crotonoleic acid, phorbol derivatives, and glyceryl crotonate,	Sinsinwar et al. (2016)

(Continued)

TABLE 4.2 (CONTINUED)
Phytochemical Compounds, Derived from Medicinal Plants, as Immunity Boosters

S. No	Plant	Phytochemical Compounds	References
31.	<i>Nardostachys jatamansi</i>	Alpha-patchoulene, angelicin, calarene, elemol, β -patchoulene, jatamansone, valeranal, nardostachone, valeranone, β -sitosolol, jatamansinol, jatamansone, nardostachnol, hexacosane, patchouli alcohol, <i>N</i> -seychellene, <i>N</i> -hexaco-sanyl β -eudesmo, jatamansin, seychelane, and orosolol	Sahu et al. (2016)
32.	<i>Allium cepa</i>	Adenine riboside, allylsulfides, beta-sitosolol, 3-beta-glucopyranoside-6'-palmitate, cycloallin, daucosterol, sitosterol, fructose, flavonols, flavonoids, organosulphur compounds, sulphur, selenium, seleno compounds, S-alk(en)yl cysteine sulphoxides, <i>N-trans</i> -feruloyl tyramine, tryptophane, thiosulphinates, tianshic acid, quercetin, quercetin-3-glucoside, xylose, glucose, glucoside, galactose, and isorhamnetin-4-mannose	Upadhyay et al. (2016)
33.	<i>Asparagus racemosus</i>	Quercitin, racemosol, arsaopogenin, asparagamine, kaempferol, flavonoids, racemoside A, B, C steroidal saponin, racemofuran, (α , α -diphenyl- β -picrylhydrazyl), hyperoside, sitosterol, 8-methoxy-5, 6, 4'-trihydroxyisoflavone, 4,6-dihydroxy benzaldehyde, 7- <i>O</i> - β -D-glucopyranoside, rutin, and saponins.	Hasan et al. (2016)
34.	<i>Zingiber officinale</i>	α -curcumene, β -bisabolene, α -farnesene, 6-dehydrogingerdione, gingerone-A, β -sesquiphellandrene, quercetin, zingerone and zingiberone	Dhanik et al. (2017)
35.	<i>Clitoria ternatea</i>	Tannins, phlobatannin, carbohydrates, saponins, triterpenoids, phenols, flavonoids, flavonol glycosides, proteins, alkaloids, anthraquinones, anthocyanins, cardiac glycosides, stigmast-4-ene-3,6-dione, volatile oils and steroids	Chauhan et al. (2017)
36.	<i>Bacopa monnieri</i>	Bacosides A and B, betulinic acid, brahmine, nicotine, stigmastrol, stigmastanol, triterpenoid saponins, D-mannitol, herpestine, saponins A, B, C, β -sitosolol, serine, glutamic acid, α -alanine, aspartic acid, and glycoside compounds	Rai et al. (2017)
37.	<i>Catharanthus roseus</i>	Ajmalicine, actineo plastidemicric, catharanthine, rosimidin, raubasin, vindeline vineamine, vinceine, vincristine, vinblastine, vindesine, reserpine, and tabersonine	Gupta et al. (2017)
38.	<i>Hyoscyamus niger</i>	Atropine, choline, albumin, hyoscytricin, hyoscine, hyoscyamine, mucilage, and calcium oxalate	Al-Snafi (2018)

(Continued)

TABLE 4.2 (CONTINUED)
Phytochemical Compounds, Derived from Medicinal Plants, as Immunity Boosters

S. No	Plant	Phytochemical Compounds	References
39.	<i>Cymbopogon martini</i>	Camphene, carvone, <i>cis</i> -carveol, <i>trans</i> -carveol, durenol, delphone, limonene, <i>cis-p</i> -mentha-2,8-dien-1-ol, sabinol, and <i>trans-p</i> -mentha-2,8-dienol	Promila (2018)
40.	<i>Jatropha curcas</i>	α -cadinol, α - <i>epi</i> -cadinol, δ -cadinene, chrysanthenyl acetate, thymol, and pulegone,	Abobatta (2019)
41.	<i>Terminalia chebula</i>	Ascorbic acid, corilagin, chebulagic acid, chebulic acid, ellagic acid, ethyl gallate, gallic acid, tannic acid, and mannitol	Kolla and Kulkarni (2018)
42.	<i>Cinnamomum zeylanicum</i>	Caryophyllene oxide, (<i>E</i>)-cinnamyl acetate, and <i>trans</i> - α -bergamotene	Rawat et al. (2019)

still focuses on the single compounds as the key compounds that focus on a specific target associated with a particular disease (Thoppil et al. 2011; Swallah et al. 2020).

4.5 POTENTIAL OF LOCAL MEDICINAL PLANTS AS AN IMMUNITY ENHANCER

The immune system is the working house of the human body to maintain homeostasis. The function and efficacy of the immune system are regulated by several endogenous and exogenous factors in order to achieve immunostimulation or immunosuppression. The agent which has the potential to modulate or normalize the pathophysiological processes is known as an immunomodulator (Jantan et al. 2015). Over the past several years, the immunomodulatory properties of numerous plant-derived compounds have been confirmed. The plant-based immunomodulators have a selective advantage over synthetic immunomodulators because of their minimal side effects and toxicity. There is a need for the discovery, identification, and isolation of specific immunomodulatory agents of plant origin with the potential to overcome the side effects of high-cost synthetic compounds. Thus, natural immunomodulators have great potential as substitutes for use in therapeutic procedures. The organic or synthetic biomolecules able to stimulate, suppress, or modulate the components of innate or adaptive immunity are known as immunomodulators, immune-augmenters, immunorestoratives, or biological response modifiers.

There are approximately 122 plant-derived chemicals which have been identified as therapeutic substances, which are used as commercially exploited drugs (Sorokina et al. 2020). For instance, willow tree bark is rich in the salicylic acid phytohormone, which is related to an active compound (acetyl salicylate) of aspirin. In the traditional medicinal system, the bark has been used as a painkiller and antipyretic substance from ancient times. The most frequent drugs prescribed by physicians are derived from plant sources, such as opium, quinine, digoxin, aspirin, etc. The immunomodulatory chemicals derived from plants are alkaloids, terpenoids, flavonoids, lactones, polysaccharides, and glycosidic products (Tiwari et al. 2018). The immunomodulators can be classified into immunostimulants, immunosuppressants, or immuno-adjuvants, examples of which have been listed in Table 4.2.

4.5.1 IMMUNOSTIMULANTS

The chemicals that induce or activate the components or mediators of the immune system are known as immunostimulants (Paul et al. 2020). Immunostimulants enhance the resistance against infection, allergy, cancer, and autoimmunity. Immunostimulants can be categorized into two categories, namely a) specific and b) non-specific immunostimulants. Specific immunostimulants can trigger the immune response, particularly with respect to antigenic type. Non-specific immunostimulants are not antigen-specific and are generally used for treatment of chronic

infections, immune-deficiency diseases, and malignant or auto-immune diseases. The immunostimulants are recognized by the Toll-like receptors (TLR) to induce the TLR signalling for immune system initiation. Extracts of plants showing immunostimulant activity are *Allium sativum*, *Asparagus racemosus*, *Achyranthes aspera*, *Azadirachta indica*, *Aloe vera*, *Abutilon indicum*, *Andrographis paniculata*, *Aristolochia indica*, *Berberis aristata*, *Clitoria ternatea*, *Catharanthus roseus*, *Cymbopogon martini*, *Hyoscyamus niger*, *Nardostachys jatamansi*, *Picrorhiza kurroa*, *Cynodon dactylon*, *Curcuma longa*, *Embelia ribes*, *Ocimum sanctum*, *Sida cordifolia*, *Punica granatum*, *Piper longum*, *Nuctanthes arbor-tristis*, *Panax ginseng*, *Phyllanthus emblica*, *Saussurea costus*, *Withania somnifera*, and *Tinospora cordifolia* (Figure 4.2; Table 4.2).

4.5.2 IMMUNOSUPPRESSANTS

Immunosuppressants are the chemicals that inhibit the immune system and can be used to prevent pathological immune reactions after organ transplantation. These substances are used to treat infections related to immunopathology, auto-immune diseases, and hypersensitive reactions (Romanelli and Mascolo 2020). The activation of B and T lymphocytes, macrophages, and the imperfect apoptosis of immune effector cells play important roles in the pathogenesis of various disorders (Turner et al. 2016). Plants showing immunosuppressant activity include *Linum persicum*, *Salvia mirzayanii*, *Stachys obtusirena*, *Andrographis paniculata*, *Bupleurum falcatum*, *Glycyrrhiza glabra*, *Dracocephalum kotschyi*, *Periploca sepium*, *Tripterygium wilfordii*, *Echium amoenum*, *Salvia miltiorrhiza*, *Argyrolobium roseum*, *Clerodendron trichotomum*, and *Campylotropis hirtella* (Figure 4.2).

4.5.3 IMMUNO-ADJUVANTS

Immuno-adjuvants are the specific stimulators of the immune system which boost the efficacy of a vaccine and hence can be considered to be true modulators of the immune response. They can be exploited as immunoprotectives, immunodestructives, or selectors between the cellular and humoral helper (Th1 and Th2) cells (Banstola et al. 2020). The plants showing such activity include *Ziziphus jujube*, *Withania somnifera*, *Achyranthes bidentata*, *Astragalus membranaceus*, *Allium sativum*, *Calliandra pulcherrima*, *Hedera taurica*, *Aesculus hippocastanum*, *Bupleurum falcatum*, *Andrographis paniculata*, *Anemone raddeana*, *Echinacea purpurea*, *Grifola frondosa*, *Nigella sativa*, *Panax ginseng*, *Tinospora cordifolia*, *Platycodon grandiflorum*, *Astragalus membranaceus*, *Asparagus racemosus*, *Curcuma longa*, and *Hypericum perforatum* (Table 4.2; Figure 4.2) (Goldman 2001; Balunas 2005; Licciardi and Underwood 2011; Patel 2012; Banstola et al. 2020).

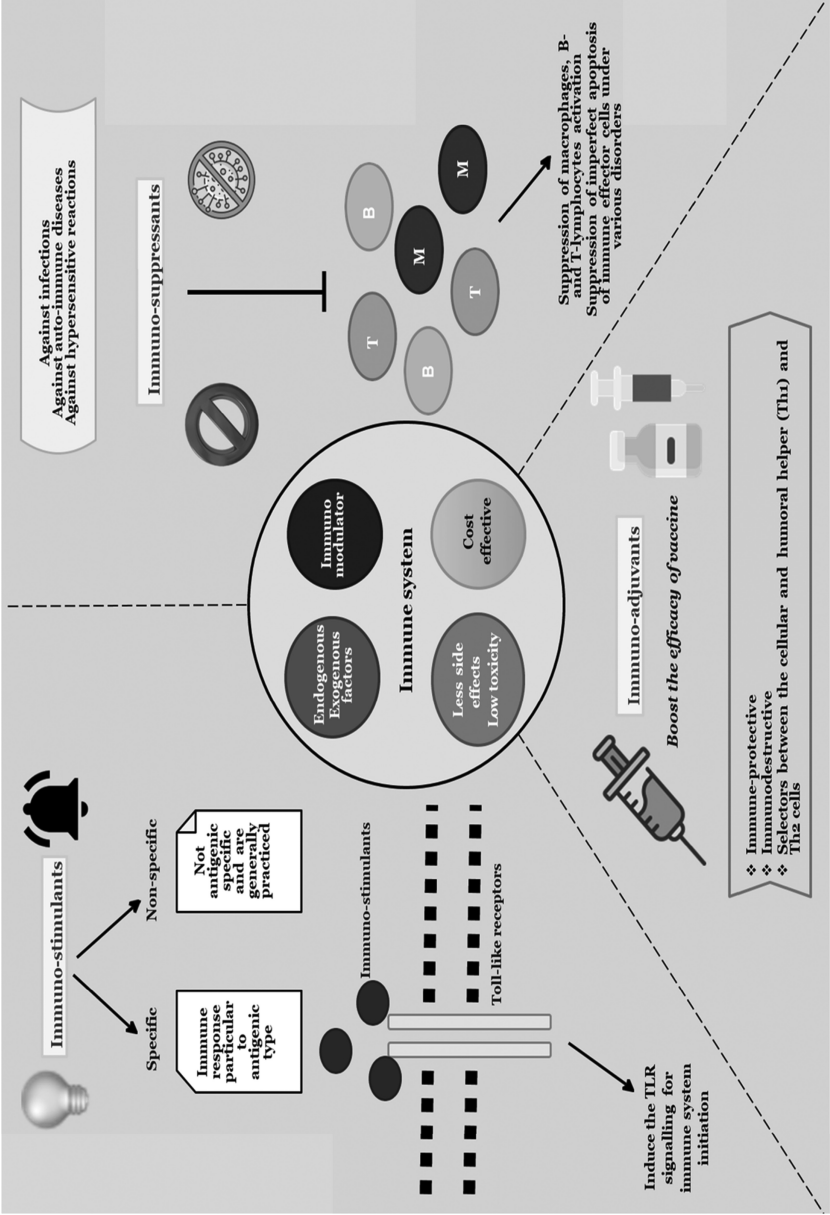


FIGURE 4.2 Different types of immunity-related chemicals and their role in disease treatment associated with weak immune systems.

4.6 PHYTOCHEMICAL EVIDENCE ASSOCIATED WITH TRADITIONAL MEDICINAL SYSTEMS

Plant-derived natural products have been used in medicine for more than 5,000 years, whereas Western medicines date back only a few hundred years ago (Goldman 2001; Atanasov et al. 2015). The medicinal use of > 85,000 plant species has been documented throughout the world (Balunas and Kinghorn 2005). According to WHO, more than 80% of people in the world rely on herbal medicines for treating several disorders, including immune disorders, mostly in the developing countries (Licciardi and Underwood 2011). Approximately 30% of the drugs approved by the Food and Drug Administration (FDA) of the USA are of botanical origin. Thus, it is crucial to determine the chemical structures of traditionally used phytomedicinal compounds to assess their potential for immunomodulatory activity against immune disorders.

Biochemists in the past developed an interest in extracting the active chemical molecules from traditional herbal medicines and examining them for their potential activities, and they began to notice additional roles for phytochemicals. Numerous phytochemicals have been identified with potential as an immunomodulator, a chemoprotective, or an adaptogenic. These chemicals include saponins, terpenoids, flavonoids, and polysaccharides, such as pectin and arabinogalactan (Sharma 2006; Rajput et al. 2007; Thoppil et al. 2011; Islam et al. 2020).

4.6.1 PHYTOCHEMISTRY

4.6.1.1 Flavonoids

More than 4,000 different kinds of flavonoids have been reported in plants and are known to contribute to leaf and flower colour. They are members of the phenolic group of secondary plant metabolites and are derivatives of the shikimic acid pathway (Cook and Samman 1996). This category of phytochemicals has gained much attention due to their antioxidant activity in scavenging oxygen free radicals and they have proven to be promising agents for anticancer therapy and anti-ageing properties (Bose et al. 2018). Apigenin poses tumour-suppressing activity by inhibiting TNF- α intra-cellular adhesion to inhibit tumour metastasis, while also suppressing angiogenesis (Patel et al. 2007). Plant genera such as *Artemisia*, *Achillea*, *Tanacetum*, and *Matricaria* belong to the family Asteraceae, which acts as the main source of apigenin (Table 4.1). Additionally, members of the Lamiaceae, such as *Sideritis* and *Teucrium*, and species of *Genista* from the Fabaceae also show the presence of apigenin in its aglycone form (Venditti et al. 2015, 2016a, 2016b, 2017; Ornano et al. 2016; Sharifi-Rad et al. 2018; Venditti et al. 2018). Apigenin decreases the expression of cytokines (IL-1 α , IL-8, TNF- α) (in the case of *Cynodon dactylon*) and reduces the response of Th1 and Th17 cells (in the case of *Salvia officinalis*), as well as downregulating the expression of pro-inflammatory mediators such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) (in *Portulaca oleracea*). Additionally, apigenin reduces the expression of the intracellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM) (in *Mentha longifolia*), resulting in lowered neutrophil chemotaxis (Nicholas et al. 2007; Kang

et al. 2009). Similarly, quercetin decreases the expression of pro-inflammatory factors, such as cytokines, NF- κ B, and iNOS. Luteolin (a type of flavone) adjusts the inflammatory environment of the brain by targeting brain chemistry. It inhibits the release of microbial IL-6 and mimics the activity of the brain-derived neurotrophic factor. There is a decrease in the secretion of INF- γ , IL-6 inflammatory mediators and in the expression of COX-2 and ICAM-1 following exposure to a preparation of *Lonicera japonica* (Ziyan et al. 2007; Chen et al. 2014).

4.6.1.2 Terpenoids

Terpenoids are considered to be the largest family of natural phytochemicals, consisting of more than 30,000 compounds that vary and show specificity to particular plants (Dubey et al. 2003; Stephane and Jules 2020). Many herbal medicines include combinations of terpenoids and saponins (examples of triterpenes) that inhibit the faulty immune inflammation response during the development of neoplastic disease. Similarly, limonene, the monoterpene obtained from apricots, cherries, and citrus fruits, suppress NF- κ B activation (Berchtold et al. 2005; Younis et al. 2020). Genopsida, obtained from *Gardenia jasminoides* fruits, can suppress the expression of iNOS and NF- κ B expression, and is traditionally used in the treatment of headache, fever, inflammation, and hepatic disorders (Koo et al. 2004). Sesquiterpene lactones are potent medicinal phytochemicals and are used against inflammatory diseases and cancers (Salminen et al. 2008). The artemisinin isolated from the leaves of *Artemisia annua* (a traditional Chinese medicinal plant) is used as an effective antimalarial drug. Artemisinin and its derivatives show anticancer, antifungal, anti-angiogenesis, and immunosuppressive properties. It inhibits the NF- κ B signalling system, with strong inhibition of inflammation (Cui and Su 2009). The elephantopin derivatives (isodeoxyelephantopin and deoxyelephantopin) isolated from *Elephantopus scaber* induce anti-inflammatory activities and anticancer activities *via* negatively targeting NF- κ B activation (Huang et al. 2010; Su et al. 2011a). Similarly, paclitaxel, marketed under the brand name Taxol, is a polyoxygenated diterpenoid alkaloid originating from *Taxus brevifolia* (Pacific yew) bark, being used clinically as a drug against ovarian cancer and other cancers (Weaver 2014). Tanshinone IIA (a diterpenoid quinone), extracted from the roots of *Salvia miltiorrhiza*, is traditionally used against immunological disorders, osteoporosis, breast cancer, and cardiovascular diseases. It inhibits NF- κ B signalling in the inflammation pathway (Gao et al. 2012). Carnosol and carnosic acid (abietane-type diterpenoids) are abundant in *Rosmarinus officinalis* and are frequently used traditionally as a result of their activity in inhibiting NF- κ B signalling and inducing expression of the Nrf-2-activated HO-1 (Pan and Ho 2008; Yousef et al. 2020). Celastrol (a quinone methide pentacyclic triterpenoid) has shown anticancer and anti-inflammatory activities (Pinna et al. 2004). It suppresses NF- κ B signalling in tumour growth and inflammation (Kim et al. 2009). Ursolic acid (a pentacyclic triterpene) is the main active ingredient in some traditional remedies used as an anticancer agent, with hepatoprotective activities, and for antihyperlipidaemia (Ikeda et al. 2008; Salminen et al. 2008). Ursolic acid inhibits the NF- κ B activation that is involved in the inhibition of TPA-induced skin tumours and lipid polysaccharide (LPS)-induced pro-inflammatory mediators (Ikeda et al. 2008).

Betulinic acid (a lupane-type triterpenoid) and its derivatives show therapeutically potent activity against cancer, pathogen infections, and various kind of inflammations (Fulda 2009). Lupeol (a triterpenoid derivative) inhibits the Akt-dependent pathway, contributing to anti-inflammatory and anticancer activities (Fernandez et al. 2001; Salminen et al. 2008; Wang et al. 2020). The tetraterpenoid derivatives, such as lutein, lycopene, and β -carotene, modulate the redox-sensitive signalling pathways, including ROS signalling and NF-kB signalling pathways (Chew and Park 2004; Huang et al. 2007).

4.6.1.3 Organosulphur Compounds

The organosulphur compounds, derived from garlic and onion, have been shown to result in suppressed activities of cyclooxygenase and lipoxygenase (inflammatory enzymes) and decreased levels of inhibitory iNOS expression in the inflammatory macrophages (Dirsch et al. 1998; Ali et al. 2000; Ruhee et al. 2020). Garlic extract inhibits receptor NF-kB activity induced in response to receptor agonists, such as TNF-an and LPS, under anti-inflammatory responses (Keiss et al. 2003; Jo et al. 2020). Garlic extract can also modulate inflammatory responses through inhibition of TLR activation (Youn et al. 2008; Table 4.2; Figure 4.3).

4.6.2 PHARMACOLOGY

The use of plants as medicines for treating disease has been recorded since ancient times (Singh et al. 2016). In India, in particular, it has become an important system of health care, and approximately 70% of rural people in India use the traditional herbal medicinal system for treating disease. There are various medicinal systems mentioned in Vedas and other scriptures, dating from ancient times. Many conventional systems, such as Siddha, homoeopathy, naturopathy, Unani, Yoga, Ayurveda, Chinese, or Amachi medicines, have been well known and widely adopted for many years. Ayurveda is also known as the “science of longevity” because it helps to maintain a long, healthy life for any individual (Kumar et al. 2012).

In the conventional medicine system, there are easy and cheap treatment methods (derived from herbs and various plant parts) to treat many common diseases, such as cancer, food allergies, and another immune diseases, for which there are few modern treatments. The medicinal attributes of many plants are found in leaves, rhizomes, and roots, and can be used as a tonic, diuretic, blood purifier, and antiphlogistic. These are used as remedies for treating various diseases, like chronic eczema, chronic rheumatism, chronic nervous diseases, cholera amenorrhoea, chronic ulcers, etc. The powder of dried leaves of plants like *Catharanthus roseus*, *Clitoria ternatea*, etc., is used for the treatment of depression and for improving memory when the powder is consumed with milk. Similarly, the juice of the leaves of plants like *Ocimum sanctum* and *Tinospora cordifolia* are used as an alternative treatment of cases of jaundice, fever, or gonorrhoea. These plants are also helpful in improving the nervous system in children and for treating cutaneous diseases. There are more than 3,000 medicinal-value plant species in India that are used to prepare medicinal drugs, of which a number have been highlighted in Table 4.1.

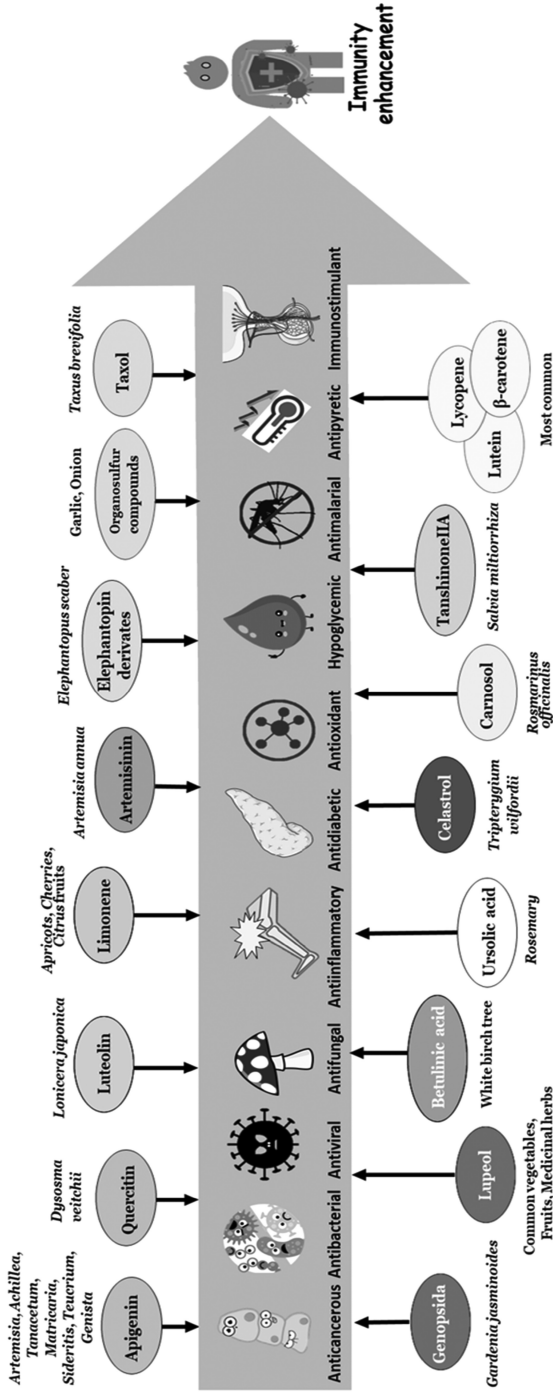


FIGURE 4.3 Phytochemical constituents obtained from various medicinal plant parts with special reference to immunity enhancement.

The effectiveness of medicinal plants varies from species to species and for the treatment of different conditions. For example, in the treatment of nervous disorders, the brain tonic, brahmi, is more effective than mandukparni. The brahmi plant is also used to reduce fatigue, and to treat asthma and depression. It energizes the central nervous system and improves the circulatory system, soothes and minimizes varicose veins, and helps to minimize scarring. Brahmi also proves useful in repairing skin and connective tissues in the body as well as smoothing out cellulite. In India, this plant has been used by Ayurvedic medicine for 3,000 years. The Ayurvedic treatise, the Charaka-samhita (100 AD) recommends Brahmi in formulations for a range of mental conditions, including treating anxiety and improving concentration.

Most of the valuable medicinal plants, like punarnava (*Boerhaavia diffusa*), gokhru (*Tribulus terrestris*), and ark (*Calotropis procera*), etc., grow in the wild, mainly because of the favorable climatic and edaphic conditions, as well as the reduced urbanization in these regions. Another important plant, ashwagandha (*Withania somnifera*) is widely used in the treatment of psoriasis, arthritis, and rheumatism. It is rich in valuable phytochemical constituents, like alkaloids (isopelletierine and anaferine), steroidal lactones (withanolides, withaferins), and saponins (sitoindosides VII and VIII). For treatment of arthritis, ginger (*Zingiber officinale*) is used because of its chemical constituent zingiberene, which is mainly responsible for reducing pain and inflammation by inhibiting the cyclooxygenase (COX) and lipoxygenase (LOX) pathways. Onion (*Allium cepa*) is also widely used to decrease the numbers of cancer cells, to effectively heal stomach ulcers, and inhibit the proliferation of cultured ovarian, breast, and colon cancer cells. This plant also reduces levels of cholesterol and blood pressure, and decreases symptoms associated with diabetes mellitus, inhibits platelet aggregation, and prevents inflammatory processes associated with asthma (Upadhyay et al. 2016). The fruit extract of the plant *Phyllanthus emblica* possesses antidiarrhoeal and spasmolytic activity, which is mediated possibly through the dual blockage of muscarinic receptors and Ca²⁺ channels, thus explaining its medicinal use in the treatment of diarrhoea. In addition, *P. emblica* has great potential to check cancer and tumour growth. In addition, extracts of sunflower (*Helianthus annuus*) seeds are used as a diuretic and to effectively cure coughs and lung infections. They are also used as an antiseptic, aphrodisiac, emollient, and as an anti-malarial. Leaves of neem (*Azadirachta indica*) are used in the treatment of numerous diseases, like eczema, ringworm, and acne, and they possess anti-inflammatory and antihyperglycaemic activities (Srivastava et al. 2020). Neem is used to treat chronic wounds, diabetes, and gangrene. It also helps to remove toxins from the body, quench free radicals, and to purify the blood (Dubey et al. 2014).

The high value of the conventional medicinal system, and its application in terms of derived drug phytochemistry, gained much attention in 2011 following a paper published by Dr. YY Tu in Nature Medicine. The discovery of artemisinin, from *Artemisia annua* plant, for the treatment of malaria resulted in the author winning the Lasker Award for medicinal research in 2011. The article explained the need for the re-recognition of the traditional medicinal system and its background

to the identification of immunity boosters. In another report, published in Science Translation Medicine by YC Cheng and coworkers, highlighted the use of TCMs containing multiple formulations, including extracts of more than three or four plants, for the treatment of cancer instead of the use of a single chemical constituent. This report described experiments that provide strong evidence for identification of preparations with anti-inflammatory, anticancer, and molecular patterning activities based solely on metabolite profiling. The above reports, supported by clinical trials, attracted greater belief and interest from the medical community. In a case study, a methanolic extract of *Ocimum sanctum* samples (100 mg/kg body wt.) showed increased concentration of red blood cells (RBC) in sheep. The extract had a promotional effect on humoral-mediated immunity and expressed an immunomodulatory effect, enhancing the level of RBCs in sheep, and decreasing the amount of histamine released from the mast cells. The findings indicated the responses of both humoral- and cell-mediated immune responses to this herbal plant preparation. An alcoholic extract of *Achillea millefolium* (100 mg/kg, i.p.) exhibited a significant stimulatory effect on both cellular and humoral function in mice. The enhanced carbon clearance and neutrophil adhesion, and the decreased level of cyclophosphamide-induced neutropaenia reflects an immunomodulatory effect (Licciardi et al. 2011; Kumar et al. 2012) In mitogen-induced lymphocyte proliferation, the andrographolide compounds from *Andrographis paniculata* act as an inhibitor of TNF- α and a stimulator of both non-specific and antigen-specific types of immunostimulatory response in mice, exhibiting responses to a range of oncogenic and infectious agents. Treatment with an extract of *Gymnema sylvestre* showed immunomodulation *in vivo* and *in vitro*, with significant immunostimulatory activity, affecting the activities of neutrophils and phagocytes, as well as chemotaxis responses (Kumar et al. 2012; Table 4.3). The herbs used in conventional formulations or Rasayana seem to function by affecting the effector arm that regulates immunosuppressants, immunoadjuvants, and immunostimulant activities. Immunomodulation activities can be used to create a pathogen-free state inside the body of a diseased person.

Immunomodulation mechanisms are mainly regulated *via* the activities of various cellular functions, such as macrophage activation, increased antigen-specific immunoglobulin production, enhanced numbers of non-specific immunity mediators and natural killer cells, increased cellular immune function, increased non-specific cellular immune system effect, phagocytosis stimulation, immunostimulatory effect on peritoneal macrophages, lymphoid cells stimulation, reduction in chemotherapy-induced leukopaenia, and increased total white cell counts *via* circulating and interleukin-2 levels (Kumar et al. 2012).

It has become our main responsibility to highlight these valuable plant species, which would help herbal practitioners, conservationists, and environmentalists to narrow down their focus to such indigenous plant species, thereby ensuring protection of the medicinal flora. Many commercial products derived from herbal plants are sold in the markets these days (Table 4.3) and their demand, production, and consumption have been significantly boosted in the present COVID-19 situation.

TABLE 4.3
Commercially Available Products Derived from Traditional Medicinal Plants. Used as Immuno-protectants

S. No.	Plant Name	Market Products	References
1	<i>Withania somnifera</i> (ashwagandha)	 <p>The image shows four different Ashwagandha products: a white bottle of 'MORPHINE REMEDIES ASHWAGANDHA' capsules, a white bottle of 'Himalaya Ashwagandha' capsules, a black bottle of 'Ashwagandha Extract' capsules, and a white bottle of 'Ashwagandha' liquid supplement.</p>	Gupta and Rana (2007)
2	<i>Aloe barbadensis</i> (aloe vera)	 <p>The image shows five different Aloe Vera products: a white bottle of 'UNI Aloe Vera' liquid, a white bottle of 'FOREVER ALOE VERA GEL', a white box of 'Juno's Pure Organic Aloe Vera' capsules, a white bottle of 'Juno's Pure Organic Aloe Vera' capsules, and a white bottle of 'Aloe Vera Essential Oil'.</p>	Christaki and Panneri (2010)

(Continued)

TABLE 4.3 (CONTINUED)
Commercially Available Products Derived from Traditional Medicinal Plants. Used as Immuno-protectants

S. No.	Plant Name	Market Products	References
3	<i>Ocimum tenuiflorum</i> (tulsi)		Vishwabhan et al. (2011)
4	<i>Aegle marmelos</i> (bael)		Atul et al. (2012)

(Continued)

TABLE 4.3 (CONTINUED)
Commercially Available Products Derived from Traditional Medicinal Plants. Used as Immuno-protectants

S. No.	Plant Name	Market Products	References
5	<i>Azadirachta indica</i> (neem)		Dubey et al. (2014)
6	<i>Tinospora cordifolia</i> (giloy)		Mittal (2014)

(Continued)

TABLE 4.3 (CONTINUED)
Commercially Available Products Derived from Traditional Medicinal Plants. Used as Immuno-protectants

S. No.	Plant Name	Market Products	References
7	<i>Mentha arvensis</i> (mint)		Choudhary and Shah (2017)
8	<i>Olea europaea</i> (olive)		Sahin and Bilgin (2017)

(Continued)

TABLE 4.3 (CONTINUED)
Commercially Available Products Derived from Traditional Medicinal Plants. Used as Immuno-protectants

S. No.	Plant Name	Market Products	References
9	<i>Zingiber officinale</i> (ginger)		Bag (2018)
10	<i>Moringa oleifera</i> (moringa)		Sekhar and Arumugam (2019)

4.7 CONCLUSION

Herbalists widely recommend the use of specific traditional medicinal plants to enhance immunity and restrict the activities of cancer, HIV, and other conditions associated with pathogenic microbes. The reason for the importance of these medicinal-value plants is that they contain chemicals exhibiting important pharmacological properties. The repeated, conclusive findings on the various properties, including anti-inflammation, antioxidant, antitumour activities, serve as an effective way of boosting the immune system. Modern-day validations are based on the activities of secondary plant metabolites. As a result, the true specificity of the traditional medicinal system was questioned by Western medicine, which later confirmed it on the basis of bioactive plant extracts containing physiologically active phytochemicals. In a nutshell, the potent immunity-based anti-inflammation and anti-tumour activities can be harmful if not evaluated over a range of doses. By the same token, different herbal formulations are often recommended in conventional medicines for the treatment of specific diseases by targeting particular cellular and molecular pathways. The use of many plants in a single drug preparation in a conventional medicinal system lacks information on the primary drug, the adjuvant, and the delivery systems within the body. Therefore, it cannot be specific for particular targets and treats the problem indirectly. Firstly, the incomplete understanding of the chemical constituents and their mode of action needs clinical trialling, to identify the exact profile of immunomodulatory activities of various herbal formulations used in the conventional medicinal system. Secondly, the majority of herbal formulations and their extracts are typically considered to be less toxic than modern-day single-chemical pharmaceutical products. Thirdly, the drawback of the conventional medicinal system is hypersensitivity and allergies, such as skin allergies caused by the intake of products from chamomile and other members of the Asteraceae due to the high concentration of sesquiterpene lactones, although this response occurs in only a few patients. Fourthly, there is an issue with the misidentification of plants with similar phenologies, such as *Compendia* by most of the herbalists which confuse the identity of *Parthenium integrifolium*. Fifthly, herbal formulations can effectively penetrate dermal regions and their immunomodulatory region as a drug delivery system. However, several compounds, such as ginsenosides and anolides, are able to enhance the inflammatory system during healing, infections, and to suppress chronic inflammation. The importance of ethnobotanists is underrated as much usage of the knowledge on medicinal plants comes from early cultures, which evaluated the potential role and effectiveness of herbal preparations based on information passed down from the ancestors. Most of these properties of medicinal herbs are positive, but why they are not completely accepted by the modern-day medicinal system is an unsolved question which needs resolution in the future. Properly conducted research and clinical trialling, carried out under strict guidelines, must be performed that will ultimately result in the acceptance of the value of medicinal herbs to Western medicine, in particular as well as in the appropriate recognition of ethnobotanists.

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5 Medicinal Plants for Strong Immune System and Traditional Skin Therapy in South Africa

An Overview

Learnmore Kambizi and Callistus Bvenura

CONTENTS

5.1	Introduction	123
5.2	Classification of Skin Diseases.....	126
5.3	Literature Survey of Plants of Dermatological Significance in South Africa	127
5.4	Indigenous Knowledge of South African Plants for Use in Skin Beauty, Therapy, and the Immune System	127
5.5	Common Methods of Preparation	166
5.6	Sustainable Utilization and Conservation of Plants for Skin Therapy	166
5.7	Conclusion	169
	References.....	169

5.1 INTRODUCTION

Without a doubt, skin care/therapy is one of the leading global markets and contributes significantly to economies today. The global value is estimated at 128.38 billion USD and is expected to rise to 189.3 billion USD by 2025 (Statista 2020a). The South African market, which was valued at 581.7 million USD in 2017, will have an estimated value of 839.2 million USD by the year 2023 (Statista 2020b). In fact, South Africa holds the largest share of the market in Africa. The major divisions of this market include anti-ageing, antipigmentation, antidehydration, and sun protection, with applications in beauty salons, medical institutions, and retail stores, among others. These figures are reflective of the role of the skin in the human body. The skin is indeed the human body's largest organ and acts as a gateway to the rest of the body. It is the body's first line of defence against pathogens and water loss,

regulating temperature and sensation, and providing insulation among its myriad functions. Nevertheless, the skin is also home to millions of complex communities of fungi, viruses, and bacteria, with most of the bacteria playing a beneficial role to the body and immune system. The communities of fungi, viruses, and bacteria are informed by a host of factors, which depend largely on environmental conditions and the ecology of the skin surface itself (Grice and Segre 2011). More specifically, Chen and Tsao (2013) reported that skin moisture content, temperature, skin physiology, including sebaceous gland density, and host genetics, as well as exogenous environmental factors are the major determinants of the composition of these communities. Furthermore, adaptive and cutaneous immune responses can moderate microbial communities, while they also inform the immune system (Grice and Segre 2011). An understanding of the skin microbiota would therefore open a window into the microbiota–skin interactions which lead to diseases and abnormalities, so that researchers can develop appropriate treatment approaches. Since the dawn of time, visible alterations of the skin surface have been recognized, with some being treated and others not.

Although medicinal plant use is as old as the story of civilisation, the specific modes of action involved in individual treatments have not always been fully understood (Grierson and Afolayan 1999). Mantle and Gok (2001) reported that almost one-third of known herbal medicines are used in the treatment of wounds and an assortment of skin disorders. The antioxidant and antimicrobial properties of the volatile compounds of these plants have proven effective in many herbal medicines used for dermatological purposes when topically applied to the skin (Quave et al. 2008). These compounds inhibit and/or eliminate pathogenic activities in the cells (Perumal Samy and Gopalakrishnakone 2010). The protective effects of antioxidants against cell damage caused by free radicals generated by metabolic processes have been widely reported (Adedapo et al. 2008), with antioxidants having a neutralizing effect on the free radicals. More recently, however, due to the recognized role of plant antioxidants in ameliorating skin damage from UV light, plants containing phytochemicals with antioxidant activity are receiving increased attention (Katiyar et al. 2001). Some of the compounds found in these plants also ameliorate the negative reactions caused by stings or insect bites by restricting diffusion of toxins, while they also reduce the effects of skin irritation and itching (Dawid-Pač 2013).

Statistics indicate that, currently, the largest antiretroviral (ARV) program globally is administered in South Africa. In fact, it is estimated that, in 2019, about 7.5 million people were infected with HIV and 70% (5,250,000) of these were on ARVs (UNAIDS 2020). However, the first-line ARVs, such as stavudine, lamivudine, and efavirenz, have been linked to both cutaneous and subcutaneous tissue disorders because of hypersensitivity reactions (Ranbaxy 2006; Adcock Ingram 2007). In addition to post-inflammatory hyperpigmentation and serious discomfort, some of the side effects of these ARVs include eczema, fungal dermatitis, itches, irritations, nail disorders, lesions and skin rashes, skin nodules, skin ulcers, herpes simplex pustular rash, and herpes zones (Pharmacare Limited 2003).

The global use of folkloric herbal medicines for ritual purposes and improvement of skin complexion and texture, as well as in the treatment of skin diseases, is

prevalent, including in South Africa. The use of herbal medicines such as *Cassipourea flanaganii* in reducing blemishes, as well as pimples, and increasing complexion clarity and skin lightening have been widely reported in South Africa (Cocks and Dold 2000). Furthermore, annually, in various provinces/ regions in South Africa and according to traditions, young initiates (Abakhwethwa – Eastern Cape province; nghomeni – xiTsonga; bagadikana – siPedi) are circumcised, and the resultant wounds are treated and dressed using medicinal plants. The use of Western medicine and practices in traditional circumcision ceremonies is viewed as meaningless, unacceptable, and a taboo. South African traditional herbal medicinal knowledge has been handed down through generations and for centuries, making the country a rich source of this knowledge (Thirumalai et al. 2009). Herbalists, traditional healers, and spiritualists, including ordinary local people, exploit this knowledge in the treatment of various ailments. This knowledge is known to have been passed down through generations by oral tradition without the need for documentation (Perumal Samy and Ignacimuthu 2000). Therefore, fears that this knowledge might be lost because of the lack of documentation or if the current holders of the knowledge die without passing it on are not far fetched. In the worst cases, there are fears that the rural healthcare systems in South Africa could eventually fail.

Nevertheless, one of the most effective and reliable methods of bioprospecting for herbal medicines and their uses is through ethnobotanical surveys. These surveys have led to the incorporation of numerous herbal medicines into the mainstream healthcare systems. Interestingly, the use of herbal medicines, which are effective as well as affordable, is gaining attention in both urban and rural areas (Katewa et al. 2004). According to Grierson and Afolayan (1999), to protect traditional herbal knowledge from extinction, its documentation is essential. Although the ethnobotanical documentation may not provide an exhaustive list, these studies are essential not only in ensuring the continued existence of this important knowledge but also for biodiversity conservation and the sustainable utilization of scarce resources (Revathi and Parimelazhagan 2010).

Although several articles have documented some of these ethnobotanical surveys to reveal the plants of dermatological significance in South Africa, they have largely been regional, with a comprehensive national study being lacking. This chapter seeks, therefore, through an extensive literature survey, to reveal and document plants of dermatological significance in South Africa at a national level. To achieve this, Google Scholar, Europe PMC, PubMed, and Science Direct search engines were used. Phrases such as “plants used for the treatment of skin/wounds in the Eastern Cape/ Western Cape/ Northern Cape/ North West/ Gauteng/ Free State/ Limpopo/ Mpumalanga/ KwaZulu Natal”, “plants of dermatological significance in South Africa”, “herbal medicines for skin treatment in South Africa”, “skin lightening in South Africa”, “skin care in South Africa”, “cosmetics in South Africa”, and “herbal plants and the immune system”, as well as “the skin, human immune system and herbal medicines”, were used, among others. Although each search generated millions of hits at a time, these were further streamlined until, eventually, a total number of 26 articles published over a period of 21 years (1999–2020) were considered relevant and therefore used for purposes of the present study. Altogether, a total

number of 57 articles are cited in the entire manuscript. Although these additional citations are relatively modern, some of the original ethnobotanical surveys cited in the present work date back fifty years.

5.2 CLASSIFICATION OF SKIN DISEASES

Diseases affecting the skin are so diverse and complex that there is a need to classify them. In fact, the Scottish Dermatological Society (2020) estimates that over 11,000 individual skin disease cases have been recorded, based on Thomas McCall Anderson's work, as shown in Table 5.1 (1887). The British Association of Dermatologists (Dermnet-NZ 2008) developed an index of twenty-five classification codes, whereas the American Academy of Dermatology (1999) developed sixteen classification codes. Furthermore, Dermnet-NZ (2008) considered (i) the site of involvement, (ii) the pathogenesis and (iii) the main structure affected as their main parameters for classification of skin diseases. The work to classify skin diseases is seemingly never ending. Tabassum and Hamdani (2014) reported nine common types of infections, including rashes, viral, bacterial, fungal, and parasitic infections, pigmentation disorders, tumours and cancers, and traumas, as well as other conditions that could not neatly be classified. These latter conditions include rosacea, spider and varicose veins, and wrinkles. But, more recently, due to advances in technology and the use of data mining and machine-learning techniques, some researchers have developed what are known as dermatological predictive classifications, which, in effect, classify skin diseases more accurately and effectively. For example, Verma et al. (2019) merged the Gradient Boosting Decision Tree, Random Forest, Decision Tree, Support Vector Machines, and the Classification and Regression Tree data mining techniques to develop an ensemble supervised learning model to predict skin diseases. These authors concluded that, although the individual data mining techniques worked in terms of skin disease prediction, the ensemble model was more accurate than the individual techniques.

Permanent skin diseases and conditions can be treated or managed using various means. Treatment can either be topical (application of creams to the affected body

TABLE 5.1
Major Classes of Skin Diseases

Organic	Functional
Inflammations	Affections of the skin
New formations and tumours	Affections of hair
Haemorrhages	Affections of the sebaceous glands
Diseases produced by uniform causes:	Affections of the sudoriparous glands
<ul style="list-style-type: none"> • Parasitic affections • Syphilitic affections • Strumous affections • Eruptive fevers 	

part) or by oral ingestion of medication. Topical applications include antibacterials, anthralin, antifungal agents, benzoyl peroxide, coal tar, corticosteroids, retinoids, and salicylic acid (Tabassum and Hamdani 2014). Oral treatments include the use of antibiotics, antifungal agents, antiviral agents, immunosuppressants, and corticosteroids. More recently, some new oral therapies, known as biologics, have been developed to treat conditions such as psoriasis. Biologic drugs are produced from living organisms, such as microorganisms, animals and/or humans using biotechnology, or might themselves contain components of living organisms. Some common examples of biologics are Amevive, Enbrel, Stelara, Remicade and Humira. However, biologics are not exclusive to skin treatment but treat a host of other diseases and conditions that may not be related to the skin. On the other hand, temporary and/or cosmetic skin conditions can be treated by the application of medicated makeup, over-the-counter skin care products, good hygiene practices, and lifestyle adjustments, such as dietary changes. Medicinal plants, therefore, become the basis of development of the treatments.

5.3 LITERATURE SURVEY OF PLANTS OF DERMATOLOGICAL SIGNIFICANCE IN SOUTH AFRICA

Numerous South African studies have reported on the pharmacological aspects of some common plants used in skin therapy, while a handful of ethnobotanical surveys have been conducted under the same theme. The ethnobotanical surveys are notably provincial/ regional, with a lack of a comprehensive national study. We present here the first comprehensive list of plants of dermatological significance in South Africa (Table 5.2). The literature search revealed 431 species from 117 families that have been documented to date in South Africa as being used in skin therapy (Figure 5.1). In general, South Africa contains some 41,983 flowering plant species, of which well over 2,000 are of medicinal value or use (Street and Prinsloo, 2013; Raimondo 2015; SANBI 2020). Of the nine provinces, the Eastern Cape and KwaZulu Natal dominate this list, with the Gauteng and Northern Cape provinces being barely mentioned.

5.4 INDIGENOUS KNOWLEDGE OF SOUTH AFRICAN PLANTS FOR USE IN SKIN BEAUTY, THERAPY, AND THE IMMUNE SYSTEM

Although most plants reported in this survey are used for the treatment of skin diseases and conditions, about 8% are used for cosmetics. This is a significant proportion against the backdrop of the percentage of plants used for the treatment of wounds, making up 18% in the present study. Skin beauty plays an important role in current South African society, as it has for years. According to Davids et al. (2016), the perceived social benefits, including beauty, historical racism, and marketing strategies of multinational companies drive this industry's growth. The marketing strategies often involved local celebrities from whom most young people draw inspiration. In fact, despite the toxic systemic effects of skin lighteners, South Africa remains the

TABLE 5.2
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Acacia burkei</i> Benth.	Fabaceae	Umkhaya wehlalahlathi (KZN)	Bark and leaves	Sores	Topical	10, 11
<i>Acacia cinerea</i> (L.) Spreng	Fabaceae	Murenzhe (L)	Twigs, fruits, bark	Ringworms, and wounds	Topical	16
<i>Acacia erioloba</i> Edgew.	Fabaceae	Kameeldoring (NC/WC)	Bark	Wounds	Topical	22, 26
<i>Acacia karroo</i> Hayne	Fabaceae	Umgga (EC)	Bark	Ringworm, clean, soften, and facial skin	Topical	5, 6, 9
<i>Acalypha glabrata</i> Thunb.	Euphorbiaceae	Umthombothi (EC)	Bark	Clean skin and rashes	Topical	5
<i>Acmella caulirhiza</i> Delile	Asteraceae	Tshishengeraphofu (L)	Leaves	Wounds and sores	Topical	16
<i>Acockanthera oppositifolia</i> (Lam.) Codd	Apocynaceae	Boesmansgif (WC/ NC)	Leaves	Accelerate hair growth, and snake bites	Topical	5, 6, 19, 22, 26
<i>Acridocarpus natalitius</i> A. Juss.	Malpighiaceae	Umabophe (EC)	Leaves	Skin allergies	Bathing	4
<i>Acrotome inflata</i> Benth.	Lamiaceae	Mogato (NW)	Rhizome	Albinism, burns, chickenpox, fleabites, sores, rash, and wounds	Topical	23
<i>Adansonia digitata</i> L.	Malvaceae	Ximuwu (L)	Fruit, bark	Toothache	Oral	14
<i>Afroaster hispida</i> (Thunb.) J.C. Manning & Goldblatt	Asteraceae	Phoa (FS)	Leaves	Sores, syphilitic sores, and wounds	Topical	24
<i>Azelaia quanzensis</i> Welw.	Fabaceae	Mdlavuzza (KZN)	Bark	Eczema	Topical	19
<i>Agapanthus africanus</i> (L.) Hoffmanns	Amaryllidaceae	Isicakathi (EC)	Rhizome	Scabies, and boils	Bathing	5
<i>Agapanthus campanulatus</i> Leighton ssp. <i>campanulatus</i>	Amaryllidaceae	Leta-laphofu (FS); Bloulolie (WC/NC)	Leaves	Rash, and crust on infants' heads	Topical	24, 26

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Agathosma betulina</i> (Berg.) Pillans	Rutaceae	Buchu (WC)	Leaves	Wounds, and bruises	Topical	20
<i>Agave americana</i> L.	Asparagaceae	Garamboom (NW); Lekhala (FS)	Leaves	Eczema	Topical	23, 24
<i>Agave angustifolia</i> Haw.	Asparagaceae	Xikwenga xa nhova (L)	Leaves	Sores	Topical	14
<i>Agave sisalana</i> Perrine.	Asparagaceae	Xikwenga (L)	Leaves	Black leg	Topical	14
<i>Agrimonia eupatoria</i> L.	Rosaceae	Inzinzinaba (EC)	Leaves	Burns	Topical	5
<i>Albizia adianthifolia</i> (Schumach.) W. Wight	Fabaceae	Umhlandlothi (EC); Umgadankawu/ igowane, umnalahanga/ umnebelele/ usolu (KZN)	Bark	Improves skin beauty, acne, eczema, and eye inflammation	Topical	9, 11
<i>Albizia anthelmintica</i> (A. Rich.) Brongn.	Fabaceae	Ummala (MP)	Stem	Lymphatic filariasis	Oral	25
<i>Albizia harveyi</i> E. Fourn.	Fabaceae	Molela (L)	Roots	Rash	Topical	16
<i>Albizia versicolor</i> Welw. ex Oliv.	Fabaceae	Umvangazi (KZN)	Bark	Sores	Topical	11
<i>Albuca setosa</i> Jacq.	Asparagaceae	Inqwebeba (EC); Wakgobaka-wa-seso (NW)	Leaves	Wounds, and Kaposi sarcoma	Topical	5, 23
<i>Alepiidea amatymbica</i> Eckl. & Zeyh.	Apiaceae	Iqwili (EC)	Rhizome	Perfume skin		5, 9
<i>Allium cepa</i> L.	Amaryllidaceae	Onion	Bulb	Yaws	Topical	23
<i>Aloe arborescens</i> Mill.	Aphodelaceae	Ikalene (EC)	Leaves	Wounds, burns, acne, deadlocks, skin moisturizer, and various skin ailments	Topical	6, 9, 13, 19, 22

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Aloe aristata</i> Haw.	Asphodelaceae	Umathithibala (KZN)	Leaves	Dermatitis, wounds, burns, cuts and eczema, sunburn, insect stings, poison ivy skin irritations, abrasions, and numerous dermatological conditions	Topical	12, 13
<i>Aloe barbadensis</i> Mill.	Asphodelaceae	Mhangani/ Tshikopa (L)	Leaves	Ringworms, moisturize the skin, remove stretch marks, rash, burns, and wounds	Topical	16
<i>Aloe ferox</i> Mill.	Asphodelaceae	Umlhlab (EC), iNhlaba (KZN); Hlabal/ Lekhala La Quthing (FS)	Leaves, juice, Jel	Eczema, irritations, burns, wounds, insect bites, ringworm, boils pimples. Soften hair, foster hair growth, and prevent hair loss, and skin cleansing	Bathing	5, 6, 9, 12, 13, 24
<i>Aloe grahamii</i> var. <i>davyana</i> (Schonland) Glen & D.S Hardy	Asphodelaceae	Kgopane	Leaf juice	Baruli ulcers, boils, chickenpox, eczema, and Steven Johnson syndrome	Topical	23
<i>Aloe marlothii</i> A. Berger	Asphodelaceae	Mhangane (L)	Leaves	Wounds	Topical	14, 17
<i>Aloe turkanensis</i> Christian	Asphodelaceae	Lekgala (NW)	Leaf juice	Eczema	Topical	23
<i>Aloe vera</i> (L.) Burm.f.	Asphodelaceae	Mhangani/ Tshikopa (L); Legkala (NW)	Leaves	Ringworms, moisturize the skin, remove stretch marks, rash, burns, and wounds	Topical	16, 23

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Aloe striatula</i> Haw. var. <i>striatula</i>	Asphodelaceae	Serelei (FS)	Leaves	Burns, and wounds	Topical	24
<i>Amaranthus caudatus</i> L.	Amaranthaceae	Utyuthu (EC)	Leaves	Clean teeth	Bathing	5
<i>Amaranthus hybridus</i> L.	Amaranthaceae	Imbuya (EC)	Leaves	Clean facial skin	Bathing	5
<i>Anagallis arvensis</i> L.	Myrsinaceae	Umsobo (EC)	Leaves	Boils	Topical	5
<i>Annona senegalensis</i> Pers. ssp. <i>senegalensis</i>	Annonaceae	Umhlalajuba/ umphofu/ umthofa (KZN); Mueembe (L)	Roots, twigs	Sores, and cleaning teeth	Topical, oral	11, 16
<i>Aptenia cordifolia</i> (L.f.) Schwant.	Mesembryanthemaceae	Ibohloholo (KZN/ MP)	Whole plant	Lymphatic filariasis	Topical	25
<i>Aptosimum procumbens</i> (Lehm.) Steud.	Scrophulariaceae	Brandbos	Leaves	Burns, and eczema	Topical	19
<i>Aptosimum elongatum</i> Engl.	Scrophulariaceae	Ditantanyane (NW)	Whole plant	Chicken pox, and yaws	Topical	23
<i>Arctotis arctotoides</i> (L.f.) O. Hoffm.	Asteraceae	Ubushwa (EC)	Leaves, juice,	Ringworm, insect bite, wound, pimples, and boils	Topical	5
<i>Argyrolobium argenteum</i> Eckl. & Zeyh.	Fabaceae	Umfanujacile (EC)	Leaves, juice,	Boils	Topical	5
<i>Aristea ecklonii</i> Baker	Iridaceae	Umhushuza (EC)	Whole plant	Shingles	Topical	22
<i>Artemisia afra</i> Jacq. ex Willd	Asteraceae	Umhloniyane (EC); Legana (NW)	Leaf decoctions	Acnes, boils, chicken pox, and rash	Bathing	6, 23
<i>Arundinella nepalensis</i> Trin.	Poaceae	Mahlakamane (FS)	Leaves	Wounds	Topical	24
<i>Asclepias concolor</i> (Decne.) Schltr.	Asclepiadaceae	Itshongwe (EC)	Leaves	Pimples	Topical	5
<i>Asclepias fruticosa</i> L.	Asclepiadaceae	Igontsi (EC)	Leaves	Prevent hair loss	Topical	5

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Asparagus aethiopicus</i> L.	Asparagaceae	Lelala-tau-le-leholo/ leunyeli (L)	Roots	Skin protection against albinism	Topical	15
<i>Asparagus africanus</i> L.	Asparagaceae	Umathinga (EC)	Leaves	Eczema, and wounds	Topical	5, 6
<i>Asparagus exuvialis</i> Burch	Asparagaceae	Tlhkobotshwaro (NW)	Whole plant	Leprosy, impetigo, condylomata acuminata, and Madura foot	Topical	23
<i>Asparagus nodulosus</i> (Oberm) J.P. Lebrun & Stock	Asparagaceae	Radipolopolwane (NW)	Roots	Boils	Topical	23
<i>Asparagus suaveolens</i> Burch	Asparagaceae	Mothantanyane (NW)	Leaves	Leprosy, impetigo, and Madura foot	Topical	23
<i>Athrixia phylloides</i> DC.	Asteraceae	Icholocholo (EC)	Leaves	Sores, and boils	Topical	6, 9, 22
<i>Babiana hypogaea</i> Burch.	Iridaceae	Thuge (NW)	Leaves	Burns	Topical	23
<i>Barleria macrostegia</i> Nees.	Acanthaceae	Magata (NW)	Rhizomes	Boils, burns chickenpox, and athlete's foot	Topical	23
<i>Barleria obtusa</i> Nees	Acanthaceae	Inzinzimba (EC); Thotshana tonya (NW)	Leaves	Burns	Topical	5, 23
<i>Bauhinia bowkeri</i> Harv.	Fabaceae	Umdlandlovu (EC)	Leaves and bark	Steaming, and bathing	Bathing	5
<i>Bauhinia macranthera</i> Benth. ex Hems!	Fabaceae	-	Leaves	Wounds	Topical	22
<i>Bauhinia thomningii</i> Schum.	Fabaceae	Xidengana (L)	Fruit	Ringworms, sores, and skin irritation	Topical	16
<i>Behnia reticulata</i> (Thunb.) Dietr.	Asparagaceae	Isilawu (EC)	Rhizome	Against hair loss	Bathing	5

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Berchemia discolor</i> (Klotzsch) Hemsl.	Rhamnaceae	Ubalatshemi-omkhulu/ umadlozane/ umhlungulo/ uvuku (KZN)	Stem and twigs	Sores	Topical	10, 18
<i>Berkheya setifera</i> DC.	Asteraceae	Lelelemla-khomo/ ntsoantsane (FS); Mavumbuka (MP)	Whole plant	Herpes sores/ skin ulcers	Topical	24, 25
<i>Bidens pilosa</i> L.	Asteraceae	Uqaqadolo (KZN); Mushidzhi (L)	Leaves	Ringworms	Topical	10, 16
<i>Boophone disticha</i> (L.f.) Herb.	Amaryllidaceae	Gifbol (WC); Inewadi (KZN); kxutsana-yanaha/ molatsisa (FS)	Bulb	Post-circumcision rites, wounds and draws out pus, boils, cuts, grazes, and abscesses	Topical	9, 12, 19, 22, 24
<i>Bowiea volubilis</i> Ex Hook.f. ssp. <i>volubilis</i>	Asparagaceae	Umagaqana (EC)	Bulb	Painkilling effect on skin	Topical	6, 9, 12
<i>Brachylaena discolor</i> DC.	Asteraceae	Isiduli (EC), Phahla (KZN)	Roots	Burns, wounds, and to clean facial skin	Topical	5, 11
<i>Bridelia micrantha</i> (Hochst.) Baill.	Euphorbiaceae	Umhlahimakwaba/ umshonge (KZN)	Leaves	Wounds, burns, and toothache	Topical	18, 22
<i>Buddleja saligna</i> Willd.	Scrophulariaceae	Igqange (EC)	Roots, leaves	Protect facial skin	Topical	5
<i>Buddleja salviifolia</i> (L.) Lam.	Scrophulariaceae	Bergsalie/ Kleinsalie (WC); Lelothwane (FS)	Leaves and stem	Sores	Topical	21, 24
<i>Bulbine asphodeloides</i> (L.) Spreng	Asphodelaceae	Uyakayakane/Intelezi (EC); Pekane (FS)	Leaves or leaf gel	Wounds, itches, burns, sunburns, rough skin, and insect bites	Topical	6, 9, 24
<i>Bulbine abyssinica</i> A. Rich	Asphodelaceae	Kgomo ya badisa (NW)	Leaves, roots	Chickenpox	Topical	23

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Bulbine capitata</i> Poelln.	Asphodelaceae	Kgomo (NW)	Leaves	Chickenpox	Topical	23
<i>Bulbine frutescens</i> (L.) Willd.	Asphodelaceae	Itswelana (EC); Maqgabinwane (NW)	Fresh leaf juice, slimy leaves	Cracked lips, wounds, and rash	Topical	6, 8, 9, 12, 13, 23, 24
<i>Bulbine lagopus</i> (Thumb.) N.E.Br.	Asphodelaceae	-	Leaves	Wounds, sores, and skin conditions	Topical	20
<i>Bulbine latifolia</i> (L.f.) Roem. et Schult.	Asphodelaceae	Ibhucu (EC)	Leaf sap	Wound, burns, eczema rashes, and itches	Topical	6
<i>Bulbine natalensis</i> Baker	Asphodelaceae	Ibhucu (KZN)	Leaves, bulbs, roots	Wounds, sores, burns, rashes, itches, ringworm, cracked lips and herpes, rheumatism, sunburn, itches, and mouth ulcers	Topical and oral	13
<i>Buxus natalensis</i> (Oliv.) Hutch.	Buxaceae	Isixhaza (EC)	Leaves	Ringworm, and boils	Topical	5
<i>Cadaba aphylla</i> (Thumb) Wild.	Capparaceae	Sekgalofatshe (male) (NW)	Whole plant	Sores, rashes, common warts, yaws	Topical	23
<i>Cadaba aphylla</i> (Thumb) Wild.	Capparaceae	Monnamontsho (female) (nW)	Leaves, roots	Chickenpox, Herangioma, Kaposi sarcoma, and malignant melanoma	Topical	23
<i>Calodendrum capense</i> (L.f.) Thunb.	Rutaceae	Umemezi (EC)	Fruits	Soften hair, clean skin, clean teeth, and rashes	Topical	5, 6, 19
<i>Calpurnia aurea</i> (Ait.) Benth.	Fabaceae	Umbethe (EC)	Leaves, roots, Seeds	Accelerate hair growth, skin irritation, rashes, and boils	Topical	5

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Canthium inerme</i> (L.f.) Kuntze	Rubiaceae	Isiphingo (EC); Isitobe (KZN)	Leaves	Ringworm, soften facial skin, pimples, Clean facial skin, and acne vulgaris	Bathing, topical	5, 10, 11
<i>Capparis tomentosa</i> Lam.	Capparaceae	Intshilo (EC); Indoda-ebomvu (MP)	Roots, Powder	Sore throat, and wounds	Oral, topical	5, 25
<i>Capsicum annuum</i> L.	Solanaceae	Itshlisi (EC)	Fruits, Leaves	Sore throat	Oral	5
<i>Carissa bispinosa</i> (L.) Desf. Ex. Brenan	Apocynaceae	Isabetha (EC)	Fruits, juice	Soften facial skin	Topical	5
<i>Caribrotus dimidiatus</i> (Haw.) L. Bolus	Apocynaceae	Mothokolo/ murungulu (L)	Leaves	Wounds	Topical	17
<i>Carpobrotus edulis</i> L. Bolus	Mesembryanthemaceae	-	Leaf juice	Wounds, and burns	Topical	6, 20
<i>Cassipourea flanaganii</i> (Schinz) Alston	Aizoaceae	Unomatyumtyum (EC); sourfig/ suury (WC)	Leaves	Eczema, wounds, burns, and skin ulcers.	Topical	5, 6, 9, 19, 20
<i>Cassipourea flanaganii</i> (Schinz), Alston	Rhizophoraceae	Umemeze (EC/WC)	Bark	Skin lightening, moisturizer, and pimples	Topical	2, 9, 19
<i>Cassipourea flanaganii</i> Alston.	Rhizophoraceae	Umemezi (EC)	Bark, powder	Soften hair, and lighten skin	Topical	5, 6
<i>Catha edulis</i> (Vahl) Forssk. ex Endl.	Celastraceae	Igwakra (EC)	Bark	Sunburn	Topical	3
<i>Catharanthus roseus</i> (L.) G. Don	Apocynaceae	Lepolomo (L); Dabula (NW)	Fruits and leaves	Pimples	Topical	5
<i>Centaurea benedicta</i> (L.) L.	Asteraceae	Ifinifini (EC)	Whole plant	Skin infections	Topical	17, 23

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Centella asiatica</i> (L.) Urban	Apiaceae	Imvumvu (EC); Setimamollo/pemmywort (NW)	Whole plant	Wounds, insect bites, burns, genital warts, and skin itch	Topical	5, 6, 23
<i>Cheilanthes viridis</i> (Forssk.) Sw.	Pteridaceae	Unomlindana (EC)	Whole plant	Burns, wounds, and sores	Topical	6
<i>Cheilanthes hastata</i> (L.f.) Kunze	Pteridaceae	Isisefo (EC)	Leaves	Soften hair	Topical	5
<i>Cheilanthes hirta</i> Sw.	Pteridaceae		Leaves	Herpes sores/skin ulcers	Topical	24
<i>Cheilanthes viridis</i> (Forssk.) Sw.	Pteridaceae	Unomlindana (EC)	Fronds	Burns, wounds, and sores	Topical	7
<i>Chenopodium ambrosioides</i> Bert. ex Steud.	Amaranthaceae	-	Leaves	Eczema, wounds, and skin infections	Topical	22
<i>Chenopodium multifidum</i> L.	Amaranthaceae	Schalalahasamalaka (NW)	Whole plant	Eczema, sores, and rash	Topical	23
<i>Chironia baccifera</i> L.	Gentianaceae	Aambetbossie (WC)	Leaves, stems Tubers	Acne, sores, and stiff muscles Scabies	Topical	20 5
<i>Chlorophytum comosum</i> (Thunb.) Jacques	Asparagaceae	Isicakathi (EC)	Tubers	Scabies	Topical	5
<i>Chrysanthemum parthenium</i> (L.) Pers.	Asteraceae	Ubushwa (EC)	Leaves	Wounds, and sores	Topical	3
<i>Cinnamomum camphora</i> L. Steb.	Lauraceae	Urosalina (KZN)	Bark	Irritated skin, and perfume	Topical	19
<i>Cissampelos capensis</i> L.f.	Menispermaceae	Umayisake (EC); Dawidjies/ Dawidjieswortel/ Fynblaarklimop (WC)	Root, leaf	Wounds, sores, boils, and skin cancer	Topical	6, 21, 22

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Cissampelos torulosa</i> E. Mey. Ex	Menispermaceae	Isitorhom (EC)	Roots	Toothache	Topical	6
<i>Citrullus lanatus</i> (Thunb.) Matsum. and Nakai	Cucurbitaceae	Umoxoxozi (EC)	Flesh of fruits	Lotions, and sunburns	Topical	6
<i>Citrus limon</i> (L.) Burm.f.	Rutaceae	Lemon (EC); Tshikavhave (L)	Fruits, juice	Pimples, soften facial skin, wrinkles, and to clean facial skin	Bathing, topical	5, 16
<i>Citrus reticulata</i> Blanco.	Rutaceae	Swiri (L)	Fruit	Clean and soften skin	Topical	16
<i>Clausena anisata</i> (Willd.) Hook.f. ex Benth.	Rutaceae	Umfutho/Umtuto (EC)	Leaves, twigs, juice	Wounds, clean teeth	Topical	2, 5, 6
<i>Clematis brachiata</i> Thunb.	Ranunculaceae	Ityolo (EC)	Leaves, juice	Clean skin, perfume skin, and wrinkles	Bathing	5, 6
<i>Clerodendrum glabrum</i> E. Mey.	Lamiaceae	Umqwaqwanam (EC); Moswaapeba (FS)	Decoctions of leaves	Wounds	Topical	6, 24
<i>Coddia rudis</i> (E. Mey. ex Harv.) Verdc.	Rubiaceae	Intsinde (EC)	Twig, juice, fruit	Clean teeth; soften facial skin, and skin ulcer	Bathing, topical	5
<i>Coleus kirkii</i> (Baker) A.J. Paton	Lamiaceae	Umvuthuza/ uhlalawane (KZN)	Roots	Sores	Topical	10

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Combretum apiculatum</i> Sond. ssp. <i>apiculatum</i>	Combretaceae	Tsholakhudu / Kgosi ya di thlare (NW)	Bark	Chickenpox, Kaposi sarcoma, flea bites, incision, molluscum contagiosum, malignant melanoma, rash, and sores	Topical	23
<i>Combretum imberbe</i> Wawra.	Combretaceae	Mondzo (L)	Bark	Sores	Topical	16
<i>Commelina africana</i> L.	Commelinaceae	Isicakathi (EC)	Roots	Scabies	Bathing	5
<i>Commicarpus pentandrus</i> (Burch) Heimerl	Nyctaginaceae	Moetapele (NW)	Whole plant	Burns, sores, warts, and wounds	Topical	23
<i>Cotyledon orbiculata</i> L.	Crassulaceae	Imphewula/kouterie/ plakkie (EC/WC); Seredite (FS)	Leaves	Warts, corns, and sores	Topical	2, 6, 9, 19, 20, 22, 24
<i>Crinum moorei</i> Hook.F	Amaryllidaceae	-	Bulbs	Sores, and acne	Topical	6
<i>Crossyne guttata</i> (L.) D. Mull. -Doblies & U. Mull. -Doblies	Amaryllidaceae	Gifbol (WC)	Bulb	Post- circumcision rites, wounds and draws out pus	Topical	19
<i>Croton sylvaticus</i> Hochst.	Euphorbiaceae	Umfeze/Umagwagane (EC)	Bark	Bleeding gums	Oral	6
<i>Cryptocarya woodii</i> Engl.	Lauraceae	Ummquma (EC)	Bark, infusion of powder	Eczema	Topical	5
<i>Cucumis hirsutus</i> Sond.	Cucurbitaceae		Leaves and roots	Inflammation	Topical	6
<i>Cullen tomentosum</i> (Thumb) J.W. Grimes	Fabaceae	Mojakubu (NW)	Whole plant	Rash, and sores	Topical	23

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Curtisia dentata</i> C.A.Sm.	Curtisiaceae	Uzintwa (EC)	Bark, infusion of powder	Eczema	Topical	5, 6, 9
<i>Cussonia paniculata</i> Eckl. & Kok	Araliaceae		Leaves	Sores, and wounds	Topical	24
<i>Zeyh. ssp. sinuata</i> (Reyneke & Kok) De Winter						
<i>Cussonia spicata</i> Thunb.	Araliaceae	Musenzhe (L)	Leaves	Ringworms	Topical	16
<i>Cycnium racemosum</i> Benth.	Orobanchaceae	Injanga (EC)	Leaves	Skin ulcers	Topical	5
<i>Cymbopogon caesius</i> (Hook. & Arn.) Stapf	Poaceae	Umqungu (EC)	Leaves	Skin itch	Topical	5
<i>Cymbopogon dieterlenii</i> Stapf. ex E. Phillips	Poaceae	Khotsoana (FS)	Whole plant	Wounds	Topical	24
<i>Cymbopogon marginatus</i> (Steud.) Stapf ex Burtt Davy	Poaceae	Umqungu (EC)	Leaves	Skin irritation	Bathing	5
<i>Cynoglossum lanceolatum</i> Forsk.	Boraginaceae		Roots	Wounds	Topical	24
<i>Cyperus exilis</i> Thunb.	Cyperaceae	Imizi (EC)	Leaves	Eczema	Topical	5
<i>Cyrtanthus obliquus</i> (L.f.) Aiton	Amaryllidaceae	Umathinga (EC)	Roots	Wounds	Topical	2
<i>Dalbergia obovata</i> E. Mey	Fabaceae	Umzungulu (EC); Udukuduku/isibandhlube/ uphandlazi (KZN)	Stem	Sore mouths in infants		6, 11
<i>Datura stramonium</i> L.	Solanaceae	Umhlavuthwa (EC); Stinkblaar (WC)	Leaves	Boils, and wounds	Topical	5, 6, 9, 20, 24

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Dialium schlechteri</i> Harms	Fabaceae	Umthiba (KZN)	Bark	Boils, burns, and wounds	Topical	11
<i>Dianthus moitenensis</i> F.N Williams ssp. <i>kirikii</i> (Burt Davys) S.S Hooper	Caryophyllaceae	Tlhokatsela (NW)	Rhizome	Genital warts	Topical	23
<i>Dianthus thunbergii</i> (Thumb.) S.S. Hooper.	Caryophyllaceae	Ungcane (EC)	Leaves Infusion	Remove body odour	Bathing	5
<i>Dicerocaryum zanguebarium</i> (Lour.) Merr.	Pedaliaceae	Dinda (L)	Leaves	Shampoo	Bathing	14, 16
<i>Dichrostachys cinerea</i> (L.) Wight & Arn.	Fabaceae	Ugagane (KZN); Murenzhe (L)	Twigs, fruits, bark	Acne vulgaris, and wounds	Topical	10, 11, 16
<i>Dicoma anomala</i> Sond.	Asteraceae	Tlhonya (NW); Hloenya (FS)	Tuber	Wounds, skin ulcers, ringworm and head sores, albinism, boils, burns, flea bite, herpes zoster, condylomata acuminata, impetigo, Kaposi sarcoma, rash, and skin itching	Topical	22, 23, 24
<i>Digitaria eriantha</i> Steud.	Poaceae	Injica (EC)	Leaf decoction	Pimples	Topical	5
<i>Dioscorea dregeana</i> T. Durand & Schinz.	Dioscoreaceae	-	Tuber	Cuts and sores	Topical	22
<i>Dioscorea elephantipes</i>	Dioscoreaceae	Olifant foot (WC)	Bulb	Tired feet, athlete's foot, and blisters	Topical	19

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Dioscorea sylvatica</i> (Kumth) Eckl.	Dioscoreaceae	Olifant foot (WC); Marakalla/Leeto la tlou (FS)	Roots	Wounds	Topical	21, 25
<i>Diospyros lyciooides</i> Desf.	Ebenaceae	Umbhongisa (EC); Muthala (L)	Bark and root	Inflammation, and wounds	Topical	6, 16
<i>Diospyros mespiliformis</i> Hochst.	Ebenaceae	Nioma/ Musuma (L)	Bark, roots	Toothache	Oral	14, 16, 22
<i>Diospyros natalensis</i> (Harv.) Brenan	Ebenaceae	Xintomatomane (L)	Twigs	Clean teeth	Oral	16
<i>Diospyros pubescens</i> Pers.	Ebenaceae	Umbhongisa (EC)	Leaves	Strengthen nails	Topical	5
<i>Dodonaea viscosa</i> Jacq var. <i>angustifolia</i> (L.f) Benth.	Sapindaceae	-	Twigs, whole plant	Clean the teeth, and oral thrush	Oral	6, 22
<i>Dombeya rotundifolia</i> (Hochst.) Planch	Malvaceae	Tshiluvhari (L)	Leaves	Wash and dry hair	Bathing	16, 18
<i>Drima capensis</i> (Burm.f.) Wijnands	Asparagaceae	Gifbol (WC)	Bulb	Post- circumcision rites, wounds, and draws out pus	Topical	19
<i>Drimia altissima</i> (LF) Ker Gawl.	Asparagaceae	Thobega (NW)	Leaves	Sores	Topical	23
<i>Drimia delagoensis</i> (Baker) Jessop	Asparagaceae	-	Bulb	Sores	Topical	10, 20
<i>Drimia elata</i> Jacq.	Asparagaceae	Red onion/ jeukoi/ rojjukei (WC); Intelezi/ Mascaban (KZN)	Bulb	Opens pores, and swelling	Topical	19, 20

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Drimys sanguinea</i> (Schinz) Jessop	Asparagaceae	Sekaname (NW)	Bark	Candidiasis, common warts, condylocromata acuminata, genital warts, syphilis, and yaws	Topical	23
<i>Dysphania ambrosioides</i> (L.) Mosyakini & Clements	Amaranthaceae	Imboya (EC); Hlahlabadimo (NW)	Leaves, lotion	Skin itch, eczema, pimples, and clean skin	Bathing, topical	5, 23
<i>Ekebergia capensis</i> Sparrm.	Meliaceae	-	Bark	Boils, and acne	Topical	22
<i>Elephantorrhiza elephanthina</i> (Burch.) Skeels.	Fabaceae	Intolwane (EC, KZN); Mositsane (FS/NW)	Roots and rhizomes	Acne, wounds, and burns	Topical	7, 9, 10, 11, 22, 24
<i>Elephantorrhiza burchellii</i> Benth (Burch). Skeels	Fabaceae	Mositsane (NW)	Roots	Chickenpox, condylocromata acuminata, squamous carcinoma, malignant melanoma, infantile acropustulosis, Herangioma, keratosis, Kaposi sarcoma, pearl penile papules, genital warts, madura foot, keratosis, and herpes simplex	Topical	23
<i>Elytropappus rhinocerotis</i> (L.f.) Less.	Asteraceae	Renosterbos (WC)	Leaves	Swollen hands and feet	Topical	19, 20
<i>Embelia ruminata</i> (E. Mey. ex A.Dc.) Mez	Myrsinaceae	-	Leaves	Wounds and leprosy	Topical	22

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Emex australis</i> Steinh.	Polygonaceae	Inkunzane (EC)	Leaf decoction	Prevent hair loss	Topical	5
<i>Eriocapitatus africanus</i> L.	Asteraceae	-	Essential oil	Skin care	Topical	16
<i>Eriosepermum lancifolium</i> Jacq.	Asparagaceae	Babbejaanore (WC)	Bulb	Skin softening	Topical	19
<i>Erythrina latissimi</i> E. Mey.	Fabaceae	Umgwabagqwaba/ umqonqazi (KZN)	Bark	Sores	Topical	18
<i>Erythrina lysistemon</i> Hutch.	Fabaceae	Umkwane (EC); Umsinsi/ umisi (KZN)	Bark powder	Wounds, skin irritation, abscesses, and sores	Topical	5, 6, 18, 22
<i>Eucalyptus camaldulensis</i> Dehm.	Myrtaceae	-	Bark	Acne	Topical	22
<i>Eucalyptus globulus</i> Labill.	Myrtaceae	Eucalyptus	Leaves	Wounds, muscle aches and pains, washing, and relaxation	Topical	19
Subsp. maidenii (F. Muell.) Kirkp.						
<i>Euclea divinorum</i> Hiern	Ebenaceae	Nhlangu/ mutangule (L); Mokwere (NW)	Leaves	Skin irritation, ringworms, rash, pimples, chickenpox	Topical	16, 23
<i>Euclea natalensis</i> A.DC.	Ebenaceae	Umshekesane (EC)	Root decoction, Wood	Sore throat and clean teeth	Oral	5
<i>Eucomis autumnalis</i> (Mill.) Chitt	Amaryllidaceae	Umathunga (EC); Mathubadihala (NW)	Bulbs	Improve beauty and treat wounds	Topical	6, 9, 23
<i>Eugenia capensis</i> ssp. <i>natalita</i> (Sond.) F. White	Myrtaceae	Tshitanzwanzwane (L)	Roots	Sores	Topical	16
<i>Eugenia natalita</i> Sond.	Myrtaceae	Tshitanzwanzwane (L)	Roots	Sores	Topical	16

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Euphorbia bupleurifolia</i> Jacq.	Euphorbiaceae	Intsema (EC)	Latex, leaves, twig	Pimples, wounds, rashes, and clean teeth	Bathing, topical	5
<i>Euphorbia clavarioides</i> Boiss var. <i>clavarioides</i>	Euphorbiaceae	Sehlehle/ Sehloko/ Thehebele (FS)	Stem	Acne, cancerous sores, cracked heels, herpes sores, leprosy, and skin rash in children	Topical	24, 25
<i>Euphorbia hirta</i> L.	Euphorbiaceae	Intsema (EC)	Roots	Wounds	Topical	2
<i>Euphorbia inaequilatera</i> Sond. var. <i>inaequilatera</i>	Euphorbiaceae	-	Rhizomes	Burns, sores, and rash	Topical	23
<i>Euphorbia ingens</i>	Euphorbiaceae	Umlonhlo (EC)	Stem	Skin rash post-inflammatory spots and promote healing without hyper pigmentation	Topical	9
<i>Euphorbia mauritanica</i> L. var. <i>mauritanica</i>	Euphorbiaceae	Milk thistle (WC)	Leaves	Warts	Topical	19
<i>Euphorbia prostrata</i> Aiton.	Asparagaceae	Letswetlane (NW)	Rhizomes	Candidiasis, syphilis, infantile cropustulosis, and chickenpox	Topical	23
<i>Euphorbia serpen</i> Kunth	Euphorbiaceae	Lwetsane (NW)	Leaves, roots	Athlete's foot and ringworm	Topical	23
<i>Euphorbia tirucalli</i> L.	Euphorbiaceae	Ingotsha (KZN)	Modified stem	Sores	Topical	10, 11
<i>Euphorbia tuberosa</i> L.	Euphorbiaceae	Milk root/ fennel (WC)	Root, whole plant	Warts	Topical	19
<i>Ficus capensis</i> Thunb.	Moraceae	Ikhwane (EC)	Leaves	Pimples	Topical	3

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Ficus ingens</i> (Miq.) Miq.	Moraceae	Mohlatsa/ molhatsa/ tshikululu (L)	Bark	Sores	Topical	15
<i>Ficus natalensis</i> Hochst.	Moraceae	Umthombe (EC)	Leaf decoction	Clean skin	Bathing	5, 6, 22
<i>Ficus sur</i> Forssk.	Moraceae	Umkhiwane (KZN)	Bark	Sores	Topical	10, 22
<i>Ficus sycomorua</i> L.	Moraceae	Xirhombethombe (L)	Leaves, bark, roots, sap	Dermatitis	Topical	14
<i>Foeniculum vulgare</i> Mill.	Apiaceae	-	Green dye from leaves	Fragrance component	Topical	6
<i>Galenia africana</i> L.	Aizoaceae	Kraalbos (WC)	Leaves	Skin ailments and toothache	Topical	19
<i>Garcinia livingstonei</i> T. Anderson.	Clusiaceae	Umphimbi/ ugobandlovu (KZN)	Bark	Burns	Topical	11
<i>Gardenia volkensii</i> K. Schum.	Rubiaceae	Tshiralala (L)	Flowers	Body odour	Bathing	16
<i>Gasteria croucheri</i> (Hook.f.) Baker	Asphodelaceae	Kannedot (WC); Intelezi (EC); Umathithibala (KZN)	Whole plant	Skin rash, warts, and ringworm.	Topical	19
<i>Gasteria obliqua</i> (Aiton) Duval	Asphodelaceae	Intelezi (EC)	Leaf decoction	Skin irritation, clean skin, eczema, and scabies	Bathing, topical	5
<i>Gerbera piloselloides</i> (L.) Cass	Asteraceae	Umsa (EC)	Root infusion	Post-inflammatory spots and pimples	Topical	6, 9
<i>Gnuidia anthyloides</i> (L.f.) Gilg	Thymelaeaceae	Intozwane (EC)	Roots	Wounds and burns	Topical	6, 9
<i>Gnuidia capitata</i> L.f.	Thymelaeaceae	Umsila (EC)	Roots	Wounds, rashes, fractures, snake bites, and sore throat	Topical	7, 9

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Gnidia gymnostachya</i> (C.A. Mey) Gilg.	Thymelaeaceae	-	Leaves	Bruises and wounds	Topical	24
<i>Gnidia kraussiana</i> Meisn.	Thymelaeaceae	Igamma (EC)	Leaves	Protect facial skin, wounds, burns, boils, rashes, and sore throat	Topical, oral	5
<i>Gomphocarpus fruticosus</i> (L) Aiton.f. ssp. <i>fruticosus</i>	Apocynaceae	Moetimolo (NW)	Whole plant	Burns, sores, and rash	Topical	23
<i>Grewia occidentalis</i> L.	Malvaceae	Umqqabaza (EC)	Bark	Wounds and shampoo	Topical and bathing	7, 18
<i>Grewia caffra</i> Meisn.	Tiliaceae	Ikholo/ ilalanyathi/ iphata (KZN)	Bark	Wounds and shampoo	Topical and bathing	18
<i>Grewia flava</i> DC.	Malvaceae	Moretlwa (NW)	Roots	Pearl penile papules	Topical	23
<i>Grewia flavescens</i> Juss.	Malvaceae	Motsotsojane (NW)	Leaves	Candidiasis, common warts, and sores	Topical	23
<i>Grewia occidentalis</i> L.	Malvaceae	Umqqabaza (EC)	Bark	Wounds	Bathing	6
<i>Grewia flanaganii</i> Bolus	Francoaceae	Usinga/Lwamaxhegokazi (EC)	Leaves	Skin ailment	Topical	6
<i>Gunnera perpensa</i> L.	Gunneraceae	Iphuzi (EC); Qobo (FS)	Leaves	Insect bite	Topical	5, 9, 22, 24
<i>Haemanthus albiflos</i> Jacq.	Amaryllidaceae	Umathinga (EC)	Paste, leaf decoction	Skin ulcers, burns, and remove body odour	Bathing, topical	5
<i>Halleria lucida</i> L.	Stilbaceae	Inkobe (EC)	Leaf decoction	Scabies	Bathing	5, 6, 22
<i>Haplocarpha scaposa</i> Harv.	Asteraceae	Isicwe (EC)	Paste, leaves decoction	Scabies and wounds	Bathing	5
<i>Harpephyllum caffrum</i> Benth.	Anacardiaceae	Umgwenye (EC)	Bark decoction	Wounds, eczema, and pimples	Topical	5, 6, 9, 12, 22

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Haworthia limifolia</i> Marloth.	Asphodelaceae	Isihlalakahle (KZN)	Leaves, stem, roots	Burns and sun burn	Topical	13
<i>Haworthia fasciata</i> (Willd.) Haw.	Asphodelaceae	Kannedot (WC); Intelezi (EC)	Whole plant	Skin rash warts and ringworm	Topical	19
<i>Helichrysum nudifolium</i> (L.) Less.	Asteraceae	Indlebe (EC); Imphepho (NW)	Leaves, twig powder	Improve skin beauty and genital warts	Topical	6, 23
<i>Helichrysum appendiculatum</i> Less.	Asteraceae	Isicwe (EC)	Leaves	Circumcision wounds and sores	Topical	3, 21
<i>Helichrysum leiopodium</i> DC.	Asteraceae	Letapiso (EC)	Whole plant	Swollen feet	Bathing and Topical	3, 21
<i>Helichrysum nudifolium</i>	Asteraceae	Indlebe zebhokwe/Isicwe/Ichola chola (EC)	Leaves and twigs	Wound and improves skin beauty	Topical	9, 21
<i>Helichrysum odoratissimum</i> (L.) Sweet.	Asteraceae	Impepho (EC)	Infusions, lotion, leaves	Wounds, skin ulcers, scabies, protect facial skin, and perfumes of the skin	Topical	5, 6
<i>Helichrysum paronychioides</i> DC. Humbert	Asteraceae	Phate-ya-ngaka (NW)	Whole plant	Boils, candidiasis, eczema, Kaposi sarcoma, soils, rash, yaws, herpes zoster, ringworm, condylomata acuminata, eczema, and pearl penile papules	Topical	23
<i>Helichrysum pedunculatum</i> Hilliard & B.L. Burtt	Asteraceae	Isicwe (EC)	Leaves	Circumcision wounds	Topical	4

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Helichrysum petiolare</i> Hilliard and B.L. Burt	Asteraceae	Imphepho (EC)	Leaves	improve skin texture and beauty and to treat wounds	Topical	6, 9, 21
<i>Helinus integrifolius</i> (Lam.) Kuntze.	Rhamnaceae	Isilawu (EC); Mpupungwa/Mugumwa (L)	Leaves	Against hair loss	Topical	5, 16
<i>Hermannia depressa</i> N.E. Br	Malvaceae	Selejane (NW)	Whole plant	Sores	Topical	23
<i>Hermannia</i> spp.	Malvaceae	8-days/ agdaegeeneebos (WC)	Leaves	Ringworm, skin ailments, and sores	Topical	19
<i>Hermannia coccocarpa</i> K.Schum.	Malvaceae	-	Roots	Burns and wounds	Topical	24
<i>Hermannia geniculata</i> Eckl. & Zeyh.	Malvaceae	Imphepho (EC)	Leaf paste	Boils	Topical	5
<i>Heteromorpha arborexscens</i> (Spreng.) Cham. & Schltdl.	Apiaceae	Muthathavhama (L)	Leaves	Skin burns	Topical	16
<i>Hewittia malabarica</i> L. (Suresh).	Convolvulaceae	Ihlanzandulo (KZN)	Leaves	Abscesses and boils	Topical	11
<i>Hibiscus surattensis</i> L.	Malvaceae	Indola ebomvu (KZN)	Roots	Burns and sores	Topical	11
<i>Hillardiella elaeagnoides</i> (DC) Swelank & J.C. Manning	Asteraceae	Nshikologa (NW)	Rhizomes	Scabies and eczema	Topical	23
<i>Hydnora africana</i> Thunb.	Hydnoraceae	Umavumbuka (EC)	Dried fruiting body	Acne and other skin blemishes	Topical	6
<i>Hyperacanthus amoenus</i> (Sims) Bridson.	Rubiaceae	Murombe (L)	Fruit	Pimples	Topical	16

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Hypericum aethiopicum</i> Thunb.	Hypericaceae	Isimayisane/ Isimonyo/ Isivumelwane (KZN)	Leaves, stem, roots	Wounds and first-degree burns	Topical	13
<i>Hypericum perforatum</i> L.	Hypericaceae	-	Leaves	Wounds and first-degree burns	Topical	22
<i>Hyphaene coriacea</i> Gaertn.	Arecaceae	Itala (EC)	Fruits, lotion, leaves, midrib	Soften hair and clean teeth	Bathing, topical	5
<i>Hypoxis hemerocallidea</i> Fisch. C.A. Mey. and Ave-Lall.	Hypoxidaceae	Inongwe (EC); Tshupoo ya poo (NW)	Corn	Pimples and improvement of beauty	Topical	6, 9, 23
<i>Hypoxis argentea</i> Harv. ex Baker	Hypoxidaceae	Inongwe (EC); Lotsane (FS)	Corn Infusion	Ringworm, eczema, pimples and to clean, and protect facial skin.	Topical	5, 24
<i>Hypoxis hemerocallidea</i> Fisch., C.A. Mey. & Ave-Lall.	Hypoxidaceae	Inkomfe/ inkomfe enkulu (KZN)	Corns	Boils, sores, and ringworm	Topical	10, 11
<i>Hypoxis rigidula</i> Baker var. <i>rigidula</i>	Hypoxidaceae	Moli-teane (FS)	Leaves	Wounds and rash	Topical	24
<i>Ilex mitis</i> (L.) Radlk.	Aquifoliaceae	Isidumo (EC); iphuphuma/ umdumo/ umdumowazo (KZN)	Leaf decoction	Rash and facial sores	Topical	5, 6, 18, 22
<i>Indigofera arrecta</i> Hochst. A. Rich	Fabaceae	Muswiswa (L)	Twigs and leaves	Cleaning and bathing	Orla and bathing	16
<i>Ipomoea bolusiana</i> Schinz.	Convolvulaceae	Mokutu (L)	Bulb	Foot ache	Topical	17

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Ipomoea oblongata</i> E. Mey. ex Chiosy A.	Convolvulaceae	Morebe / Mokatelo (NW); Ubhoqo (MP); Mothokho (FS)	Rhizomes	Genital warts, leprosy, and scabies	Topical	23, 25
<i>Ipomoea simplex</i> Thunb.	Convolvulaceae	Igontsi (EC)	Corn, leaves	Hair loss, Clean skin, and protect facial skin	Topical	5
<i>Jatropha brachyadenia</i> Pax & K.Hoffm.	Euphorbiaceae	Xidemeja (L)	Leaves	Wounds	Topical	16
<i>Jatropha curcas</i> L.	Euphorbiaceae	Mupfure donga (L)	Stem, leaves, Roots	Skin moisturiser and wounds	Topical	16
<i>Jatropha zeyheri</i> Sond.	Euphorbiaceae	Modomeja/ Xidemeja (L); Seswagadi (NW)	Leaves	Wounds, acne vulgaris, albinism, boils, herpes zoster, genital warts, and yaws	Topical	14, 16, 23
<i>Kedrois nana</i> var. <i>zeyheri</i>	Curcubitaceae	Mpitike (NW)	Bulb	Eczema	Topical	23
<i>Kigelia africana</i> (Lam.) Benth.	Bignoniaceae	Umvunguta/ umfongothi (KZN); Umvongotsi (MP)	Bark	Ringworm	Topical	10, 11, 22, 25
<i>Knifophia laxiflora</i> Kunth	Asphodelaceae	Inxonya (WC)	Root	Pimples	Topical	19
<i>Kniphofia drepanophylla</i> Baker.	Asphodelaceae	Ixonyi (EC)	Rhizomes	Ringworm, wounds, pimples, acne, and eczema	Topical	6, 9
<i>Lansea discolor</i> Engl.	Anacardiaceae	-	Bark	Boils and abscesses	Topical	22
<i>Lansea schweinfurthii</i> var. <i>stuhlmannii</i> (Engl.) Kokwaro	Anacardiaceae	Ndivata (L)	Leaves	Wounds	Topical	16
<i>Lansea stuhlmannii</i> Engl.	Anacardiaceae	Ndivata (L)	Leaves	Wounds	Topical	16
<i>Lantana angolensis</i> Moldenke	Verbenaceae	Selaole (NW)	Rhizome	Ringworm	Topical	23

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Lantana rugosa</i> Thunb.	Verbenaceae	-	Leaves, stem, ripe fruits	Sores and cuts	Topical	22
<i>Lasiosiphon kraussianus</i> Hutch. & Dalz.	Thymelaeaceae	-	Whole plant	Wounds and bruises	Topical	24
<i>Ledebouria revoluta</i> (L.f.) Jessop	Hyacinthaceae	Icubudwana (KZN)	Bulb	Ringworm	Topical	10
<i>Leonotis leonurus</i> (L.) R.Br.	Lamiaceae	Umfincafinca/Umunyamunya (EC); Wild dagga (WC)	Leaves and stems	Itching, boils, eczema, and dandruff	Topical	6, 8, 9, 19
<i>Leucosidea sericea</i> Eckl. and Zeyh.	Rosaceae	Isidwadwa/Umyityi (EC); Mosimo (FS)	Leaves	Acne	Topical	6, 24
<i>Lippia javanica</i> Burm.f. Spreng.	Verbenaceae	Inzinziniba (EC); Umsuzwane/umswazi (KZN); Musudzungwane (L); Selaole / fever tea (NW)	Leaves	Boils, scabies, and wounds	Topical	5, 6, 9, 10, 11, 12, 16, 23
<i>Lyctium horridum</i> Thunb.	Solanaceae	Mothalawadikonyana (NW)	Whole plant	Kerotosis	Topical	23
<i>Macaranga capensis</i> (Baill.) Benth. ex Sim	Euphorbiaceae	Umpumelelo (EC)	Bark	Pimples, wounds eczema, and acne	Topical	6, 9
<i>Mahua neglecta</i> Wallr.	Malvaceae	Tikamotose (NW)	Whole plant	Albinism, bullous dermatosis, herpes simplex, sores, and yaws	Topical	23
<i>Mahua parviflora</i> L.	Malvaceae	Ijongilanga (EC)	Leaves	Pimples, insect bite, and wound boils	Topical	5, 6, 7, 22, 24
<i>Melia azedarach</i> L.	Meliaceae	Mosara (L)	Leaves	Shingles	Bathing	17

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Melanthus comosus</i> L.	Melanthaceae	Ubuhlungu bemamba (EC); Kruidjie roer my nie (WC)	Leaves	Wounds and Sores	Topical	6, 20, 22
<i>Melanthus major</i> L.	Melanthaceae	Ubuhlungubemamba/Ubutyayi (EC); kruidjie-roer-my-nie (WC)	Leaves	Wounds, sores and bruises	Topical	6, 8, 19, 21, 22
<i>Mentha longifolia</i> (L.)	Lamiaceae	Inixina/Inzininiba (EC); Kruisement (WC)	Leaves	Wounds	Topical	6, 20, 22
<i>Merrillia plumbea</i> (Lindl.) Speta.	Asparagaceae	Ichitha/ Imbizenkulu/ Inguduza/ Ubulika (KZN)	Leaves, bulbs, roots	Boils, sores, wounds healing, sprains, and to remove scar tissue	Topical	13
<i>Miscanthus capensis</i> (Nees) Andersson.	Poaceae	Umpumelelo (EC)	Bark	Pimples, wounds eczema, and acne	Topical	6, 9
<i>Monardica balsamina</i> L.	Cucurbitaceae	Intshungu/ intshungwana yehlathi (KZN)	Leaves	Rash	Topical	11
<i>Monadenium lugardiae</i> N.E.Br.	Euphorbiaceae	Umhuwa (KZN)	Bark	Sunburn	Topical	19
<i>Monsonia brevistriata</i> Knuth.	Geraniaceae	-	Leaves	Syphilitic sores	Topical	24
<i>Musa acuminata</i> Colla.	Musaceae	Muova (L)	Flowers, leaves	Skin burns and wounds	Topical	16
<i>Myrsine africana</i> L.	Myrsinaceae	Moroko-pheleu/ semapo, sethakhisa/ thakisa (FS)	Leaves, fruits	Ringworm and skin diseases	Topical	24
<i>Myrsine melanophloeos</i> (L.) R. Br. Adamson	Primulaceae	Umaphipha (KZN)	Bark	Hair shampoo	Topical	19

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Nasturtium officinale</i> W.T. Aiton	Brassicaceae	Umsobo (EC)	Whole plant	Antiseptic and blemishes	Topical	4
<i>Nerium oleander</i> L.	Apocynaceae	Five roses	Leaves	Toothache	Oral	17
<i>Nicotiana tabacum</i> L.	Solanaceae	Icuba (EC)	Paste	Wound	Topical	5
<i>Obetia tenax</i> Friis. Syn: <i>Ureva tenax</i>	Urticaceae	Thanga (L)	Seeds	Skin moisturiser	Topical	16
<i>Ochna serrulata</i> (Hochst.) Walp.	Ochnaceae	Ilitye (EC)	Paste, leaves	Soften hair, strengthen nails, and to soften facial skin	Topical	5
<i>Ocotea bullata</i>	Lauraceae	Ummukani (KZN)	Bark	Pimples	Topical	12
<i>Olea europaea</i> L.	Oleaceae	Umquma (EC); Wild olive/olienhout (WC); Modukguhlu (FS)	Leaf decoction	Remove body odour, sores, and skin ulcers	Bathing	5, 6, 21, 24
<i>Ophioglossum vulgatum</i> L.	Ophioglossaceae		Rhizomes	Boils	Topical	24
<i>Opuntia aurantiaca</i> Lindl.	Cactaceae	Itolofiya (EC)	Gel, Leaves	Soften hair, treat skin ulcers, and to protect facial skin	Topical	5
<i>Opuntia ficus-indica</i> (L.) Mill.	Cactaceae	Midthoro (L); Prickly pear (WC)	Leaves	Toothache	Oral	14, 17, 19, 22
<i>Opuntia vulgaris</i> Mill.	Cactaceae	Itolofiya (EC)	Stem	Wounds	Topical	2
<i>Ozoroa engleri</i> R. Fern. & A. Fern.	Anacardiaceae	Isifice/ Isifico (KZN)	Bark and leaves	Sores	Topical	10
<i>Ozoroa engleri</i> R. Fern. & A. Fern.	Anacardiaceae	-	Bark	Sores	Topical	11

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Ozoroa sphaerocarpa</i> R. & A. Fern.	Anacardiaceae	Isifice/ isifico (KZN)	Bark	Wounds	Topical	18
<i>Parapodium costatum</i> E. Mey	Poeyniaceae	-	-	External tumours	Topical	24
<i>Parinari capensis</i> Harv. subsp. <i>capensis</i>	Chrysobalanaceae	-	Roots	Sores	Topical	11
<i>Povetta lanceolata</i> Eckl.	Rubiaceae	Umhleza (EC)	Paste, leaves	Skin itch	Topical	5
<i>Pelargonium lubricum</i> (Andrews) Sweet	Geraniaceae	Thotamadi (NW)	Roots	Acne vulgaris, burns, eczema, pimples, and yaws	Topical	23
<i>Pelargonium peltatum</i> (L.) L'OHér. ex	Geraniaceae	Ityolo (EC)	Tuber decoction	Clean the skin	Bathing	5, 20
<i>Pelargonium sidoides</i> DC.	Geraniaceae	Umsangela (EC)	Whole plant	Various skin disorders	Topical	6, 20
<i>Pellaea calomelanos</i> Link.	Adiantaceae	-	Leaves, rhizomes	Boils and abscesses	Topical	22
<i>Peltophorum africanum</i> Sond.	Fabaceae	Musese (L); Mosestha (NW)	Bark, roots	Mouth sores, Kaposi sarcoma, and heat rash	Oral, topical	16, 17, 23
<i>Pentstemon prunelloides</i> (Klotzsch ex Xkl. and Zeyh.) Walp.	Rubiaceae	Icimamilo/irhubuxa (EC); Iscimamilo (KZN)	Roots	Blisters, bruises, burns, cuts, insect, and stings/bites	Topical	1, 6, 9, 19, 22, 24
<i>Persea americana</i> Mill.	Lauraceae	Avocado (EC); Afukhada (L)	Seed, leaves	Clean facial skin, protect facial skin, and wrinkles	Bathing, topical	5, 16
<i>Phragmites australis</i> (Cav.) Trin.ex Steud.	Poaceae	Ingcongolo (EC)	Paste of leaves	Protect facial skin	Topical	5

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Phragmites mauritianus</i> Kunth.	Poaceae	Lutanga (L)	Thorns and whole plant	Moles and stretch marks	Topical	16
<i>Phygelius capensis</i> E. Mey.	Scrophulariaceae	Metsi-matsho (FS)	Leaves	Sores and skin ulcers	Topical	24
<i>Phyllanthus maderaspatensis</i> L.	Phyllanthaceae	Leestane (NW)	Leaves	Ringworm and eczema	Topical	23
<i>Physalis angulata</i> L.	Solanaceae	Itywabotywabo (EC)	Paste of leaves	Burns	Topical	5
<i>Phytolacca americana</i> L.	Phytolaccaceae	Umsobosobo (EC)	Paste of leaves	Boils	Topical	5
<i>Phytolacca octandra</i> L.	Phytolaccaceae	Amahashe ayatsala (EC)	Fruits	Wounds and sores	Topical	4
<i>Ptilostigma thommingii</i> (Schum.) Milne-Redh	Fabaceae	Denga (L)	Fruit	Pimples and wounds	Topical	16
<i>Pittosporum viridiflorum</i> Sims.	Pittosporaceae	-	Roots, leaves	Boils	Topical	22
<i>Plumbago auriculata</i> Lam.	Plumbaginaceae	Umabophe (EC)	Roots /leaves	Warts, rashes, acne, and pimples	Topical	6, 9
<i>Podocarpus latifolius</i> (Thunb.) R.Br. ex Mirb.	Podocarpaceae	Umkhaba (EC)	Juice of leaves	Eczema	Topical	5
<i>Polystichum pungens</i> (Kaufl.) Presl.	Dryopteridaceae	Shield ferns (WC)	Leaves	Pain and inflammation	Topical	7, 26
<i>Portulacaria afra</i> Jacq.	Portulacaceae	Intelezi/ isidondwane/ isambilane/ indibili/ isicococo (KZN)	Leaves	Rash and chronic sores	Topical	11

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Pouzolzia mixta</i> Solms	Urticaceae	Muthanzwa (L); Moreba (NW)	Roots	Wounds, abscess, boils, eczema, infantile acropustolosis, and penile papules	Topical	16, 23
<i>Protea repens</i> (L.) L.	Proteaceae	Isadlungi (EC)	Whole plant	Inflammation	Topical	6
<i>Protea simplex</i> E. Phillips	Proteaceae	Isadlungi (EC)	Whole plant	Inflammation	Topical	6
<i>Protorhus longifolia</i> (Bernh.) Engl.	Anacardiaceae	Ikhubalo (EC)	Bark	Wounds, cuts, bruise, and graze ringworm, ache, and eczema	Topical	6
<i>Pseudocrossidium crinitum</i> (Schultz) R.H. Zander.	Pottiaceae	Ixolo lamatye (EC)	Infusion of leaves	Skin irritation	Topical	5
<i>Pseudophyllanthus ovalis</i> (E. Mey. ex Sond.) Voronts. & Petra Hoffm.	Phyllanthaceae	Umbezo (EC)	Root decoction	Perfume skin	Topical	5
<i>Psidium guajava</i> L.	Myrtaceae	Gwabisi (KZN)	Leaves	Wounds	Topical	12
<i>Psoralea pinnata</i> L.	Fabaceae	Umhlonishwa (KZN)	Leaves	Shingles	Topical	10
<i>Ptaeroxylon obliquum</i> (Thumb.) Radlk.	Rutaceae	Umthathe (EC)	Bark Infusion	Remove body odour	Bathing	5
<i>Pterocarpus angolensis</i> DC.	Fabaceae	Indlandlovu/ umbilo/ umvangazi (KZN)	Bark	Sores	Topical	18
<i>Pterocelastrus tricuspidatus</i> (Lam.) Sond.	Celastraceae	Ibholo (EC)	Leaves, shrub Infusion	Sore throat and to protect facial skin	Topical	5
<i>Ranunculus multifidus</i> Forssk.	Ranunculaceae	Ishashakazane/ Isijojokazana/ Uxhaphozi (KZN),	Whole plant	Sores	Topical	10, 11

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Rapanea melanophloeos</i> (L.) Mez.	Myrsinaceae	Umaphipha (EC); Ikhubalwane/inhluthe (KZN)	Bark	Cosmetic paste to protect against evil, and wounds	Topical	6, 15, 18
<i>Rauwolfia caffra</i> Sond.	Apocynaceae	-	Bark	Measles, urticaria and other skin rashes	Topical	22, 23
<i>Rawsonia lucida</i> Harv. & Sond.	Achariaceae	Umlongo (EC)	Paste offleaves	Ringworm	Topical	5
<i>Rhamnus prinoides</i> L'Her.	Rhamnaceae	Mofifi (FS)	Leaves	Sores	Topical	24
<i>Rhus lucida</i> L.	Anacardiaceae	Intlokoshane (EC)	Bark Infusion	Scabies	Topical	5
<i>Ricinus communis</i> L.	Euphorbiaceae	Umthlakuva (EC); Nhlampfurha/mupfure (L); Oliveblare/kastorolie boom (WC); Mokhura (NW)	Roots and leaves	Wounds and sores	Topical	2, 16, 20, 23
<i>Rothmannia capensis</i> Thunb.	Rubiaceae	Ibolo (EC)	Fruit juice	Wounds and burns	Topical	6, 22
<i>Rubia horrid</i> (Thunb.) Puff	Rubiaceae	Madi-a-phalane (NW)	Roots	Albinism	Topical	23
<i>Rumex acetosella</i> L.	Polygonaceae	Ubuhlunga (EC)	Roots	Wounds and bruises	Topical	24
<i>Rumex crispus</i> L.	Polygonaceae		Decoction of leaves	Treat hair loss	Topical	5
<i>Rumex lanceolatus</i> Thunb.	Rubiaceae	Dolonyana (EC)	Roots/leaves	Abscesses, boils, and bruises	Topical	7, 9, 24
<i>Salacia rehmannii</i> Schinz.	Celastraceae	Phathatsimima (L)	Roots	Sores	Topical	16
<i>Salix mucronata</i> Thunb.	Salicaceae	Mogokare (FS)	Leaves	Burn wounds	Topical	24
<i>Salix babylonica</i> L.	Salicaceae	Umngecunube (EC)	Bark	Wounds	Topical	2
<i>Salvia africana-lutea</i> L.	Lamiaceae	Red sage (WC)	Leaves	Sore legs	Topical	19, 21

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Salvia stenophylla</i> Burch. ex Benth	Lamiaceae	-	Leaves	Wounds and sores	Topical	6
<i>Sansevieria hyacinthoides</i> (L.) Druce	Asparagaceae	Isikholokotho (EC); Mosekela tsebeng (NW)	Leaves	Swellings, burns, and wounds	Topical	6, 23
<i>Sarcophyte sanguinea</i> Sparrm. ssp. <i>sanguinea</i>	Balanophoraceae	Umavumbuka (EC)	Dried fruiting body	Acne and other skin blemishes	Topical	6, 25
<i>Sarcostemma viminale</i> L.	Apocynaceae	Umbelebele (EC)	Decoction of leaves	Skin itch	Topical	5
<i>Scabiosa columbaria</i> L.	Dipsacaceae	Makgha (EC); Thakoa-pitsi/selomi/ mamokhale/ moholungoane (FS)	Leaves, roots	Wounds, bruises, and cuts	Topical	6, 9, 24
<i>Scadoxus multiflorus</i> (Martyn) Raf.	Amaryllidaceae	Inkuphulwana (EC)	Bulb Infusion	Wounds and bruises	Topical	5
<i>Scadoxus puniceus</i> (L.) Frits and Nordal	Amaryllidaceae	Inkuphulwana (EC)	Bulbs and roots	Wound and skin ulcers	Topical	6, 22
<i>Schinus molle</i> L.	Anacardiaceae	Ipepile (EC); Pepper tree (WC)	Lotion of fruits	Eczema	Topical	5, 19
<i>Schofia afra</i> (L.) Thunb.	Fabaceae	Umquqoba (EC)	Bark decoction	Skin ulcers	Topical	5
<i>Schofia brachypetala</i> Sond.	Fabaceae	Ihluze/umgxamu/uvovovo (KZN)	Bark	Sores	Topical	10, 11, 12
<i>Scilla natalensis</i> Planch	Hyacinthaceae	-	Fresh bulbs	Boils and sores	Topical	6
<i>Scilla nervosa</i> (Burch.) Jessop	Asparagaceae	Inkwitelu (EC)	Bulb ointment	Wounds and ringworm	Topical	5

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Sclerocarya birrea</i> (A. Rich) Hochst., ssp. <i>caffra</i>	Anacardiaceae	Umganu (KZN)	Bark and leaves	Sores	Topical	10, 11, 16, 23
<i>Scutia myrtila</i> (Burm.f.) Kurz	Rhamnaceae	Isiphingo (EC)	Paste Leaves	Ringworm	Topical	5
<i>Searsia lancea</i> (L.f.) F.A. Barkley	Anacardiaceae	Mushakaladzane (L); Mosinabele/ mositabele (FS)	Leaves	Rash and pimples	Topical	16, 24
<i>Selaginella caffrorum</i> (Milde) Hieron	Selaginaceae		Leaves	Herps and ulcers	Topical	24
<i>Senecio asperulus</i> DC.	Asteraceae	Moferefer/ Letapisa (FS)	Whole plant	Herpes sores/skin ulcers, and mouth ulcers	Topical, oral	24
<i>Senecio deltoideus</i> Less.	Asteraceae	Ityolo (EC)	Leaf lotion	Scabies and burns	Topical	5
<i>Senecio longiflorus</i> (DC). Sch. Bip	Asteraceae	Mosiama (NW)	Whole plant	Athlete's foot, chicken pox, eczema, Kaposi sarcoma, molluscum contagiosum, rash syphilis, and yaws	Topical	23
<i>Senecio serrnutooides</i> DC.	Asteraceae	Ichazampukane/ Insukumbili/ Umaphozisa/ Umkhuthelo (KZN)	Leaves	Sores and shingles	Topical	10, 11
<i>Senecio speciosus</i> Willd.	Asteraceae	Ustukumbini (EC)	Leaves, stem	Swellings, cuts, burns, and sores		7, 9
<i>Senna italica</i> Mill ssp. <i>arachoides</i> Burch Lock.	Fabaceae	Sebetebete (NW)	Whole plant	Chickenpox	Topical	23
<i>Senna occidentalis</i> (L.) Link	Fabaceae	Nembenembe/ Munembenembe (L)	Leaves	Skin burns and wounds	Topical	16

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Setaria acromelaena</i> (Hochst.) T. Durand & Schinz	Poaceae	Xihovane (L)	Stem	Sores	Topical	16
<i>Sida pseudocardifolia</i> Hochr.	Malvaceae	Mutudo (L)	Whole plant	Ringworm	Topical	10, 16
<i>Sideroxylon inerme</i> C.A.Sm.	Sapotaceae	Unqwashu (EC)	Decoction of leaves	Remove body odour	Bathing	5, 6
<i>Siphonochilus aethiopicus</i> Schweif.	Zingiberaceae	Ingungulo/ isiphephetho (KZN); Serokolo (NW)	Leaves	Oral thrush and chickenpox	Oral, topical	6, 23
<i>Solanum aculeastrum</i> Dunal.	Solanaceae	Umthuma (EC); Gifapple (WC)	Decoction of fruit	Insect bite, strengthen nails, perfume skin, and skin ulcers	Topical	5, 19
<i>Solanum aculeatissimum</i> Jacq.	Solanaceae	-	Leaves	Wounds	Topical	24
<i>Solanum catombelense</i> Peyr	Solanaceae	Morolwana (NW)	Whole plant	Chickenpox, fleabites, Kaposi sarcoma, rash, and sores	Topical	23
<i>Solanum incanum</i> L. Ruiz and Pav.	Solanaceae	Umthuma (EC)	Leaves, roots, fruits	Wounds, furuncles, and ringworm, and scars	Topical	6, 9, 22
<i>Solanum lichtensteinii</i> Willd.	Solanaceae	Tolwane (NW)	Whole plant	Burns	Topical	23
<i>Solanum nigrum</i> L.	Solanaceae	Umsobosobo (EC); Morotho (FS)	Paste of leaves	Ringworm	Topical	5, 24
<i>Solanum panduriforme</i> E. Mey.	Solanaceae	Mututulwa (L)	Fruits	Warts	Topical	11, 14, 16
<i>Solanum rigescens</i> Jacq.	Solanaceae	Mtuma (KZN)	Fruits	Boils	Topical	10, 11
<i>Solanum tuberosum</i> L.	Solanaceae	Potato	Tubers	Rash	Topical	16

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Sonchus oleraceus</i> DC.	Asteraceae	Leshoabe/ sentlokojane/ sethokojane (FS)	Leaves	Rash	Topical	24
<i>Sorghum bicolor</i> (L.) Moench	Poaceae	Mabele (NW)	Grains	Chickenpox	Topical	23
<i>Sporostachys africana</i> Sond.	Euphorbiaceae	Umthombothi (EC)	Bark	Rashes on newborn babies, nappy rashes, wounds, birth wounds, and pimples	Topical	9
<i>Stapelia gigantea</i> N.E. Br	Apocynaceae	Menoanoga (NW)	Whole plant	Kaposi sarcoma and molluscum contagiosum	Topical	16
<i>Striga asiatica</i> (L.) Kuntze	Orobanchaceae	Vhuri (L)	Whole plant	Wounds	Topical	10, 11
<i>Strychnos madagascariensis</i> Poir.	Loganiaceae	Umgluguzal/ umkwakwa (KZN)	Bark	Sores, burns, sores, and ringworm	Topical	10, 11, 16
<i>Strychnos spinosa</i> Lam.	Loganiaceae	Ihlala (KZN); Muramba (L)	Fruit sap	Sores	Topical	10, 11, 16
<i>Sutherlandia frutescens</i> (L.) R.Br.	Fabaceae	Ummwele (EC); Cancer bush/ kankerbos (WC); Lerumolamadi (NW)	Leaves	Wounds and skin cancer	Topical	6, 9, 19, 23
<i>Synadenium cupulare</i> (Boiss.) L. C. Wheeler	Euphorbiaceae	Muswoswo (L)	Stem	Moles	Topical	16
<i>Syzygium cordatum</i> Hochst.ex C. Krauss	Myrtaceae	Umswi (EC); Umdoni (KZN)	Bark, leaves	Blisters, pimples, inflammations, acne, and eczema	Topical	6, 9, 10, 11, 18
<i>Tabernaemontana elegans</i> Stapf.	Apocynaceae	Umkhahlwana/umkhadlu (KZN); Mubatu (L)	Bark and leaves	Sores and ringworms	Topical	10, 11, 16
<i>Talinum portulacaifolium</i> (Forssk.) Asch. ex Schweinf.	Talinaceae	Umhlabelo (EC)	Paste of leaves	Skin itch	Topical	5

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Taraxacum officinale</i> F.H. Wigg	Asteraceae	Ikhokhoyi (EC)	Decoction of leaves	Remove body odour	Bathing	5
<i>Tarchoananthus camphoratus</i> L.	Asteraceae	Mohatla Wadikonyana (NW)	Roots	Albinism	Topical	23
<i>Tecomaria capensis</i> (Thunb.) Spach.	Bignoniaceae	Umsilingi/leakatha (EC)	Bark	Inflammation	Topical	6
<i>Terminalia sericea</i> Burch. ex DC.	Combretaceae	Nkonono (L)	Leaves	Burns	Topical	11, 16, 22
<i>Tetradenia riparia</i> (Hochst)	Lamiaceae	Iboza (EC)	Leaves	Mouth ulcers	Oral	6
<i>Thesium strictum</i> P.J. Bergius	Santalaceae	Umbiza (EC)	Paste of leaves	Boils, wounds	Topical	5
<i>Trachyandra muricata</i> (L.f.) Kunth	Asphodelaceae	Olifant foot (WC)	Rhizome	Tired feet, athlete's foot, and blisters	Topical	19
<i>Tribulus terrestris</i> L.	Zygophyllaceae	Tshetho (NW); Inkunzane (EC)	Seeds, leaves	Chickenpox, eczema, infantile acropustulosis, hair loss, and scabies	Topical	5, 23
<i>Trichilia dregeana</i> Sond.	Meliaceae	Umkhuhlu (EC)	Seeds	Body ointment and hair oil	Topical	6
<i>Trichilia emetica</i> Vahl.	Meliaceae	Umkhuhlu (EC); Nkuhlu (L)	Leaves or fruits	Bruises and eczema	Topical	6, 9, 16, 22
<i>Tulbaghia alliacea</i> (L.f.) Thunb.	Amaryllidaceae	Itswele (EC)	Bulb	Boils, wounds, pimples, eczema, and herpes	Topical	6, 9
<i>Tulbaghia violacea</i> Harv.	Amaryllidaceae	Wildeknoffel/ wildeknoffok (WC); Uiswelane (EC); Isihaqa/ incinsini (KZN)	Whole plant	Wounds	Topical	21, 23
<i>Ursinia nana</i> DC. ssp. <i>nana</i>	Asteraceae		Whole plant	Wounds	Topical	24

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Mode of Administration	Ref
<i>Urtica urens</i> L.	Urticaceae		Whole plant	Wounds	Topical	24
<i>Vepris undulata</i> (Thunb.) I. Verd.	Rutaceae	Ilatile lokuqumisa (EC)	Decoction of leaves	Accelerate hair growth	Topical	5
<i>Vernonia fastigiata</i> Oliv. & Hiem	Asteraceae	Tany'i (L)	Leaves	Wound scars	Topical	16
<i>Vernonia natalensis</i> Sch.Bip. ex Walp	Valerianaceae	Umthi wezulu (EC)	Roots and leaves	Boils	Topical	6, 22
<i>Viscum capense</i> L.f.	Santalaceae	-	Whole plant	Warts	Topical	22
<i>Viscum meryharthii</i> Engl. & Schinz	Santalaceae	Lephakama (NW)	Stem	Kaposi sarcoma	Topical	23
<i>Wahlbergia banksiana</i> A.DC.	Campanulaceae		Roots	Syphilitic sores	Topical	24
<i>Waltheria indica</i> L.	Malvaceae	-	Roots	Burns and wounds	Topical	11
<i>Warburgia salutaris</i> (Bertol. F.) Chiov.	Canellaceae	Manaka/ shibaha (L)	Bark	Various skin complaints	Topical	6, 15
<i>Warburgia salutaris</i> (G. Bertol.) Chiov.	Canellaceae	Isibhaha (KZN)	Bark	Mouth sores	Oral	12, 18, 22
<i>Withania somnifera</i> (L.) Dunal	Solanaceae	Ubuvimba/Ubushwa (EC, KZN); Geneesbos (WC); Bofepha (FS)	Leaves and berries	Cuts, wounds, abscesses, inflammation, and soap, douche	Topical	6, 9, 11, 19, 24
<i>Ximения americana</i> L.	Oliaceae	Nisenghele	Roots, leaves	Inflamed eyes	Bathing	14
<i>Ximения caffra</i> Sond.	Oliaceae	Umthunduluka obomvu (KZN)	Twigs	Sores	Topical	11
<i>Xyssmalobium undulatum</i> (L.) Aiton F.	Poeynaceae	Nwachaba/Ishongwane (EC)	Roots	Cuts and wounds	Topical	6

(Continued)

TABLE 5.2 (CONTINUED)
South African Ethnomedicinal Plants of Dermatological and Immune Significance

Botanical Name	Family	Local Name	Part Used	Condition for Treatment	Administration	Ref
<i>Zantedeschia albomaculata</i> (Hook.) Baill ssp. <i>albomaculata</i>	Araceae	Mohalalaitoe (FS)	Leaves	Mouth ulcers	Oral	24
<i>Zantedeschia aethiopica</i> (L.) Spreng.	Araceae	Inyibiba (EC)	Leaves, rhizome	Wounds, burns, and sore throat	Topical	2, 6, 8, 13, 22
<i>Zanthoxylum capense</i> Harv.	Rutaceae	Isifutho (EC); Ummungamabele (KZN); Monokwane/khukungorupa (L); Knobwood (WC)	Leaves, roots, bark	Sores and toothache swollen feet	Topical	6, 11, 15, 19
<i>Zanthoxylum davyi</i> Waterm.	Rutaceae	Munungu (L)	Roots, Leaves, Stem	Wounds and teeth cleaning	Topical and oral	16
<i>Zea mays</i> L.	Poaceae	Umbona (EC); Mufhumbu ha mavhele (L)	Leaves, seeds	Wound, rash, and pimples	Topical	6, 16
<i>Ziziphus mucronata</i> Willd.	Rhamnaceae	Umphafa (EC); Umphafa/umlahlankosi/isilahla (KZN); Mokgalo/ mutsheishele/ mphasanhala/ mokgal6/ moonaona (L)	Leaves, roots, bark	Boils and swellings	Topical	6, 11, 15, 17, 22

Key: EC – Eastern Cape; FS – Free State; KZN – KwaZulu Natal; L – Limpopo; MP – Mpumalanga; NC – Northern Cape; NW – North West; WC – Western Cape
 1. Maroyi (2019); 2. Buwa-Komoreng et al. (2019); 3. Bhat (2013); 4. Bhat (2014); 5. Afolayan et al. (2014); 6. Sagbo and Mbeng (2018); 7. Grierson and Afolayan (1999); 8. Weideman (2005); 9. Mahachi (2013); 10. de Wet et al. (2013); 11. Nciki et al. (2016); 12. Coopoosamy and Naidoo (2012); 13. Ghuman et al. (2016); 14. Shikwambana and Mahlo (2020); 15. Rasethle et al. (2019); 16. Setshego et al. (2020); 17. Mongalo and Makhafola (2018); 18. Grace et al. (2003); 19. Aston Philander (2011); 20. Thring and Weitz (2006); 21. Mntsa Mi Nzue (2009); 22. Mabona et al. (2013); 23. Asong et al. (2019); 24. Moteete and Kose (2017); 25. Komoreng et al. (2019); 26. Lall and Kishore (2014).

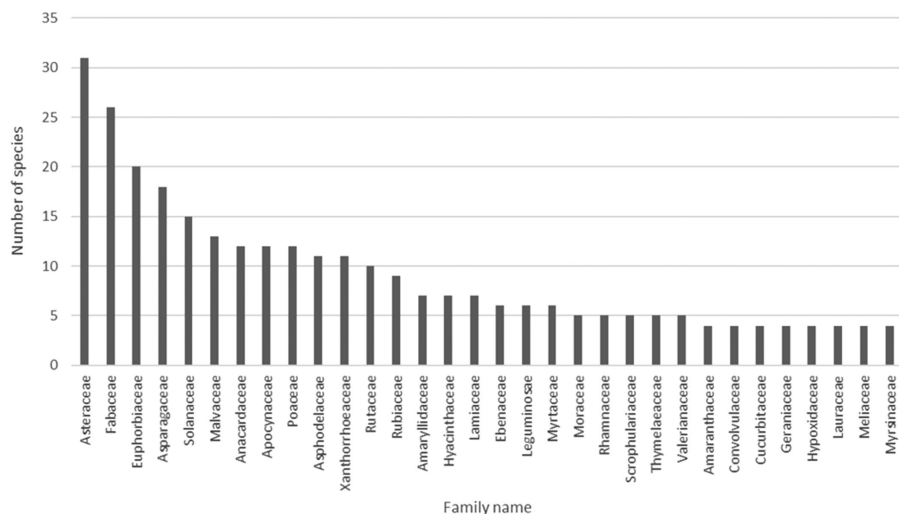


FIGURE 5.1 Some plant species of dermatological significance in South Africa.

world's largest documented consumer of these products (Davids et al., 2016). The use of chemicals, such as mercury and hydroquinone, are the major causes of these toxic effects. This led to the banning of hydroquinone in cosmetics in draft legislation in 1988 (Thomas, 2012). Nevertheless, history indicates the use of medicinal plants for skin lightening with little or no side effects. However, the use of herbs to boost the immune system achieves this goal by softening the skin and protecting the skin against ultraviolet (UV) radiation from the sun. Some compounds from these medicinal plants have been shown to inhibit UV-induced development of squamous cell carcinomas, or simply to guard against cutaneous damage caused by UV irradiation (Tabassum and Hamdani 2014). The study of Heo et al. (2001) was able to show that the ethanol extract of *Prunus persica* was able to inhibit UVB- or UVC-induced lipid peroxidation in skin fibroblast cells. Perhaps the revitalization of medicinal plant use in cosmetics could lead to other avenues, such as their domestication and eventual cultivation. These plants have little or no side effects, even after long-term use, in comparison with the harsh synthetic chemicals that often leave the skin without melanin and damaged beyond any prospects of repair. Most of the users of skin lightening products are poor and cannot afford the expensive treatment regimes. Some of the medicinal plants, such as lemons, avocados, potatoes, sorghum, and others reported in this work, are common foods which are highly nutritious and therefore play a dual role, as topical skincare applications and as a source of nutrition to boost the immune system. Orally administered medicines have, in times past, been reported to also possess nutritional benefits, so that, whereas the compounds target the pathogens, the nutritional composition of the medicine boosts the immune system, leading to a quicker recovery.

5.5 COMMON METHODS OF PREPARATION

The literature survey revealed that the medicinal plants identified as being effective in skincare strategies are used for wounds (18%), sores (11%), cosmetics (8%), burns (8%), allergies (8%), boils (6%) and eczema (5%), among other conditions, as shown in Figure 5.2. Other conditions that are treated by these medicinal plants and that appear in the literature search, as shown in Table 5.2, include leprosy, impetigo, condylomata acuminata, madura foot, painkilling effect on skin, sore throat, corns, drawing out pus, sore mouth, keratosis, pearl penile papules, and molluscum contagiosum.

Topical administration (84%) is the most common form of administering the medicinal plant preparation, followed by bathing (6%) and oral consumption (3%), as shown in Figure 5.3. The same plant preparation can be administered both topically and orally or in a bath and orally. However, *Albizia anthelmintica*, a plant mentioned in the treatment of lymphatic filariasis is also administered orally. Other orally administered plants are used either for cleaning teeth or for the treatment of gums, sore throat, oral thrush, and/or mouth ulcers. A total of six plant species are reportedly mixed with lotion/ glycerin to ensure that the product sticks to the skin. Several authors, including Lordani et al. (2018), reported on this mode of application of medicinal plant preparations.

5.6 SUSTAINABLE UTILIZATION AND CONSERVATION OF PLANTS FOR SKIN THERAPY

This current literature survey reveals that the leaves are the plant parts most used for herbal preparations, accounting for 47% of usage, while the bark (14%) and roots

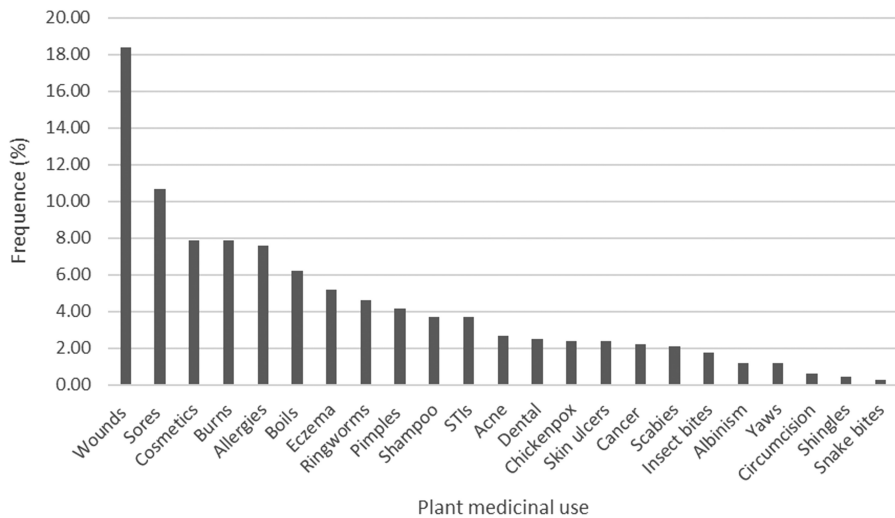


FIGURE 5.2 The medicinal uses of the plants.

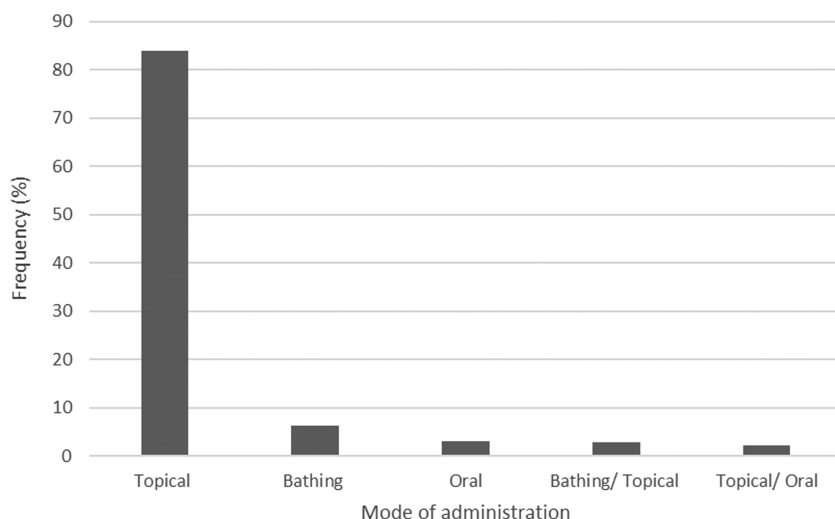


FIGURE 5.3 Mode of administration of medicinal plants.

(13%) also play a significant role (Figure 5.4), with other plant parts contributing less than 10% each. The use of the whole plant and roots is of significance. This is because these harvesting methods are destructive and therefore pay little attention to biodiversity conservation. In fact, the greatest proportion of documented plant species becoming extinct in the world has been reported in South Africa. A total of sixty-four plant species has not been seen in more than fifty years and their habitat has been destroyed, while thirty-nine species are extinct (Raimondo et al. 2013). As of 2020, SANBI (2020) lists South Africa's threatened flora in the order: Western Cape (63.8% species are threatened) > Northern Cape (13.9 %) > Eastern Cape (9.7%) > KwaZulu Natal (8.1%) > Mpumalanga (4.6%) > Limpopo (3.3%) > Gauteng (0.8%) > North West (0.7%) > Free State (0.2%). As of 2014, about 172 plant taxa had been listed as "protected" under the South African National Environmental Management: Biodiversity Act (NEMBA); Act No. 10 of 2004 (Raimondo 2015). However, the updated list (SANBI 2020) shows the proportion of protected taxa in each of South Africa's nine biomes as follows: Albany Thicket (11.9%), Desert (30.3%), Forest (40.8%), Fynbos (22.7%), Grassland (4.5%), Indian Ocean Coastal Belt (7.1%), Nama Karoo (1.6%), Savanna (13.4%), and Succulent Karoo (7.8%). Habitat loss, habitat degradation, invasive alien species, overharvesting of medicinal plants, demographic factors, pollution, climate change, and natural disasters are the major driving forces behind medicinal plant extinction in South Africa. Current SANBI (2020) statistics indicate that, between 1990 and 2018, about 5% of the taxa increased in threat status. Furthermore, about 40% of the increased threat to medicinal plants over the past twenty years has been caused by invasive species. Other threats, such as habitat invasion due to livestock overgrazing, urban development, and crop cultivation, has contributed 11, 20, and 33%, respectively.

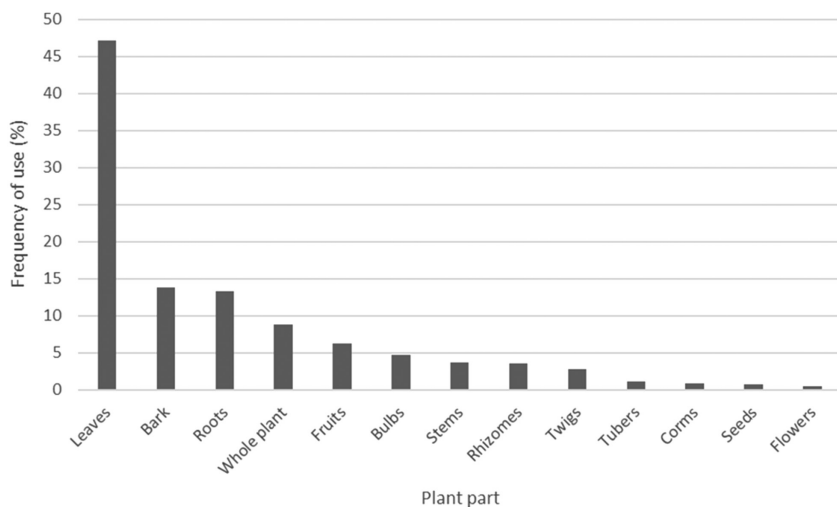


FIGURE 5.4 Plant parts used of plant species of dermatological significance in South Africa.

The need for protection of South Africa's biodiversity and for implementation of the various conservation strategies is clear. In fact, the draft policy on African Traditional Medicine Notice 906 of 2008 (South Africa 2008) is an attempt to protect not only biodiversity but also the African traditional herbal medicine knowledge. This legislation specifically makes it illegal to harvest plants from the wild without permission from the relevant authorities. To ensure protection of biodiversity due to habitat loss or degradation, *in-situ* and *ex-situ* conservation strategies have been put in place. South Africa currently has seventeen national parks, eight natural Transfrontier Conservation Areas, and numerous private parks, wild nurseries, and forest reserves. These *in-situ* conservation areas play a huge role in the protection of biodiversity, including that of medicinal plants. *Ex-situ* conservation strategies in place in South Africa include seventeen national botanic gardens and numerous seed banks. Research on the domestication of medicinal plants in South Africa has been on-going for more than ten years. This research aims to bring medicinal plants under cultivation to put less pressure on harvesting these resources from the wild. Although these strategies may not be able to replicate the exact growing conditions of plants in the wild, this a step in the right direction. Researchers now know that the polyphenolic compounds produced by plants in the wild change when these plants are cultivated either under controlled conditions or in environments other than their original habitats. Scientists therefore need to focus more on how to stimulate the production of specific bioactive compounds under controlled environments or in other habitats. More importantly, biodiversity protection rules and regulations put in place by the government need to be adhered to.

5.7 CONCLUSION

South Africa is richly endowed with numerous medicinal plants that are used in the treatment of various skin-related diseases and conditions. Most of the plants are used to treat wounds, although a sizeable proportion has immunological functions, for use, for example, in cosmetics. The preferred mode of administering medicinal plant preparations is topical, and the leaves are the most used plant parts. Although South Africa contains more than 400 species with dermatological uses, care needs to be taken to ensure that the legislation put in place by the government to protect these species is adhered to and administered. Habitat degradation and/or loss, overharvesting and natural disasters are some of the major threats to these plants' survival. There is therefore a need to constantly raise awareness of these important species by educating the public on the importance of protecting them. If these species are neglected and their knowledge is not passed on to future generations, their risk of extinction, which is already high, will increase further, and this will leave future generations with nothing.

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6 Traditional African Medicinal Plants for a Strong Immune System

Anywar Godwin

CONTENTS

6.1	Introduction	173
6.2	Immunomodulatory Agents from Plants	174
6.3	Mechanisms of Action of Immunomodulatory Agents from Plants	175
6.4	Medicinal Plants Used in African Traditional Medicine for Immunomodulation	175
6.5	Commercial Formulations of African Medicinal Plants for Strengthening Immunity.....	186
6.6	Conclusion	186
	References.....	187

6.1 INTRODUCTION

Africa is disproportionately affected by diseases such as HIV/AIDS, which attack and destroy the immune system. More than 68% of the 38 million people globally affected by HIV/AIDS reside in sub-Saharan Africa (UNAIDS 2020). Furthermore, many of them do not have access to modern treatment facilities or medicines.

The immune system consists of a highly complex mechanism for defending the body against disease by identifying and killing pathogens or tumour cells (Gertsch et al. 2011; Wen et al. 2012; Wynn et al. 2013). It is composed of the innate and adaptive immune systems. The former is characterized by a non-specific response of cells *via* molecular interactions and the expression of inducible cytokines and chemokines, whereas the latter consists of specialized effector cells (T and B cells) which recognize antigens, that are processed and presented by macrophages and dendritic cells. This leads to the activation of cytotoxic T cells and generation of antibodies which are pivotal in eliminating or preventing pathogenic insults (Gertsch et al. 2011; Kuwabara et al. 2017).

Conventionally, disorders of the immune system are categorised as: (i) primary immune deficiencies, which occur when one is born with a weak immune system, such as severe combined immunodeficiency (SCID), (ii) acquired immune

deficiencies, which occur when one catches a disease that weakens the immune system, such as HIV/AIDS, (iii) overactive immune systems, which occur when one's immune system is too active, e.g., in allergic reactions, and (iv) autoimmune diseases, which occur when one's immune system attacks itself, e.g., type 1 diabetes and rheumatoid arthritis (Murphy and Weaver 2016). However, in African traditional medicine, diseases of the immune system are looked at from the perspective of immune deficiencies, particularly HIV/AIDS or cancer. This chapter focuses on the use of medicinal plants on immune disorders only in the category of acquired immune deficiencies.

Immunomodulators are biological or synthetic biomolecules which have the ability to regulate, suppress, or stimulate any components of the immune system (Puri et al. 1994; Jantan et al. 2015). They are also referred to as immunorestoratives, immunoaugmentors, or biological response modifiers (Jantan et al. 2015). Immunomodulators are categorized as immunostimulants, immunoadjuvants, or immunosuppressants. Immunostimulants activate or stimulate the immune system mediators, resulting in improved resistance against various infections and restoration of compromised immunity (Saxena et al. 2008; Kumar et al. 2011; Jantan et al. 2015; Raj and Gothandam 2015). Immunomodulators can be used to stimulate the immune system to reduce drug side effect (Prendergast and Jaffee 2007). Immunoadjuvants are specific immune stimulators which boost vaccine efficacy (Leroux-Roels 2010). Immunosuppressants inhibit the immune system and can be used to control pathological immune reactions (Chatterjee et al. 1988; Jantan et al. 2015). Overall, the present chapter explores the most recent scientific evidence supporting the employment of some widely used African medicinal plant species with proven immunomodulatory activity. Additionally, the phytochemistry, mode of action, and toxicity of these plant species are discussed in relation to traditional uses of these plant species.

6.2 IMMUNOMODULATORY AGENTS FROM PLANTS

Unfortunately, most immunostimulants and immunosuppressants in clinical use are cytotoxic (Leroux-Roels, 2010; Jantan et al. 2015). Many of the immunomodulating biological agents approved for use by the Food and Drug Authority in the USA have been reported to have a wide array of unintended, sometimes fatal side effects. For instance, rituximab use was associated with a higher incidence of serious infections, particularly in patients with profound CD4 lymphopaenia (Koo et al. 2010). On the contrary, natural products are known to have many advantages, such as nontoxicity, ease of preparation and application, and greater safety, and accessibility (Oršolić & Bašić 2003; Lotter-Stark et al. 2012; Mukherjee et al. 2014).

Several plant species have been regularly used in traditional medicine to treat immune system disorders (Fernandez et al. 2002; Sultan et al. 2014; Anywar et al. 2020a) and are a potential source of immunomodulating agents (Williams 2001). Different studies have shown novel and significant immunomodulatory activities from various plant species (Puri et al. 2000; Reis et al. 2008; Karunai Raj et al. 2012; Arthanari et al. 2013; Sultan et al. 2014; Mukherjee et al. 2015; Raj & Gothandam 2015;

Hasson et al. 2019; Olwenyi et al., 2021). This emphasizes the need to search for novel immunomodulatory agents from natural sources (Raj and Gothandam, 2015).

6.3 MECHANISMS OF ACTION OF IMMUNOMODULATORY AGENTS FROM PLANTS

A compromised immune system can lead to the development of several serious chronic diseases (Gertsch et al. 2011; Wen et al. 2012; Abbas et al. 2019) such as AIDS, the most widespread immunosuppressive disease globally (Gea-Banacloche 2006). In such cases, maintenance of the immune system by means of medication can be achieved, using herbal medicines. Herbal medicines which function as immunomodulators alter the activity of immune function through the dynamic regulation of informational molecules, such as cytokines (Spelman et al. 2006).

Cytokines are secreted proteins that regulate immune responses through growth, differentiation, and activation functions. They are involved in almost all aspects of immunity and inflammation. Different combinations of cytokines are produced in response to specific immune insults (Steinke and Borish 2006). The modulation of cytokine secretion may offer novel approaches in the treatment of a variety of diseases. The cytokines include interleukins (IL), such as IL-2, IL-4, IL-17 (Vitetta et al. 1985; Dembic 2015; Kuwabara et al. 2017), interferons (IFNs) such as IFN- γ (Tau and Rothman 1999; Kak et al. 2018) and TNF- α (Pfeffer 2003; Bradley 2008). Some of the better known and more widely used medicinal plant species in Africa for stimulating or modulating the immune system exert their immunomodulatory effects through various mechanisms, as illustrated in Table 6.1. Some of these mechanisms include the induction of various cytokines, such as IFN- α and - β (Beuscher et al. 1994; Ngure et al. 2014), triggering the alternative complement pathway, raising the number and distribution of white blood cells, stimulating phagocytosis, T-cell production, or lymphocytic activity (El-Ashmawy et al. 2015), inducing apoptosis, suppression of cell proliferation, inhibition of pro-inflammatory cytokine/chemokine production, and increasing anti-inflammatory cytokine production (Rieder et al. 2010).

6.4 MEDICINAL PLANTS USED IN AFRICAN TRADITIONAL MEDICINE FOR IMMUNOMODULATION

This review was carried out on the relevant articles, books, theses, dissertations, patents, and other English-only reports on ethnobotany, immunomodulatory profiles, pharmacological or biological activity, toxicity, or phytochemistry, of selected medicinal plant species in Africa used by herbalists in boosting or modulating the immune system. We searched databases, such as PubMed, Web of Science, Scopus, and Science Direct, and search engines, such as Google Scholar. **Table 6.1** shows nineteen medicinal plant species with proven immunomodulatory activity used in African traditional medicine for immune-related disorders. The table also shows their mode of action, the identity of their bioactive molecules, as well their toxicity *in vitro*.

TABLE 6.1
Medicinal Plant Species Used in African Traditional Medicine for Strong immunomodulation

Scientific name and Family	Traditional Uses Related to Immune Disorders	Immunomodulatory Activity and Mode of Action	Phytochemical Composition	Toxicity /cytotoxicity
1. <i>Aerva lanata</i> (L.) Juss. Amaranthaceae	Low/compromized immunity to HIV (Anywar et al. 2020a).	The ethanolic extract of the whole plant produced an increase in total WBC count, bone marrow cellularity, number of α -esterase-positive cells in BALB/c mice, proliferation of splenocytes, thymocytes and bone marrow cells (Nevin and Vijayammal, 2005; Siveen & Kuttan, 2011).	Phenolic compounds e.g. gallic acid, apigeitin, rutin, myricetin, saponins, flavonoids, tannins and phytosterols (Kumar et al. 2013)	The aqueous whole plant extract is relatively safe ($LD_{50} = 22.62$ g/kg bw) in albino mice (Omotoso et al. 2017). The aqueous stem extract was nontoxic to human erythrocytes ($IC_{50} = 24.89$ mg/ml) (Kumar et al. 2013). The ethanol extract is cytotoxic to Dalton's lymphoma ascites and Ehrlich ascites carcinoma cells at 500 μ g/ml. The extract was also cytotoxic to L929 and HeLa cells at higher concentrations (Siveen and Kuttan, 2011).

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TABLE 6.1 (CONTINUED)
Medicinal Plant Species Used in African Traditional Medicine for Strong immunomodulation

Scientific name and Family	Traditional Uses Related to Immune Disorders	Immunomodulatory Activity and Mode of Action	Phytochemical Composition	Toxicity /cytotoxicity
2. <i>Aloe vera</i> (L.) Burm.f. <i>Asphodelaceae</i>	Low/compromized immunity to HIV (Anywar et al. 2020a)	The decolorized leaf extract of <i>A. vera</i> showed immunomodulatory activity by significantly increasing the activation of T lymphocytes, monocytes and expression of CD25 & CD69 glycoproteins of NK cells in PBMCs (Ingles et al. 2017). <i>A. vera</i> gel ameliorates cyclophosphamide-induced immunotoxicity in rats by activating Peyer's patch cells to produce cytokines (Im et al. 2014). Acemannan from <i>A. vera</i> reduced mortality in irradiated Swiss albino mice by inducing haematopoiesis and upregulation of cytokines e.g. TNF- α and IL-1 (Kumar and Tiku 2016).	Polysaccharides: glucomannan and acemannan; carboxypeptidase, saponins, sterols, amino acids, anthraquinone, enzymes, glycosides: aloin, aloe-emodin, barbaloin (Reynolds & Dweck, 1999; Reynolds, 2004; Augustino et al. 2011)	Acute and sub-acute tests on Wistar rats using the methanol extract (16 g/kg bw) did not show significant toxic effect (Saritha and Anilakumar, 2010). The aqueous leaf extract is toxic (LD ₅₀ = 120.65 g/kg bw) in Swiss albino mice (Lagarto et al. 2001) and induces toxic hepatitis (Lee et al. 2014).
3. <i>Allium cepa</i> L. Amaryllidaceae	Tuberculosis (TB) (Nguta et al. 2015), low immunity in HIV (Anywar et al. 2020b)	Onion fructo-oligosaccharides from <i>A. cepa</i> significantly increased the proliferation of mouse splenocytes/thymocytes, enhanced the production of NO, intracellular free radicals and phagocytic activity in Wistar rats (Kumar et al. 2015).	Quercetin, phenolics (Prakash et al. 2007).	The crude extract is cytotoxic against tumoral Lucena multidrug-resistant (MDR) human erythroleukaemic and K562 cell lines (Votto et al. 2010). Excessive

(Continued)

TABLE 6.1 (CONTINUED)
Medicinal Plant Species Used in African Traditional Medicine for Strong immunomodulation

Scientific name and Family	Traditional Uses		Phytochemical Composition	Toxicity /cytotoxicity
	Related to Immune Disorders	Immunomodulatory Activity and Mode of Action		
4. <i>Allium sativum</i> L. Amaryllidaceae	Infections (Koch and Lawson, 1996), cough, low immunity (Anywar et al. 2020a)	Garlic organo-sulphur compounds cause various immune responses (Schafer and Kaschula, 2014). Incubation of PBMCs with alliin produced a significant increase in spontaneous IL-1b production (Salman et al. 1999).	Diallyl thio-sulphinate (allicin), allyl methyl thiosulphinate, methyl allyl thiosulphinate, ajoene, alliin, deoxyalliin, diallyl disulphide and diallyl trisulphide (Weber et al. 1992).	Generally safe (Borrelli et al. 2007) but can cause gastrointestinal discomfort, nausea, bloating, headache, dizziness, profuse sweating when excessively consumed (Rose et al. 1990; Beck and Grunwald 1993; Borrelli et al. 2007).
5. <i>Carica papaya</i> L. Caricaceae	Cough, low immunity (Tugume et al. 2016), skin infections (Anywar et al. 2020a).	The aqueous extract of <i>C. papaya</i> (150 mg/kg) caused an increase in thrombocytes, delayed-type hypersensitivity response, and mediated the release of platelets in rats (Anjum et al. 2017). The extract caused a reduction in the production of IL-2 and IL-4, and an increase in IL-12p40, IL-12p70, IFN- γ and TNF- α in PBMC (Otsuki et al. 2010).	Polysaccharides, glycosides, saponins, flavonoids and phytosterols (Saeed et al. 2014), myricetin, caffeic acid, <i>trans</i> -ferulic acid and kaempferol (Anjum et al. 2017)	Sub-acute oral toxicity tests of the leaf extracts in Sprague Dawley rats at 14 times the levels used in traditional medicine in Malaysia is safe (Afzan et al. 2012; Ismail et al. 2014).
6. <i>Cannabis sativa</i> L. Cannabaceae	TB, low/compromized immunity in HIV (Anywar et al. 2020a; 2020b).	Cannabinoids modulate immune responses during inflammatory processes <i>via</i> (i) cell proliferation, (ii) inhibition of pro-inflammatory cytokine/chemokine production, (iii) increase in anti-inflammatory cytokines, (iv) induction of regulatory T cells (Rieder et al. 2010) and (v) epigenetic regulation involving histone modifications (Yang et al. 2014).	Phytocannabinoids, e.g., delta8-tetrahydrocannabinol, cannabigerol, cannabidiol (Russo 2011).	Frequent and prolonged use produces both mental and physical impairment, mood disorders, exacerbation of psychotic disorders in vulnerable people, cannabis use disorders, withdrawal syndrome, neurocognitive impairments, cardiovascular, and respiratory diseases (Smith, 1968; Karila et al. 2014).

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TABLE 6.1 (CONTINUED)
Medicinal Plant Species Used in African Traditional Medicine for Strong Immunomodulation

Scientific name and Family	Traditional Uses		Phytochemical Composition	Toxicity /cytotoxicity
	Related to Immune Disorders	Immunomodulatory Activity and Mode of Action		
7. <i>Centella asiatica</i> (L.) Urb. Apiaceae	Dermatitis (Ssegawa and Kasenene 2007), skin infections, low/compromized immunity in HIV (Anywar et al. 2020a; 2020b)	<i>C. asiatica</i> produced non-specific cellular and humoral immune responses in PBMCs, significantly increased proliferation and production of IL-2 and TNF- α and showed higher responses to both primary and secondary antibodies against Bovine Serum Albumin antibodies in BALB/c mice (Punturee et al. 2005).	Asiaticoside, asiatic and madecassic acids (Kwon et al. 2014). Tannins, essential oils, phyosterols, mucilages, resins, flavonoids, alkaloids (hydrochotone), vallerine, fatty acids (linoleic, linoleic, oleic, palmitic, and stearic acids) (Srivastava and Vaidya 1999)	The acetone extract was non-toxic in Swiss mice (LD ₅₀ < 4000mg/kg bw) (Chauhan and Singh 2012) and the crude extracts were non-toxic to normal human lymphocytes (Babu et al. 1995).
8. <i>Curcuma longa</i> L. Zingiberaceae	Low/compromized immunity in HIV (Anywar et al. 2020a)	Alpha-turmerone and aromatic-turmerone showed stimulatory effects on human PBMC proliferation & cytokine production (Yue et al. 2010).	Curcuminoids, e.g., curcumin, demethoxycurcumin, bisdemethoxycurcumin and α -turmerone (Yue et al. 2010; Ankur et al. 2015), fisetin, quercetin, and myricetin (Lako et al. 2007), α - and β -turmerone, α -santalene, aromatic-curcumene, oleoresins (Singh et al. 2010).	Powder/ alcoholic extract is not toxic at 10 g/kg bw (LD ₅₀ > 15 g/kg bw) in Swiss albino mice (Sittisomwong et al. 1990) or guinea pigs and monkeys (300 mg/kg – 2.5 g/kg, respectively) (Shankar et al. 1980). The essential oil is safe up to 0.5 g/kg bw in Wistar rats and is not mutagenic/genotoxic when orally administered (Liju et al. 2013).

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TABLE 6.1 (CONTINUED)
Medicinal Plant Species Used in African Traditional Medicine for Strong immunomodulation

Scientific name and Family	Traditional Uses		Phytochemical Composition	Toxicity /cytotoxicity
	Related to Immune Disorders	Immunomodulatory Activity and Mode of Action		
9. <i>Jatropha curcas</i> L. Euphorbiaceae	Low/compromized immunity in HIV (Anywar et al. 2020ba)	An 80% aqueous methanol extract & some of its compounds, e.g., biapigenin, apigenin, orientin and vitexin stimulated both humoral and cell-mediated seroresponse in one-day-old specific pathogen-free chicks (Abd-Alla et al. 2009).	Jatrophalactone, jatrophalone, jatrophadiketone (Liu et al. 2012), curcuseone B (Devappa, et al. 2011), curcin (Luo et al. 2007), phorbol esters (Li et al. 2010), biflavone di-C-glucoside, apigenin 7-O- β -D- galactoside, orientin, vitexin, vicenin and apigenin (Abd-Alla et al. 2009), Protocatechic acid, catechin, mangiferin, alanine, glycine, γ -aminobutyric acid (Scartezzini and Speroni 2000), triterpenoids and flavonoids.	Known to be toxic and causes nausea, vomiting, and abdominal cramps (Joubert et al. 1984; Mampane et al. 1987). The purified phorbol esters from the oil are highly toxic to Swiss Hauschka mice (LD ₅₀ = 27.34 mg/kg bw (Li et al. 2010).
10. <i>Mangifera indica</i> L. Anacardiaceae	Skin infections, low/compromized immunity in HIV (Anywar et al. 2020a; 2020b)	Has immunomodulatory properties (Núñez-Sellés 2005). An extract with 2.6 % mangiferin caused an increase in humoral antibody titre and delayed type- hypersensitivity in mice (Makare et al. 2001). Vimang, an extract from <i>M. indica</i> containing mangiferin, a glucosylxanthone, modulates the activation and functionality of macrophages, through partial inhibition of chemotactic migration, phagocytic activity, ROS & RNS production (García et al. 2002).		Leaf extracts are non-toxic in ICR mice in acute and long-term toxicity studies up to 18.4 g/kg bw (Zhang et al. 2014) and are not genotoxic or clastogenic <i>in vivo</i> (Reddeman et al. 2019).

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TABLE 6.1 (CONTINUED)
Medicinal Plant Species Used in African Traditional Medicine for Strong immunomodulation

Scientific name and Family	Traditional Uses Related to Immune Disorders	Immunomodulatory Activity and Mode of Action	Phytochemical Composition	Toxicity /cytotoxicity
11. <i>Moringa oleifera</i> Lam Moringaceae	Low/compromized immunity in HIV (Anywar et al. 2020b)	The methanolic leaf extract caused an increase in WBC, lymphocyte and neutrophil counts at 1000 mg/kg bw comparable to levamisole, the standard drug (Nfambi et al. 2015). The ethanolic extract stimulates IgG, IgM and IgA production in Sprague Dawley male rats and neutralized haematoimmune toxic hazards (Abd-Elhakim et al. 2018). <i>M. oleifera</i> seed lectin protein induced the release of TNF- α , IL-2, IL-6, IL-10 and NO, and achieved activation of CD8+ T lymphocytes in PBMCs, promoting immunomodulation (Coriolano et al. 2018). A 50% ethanolic leaf extract caused a significant increase in WBC, neutrophils, thymus, and spleen weight in normal and cyclophosphamide-immunosuppressed mice (Anamika et al. 2010).	Alkaloids, polyphenols, flavonoids, anthraquinones, coumarins, tannins, triterpenes, sterols, and saponins (Dzotam et al. 2016).	Leaves are genotoxic at supra-supplementation levels of 3000 mg/kg bw but are safe at \leq 1000 mg/kg bw in rats (Asare et al. 2012), in male Wistar albino mice (LD_{50} = 1585 mg/kg) (Awodele et al. 2012) and in Swiss albino mice (LD_{50} = 17.8 g/kg) (Kasolo et al. 2011).

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TABLE 6.1 (CONTINUED)
Medicinal Plant Species Used in African Traditional Medicine for Strong immunomodulation

Scientific name and Family	Traditional Uses		Phytochemical Composition	Toxicity /cytotoxicity
	Related to Immune Disorders	Immunomodulatory Activity and Mode of Action		
12. <i>Pelargonium sidoides</i> DC. Geraniaceae	Respiratory tract infections, e.g., TB (Brendler and van Wyk, 2008)	EPs® 7630, an aqueous-ethanolic formulation of <i>P. sidoides</i> extracts, induced TNF and IF in activated bone marrow-derived macrophages (Kolodziej et al. 2003). Has significant immunomodulatory properties (Kolodziej and Kiderlen 2007)	Coumarins, simple phenolics, gallic acid and proanthocyanidins (Kolodziej and Kayser 1998).	No evident toxic effect in mice (Theisen and Muller 2012)
13. <i>Persea americana</i> Mill. Lauraceae	HIV/AIDS infections (Nyamukuru et al. 2017), TB (Anywar et al. 2020a).	An arabinogalactan-protein-rich fraction showed inhibitory effects on the complement system (Yamassaki et al. 2018).	Quercetin, rutin, luteolin, apigenin (Owolabi et al. 2010).	Seed (LD ₅₀ > 10 g/kg) and leaf extracts (LD ₅₀ > 10 g/kg) were not toxic in rats (Adeyemi et al. 2002; Ozolua et al. 2009).
14. <i>Psidium guajava</i> L. Myrtaceae	Low/compromized immunity in HIV (Anywar et al. 2020b)	A fraction of guava seed polysaccharide (GSPS), GSF3, has potent immunomodulatory effects in female BALB/c mice against LPS-stimulated inflammation in macrophages <i>via</i> decreasing IL-6/IL-10 secretion ratio (Lin and Lin 2020)	Meroterpenoids (Qin et al. 2017).	The aqueous leaf extracts were not-toxic to rats/mice (LD ₅₀ > 5 g/kg, p.o.) at 100 times the recommended dose for treatment of diarrhoea (Jaiarj et al. 1999).

(Continued)

TABLE 6.1 (CONTINUED)
Medicinal Plant Species Used in African Traditional Medicine for Strong immunomodulation

Scientific name and Family	Traditional Uses Related to Immune Disorders	Immunomodulatory Activity and Mode of Action	Phytochemical Composition	Toxicity /cytotoxicity
15. <i>Punica granatum</i> L. Lythraceae	Inflammation, infections (Cowan 1999; Braga et al. 2005), low/compromized immunity in HIV (Anywar et al. 2020a)	The fruit rind powder stimulates cell-mediated and humoral components of the immune system in rabbits by provoking an increase in antibody titre to typhoid-H antigen and enhanced the inhibition of leucocyte migration (Gracious et al. 2001). A polysaccharide (PSP001) from <i>P. granatum</i> showed a stimulatory effect on the growth of isolated normal lymphocytes and haemagglutinating antibodies in Wistar male rats (Sin et al. 2019).	Phenolics (Rout & Banerjee 2007), galloitanins, ellagitannins, ellagic acid, and anthocyanins (Madrigal-Carballo et al. 2009).	The fruit extract was not toxic to the chick embryo model or at doses < 0.1 mg/g in either male or female OF-1 mice (LD ₅₀ = 731 mg/kg) i.p (Vidal et al. 2003).
16. <i>Sutherlandia frutescens</i> (L.) R.Br. Fabaceae	Cancers, infections, and inflammatory conditions insouthern Africa (Lei et al. 2016).	The crude aqueous extract or polysaccharide- enriched fraction of <i>S. frutescens</i> increased macrophage production of ROS and NO. <i>S. frutescens</i> activated NF- κ B signalling in murine macrophages, resulting in an increased production of TNF- α (Lei et al. 2016).	Triterpenoids, saponins, flavonoids, c-aminobutyric acid, pinitol and L-canavanine (van Wyk & Albrecht, 2008).	Potentially toxic because of L-canavanine (Rosenthal 1977). However, no toxicity or side effects were observed at the maximal dose of 81 mg/kg in vervet monkeys (Fernandes et al. 2004).

(Continued)

TABLE 6.1 (CONTINUED)
Medicinal Plant Species Used in African Traditional Medicine for Strong immunomodulation

Scientific name and Family	Traditional Uses Related to Immune Disorders	Immunomodulatory Activity and Mode of Action	Phytochemical Composition	Toxicity /cytotoxicity
17. <i>Tamarindus indica</i> L. Fabaceae	Low/compromized immunity in HIV (Godwin Anywar et al. 2020b)	Galactoxyloglucan (PST001), isolated from seed kernel stimulates the immune system (Manu et al. 2016). Another polysaccharide exhibited immunomodulatory activity by enhancing phagocytic activity, inhibition of leukocyte migration, and cell proliferation (Streelekha et al. 1993). The seed kernel extract increased total WBC, CD4+ T-cell population, and bone marrow cellularity (Manu et al. 2013; 2016).	Phenolics, proanthocyanidins, arabinose, triterpenes, apigenin, luteolin (Bhadoriya et al. 2012).	Generally safe with no signs of toxicity up to 2000 mg/kg/p.o (Martiniello et al. 2006; Agnihotri & Singh, 2013; Martiniello et al. 2017)
18. <i>Warburgia ugandensis</i> Sprague Canellaceae	TB and HIV/AIDS, low immunity (Nyamukuru et al. 2017; Anywar et al. 2020a; 2020b), cancer (Schultz et al. 2020).	Stimulated moderate production of IFN- γ and low levels of IL-4 in BALB/c mice (Ngure et al. 2014)	Ugandensolide, ugandensidial, muzigadial, polygodial, warburganal, cinnamolide, mukaadial, muzigadiolide (Kiyo et al. 1990; Wube et al. 2005).	Extracts are safe to use (LD ₅₀ > 5000 mg/kg bw) in BALB/c mice (Karani et al. 2013). Different extracts of <i>W. ugandensis</i> were non-cytotoxic to human keratinocyte cells (IC ₅₀ > 512 μ g/ml) (Schultz et al. 2020). Anywar et al. 2021 found the the DMSO (CC ₅₀ = 1.5 μ g/ml) and the ethanol (CC ₅₀ = 7.6 μ g/ml) root extracts were highly cytotoxic to U87CD4CXCR4 cells.

(Continued)

TABLE 6.1 (CONTINUED)
Medicinal Plant Species Used in African Traditional Medicine for Strong immunomodulation

Scientific name and Family	Traditional Uses Related to Immune Disorders		Immunomodulatory Activity and Mode of Action	Phytochemical Composition	Toxicity /cytotoxicity
<i>Azadirachta indica</i> <i>A. Juss.</i> Meliaceae	HIV/AIDS opportunistic ailments (Anywar et al. 2020a)	Neem extract leaf has immunostimulating activity in BALB/c-mice. It caused spleen and thymus enlargement (Beuth et al., 2006). The ethanol-aqueous extract of <i>A. indica</i> contains down-regulates chronic HIV associated CD4+ T cell activation/ exhaustion (Olweny et al., 2021).	triterpenes, flavonoids and saponins, limonoids, tannins, alkaloids, sterols and gallic acid catechins and nimbins (Cesa et al., 2019; Schumacher et al., 2011; van der Nat et al., 1991).	An aqueous extracts of <i>A. indica</i> leaves was not toxic in mice (LD ₅₀ < 2500 mg/kg) (Dorababu et al., 2006). Another study showed the LD ₅₀ values of neem oil to be 31.95 g/kg (Deng et al., 2013). The queous wood ash extract posses damaging effects on sperms and testicular tissues in male albino mice (Auta and Hassan, 2016). Different biochemical parameters of toxicity indicated that the aqueous stem bark has some oral toxicity at the doses of 50, 100, 200 and 300 mg/kg body weight in mice (Auta and Hassan, 2016).	

Key: PBMCs = Peripheral Blood Mononuclear Cells; bw= body weight, NO = nitric oxide, WBC = White Blood Cells, i.p = Intraperitoneal, ROS = reactive oxygen species, RNS= Reactive Nitrogen Species

All the medicinal plant species recorded are either traditionally used to treat an immunity-related disorder, such as immunodeficiency, especially HIV/AIDS, or to treat symptoms associated with low immunity and cancer. All the plant species are also widely used across the continent and have been scientifically researched to confirm their immunomodulatory properties and modes of action. However, despite several other medicinal plant species being recorded as immune boosters in African traditional medicine, they have not been subjected to any scientific investigations to verify these claims (Nalumansi et al. 2016; Anywar et al. 2020b, 2020c). Unfortunately, even when some plant species have been scientifically shown to possess immunomodulatory properties, such as *Tamarindus indica*, they have generally not been fully exploited and are often underutilised (Tugume et al. 2020).

6.5 COMMERCIAL FORMULATIONS OF AFRICAN MEDICINAL PLANTS FOR STRENGTHENING IMMUNITY

Different herbal formulations of African medicinal plants have been tested for improving immunity and approved by regulatory authorities in some countries. Such products are now commercially available in different countries. Two prominent examples from South Africa are a traditional energy tonic formulation and *uMakhonya*[®].

A traditional South African energy tonic formulation of equal measures of six different medicinal plants (*Eriosema salignum* E. Mey., *Tragia meyeriana* Müll.Arg., *Gladiolus sericeovillosus* Hook.f., *Rapanea melanophloeos* (L.) Mez, *Grewia occidentalis* var. *occidentalis* L., and *Zanthoxylum capense* (Thunb.) Harv.) produced immunomodulatory effects on isolated immune cells and modulated the immune response of rat models infected with *Staphylococcus aureus*. It further stimulated secretion of cytokines and increased sIL-2R levels at doses of 10–100 µg/ml. It also caused an increase in Nuclear Factor Kappa Beta (*NF-κβ*) transcription in lipopolysaccharide-stimulated THP-1 cells with minimal cytotoxicity in mitogen- and peptidoglycan-stimulated PBMCs, with no significant toxicity at doses of up to 2000 mg/ml/kg of body weight (Ngcobo et al. 2017).

Another herbal immune booster from South Africa called *uMakhonya*[®], containing *Artemisia afra* Jacq., menthol, guava (*P. guajava*), the seaweed *Chondrus crispus*, and *Uncaria tomentosa* induced a significant increase in secretion of chemokines in unstimulated THP-1 cells when compared with untreated or cyclosporine-treated cells at lower doses. The lowest dose of *uMakhonya*[®] increased transcriptional activity of the *NF-κβ* gene in both unstimulated and lipopolysaccharide-stimulated THP-1 cells. This may explain the increase in chemokines secretion observed. However, *uMakhonya*[®] significantly induces dose-dependent cytotoxicity with high-dose cytotoxicity to monocytes (half maximal inhibitory concentration, $IC_{50} = 100.08$ and 107.68 µg/ml for normal and LPS-stimulated THP-1 cells, respectively) (Ngcobo et al. 2016).

6.6 CONCLUSION

Medicinal plant species with proven immunomodulating properties have great potential in treating cancer patients or people with low or compromised immune systems, without having to resort to expensive and sometimes toxic conventional

medicines. Such medicinal plants have the potential to be developed into modern drugs or improved herbal medicine products, as has been demonstrated with individual medicinal plant species, such as *P. sidosides*, in polyherbal formulations, especially in poor African nations.

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7 Traditional Brazilian Medicinal Plants for a Strong Immune System

*José Crisólogo de Sales Silva,
Solma Lúcia Souto Maior de Araújo Baltar,
and Maria Lusía de Moraes Belo Bezerra*

CONTENTS

7.1	Introduction	199
7.2	Brazilian Medicinal Flora: Native and Exotic.....	200
7.2.1	Ethnobotanic Aspects of Brazilian Medicinal Plants	201
7.3	Medicinal Plants within the Scope of the Brazilian Health System	202
7.4	Immunomodulatory Properties of Medicinal Plants	203
7.5	Conclusion	206
	References.....	206

7.1 INTRODUCTION

On the South American continent, Brazil is the largest country, with regard to both its population size and its geographic dimensions. Brazil is not only a large country, but, because of its diverse topographic conditions and habitats, it also has a diverse flora, which are of medicinal interest and are strongly associated with human and animal immunity in general.

Public knowledge of the extreme and unique plant diversity, as well as the rich traditions of their use by the native, and later settler, populations in Brazil is relatively scarce in relation to its value. The aim of the present chapter is to serve as a modest introduction to this wonderful natural resource, with a special focus on medicinal plants and the immune system. In this sense, Brazil is presented as the richest country in terms of flora, with 40,989 species, of which 18,932 are endemic, according to Mathé and Silva (2018).

We can highlight that all plants contain bioactive chemicals which can be useful for conventional and/or traditional medicine. Even plants called weeds in the diverse biomes of Brazil can have an important function, and can be valued according to their specific contribution to the development of the ecosystems present there.

An herbaceous plant in a pasture can be invasive, whereas, in another context, it can heal an animal or a human being. On the other hand, it can be toxic at high dosages, whereas, in lower dosages, it can function, say, as a vermifuge or as a booster of immunity.

The Brazilian nation, having indigenous roots in people who valued and healed diseases and other conditions through their knowledge of the many useful species from the local flora, has, in its health system, many plants authorized for use in traditional medicine. In the *Atenção Básica à Saúde* (Primary Health Care) system, some native species have been recognized for treatment of certain conditions as the first step of emergency care. Local populans use teas and infusions of specific medicinal plants, for example, for the treatment of inflammatory symptoms.

This chapter provides a quick overview of the Brazilian medicinal flora and of those species that have an important phytotherapeutic property to treat particular conditions, as a source of drugs and useful substances for treating people, with particular reference to the maintenance of immunological health.

7.2 BRAZILIAN MEDICINAL FLORA: NATIVE AND EXOTIC

Endemic Brazilian plants, that compose much of its flora, have medicinal tendencies or are suppliers of substances of value in medicine. The fact that there are no scientific references to the medicinal function of a particular plant does not mean that it cannot be used with these objectives in the future. In principle, all plants from the Brazilian flora could have active components that are essential for the development of either medicines or nutrition, which, consequently, could strengthen human immunity; even toxic plants could have a function in parasite control. Most plants that compose the Brazilian medicinal flora are species endemic to South America, particularly from the biomes of the Atlantic Forest, the cerrado, and the caatinga, with some being from the Pantanal tropical wetlands or the Amazon tropical rainforests. Some plants can carry out important immunological functions through their active principles, acting in a partial or indirect way, combating diseases, particularly those related to the urban environment. Some of these species are listed in Table 7.1, with their scientific and popular names and the conditions which they are used to treat.

In this sense, plants with the ability to stimulate the immunoregulatory action of the liver and pancreas present themselves as natural, cheap alternatives, that, in safe dosages, contribute to the preventive balance of the health of many organs. However, for this to happen, it is necessary to return to the traditions of using plant teas and infusions to promote natural health. These immunity regulators need to be present daily in the diet of both the urban and rural people, in the form of refreshing drinks, without preservatives or industrialized products, so that they can regulate, slowly and in keeping with the body's timing, any dysfunctions provoked by the consumption of fibre-free food, by excessive work, sleepless nights, and the fast-paced routine which is part of the modern day. Daily breaks can be accompanied by teas and infusions that reduce inflammation of the cardiovascular, hepatic, pancreatic, and urinary systems, as healthy organs and bowels are rarely affected by infections and diseases. As

TABLE 7.1
Native and Exotic Brazilian Plants With Medicinal Potential to Strengthen the Immune System (adapted from Americano 2015)

Scientific Name	Popular Name in Brazil	Principal Use
<i>Aloe vera arborensis</i> Miller	Babosa	Immunological, vitamin A, B and C tonic
<i>Annona muricata</i> L.	Graviola	Antibiotic, anticancer, hypotensive, hypoglycaemic
<i>Annona sylvatica</i> A. St. Hill.	Araticum-do-campo	Immunogenic, antihypertensive
<i>Baccaris dracunculifolia</i> DC	Alecrim silvestre	General tonic, digestive
<i>Baccharis trimera</i> (Less) DC	Carqueja	Immunity control, cardiovascular, and glycaemic
<i>Bidens pilosa</i> L.	Picão	Antibiotic, hypoglycaemic, hypotensive
<i>Chiococa racemose</i> Jacq.	Cainana, Cainca	Anti-inflammatory and antibiotic
<i>Cochlospermum insigne</i> St. Hill.	Algodão-do-campo	Anti-inflammatory and antibiotic
<i>Copaifera officinalis</i> L.	Copaiba	Anti-inflammatory, immunogenic
<i>Dipteryx alata</i> Vog.	Baru	Antitumour, anti-inflammatory
<i>Hancornia speciosa</i> Muell.	Mangabeira	Hormonal control, protective effect on the liver and pancreas
<i>Lychnophora ericoides</i> Mart.	Arnica campestre	Anti-inflammatory, general tonic
<i>Macrosiphonia velama</i> St. Hill.	Velame	Antibiotic, tonic, immunoregulator
<i>Maytenus ilicifolia</i> Martius ex Reiss	Espinheira santa	Antibiotogenic, liver tonic
<i>Myracrodruon urundeuva</i> Allem.	Aroeirinha-do-campo	Anti-inflammatory, anti-diarrhoeal
<i>Ocimum gratissimum</i> Fr. All.	Alfavaca	General tonic, antimicrobial
<i>Persea americana</i> Will.	Abacateira	Antioxidant, cholesterol control
<i>Rosmarinus officinalis</i> L.	Alecrim	Hepatotonic, digestive
<i>Stryphnodendron adstringens</i> (Mart.) Coville	Barbatimão	Anti-inflammatory, antibiogenic
<i>Vernonia condensata</i> Baker	Alumã	Protective of the liver

a reflection of the power of the native and exotic plants of the Brazilian flora plants, Table 7.1 lists some species that have medicinal properties that can strengthen the immune system.

7.2.1 ETHNOBOTANIC ASPECTS OF BRAZILIAN MEDICINAL PLANTS

Ethnobotany involves the study of human societies, with its main characteristic being the direct contact with traditional populations through knowledge of the interaction between people and local plants from a community, and their mores, uses, and peculiarities, searching for information that can be beneficial with regard to the use of the medicinal plants (Rodrigues and Andrade 2014; Tomazi et al. 2014). This relationship involves ecological, evolutionary, genetic, and cultural interactions, and

contributes to our understanding of the many plant species with medicinal properties (Alves and Povh 2013).

In the communities, local knowledge about the use of medicinal plants is transmitted from generation to generation, through contact between older and younger members, socialization within the family group, or between individuals from the same generation (Amorozo 1996; Lozada et al. 2006). However, the conservation of this local knowledge represents a medicinal alternative for families, particularly for those with low purchasing power, since herbal medicine is cheaper and more accessible than pharmaceutical medicines (Silva and Proença 2008).

In this context, Brazil stands out as the country with the greatest diversity of biological species in the world, and its importance for ethnobotanical research is related to its botanical and cultural diversity, represented by indigenous peoples, quilombola communities of artisanal fishermen, family farmers, sertanejos and riverside dwellers, that, through their human and environmental relationships (Albuquerque et al. 2011), discover the potential of local plants for the development of new drugs, and develop information on the different ways of the handling and use of plant preparations (Feijo et al. 2013; Ribeiro et al. 2014; Vasquez et al. 2014).

Research shows that most of the medicinal species known and studied today were identified with the help of ethnobotanical surveys. The contribution of these studies highlights the practices of medicinal plant use, explaining the traditional medicinal systems of the local populations (Albuquerque et al. 2010; Oliveira and Menini Neto 2012; Ribeiro et al. 2014). However, some medicinal plants require special care in their administration, and this care is directly related to their medicinal and toxicological characteristics, and to the way the natural remedy is prepared and applied (Rehman et al. 2017).

According to the Brazilian Institute of Geography and Statistic (IBGE, in Portuguese), Brazil is formed of six natural regions, known as biomes (the Amazon, caatinga, cerrado, Atlantic forest, pampa, and wetland). These biomes harbor different types of vegetation, each with their own characteristics, and this biodiversity has allowed separate ethnobotanical studies to be carried out in different Brazilian regions (Albuquerque and Andrade 2002; Pasa et al. 2005; Miranda and Hanazaki 2008); among the many categories of use of these plants, the work with medicinal plants dominates (Oliveira et al. 2009). The approach to this topic allows the research to be planned from a pre-existing empirical knowledge, confirmed many times by regular medicinal use of these plants, which should then be tested on a scientific basis (Amorozo 1996).

7.3 MEDICINAL PLANTS WITHIN THE SCOPE OF THE BRAZILIAN HEALTH SYSTEM

Brazilian's Health System, SUS in Portuguese, is one of the world's largest and most complex systems of public health. It was created in 1998 by the Brazilian Federal Constitution to address the constitutional article that classifies health as a people's right and a state duty, regulated by the law n°. 8.080/1990 (Brasil 2000).

From the creation of the Brazilian Federal Constitution, all of the Brazilian populations were guaranteed the right to universal free healthcare, financed by the Union

resources, the states, the Federal District, and the counties, according to article 195 of the Constitution, that establishes five basic principles: the universality (article 196), integrality (article 198–II), equity (article 196–‘universal and egalitarian access’), decentralization (article 198–I), and social participation (article 198–III).

SUS care is performed in health centres and unities, in public hospitals, including the university hospitals, and the laboratories and blood banks in the service of the health, epidemiological, and environmental departments, other than academic and scientific research foundations and institutes. With the goal of offering a wider service to the population, SUS has been opening opportunities for treatments with alternative medicine, such as aromatherapy, meditation, and yoga, and expanding the accessibility to patients of medicines based on medicinal plants and herbal medicines (<http://bvsmms.saude.gov.br>).

For the Ministry of Health, the benefits of natural treatments are recognized throughout the country for their relevance in preventing diseases, promoting health, and aiding recuperation from illness. To this end, the federal government published, in 2006, the National Policy of Integrative and Complementary Practices (PNPIC, in Portuguese), and, two years later, approved the National Program of Medicinal Plants and Phytotherapies, that details the guidelines of the policy in the form of concrete actions. The goal of this regulation is to guarantee safe access to medicinal plants and phytotherapy for the population, to assure the rational use of these resources, to promote the sustainable use of the biodiversity, and to develop the chain of production and the national industry.

To the National Health Surveillance Agency (Anvisa, in Portuguese), a medicinal plant is every plant or part of a plant that contains substances or classes of substance responsible for therapeutic action (Brasil 2009), and phytotherapy is the result of the transformation of the properties of a medicinal herb into a medicine.

Medicinal plants and phytotherapy are important for treatment of numerous conditions (infection, inflammation, pain, and control of blood pressure, among others). The regulation of the medicinal herbal products is done by Anvisa and by the County and State Health Surveillance agencies; therefore, all industrialized phytotherapies are regulated by Anvisa before being made available on the market. Nowadays, SUS lists 71 medicinal plants and phytotherapies that are disseminated by the National Program of Medicinal Plants and Phytotherapies from the Health Ministry.

SUS phytotherapies are approved by Anvisa, and are considered safe and effective for the population. This list has the goal of guiding studies and research that can subsidize the preparation of phytotherapies available to the population to be used safely and effectively for the treatment of a certain condition (<http://bvsmms.saude.gov.br>).

7.4 IMMUNOMODULATORY PROPERTIES OF MEDICINAL PLANTS

From what has been described here, it is undeniable that the Brazilian flora contains a wide range of species with considerable medicinal potential, capable of generating innovative products, and which has benefitted many people throughout the national territory. Popular wisdom on the therapeutic effects of many Brazilian plants, especially those associated with the immune system, has been confirmed by numerous scientific studies (Zandonai et al. 2010; Seyfried et al. 2016; Ribeiro Neto et al. 2020).

The ability that the human body has to respond, in a protective way, against many biotic attacks, especially by bacteria, viruses, fungi, and parasitic infections (protozoa, helminths, and ectoparasites), is essential for its maintenance (Coelho-Castelo et al. 2009; Chen et al. 2018). The functional complexity of the immune system involves molecules, cells, and organs, integrating two types of immunity, the innate, and the acquired or adaptive, that act simultaneously during the control of an infection.

The innate response constitutes the first defensive line in a tissue, with the involvement of physical, chemical, and biological barriers, as well as the effects of local cells and molecules. In this way, the inflammatory response, phagocytosis (by dendritic cells, neutrophils, and macrophages), and the liberation of mediators (complement system molecules, cytokines, and chemokines) are mechanisms of innate immunity. In addition to acting as an alert for the immune system, innate immunity allows a quick response against the pathogen, until the activation of the adaptive immune response can happen (Nunes-Pinheiro et al. 2003; Coelho-Castelo et al. 2009; Cruvinel et al. 2010).

In turn, the adaptive immunity response involves humoral and cellular immune actions. The first is characterized by the production and secretion of antibodies by B lymphocytes. The antibodies facilitate phagocytosis and activate cytotoxicity mechanisms mediated by the complement system, neutrophils, macrophages, and natural killer cell (NK). The cellular immune action, on the other hand, is mediated by various types of T lymphocytes (Nunes-Pinheiro et al. 2003; Cruvinel et al. 2010).

In popular herbal medicine, numerous phytochemicals stand out, such as peptides, polysaccharides, lectins, terpenoids, saponins, oils, alkaloids, flavonoids, and others, with properties that act on the immune system (Nunes-Pinheiro et al. 2003; Seyfried et al. 2016). The immunomodulatory activity of primary and secondary metabolites from extracts of medicinal plants has been confirmed by research from Brazil and around the world (Zandonai et al. 2010; Seyfried et al. 2016; Wangchuk et al. 2018; Andrade et al. 2020). In this modulation process, the substances act as immunoregulatory, immunostimulatory, and/or immunosuppressive factors, heightening or lowering the immune response (Amirghofran et al. 2009; Zandonai et al. 2010).

Pereskia aculeata Miller is a scrambling plant from the Cactaceae family, common in the Atlantic forest, and popularly known in Brazil as Ora-pro-nobis. Its leaves, apart from being used in cooking, are used to help in the reduction of signals and inflammatory symptoms, and in wound healing (Pinto and Scio 2014; Ribeiro Neto et al. 2020). The immunomodulatory effect of this plant's leaves has been demonstrated by Andrade and collaborators (Andrade et al. 2020), and is related to its capacity to stimulate the proliferation of human peripheral blood mononuclear cells.

Plantago major L., known as tanchagem in Brazil, is an herb native to Europe, but naturalized in the south of Brazil. In addition to immunostimulatory biological properties, the *P. major* extract exhibits healing, analgesic, antioxidant, anti-ulcerogenic, antibiotic, and anti-inflammatory activities (Samuelsen 2000; Lorenzi and Matos 2002). Studies show that polysaccharides extracted from the African locust bean (*Parkia biglobosa*), the cashew nut (*Anacardium occidentale*), and from noni (*Morinda citrifolia*) show promising immunomodulatory properties, regulating mainly the activity of macrophages and the release of effector cell mediators (Hirazumi and Furuzawa 1999; Zou et al. 2014; Yamassaki et al. 2015). Table 7.2

TABLE 7.2
Immunomodulatory Activities of Herbaceous, Shrub, and Tree Plants of Native and Exotic Brazilian Flora

Type of Plant/ Popular Name in Brazil	Scientific Name	Immunomodulatory Activity	References
Herbs			
Salsa-de-praia, pé-de-cabra	<i>Ipomea pés-caprae</i> (L.) R. Br.	Increased proliferation of T lymphocytes	Zandonai et al. (2010)
Unha de gato	<i>Uncaria tomentosa</i> (Willd.) DC	Immunostimulatory activity in macrophages, T and B lymphocytes with induction of cytokine production	Lenzi et al. (2013); Domingues et al. (2011)
Marcela	<i>Achyrocline</i> <i>satureioides</i> (Lam.) DC.	Operates in the complement system	Puhlmann et al. (1992)
Tanchagem	<i>Plantago major</i> L.	Immunostimulant. Complement system activator	Samuelsen (2000); Michaelsen et al. (2000)
Shrubs			
Ora-pro-nobis	<i>Pereskia aculeata</i> Miller	Proliferation of human peripheral blood mononuclear cells	Andrade et al. (2020)
Amoreira-rosa	<i>Rubus imperialis</i> Cham. & Schltldl.	T lymphocyte inhibition	Zandonai et al. (2010)
Malva branca	<i>Althaea officinalis</i> L.	Effect on the complement system	Al-Snafi (2013)
Erva-preá, Erva-de-são-Simeão	<i>Vernonia scorpioides</i> (Lam.) Pers.	Reduces T lymphocyte proliferation	Zandonai et al. (2010)
Trees			
Guanandi or jacareúba	<i>Callophyllum</i> <i>brasiliensis</i> Cambess.	Induces T lymphocyte proliferation	Zandonai et al. (2010)
Noni	<i>Morinda citrifolia</i> L.	Production of cytokines by macrophages. Stimulates the release of chemical mediators	Hirazumi and Furuzawa (1999); Mufidah et al. (2013)
Miguel-pintado, Cambuatá-branco	<i>Matayba</i> <i>elaeagnoides</i> Radlk.	Stimulates T lymphocyte proliferation	Zandonai et al. (2010)
Cajueiro	<i>Anacardium</i> <i>occidentale</i> L.	Regulation of macrophage activity	Yamassaki et al. (2015)
Coração-de-bugre, cafezinho-do- mato	<i>Maytenus robusta</i> Reissek.	T lymphocyte inhibition	Zandonai et al. (2010)

(Continued)

TABLE 7.2 (CONTINUED)

Immunomodulatory Activities of Herbaceous, Shrub, and Tree Plants of Native and Exotic Brazilian Flora

Type of Plant/ Popular Name in Brazil	Scientific Name	Immunomodulatory Activity	References
Visgueiro	<i>Parkia biglobosa</i> (Jacq.) R.Br. ex G. Don	Complement system effect, macrophage activation	Zou et al. (2014)
Aroeira	<i>Myracrodruon</i> <i>urundeuva</i> Allem.	Modulates macrophage activation	Carvalho et al. (2017)
Babosa	<i>Aloe arborescens</i> Mill.	Induces the production of various cytokines and the tumour necrosis factor	Nazeam et al. (2020)
Carqueja	<i>Baccharis trimera</i> (Less.) DC.	Inhibitory effect on T lymphocyte proliferation	Paul et al. (2009)

lists various herbaceous, shrub, and tree species, native and exotic, in the Brazilian flora that contain substances with immunomodulatory properties. Countless plant species have been indicated and used in traditional medicine and have had their medicinal properties confirmed, but many are still unknown, especially with reference to those with immunomodulatory activity. Conducting medicinal plant research focused on immunomodulatory activity is essential, though challenging, since it involves high costs, considering that such research requires both *in vivo* and *in vitro* experiments. To achieve developments in this scientific field, greater investment is needed, whether from governmental or other funding agencies.

7.5 CONCLUSION

Medicinal Brazilian flora is a source of powerful therapeutic chemicals capable of acting on the molecular and cellular mechanisms of organic defence, either stimulating or inhibiting the immune system. Biologically active compounds can be obtained from fruit plants, ornamental plants, and species of no current economic importance, which are used daily for medical purposes by the local populations distributed throughout the national territory. In view of the great botanical diversity in this country, studies on the immunomodulatory properties of Brazilian plant extracts are still preliminary, representing a research niche that urgently needs to be expanded and increasingly explored.

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8 Traditional Himalayan Plants

Nature's Gift for Maintaining a Strong Immune System

Antul Kumar, Anuj Choudhary, Harmanjot Kaur, Atul Arya, Baljinder Singh, and Sahil Mehta

CONTENTS

8.1	Introduction	211
8.2	Background.....	213
8.3	Traditional Himalayan Medicinal Plants.....	215
8.4	Roles of Himalayan Medicinal Flora in Disease Treatment.....	229
8.4.1	<i>Astragalus membranaceus</i>	230
8.4.2	<i>Allium sativum</i>	230
8.4.3	<i>Tylophora asthmatica</i>	230
8.4.4	<i>Withania somnifera</i>	231
8.4.5	<i>Panax ginseng</i>	231
8.4.6	<i>Tinospora cordifolia</i>	231
8.4.7	<i>Boerhaavia diffusa</i>	232
8.4.8	<i>Picrorhiza scrophulariiflora</i>	232
8.4.9	<i>Actinidia eriantha</i>	232
8.4.10	<i>Rhus toxicodendron</i>	234
8.5	Ethanopharmacology	234
8.6	Recent Advances in Immunomodulatory Research	235
8.7	Himalayan Medicinal Plants and Their Decline	236
8.8	Conclusion	236
	References	237

8.1 INTRODUCTION

In the past fifty years, climate change has become the most recognized challenge to Sustainable Development Goal 15 (or Global Goal 15) that relates to the halting of biodiversity loss. It not only affects plant distribution, global temperature, and ice cover, but also pushes the vulnerable species towards extinction (Mehta et al. 2019;

Sharma et al. 2020; Bharti et al. 2021). The Himalayas ('Third Pole of the Earth'), harboring around 600 BT (billion tons) of ice glaciers, seems to have been affected by unpredictable changes in temperature since the 20th century, where the global warming trend began at 0.16°C (Viste and Sorteberg 2015). Later on, the temperature increase rate doubled by the start of the 21st century leading to further melting of glaciers. This has been highlighted by reports presented by many agencies and international organizations. For example, China, India, Bhutan, Nepal, and Pakistan account for the most glacier losses, occurring at a pace that has been accelerating since the year 1975. Significant increases in surface temperature have been reported from each of the past six decades and currently there is an annual mean temperature increase of 0.2°–0.3°C across the Hindu Kush Himalayan (HKH) Region (Mohamed et al. 2017; Islam et al. 2018). The Tibetan Plateau and the Himalayas have experienced a temperature increase of 0.5°C/decade, termed the EDW (elevation-dependent warming). The resulting increase in the glacial melt (especially of the HKH) has also resulted in increased (by nearly 17.4%) river flows for ten major Himalayan-region-dependent rivers, namely the Tarim, Amu Darya, Indus, Brahmaputra, Irrawaddy, Yangtze, Yellow, Mekong, Salween, and Ganges. Together, these rivers contribute more than 50% of the total utilizable water. The changes in the glacier melting pace and water levels, coupled with varying rainfall, climate, and soil degradation, have resulted in the Himalayan region rapidly losing its precious flora and fauna (Ridley et al. 2013; Hui et al. 2018; Dimri and Allen 2020).

One of the most frightening recent observations is the influence of ice melting, inadequate water supply, dry summers, and intense climatic conditions on the flowering of many medicinal plants in the Himalayan regions. All these factors together affect the plant's morphology, phenology, reproduction, and ability to complete their life cycle. Furthermore, these factors indirectly impact tree lines, ecosystem compositions, tribal livelihoods, and faunal diversity (Durcan et al. 2016; Bitew et al. 2019). In this regard, conserving the medicinal plants of the Himalayan regions under the changing climate is of utmost priority. The reason lies in the fact that many medicinal plants, including *Fritillaria roylei*, *Lilium polyphyllum*, *Habenaria edgeworthii*, *Habenaria intermedia*, *Malaxis muscifera*, *Malaxis acuminata*, *Polygonatum verticillatum*, and *Polygonatum cirrhifolium* (together termed Astavarga), have been used in Ayurveda for many centuries. Astavarga is important in treating seminal weakness, abnormal thirst, and fever, in healing fractures, reducing elevated body fat, and improving diabetic conditions. Plants listed in Astavarga are described as having rich antioxidant properties and can restore a range of health issues (Dhyani et al. 2010). Due to their potent medicinal properties, Astavarga plants are used in various forms, such as powder (churana), butter (clarified butter), extracted oils (taila), and other herbal formulation in the conventional herbal medical system (CMS), such as chyavanprasha, a well-known, immunostimulatory, and health-promoting agent. Taking together, these species are regarded as valuable 'Rasayana', with considerable health-improving and rejuvenating properties that together strengthen the immune system, including the capacity for cell regeneration.

Over the past two decades, many exploration-cum-documentation surveys have been conducted on tribal and conventional knowledge of Himalayan medicinal

plants (Samal and Dhyani 2006; Kala and Sajwan 2007; Singh et al. 2018; Kumar et al. 2020). Findings indicate that the western Himalayas (including India, Pakistan, Nepal, and Bhutan) hold a prime position in harbouring high concentrations of medicinal plant species, as compared with the global distribution of such plants. This knowledge has been conserved and passed on to the next generation by the tribal communities as a result of the area's inaccessibility to tourism, its harsh environmental conditions, difficult survival conditions, and comparatively low rate of development (Kala et al. 2006; Rai 2017).

8.2 BACKGROUND

The tradition of treating diseases with preparations of plants growing at high altitude is not a new concept. The use of Himalayan medicinal plants was already documented early in the Vedic period in the Charaka Samhita (300 BC), Sushruta Samhita (1300 BC), Atharvaveda (2000 BC), and other Brahminic treatises (Figure 8.1). Over the years, the tribal communities relied on traditional practitioners who developed medicinal plant preparations of various compositions to treat a number of diseases, like diabetes, renal disorders, hepatic ulcers, sexual debility, and neurological disorders that suppress immune function. The Himalayas are often known as the "Rooftop of the World" and contain a very high biodiversity of medicinal plants, and they are considered to be repositories of unique medicinal plants (Hemant and Aitken 2003; Yadav et al. 2017). Due to the remoteness of the area and the lack of conventional medical resources and facilities, the local communities are treated by traditional medicinal healers, known as Amachis or vaidas, who are experts in herbal formulations based on local plants. According to a Chinese proverb:

'If you are thirsty and digging a well is like you start boosting your immune system when you are ill'.

Archaeological findings on folk medicines which are still in use, such as *Papaver somniferum*, date back more than 8,000 years. Concomitantly, the documentation on traditional plants obtained from the Himalayas is also found in the Atharvaveda, Rigveda, and Ayurveda. Hippocrates (c.460–c.370 BC) explained the role of a willow tree in curing fever, cold, and energy flow *via* an elevated immune system. Even before the 19th century, these plants were the major agents used by communities to treat sick people, and still, their importance is immense. Several plant-derived drugs, such as colchicine (an immunomodulator, preventing the development of a 'cytokine storm'), ephedrine (an immunostimulant), and quinine (an antimalarial drug), which were used in herbal preparations by tribal communities, are currently being manufactured by pharmaceutical companies commercially. Various other conventional healing therapies based on Himalayan plants, like *Rauwolfia serpentina* (to treat hypertension), *Mucuna pruriens* (Parkinson's disease), *Artemisia annua* (an anti-malarial), *Holarrhena* sp. (amoebiasis), and *Commiphora* (an hypolipidaemic) are currently being used too. Furthermore, some renowned bioactive compounds present in Himalayan medicinal plants are also used in folk medicine practices, including

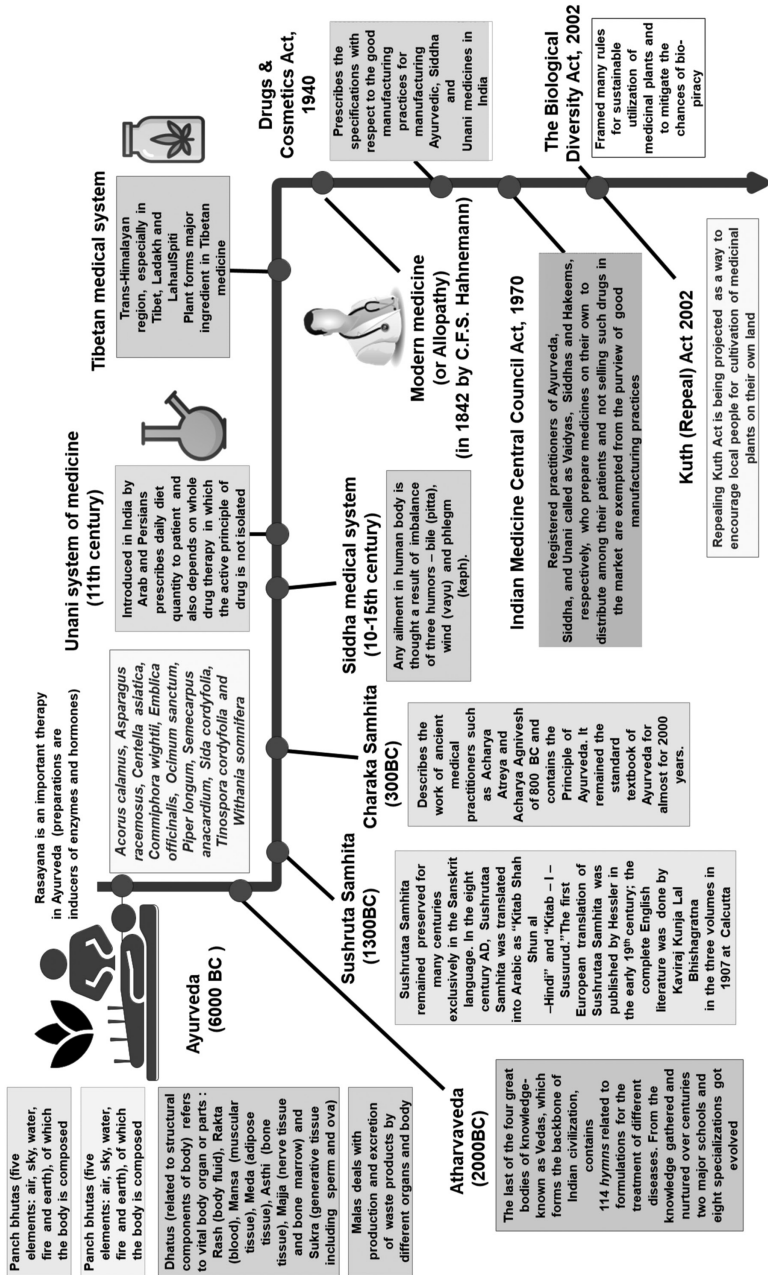


FIGURE 8.1 Historical milestones in immunity-boosting research-cum-exploration mining of Himalayan plants.

guggulsterones (an hypolipidaemic), curcumin (an anti-inflammatory), asclepias (for mental retention), psoralens (for vitiligo), asarone (against hallucinations and for mental stability), picosides (as a cardiogenic), withanolides (anticancer agents) and dirubin (an anti-tumour agent and to treat other immunomodulatory disorders). According to charaka system of medicine, exogenous diseases, or Agantuja Vyadhi and Rasayana chikitsa, are explained in Ayurveda in terms of diseases related to the immune system (Dhyani et al. 2010; Rana and Samant 2011; Sharma et al. 2017). At the medical level, modulation of cytokine activity is seen to be primarily targeted in both *in-vivo* and *in-vitro* studies that were conducted to assess the effect of herbal formulations on the immune system. These cytokines are glycoproteins or extracellular soluble proteins in the form of chemokines, interferons, and interleukins (ILs), which play a central role in both acquired and innate types of immune response (Joshi et al. 2010; Sharma et al. 2010). Furthermore, immunomodulation mediated by Himalayan medicinal plants was also observed to be associated with polysaccharides in the preparation, which caused a release of cytokines from IDCs (intestinal dendritic cells), reduced the levels of IL-6, IL-10, IL-1, IL-12, IL-8, IL-6, MCP-1 (monocyte chemoattractant protein-1), and lipopeptides. There was also an increase in levels of CD3-CD4-CD8-triple-negative thymocytes and natural killer (NK) cells, as well as in the activity of B lymphocytes, helper, and killer T cells (Ernst 2003; Namtak et al. 2018).

8.3 TRADITIONAL HIMALAYAN MEDICINAL PLANTS

More than 130 chemical compounds derived from medicinal plants have been recognized as valuable therapeutic agents and a number are established as well-known drugs in conventional medicine. For example, salicylic acid, extracted from the bark of the willow tree, is an important ingredient of skin ointments, pain killers, and as an antipyretic substance, marketed as aspirin. The bark has been used as an important herbal preparation for treating fever and pain by local communities since ancient times. Many drugs like opium, quinine, digoxin, etc. are frequently used by both herbal medicinal practitioners and conventional physicians for treating the same diseases.

Extracts of a number of medicinal plants have been used for studies on tumour necrotic factors, interleukins 1, IL-6, and interferons (Spelman et al. 2006; Wu et al. 2007; Dhyani et al. 2010; Chaurasia and Singh 2010; Kumar et al. 2019; Janifer et al. 2020), and are listed in Table 8.1: *Aconitum heterophyllum*, *Tinospora cordifolia*, *Atropa acuminata*, *Acalypha wilkesiana*, *Rheum australe*, *Fritillaria cirrhosa*, *Picrorhiza kurroa*, *Withania somnifera*, *Dactylorhiza hatagirea*, *Podophyllum hexandrum*, *Acanthopanax gracilistylus*, *Swertia chirayita*, *Allium sativum*, *Saussurea gossypiphora*, *Pleurospermum brunonis*, *Harpagophytum procumbens*, *Dioscorea deltoidea*, *Nardostachys grandiflora*, *Echinacea purpurea*, *Saussurea roylei*, *Uncaria tomentosa*, *Saussurea obvallata*, *Ananus comosus*, *Cissampelos sympodialis*, *Valeriana hardwickii*, *Silybum marianum*, *Polygala tenuifolia*, *Codonopsis ovata*, *Polygonatum cirrhifolium*, *Curcuma longa*, *Poria cocos*, *Jurinea dolomiaea*, *Smilax glabra*, *Panax ginseng*, *Grifola frondosa*, and *Coriolus versicolor*

TABLE 8.1
Comparison of Medicinal Plants, Based on Characters Like Pharmacological Properties, Folk Uses, and Herbal Formulations Used During Treatment of Various Health Issues

Botanical Name	Vernacular Name	Family	Part Used	Medicinal System	Part Administered	Uses/properties	References
<i>Corydalis gowaniana</i> Wall.	Bhuijatta	Fumariaceae	Juice/ Roots	Tibetan	Root extract	Antiperiodic, diuretic, alterative antisyphilitic properties, to treat dermal allergies, and infections	Mukhopadhyay et al. (2004)
<i>Inula orientalis</i> Lam.	Poshkar/ Puskarmool (H) Manu (L)	Asteraceae	Roots	Ayurveda	Root extract	Anti-inflammatory, antiseptic, expectorant, and diuretic properties To treat cardiovascular diseases, epilepsy, hysteria, antipyretic, to treat rheumatism, sleeping syndromes, tooth-ache, and bleeding piles	Wani et al. (2006)
<i>Achillea millefolium</i> L.	Chuang/ biranjasi/ yarrow/ millefoeil	Asteraceae	Leaves/ flowers	Ayurveda	Crushed herb formulation (flowers and leaves)	To treat cardiovascular diseases, epilepsy, hysteria, antipyretic, to treat rheumatism, sleeping syndromes, tooth-ache, and bleeding piles	Benedek et al. (2008)
<i>Rubia cordifolia</i> L.	Manjith (H), Indian Maddar (E), Btsod (L)	Rubiaceae	Stems and roots	Ayurveda	Leaf extract	To treat urino-genital problems, stomach ache, chest complaints, menstrual disorders, ulcers, leukoderma, and blood-related diseases	Patil et al. (2009)

(Continued)

TABLE 8.1 (CONTINUED)
Comparison of Medicinal Plants, Based on Characters Like Pharmacological Properties, Folk Uses, and Herbal Formulations Used During Treatment of Various Health Issues

Botanical Name	Vernacular Name	Family	Part Used	Medicinal System	Part Administered	Uses/properties	References
<i>Xanthium strumarium</i> L.	Banokra	Asteraceae	Leaves, roots, fruits, and seeds	Chinese Medicine	Plant extract	To treat urinary diseases, diaphoretic properties, antimalarial, and leucorrhoea	Kamboj et al. (2010)
<i>Piper longum</i> L.	Pippali	Piperaceae	Fruits	Ayurveda	Plant extract	Immunomodulatory, antidiarrhoeal, antimicrobial, and antitumour activity	Khandhar et al. (2010)
<i>Arctium lappa</i> L.	Burdock/bankuth /jari	Asteraceae	Leaves, fruits, flowers, and roots	Tibetan	Root extract, crushed seeds	To treat cutaneous eruptions, rheumatism, eczema skin allergies, psoriasis inflammations, cystitis, gout, urinary infections, toothaches, and to maintain blood sugar levels	Chan et al. (2011)
<i>Piper kadsura</i> L.	Pippali	Piperaceae	Stem	Tibetan	Plant extract	Anti-irritant, analgesic, anti-asthmatic properties, and to treat bronchitis	Kim et al. (2011)

(Continued)

TABLE 8.1 (CONTINUED)
Comparison of Medicinal Plants, Based on Characters Like Pharmacological Properties, Folk Uses, and Herbal Formulations Used During Treatment of Various Health Issues

Botanical Name	Vernacular Name	Family	Part Used	Medicinal System	Part Administered	Uses/properties	References
<i>Fritillaria cirrhosa</i> D. Don	Hadjod	Liliaceae	Bulbs	Tibetan	Bulb paste	To treat respiratory syndromes, tuberculosis, asthma, fractured bones, joints, and bronchitis	Konchar et al. (2011)
<i>Withania somnifera</i> (L.) Dunal	Ashgandh/ ashwagandha	Solanaceae	Leaves, stem, flower, root, seeds, bark	Ayurveda	Dried root powder (mixed in milk)	Diuretic, hypnotic, sedative, abortifacient, immunostimulant, restorative, aphrodisiac, narcotic properties; to treat dropsy, weakness, rheumatism, coughs, and constipation	Verma et al. (2011)
<i>Ferula jaeskiana</i> L.	Jangli Heeng/ chuklam (L)	Apiaceae	Stem/roots	Ayurveda	Plant extract	To treat septic wounds, diabetes, antipyretic, rheumatism, and tooth problems	Mahendra et al. (2012)
<i>Dactylocteniza ahatagirea</i> (D. Don) Soó	Hathpanja/ salampanja	Orchidaceae	Root/flowers	Unani/Ayurveda and Chinese medicine	Tubers	To treat chronic diarrhoea, dysentery, nerve debility, nerve stimulation, seminal debility, weakness in women after delivery, and other sexual problems	Pant et al. (2012)

(Continued)

TABLE 8.1 (CONTINUED)
Comparison of Medicinal Plants, Based on Characters Like Pharmacological Properties, Folk Uses, and Herbal Formulations Used During Treatment of Various Health Issues

Botanical Name	Vernacular Name	Family	Part Used	Medicinal System	Part Administered	Uses/properties	References
<i>Anaphalis contorta</i> (D. Don) Hook. f.	Rui-ghas	Asteraceae	Leaves, roots, flowers, and seeds	Ayurveda and Chinese medicine	Flower extract	Anti-bacterial properties, to treat burns, sores, ulcers, swellings, and rheumatic joints	Joshi (2013)
<i>Scutellaria angulosa</i> Benth.	Skullcap	Lamiaceae	Stem, flower	Tibetan	Plant extract	Febrifuge, nervine, antispasmodic, stomachic, laxative properties, microbiome modulation, and stimulation of immunoreactivity	Joshee et al. (2013)
<i>Aloe vera</i> (L.) Burm. F.	Aloe vera	Aloaceae	Leaves	Ayurvedic/homoeopathic	Aloe vera gel is used both, topically (treatment of wounds, minor burns, and skin irritation). Plant extract	Used to treat ulcers, arthritis, abdominal tumours, and burns	Sahu et al. (2013)
<i>Jurinea dolomiaea</i> Boiss.	Dhoop	Asteraceae	Roots/leaves	Tibetan	Plant extract	Antipyretic, to treat rheumatism, joint pains, colic, and gout	Asma et al. (2014)

(Continued)

TABLE 8.1 (CONTINUED)
Comparison of Medicinal Plants, Based on Characters Like Pharmacological Properties, Folk Uses, and Herbal Formulations Used During Treatment of Various Health Issues

Botanical Name	Vernacular Name	Family	Part Used	Medicinal System	Part Administered	Uses/properties	References
<i>Fragaria vesca</i> L.	Wild strawberry	Rosaceae	Roots/fruits	Ayurveda	Root extract	Antibacterial, angioprotective, to improve blood circulation, and treat urinary problems	Dhole et al. (2014)
<i>Arnebia benthamii</i> (Wall. ex G. Don)	Ratanjot	Boraginaceae	Roots, flowers	Ayurveda / Chinese medicine	Extract of plant aerial parts	Antiseptic, antibiotic, and anti-microbial properties	Ganie et al. (2014)
<i>Arisaema tortuosum</i> (Wall.) Schott	Samp ki kumb/ kidajadi	Araceae	Roots, seeds	Chinese medicine	Seeds, tubers	Antidote, neurotoxic injuries, and to maintain blood flow	Nile et al. (2015)
<i>Thymus serpyllium</i> L.	Banjwain	Lamiaceae	Stem, roots	Ayurveda	Dried root powder (mixed in tea)	Antispasmodic, anthelmintic, antiseptic, expectorant, carminative, cell regeneration, stimulant properties, to treat colds, coughs, fever, and stomach-ache	Jaric et al. (2015)

(Continued)

TABLE 8.1 (CONTINUED)
Comparison of Medicinal Plants, Based on Characters Like Pharmacological Properties, Folk Uses, and Herbal Formulations Used During Treatment of Various Health Issues

Botanical Name	Vernacular Name	Family	Part Used	Medicinal System	Part Administered	Uses/properties	References
<i>Malaxis muscifera</i> (Lindl.) Kuntze	Rishbhak	Orchidaceae	Leaves, flowers, fruits	Ayurveda	Plant extract	Antipyretic, to treat, dysentery, fever, burning, haematemesis, seminal weakness, dipsia, and enaciation	Kant (2015)
<i>Lilium polypetalum</i> D. Don	Ksirakakoli	Liliaceae	Leaves, stem	Ayurveda	Plant extract	Anti-inflammatory, antipyretic, galactagogue, expectorant, aphrodisiac, diuretic, seminal weakness, haematemesis, to treat intermittent fever, and rheumatism	Sourabh (2015)
<i>Prunella vulgaris</i> L.	Ustakha-ddus	Labiatae	Leaves, flowers, roots	Chinese medicine	Plant juice (mixed with rose oil)	To treat haemorrhages, spasmodic, bleeding piles, fevers, cough stimulant; antiseptic, anti-rheumatic, carminative, diarrhoea, headache tonic, astringent, and expectorant property	Bai et al. (2016)

(Continued)

TABLE 8.1 (CONTINUED)
Comparison of Medicinal Plants, Based on Characters Like Pharmacological Properties, Folk Uses, and Herbal Formulations Used During Treatment of Various Health Issues

Botanical Name	Vernacular Name	Family	Part Used	Medicinal System	Part Administered	Uses/properties	References
<i>Mecanopsis aculeata</i> Royle	Blue poppy	Papaveraceae	Roots/flower	Tibetan	Plant extract	To treat inflammation, fractures, and pain	Ganaie et al. (2016)
<i>Roscoea capitata</i> Sm.	Kakoli	Zingiberaceae	Tuber/rhizome	Ayurveda	Plant extract	Diabetes, diarrhoea, malaria, and antioxidants	Rawat et al. (2016)
<i>Geranium wallichianum</i>	Ratanjot	Geraniaceae	Rootstock	Chinese medicine	Plant extract	Mouth ulceration, joint pain, dysentery, diarrhoea, passive toothache, colic, jaundice, haemorrhage, kidney disorder, and eye troubles	Shaheen et al. (2017)
<i>Swertia chirata</i> L.	Chirayita	Gentianaceae	Leaves, fruit	Ayurveda	Plant extract	To treat anaemia, antipyretic, liver disorders, and respiratory disorders	Aleem et al. (2018)
<i>Rosa webbiana</i> Wall. ex Royle	Wild rose (E) / Siah (L)	Rosaceae	Seed/ fruit	Chinese medicine	Plant extract	To treat antidote, jaundice, viral fever, hepatitis, and liver inflammation	Ayati et al. (2018)

(Continued)

TABLE 8.1 (CONTINUED)
Comparison of Medicinal Plants, Based on Characters Like Pharmacological Properties, Folk Uses, and Herbal Formulations Used During Treatment of Various Health Issues

Botanical Name	Vernacular Name	Family	Part Used	Medicinal System	Part Administered	Uses/properties	References
<i>Origanum vulgare</i> L.	Sathra/Sathra/ Banajwain, Baslughas/Wild oregano / marjoram	Lamiaceae	Leaves	Chinese medicine	Leaves, root paste	Diaphoretic, carminative, diuretic, emmenagogue properties; to treat diarrhoea, whooping cough, tuberculosis, bronchitis, spasmodic earache, and conjunctivitis	Bahmani et al. (2018)
<i>Rhodiola imbricata</i> Edgew.	Rose root or stonecrop (E)/ Shrolo (L)	Crassulaceae	Leaves/roots	Anchi	Plant extract	Anti-inflammatory properties, to treat lung problems, colds, coughs, to restore memory, and to maintain blood cell number during altitude sickness	Bhardwaj et al. (2018)
<i>Carum carvi</i> L.	Konyot/ban jeera	Apiaceae	Seeds	Chinese medicine	Seeds (mixed with butter)	Febrifuge, digestive problems, eye syndromes, and to prevent cardiac arrest	Goyal et al. (2018)

(Continued)

TABLE 8.1 (CONTINUED)
Comparison of Medicinal Plants, Based on Characters Like Pharmacological Properties, Folk Uses, and Herbal Formulations Used During Treatment of Various Health Issues

Botanical Name	Vernacular Name	Family	Part Used	Medicinal System	Part Administered	Uses/properties	References
<i>Bistorta affinis</i> L.	Banmundu/ sarbguni	Polygonaceae	Flowers/roots	Ayurveda/unani	Plant extract	To treat coughs, cold, tonsillitis, fever, diarrhoea, abdominal, and back pain	Paul et al. (2018)
<i>Bergenia ciliata</i> (Haw.) Sternb.	Pashanbhed/ patharchatta/ takli	Saxifragaceae	Leaves, rhizomes	Chinese medicine	Root extract (mixed with milk or curd), rhizome paste	To treat piles, as a laxative, heart diseases, spleen enlargement, diarrhoea, respiratory diseases, diuretic affections, renal stones and diabetes	Singh et al. (2018)
<i>Plantago major</i> L.	Isabgol	Plantaginaceae	Roots, leaves, flowers	Homoeopathy	Seeds	Dermatological inflammation, earache, toothache, and gastric allergies	Najafian et al. (2018)

(Continued)

TABLE 8.1 (CONTINUED)
Comparison of Medicinal Plants, Based on Characters Like Pharmacological Properties, Folk Uses, and Herbal Formulations Used During Treatment of Various Health Issues

Botanical Name	Vernacular Name	Family	Part Used	Medicinal System	Part Administered	Uses/properties	References
<i>Rheum australe</i> L.	Chuchi, chukri, leechu	Polygonaceae	Roots/flowers	Unani, Tibetan, homoeopathy	Dilute extract	Astringent, laxative properties; to treat muscular injury, Stomach pains, constipation, mumps dysentery, headache inflammation, blood purification, rheumatic earache and swelling of throat	Pandith et al. (2018)
<i>Zanthoxylum armatum</i> DC.	Tirmira/timru	Rutaceae	Leaves, bark, root	Ayurveda/Chinese Medicine	Leaf extract, bark	Dyspepsia, abdominal pains, dysentery, diarrhoea, asthma, antiplaque, diaphoretic, spasmolytic, hepatoprotective, anti-inflammatory, skin diseases, antihelminthic and antispasmodic properties	Paul et al. (2018)
<i>Hedychium spicatum</i> Sm.	Kapur-Kachri	Zingiberaceae	Rhizomes	Tibetan	Rhizome extract	Dyspepsia, carminative, and spasmodic disorders	Utami et al. (2018)

(Continued)

TABLE 8.1 (CONTINUED)
Comparison of Medicinal Plants, Based on Characters Like Pharmacological Properties, Folk Uses, and Herbal Formulations Used During Treatment of Various Health Issues

Botanical Name	Vernacular Name	Family	Part Used	Medicinal System	Part Administered	Uses/properties	References
<i>Tinospora cordifolia</i> (Willd.) Miers	Giloe, gurcha, guluichi, amrita, gilo	Menispermaceae	Stem, leaves, roots	Ayurveda	Root extract	Gastrointestinal, anti-ulcer activity, chronic cough treatment, diabetes, rheumatoid arthritis, cardiac disorder, diuretic, stomachic, antidote, neuro-pharmacological activities, anaemia, stimulates bile secretion, gout, respiratory tract infections, antidote, anti-inflammatory activity, maintain cholesterol content, anti-asthmatic, antileprotic, anti-hyperglycaemic, hepatoprotective activity, and anticancer activity	Kumar et al. (2019)

(Continued)

TABLE 8.1 (CONTINUED)
Comparison of Medicinal Plants, Based on Characters Like Pharmacological Properties, Folk Uses, and Herbal Formulations Used During Treatment of Various Health Issues

Botanical Name	Vernacular Name	Family	Part Used	Medicinal System	Part Administered	Uses/properties	References
<i>Echinops niveus</i> Wall. ex Wall.	Umtkandara	Asteraceae	Fruits/roots	Ayurveda	Root bark (mixed with honey)	Ophthalmia, indigestion, urinary, neural, respiratory and mild antibiotic properties, to treat asthma, cough, and chest infections	Bitew et al. (2019)
<i>Artemisia dracunculus</i> L.	Burtse/kundial/ Shersing	Asteraceae	Leaves/roots	Ayurveda/Chinese Medicine	Root extract	To treat urinary diseases, toothache, sexual problems, respiratory problems (especially lung infections), and menstrual problems	Fildan et al. (2019)
<i>Dracocephalum heterophyllum</i> Benth.	Zinkzer	Laminaceae	Leaves/ flowers	Ayurveda/Tibetan	Plant extract	To treat cold, headache, cough, and fever	Raj et al. (2009)
<i>Ficus benghalensis</i> L.	Banyan	Moraceae	Aerial roots	Ayurveda	Bark extract	Treatment of gonorrhoea, vomiting, and diabetes	Tripathi et al. 2019
<i>Sinopodophyllum hexandrum</i> (Royle) T.S. Ying	Bankakri	Berberidaceae	Roots, Rhizomes	Ayurveda	Dried root powder, fruits	Anticancer, gastric ulcers, hepatic problems, and tissue regeneration properties	Kumar et al. (2020)

(Continued)

TABLE 8.1 (CONTINUED)
Comparison of Medicinal Plants, Based on Characters Like Pharmacological Properties, Folk Uses, and Herbal Formulations Used During Treatment of Various Health Issues

Botanical Name	Vernacular Name	Family	Part Used	Medicinal System	Part Administered	Uses/properties	References
<i>Hippophaë rhamnoides</i> L.	Sea buckthorn, Tsermang	Elagnaceae	Leaves, berries, pulp, and seed residue	Ayurveda/Chinese edicine	Berries	Inflammatory, lung disorders, blood purifier, peptic ulcer, antiseptic, antimicrobial activities, improves digestion, nutrient deficiencies, and blood circulation	Kumar et al. (2020)
<i>Polygonatum verticillatum</i> (L.) All.	Mahameda, salammisri	Asparagaceae	Rhizomes	Ayurveda/Chinese medicine	Rhizomes	Used for urino-genital disorders, nerve tonic, general weakness, spermatorrhoea, haemorrhoids, leucorrhoea, anaemia, gastric problems, wounds, rheumatism, aphrodisiac, kidney problems (stones), and fever	Kumar et al. (2020)

These reports validate the therapeutic success of traditional medicinal theories in treatment of a range of autoimmune illnesses and cytokine-associated syndromes or diseases. The treatment based on conventional medicinal plants, including immunomodulation, is effective due to the presence of different phytochemical compounds in a single dose of the preparation given to the patient. So, researchers are working on the isolation of single compounds that target particular diseases, using phytotherapy. Herbal practitioners use herbal compositions; single compounds may not work, and this has always been a point of criticism for conventional medicinal systems (Kala et al. 2006; Sharma et al. 2010; Rai 2017). The hypothesis underlying multi-component remedies proposes that dilute mixtures of more than four or five traditional medicinal plants representing the 'crude drug', consisting of many chemical constituents, show therapeutic and pharmacological effect as a result of synergistic activity. Equally, this complex combination of compounds is reflected in the effect of many compounds, regulating signalling cascades, cytokine receptors, and protein regulation. Studies on the dilution of biologically active chemical compounds suggest that subclinical concentrations of oral interferon- α can provide a wide range of useful benefits (Sharma et al. 2010). The strategy of using multiple immunomodulatory compounds in a single dose regulates the activity of various cytokines. Currently, this knowledge is restricted to phytochemicals used by people in tribal regions in treatments based on multi-component plant extracts. Recently, due to the onset of the global COVID-19 pandemic, there has been increased attention being paid towards employing such immunomodulatory plants to boost the immune system (Ernst 2003; Rastogi et al. 2020).

8.4 ROLES OF HIMALAYAN MEDICINAL FLORA IN DISEASE TREATMENT

Plant extracts of various Himalayan herbal formulations have been regularly evaluated for their role as chemoprotective and immunomodulation agents (Mohan et al. 2019). The compounds in these plants modify and induce anti-tumour effects by enhancing the activities of the host immune response against the tumour. These plants show direct antiproliferative roles on cyst-like cells and also increase the ability of the host cells to resist or counteract toxic damage that may be crucial to the damage caused by the tumour cells (Janifer et al. 2020).

Immunomodulatory therapy could offer an efficient and effective approach over conventional chemotherapy for numerous conditions resulting from poor immune responsiveness or where targeted immunosuppression has to be initiated to treat the condition, as in auto-immune disorders, inflammatory diseases, or following bone marrow or organ transplantation. Numerous medicinal plants from temperate and sub-temperate zones have been claimed to exhibit immunostimulatory activities, supporting the evidence of local herbal medicinal practitioners. These well-known medicinal plants include *Achillea wilhelmsii*, *Caesalpinia bonducella*, *Astragalus membranaceus*, *Jatropha curcas*, *Picrorhiza scrophulariiflora*, *Bergenia ciliata*, *Tinospora cordifolia*, *Plantago asiatica*, *Panax ginseng*, *Sophora subprostrata*, *Mangifera indica*, *Morus alba*, and *Withania somnifera* (Singh et al. 2018; Kumar et al. 2020; Niraj and Varsha 2020). Several of these plants are described below:

8.4.1 *ASTRAGALUS MEMBRANACEUS*

In the Chinese medicine system, the roots are well known as a spleen tonic and for treating different wasting or deficiency conditions. Using an extract of *A. membranaceus*, *in-vitro* experiments showed lower levels of interleukin-6, one of the best-known signalling compounds involved in inflammatory disorders. The decline in content of interleukin-6 validates the long-held rationale of their role in wasting and deficiency disorders. Moreover, increased concentrations of C-reactive proteins and interleukin-6 are associated with significant increases in cardiovascular disorders (Hong et al. 2018; Riaz et al. 2019). The tribal communities use these plants in the treatment of oedema and respiratory syndromes, which could be associated with cardiovascular disorders due to poor immune response. Thus, a predictable mechanism of reduced interleukin-6 content in cardiovascular disorders underlines the effective role of *A. membranaceus* as an immunomodulatory agent (Rios 2010; Sharma et al. 2017; Niraj and Varsha 2020).

8.4.2 *ALLIUM SATIVUM*

Allium sativum, or garlic, is one of the most commonly used cooking ingredients as well as one of the most widely used medicinal plants available in the temperate, sub-temperate, and tropical areas of Asia. Garlic is effective at regulating the functions of multiple cytokines. Studies on the addition of garlic extract to *in-vitro* cell cultures showed a lowering in the concentration of interleukin-6 and lower antioxidant activity, lower cholesterol level, and lower acetylcholinesterase (ACE)-inhibition activity, which are associated with improved cardiovascular activity (Sharma et al. 2017). However, in another model, the use of *A. sativum* extract caused a decrease in the concentration of the pro-inflammatory cytokine-like interleukin-1 that is involved in the elimination of pancreatic β cells. Garlic extract also induced changes in alloxan-based diabetes and activity towards hypoglycaemia, which may cause inhibition of IL-2. It also reduced the activities of interleukin-1, IL-8, and TNF but increased the production of IL-10 (an antiproinflammatory cytokine). Moreover, interleukin-10 also plays a role in immunopathological (inflammatory bowel and microbial infection) and immunomodulatory disorders (Alzheimer's disease), both of which support the finding that *A. sativum* acts as a cytokine stimulatory agent (Villinger 2003; Spelman et al. 2006; Rastogi et al. 2020).

8.4.3 *TYLOPHORA ASTHMATICA*

This medicinal plant is traditionally used for treating respiratory disorders, such as asthma, chest infections, allergies, and other immune-related disorders. In the Ayurveda medicinal system, *T. asthmatica* is known as anthrapachaka and is used to boost circulation in terms of internal energy flow. *T. asthmatica* shows a biphasic effect in *in-vitro* studies; it increases the interleukin-2 level when used at a lower dosage, but a decline in interleukin-2 level is observed on application of high dosages of *T. asthmatica* extract (Nair et al. 2004; Chlubnova et al. 2011; Jantan et al. 2015;

Abbas et al. 2016). This paradoxical effect of the plant suggests that researchers need to maintain an optimum concentration during drug formulation (Sotto et al. 2020). However, the high dosage may lead to activation of the mechanism that upregulates cytokine activity. The *T. asthmatica* dosage recommended by herbal practitioners is still questionable, given the contradictory effects of other plant compounds in a single dose (Ganguly et al. 2001; Gilbert and Alves 2003; Villinger 2003; Nazar et al. 2020).

8.4.4 *WITHANIA SOMNIFERA*

W. somnifera (ashwagandha) has held a prime position in terms of health benefits from ancient times and its use is well documented in Ayurveda, Chinese, Siddha, Unani, and almost all medicinal systems, as well as being a well-known immunity booster plant. *W. somnifera* also shows biphasic dosage-response effects, and influences TNF expression in a concentration-dependent manner, thus restoring chemotactic activity (Cundell et al. 2014; Chandran et al. 2017; Kalra and Kaushik 2017). An *in-vitro* investigation showed the suppression of TNF and IL-1 activity against murine macrophages, using the carcinogenic ochratoxin A (OTA). The immunosuppressive action of ochratoxin A, elevating TNF expression, confirms the chemotactic role of *W. somnifera* (Singh et al. 2016). The above findings confirm the immunological properties of an extract of *W. somnifera*, which is exploited as an immunomodulatory agent in folk medicinal systems (Davis and Kuttan 1999; Niraj and Varsha 2020).

8.4.5 *PANAX GINSENG*

Ginseng plant parts are one of the most common ingredients of many local Chinese herb formulations used by the Tibetan herbal practitioners, the Amchis, and are also well represented in the soya-rigpa medicinal systems of Ladakh. The ginsenosides are active constituents and are believed to have a diverse role in addressing health issues. *P. ginseng* is prescribed to treat inflammation and is thus predicted to exert possible functionality in terms of immunomodulatory activities. In clinical studies, the ginseng extract inhibits the stimulation of cytokine-like TNF- α levels and decreases the expression and secretion expression of C-X-C motif chemokine ligand 10 (CXCL-10) (Sun et al. 2018). In another study, seven out of nine ginsenosides (Rh1, Rf, Rg1, Rb1, Rb2, Rd, Rg3, Rc, and Re) caused stimulation of the cytokine-like TNF- α and decreased the production and secretion of CXCL-10. Such suppression of CXCL-10 can directly be inter-linked with the inactivation of several oncogenes and could ultimately activate immune responses (Singh et al. 2016; Sotto et al. 2020).

8.4.6 *TINOSPORA CORDIFOLIA*

Historically, guduchi (or giloy) is considered to be the first medicinal plant that appeared in the Vedic period during samundra manthna, as explained in

bhagavata-purana (the oldest Hindu scripture), so is referred to as amrita booti. *T. cordifolia* is used in many traditional healing therapies, conferring chemoprotectivity and treating immunological disorders (Aranha et al. 2012). The diverse range of functionalities of *T. cordifolia* is well known and helps to treat hyperglycaemia, alopecia, diabetes, hirsutism, hyperuricaemia, hyperkalaemia, renal dysfunction, hypercholesterolaemia, hypertension, elevated low-density lipoprotein (LDL) cholesterol, hyperlipidaemia, gum hyperplasia, nephrotoxicity, pulmonary toxicity, hepatic fibrosis, lymphoma nephrotoxicity, neurotoxicity, and to lower the risk of infection. Studies confirmed that macrophage activation and lymphoproliferative activities occurred in response to giloy preparations in the various herbal formulations, supporting the concept of an immunoprotective agent (Kumar et al. 2019; Sotto et al. 2020; Figure 8.2).

8.4.7 BOERHAAVIA DIFFUSA

Punarnavine is a commercial drug obtained from *B. diffusa* and is considered to play a valuable role in immunity enhancement. Several folk communities ingest leaves of this plant in the form of a herbal formulation as well as in the raw form. In sheep, treatment with the punarnavine extract causes increases in the circulation of antibodies, red blood cell (RBC) count, and numbers of plaque-forming cells (PFC) in spleen tissue. It also results in an increased number of bone marrow cells and thymocytes, as well as increased splenocyte proliferation under both *in-vitro* and *in-vivo* conditions. Punarnavine significantly reduces the concentrations of various proinflammatory cytokines like interleukin-6, IL-1 β , and TNF- α in mice. The above findings suggest an immunomodulatory function of *B. diffusa* extracts (Rios 2010; Sharma et al. 2017; Thangadurai et al. 2018; Sotto et al. 2020).

8.4.8 PICRORHIZA SCROPHULARIIFLORA

Species of the genus *Picrorhiza* are mainly found in high-altitude regions and are utilized by tribal people of the Himalayan regions. The scrocaffeside A present in the *P. scrophulariiflora* extract induces immunostimulatory functions under laboratory conditions. The compound scrocaffeside A increased splenocyte proliferation and their effect on lipopolysaccharides (LPS) and ConA (concanavalin A), along with increased activity of NK (natural killer) cells, mature T cells, and peritoneal macrophage cells. The concentration of interferons and interleukins (IL12, IL-2, IL-4) responded *via* splenocytes to the extract containing scrocaffeside A, identifying a functional role for scrocaffeside A in stimulating the immune system (Spelman et al. 2006; Aranha et al. 2012; Singh et al. 2016; Smit 2020).

8.4.9 ACTINIDIA ERIANTHA

This plant species has been used for treating several serious diseases, such as cancer, as described in the traditional Chinese medicine system. The roots of *A. eriantha* are rich in polysaccharides, that suppress tumour activity in mice, indicating their

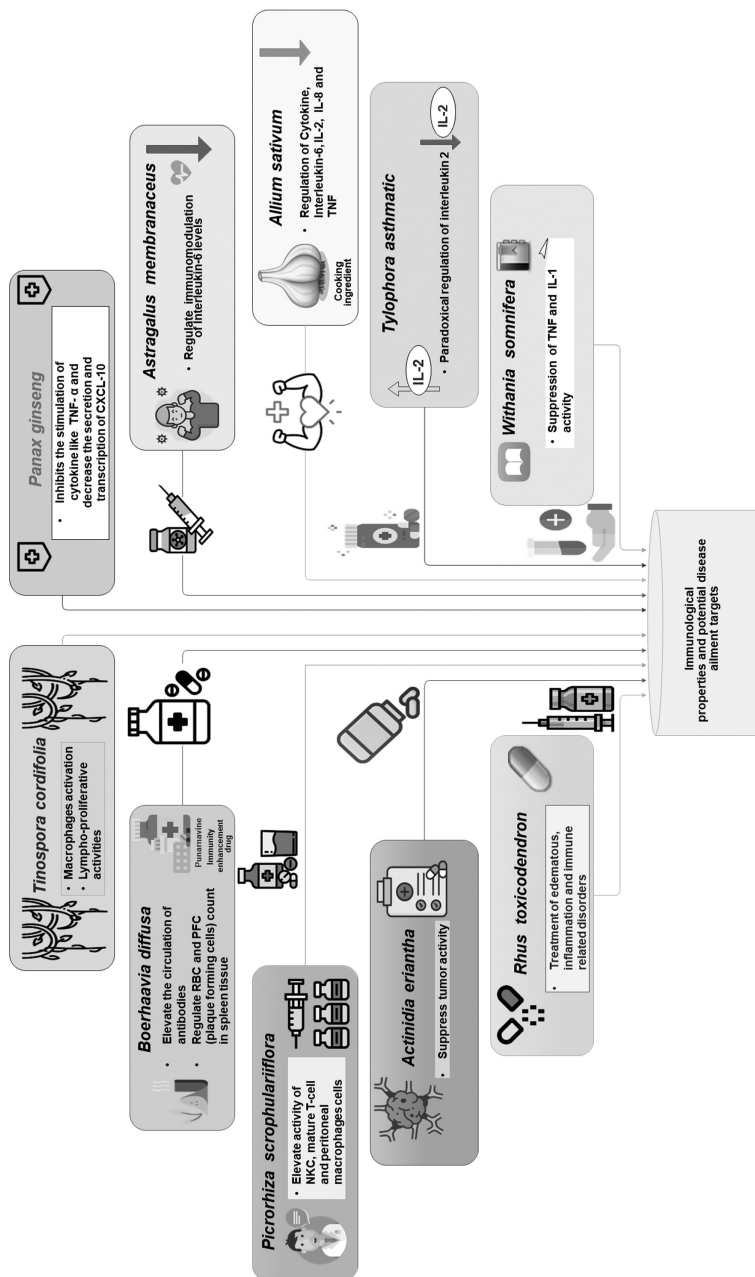


FIGURE 8.2 Immunological properties and potential disease treatment targets of Himalayan medicinal plants.

positive role in the immunostimulatory mechanism. In mice, the extract shows anti-tumour activity *via* improving immune response and is rich in uronic acid, several monosaccharides, and polysaccharides, which exhibit immunostimulatory activities (Thangadurai et al. 2018; Hasson et al. 2019; Sotto et al. 2020).

8.4.10 *RHUS TOXICODENDRON*

This plant is present in the Rhus Tox herbal formulation used by homoeopathic medicine practitioners and is used for the treatment of oedematous, inflammatory, and immune-related disorders. Treatment of mice with various concentrations of the derived compounds resulted in stimulation of both cellular and humoral types of immune response. Similar findings were also reported in humans, showing enhanced phagocytosis and chemotactic activities, confirming *R. toxicodendron* to be an important plant in conventional medicinal systems (Singh et al. 2000; Rios 2010; Hasson et al. 2019; Sotto et al. 2020).

8.5 ETHANOPHARMACOLOGY

Himalayan medicinal plants, such as *Inula racemosa*, *Rosa macrophylla*, *Mentha longifolia*, *Nepeta podostachys*, *Peganum harmala*, *Origanum vulgare*, *Utrica hyperborea*, *Gallium pauciflorum*, *Heracleum pinnatum*, *Rosa webbiana*, *Hippophaë rhamnoides*, *Dracocephalum heterophyllum*, *Tanacetum gracile*, *Artemisia dracunculus*, *Achillea millefolium*, *Bidens pilosa*, *Carum carvi*, *Ferula jaeskiana*, *Rubia cordifolia*, *Rhodiola imbricata*, and *Rhodiola heterodonta*, are endemic to high-altitude regions and are well utilized by folk medicinal practitioners, such as Amachis and Ladhakis (Wangchuk et al. 2018; Sotto et al. 2020). These plants are rich in flavonoids, tannins, alkaloids, steroids, saponins, terpenoids, cardiac glycosides, and other phytochemical compounds. These compounds have demonstrated promising results in the treatment of microbial infections, wounds, deficiencies, syndromes, and immune-related disorders. The herbal formulations of high-altitude plants contain phenolic compounds like flavanones, flavones, isoflavones, flavonols, and chalcones that help in the treatment of several diseases; these preparations include roots of *Ferula jaeskiana* (to treat rheumatism), *Heracleum pinnatum* (inflammation), and *Hippophaë rhamnoides* (to achieve immunostimulation). Therapeutic and ethnobotanical studies report the claims by traditional healers of the potential of these preparations to treat diseases like diabetes, cancer, and immune-related syndromes. Saponins in root extracts show anti-diabetic properties, whereas root extracts show other medicinal effects, as with *Dracocephalum heterophyllum* and *Inula racemosa* (to treat coughs, cold, and fever) and *Peganum harmala* (to treat cardiac arrhythmia and cardiac arrest). Tannins and flavonoids show astringent properties (leaves of *Achillea millefolium*), antifungal, and antimicrobial properties, and are used to treat toothache, menstrual problems (*Artemisia dracunculus*), gum problems (resin and stem gum of *Ferula jaeskiana*), and circulatory system problems, and to increase blood cell concentrations (*Rubia cordifolia*) (Surya et al. 2017). Some other pharmacological activities reported are antimicrobial effects, and protection from mutagenesis, carcinogenesis and ageing (*Rhus parviflora*), as well as anti-inflammatory

effects, maintenance of blood glucose level, and treatment of hypertension (*Inula racemosa*). Polysaccharides show immunomodulatory properties, activating macrophages, dendritic cells, NK cells, B cells, T cells, and inflammatory pathways, and regulating cytokine gene expression (Joshi et al. 2016; Rastogi et al. 2020).

8.6 RECENT ADVANCES IN IMMUNOMODULATORY RESEARCH

Recently, the interest in immunity booster plants has gradually increased, and sales of such herbal plant-based medicines have increased, with annual growth of 20% in the Indian market, as well as increases in the international herbal market *via* indigenous and ethnopharmacological expansion. With enhanced conventional herbal therapies based on Himalayan plants, the documents confirming their efficacy require the verification of modern-day phytochemical extraction. The tribal therapies, based on diet, drug, and treatment, have been questioned, due to scarce research, poor document evaluation, and limited *in-vivo* studies. Several Himalayan plants which have recently been overexploited for immunomodulatory drug extraction include *Rubus ellipticus* for its abortifacient activity and its action as an anti-implantation agent, whereas the caterpillar fungus, *Ophiocordyceps sinensis*, is used to enhance memory, as a haemostatic, anticancer, anti-asthmatic, antioxidant, mycolytic, or antitumour agent, as well as stimulating the immune response (Janifer et al. 2020). Another plant species, *Plantago major*, is used in herbal medicine for its antibacterial, oestrogenic, anti-inflammatory, antitumour, and antiviral activities, and its functions as a wound healer, diuretic, as an agent to achieve renal stone disintegration, and to treat hypotension. *Tinospora cordifolia* is used to inhibit COX-2, IL-6, IL-1 β , and TNF- α , increase the level of NF- κ B in the blood, increase TNF- α /DNA binding, cell-cycle arrest, and to treat Parkinsonism. The immunomodulatory drug derived from *T. cordifolia* enhances the number of T cells (Spelman et al. 2006; Chaurasia and Singh 2010; Haque et al. 2017; Kumar et al. 2019). *Boerhaavia diffusa* is a well-known immunomodulatory plant that inhibits cell proliferation, while the root extract inhibits the production of tumour necrosis factors, shows cytotoxicity towards natural killer cells, and interleukins (Janifer et al. 2020). *Centella asiatica* increases the concentration of antibodies, phagocytosis cells, and white blood cells (Kumar et al. 2020). A rhizome extract of *Rhodiola imbricata* causes stimulation of TNF- α and IL-6, and inhibits expression of the NF- κ B transcription factor, demonstrating the immunosupportive properties of *R. imbricata* (Niraj et al. 2020). *Boswellia serrata*, a Chinese herb, is used to treat inflammatory arthritis and to inhibit the cellular toxicity of various cytokines, like IFN- γ , TH2, IL-2, IL-4, and IL-10. The inhibition is based solely on the anticancer properties that help to suppress carcinogenic cells *via* influence on the immune system (Sotto et al. 2020). Ginsenosides obtained from the ginseng plant *Panax ginseng* regulate the gene expression involved in cell growth, coagulation, cell adherence, and vascular contractions, and stimulates signalling by TNF- α (Sun et al. 2018; Riaz et al. 2019). In *Astragalus membranaceus*, the polysaccharides in the extract increase the nitrous oxide concentration in macrophage cells to increase phagocytic activity *via* activating transcription factors like NF- κ B. Furthermore, the extract enhances the activity of NK cells, complement defence

systems in peripheral lymphocytes, and upregulated B lymphocyte proliferation (Zheng et al. 2020). *Andrographia paniculata* shows antinociceptive, anticancer, antiplatelet-aggregation, anti-inflammatory, and antihyperglycaemic pharmacological activities and is also used for treating encephalomyelitis immune diseases, suppressing LPS-induced expression, and inhibiting levels of IL-6, TNF, and IL-1. To date, labdane diterpenes, polysaccharides, and fatty acids are mainly responsible for the immunomodulation properties from *A. paniculata*, where labdane diterpenes and polysaccharides are immunosuppressors, and fatty acids show immunostimulatory and immunosuppressive activities (Hong et al. 2018; Riaz et al. 2019). Much research of higher quality is needed to support the concepts and validity of the use of these plants in the fields of immunology and pharmaceutical sciences (Islam et al. 2017; Thangadurai et al. 2018; Sotto et al. 2020).

8.7 HIMALAYAN MEDICINAL PLANTS AND THEIR DECLINE

The survival of humans depends upon their capability to defend themselves against foreign particles or organisms, external factors, and toxic or allergenic compounds *via* a strong immune system. Once the infectious agent penetrates the host after suppressing its defence barriers, only the immune system can protect the body from severe damage. Without doubt, the native medicinal plants have a great ability to heal diseases exogenously as well as endogenously. The various plant parts, such as roots, shoots, leaves, and fruits, are used to increase the concentrations of specialized cell types associated with boosting the immune system and hence cope with disease and energy loss (Abbas et al. 2016). The fragile melting glacier in the Himalayas has resulted in the decline of many wild species, evolving into subspecies that remained stationary. The combination of habitat isolation, elevation gradient, and climate compression often increase endemism at a single topographical level. Among species, the endemic plants of some regions in the Himalayas face barriers to migrating further up the mountains to avoid the increasing temperatures, and become extinct (Ayati et al. 2018). Plant genera, such as *Meconopsis*, *Aconitum*, *Pedicularis*, and *Pleurospermum*, and many more, face the situation of ‘climb or die’: either they trek towards higher altitudes or die out at their native growing level (Khuroo et al. 2020). The species extinction rate in high-altitude regions is high, with two drug plants disappearing from their native habitat globally.

Climate change, overgrazing, and the unsustainable overexploitation of medicinal plants are major threats concerning the ecology of these high-altitude regions. As the global market for herbal plants expands, the population pressure on native herbal farming becomes more intense. The increase in farming of vegetables and exotic varieties also affects the farming of local wild medicinal plants.

8.8 CONCLUSION

At present, the global warming trends are visible in Himalayan regions in terms of the loss of species habitat, species shifts, and increasing dominance of sub-temperate species, habitat fragmentation, and endemism at high altitudes. These

warming changes threaten not only the local ecology but also the survival of tribal communities that depend on local resources for their livelihood. Across the globe, but especially in the Asian Himalayas, communities living at high altitude, and which depend primarily on local flora for their disease treatment systems, are facing many problems. These plant resources are used effectively and sustainably by local communities and are an integral part of their life cycle. The use of medicinal plants also depends upon reachable sources, livelihood strategies, customs, and spiritual mythologies. Immunostimulation using Himalayan medicinal plants can achieve valuable treatment sources for chemotherapy of several diseases involving poor immune responses or immune-related disorders. In modern times, the pharmacological analysis of traditional immunomodulatory plants are playing an important role in the inhibition of several inflammatory factors, such as interleukins, tumour necrotic factors, cyclooxygenase, lipoxigenase, prostaglandins, and leukotrienes. These plants hold promise for the development of new drugs capable of relieving, reducing, or suppressing inflammation as well as pain. Still, many high-altitude plants are unavailable for research due to their endemicity to tribal regions, and these can have properties that antagonize the effects of interleukins and cytokines by improving the immune system. Conventional herbal formulations are very effective and act in multiple ways to target different ligands associated with various cellular receptors. However, the hidden fact of potency and effectiveness of the herbal formulation is that many chemical constituents are involved in treatment, rather than a single, active compound. Advances in biotechnologies and genetics can help to decipher the concept of ethnomedicine in terms of differential gene expression involved in an immune response. Polysaccharides show immunomodulatory properties, by activating macrophages, dendritic cells, natural killer cells, B cells, T cells, and inflammatory pathways, and by regulating cytokine-related gene expression. In the future, proper research with strict guidelines needs to be carried out that will ultimately result in conserving every Himalayan medicinal plant as well as generating a curated compendium of Himalayan medicinal herb knowledge, combining local medicinal knowledge with modern, pharmacological, and genetic knowledge, to include their bioactives, medicinal uses, and growing areas.

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9 Traditional South Indian Herbal Plants for a Strong Immune System

Mani Divya and Sekar Vijayakumar

CONTENTS

9.1 Introduction	245
9.2 Herbal Plants.....	246
9.3 Immune System	246
9.4 Traditional South Indian Herbal Plants and the Immune System	247
9.4.1 Medicinal Value of Herbal Plants.....	249
9.5 Conclusion	250
Acknowledgements.....	251
References.....	251

9.1 INTRODUCTION

In recent times, the World Health Organization (WHO) estimated that approximately 80% of people globally depended on herbal medicines for primary health care requirements (WHO 1993). Approximately 21,000 plant species have potential for use as medicinal plants. The use of plants is mankind's oldest approach to health care. Herbal remedies are occasionally called traditional medicines. Various herbal plants which are recognized in the traditional structure of medicine contain a large number of pharmacologically active chemicals bioactives (Ford and Roach, 2009). In the period of globalization, health-conscious individuals around the world began to emphasize the use of medicinal herbs of Indian origin (Sarkar et al. 2015). Increasingly, herbal plants have gained a good reputation as a result largely of the work of local traditional herbal practitioners. It is noteworthy to point out here that the majority of the Indian herbal plants are found throughout South India (Rajan et al. 2005). In light of the significance of traditional herbal medicinal plants of southern India as a resource to fight against infectious diseases, there is the likelihood that some function by stimulating the immune response of the host. As a consequence, plant extracts used in traditional herbal remedies should be assessed for immunomodulatory activities (Upadhyay, 1997).

The basic structural design of the immune system is multifaceted, with fortifications at several different stages (Kumar et al. 2012). If pathogens have effectively entered the body of the host, then they are faced with the rapid but short-lived non-specific innate immune response or the slower-acting but longer-lasting specific adaptive immune response (Hofmeyr, 2001). It should be obvious that there are many healing plants that make use of immunomodulatory activity. The range of phytochemicals in herbal formulations may lead to a cooperative effect in achieving greater defence through inducing both innate and adaptive immunities, with both defensive antibodies and the development of effective cell-mediated immune responses (Vimalanathan et al. 2009). There are a large number of herbal products with prospective therapeutic applications because of their high effectiveness, low cost, and low toxicity. Such herbal formulations may consequently be recommended as a positive immunomodulator. The exhibition of increased immunity by the use of herbal plants and their extracts or derivatives shows potential as a promising health care strategy for the future (Singh et al. 2016).

9.2 HERBAL PLANTS

'Herbs' refer to the use of some or all parts of the plant, such as seed, bark, stem, leaf, stigma, flower, fruit, root, or whole plant. Over the past two decades, there has been a marked increase in the use of herbal medicines. Consequently, since 1999, WHO has published three volumes of monographs on herbal plants (<http://WHO>). Treatment with preparations of confirmed medicinal herbs increases the resistance of the patient to disease and other conditions. Plant-based herbal therapies are potent, with low toxicity and low cost, and are accessible to the local community. Problems of traditional herbal medications are often associated with the presence of natural or man-made contaminants, which may result in poor response by the patient and even death (van Wyk and Prinsloo, 2020). Studies on traditional healing plants have turned out to be even more valuable with respect to the expansion of healthcare programmes throughout the world (Shil et al. 2014). Traditional medicine systems are based on plant-derived bioactive molecules with pharmaceutical activities (Rehechoa et al. 2011). Treatment of some diseases by means of herbal plant preparations is considered to be superior to conventional medicines because of the negligible side effects. Medicinal herbs can show therapeutic superiority over conventional single-compound medicines, especially with respect to hard-to-treat or chronic diseases. Numerous modern pharmaceutical drugs are derived in some way from phytochemicals. The use of conventional herbal medicines occurs predominantly in developing countries (UNESCO, 1996), though their adoption in the developed countries is increasing markedly. Current estimates list more than 9,000 plants with recognized therapeutic relevance in different traditions and countries.

9.3 IMMUNE SYSTEM

In recent times, there has been steady progress in our understanding of the immune system, and its ability to defend the body from infection, identifying each phase of

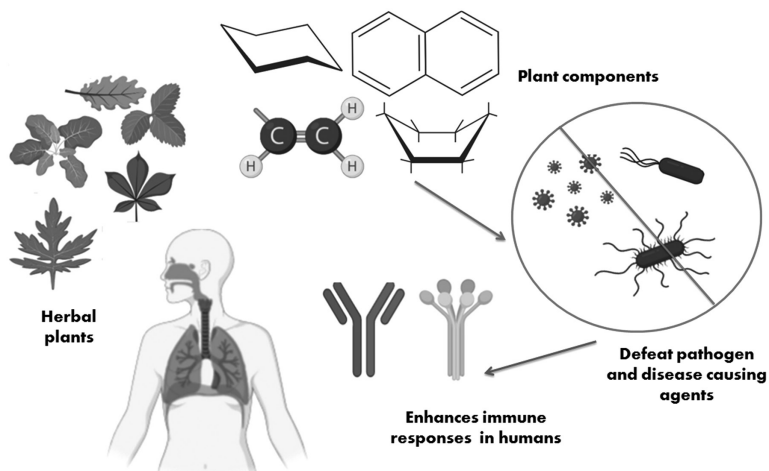


FIGURE 9.1 Traditional herbal plants which suppress disease-causing pathogens and stimulate the human immune system.

immunology (Murphy et al. 2007). The immune system involves a network of genes, molecules, cells, and pathways to defend the membrane, intestinal tract, respiratory channel, and other parts from antigens from the attacker (Figure 9.1).

The innate and adaptive immune systems are expressed *via* different pathways, though they typically perform as one. The innate reaction reflects the initial barrier of the host defence, with the adaptive immune reaction peaking later, by which time antigen-specific T and B cells have undergone clonal extension (Huston, 1997). The innate immune system uses receptors that are encoded by intact genes inherited through the germline, whereas the adaptive immune system uses antigen receptors encoded by genes that are assembled from individual gene segments during lymphocyte development, a process that leads to each individual cell expressing a receptor of unique specificity (Holmskov et al. 2003). A major problem faced with the immune classification involves recognition of host cells that have been contaminated by microorganisms (Chaplin, 2010). Innate and adaptive immunities are not reciprocally elite methods of host defence, although they can quite harmonize together. Innate immunity is the initial immunological, non-specific means for defending against a pathogen (Turvey and Broide, 2010). This resistant reaction is rapid and is carried out between numerous cells, including eosinophils, phagocytes, basophils, and the complement system. Adaptive immunity expands through innate immunity to eradicate transferable agents (Bonilla and Oettgen, 2010).

9.4 TRADITIONAL SOUTH INDIAN HERBAL PLANTS AND THE IMMUNE SYSTEM

Some of the important traditional herbal plants distributed within India, and particularly in India, are listed in Table 9.1. The plants are recognized to exhibit several

TABLE 9.1
Traditional South Indian Herbal Plants and their Healing Properties

South Indian Herbal Plant	Diseases Treated and Activities Exhibited	References
<i>Andrographis paniculata</i>	Anti-inflammatory, immunostimulant, antiparasitic, hepatoprotective, antihyperglycaemic and antihypoglycaemic	Sagadevan and Suresh, (2015)
<i>Acalypha indica</i>	Anthelmintic, antibacterial, anti-ulcer, to treat wounds, asthma, and bronchitis	Zahidin et al. (2017)
<i>Cassia auriculata</i>	Anti-tumour, anti-diabetic, and immunomodulatory	Chakraborty, (2009)
<i>Calotropis gigantea</i>	Antifertility, vermifugal activity, and pregnancy interceptive	Kumar et al. (2013)
<i>Cardiospermum halicacabum</i>	Immunomodulatory and anti-arthritic activities	Saravandaa et al. (2018)
<i>Catharanthus roseus</i>	Anti-helminthic, pesticidal, and antidiabetic activities	Kaushik et al. (2017)
<i>Cynodon dactylon</i>	Immunomodulatory effects	Mangathayan et al. (2009)
<i>Datura metel</i>	Antimicrobial, antipyretic, anti-asthmatic, analgesic, and nephroprotective activities	Alam et al. (2020)
<i>Euphorbia susanholmesiae</i>	To treat skin cancer and actinic keratosis	Ernst et al. (2015)
<i>Gloriosa superba</i>	Antidote for snake bite, as a laxative, to treat ulcers, arthritis, cholera, colic, kidney problems, and typhus	Zahir et al. (2012); Kavithamani et al. (2013)
<i>Lufa acutangula</i>	Immunomodulatory, analgesic, and gastroprotective effects	Al- Snafi, (2019)
<i>Lyngodium flexuosum</i>	Jaundice, wound healing, and eczema	Esha et al. (2011)
<i>Morinda pubescens</i>	Antimicrobial activity	Ravikumar et al. (2012); Tyagi et al. (2015)
<i>Myrtus communis</i>	Immunostimulant	Tae et al. (2017)
<i>Opuntia ficus-indica</i>	Anti-inflammatory and hypoglycaemic effects, delay of stomach ulceration, and neuroprotective effects	Kaur et al. (2012)
<i>Phyllanthus emblica</i>	Antiviral, antimicrobial, anticancer, hepatoprotective, and antidiabetic properties	Khan (2009)
<i>Phyllanthus niruri</i>	Antispasmodic, analgesic, anticonvulsant, aphrodisiac, and contraceptive activities	Kamruzzaman and Hoq (2016);
<i>Physalis angulata</i>	Antitumour and immunomodulatory effects	Chiang et al. (1992); Lin et al. (1992)
<i>Piper longum</i>	To treat cough, stomach-ache, diseases of the spleen, bronchitis, and tumours	Kumar et al. (2011)
<i>Ruellia tuberosa</i>	To treat stomach cancer, gonorrhoea, and bladder diseases	Chothani et al. (2010)

(Continued)

TABLE 9.1 (CONTINUED)

Traditional South Indian Herbal Plants and their Healing Properties

South Indian Herbal Plant	Diseases Treated and Activities Exhibited	References
<i>Thevetia peruviana</i>	Larvicidal, antidiabetic, antifertility, antimicrobial, and anticancer properties	Ahmad et al. (2017)
<i>Tridax procumbens</i>	Immunomodulatory effects	Tiwari et al. (2004)
<i>Vitex negundo</i>	Anti-inflammatory and antioxidant activities	Utpalendu et al. (1999); Tiwari (2007)
<i>Withania somnifera</i>	Chemopreventive, used to treat Alzheimer's disease and Parkinson's disease, as a memory enhancer and an immunomodulator	Umadevi et al. (2012)

activities which enables them to treat human diseases, including stimulation of the immune system (Nath et al. 2011). The goal of this study was to screen the methanol or acetone extracts of four plant species from South India for antileishmanial activity. This provided the primary details on the *in-vitro* activity of certain plants towards the intracellular human parasite *Leishmania donovani*. The effectiveness of the effective herbal plants will be further explored extensively with regard to a number of activities, because it is obligatory to follow up these findings with pharmacological and phytochemical analysis of the traditional herbal plants. The major focus of these traditional herbal plants on the immune system highlights the need to evaluate the potential of South Indian herbal plants to offset the side effects of modern therapies by stimulating the immune systems of the host.

9.4.1 MEDICINAL VALUE OF HERBAL PLANTS

Medicinal plants have been used since ancient times to treat a wide range of diseases, ailments and conditions. Herbal medicinal plants are gaining a positive reputation among individuals in both urban and rural areas (Katic, 1980). The most famous author on plant drugs was Dioscorides, “the father of pharmacognosy,” who, as an army doctor and pharmacognosist with Nero’s army, studied medicinal plants everywhere he travelled with the Roman Army (Nikolovski, 1961). Subsequently, as society and cultures evolved, the curative properties of confirmed herbal plants were noted, recognized, and directed towards the appropriate age group (Petrovska, 2012).

The significance of the contribution of herbal plants to human health cannot be overestimated. These plants contain curative phytochemicals in individual organs or in several of them. The use of these plants is increasing globally in terms of the expansion of established medicine and the increasing interest in herbal medicine. Plants are used as a source of natural drugs to sustain and expand the patient’s physical and mental condition (Idu, 2009). For instance, the use of herbal medicine to treat

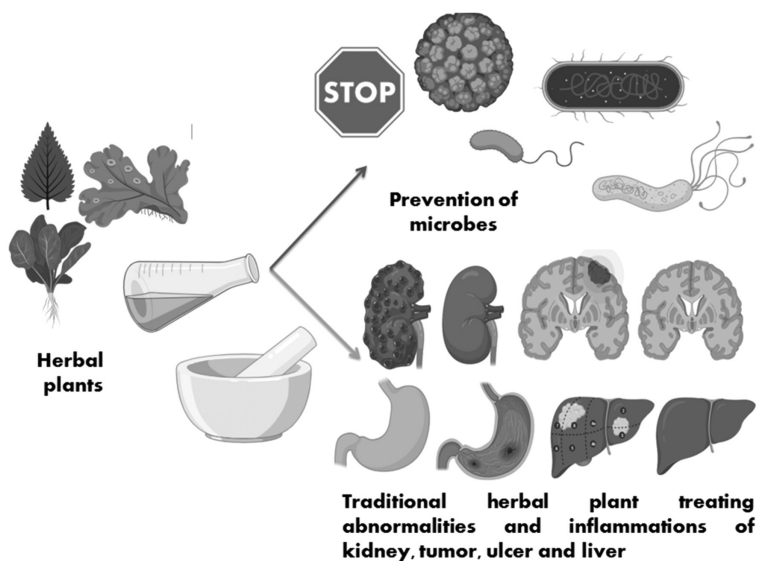


FIGURE 9.2 Herbal plants which helps to inhibit the pathogen and combat several diseases.

diseases related to asthma, cancer, neurological and hepatic diseases is estimated to be approximately 80%, 55%, 42%, and 90% of people, respectively (Al-Moamary, 2008; Jazieh et al. 2012; Mohammad et al. 2015) (Figure 9.2). Each part of the medicinal plant possesses healing properties, including activities, such as anti-inflammatory, anti-insecticidal, antioxidant, antibiotic, antiparasitic, and antihemolytic properties, and so on (Neelam Bamola et al. 2018). The medicinal value of plants lies in their secondary plant metabolites for treatment of numerous illnesses (Modak et al. 2007).

Phytochemicals are pharmacologically active compounds of several different types: terpenoids, which are recognized for their antihelmintic, antiviral, anticancer, antibacterial, anti-inflammatory, and antimalarial properties; alkaloids, which have antispasmodic, analgesic, antimalarial, and diuretic activities; and phenolics and flavonoids, which have antioxidant, antibacterial, and antiallergic properties (Maurya et al. 2008). In addition, saponins (a type of terpenoid) are known to exhibit anti-inflammatory, antiviral, and plant defence activities, whereas glycosides of other groups of secondary metabolites can show antifungal and antibacterial properties (Chopra et al. 2002). Thus, traditional knowledge of herbal plants assists the pharmaceutical industries in developing novel drugs and to employ them to achieve the treatment of different diseases (Forouzan et al. 2012; Bahmani et al. 2013; Divya et al. 2020).

9.5 CONCLUSION

As our way of life becomes increasingly dominated by technology, we are becoming more widely separated from the natural world. As herbs are natural products, their availability is reasonably secure, recyclable, and accessible. By tradition, there are

groups of herbs used for treating particular disorders during a specific season of the year. Herbs had been exploited for flavouring, medicinal, and scented characteristics for centuries, but the synthetic chemicals used for the same ends in the modern age have become predominant. This chapter deals only with the traditional knowledge of medicinal plants from the South Indian region, as directly related to medicinal research with respect to the practice of traditional medicines in that region as well as in neighbouring areas. To conclude, this book chapter focuses on a range of natural traditional herbal medicines to stimulate the immune system of humans. This also emphasizes the progress achieved in medicinal innovation dealing with the medicinal plants of South India, with a number of suggestions, recommendations, and future goals for this aspect of herbal medicine.

ACKNOWLEDGEMENTS

The corresponding author, Dr. Sekar Vijayakumar, is grateful to Shandong University, Weihai, P.R. China, for providing a post-doctoral research fellowship.

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10 Sacred Medicinal Plants and their Use by Indigenous People for Strengthening the Immune System

Jamal Akhtar and Fouzia Bashir

CONTENTS

10.1	Introduction	256
10.2	Plants Mentioned in Sacred Books	257
10.2.1	Khajoor	260
10.2.1.1	Evidence-based Research	261
10.2.2	Zaitoon	262
10.2.2.1	Evidence-based Research	263
10.2.3	Maweez	263
10.2.3.1	Evidence-based Research	264
10.2.4	Rumman	264
10.2.4.1	Evidence-based Research	265
10.2.5	Kalonji	265
10.2.5.1	Evidence-based Research	266
10.2.6	Kafoor	267
10.2.6.1	Evidence-based Research	268
10.2.7	Zanjabeel	268
10.2.7.1	Evidence-based Research	268
10.2.8	Anjeer	269
10.2.8.1	Evidence-based Research	270
10.2.9	Mauz	270
10.2.9.1	Evidence-based Research	270
10.2.10	Ber	271
10.2.10.1	Evidence-based Research	271
10.2.11	Rehan	272
10.2.11.1	Evidence-based Research	272
10.2.12	Peepal	273
10.2.12.1	Evidence-based Research	273

10.2.13	Bael	274
10.2.13.1	Evidence-based Research	275
10.2.14	Neem	275
10.2.14.1	Evidence-based Research	276
10.2.15	Sandal	276
10.2.15.1	Evidence-based Research	277
10.2.16	Qinnab	277
10.2.16.1	Evidence-based Research	278
10.2.17	Ashok	278
10.2.17.1	Evidence-based Research	278
10.2.18	Sumbul-ut Teeb	279
10.2.18.1	Evidence-based Research	279
10.2.19	Zoofa	279
10.2.19.1	Evidence-based Research	280
10.2.20	Foful	280
10.2.20.1	Evidence-based Research	281
10.2.21	Nilofar	281
10.2.21.1	Evidence-based Research	282
10.4	Conclusion and Future Perspectives	282
	Acknowledgements	286
	Bibliography	286

10.1 INTRODUCTION

India, the second most heavily populated country in the world, with twenty-eight states and eight Union territories, is also one of the most diverse nations in the world in terms of religions and cultures. Religion plays a vital and absolute role in the life of many of its people. Although India is a secular country, it has several different religions, i.e., Hindus, Muslims, Christians, Sikhs, Buddhists, Jains, and various tribal populations in India. According to the census of India (2011), the Indian population comprises 79.80% Hindus, 14.23% Muslims, 2.3% Christians, 1.72% Sikhs, 0.70% Buddhists, 0.4% Jains, and 0.9% others (Anonymous 2004). Every religion has their ‘Sacred’ books and places, which demand deep respect and are ‘set aside’ for purposes of the spiritual or religious.

In the Qur’an, the holy book of Muslims, many plants, like Teen (*Ficus carica*), Zaitoon (*Olea europaea*), Khurma (*Phoenix dactylifera*), Munaqqa (*Vitis vinifera*), Anar (*Punica granatum*), Kafoor (*Cinnamomum camphora*), Ber (*Zizyphus jujuba*), Mauz (*Musa paradisiaca*), and Kalonji (*Nigella sativa*), etc., are quoted as being part of a diet for the preservation of health and the management of diseases. According to Vedas in Hindu mythology, various ‘Sacred’ plants are described for improving health and for curing diseases, such as Tulsi (*Ocimum sanctum*), Peepal (*Ficus religiosa*), Bael (*Aegle marmelos*), Neem (*Azadirachta indica*), Sandal (*Santalum album*), Bhang (*Cannabis sativa*), and Ashok (*Saraca asoca*), etc. Similarly, in the Bible, the holy book of Christians, Teen (*Ficus carica*), Nard/Sumbul-ut-Teeb

(*Nardostachys jatamansi*), Zoofa (*Hyssopus officinalis*), Foful (*Areca catechu*), and Nilofar (*Nymphaea alba*), etc. are mentioned for the maintenance of health.

These medicinal plants have been given so much importance for health maintenance that people even worship them, an act which attracted scientists from different fields, namely botanists, pharmacologists, biochemists, and pharmacognosists, to determine the science behind these sacred medicinal plants. They tried to identify the active ingredients and the molecular mechanisms between these phytochemicals and health issues, which not only cause the health benefits and health-promoting effects but which are also used in the management of diseases. This chapter highlights some of the readily accessible sacred plants mentioned in the holy Qur'an/Ahadith and other religious books to identify established immunomodulatory and other medicinal effects.

10.2 PLANTS MENTIONED IN SACRED BOOKS

The sacred book of Islam, the Qur'an, is the Word of God, as it was revealed to Prophet Muhammad (PBUH). With its unique composition and style, the Qur'an is also considered to be the pre-eminent literary masterpiece of the Arabic language. Its contents provide the basics of the doctrinal tenets and principles of Islam. The Qur'an comprises 6,236 verses (ayahs) which are divided into 114 chapters or surahs, each of which takes its name from a prominent event, theme, or topic relevant to the chapter. A report of the sayings or actions of Muhammad or his companions, together with the tradition of its chain of transmission, is called Ahadith.

The Hindu sacred text has been divided into the revealed and the remembered texts, and the original language of the early Hindu sacred books is Sanskrit. The revealed texts are found in the Veda, which may be divided into four parts, the Rig Veda, the Yajur Veda, the Sama Veda, and the Atharva Veda, while the remembered texts consist of post-Vedic texts, including two epics, the Mahabharata and the Ramayana; the Bhagavad Gita, based on the god Krishna, a script inserted into the Mahabharata, and the Dharam sastras based on dharma. The Bible for Christians, the Guru Granth Sahib for the Sikhs, the Tipitaka for the Buddhists, and the Agam Sutras for the Jains are the sacred books of different religions practised in India.

In Islam, according to the Qur'an and Ahadith, the importance of various plants is mentioned, e.g., Teen (*Ficus carica*), Zaitoon (*Olea europoea*), Khurma (*Phoenix dactylifera*), Maweez (*Vitis vinifera*), Anar/Rumman (*Punica granatum*), Balsan (*Ocimum basilicum*), Kafoor (*Cinnamomum camphora*), Miswak (*Salvadora persica*), Khardal (*Brassica nigra*), Ber (*Zizyphus jujuba* Lam.), Hanzal (*Citrulus colocynthis*), Mauz (*Musa paradisiaca*), and Kalonji (*Nigella sativa*).

The Qur'anic verses which contain description of plants and their parts are to inspire people to think about Allah's creation and to aid them to reach a level of faith based on conviction. These verses also remind people of Allah's blessings and the need to thank Him for what He has offered them.

وَمِنْ ثَمَرَاتِ النَّخِيلِ وَالْأَعْنَابِ نَتَّخِذُونَ مِنْهُ سَكَرًا وَرِزْقًا حَسَنًا إِنَّ فِي ذَلِكَ لَآيَةً لِّقَوْمٍ يَعْقِلُونَ ﴿١٧﴾

'And from the fruits of the palm trees and grapevines you take intoxicant and good provision. Indeed, in that is a sign for a people who reason'. (Qur'anic Verse, 16:67)

وَالنِّينِ وَالزَّيْتُونِ ﴿١﴾

'By the fig and the olive' (Qur'anic Verse, 95:1)

وَإِذْ قُلْتُمْ يَا مُوسَىٰ لَنْ نَصْبِرَ عَلَىٰ طَعَامٍ وَاحِدٍ فَادْعُ لَنَا رَبَّكَ يُخْرِجْ لَنَا مِمَّا تُنْبِتُ الْأَرْضُ
مِنْ بَقْلِهَا وَقِثَّائِهَا وَفُومَهَا وَعَدْسَهَا وَبَصِلَهَا ۗ قَالَ أَتَسْتَبْدِلُونَ الَّذِي هُوَ
أَدْنَىٰ بِالَّذِي هُوَ خَيْرٌ ۗ أَهَيِّطُوا مَصْرًا فَإِنَّ لَكُمْ مَآسًا أَنْتُمْ وَضَرَبْتُمْ عَلَيْهِمُ
الذِّلَّةَ وَالْمَسْكَنَةَ وَبَاءَ أَوْ يَغْضَبُ مِنَ اللَّهِ ذَٰلِكَ بِأَنَّهُمْ كَانُوا يَكْفُرُونَ بِآيَاتِ اللَّهِ
وَيَقْتُلُونَ النَّبِيِّنَ بِغَيْرِ الْحَقِّ ذَٰلِكَ بِمَا عَصَوْا وَكَانُوا يَعْتَدُونَ ﴿٦١﴾

'And [recall] when you said, "O Moses, we can never endure one [kind of] food. So, call upon your Lord to bring forth for us from the earth its green herbs and its cucumbers and its garlic and its lentils and its onions". [Moses] said, "Would you exchange what is better for what is less? Go into [any] settlement and indeed, you will have what you have asked". And they were covered with humiliation and poverty and returned with anger from Allah [upon them]. That was because they [repeatedly] disbelieved in the signs of Allah and killed the prophets without right. That was because they disobeyed and were [habitually] transgressing'. (Qur'anic Verse, 2:61)

وَهُوَ الَّذِي أَنْزَلَ مِنَ السَّمَاءِ مَاءً فَأَخْرَجْنَا بِهِ نَبَاتَ كُلِّ شَيْءٍ فَأَخْرَجْنَا مِنْهُ خَضِرًا
تُخْرِجُ مِنْهُ حَبًّا مُتَرَاكِبًا وَمِنَ النَّخْلِ مِنَ طَلْعِهَا قِنَوَانٌ دَانِيَةٌ وَجَنَّاتٍ مِّنْ أَعْنَابٍ
وَالزَّيْتُونِ وَالرُّمَّانِ مُشْتَبِهًا وَغَيْرَ مُتَشَبِهٍ ۗ انظُرُوا إِلَىٰ ثَمَرِهِ إِذَا أَثْمَرَ وَيَنْعِهِ ۗ إِنَّ فِي ذَٰلِكُمْ
لَآيَاتٍ لِّقَوْمٍ يُؤْمِنُونَ ﴿١١﴾

'It is He Who sends down water [rain] from the sky, and with it We bring forth vegetation of all kinds, and out of it We bring forth green stalks, from which We bring forth thick clustered grain. And out of the date palm and its spathe come forth clusters of dates hanging low and near, and gardens of grapes, olives, and pomegranates, each similar (in kind) yet different (in variety and taste). Look at their fruits when they begin to bear, and the ripeness thereof. Verily! In these things there are signs for people who believe'. (Qur'anic Verse, 6:99)

﴿١١﴾ وَهُوَ الَّذِي أَنْشَأَ جَنَّاتٍ مَّعْرُوشَاتٍ وَغَيْرَ مَعْرُوشَاتٍ وَالنَّخْلَ وَالزَّرْعَ مُخْتَلِفًا
أُكْلُهُ، وَالزَّيْتُونَ وَالرُّمَّانَ مُتَشَبِهًا وَغَيْرَ مُتَشَبِهٍ ۗ كُلُوا مِنْ ثَمَرِهِ إِذَا
أَثْمَرَ ۗ وَأَتُوا حَقَّهُ يَوْمَ حَصَادِهِ ۗ وَلَا تُسْرِفُوا ۗ إِنَّهُ لَا يُحِبُّ الْمُسْرِفِينَ ﴿١٤١﴾

‘And He it is who causes gardens to grow, [both] trellised and untrellised, and palm trees and crops of different [kinds of] food and olives and pomegranates, similar and dissimilar. Eat of [each of] its fruit when it yields and give its due [zakah] on the day of its harvest. And be not excessive. Indeed, He does not like those who commit excess’. (Qur’anic Verse 6:141)

According to Hindu mythology, various ‘Sacred’ plants and herbs are described for improving health and for curing diseases, e.g., Tulsi (*Ocimum sanctum*), Peepal (*Ficus religiosa*), Bael (*Aegle marmelos*), Neem (*Azadirachta indica*), Sandal (*Santalum album*), Bhang (*Cannabis sativa*), Ashok (*Saraca asoca*), and Coconut (*Cocos nucifera*).

क्षुधामारं तृष्णामारमृगोतामनपुत्यताम् । अपामार्गं त्वया व्ययं सर्वं तदपं मृज्महे ॥

‘We cleanse and wipe away, through Apamarga, the harm caused by hunger, harm caused by thirst, debility of limbs, and childlessness’. (Atharvaveda, 4, 17, 6)

शतवारो अनीनशुद्धक्ष्मात्रक्षांसि तेजसा । आरोहन्वर्चसा सह मणिर्दुर्गामिचातनः ॥

‘The praiseworthy germicidal shatavara [the name of herb which prevents one hundred diseases] mounting over the disease with splendour vanishes the tuberculosis and its germs with power’. (Atharvaveda, 19, 36, 1)

पिप्पुल्यं¹ समंवदन्तायुतीर्जनादधि । यं जीवमुश्रवांमहे न स रिष्याति पूरुषः ॥

‘These *Piper longum*, as if confabulating mutually tell them that from their origin, the alive man whom they were applied to, does not feel troubled by rheumatic pain’. (Atharvaveda, 6, 109, 2)

यथाह्वल्पेनयत्नेनच्छिद्यतेतरुणस्तरुः।

सएवाऽतिप्रवृद्धस्तुच्छिद्यतेऽतिप्रयत्नतः॥

एवमेवविकारोऽपितरुणःसाध्यतेसुखम्।

विवृद्धःसाध्यतेकृद्भादसाध्योवाऽपिजायते॥

‘Just as a tender plant is easy to cut down, the same requires much more effort when fully grown. Likewise, any disease is manageable in the early stage; it becomes almost incurable when it grows’ (Charak Nidaan 5/13–16).

Some plants with medicinal value are mentioned in the Bible, such as Teen (*Ficus carica*), Nard/Sumbul-ut-Teeb (*Nardostachys jatamansi*), Zoofa (*Hyssopus officinalis*), Ood Balsam (*Commiphora opobalsamum*), and Foful (*Areca catechu*). In Buddhism, some flowers, like Nilofar (*Nymphaea alba*), Champa (*Michelia champaca*), and Chameli (*Plumeria rubra*), are also said to have medicinal value.

‘Now Isaiah had said, “Let them take a cake of figs and apply it to the boil that he may recover’. (Isaiah 38:21 ESV/157)

‘Mary therefore took a pound of expensive ointment made from pure nard and anointed the feet of Jesus and wiped his feet with her hair. The house was filled with the fragrance of the perfume’. (John 12:3 ESV/9)

‘Purge me with hyssop, and I shall be clean; wash me, and I shall be whiter than snow’. (Psalm 51:7 ESV/39).

The different parts of these sacred plants have been used medicinally by indigenous people to treat different ailments. These plants have also been mentioned by the ancient Hakims and Vaidis for the treatment of several diseases, as well as to improve immunity or to act as a tonic. While centuries of use of these sacred medicinal plants is the basis of the testimony, nowadays, more specific and reproducible results are needed to certify the quality, safety, and reliability of the phytomedicines, as well as scientific evidence in relation to health claims, according to international guidelines. These plants have been scientifically evaluated for different activities, e.g., immunostimulant, cardioprotective, anti-arrhythmic, spasmolytic, hypotensive, antihyperglycaemic, antimicrobial, and anti-inflammatory effects.

According to the World Health Organization (WHO), 80% of the world’s population still relies on botanical medicines for primary health care (Mukherjee et al. 1998a; Mukherjee 2002a). There is a need for experimental data, proper documentation on mechanisms of action, standardization and fractionation by modern techniques, and *in-vitro* and *in-vivo* studies to check safety and efficacy assurance and to identify the molecular mechanism behind the medicinal effects of these sacred plants. Therefore, evidence for the potential immunomodulatory effects of these sacred medicinal plants, based on research demonstrating a biological activity in relevant *in-vitro* and/or *in-vivo* bioassays, using animal models, is necessary. These plants have been studied scientifically to establish the link between traditional knowledge and modern science. Various investigations on these sacred plants have confirmed the immunomodulatory effects of these plants.

10.2.1 KHAJOUR

Botanical Name *Phoenix dactylifera* L.

Kingdom/Subkingdom – Plantae/Tracheobionta
 Super division/Division – Spermatophyta/Magnoliophyta
 Class/Subclass – Liliopsida/Arecidae
 Order/Family – Arecales/Arecaceae
 Genus/Species – *Phoenix/dactylifera*

Vernacular Names

Arabic – Tammar, Nahal, Balah, Rutab
 Urdu – Khajur
 Hindi – Khajoor
 English – Date palm
 Persian – Khurma

Khajoor (*P. dactylifera*) is one of the sacred plants mentioned in the Holy Qur'an and belongs to the Arecaceae family. It has been cultivated in the deserts of Iraq, the Arab world, North Africa, Pakistan, and India. The fruit is commonly available and is a rich source of dietary fibre, and also contains large amounts of lipids, minerals, protein, and certain essential vitamins (Figure 10.1a). It is used in the diet to improve health. The dates have also been used to treat a variety of ailments in the various traditional systems of medicine, e.g., heart diseases, skin diseases, as an antidote, to treat intestinal colic, as a wound healer, to treat diarrhoea, stomach-ache, sexual weakness, piles, physical debility, a shrill voice, and liver disorders (Anonymous 1986; Qarshi 2011).

10.2.1.1 Evidence-based Research

Khajoor (*P. dactylifera*) were evaluated scientifically for immunomodulatory effects. Polyphenols, identified as chlorogenic acid, caffeic acid, pelargonin, and ferulic

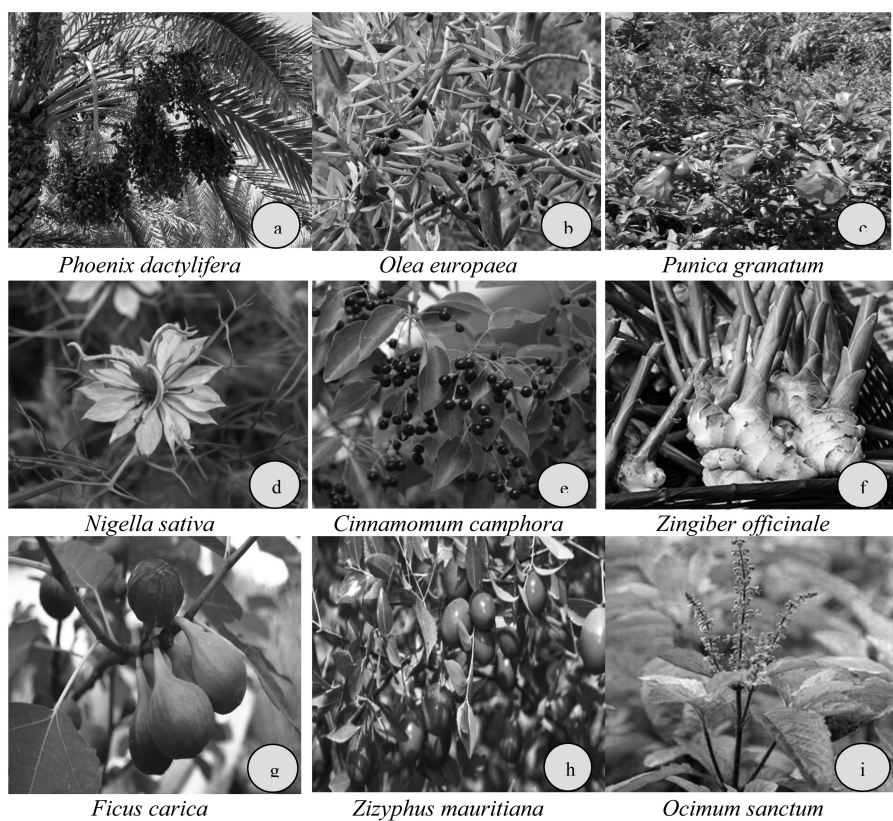


FIGURE 10.1 Sacred medicinal plants for a strong immune system: (a) *Phoenix dactylifera*–Khajoor, (b) *Olea europaea*–Zaitoon, (c) *Punica granatum*–Rumman, (d) *Nigella sativa* – Kalonji, (e) *Cinnamomum camphora* – Kafoor, (f) *Zingiber officinale* – Zanjabeel, (g) *Ficus carica* – Anjeer, (h) *Zizyphus mauritiana* – Ber, and (i) *Ocimum sanctum* – Rehan.

acid, from the hot water extract of matured fruit of the date palm tree, stimulated the expression of interferon IFN- γ mRNA significantly in experimental animals by stimulating the cell-mediated immune mechanism (Koji 2011). Similarly, the immunomodulatory effects of hot water extracts of date, prune, or fig were investigated, and it was observed that date extract stimulated the cellular system more than did the prune or fig extracts (Mansouri 2005). Khajoor extract at a dosage of 50 mg/kg body-weight showed an immunostimulatory effect on the reticulo-endothelial system and antioxidant activity (Eddine 2014). It was also observed that Khajoor extract normalized the level of circulatory CD161 natural killer (NK) cells, and breast tissue TNF-alpha, cell size, and proliferation, and improved overall survival rates (Elhemeidy 2018). Tahneeq is a traditional method in which pre-masticated Ajwa palm dates are rubbed manually onto the palatal mucosa of newborn babies. A study was conducted to investigate the effects of Ajwa palm dates on interleukin IL-12 expression in dendritic cells and blood T lymphocytes expressing CD8⁺ in experimental rats. They were divided into three groups of neonatal Wistar rats immediately after birth: the control group received breastmilk, the first treatment group (T1) received breast milk and mild-scratched intensity of tahneeq, whereas the second treatment group (T2) received breast milk and strong-scratched intensity of tahneeq on the palatal and gingival mucosa. It was observed that treatment groups 1 and 2 had significantly higher interleukin-12 (IL-12) expression than the control group. The increased IL-12 expression in T2 group was significantly higher than IL-12 expression in the T1 and control groups.

10.2.2 ZAITOON

Botanical Name *Olea europaea* L.

Kingdom/Subkingdom – Plantae/Tracheobionta
Superdivision/Division – Spermatophyta/Magnoliophyta
Class/ Subclass – Magnoliopsida/Asteridae
Order/Family – Scrophulariales/Oleaceae
Genus/Species – *Olealeuropaea*

Vernacular Names

English – Olive
Hindi – Jaitoon
Urdu – Zaitoon
Arabic – Zaitoon
Persian – Zaitoon

Zaitoon (*O. europaea*) plants have religious importance and are usually found in northern Iran, coastal areas of the eastern Mediterranean region, south-eastern Europe, the western part of Asia, and northern Africa (Ali 2004). Olives are mentioned many times in the Bible, both in the New and Old Testaments. The olive tree has also been praised as a blessed tree and fruit in the Holy Qur'an. The Prophet

Muhammad (PBUH) recommended various plants e.g., dates, black seed, and olive, for the management of different diseases (Anonymous 2000; Maryam et al. 2009). The plant has laxative, mouth cleanser, tonic, and vasodilator properties, and is known to reduce blood sugar, cholesterol, and uric acid levels (Figure 10.1b). It has also been used to treat various disorders, e.g., hypertension, diabetes, inflammation, haemorrhoids, diarrhoea, respiratory diseases (including bronchial asthma), urinary tract infections, gastrointestinal disorders, and musculo-skeletal disorders (Nadkarni 1986; Anonymous 1999; Nigrami 2009).

10.2.2.1 Evidence-based Research

Leaves, fruits, and oil of Zaitoon play an important role in the management of different diseases, which may be due to the presence of simple phenolics (hydroxytyrosol, tyrosol) and polyphenols. Different research studies conducted on *in-vitro* and *ex-vivo* models have revealed that phenolics present in olive oil have antioxidant activity towards lipids and DNA oxidation greater than the industrial standard, vitamin E (Owen 2000). Extracts of leaves collected from three olive cultivars were investigated for phenolic compounds, using a high-performance liquid chromatography system coupled to a diode array detector time-of-flight mass spectrometer (HPLC-DAD-TOF-MS). Thereafter, an *in-vitro* study was carried out on RAW 264.7 mouse macrophages to investigate the immunomodulatory properties of the crude phenolic extracts. A total number of 28 phenolic compounds were identified in the olive leaf extracts. It was also observed that all olive leaf extracts exhibited immunomodulatory properties, as they inhibited the release of nitric oxide from RAW 264.7 cells treated with lipopolysaccharide (LPS), which is a pro-inflammatory mediator. It may be concluded that the inhibition of nitric oxide by the leaf extracts of Zaitoon depends more on the type of phenolic compounds present in the extract than on the total phenolic concentration (Talhaoui 2015).

10.2.3 MAWEEZ

Botanical Name *Vitis vinifera* L.

Kingdom/Subkingdom – Plantae/Tracheobionta
 Superdivision/Division – Spermatophyta/Magnoliophyta
 Class/Subclass – Magnoliopsida/Rosidae
 Order/Family – Rhamnales/Vitaceae
 Genus/species – *Vitis/vinifera*

Vernacular Names

Arabic – Inab
 Persian – Kishmish
 Urdu – Maweez, Zabeeb, Munaqqaa, Kishmish
 Hindi – Angur
 English – Grape
 Sanskrit – Draksha

Maweez (*V. vinifera*) is a woody and shrubby climber, which is usually found in Southeastern Europe, but nowadays is widely cultivated in Europe, Australia, California, and other parts of North America. It is cultivated for agricultural purposes in many states across India, e.g., Punjab, Rajasthan, Delhi, Uttar Pradesh, Maharashtra, Karnataka, Andhra Pradesh, and Tamil Nadu. The flowers are small, pale, and green in colour which appear in the summer season, followed by bunches of green to purple-black berry fruits. Ripe berries are often used as a mild laxative and nutrient, while unripe berries are used to neutralize excessive bile and thus improve ailments of the gastro-intestinal system. Dried berries have stomachic, anti-emetic, hepatoprotective and blood-purifying properties. Maweez is used to treat coughs and other respiratory tract diseases. It is also beneficial in the treatment of liver disorders, gastro-intestinal problems, haemorrhagic diseases, and gout, as well as dyspnoea (Ghani YNM; Gruner 1970; Nadkarni 1976, 1982).

10.2.3.1 Evidence-based Research

An *in-vivo* and an *in-vitro* study were conducted to explain the molecular mechanisms involved in the immunomodulation effects and antitumour therapeutic effect of grape seed proanthocyanidins (GSPs). The *in-vivo* study revealed that GSPs inhibit the growth of Sarcoma 180 tumour cells significantly and increase the thymus and spleen weight of Sarcoma 180-bearing mice remarkably, elevating the secretion level of serum Tumour Necrosis Factor- α (TNF- α). It was also observed that exposure to GSPs could increase the lysosomal enzyme activity, stimulate the lymphocyte transformation and the phagocytic capability of peritoneal macrophages, and markedly promote the production of TNF- α . The results of this study suggest that GSPs improve the immune system (Tong 2011).

10.2.4 RUMMAN

Botanical Name *Punica granatum* L.

Kingdom – Plantae

Division – Spermatophytina

Class – Magnoliopsida

Superorder/Order – Rosanae/Myrtales

Family – Lythraceae

Genus/species – *Punica/granatum*

Vernacular Names

Arabic – Rummän, Shajarätur-Rummän

Urdu – Anar Mitha

English – Pomegranate tree

Hindi – Anaar, Dhalim

Persian – Darakht-e-Anar, Gulnar, Anar

Sanskrit – Bijapura, Dadima, Shuka-dana, Kuchaphala

Anar/Rumman (*P. granatum*) is an ancient, mystic, distinctive fruit, borne on the long-lived pomegranate tree. It is a large, deciduous shrub or small tree, having

smooth grey bark, and is often armed with small axillary or terminal thorns. It is found throughout India from the Balkans to the Himalayas. Nowadays, it is cultivated in most regions of the world, e.g., Iran, Spain, Italy, Afghanistan, USA, India, China, Russia, Uzbekistan, Morocco, and Greece (Figure 10.1c). Pomegranate is used to treat various ailments in the Unani system of medicine. Extract of pomegranate flowers acts as an astringent, checking haemorrhage from all internal organs. Its desiccant properties dry up morbid bodily secretions. Application of the powder or its decoction is useful in treating stomatitis, and also prevents various oro-dental disorders, like bleeding gums, shaky teeth, bad odour, mouth ulcer, etc. The ointment is effective in wound healing because of its cicatrizing (scar development) properties. It is also effective in the treatment of diarrhoea and dysentery. The flower extract is also beneficial in treating skin diseases, such as scabies, pruritus, etc. Either root or stem bark, being anthelmintic in action, expel intestinal worms when administered in the form of decoction. Whole fruit is used as a cardiac and liver tonic and as an aphrodisiac in cases of sexual debility. Seeds are anti-emetic and diuretic in action (Ghani 1921; Momin YNM; Baitar YNM; Hamdani 2001).

10.2.4.1 Evidence-based Research

Investigations on fruit rind powder were carried out to evaluate the immunomodulatory activity of Rumman. An aqueous suspension of fruit rind powder in a dose of 100 mg/kg bodyweight was administered orally, which stimulated the cell-mediated and humoral components of the immune system. Antibody titre to the typhoid-H antigen (HA) was also increased (Ross et al. 2001). An *in-vitro* assay, using four separate antioxidant testing methods, demonstrated that extracts of pomegranate juice and seed exhibited two to three times the antioxidant activity (Gil et al. 2000). The immunomodulatory effect on cell-mediated immunity of an ethanolic extract of the peel and fruit juice of *P. granatum* was evaluated. The neutrophil adhesion test and cyclophosphamide-induced myelosuppression activity assay were also used as testing methods. HA titres were used to determine the effect on antibody-mediated immunity. It was observed that the effects of the extract on the percentage neutrophil adhesion, cyclophosphamide-induced myelosuppression, and HA titre were significant, when compared to the standard (Levamisole) group. The study revealed that the peel extract and the fruit juice had significant effects on cell-mediated and humoral immunity (Ittiyavirah 2014). *In-vitro* studies were conducted to investigate the radical scavenging and antitumour activities of polysaccharides (PSP001) isolated from *P. granatum*. It was shown that an *in-vitro* growth stimulatory effect on isolated normal lymphocytes, and a proliferative index of 1.21 ± 0.01 at a concentration of 1000 $\mu\text{g/ml}$ was obtained, indicating immunomodulatory activity. The results of this study indicated that further studies are required on PSP001 in order to use this compound as an antitumour agent (Joseph et al. 2012).

10.2.5 KALONJI

Botanical Name – *Nigella sativa* L.

Kingdom/Subkingdom – Plantae/Tracheobionta

Superdivision/Division – Spermatophyta/Magnoliophyta

Class/Subclass – Magnoliopsida/Magnoliidae

Order/Family – Ranunculales/Ranunculaceae

Genus/Species – *Nigella/sativa*

Vernacular Names

Arabic – Kamun Aswad, Habbatussauda

Persian – Shooneez

Hindi – Kalonji, Mungrela

Urdu – Kalonji

English – Black Cumin, Small Fennel, Nigella Seed

Kalonji (*N. sativa*) is an annual flowering plant which grows to 20–90 cm tall. It is commonly grown in Saudi Arabia, northern Africa, and Asia. Kalonji seeds are widely used as spices and food preservatives, as well as being used as medicine for centuries around the world. The leaves are finely divided. The flowers have 5–10 petals and are yellow, white, pale blue, or pale purple in colour (Figure 10.1d). Seeds are dark, thin, and crescent shaped, with a pungent smell and a bitter taste. Prophet Muhammad (PBUH) stated that Habbatus sauda/Kalonji (Nigella seeds) can cure every disease except death. Seeds were prescribed by ancient Unani physicians to treat headache, nasal congestion, toothache, and intestinal worms, as well as acting as a diuretic, to regulate menstruation, and to promote milk production (Maseehi 2008; Husain 2010; Bashir et al. 2018).

10.2.5.1 Evidence-based Research

Methanolic extracts of the shoots, roots, or seeds of Kalonji were assessed for antioxidant, anti-inflammatory, anticancer and antibacterial activities. The results showed that all these extracts exhibited strong antioxidant activity (Bourgou et al. 2008). It was also observed that Kalonji powder inhibited the oxidative stress caused by administration of oxidized corn oil to experimental animals (Al-Othman et al. 2006). Thymoquinone (TQ) is one of the major bioactive components extracted from the volatile oil of *N. sativa* seeds. It was evaluated for antioxidant and anti-arthritis activity in collagen-induced arthritis. It was found that oral administration of TQ reduced the levels of pro-inflammatory mediators [IL-1 β , IL-6, TNF- α , IFN- γ and PGE (2)] and increased the IL-10 level (Umar et al. 2012). It was also observed that treatment with Nigella seed for six weeks protected the liver of broiler chicks from oxidative stress by increasing the activities of enzymes such as glutathione-S-transferase, myeloperoxidase, adenosine deaminase, and catalase and by decreasing hepatic lipid peroxidation (Sogut 2008). The crude methanolic extract of Nigella seed cake was found to exhibit significant antioxidant properties under an *in-vitro* system (Mariod 2009). The effect of *N. sativa* oil on the selected T cell subset percentage in females with rheumatoid arthritis (RA) was investigated. A significant decrease was observed in serum high-sensitivity C-reactive protein (hs-CRP) level and DAS-28 score and there was a decreased number of swollen joints compared with baseline and placebo groups. A comparable CD4+T-cell percentage

was observed in the *N. sativa* and placebo groups either in the baseline or at the end of the study. The treatment also resulted in a reduction in CD8+, and an increase in CD4+CD25+T cell percentage, with the CD4+/CD8+ ratio being observed in the treatment group as compared with the placebo (Kheirouri et al. 2016). The effects of three different concentrations of each of the ethanolic extract of *N. sativa*, thymoquinone (TQ), dexamethasone, and saline were investigated, and it was observed that the ethanolic extract of *N. sativa* and TQ had cytotoxic activity and immunomodulatory effects, especially at the higher concentrations. The highest concentration of *N. sativa* extract increased the IFN γ /IL-4 ratio in both non-stimulated and stimulated cells, while the higher concentrations of TQ increased the IFN γ /IL-4 ratio in stimulated cells only (Gholamnezhad et al. 2015). The immunomodulatory effect of *N. sativa* was studied, and it was observed that extracts of *N. sativa* had an immunostimulating effect on non-PHA (Phytohaemagglutinin)-stimulated proliferation of human PBMCs (Peripheral blood mononuclear cells) (Alshatwi 2014).

10.2.6 KAFOOR

Botanical Name *Cinnamomum camphora* L.

Kingdom/Subkingdom – Plantae/Tracheobionta
Superdivision/Division – Spermatophyta/Magnoliophyta
Class/Subclass – Magnoliopsida/Magnoliidae
Order/Family – Laurales/Lauraceae
Genus/species – *Cinnamomum/camphora*

Vernacular Names

Arabic – Kafoor
Urdu – Kafoor
English – Camphor tree
Hind – Kapoor

Kafoor or camphor is a white, crystalline substance with a strong odour and a pungent taste. It is obtained from the wood of camphor laurel and other related trees of the laurel family. The Kafoor tree (*C. camphora*) is found in India, China, Mongolia, Taiwan, and Japan, with a variety of this fragrant, evergreen tree being grown in the southern United States, especially in Florida (Figure 10.1e) (Frizzo 2000). Kafoor is obtained by steam distillation, purification, and sublimation of wood, twigs, and bark of the tree (Zuccarini 2009). There are many pharmaceutical activities of Kafoor, such as a topical analgesic, and anti-inflammatory, antispasmodic, antiseptic, antipruritic, anti-infective, contraceptive, rubefacient, nasal decongestant, mild expectorant, cough suppressant activities, etc. (Chelliah 2008; Zuccarini 2009). Kafoor is easily absorbed through the skin and can also be administered by injection, inhalation, or ingestion (Sydney 1978; Zuccarini 2009). It is used in medicine in preparations of toothpaste, powder, as a diaphoretic or antiseptic, and to treat hysteria and dysmenorrhoea (Kabeeruddin 2009; Jurjani 2010; Lone 2012).

10.2.6.1 Evidence-based Research

Immunomodulatory effects of Kafoor and Kakuti (*Ziziphora tenuior*) were studied, and it was found that the extracts had a non-significant macrophage cytotoxicity in the dimethylthiazol-diphenyltetrazolium bromide (MTT) cell metabolic activity assay (Kanan 2020).

10.2.7 ZANJABEEL

Botanical Name *Zingiber officinale* Roscoe

Kingdom – Plantae
 Division – Magnoliophyta
 Class/Sub Class – Liopsida/Zingiberidae
 Order – Zingiberales
 Family – Zingiberaceae
 Genus/species – *Zingiber/officinale*

Vernacular Names

Arabic – Qafeer, Zanjabeel
 Urdu – Sonth, Zanjabeel
 Persian – Sahangrez, Zanjabil
 English – Ginger
 Hindi – Sonth, Adrak
 Sanskrit – Naara, Visva, Adraka, Anupama

Zanjabeel (*Z. officinale*) is an important medicinal plant which is cultivated on a large scale in different parts of India, especially in the warm, moist regions, e.g., Chennai, Cochin, and Travancore, and, to a somewhat lesser extent, in Bengal and Punjab. It is also found at some places in the western Ghats. Ginger requires a warm and humid climate. The plant thrives well from sea level up to an altitude of 1500 m in the Himalayas, the optimum elevation being between 300 and 900 m. The crop needs adequate rainfall and high temperatures during the growing period (Figure 10.1f). According to Unani literature, ginger acts as carminative, digestive, expectorant, and detergent (Ghani 1921). Many commentators have said that Arabs were pleased with drinking wine mixed with ginger, because it made the wine tastier. Now, the Holy Qur'an speaks about 'a cup (of pure drink)' which is mixed with Zanjabeel, but it is obvious that this mixed drink is completely different from that of wine. In other words, the difference between these two kinds of drink is as far as the distance between this world and the next world (Kabeeruddin 1954, 1994).

10.2.7.1 Evidence-based Research

Z. officinale has antioxidant activities as it scavenges peroxide and hydroxyl ions, as well as suppressing lipid peroxidation (Kabuto 2005). The immunomodulatory effects of *Z. officinale* and some other plant oils were evaluated by studying humoral

and cell-mediated immune responses, and it was found that ginger essential oil recovered the humoral immune response in immunosuppressed mice (Carrasco et al. 2009). An *in-vitro* study was conducted to determine the immunomodulatory effect of *Z. officinale* and it was found that the plant extract inhibited lymphocyte proliferation, which was mediated by reductions in IL-2 and IL-10 production (Wilasrusmee et al. 2002). An aqueous extract of ginger was investigated for immunomodulatory effects, and significant increases in the production of IL-1 β , IL-6, and TNF- α were observed in activated peritoneal mouse macrophages, and increases occurred with respect to splenocyte proliferation and cytokine production (Ryu and Kim 2004). Ginger rhizome powder was found to be capable of improving non-specific immune response in rainbow trout (Haghighi and Rohani 2013). The therapeutic efficacy and mechanisms of action of ginger on key immunopathogenic mechanisms was relevant to psoriasis treatment (Nurul et al. 2013). The successful isolation of pure bioactive compounds from *Z. officinale* confirmed the traditional use of the plant to stimulate the immune system (Tan and Vanitha 2004).

10.2.8 ANJEER

Botanical Name *Ficus carica* L.

Kingdom – Plantae
Division – Magnoliophyta
Class – Magnoliopsida
Order – Urticales
Family – Moraceae
Genus – *Ficus*

Vernacular Names

Arabic – Teen
English – Common Fig, Fig
Indian – Anjir

Anjeer (*F. carica*) is a large tree or shrub 4.5–9.0 m high, which has been cultivated throughout the world since ancient times, both for its decorative purposes as well as for the usefulness of its fruit. The plant produces several branches from the trunk, and the bark of the tree is grey or dull white, smooth or hairy. The leaves are broad, lobed, ovate or nearly orbicular, with a blade 10–20 cm long and petioles 5.0–7.5 cm long with a rough surface (Figure 10.1g). In classical Unani literature, it has been mentioned that fruits of Anjeer can be eaten fresh as well as dried and used as jam. It has a high nutritive value and provides energy to the human body. Pharmacologically, Anjeer fruit has diuretic, detergent, laxative, de-obstruent, and anti-inflammatory properties, and it can be used in the treatment of chickenpox, measles, respiratory diseases, palpitations, etc. (Kabeeruddin 2006; Qamri 2010; Khan 2011).

10.2.8.1 Evidence-based Research

An ethanolic extract of the leaves of *F. carica* was assessed for immunomodulatory effect and it was revealed that the extract of the leaves had significantly ameliorated the cell-mediated and humoral antibody response. The results indicated that the extract possessed immunostimulant properties (Patil 2010). Anjeer fruits from six commercial fig varieties of different colours (black, red, yellow, or green) were evaluated for total polyphenols, total flavonoids, antioxidant capacity, and profile of anthocyanins, and it was found that the fruits contained the highest levels of polyphenols, flavonoids, and anthocyanins, and exhibited the highest antioxidant capacity (Çalışkan 2011). The antioxidant potential of fig extract was determined by the ABTS assay and it was found to be very high (19.8 mg/ml) (Soni et al. 2014). A novel polysaccharide (FCPW80-2) was isolated from *F. carica* through hot water extraction and several chromatographic methods. The results showed that MAPK and NF- κ B signalling pathways contributed to FCPW80-2-induced macrophage activation, so that FCPW80-2 has potential to be used as an immunomodulating functional food (Du et al. 2018). Antioxidant activity and the effect on the immune response by fermented fig extracts were investigated in mice. It was observed that the extracts enhanced immune organ indexes, improved immune organ injuries, helped in the production of immune-related cytokines, and improved the histopathological state of immune organs (Zhao et al. 2020).

10.2.9 MAUZ

Botanical Name *Musa paradisiaca* L.

Kingdom/Subkingdom – Plantae/Tracheobionta
Superdivision/Division – Spermatophyta/Magnoliophyta
Class/ Subclass – Liliopsida/Zingiberidae
Order/Family – Zingiberales/Musaceae
Genus/Species – *Musa/paradisiaca*

Banana (*M. paradisiaca*) is a very important fruit crop in India. Its accessibility, affordability, taste, range, nutritional, and medicinal values make it the favourite fruit among all classes of people. Bananas are spread over almost the entire world. In India, it is cultivated in particular in Andhra Pradesh, Assam, Gujarat, Jharkhand, Karnataka, Kerala, Madhya Pradesh, Maharashtra, Orissa, Tamil Nadu, and West Bengal. It is used as food, medicine (*Ilaj Bil Ghiza*) for treatment of several diseases, like diarrhoea, dysentery, constipation, etc. The fruit is a very rich source of valuable phytochemicals, including phenolic compounds and vitamins. (Khare 2007; Imam 2011; Deepthi 2012; Sampath 2012).

10.2.9.1 Evidence-based Research

A study was carried out on powdered CandI banana (*M. × paradisiaca*) extracted with ethanol or ethyl acetate in an ultrasonic bath and it was observed that these extracts had antioxidant activities which were higher in the ethanolic extract than

in the ethyl acetate extract (Laeliocattleya 2018). Flavonoids isolated from peels of *M. × paradisiaca* were investigated for immunomodulatory properties. It was revealed that these flavonoids showed dose-dependent increases in antibody titre at higher doses, which confirmed the immunomodulatory activities of these flavonoids isolated (Abhijit et al. 2017).

10.2.10 BER

Botanical Name *Ziziphus mauritiana* (Lamk.)

Kingdom – Plantae

Division/Subdivision – Magnoliophyta/Angiosperm

Class – Magnoliopsida

Order/ Family – Rosales/Rhamnaceae

Genus – *Ziziphus/mauritiana*

Vernacular Names

Urdu – Annab, Baer, Ber, Unab, Unnab

Arabic – Annab, Aunnab e hindi, Nabig, Nabiq

Persian – Kanar, Kunar

English – Chinese Apple, Cottony Jujube, Indian Cherry, Indian Jujube

Hindi – Ber

Sanskrit – Ajapriya, Badara, Karkandhu

Ber (*Z. mauritiana*) is a very common plant, which is cultivated throughout India and other countries on the Indian subcontinent. It is a spiny, evergreen shrub or small tree with a height up to 15 m, with a trunk diameter of 40 cm or more, a spreading crown, stipular spines, and many drooping branches. It is a multi-purpose tree grown mainly for its fruits. Bearing of fruits starts after 6–8 years of growth. The fruit can be eaten fresh or dried like dates, candied, salted, or pickled (Figure 10.1h). It can also be used as flour meal, paste, juice, syrup, or as a beverage. It may be used in the treatment of insomnia, chronic bronchitis, constipation, liver diseases, fever, bronchial asthma, urinary diseases, and gastro-intestinal disorders (Mediratta 2002; Tabri 2003; Akassh 2020).

10.2.10.1 Evidence-based Research

Root of *Z. mauritiana* were investigated and it was found that the root extract, particularly that extracted in dichloromethane, had immunomodulatory, cytotoxic, and antioxidant activities (Afzal 2017). Twenty-eight varieties of Indian jujube were investigated for different compounds, e.g., ascorbic acid, total phenolics, flavanols, total flavonoids, and dihydric phenol. It was observed that cv. ZG₃ was found to exhibit the highest DPPH free radical scavenging activity, followed by ‘Katha Phal’ and ‘Thar Sevika’. Variation in relation to their phenolic content and antioxidant activity among the genotypes was also observed (Krishna 2013). *Ficus religiosa* (sacred fig) and *Z. mauritiana* were investigated for immunostimulatory effect and it was found that both extracts in higher doses increased paw oedema in comparison with the control group. This revealed the immunostimulatory effect of the selected plant

extracts on the cell-mediated immune response (Maity et al. 2012). The aqueous or ethanolic extracts of *Z. mauritiana* seed were studied for immunomodulatory activities, with results indicating that up-regulation of cell-mediated humoral immune response, as well as in Th-1-mediated cytokine IFN-gamma levels, and decreases in Th-2-mediated cytokine IL-4 were the most significant changes (Mishra 2010).

10.2.11 REHAN

Botanical Name *Ocimum sanctum* L.

Kingdom/ Subkingdom – Plantae/Tracheobionta
Superdivision/Division – Spermatophyta/Magnoliophyta
Class/Subclass – Magnoliopsida/Asteridae
Order/Family – Lamiales/Lamiaceae
Genus/species – *Ocimum/sanctum*

Vernacular Names

Urdu – Rehaan
Arabic – Rehan
Persian – Jasaspermum
English – Holy Basil, Sweet Basil
Hindi – Tulsi
Sanskrit – Tulsipatr, Tulsidal, Vrinda

Rehan (*O. sanctum*) is a tropical plant which grows as a weed or is cultivated. Rehan or Tulsi is worshipped by Hindus and is considered to be very important in the Hindu faith. It is a branched, fragrant, and erect herb which has hairs all over. Mature plants may grow up to a height of 75–90 cm (Figure 10.1i). Different parts (leaves, stems, flowers, roots, seeds, and even whole plants) of Tulsi have been used widely by the traditional medical practitioners for the treatment of various diseases in their day-to-day practice, such as malaria, bronchial asthma, bronchitis, diarrhoea, chronic fever, dysentery, arthritis, skin diseases, painful eye diseases, insect bite, etc. (Anonymous 1989; Hakeem 2002; Zaidi 2011; Gupta 2018).

10.2.11.1 Evidence-based Research

O. sanctum seed oil was evaluated for immunomodulatory activity in both non-stressed and stressed animals, and it was revealed that *O. sanctum* seed oil modulated humoral and cell-mediated immune sensitivity (Mediratta 2002). An aqueous extract of *O. sanctum* leaves has shown immunotherapeutic potential in sub-clinical trials, and there was a reduction in the total bacterial count, and an increase in neutrophils and lymphocytes with good phagocytic activity (Mukherjee 2005). Aqueous and ethanolic extracts of *O. sanctum* leaves were evaluated for immunomodulatory activity, which stimulated both specific and non-specific responses assessed by the Haemagglutination Antibody (HA) titre assay, the neutrophil adhesion test, and the Delayed Type Hypersensitivity (DTH) test (Das et al. 2015). The aqueous or methanolic extracts of *O. sanctum* leaves produced clinically significant immunostimulation of the humoral immunological response (Godhwani 1988). Methanolic and

aqueous extracts of *O. sanctum* leaves exhibited immunoregulatory activity (Kelm 2000; Dashputre 2010). Aqueous leaf extracts of *O. sanctum* were investigated *in vitro* and *in vivo* for immunomodulatory activity and it was observed that the extract increased the DTH response, the TLC (Total Leukocyte Count) and the DLC (Differential Leukocyte Count) count significantly, with the extract at 200 mg/kg bodyweight showing only a significant effect but a dose of 400 mg/kg and the standard treatment showing highly significant effects, compared with the control group (Venkatachalam 2013). A study was conducted to compare the immunomodulatory effects of *O. sanctum* with those of *Ocimum basilicum* in mice and it was observed that neither preparation caused any mortality or any signs of behavioural changes or toxicity at the dose level of 2000 mg/kg bodyweight in mice, but *O. sanctum* improved the DTH reaction in mice in T cell-dependent antigen response, which may be due to the stimulatory effect of *O. sanctum* on T cells (Jeba 2013).

10.2.12 PEEPAL

Botanical name *Ficus religiosa* L.

Kingdom/Subkingdom – Plantae/Viridiaeplantae
Class/Subclass – Magnoliopsida/Dilleniidae
Order/Family – Urticales/Moraceae
Genus/species – *Ficus/religiosa*

Vernacular Names

Hindi – Pipli, Papal, Pipar
Sanskrit – Asvattha
English – Peepal Tree, Sacred Fig

Peepal (*F. religiosa*) is one of the oldest trees mentioned in Indian literature. The tree is described in the holy books of Hinduism, such as Arthasastra, Puranas, Upanishads, Ramayana, Mahabharata, and Bhagavad Geeta, and in Buddhist literature. The tree is native to India and is believed to have originated mainly in northern and eastern India. It is also grown in neighbouring countries, like Bangladesh, Pakistan, Nepal, Sri Lanka, and China. The tree grows very large, with wide spreading branches and brown-coloured bark. The plant has thin shiny leaves and the fruit is flattened and circular in shape (Figure 10.2a). Young immature leaves are reddish-pink in colour, turning deep green on maturity. Fruits are known to cure various diseases, such as bronchial asthma and digestive disorders. The leaves are effective in the treatment of different diseases like hiccoughs, vomiting, gonorrhoea etc. The bark also shows beneficial effects with respect to diseases such as diarrhoea, dysentery, inflammation, bacterial infections, paralysis, and bleeding (Azmi 1995; Anonymous 2006).

10.2.12.1 Evidence-based Research

An alcoholic extract of the bark of *F. religiosa* was investigated for immunomodulatory activity and it was observed that the extract ameliorated both the cell-mediated and the humoral antibody response to a great degree. It was concluded that the extract possessed promising immunostimulant properties (Mallurvar 2008). The

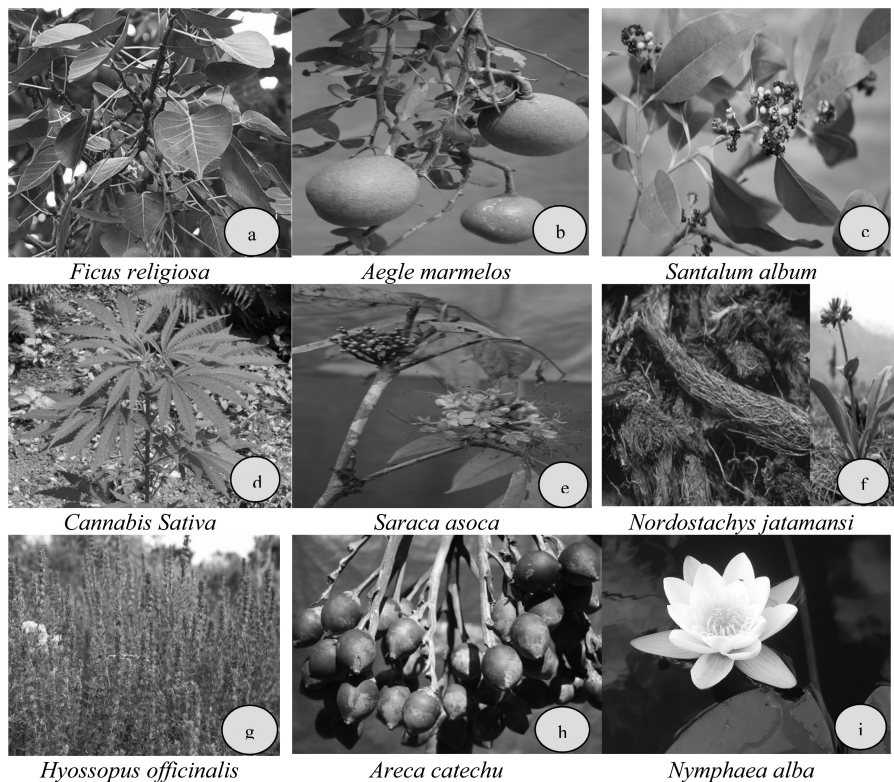


FIGURE 10.2 Sacred medicinal plants for a strong immune system: (a) *Ficus religiosa* – Peepal, (b) *Aegle marmelos* – Bael, (c) *Santalum album* – Sandal, (d) *Cannabis sativa* – Qinnab, (e) *Saraca asoca* – Ashok, (f) *Nordostachys jatamansi* – Sumbul ut Teeb, (g) *Hyossopus officinalis* – Zoofa, (h) *Areca catechu* – Foful, and (i) *Nymphaea alba* – Nilofar.

aqueous extract of *F. religiosa* reduced oxidative stress in rats with experimentally induced type 2 diabetes (You 2006).

10.2.13 BAEI

Botanical Name *Aegle marmelos* (L.) Correa

Kingdom/Subkingdom – Plantae/Tracheobionta
 Superdivision/Division – Spermatophyta/Magnoliophyta
 Class/Subclass – Magnoliopsida/Rosidae
 Order/Family – Sapindales/Rutaceae
 Genus/Species – *Aegle/marmelos*

Vernacular Names

Urdu – Bel
 English – Apple wood, Bengal Quince, Golden Apple, Japanese Orange

Hindi – Sir Phal, Bel
 Sanskrit – Shree Phal, Bilva, Asholam
 Gujrati – Billi (Baghdadi 2005)

Bael (*A. marmelos*) is a very common spiritual and religious plant, which is a native of India and Bangladesh but is cultivated throughout SouthEast Asia. Bael is sweet, aromatic, and astringent in nature (Bashir et al. 2018). It is one of the few Unani plants where all the different parts, from roots to leaves, are used for medicinal purposes against different diseases (Figure 10.2b). Due to its digestive and carminative properties, it is used for curing chronic diarrhoea and dysentery. It is also used to treat intermittent fevers and heart disorders (Bashir et al. 2018; Bhar et al. 2019).

10.2.13.1 Evidence-based Research

A study was carried out to assess the immunomodulatory activity of a methanolic extract of *A. marmelos* fruit in an experimental model of immunity. The results showed that the fruit extract at 100 and 500 mg/kg bodyweight produced significant increases in adhesion of neutrophils and an increase in phagocytic index in the carbon clearance assay in the test animals (Patel et al. 2010). Pratheepa and colleagues carried out a study where fish were challenged with pathogens through the water medium for thirty days and the immunomodulatory effect of the *A. marmelos* leaf extract was evaluated on blood samples every five days until fifteen days after infection. The results obtained from the study showed that the dosage of 25 g leaf extract/kg of feed was found to be capable of achieving the optimum immune response (Pratheepa et al. 2011).

10.2.14 NEEM

Botanical Name *Azadirachta indica*

Kingdom/Subkingdom – Plantae/Tracheobionta
 Order/Suborder – Rutales/Rutinae
 Family/Subfamily – Meliaceae/Melioideae
 Genus/Species – *Azadirachta indica*

Vernacular Names

Urdu – Neem
 Sanskrit – Nimbah, Arista, Arkapadapa
 English – Indian lilac, Margosa tree
 Tamil – Vepamaram, Vemu, Vembu
 Hindi – Balnimb, Nim, Neem, Nimb
 Persian – Azad Darakth-e-Hind, Nib, Neeb

Neem (*A. indica*) is a popular, evergreen tree, which is found commonly in India, Africa, and USA. It grows to a height of 12–18 m, with a girth of 1.8–2.4 m. Its straight, long, and spreading branches form a broad crown. (Brahmachari 2004) The leaves are alternate, imparipinnate, and 20–38 cm long. The leaflets are 8–19 cm long, alternate or opposite, and the fruit is one seeded. Neem is used in Ayurveda,

Unani, homoeopathy, and modern medicine for the treatment of many infectious, metabolic, or cancer diseases. It is a multipurpose tree with immense potential. It possesses more useful non-wood products (leaves, bark, flowers, fruits, seed, gum, oil, and neem cake) than any other tree in India. Various properties of Neem have been mentioned in classical Unani literature, such as antiseptic, antipyretic, antitussive, cicatrizant, carminative, etc., which can be used to treat skin diseases, arthritis, drowsy, earache, and other diseases (Ahmedullah 1999).

10.2.14.1 Evidence-based Research

An aqueous extract of the flowers of *A. indica* was evaluated for immunomodulatory activity on humoral and cell-mediated immune response to ovalbumin. Treatment with the extract showed a significant increase in phagocytic index, which reflects activation of the reticulo-endothelial system through release of the mediators. The extract also resulted in an increase in antibody titre against ovalbumin, with a significant effect on stimulation of T cells at the dose of 400 mg/kg bodyweight (Abhishek 2009). It was confirmed that a methanolic extract of the leaves of *A. indica* exhibited antioxidant activity (Pokhrel 2015). A study was conducted to evaluate the immunomodulatory effects of Neem oil in experimental animals, which revealed that Neem oil works as a non-specific immunostimulant by selectively activating the CMI (Cell-Mediated Immunity) mechanisms (Upadhyay et al. 1992). NIM-76, a volatile fraction from Neem oil, was assessed for its immunomodulatory properties and it was found that NIM-76 acts through cell-mediated mechanisms by activating macrophages and lymphocytes (Ram et al. 1997). An aqueous extract of the stem bark of *A. indica* showed strong anticomplement effects, which were dose- and time-dependent and most pronounced in the classical complement pathway assay (Van der Nat et al. 1987). The growth-promoting and immunomodulatory effect of a Neem leaf infusion was evaluated on broilers and it was observed that the Neem infusion significantly increased antibody titre, growth performance, and gross return (Durrani et al. 2008).

10.2.15 SANDAL

Botanical Name *Santalum album*

Kingdom/Subkingdom – Plantae/Tracheobionta
Superdivision/Division – Spermatophyta/Magnoliophyta
Class/Subclass – Magnoliopsida/Rosidae
Order/Family – Santalales/Santalaceae
Genus/species – *Santalum/album*

Vernacular Names

Arabic – Khashab ul Sandal
English – Sandalwood
Hindi – Chandan
Persian – Chob Sandal
Sanskrit – Shrigandha
Urdu – Sandal

Sandal (*S. album*) is one of the most precious trees in the world, with great sacred value. Ancient history reveals that sandalwood has been referred to in Indian mythology, folklore, and ancient scriptures. The finest sandalwood grows in the driest regions, mainly on red or stony ground; on rocky ground, the tree often remains small but gives the highest yield of oil. It is an evergreen tree that grows up to 20 m, attaining a girth of up to 2.4 m, with slender drooping branchlets (Figure 10.2c). A wide range of articles, such as boxes, jewel cases, picture frames, combs, pen holders, card cases, hand fans, and bookmarks, are made from sandalwood. As medicine, sandalwood is regarded as a coolant, sedative, astringent, and disinfectant in the genitourinary and bronchial tracts, and as a diuretic, expectorant, and stimulant. The wood, root, bark, and leaves of the tree are used to treat liver diseases, such as jaundice, by the tribal healers (Duke 2002). It is used by the Jews, the Buddhists, and the Hindus, as well as adherents to almost every other belief system for its vast diversity of attributes (Joshi 2003; Sina 2010; Arun 2012).

10.2.15.1 Evidence-based Research

The FRAP (Ferric Reducing Antioxidant Power Assay) antioxidant assay of an aqueous extract of *S. album* confirmed the antioxidant activity of the plant (Shamsi et al. 2014).

10.2.16 QINNAB

Botanical Name *Cannabis sativa*

Kingdom/Subkingdom – Plantae/Tracheobionta
Superdivision/Division – Spermatophyta/Magnoliophyta
Class/Subclass – Magnoliopsida/Hamamelididae
Order/Family – Rosales/Cannabaceae
Genus/Species – *Cannabis sativa*

Vernacular Names (Kalam 2020)

Arabic – Banj, Qinnab, Warq al-Khiyal
Persian – Bang, Hashish, Falaksair, Arshnuma, Falaktaz, Kinnab
Bengali – Bhang
English – Indian hemp.
Gujarati – Bhang, Gajna
Hindi – Bhang, Bhanga, Ganja, Charas, Shiv Booti

Qinnab (*C. sativa*) is a native of Persia, western and Central Asia. Nowadays, it is cultivated all over India and is wild in the western Himalayas from Kashmir to East of Assam. The drug is mentioned in early Hindu and Chinese works on medicine. It is an erect, much-branched 40–75 cm tall herb, which commonly grows along roadsides and on waste ground. The leaves have a strong, characteristic odour, with a somewhat acrid and pungent taste (Figure 10.2d). Because of its soothing properties, it is effectively used for the treatment of diseases related to the brain and nerves (Samarqandi 1906; Killestein 2003).

10.2.16.1 Evidence-based Research

Cannabidiol is one of the key pharmacologically active compounds of *C. sativa*. It was clinically tested on patients suffering from multiple sclerosis, and a modest increase in TNF-alpha in lipopolysaccharide (LPS)-stimulated whole blood was found in the treatment group, although no changes in other cytokines were observed (Killestein 2003). Cannabidiol protects lipids and proteins against oxidative stress damage by modulating the level of oxidative stress, by participating in cell signalling pathways (Atalay 2019).

10.2.17 ASHOK

Botanical Name *Saraca asoca* L.

Kingdom/Subkingdom – Plantae/Tracheophyta
Superdivision/Division – Spermatophyta/Magnoliophyta
Class – Magnoliopsida
Order/Family – Fabales/Fabaceae
Genus/Species – *Saraca/asoca*

Vernacular Names

Urdu – Ashok Chaal
Bengali – Asok, Asoka
English – Asoka Tree.
Gujarati – Ashopalava
Hindi – Ashok, Asok
Sanskrit – Apashoka, Ashok, Chitra, Doshahari, Gandhapushpa

Ashok (*S. asoca*) is a medium-sized, evergreen tree with glabrous branches. It is generally found in hilly areas of Assam, West Bengal, and the western Ghats of Maharashtra in India. The leaves are pinnate and rigidly coracious (Figure 10.2e). Moist and well-drained soil is very suitable for the growth of the plant. It is a moderately shade-loving tree. The bark of the plant has been described in classical Unani literature as a uterine tonic, antimenorrhagic, refrigerant, vermifugal, nervine tonic, and anti-inflammatory, which may be used in uterine debility, leucorrhoea, etc. (Kabiruddin YNM; Kirtikar 1991; Rushd 1997; Tariq 2010).

10.2.17.1 Evidence-based Research

A methanol extract of the bark of *S. asoca* showed the highest radical scavenging activity, using the DPPH assay, at a concentration of 200 µg/µl, which confirms the antioxidant activity of plant extracts of *S. asoca* (Mohan 2016). The antioxidant potential of the petroleum ether, ethyl acetate, benzene, ethanol, and methanol extracts of the flowers of *S. asoca* was also evaluated. The results showed that ethanol extract of the flowers of the plant exhibited the highest antioxidant activity (Tresina et al. 2018).

10.2.18 SUMBUL-UT TEEB

Botanical name *Nardostachys jatamansi* (D. Don) DC

Kingdom – Plantae
Division – Magnoliophyta
Class – Magnoliopsida
Order – Dipsacales
Family – Caprifoliaceae
Genus – *Nardostachys*

Vernacular Names

Urdu – Sumbul-ut-teeb, Balchar
Arabic – Sumbul-ut-teeb
Persian – Sumbul-ut Teeb
English – Muskroot, Indian Spikenard, Spikenard
Hindi – Balchar, Balchir, Jatamansi
Sanskrit – Mansi, jati, jatila Jatamansi, Janani Jatamansi

Sumbul-ut Teeb (*N. jatamansi*) is a perennial plant commonly cultivated in the hilly regions of Himachal Pradesh, Sikkim, Uttaranchal, and Jammu and Kashmir. The plant is up to 60 cm in height, with long woody rootstocks. Dark grey rhizomes are crowned with reddish brown tufted fibres internally. These rhizomes are elongated and cylindrical in shape, from 2.5 to 7.5 cm in length (Muzafar 2017). The radical and elongated leaves are sessile, oblong, or sub-ovate (Figure 10.2f). Flowers are pale pink or blue in colour. According to classical Unani literature, Sumbul-ut Teeb acts as an emmenagogue, carminative, diuretic, cardiotoxic, and brain tonic and can be used to treat insomnia, hypertension, asthma, and epilepsy (Razi 1991; Rizwan 2010).

10.2.18.1 Evidence-based Research

A methanolic extract of Sumbul-ut Teeb exhibited antioxidant activity, using the FRAP (10.18 mg ascorbic acid equivalent (AAE)/100 g dry weight, DW) and ABTS assays (4.87 mg AAE/100 g DW); on the other hand, the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay showed significantly higher antioxidant activity (5.84 mg AAE/100 g DW; Bhatt et al. 2012). The antioxidant activity of the essential oil and of different extracts of *N. jatamansi* roots, measured by DPPH radical scavenging and the chelation power assay, showed that the methanolic extract had definite antioxidant properties, which may be due to the presence of high concentrations of polyphenols and flavonoids (Sakshima et al. 2014).

10.2.19 ZOOFA

Botanical Name *Hyssopus officinalis* L.

Kingdom/Subkingdom – Plantae/Tracheobionta
Superdivision/Division – Spermatophyta/Magnoliophyta

Class/Subclass – Magnoliopsida/Asteridae

Order/Family – Lamiales/Lamiaceae

Genus/Species – *Hyssopus officinalis*

Vernacular Names

Urdu – Zufa khushk

Sanskrit – Jupha

Persian – Ushnan-e Dawood

Hindi – Zupha

English – Hyssop, Holy herb

Zoofa (*H. officinalis*) is an aromatic perennial plant which is found in the western Himalayan region from Kashmir to Kumaun. It grows to a height of 120 cm. The plant has been used for culinary and medicinal purposes since ancient times. The plant leaves are often used for their minty flavour and as a condiment in the food industry (Figure 10.2g). The oil extracted from the aerial part of the plant is used as a flavouring agent for alcoholic beverages and meat products. The benefits of Hyssop have been documented in the primary texts of Christianity and Judaism. Medicinally, it is used as a carminative, tonic, antiseptic, expectorant, and cough reliever (Rafeequddin 1985; Fathiazad 2011).

10.2.19.1 Evidence-based Research

The antioxidant activity of an ethanolic extract of Zoofa (*H. officinalis*) was determined and it was found that appreciable antioxidant activity was present in the extract as assayed by DPPH radical scavenging test, the Trolox equivalent antioxidant capacity assay, the electron paramagnetic resonance radical detection assay, and the haemoglobin ascorbate peroxidase activity inhibition assay (Vlase et al. 2014).

10.2.20 FOFUL

Botanical Name *Areca catechu* L.

Kingdom/Subkingdom – Plantae/Tracheobionta

Superdivision/Division – Spermatophyta/Magnoliophyta

Class/Subclass – Liliopsida/Arecidae

Order/Family – Arecales/Arecaceae

Genus/species – *Areca/catechu*

Vernacular Names

Urdu – Chalia, Supari

Arabic – Fufal, Fofal

English – Betel Palm

Hindi – Supari

Persian – Popal

Sanskrit – Ghonta, Kramuka, Gubak, Poogaphalam

Unani – Fufal, Chhalia, Supari (Anonymous 2007)

Foful (*A. catechu*) is a tree of up to 20 m in height, found on plains and hilly regions. In India, it is commercially cultivated on the western Coast, West Bengal, and Assam. The nut has a rounded cone-shape, 2–3 cm in height (Figure 10.2h). Its seeds can be used to strengthen the teeth and gums, can act as an anthelmintic, and improves the digestive system as it is both a digestive and a stimulant (Anonymous 2007; Rashid et al. 2015).

10.2.20.1 Evidence-based Research

An experimental study conducted on rats showed that areca nut extract increased the number of white blood cells (WBCs) and improved the activity and capacity of macrophages in rats infected with the bacterium *Staphylococcus aureus*. The immunomodulatory ability may be due to the presence of phytochemicals in the areca nut (Sari et al. 2020).

10.2.21 NILOFAR

Botanical Name *Nymphaea alba* L.

Kingdom/Subkingdom – Plantae/Tracheobionta

Superdivision/Division – Spermatophyta/Magnoliophyta

Class/Subclass – Magnoliopsida/Magnoliidae

Order/Family – Nymphaeales/Nymphaeaceae

Genus/Species – *Nymphaealalba*

Vernacular Names

Urdu – Nilofar

Hindi – Nilkamal, Nilpadma

English – European White Water lily, White lotus

Tamil – Karuneythal

Bengali – Nilshapla, Nilpadma

Gujarati – Nilkamal

Tamil – Karuneythal

Nilofar (*N. alba*) is a perennial aquatic plant which is found in ponds and lakes in Bangladesh, Africa, and warmer parts of India (Figure 10.2i). It is an important and well-known medicinal plant, which has been advocated by various systems of medicine, like Unani, Ayurveda, and Siddha, for the treatment of diabetes, inflammation, liver disorders, urinary disorders, menorrhagia, menstrual problems, and as an aphrodisiac, brain tonic, and cardiogenic (Doli et al. 2012; Lakshmi 2013).

10.2.21.1 Evidence-based Research

An ethanolic extract of the rhizomes of Nilofar (*N. alba*) has shown significant antioxidant activity, which may be due to the presence of tannins and other phenolic compounds (Bose 2012). Aqueous and ethanolic extracts of the flowers of *N. alba* were investigated for antioxidant ability by performing the DPPH radical scavenging assay, the hydroxyl radical scavenging assay, and the nitric oxide scavenging assay. The results of all three assays concluded that ethanolic extract of *N. alba* had significant antioxidant activity in comparison with the aqueous extract (Madhusudhanan et al. 2011).

More information related to sacred medicinal plants is presented in Table 10.1.

10.4 CONCLUSION AND FUTURE PERSPECTIVES

Different plants have long been believed to be sacred by communities all over the world. Various religions have different religious books, describing plants for the maintenance and the preservation of health. India has a very extensive and diverse flora, which has a special place in our rituals, worship, myths, epics, and daily life. Diseases are cured in two ways in Islam: cure of the soul through prayers and cure of ailments through medicines. The Holy Qur'an described the importance of different plants for treating various ailments. Khajoor (*P. dactylifera*) has the greatest number of references in The Holy Book. Many food products are prepared from dates these days. Zaitoon (*O. europaea*) also has many references in the Holy Qur'an and Ahadith. In the Holy Qur'an it is mentioned: 'Your God is that who has made different kinds of orchids and gardens for you, those have colourful crops of Khajoor, Zaitoon and Anar/Rumman. Eat these fruits when ripe but keep the share for poor relatives and the needy and do not waste them'. (Holy Qur'an: 141, Surah- Al-Anam). Lord Buddha meditated on the path to enlightenment under Peepal (*F. religiosa*); Sita sheltered in a grove of Ashok (*S. asoca*), when she was detained by Ravana, and no Hindu household is considered complete without Tulsi (*O. sanctum*), with the leaves of Bael (*A. marmelos*) being used for the worship of Shiva.

The need for exploration of such useful data from the Holy Qur'an, Ahadith, Vedas, and the Bible has long been felt, with the increasing need for drugs, medicines, and other useful products. This approach was adopted to record the medicinal uses of sacred plants for the welfare of human beings.

This chapter may supply the scientific knowledge of the medicinal plants mentioned in the Holy Qur'an, Vedas, and other religious books to the botanists practising both basic and applied aspects of plant research. This may ensure essential ethno-pharmacological investigations of most of these plants and may correlate botanical clarification with the unique sacred books or may denote an additional biological theme to the list of important independent subjects learned from the Holy book.

Various uses of sacred plants for food and animal feed, folk medicine, and for normal life are reported in more than one verse in the Holy Qur'an and other religious

TABLE 10.1
Medicinal Activities of Sacred Medicinal Plants

Common Name	Scientific Name	Proven Medicinal Activities	References
Khajoor	<i>Phoenix dactylifera</i>	Anti-inflammatory, antioxidant, antitumour, antimicrobial, antidiabetic, nephroprotective, and for labour relaxation	Michael et al. (2013), Eddine (2013), and Badreldin et al. (2008)
Zaitoon	<i>Olea europaea</i>	Hypoglycaemic, hypotensive, diuretic, antipyretic, anti-inflammatory, general tonic, cleanser, and laxative	Amel (2013), Ali-Shtayeh (2012), Vardanian (1978), Fujita (1995), Gastaldo (1974), Ribeiro (1986), and Khalil (1995)
Maweez	<i>Vitis vinifera</i>	Skin protective, antibacterial, anticancer, anti-inflammatory, antidiabetic, hepatoprotective, and neuroprotective	Saada et al. (2009), Lakshmi et al. (2013), Silva et al. (2015), Kang et al. (2012), Yammi et al. (2015), Porquet et al. (2013), and Giribabu et al. (2015)
Kalonji	<i>Nigella sativa</i>	Antihypertensive, liver tonic, diuretic, digestive, anti-diarrhoeal, appetite stimulant, analgesic, antibacterial, antidiabetic, anticancer, immunomodulator, and antioxidant	Abedi (2017), Adam et al. (2016), Ahmad et al. (2013), Aljabre et al. (2015), and Malik et al. (2016)
Rumman	<i>Punica granatum</i>	Anti-inflammatory, anticancer, antidiabetic, cardioprotective, and hepatoprotective	Murthy (2004), Schubert (1999), Esmailzadeh (2006), Adhami (2009), Sumner (2005), and Xu (2009)
Kafoor	<i>Cinnamomum camphora</i>	Antioxidant, anti-inflammatory, antitumour, antifungal, antimicrobial, and antihypoglycaemic	ChenLung (2009), Edris (2007), Ngadiman (2005), Agarwal (2012), Satyal (2013), Inouye (2001) and Lin (2015)
Zanjabeel	<i>Zingiber officinale</i>	Cardiotonic, powerful antioxidant, anticancer, anticoagulant, anti-inflammatory, anti-atherosclerotic, antacid, antiviral, antimicrobial, and antitussive	Khare (2007), Nadkarni (2009), Rehman (2010), Lantz (2007), and Mahmoud (2012)
Anjeer	<i>Ficus carica</i>	Anticancer, hepatoprotective, hypoglycaemic, hypolipidaemic, antipyretic, antispasmodic, antiplatelet and antihelminthic	Yancheva et al. (2005), Rubnov (2001), Gond (2008), Perez (1998), Asadi (2006), Patil (2010), Mohamad (2011), and Amorin (1999)
Mauz	<i>Musa x paradisiaca</i>	Antidiarrhoeal, anti-ulcerative, hypoglycaemic, antihypertensive, diuretic, antioxidant, and wound healer	Rabbani et al. (1999), Rabbani et al. (2001), Jain et al. (2007), Singh et al. (2007), Orie (1997), and Yin et al. (2008)

(Continued)

TABLE 10.1 (CONTINUED)
Medicinal Activities of Sacred Medicinal Plants

Common Name	Scientific Name	Proven Medicinal Activities	References
Bael	<i>Ziziphus mauritiana</i>	Anticancer, antioxidant, antihyperglycaemic, antidiarrhoeal, hepatoprotective, and antimicrobial	Mishra et al. (2011) and Jarald (2009)
Rehan	<i>Ocimum sanctum</i>	Antibacterial, antifungal, antiviral, analgesic, antipyretic, and anti-inflammatory	Joshi et al. (2011), Amadi et al. (2010), Sharma et al. (2002), Vogel (2002), and Mahima et al. (2012)
Peepal	<i>Ficus religiosa</i>	Antimicrobial, antiparasitic, anticonvulsant, hepatoprotective, nephroprotective, antidiabetic, anti-inflammatory, analgesic, anti-ulcer, and wound healer	Rahman (2014), De Amorin (1999), Singh (2014), Parameswari et al. (2013), Yadav (2015), Kirana (2009), Viswanathan et al. (1990), Gulecha (2011), Gregory et al. (2013), and Murti et al. (2011)
Bael	<i>Aegle marmelos</i>	Antidiabetic, hepatoprotective, antimicrobial, analgesic, anti-inflammatory, antipyretic, antifungal, anticancer, anti-ulcer, and antithyroid	Singanan et al. (2007), Maheshwari et al. (2009), Arul et al. (2005), Patil (2009), Leticia (2005), Goel (1997), and Panda (2006)
Neem	<i>Azadirachta indica</i>	Antioxidant, anticancer, anti-inflammatory, hepatoprotective, wound healing, antidiabetic, antimicrobial, antimalarial, and antineoplastic	Ghimeray et al. (2009), Harish (2009), Naik. (2014), Baligar et al. (2014), Osunwoke et al. (2013), and Joshi et al. (2011)
Sandal	<i>Santalum album</i>	Hepatoprotective, memory enhancement, anti-ulcer, antibacterial, antifungal, antiviral, anticancer, antihypertensive, antipyretic, sedative, cardioprotective, anti-inflammatory, and antihyperlipidaemic	Hegde (2014), Papaiah et al. (2010), Okugawa et al. (1995), Ahmed et al. (2013), Viollon (1994), and Kulkarni et al. (2012)
Qinnab	<i>Cannabis sativa</i>	Anticancer and antidiabetic	Levendal (2006) and Ramer (2015)

(Continued)

TABLE 10.1 (CONTINUED)
Medicinal Activities of Sacred Medicinal Plants

Common Name	Scientific Name	Proven Medicinal Activities	References
Ashok	<i>Saraca asoca</i>	Antimenorrhagic, antimicrobial, uterine tonic, larvicidal, anticancer, anti-oxytocic, anti-inflammatory, anti-arthritic, cardioprotective, analgesic, anti-ulcer, and antihelminthic	Teunisdie et al. (1983), Pal et al. (1985), Mitra et al. (1999), Mathew et al. (2008), Bhandary et al. (1995), Ghosh et al. (1999), Joseph et al. (2009), Verma et al. (2010), Preethi (2011), Lakshmi et al. (2013)
Sumbul ut Teeb Zoofa	<i>Nardostachys jatamansi</i> <i>Hyssopus officinalis</i>	Antifungal, hepatoprotective, anticonvulsant, antidiabetic, neuroprotective, and antioxidant Antiviral, antimicrobial, and antioxidant	Mishra et al. (1995), Ali et al. (2007), Rao (2005), and Salim et al. (2003) Gollapudi et al. (1995), Hong et al. (2005), and Ozer et al. (2006)
Foful	<i>Areca catechu</i>	Antioxidant, anti-inflammatory, hypolipidaemic, hypoglycaemic, antihypertensive, vascular relaxant, antidepressant, anti-allergenic, and anticonvulsant	Koleva et al. (2002), Chempakam (1993), Byun et al. (2001), Inokuchi et al. (1986), Hirrozo et al. (1997), Kumarnsit et al. (2005), Lee et al. (2004), and Lodge et al. (1977)
Nilofar	<i>Nymphaea alba</i>	Anxiolytic, antifungal, antitumour, and antioxidant	Thippeswamy et al. (2011) and Cudalbeanu et al. (2020)

books. The scientific studies of these sacred plants have shown the promising effect in many cases to be immunomodulatory, antioxidant, and tonic in nature. In addition, these sacred plants also possess other properties, such as anti-inflammatory, analgesic, antipyretic, blood purifier, haemopoietic, wound healing, antifungal activity, anticancer, and antidiabetic, etc., which have been confirmed by modern scientific research.

Although the research data of many eminent researchers have been included in this document, many gaps still remain to be filled, but we hope that this chapter will inspire future scientists and research scholars to take up the task of preserving, documenting, and re-establishing sacred groves to a new level, supported by scientific evidence. These findings may reach the great masses living in the Urban areas. This will also benefit the underprivileged persons residing in the remote areas of the world where it is difficult to buy expensive medicines.

ACKNOWLEDGEMENTS

Special gratitude is expressed to Dr. Sana Nafees, Aligarh Muslim University, Aligarh, Dr. Nighat Anjum and Dr. Mokhtar Alam, Research Officers, Central Council for Research in Unani Medicine, New Delhi, and Dr. Salma Jamal, Jamia Tibbiya, Deoband, for their moral support and prolific suggestions after reading earlier drafts of this manuscript.

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11 Molecular Features of Potential Herbal Products in Enhancing Human Immune System

Chandrabose Selvaraj, Chandrabose Yogeswari, and Sanjeev Kumar Singh

CONTENTS

11.1	Introduction.....	301
11.2	Roles of Medicinal Plants	303
	11.2.1 Role in Modern Medicine	303
	11.2.2 Role in Traditional Chinese Medicine	303
	11.2.3 Role in Ayurveda	304
	11.2.4 Role in Siddha	305
	11.2.5 Role in Other Regional Medicinal Systems	307
11.3	Medicinal Plants and Immunological Regulation	307
	11.3.1 Immunomodulator Agents	308
	11.3.2 Mechanism of Action of Immunomodulators	343
	11.3.3 Immunosuppressive Agents	343
11.4	Medicinal Plants as Immune Boosters	344
11.5	Molecular Chemistry of Plant-derived Immunity Boosters	346
11.6	Molecular Chemistry of Phytoconstituents	348
11.7	Pharmacology and Toxicity of Medicinal Plants.....	350
11.8	Current Developments in Immunomodulator Research	350
11.9	Limitations.....	351
11.10	Conclusion.....	351
	Acknowledgement	352
	References.....	352

11.1 INTRODUCTION

The survival of human beings is greatly influenced by the defensive mechanism of the immune system against various types of harmful pathogens and some of the elements. The immune system potentially helps the host cells to prevent the entry of microorganisms and the development of major health issues like cancer

(Mak et al. 2014). The occurrence of defects in the immune system leads to response impairment against various infectious agents and cancer. Both extrinsic and intrinsic pathways heavily influence the impairment of the immune system. Some of the pathogens, including human immunodeficiency virus or the advanced stage of some of the chronic diseases, may cause impairments (Chinen and Shearer 2010; Abbas et al. 2016). Several medical systems, like Chinese traditional medicine, traditional Thai medicine, African traditional medicine, along with Indian traditional medicine, are currently practiced all around the world by using potential medicinal plants for treating the diseases. In particular, microbial infections, insect, and reptile bites are well treated through the use of available medicinal plants. Due to the range and diversity of the various secondary plant metabolites, herbal remedies are also strongly involved in the development of conventional drugs. Most secondary metabolites are significantly active as potent immunomodulators and improve cell- and humoral-mediated immunity. Secondary metabolites with immunomodulatory properties induce immune modulation in organisms and trigger immune system stimulation against a variety of harmful pathogenic microbial infections. Similarly, they also cause the activation of specialized cells, such as macrophages, natural killer (NK) cells, and granulocytes, subsequently activating the production of cytokines. These cytokines are of core importance for the enhancement of immune response (Lesourd 2006; Vigila and Baskaran 2008). For example, the plant extract of *Mentha longifolia* (mint) has been extensively used in the pharmaceutical industry and in the food and chemical industries. It has potent activities, including antimicrobial, antioxidant, and immunomodulatory effects, with no side effects (Mikaili et al. 2013).

Many plant-derived compounds have been identified from their source plant and their structure elucidated and subsequently used as potential lead molecules for the development of commercial, single-chemical drugs to treat a number of diseases. For example, the widely used drug aspirin was purified from the willow tree bark extract and used as an important painkiller and antipyretic activity (Dias et al. 2012). The major bioactive components of traditionally used plants, including quinine and opium, are commonly used as powerful drug molecules for the treatment of several diseases (Wadood et al. 2013). As a consequence of the successful use of medicinal plants for an extended period into the current day has resulted in a number of researchers focusing on plant-derived lead molecules that have immunomodulating effects to find and develop novel and effective drug molecules to reduce the usage of toxic synthetic chemicals and to reduce the high risk of many chronic diseases. A wide variety of secondary plant metabolites, including flavonoids, terpenoids, phenolics, and curcumins, have potent effects in inhibiting DNA synthesis and stimulating the action of several protective enzymes, such as phase II enzymes. Many medicinal plants are rich in antioxidant molecules that provide efficient protection against chronic disease, maintain low-density lipoprotein (LDL)-cholesterol, and also inhibit both lipoxygenase and cyclooxygenase enzymes to prevent lipid peroxidation (Kyo et al. 2001; Gebreyohannes and Gebreyohannes 2013). This support from the scientific literature provides support for herbal medicines and their effective

action against a variety of infectious diseases as an effective alternative approach to current chemotherapy (Dutt 2013). Moreover, it is well known that plant compounds with immunomodulatory effects may also act as highly effective adjuvants to vaccines (Wilson and Warise 2008). Hence, this present book chapter describes the various plant-derived immunomodulatory compounds and their source, mode of action, and their crucial role in immune response to stimulate the immune system.

11.2 ROLES OF MEDICINAL PLANTS

11.2.1 ROLE IN MODERN MEDICINE

In recent years, medicinal plants are often used as the alternative healthcare system in both developing and developed countries. The mixture of natural compounds primarily derived from plants has great potential to treat a wide range of diseases. However, owing to poor absorption, herbal medicines have less effectiveness than other modern, synthetic medicines (Gauttam et al. 2003; Sagar et al. 2005). WHO (the World Health Organization) states that about 80% of the world population have been using medicinal plants in the traditional herbal medicine system for primary health care. The evaluation of modern drugs since the beginning of the 19th century led to the isolation of the first active compound, morphine, purified from the opium poppy by a German pharmacist, followed by the isolation and characterization of a number of plant-based compounds as effective molecules (Hamilton et al. 2000; Joo et al. 2014). Among them, a number are still used in traditional medicine. After the invention of advanced chemical technologies, the development of synthetic compounds has significantly reduced the usage and importance of natural products, although natural products are still used to find potent novel lead molecules in the treatment of cancer, hypertension, and other diseases (Newman et al. 2003). The identification of novel lead molecules in most of the pharmaceutical companies is well developed, with high-throughput synthesis and combinatorial chemistry-based approaches since the 1980s. Some of the pharma industries are facing challenges to develop novel drugs, and, over recent decades, they have focused their attention on natural products for the development of novel drugs with help of modern technology, including high-throughput screening (Zhu et al. 2012; Ngo et al. 2013).

11.2.2 ROLE IN TRADITIONAL CHINESE MEDICINE

In addition to Ayurveda and Siddha, Chinese medicine plays a significant role in boosting the immune system and its activity and function. Traditional Chinese medicine was considered to be the most advanced medical science in the late 17th century, and around 12,000 medical classics were distributed through China. In the Chinese medicinal system, several surgeries were practised, like Ayurveda, though, in recent years, only acupuncture and herbal-based therapy are used as major branches of the Chinese medicine system. Basically, two important therapeutic approaches have attracted particular attention in the field of complementary and alternative medicine.

The combination of one or more herbs in a single formulation was one of the most prominent steps in Chinese medicine. The 'Theory of the Five Elements' is widely used in Chinese medicine to describe the relationship between the human body and the five elemental qualities, namely earth, metal, water, wood, and fire. Before the 20th century, Chinese medicine was intensively used for the treatment of various pathological diseases (Xue 1991; Zhang et al. 1996).

Several studies demonstrated that Chinese medicines are highly effective at stimulation of the immune system. Wang et al. (2015) reported that the polysaccharides isolated from the medicinal plant ginseng (*Panax ginseng*) exhibited anticancer properties and also had the ability to improve the size of the organs associated with the immune system; for instance, PGFP1 is a polysaccharide from *Panax ginseng* with potent inhibitory activity in cancer-bearing mice, which reduced the size of the spleen and thymus, also suppressing lipopolysaccharide (LPS) or Concanavalin-A (ConA) -mediated T cell proliferation. The interactions between several compounds in Chinese herbal medicine result in good therapeutic effects, so that the isolation and purification of major active compounds from herbal plant preparations are carefully studied both in preclinical and clinical trials to develop potent novel anti-cancer natural compounds (Zhou et al. 2014). Polysaccharides are among the most important active molecules used in Chinese medicine, with significant anticancer and immune-enhancing properties with fewer side effects, hence the significance of polysaccharides in the widely used Chinese medicine system.

11.2.3 ROLE IN AYURVEDA

Ayurveda is one of the oldest traditional medicinal systems in India, which has been applied and organized since around 1500 BC. The system of Ayurveda is literally defined as the 'Science of Life' and contains 114 hymns and their associated formulations for the management of a number of diseases. Two major schools, Dhanvantari Sampradaya and Atreya Sampradaya, have been nurtured and have gathered the knowledge of Ayurveda over the centuries. The school Atreya Sampradaya represents the compilation of Charaka Samhita with another school of medicine and surgery (Sushruta Samhita). More than one thousand five hundred plant-derived molecules and potent molecules from animal and mineral sources have been described in this medical system. Since the medieval period, only the Ayurveda medicine system existed in the Indian sub-continent for healthcare requirements, and that period is considered to be the golden period of Ayurveda. In the 20th century, the system of Ayurveda received official recognition and a national healthcare network, based on Ayurveda was set up to treat various diseases. After independence, the Indian Government initiated several procedures to enhance the position of Ayurveda as a major health system. Recently, several colleges and hospitals for Ayurveda have been established, regulating the education and registration of Ayurveda, Siddha, and Unani systems of medicine. The use of medicinal plants in the Ayurvedic system has a strong effect on the body and activates the immune system. The classical preparations of Ayurvedic medicines are 90% made from plants with combinations of several plant products for optimal effect. Studies have demonstrated that, compared

with a single herbal formulation, the polyherbal preparation shows a longer-lasting effect. Approximately thirty plant species are used in a polyherbal combination in the Ayurveda system of medicine and the major active components are accurately combined in such a way as to make an effective formulation. In the polyherbal formulation, one or more constituents plays the main role and others will support and show different properties, or, in some cases, act as a catalyst for the proper absorption and transportation of major active molecules, to reduce the toxic effects. Generally, the Ayurvedic formulations are safer and show fewer side effects (Kurup 2004; Ravishankar and Shukla 2007).

For instance, the widely used plants, such as pippali, tulsi, and guduchi, show strong and potent activity against infectious diseases. All the plant parts, including leaves, flowers, bark, roots, and seed are selected, with the selection of a specific part of the plant also being important for the development of a good formulation. A particular combination of the plant parts results in the formulation achieving the greatest effect (Jagetia 2004). Polyherbal formulations have the potential to enhance their therapeutic effects compared to single plant products, with this interactive phenomenon being called synergy. Most of the active components of medicinal plants and some in the herb extract have potent pharmacological actions. There are two basic mechanisms of synergistic action, namely pharmacokinetic synergy and pharmacodynamic synergy, which have been employed to facilitate the ADME (absorption, distribution, metabolism, and elimination) properties of the active plant molecules (Parasuraman et al. 2014). Later, this synergistic effect of molecules can be exploited to target similar receptors. Several factors are involved in most of the disease-oriented pathways, the polyherbal formulation targeting the multiple receptors at the same time, thus providing lasting relief (Chorgade 2007). Most of the conventional medicines are preferably administered after food, but, in Ayurveda, medications are directed to be taken on an empty stomach, with the absorption of drugs occurring as part of normal metabolism. The most advanced scientific techniques are used for the identification and characterization of major active compounds from the polyherbal formulation. A combination of three herbs, like long pepper, black pepper, and ginger, significantly improves their mucus-reducing effects, whereas another combination, of neem and ginger, positively offsets any extreme effects (Ponnusankar et al. 2011).

11.2.4 ROLE IN SIDDHA

The medicinal practice belonging to the Siddha system is considered to be a great achievement of Tamil culture, which is derived from Dravidian culture and practiced in the time of the civilization of the Indus Valley, Chinese culture, and Taoism. Since ancient times, the Siddha system of medicine combines proper diet and health measures (Ajmal et al. 2017). In Tamil culture, Siddha categorized human diseases into 4448 different types, and used medicinal plants as the main source by which to treat different types of diseases. Medicinal plants greatly influence the characteristic features of physiology and have been used to alleviate the effect on the number of pathophysiological states of immunity and immunomodulatory for more than several

centuries in the history of medicine. The potent immunomodulator can significantly influence the immune system components and its associated function in either specific or non-specific ways, including both immune responses (innate and adaptive) (Figure 11.1). Hence, the immunomodulators are referred to as substances that can modify and improve the defence mechanism of host cells against pathogenic organisms, to reduce the impact of diseases. The major active components of the medicinal plants regulate the immune system by interacting with different types of immune cells and effector mechanisms. For example, the basic functions involved in the immune systems destroy the non-self cells to induce the mechanisms to detect and eliminate the harmful pathogens (Hubbard et al. 2006). Siddha medicine in India is still used to treat various diseases, including respiratory disease (asthma and chronic obstructive pulmonary disease (COPD)), which are the most important causes of human mortality (Viegi et al. 2006).

Three main sources of natural products are used in the Siddha medicinal system: products from plants (mulavargam), from an animal source (jivavargam), and inorganic materials (thathuvargam), based on the five characteristic features like the taste, quality, potency, post-digestive taste, and action (Zysk 2008). Of the three sources, plant products are dominantly used in the Siddha system and the plant sources predominantly use 108 herbs (karpa mooligai) to treat human ailments. The traditionally used medicinal plants include *Withania somnifera*, *Solanum trilobatum*, *Cuminum cyminum*, *Aloe barbadensis*, *Azadirachta indica*, *Zingiber officinale*, *Phyllanthus emblica*, and *Phyllanthus amarus*, which represent a few of those dominantly used in the Siddha system (Ram et al. 2009). These plants greatly influence the immune response and prevent chronic diseases. The medicinal plant formulations are also used in the Siddha system. In recent years in India, more plant

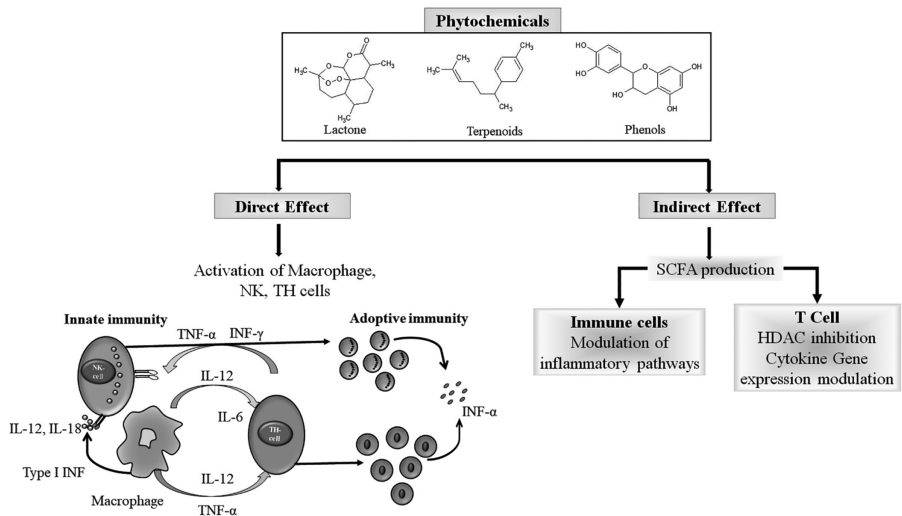


FIGURE 11.1 Schematic representation of phytochemical effects in terms of direct and indirect benefits towards the immune cells.

formulations are used and manufactured commercially by various pharmaceutical companies, including TAMPCOL, IMCOPS, and SKM SIDDHA, and prescribed by Siddha physicians (Ram et al. 2009).

11.2.5 ROLE IN OTHER REGIONAL MEDICINAL SYSTEMS

The growing popularity of traditional remedies, along with its massive commercial potential, has attracted the attention of the pharmaceutical industry, which are eyeing each medicinal system operating around the world. As stated above, the WHO reports that about 65% to 80% of the world's population uses traditional medicines. Apart from above-discussed medicinal systems, African traditional medicine is also a notable holistic discipline that uses ethnic herbalism, combined with spirituality aspects. Much research suggests that modern medicine rooted in this ancient medicine, and exploiting the traditional medicinal practice based on African biodiversity will provide new remedies to the world in the future. This policy is not limited to African traditional medicine but is also appropriate to all the regional traditional medicinal systems.

11.3 MEDICINAL PLANTS AND IMMUNOLOGICAL REGULATION

The body's immune system plays a key role in defence mechanisms and is composed of central immune organs where unique immune cells can develop and exert the effects that subsequently impact host immunity. The major immune system is composed of immune organs like bone marrow and peripheral immune organs, producing numerous immune cells like lymphocytes and a number of phagocytes that monitor cancerogenesis and influence the expression of cytokines to exert anticancer activity, becoming the principal target for cancer treatment. Hence, the status of immune organs is more important for developing novel drug molecules against cancer and other chronic diseases (Wu et al. 2016). The common assembly of the immune system is depicted as being multilayered, achieving a high level of defence. For example, the skin is recognized as a primary immune system, acting as a potent barrier against various infectious diseases as well as being involved in maintaining the temperature and pH of the body, providing an inappropriate environment for harmful organisms. Once the pathogenic microorganism has entered the host body, it is addressed by either an innate and/or an acquired immune system, which has a multitude of cells and molecules which interact with each other to form a complex to detect and attack the pathogen (Hofmeyr, 2001). Several *in-vitro* and *in-vivo* reports have demonstrated the effects of herbal medicines on cytokines, showing that they significantly influence many cytokines. Cytokines are a group of proteins present in the form of interleukins, interferons, and chemokines, which are essential for maintaining physiological stability and their secretion in cells *via* intermolecular crosstalk (Mogensen 2009). Numbers of novel molecules are needed as antagonists, agonists, and initiators. Interferons act as an agonist for hairy cell leukaemia, and tumour necrosis factor has been proposed as an agonist for rheumatoid arthritis (Gomes et al. 2016). Cytokines have diverse pleiotropic characters and play a crucial

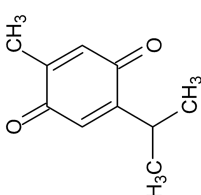
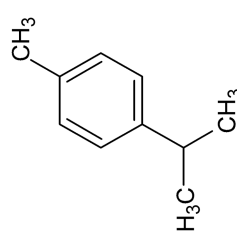
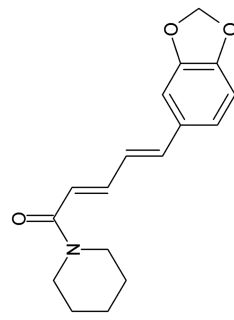
role in some disorders which are not related to the immune system. In some cases, interferon leads to depression and fatigue due to this adverse effect on patients; recently, phytotherapy has been used as an alternative to modifying the expression of cytokines. The medicinal plant *Astragalus membranaceus* is often used in the Chinese medicinal system to cure several diseases. The extract obtained from root of this plant significantly reduced the level of interleukin IL-6 in an *in-vitro* assay (Suzuki et al. 2008; Denzler et al. 2010). Another plant widely and commonly used in Indian herbal medicine is garlic (*Allium sativum*), which reduces the levels of IL-1 and IL-6 and acts as a potent anti-inflammatory, antioxidant, and angiotensin-converting enzyme inhibitor (Singh et al. 2001). Both innate and adaptive immune systems work together functionally, where the innate immune system distinguishes the signals from the infection, the adaptive system is involved in antigen production and is responsible for major histocompatibility complex proteins. The innate cells secrete the chemical signals, including cytokines and chemokines, to stimulate the adaptive immune system. Specifically, the B and T lymphocytes are well-known regulatory cells that maintain the immune response (Josefowicz et al. 2012; Mauri and Bosma, 2012).

11.3.1 IMMUNOMODULATOR AGENTS

Any biological or synthetic substance which can modulate the expression and aspect of the immune response is known as an immunomodulator, having the capability to stimulate or suppress both the innate and acquired immune systems. Clinically, immunomodulators are classified into three major categories, namely immunostimulants, immunosuppressants, and immunoadjuvants. Immunostimulants are non-specific agents that significantly improve the body's resistance to infection *via* an innate and adaptive immune response. In some cases, immunostimulants act as prophylactic and promoting agents to enhance the basic level of the immune response (Casa et al. 2014). Immunoadjuvants are effectively used for the enhancement of vaccine efficacy and can result in promising effects on the immune response. It has been reported that the immunoadjuvants may be active as selectors among the cellular and humoral helper cells 1 and 2 (Th1 and Th2). Another type of immunosuppressant is a heterogeneous group often concomitantly administered to cure several forms of organ transplant rejection and autoimmune disorders (Casa et al. 2014). A number of medicinal plants have been used as potent immunomodulators in the traditional medicine system of Rasayana to enhance the body's resistance. The medicinal plants also have various pharmacological activities, including antioxidant, anti-inflammatory, cardiogenic, hepatoprotective and antifungal properties. Various major active constituents from medicinal plants and their immunomodulatory role are listed in Table 11.1. Glycosides are one of the classes of plant-derived immunomodulators involved in enzymatic and acid hydrolysis to yield sugar molecules; structurally, they are sugar ethers which can interact with hydroxyl groups of both sugar and non-sugar molecules. A number of glycosides are known to influence immunomodulatory action, such as iridoid glycosides from *Picrorhiza scrophulariiflora*, anthraquinone glycosides, from *Andrographis paniculata*, and sesquiterpene glycosides

TABLE 11.1

Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Nigella sativa</i>	Thymoquinone		Modulates pro- and anti-inflammatory cytokines	Majdalawieh and Fayyad 2015
<i>Cuminum cyminum</i>	Cumin oil, <i>p</i> -cymene		Activate cytotoxic CD8+ and CD4+ cells	Chauhan et al. 2010
<i>Piper longum</i>	Piperine		Increases total WBC count, bone marrow cellularity, total antibody production	Sunila et al. 2004

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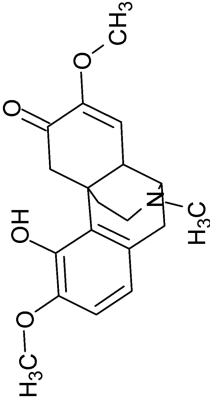
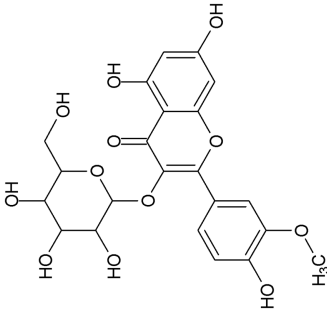
Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Hydrastis canadensis</i>	Berberine		Significant reduction of plasma TNF- α , IFN- γ , and NO levels	Li et al. 2006
<i>Stephania tetrandra</i>	Tetrandrine		Suppresses cytokine production. Inhibits NF- κ B-mediated release of inflammatory factors	Xue et al. 2008

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TABLE 11.1 (CONTINUED)

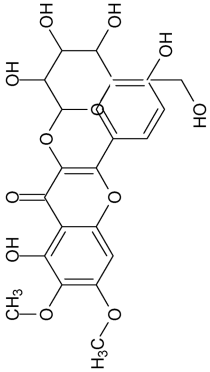
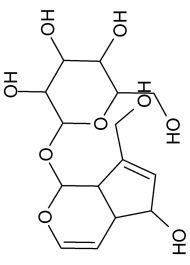
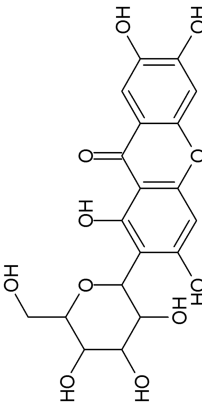
Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Sinomenium acutum</i>	Sinomenine		Graft survival	Mark et al. 2003
<i>Urtica dioica</i>	Isorhamnetin-3-O-glucoside		<i>In-vitro</i> immunomodulatory potential	Akbay et al. 2003

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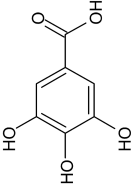
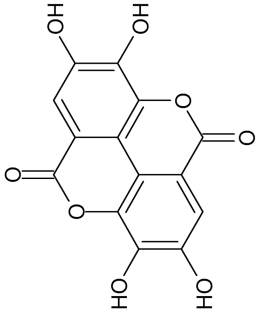
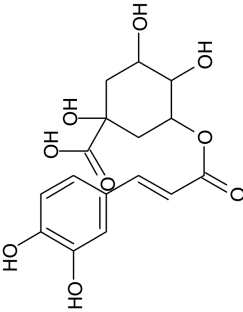
TABLE 11.1 (CONTINUED)

Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Boerhavia diffusa</i>	Betuletin		Inhibits PHA-stimulated proliferation of peripheral blood mononuclear cells, IL-2 and TNF- α	Pandey et al., 2005
<i>Plantago major</i>	Aucubin		Enhances lymphocyte proliferation and secretion of IFN- γ	Chiang et al., 2003
<i>Mangifera indica</i>	Mangiferin		Enhances the production of IgG1 and IgG2b	Garcia et al. 2003

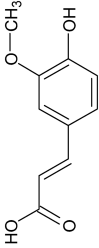
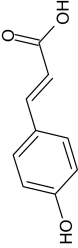
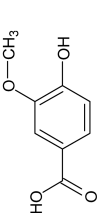
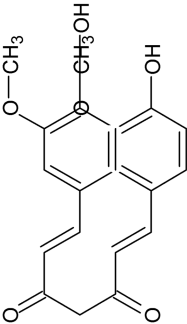
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TABLE 11.1 (CONTINUED)
Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Phyllanthus embelica</i>	Gallic acid		B cell proliferation, inhibition of mast cell degranulation	Serrano et al. 1998
<i>Punica granatum</i>	Ellagic acid		Antiproliferative and antioxidant activities	Seeram et al. 2005
<i>Plantago major</i>	Chlorogenic acid		Enhances lymphocyte proliferation and secretion of IFN	Chiang et al., 2003

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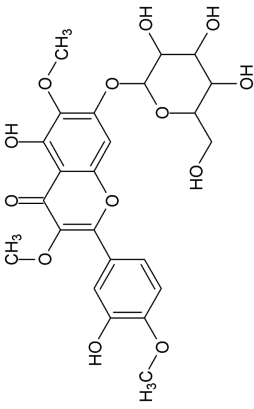
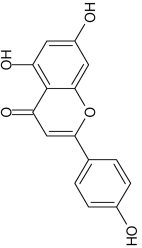
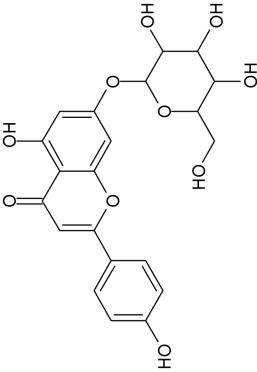
TABLE 11.1 (CONTINUED)
Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Plantago major</i>	Ferulic acid		Enhances lymphocyte proliferation and secretion of IFN	Chiang et al., 2003
<i>Plantago major</i>	<i>p</i> -Coumaric acid		Enhances lymphocyte proliferation and secretion of IFN	Chiang et al., 2003
<i>Plantago major</i>	Vanillic acid		Enhances lymphocyte proliferation and secretion of IFN	Chiang et al., 2003
<i>Curcuma longa</i>	Curcumin		Enhances bone marrow cellularity.	Yadav et al. 2005

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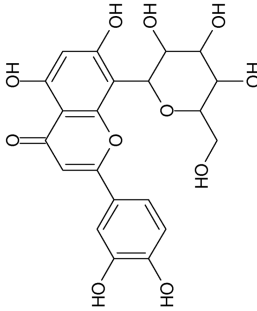
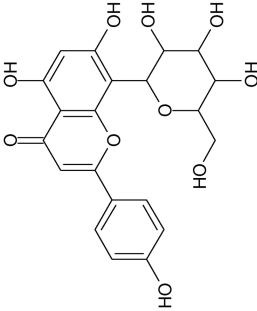
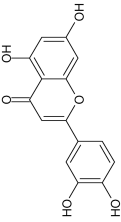
TABLE 11.1 (CONTINUED)

Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Bidens pilosa</i>	Centauraerin		Augmentation of IFN- γ promoter activity	Chang et al. 2007
<i>Jatropha curcas</i>	Apigenin		Stimulation of humoral- and cell- mediated immune response	Abd-Alla et al. 2009
<i>Jatropha curcas</i>	Apigenin 7-O- β -D-galactoside		Stimulation of humoral- and cell-mediated immune response	Abd-Alla et al. 2009

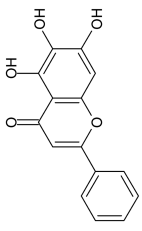
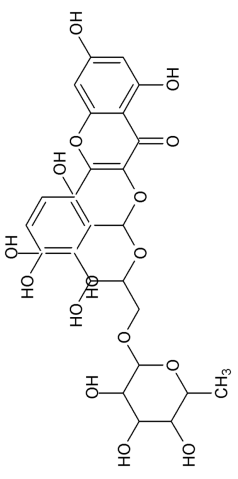
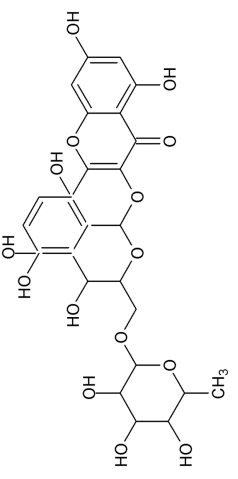
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TABLE 11.1 (CONTINUED)
Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Jatropha curcas</i>	Orientin		Stimulation of humoral- and cell-mediated immune response	Abd-Alla et al. 2009
<i>Jatropha curcas</i>	Vitexin		Stimulation of humoral and cell-mediated immune response	Abd-Alla et al. 2009
<i>Plantago major</i>	Luteolin		Enhances lymphocyte proliferation and secretion of IFN	Chiang et al., 2003

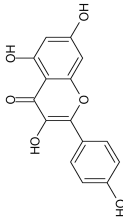
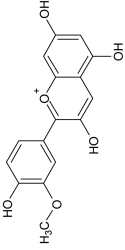
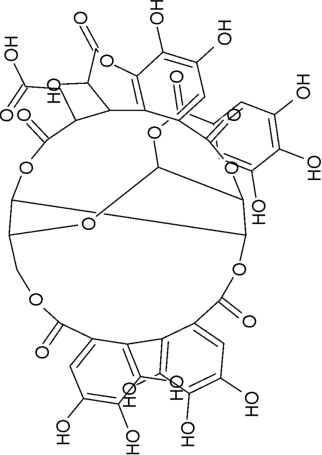
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TABLE 11.1 (CONTINUED)
Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Plantago major</i>	Baicalein		Enhances lymphocyte proliferation and secretion of IFN	Chiang et al., 2003
<i>Urtica dioica</i>	Quercetin-3-O-rutinoside		Immunomodulation	Akbay et al. 2003
<i>Urtica dioica</i>	Kaempferol-3-O-rutinoside		Immunomodulation	Akbay et al. 2003

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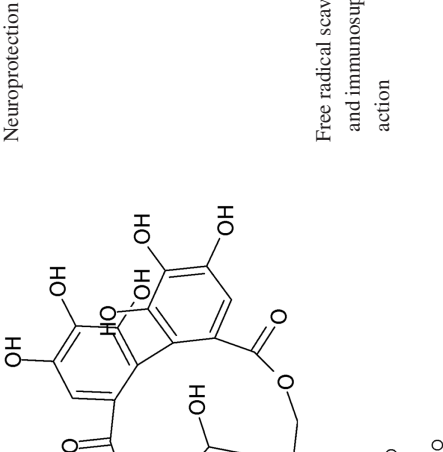
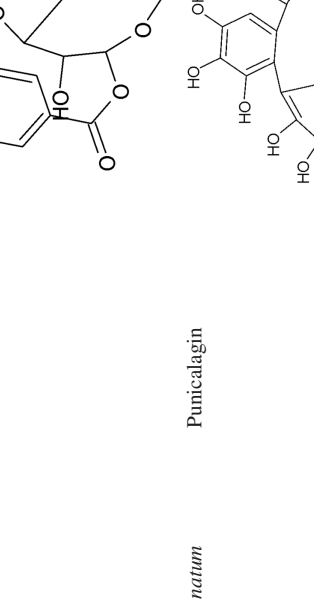
TABLE 11.1 (CONTINUED)
Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Cleome gynandra</i>	Kaempferol		Anti-inflammatory mechanism	van der Meijden, 2001
<i>Rubus fruticosus</i>	Peonidin		Antioxidant and anti-inflammatory mechanism	Rechner et al. 2005; Wang et al. 2008
<i>Terminalia chebula</i>	Chebulagic acid		Down regulation of TNF- α and IL-6	Reddy et al. 2009

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TABLE 11.1 (CONTINUED)

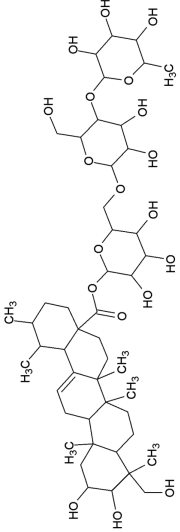
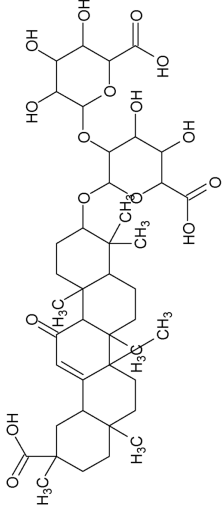
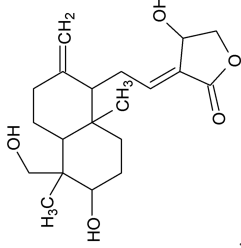
Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Terminalia chebula</i>	Corilagin Corilagin		Neuroprotection	Chang et al. 2012
<i>Punica granatum</i>	Punicalagin		Free radical scavenging and immunosuppressive action	Lee et al. 2008

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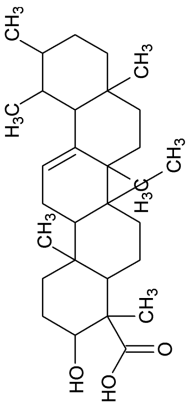
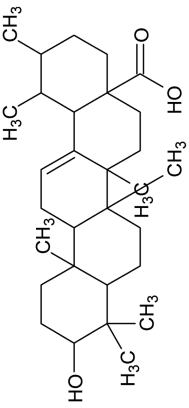
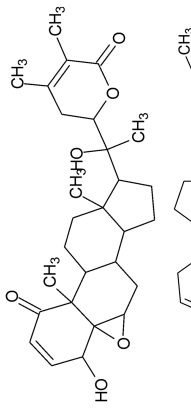
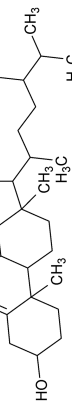
TABLE 11.1 (CONTINUED)

Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Centella asiatica</i>	Asiaticoside		Enhances phagocytic index and total WBC count	Punturee et al. 2005
<i>Glycyrrhiza glabra</i>	Glycyrrhizin		Inhibits classical complement pathway	Ablise et al. 2004
<i>Andrographis paniculata</i>	Andrographolide		Enhances the expression of IL-2. Inhibition of NO in endotoxin-stimulated macrophages	Chiou et al. 2000

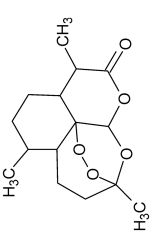
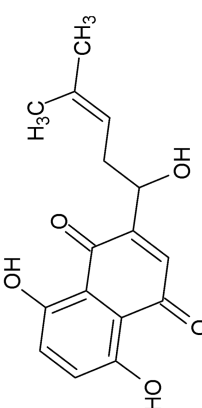
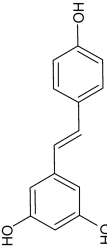
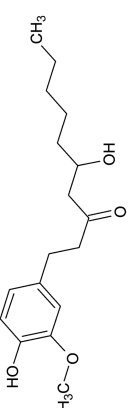
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TABLE 11.1 (CONTINUED)
Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Bowella serrata</i>	Boswellic acid		Significant inhibition of mast cell degranulation	Singh et al. 2008
<i>Rosmarinus officinalis</i>	Ursolic acid		Activates intracellular killing effect of macrophages	Podder et al. 2015
<i>Withania somnifera</i>	Withanolide		Activates murine macrophages, phagocytosis and lysosomal enzyme activity	Ghosal et al. 1989
<i>Corchorus fascicularis</i>	β -Sitosterol		Activates human peripheral lymphocyte proliferation	Boutic et al. 1996

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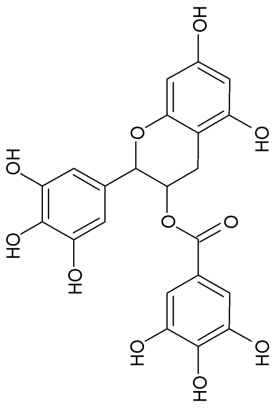
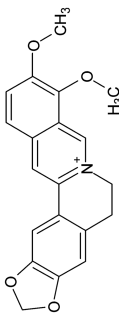
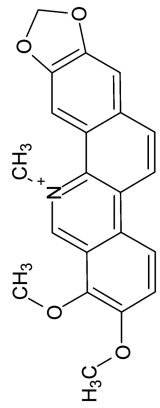
TABLE 11.1 (CONTINUED)
Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Artemisia annua</i>	Artemisinin		Inhibit iNOS transcription,	(Aldieri et al. 2003)
<i>Lithospermum erythrorhizon</i>	Shikonin		Inhibits the promoter/transcriptional activity of the pro-inflammatory cytokine TNF- α	(Staniforth et al. 2004)
<i>Polygonum cuspidatum</i>	Resveratrol		Regulates various transcription factors	(Harikumar and Aggarwal 2008)
<i>Zingiber officinale</i>	6-Gingerol		Regulates the expression of NF- κ B, AP-1, PKC α , cyclin D	Kim et al. 2004

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TABLE 11.1 (CONTINUED)

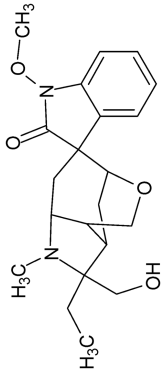
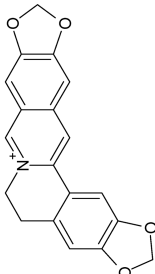
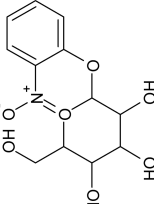
Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Camellia sinensis</i>	Epigallocatechin gallate		Activates EGFR, AKT, NF-κB, AP-	Babu and Liu (2008)
<i>Coptis chinensis</i>	Berberine		Regulates T-helper cells	Lin and Lin 2011
<i>Chelidonium majus</i>	Chelerythrine		Regulates Cox-2 activity	Yun et al. 2021

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TABLE 11.1 (CONTINUED)

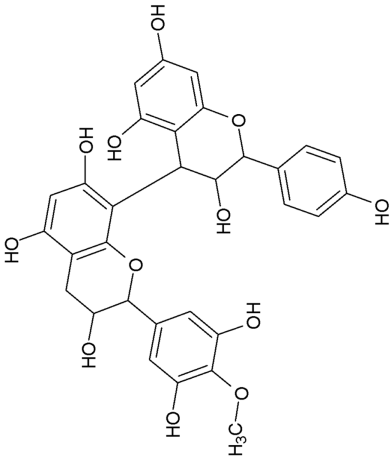
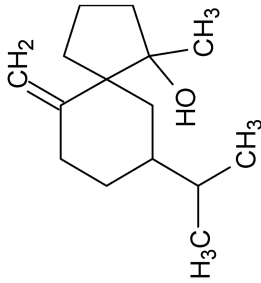
Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Gelsemium elegans</i>	Gelselegine		Inhibits NF- κ B	Xu et al. 2012
<i>Corydalis turtschaninovi</i>	Pseudo-coptisine		Inhibits NF- κ B	Yun et al. 2009
<i>Boerhavia diffusa</i>	β -D-galactopyranoside H		Activates NK cells	Pandeya et al. 2005

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TABLE 11.1 (CONTINUED)

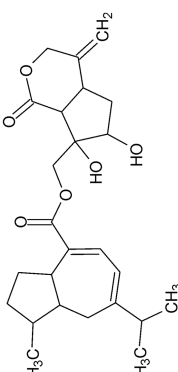
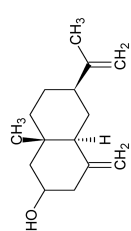
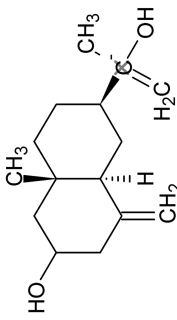
Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Rhododendron spiciferum</i>	Proanthocyanidin		Enhances the expression of NK cells	Liu et al. 2010
<i>Nardostachys jatamansi</i>	Spirojatamol,		Plays a role in central nervous system (CNS)	Chatterjee et al. 2012

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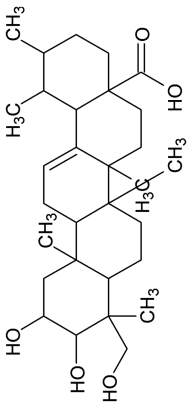
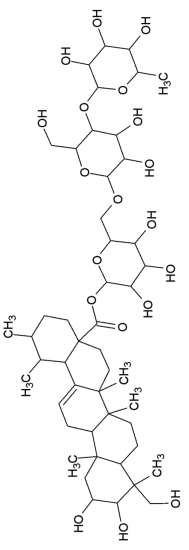
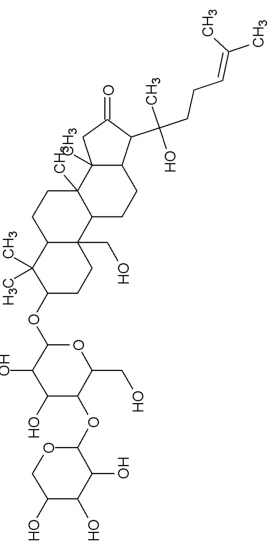
TABLE 11.1 (CONTINUED)

Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Nardostachys jatamansi</i>	Nardostachysin,		Plays a role in CNS	Chatterjee et al. 2012
<i>Nardostachys jatamansi</i>	Jatamols A		Plays a role in CNS	Bagchi et al. 1991
<i>Nardostachys jatamansi</i>	Jatamols B		Plays a role in CNS	Bagchi et al. 1991

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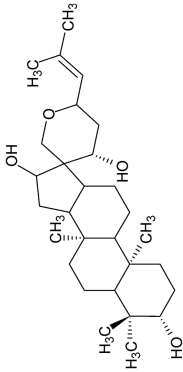
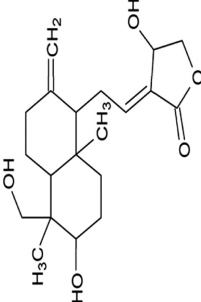
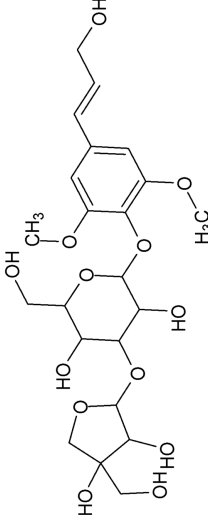
TABLE 11.1 (CONTINUED)
Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Centella asiatica</i>	Asiatic acid		Modulates oxidative stress response	Cervenka and Jahodar 2006
<i>Centella asiatica</i>	Asiaticoside		Modulates oxidative stress response	Cervenka and Jahodar 2006
<i>Bacopa monnieri</i>	Bacoside A		Modulates intracellular oxidative stress	Limpeanchob et al. 2008

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TABLE 11.1 (CONTINUED)

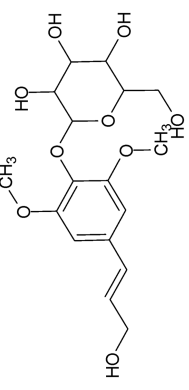
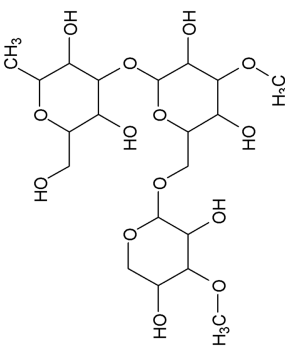
Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Bacopa monnieri</i>	Jujubogenin		Modulates intracellular oxidative stress	Limpeanchob et al. 2008
<i>Andrographis paniculata</i>	Andrographolide		Regulates proliferation of lymphocytes and production of interleukin	Varma et al. 2011
<i>Tinospora cordifolia</i>	Cordifolioside A		Immunomodulation, anticancer	Sharma et al. 2019

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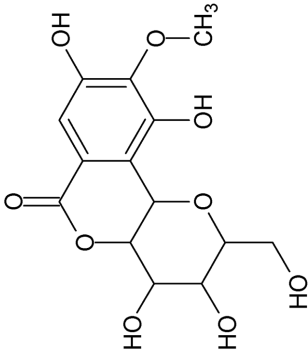
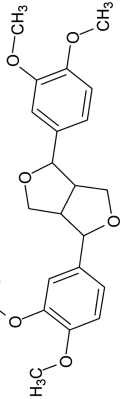
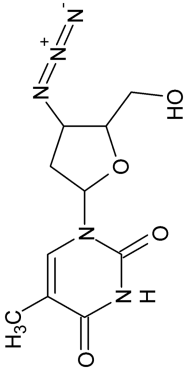
TABLE 11.1 (CONTINUED)

Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Tinospora cordifolia</i>	Syringin		Immunomodulation, anticancer	Sharma et al. 2019
<i>Syzygium guineense</i>	Arabinogalactan		Activates the cytokines	Ghildyal et al. 2010

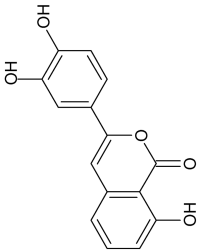
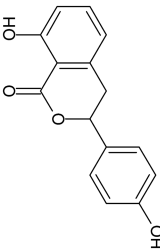
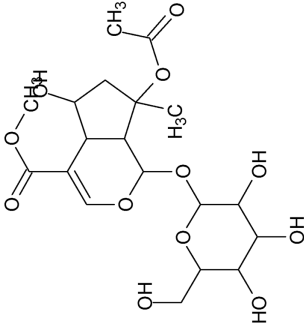
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TABLE 11.1 (CONTINUED)
Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Bergenia crassifolia</i>	Bergenin		Exhibits immunomodulatory and wound healing properties	Patel et al. 2012
<i>Stellera chamaejasme</i>	Eudesmin		Exhibits immunomodulatory activity	Xu et al. 2001
<i>Hydrangea dulcis folium</i>	Concanavalin-A		Regulates splenocyte proliferation	Matsuda et al. 1998

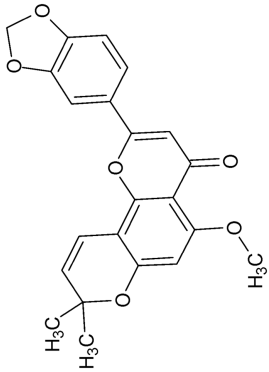
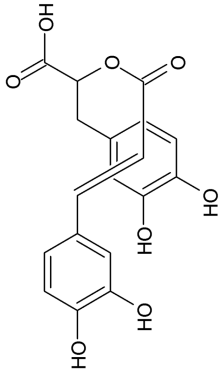
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TABLE 11.1 (CONTINUED)
Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Hydrangea dulcis</i> <i>folium</i>	Thunberginol A		Regulates splenocyte proliferation	Matsuda et al. 1998
<i>Hydrangea dulcis</i> <i>folium</i>	Hydrangenol		Regulates splenocyte proliferation	Matsuda et al. 1998
<i>Phlomis youngusbandii</i>	Barlerin		Exhibits immunomodulatory activity	Fan et al. 2010

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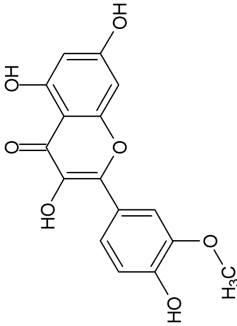
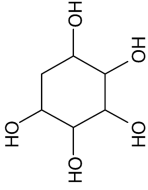
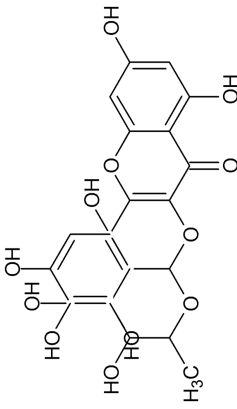
TABLE 11.1 (CONTINUED)
Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Imperata cylindrica</i>	5-Methoxy-flavone	 <p>The structure shows a flavone core with a methoxy group (-OCH₃) at the 5-position and a 3,4-dihydro-2H-pyridin-2-ylidene group at the 3-position.</p>	Exhibits immunomodulatory activity	Fu et al. 2010
<i>Polygonum aviculare</i>	Rosmarinic acid	 <p>The structure shows a central biphenyl core with two hydroxyl groups (-OH) at the 3 and 4 positions of the first ring, and a propenoic acid side chain at the 1 position of the second ring.</p>	Exhibits immunomodulatory activity	Hu et al. 2006

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TABLE 11.1 (CONTINUED)

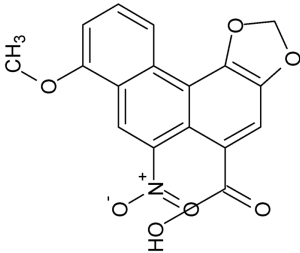
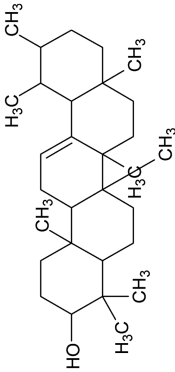
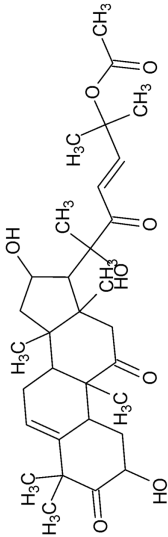
Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Prunus mume</i>	Isorhamnetin		Exhibits immunomodulatory activity	Zhang et al. 2008
<i>Euphorbia hirta</i>	Quercitol		Anti-inflammatory activity	Kumar et al. 2010
<i>Euphorbia hirta</i>	Myricitrin		Sedative and anxiolytic activity	Kumar et al. 2010

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TABLE 11.1 (CONTINUED)

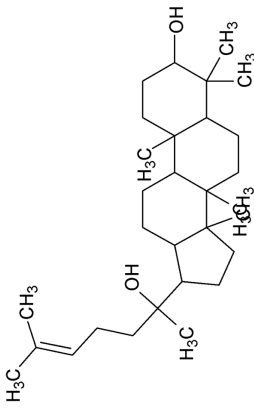
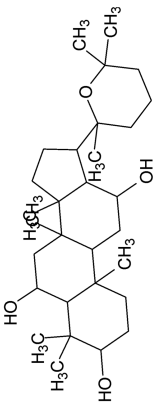
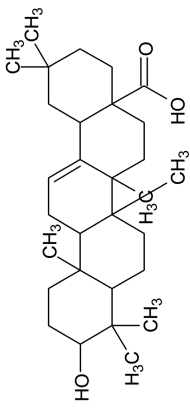
Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Aristolochia</i> spp	Aristolochic acid		Antiangiogenic activity	Wei et al. 2007
<i>Cordia superba</i>	Alpha-amyrin		Anti-inflammatory, antimicrobial activity	Jamkhande et al. 2013
<i>Lagenaria siceraria</i>	Cucurbitacin		Purgative, emetic activity	Ramalingam et al. 2010

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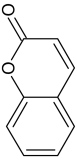
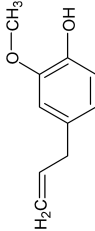
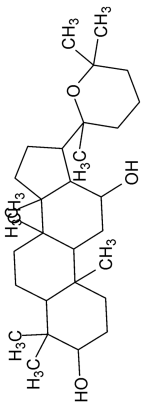
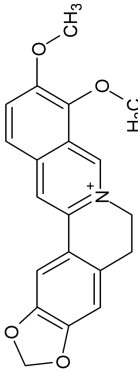
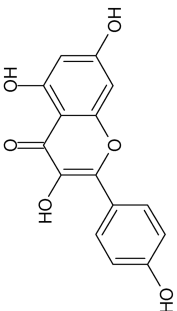
TABLE 11.1 (CONTINUED)

Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Panax ginseng</i>	Ginsenosides		Adaptogenic properties, Anti-arrhythmic	Lee et al. 2010
<i>Panax ginseng</i>	Panaxatriol		Adaptogenic properties, Anti-arrhythmic	Lee et al. 2010
<i>Panax ginseng</i>	Oleanolic acid		Adaptogenic properties, antiarrhythmic	Raphael et al. 2003

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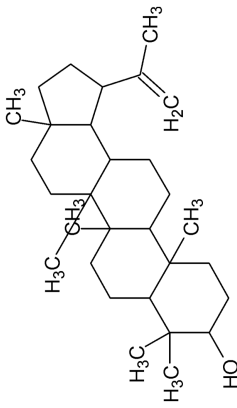
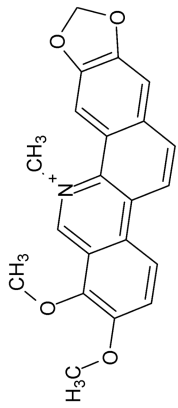
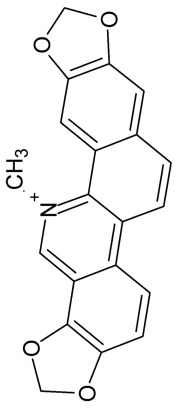
TABLE 11.1 (CONTINUED)
Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Murraya koenigii</i>	Coumarin		Antifungal	Igor et al. 2008
<i>Ocimum sanctum</i>	Eugenol		Antispasmodic,	Vaghasiya et al. 2010
<i>Panax ginseng</i>	Panaxadiol		Adaptogenic properties	Lee et al. 2010
<i>Tinospora cordifolia</i>	Berberine		Hypoglycemic agent	Sinha et al. 2004
<i>Cleome gynandra</i>	Kaempferol		Anti-inflammatory	Gaur et al. 2009

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TABLE 11.1 (CONTINUED)

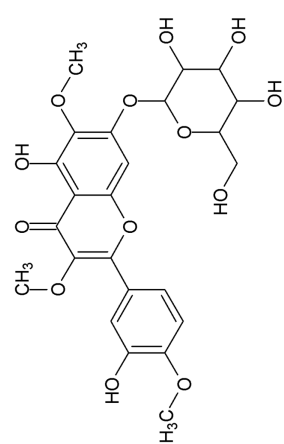
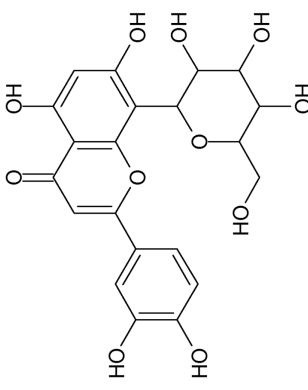
Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Hypoxis suaveolens</i>	Lupeol		Antispasmodic	Jain et al. 2005
<i>Chelidonium majus</i>	Chelerythrine		Enhances the production of IL-6, TNF- α	Li et al. 2012
<i>Chelidonium majus</i>	Sanguinarine		Inhibits degranulation	Agarwal et al. 1999

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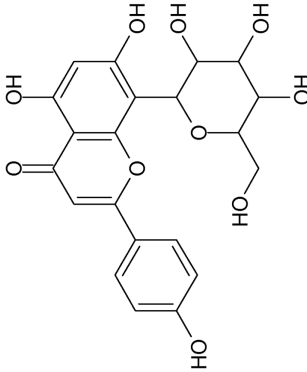
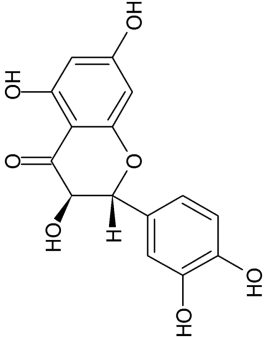
TABLE 11.1 (CONTINUED)

Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Bidens pilosa</i>	Centaurcin		Induces nuclear factor activation	Chang et al. 2007
<i>Jatropha curcas</i>	Orientin		Stimulates humoral- and cell-mediated immune response	Abd-Alla et al. 2009

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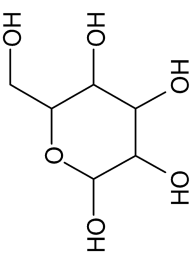
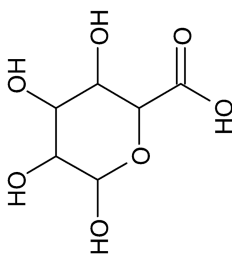
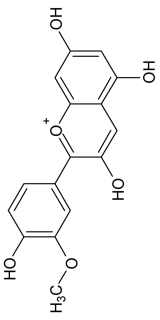
TABLE 11.1 (CONTINUED)
Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Jatropha curcas</i>	Vitexin		Stimulates humoral- and cell-mediated immune response	Abd-Alla et al. 2009
<i>Cedrus deodara</i>	Dihydroquercetin		Exhibits immunomodulatory effects	Arreola et al. 2012

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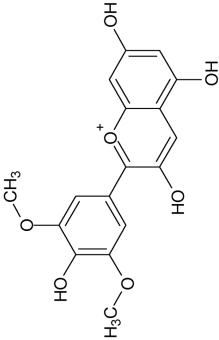
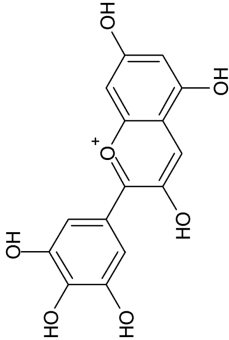
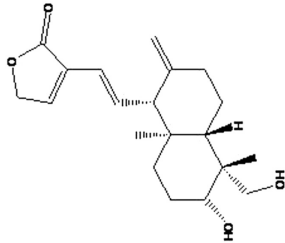
TABLE 11.1 (CONTINUED)

Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Opuntia polyacanth</i>	Galactose	 The image shows the chemical structure of galactose, a six-membered pyranose ring with hydroxyl groups at the 2, 3, 4, and 6 positions. The hydroxyl group at the 5-position is part of a CH2OH group.	Used as potent immunotherapeutic adjuvant	Igor et al. 2008
<i>Opuntia polyacanth</i>	Galactourcinic Acid	 The image shows the chemical structure of galactourcinic acid, a six-membered pyranose ring with hydroxyl groups at the 2, 3, and 4 positions. The hydroxyl group at the 5-position is part of a CH2OH group, and the hydroxyl group at the 6-position is part of a carboxylic acid group (-COOH).	Used as potent immunotherapeutic adjuvant	Igor et al. 2008
<i>Vaccinium</i> spp.	Peonidins	 The image shows the chemical structure of peonidins, a flavonoid compound. It consists of a central benzopyrone core with a methoxy group (-OCH3) and a hydroxyl group (-OH) on the benzene ring, and a hydroxyl group (-OH) on the pyrone ring. The pyrone ring is substituted with a 3,4,5-trihydroxyphenyl group.	Inflammatory response	DeFuria et al. 2009

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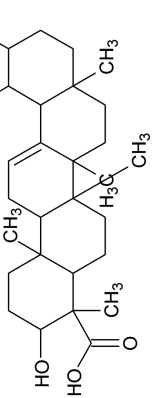
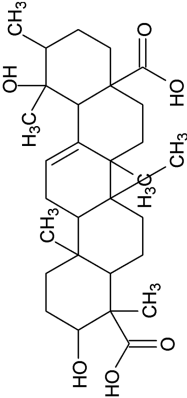
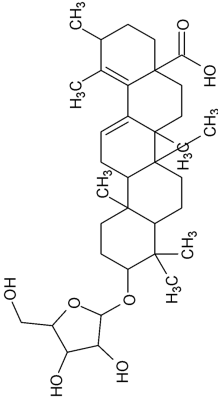
TABLE 11.1 (CONTINUED)
Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Vaccinium</i> spp.	Malvidins		Inflammatory response	DeFuria et al. 2009
<i>Vaccinium</i> spp.	Delphinidins		Inflammatory response	DeFuria et al. 2009
<i>Tinospora cordifolia</i>	14-Deoxy-11, 12-didehydroandrographolide		Immunostimulatory effect	Sinha et al. 2004

(Continued)

TABLE 11.1 (CONTINUED)

Various Types of Immunomodulators and Their Action and Source

Plant name	Active Compound(s)	2-D Structure of the Compound	Mode of Action	Reference
<i>Boswellia serrata</i>	Boswellic acid		Inhibits pro-inflammatory mediators	Singh et al. 2008
<i>Ilex hainanensis</i>	Ilexgenin A		Lipid disorders	Li et al. 2015
<i>Ilex pubescens</i>	Ilexolide A		Anti-inflammatory effect	Zhou et al. 2017

from *Dendrobium nobile*, a widely used plant in Chinese medicine. Dendrosides A and B from *D. nobile* caused significant stimulation of the proliferation of murine T and B lymphocytes (Dinesh Kumar et al. 2012).

11.3.2 MECHANISM OF ACTION OF IMMUNOMODULATORS

Immunomodulators are nutritional supplements that exert strong activity against various diseases owing to the presence of high concentrations of antioxidants. They also have antagonistic action and are involved in the formation of different free radicals. Hence, immunomodulators are mainly used to fight the effects of ageing factors, cancer, diabetes, and autoimmune diseases. The medicinal effect of this Rasayana herb is effectively mediated *via* activities of immunostimulants and immunosuppressants or is mediated through disturbing the effector arm of the immune response (Chulet and Pradhan, 2010). The mechanism of action of these immunomodulatory activities mainly occurs through the basic cellular process, including phagocytosis and macrophage activation. In addition, lymphoid cell stimulation, increase in cellular immune function, increased antigen-specific immunoglobulin production, and increases in the number of natural killer cells and white cells also play a key role in Rasayana-mediated cell response and its effect on immune systems (Singh et al. 2007; Anonymous, 2009; Vaghasiya et al. 2010). The modulatory activity of medicinal plant extracts on the immune response operates *via* stimulatory and suppressive effects and plays a crucial role in maintaining the disease-free state in normal and unhealthy persons. Phytochemicals show significant activity towards host defence mechanisms, even in an impaired immune response, and can provide supportive therapy to chemotherapy (Wagner et al. 1984). The increased level of cell proliferation in bone marrow cells is considered a potentially sensitive target for the various cytotoxic drugs because the bone marrow is one of the organs most affected during immunosuppression therapy. The plant-derived saponins play a significant role in various pharmacological activities, including antitumour, antiviral, immunomodulating, antihepatotoxic, and antifungal activity. Recently, the saponins isolated from *Paris polyphylla* showed active immunostimulant properties. Several studies have demonstrated that the saponins are considered to be important immunomodulating agents (Bafna et al. 2006; Xiu-feng et al. 2007).

11.3.3 IMMUNOSUPPRESSIVE AGENTS

Medicinal plants having strong immunosuppressive activity can be used as an alternative to conventional chemotherapy. The currently used chemotherapeutic agents shows various adverse effects. Several plant species have the ability to inhibit both the innate and the humoral immune response by activating the B and T lymphocytes. For example, *Cannabis sativa* significantly suppresses the hyperactivity of the immune system *via* activating the cannabinoid receptors such as CB1 and CB2 (Cannabinoid receptor 1 and 2). CB1 receptors are abundantly present in brain cells and CB2 are present in immune cells, which are used for the management of cancer and inflammatory disorders (Bettini and Vignali 2009). The phytochemical brasilicardin-A, purified from *Nocardia brasiliensis* IFM0406, shows effective

immunosuppressive activity; it contains amino acids and perhydro-phenanthrene as important chemical moieties, which may influence the immunosuppressive effect of the molecule. Another compound isolated from green tea (*Camellia sinensis*) acts as a potent immunosuppressive agent and is used for the treatment of autoimmune arthritis. The major active constituent of green tea is catechin, a phenolic compound possessing significant anti-inflammatory action (Kunz and Ibrahim, 2009). The extract of *Artemisia annua* has been extensively used in the treatment of autoimmune diseases, including rheumatoid arthritis and lupus erythematoses, due to the existence of major bioactive compounds artemisinins; the derivatives of artemisinin, such as artesunate and artemether, also have a significant immunomodulatory effect (Perretti et al. 2009). The steroids of the sarsaparilla plant, such as smilagenin, saponins, stigmasterol, and sarsasapogenin, are the major beneficial components extensively used in the treatment of arthritis owing to their inhibitory effect on TNF- α (De Bosscher et al. 2008). The Zingiberaceae family member turmeric (*Curcuma longa*) is one of the most widely and often used medicinal plants in Indian traditional medicine, as well as in the Indian diet. It possesses strong antimicrobial activity and significant anti-inflammatory effect. Curcumin is the major bioactive compound present in *C. longa*; it is a yellow pigment that effectively regulates the immune response *via* cell- and humoral-mediated immunity (Kunz et al. 2009). Ashwagandha is another widely used medicinal plant that has diverse inhibitory activities. The alkaloids derived from Ashwagandha, such as iso-pelletierine anaferine, lactones (withanolides, withaferin), saponins (sitoindoside VII and VIII), and withanolides are main constituents of *Withania somnifera*, which greatly influence the activation of B and T cells and produce immunosuppressive action. Another important medicinal plant used both as medicine and in the diet is ginger (*Zingiber officinale*), mainly used for the reduction of pain in arthritis (Dooley and Nair, 2008). The major bioactive component zingiberene is effectively involved the anti-inflammation effect *via* inhibiting the major pathways such as cyclooxygenase (COX) and lipoxygenase. Figure 11.2 shows that the major active compound has an immunosuppressive effect.

11.4 MEDICINAL PLANTS AS IMMUNE BOOSTERS

Several studies have reported that medicinal plants can strongly boost up the immune system, by which they can cure several pathological diseases. *Abrus precatorius* is a member of the Fabaceae, with seed and root being the key parts of the plants, with major constituents like gallic acid, hypaphorine, glycyrrhizin, squalene, and 5-beta cholanic acid. The plant extract is widely used for the treatment of helminthiasis, vomiting, cancer, malaria, and jaundice. In addition, the seed and root extract of this plant exhibits the immunosuppression effect by inhibiting the expression of antibodies and delaying the hypersensitivity response. The reports stated that the extract of *A. precatorius* significantly increased the serum immunoglobulin levels and the activity of phagocytosis, stimulating the cell-mediated immunity (Tripathi et al. 2005). Another medicinal plant, *Acacia concinna*, exhibits an immunostimulatory effect by increasing the numbers of Th1 and Th2 helper cells. Pods and leaves are mainly used in this plant, containing lupeol, nicotine, spinasterol, ascorbic acid, rhamnose, and

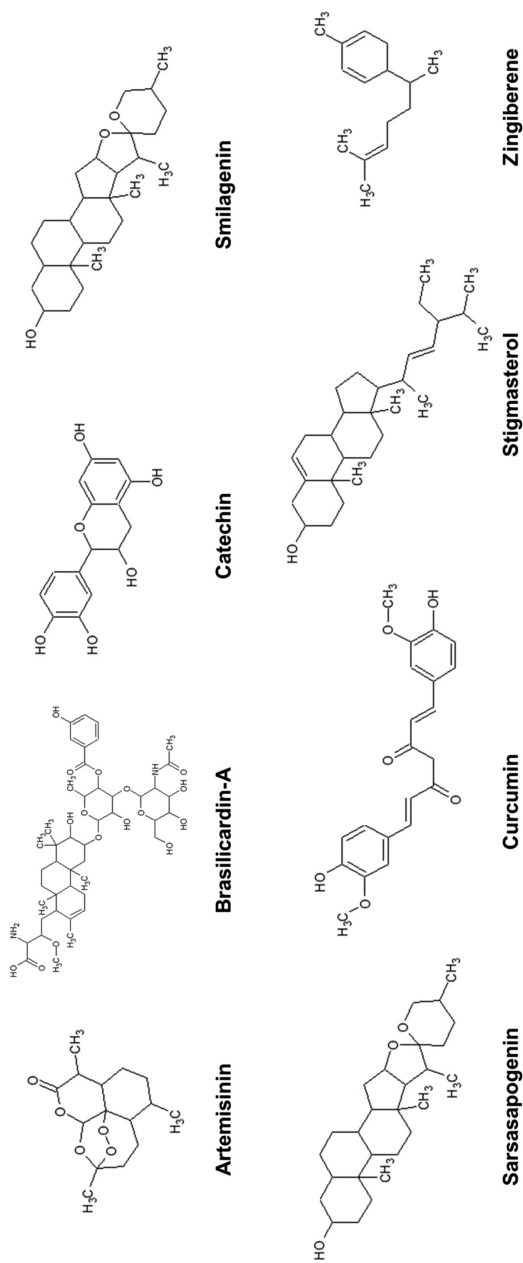


FIGURE 11.2 Major bioactive compounds with an immunosuppressive effect.

spinasterone as major active components that may be responsible for the antimalarial and anti-dandruff activity. The saponin extract from pods of *A. concinna* reported significant immunological adjuvant activity (Kukhetpitakwong et al. 2006; Ismail and Asad, 2009). The bulb extract of *Allium sativum* has major active components like allin, phytoicin, scordinin, and diallyl-disulphide, and is mainly used for treating various pathological conditions, including hyperlipidaemia, diabetes, bacterial infection, hypertension, cancer, and tuberculosis. It also exhibits antiviral, antirheumatic and antispasmodic activity. Garlic extract shows immunostimulatory activity by increasing the mitogenic activity of human peripheral blood lymphocytes, murine splenocytes, and thymocytes (Clement et al. 2010). It effectively promotes the Th2 cells like interleukin-4, -10, and -13 subsequently induce the expression of Th1 cells, such as INF- γ . The activation of IL-10 significantly suppressed pro-inflammatory cytokines like IL1, IL12, which are essential to produce antigen-presenting cells. The up-regulation of INF- γ can induce nitric oxide synthase and mRNA expression, which produce the NO and destroy *Leishmania*. Hence, the extract of *A. sativum* generates a potent immunomodulatory effect (Hodge et al. 2002; Liu and Uzonna, 2012). *Andrographis paniculata* is another widely used medicinal plant used for the management of helminthiasis, cholera, jaundice, and dyspepsia. Extracts of leaf, bark, and root of *A. paniculata* has chemical constituents like apigenin, kalmeghin, and andrographolide. Owing to the presence of these active molecules, *A. paniculata* exhibits an immunostimulatory effect and is also used for its hepatoprotective, alterative, and anthelmintic properties. It greatly influences the activation of antibody secretion and delayed-type hypersensitivity. The brown seaweed *Ascophyllum nodosum* contains tetraphlorethol C, tetrafucol A, and phlorotannins as major active compounds, hence showing a good anti-inflammatory effect, as well as acting as an immunostimulant, enhancing the production of natural killer cells. The medicinal plant *Boerhavia diffusa* is used to treat diabetes mellitus, cancer, leukaemia, and several bacterial infections. The chemical constituents include sitosterol, tetracosanoic acid, triacontanol, ursolic acid, and punarnavine. The pharmacological activities of *B. diffusa* include antioxidant, antiestrogenic, and immunomodulant properties. It effectively inhibits the natural killer cells, which prompt the production of NO, interleukin IL-2 and TNF- α (Nakano et al. 2012; Mehrotra et al. 2002). The widely used medicinal plant *Camellia sinensis* contains several essential and potent active molecules like catechin, saponins, epicatechin gallate, adenine, gallic acid, tannic acid, quercetin, and xanthine which are used to treat asthma, cancer, and bacterial infections, while also exhibiting an antioxidant effect. The essential chemical constituents of *C. sinensis*, the catechin-polysaccharide complexes, showed significant immunomodulatory activity in an animal model and in human peripheral mononuclear cells.

11.5 MOLECULAR CHEMISTRY OF PLANT-DERIVED IMMUNITY BOOSTERS

Several avenues of scientific research have reported that most of the plant-derived active molecules act as an essential source of clinical therapeutics by providing

diverse chemical molecules with effective pharmacological activity. For many years, medicinal plants have been used in the traditional way to cure various diseases (Chattopadhyay et al. 2012). Most of the natural molecules have the appropriate pharmacological activity and are used in drug discovery strategies. Polyphenols derived from medicinal plants have potent antioxidant activity, hence these molecules are often used in the human diet. A number of studies have supported the concept of the beneficial and pharmacological activity of medicinal plants (Annuzzi et al. 2014; Estrela et al. 2017). In addition, some plants also have the capacity to control the immune system response, especially those plants which are rich in polyphenols, polysaccharides, flavonoids and alkaloids, which are often studied for their immunomodulatory activities (Farzaei et al. 2015; Ferreira et al. 2015; Andreicut et al. 2018). The plant-derived immunomodulators are inexpensive and more effective molecules, so have great potential value in medicine, though, due to the lack of standardization and characterization of most active components, evaluation of both qualitative and quantitative changes and the lack of a suitable test for efficacy are limitations to reported results on immunomodulatory effects of traditional medicinal systems. The preparation of *Echinacea* is an effective flower formulation used as an herbal remedy and reduces the symptoms of a severe cold, though there are reports of both high and low therapeutic efficacy, based on formula preparation. The efficacy of this formulation was noted only in certain preparations, mainly from *Echinacea purpurea* (Karsch-Völck et al. 2015). Balan et al. (2016) compared the effects of three different formulations, namely IMMUNAL drops prepared from a succus (concentrated liquid extract) of *E. purpurea*, IMMUNAL FORTE tablets prepared from *E. purpurea* herbae succus siccum, and ECHINACEA FORTE drops prepared from the juice of fresh flowers of *E. purpurea*, and the results revealed that the three formulations showed significant differences in immunomodulatory effect in the female Balb/c mice model. The formulation IMMUNAL drops and ECHINACEA FORTE shows effective immunostimulatory activity, whereas the IMMUNAL tablet showed immunoinhibitory activity and ECHINACEA FORTE had no effect on antibody production. This study highlights that the type of preparation greatly influenced the modulatory effects. However, a lot of studies have supported the concept that *Echinacea* be used as an immunostimulant which effectively enhances both innate and specific immunity (Sultan et al. 2014). In addition, *Echinacea* also exhibits antiviral and anti-inflammatory activity and plays a crucial role in traditional medicine. This wide range of actions of *Echinacea* depends on the plant parts extracted in particular, leaves, flowers, and roots having several active constituents. The different solvents used to create the preparation, like water, alcohol, or oil, also influenced the activity due to the different components that are extracted by the different solvents formed. The standardization of preparation and testing methods is also crucial before administration for evaluation of effect on the different immune systems. The phytochemical profile of each *Echinacea* product is highly dependent on the choice of plant material and extraction methods. The traditional use of *Echinacea* is mainly shown to be effective as a therapeutic agent; Rondanelli et al. (2018) reported that the prophylactic use of an *Echinacea* extract, containing specific bioactive molecules (polysaccharides and phenylethanoid), as a source was effective at preventing colds

and enhancing the immune response. These reports suggested that *Echinacea* significantly stimulates the immune response in healthy as well in immune-suppressed animals (Di Pierro et al. 2012). It enhances the immune system *via* activation of phagocytosis, production of macrophages, and cytokine production, subsequently increasing the expression of TNF- α , interleukins, and interferons. Treatment with the *Echinacea* preparation activates the leukocyte mobility and induces the natural killer cells, which are responsible for the immunomodulatory effect on animals and humans (Vetvicka et al. 2014). The polysaccharide-rich *Echinacea* can stimulate the phenotype and maturation of dendritic cells *via* modulating pathways like JNK, MAPK and NF- κ B, which favour the polarization of macrophages (Fu et al. 2017). The study was carried out by Wang et al. (2006) comparing four different extracts of *Echinacea* (whole plant, root, aerial parts, and flower) on dendritic cells over a 24-h period. The results revealed that there was a reduced level of CD32 and HLA-DR expression following treatment. Among the four preparations, the cells treated with extracts of the whole plant or the aerial parts showed the greatest inhibitory activity on CD32 expression, suggesting that, compared with the other extracts, the whole plant and aerial parts extracts had greater ability to inhibit dendritic cell maturation. Fu et al. (2017) demonstrated that an extract of *Echinacea* with a concentration of 100 μ g/ml effectively activated the macrophages of murine bone marrow by stimulating the expression of essential markers like CD80, MHCII and CD86, and upregulating the macrophages, and was also involved in the production of interleukins, interferons and NO and in enhancing phagocytosis.

11.6 MOLECULAR CHEMISTRY OF PHYTOCONSTITUENTS

Phytochemicals are chemical compounds that are present in plants. Most of the chemical molecules have diverse pharmacology activity and biological significance. For instance, the main molecules present, flavonoids, carotenoids, and coumarins are considered essential. Approximately 4,000 different phytochemicals have been reported, all having potential biological activity. In the early period of the sixteenth century, most of the traditional medicinal systems used wild plants as their mainstream medical system (Venketeshwer Rao, 2015). In garlic extract, more than 200 chemicals have been reported with diverse properties (Fallah-Rostami et al. 2013), being particularly rich in sulphur compounds, which play the key role in the flavour of garlic and its various beneficial effects. The main constituents of garlic extract are carbohydrate and water, with organosulphur compounds, amino acids, proteins, and fibres in smaller but still significant amounts. The active molecules of garlic extracts are classified into two major categories, based on their chemical composition. The first are the nonvolatile sulphur-containing compounds and organosulphur compounds. Allin, allyl-L-cysteine sulphoxides, and γ -glutamyl-allyl-L-cysteines are the main precursors of nonvolatile sulphur-containing compounds; this category contains around 33 sulphur-containing molecules, enzymes, and amino acids, as well as lectins and glycosides (Kaku et al. 1992). The organosulphur-containing compounds are synthesized during production of the garlic preparation. Allicin is the most biologically active molecule that is not present in the normal condition,

but is generated when the garlic is damaged, crushed, pulverized or boiled, which activates the production of the enzyme alliinase, which activates metabolism of the alliin to allicin (Londhe et al. 2011). The allicin immediately decomposes into the other essential compounds, such as diallyl disulphide, ajoene, and the formation of allyl-cysteines from γ -glutamyl cysteine (Rana et al. 2011). The organosulphur-containing compounds are further classified into three subgroups based on their chemical nature, such as thiosulphinates, organosulphur volatiles, and water-soluble compounds. The thiosulphinates are formed *via* the conversion of sulphoxides in the enzymatic reaction. For example, the allicin is considered as a transient compound that decomposes into sulphur-containing compounds which are not found in an active form in undamaged garlic (Amagase et al. 2006). The second group of compounds are the organosulphur volatiles, which includes a large variety of molecules in the processed garlic form, with methyl allyl trisulphide, diallyl trisulphide, 3-dithiin, 2-dithiin, and (E,Z)-ajones being the major and typical volatiles present in the processed garlic. Around twenty sulphides have been reported in the steam-boiled garlic oil and extract; all have allyl groups and are responsible for the flavor and taste of garlic (Amagase et al. 2006). The water-soluble sulphur compounds are extracted with water and contain S-allyl-L-cysteine as the major compound formed from γ -glutamyl-S-allyl-L-cysteines (Amagase et al. 2006). Other compounds, like lectins, pectin, fructan, vitamins, and glycolipids also have important biological activities and contribute to the inhibitory effect on cancer and pathogenic microbes (Suleria et al. 2013).

Ginger is another widely used spice which is also used in traditional herbal medicine. It has a significant health-promoting effect due to its high concentration of bioactive molecules (Shukla and Singh 2007). The origin and the form of ginger (fresh or dry) greatly influence the number and concentration of the chemical constituents. The rhizome contains many phytochemicals, including minerals, carbohydrates, and phytochemicals. The proteolytic enzyme zingibain is a potent enzyme present in the rhizomes, and there are also a moderate number of vitamins, while oleoresins are basic components and are responsible for some pharmacological effects of ginger. The extraction of ginger essential oils by gas chromatography techniques shows that sesquiterpenes are the major bioactive compounds, followed by carbonyl compounds, alcohols, and terpenes. In another study, Jolad et al. (2004) reported around sixty compounds in fresh ginger, which were categorized as volatile and non-volatile compounds, contributing specifically to the spiciness, whereas the sesquiterpene and hydrocarbons provide the aroma and taste of the ginger. Gong et al. (2004) reported 140 and 136 compounds from fresh and dry ginger, respectively, using gas chromatography–mass spectrometric (GC–MS) analysis. Compounds such as α -zingiberene and β -sesquiphellandrene are the main volatile components, while other bioactive molecules, curcumene, [6]-gingerol and [6]-shogaol, are mainly responsible for the spiciness. Gingerols are phenolics present in the ginger to which are mainly attributed the spiciness, with the concentration of [6]-gingerol acting as a key component of spiciness in the fresh rhizome being converted into shogaol during drying, with hydration and this conversion being heavily influenced by temperature and pH (Wohlmuth et al. 2005).

11.7 PHARMACOLOGY AND TOXICITY OF MEDICINAL PLANTS

The development of a drug from traditional plants is valuable and is a potent alternative to the modern drug development process, but also has a wide context for use in non-Western medical approaches and their activities. A single herb or a polyherb formulation usually have several bioactive molecules that have the potential for various pharmacological activities. Most of the medicinal plants extensively used, for example, have potent inhibitory activity against pathogenic bacteria. For a long period of time, medicinal plants were extensively used for maintaining human health. The methanol extracts of *Acacia nilotica*, *Withania somnifera*, and *Sida cordifolia* also show significant antimicrobial activity against *Pseudomonas* spp., *Staphylococcus* spp., and *Xanthomonas* spp. The leaf extracts of *T. cordifolia*, *Z. mauritiana* and *A. flavus* show effective antifungal activity (Gupta et al. 1993). Some medicinal plants possess anthelmintic activity, with the alcoholic extract of *Wedelia biflora* showing effective anthelmintic activity against the Indian earthworm. The aqueous extract of *Thespesia lampas* showed inhibitory activity against tapeworms and roundworms (Satish and Ravindra, 2009). Most importantly, medicinal plants also have potent anticancer properties. The currently employed approaches like chemotherapy, surgery, and radiotherapy cause several adverse effects in normal tissues while treating cancerous tissues. Hence, there is a need for alternative medicines (Veerakumar et al. 2016). A number of studies has supported the anticancer activity of several medicinal plants in attempts to find novel therapeutic agents without toxic effects. In recent decades, herbal medicines and plants have effectively proven their anticancer properties with limited side effects. In India, only a few plants have attracted enough attention to identify the active biomolecules and assess their role in the control/prevention of cancer proliferation (Shaikh et al. 2014). The plant-based secondary metabolites such as camptothecin, flavopiridol, resveratrol, vinblastine, and vincristine are plant-based compounds used as potent anticancer agents worldwide (Ghasemzadeh et al. 2011).

11.8 CURRENT DEVELOPMENTS IN IMMUNOMODULATOR RESEARCH

Schisandra chinensis is a Chinese herb used in clinical practice owing to its effective enzyme-inhibiting and hepatoprotective activity. In the 1960s, Chinese scientists started to isolate the potent bioactive molecules from *S. chinensis* and reported that schisandrin C was the major constituent with strong pharmacological activity. It was also used to decrease enzyme levels in the treatment of the hepatitis B virus (Yang et al. 2009). The structure–activity relationship of bifendate and its analogues was studied and a series of novel derivatives were synthesized then subjected to screening with respect to a number of chemical and pharmaceutical injury modes. It was noticed that the derivatives having hepatoprotective activity showed closely related dimethylenedioxy functional group in two benzene rings with long carboxyl side chains. Finally, a new compound, bicyclol, was synthesized. Due to the presence of the carbomethoxy side chain and the hydroxymethyl group, bicyclol has great

bioavailability and biological activity (Liu et al. 2010). It also significantly inhibited the replication of the hepatitis B virus though it exhibited a more effective and it was discontinued due to fewer side effects (Bao et al. 2008; Li et al. 2011). Another plant-derived compound, paclitaxel, a potent anticancer compound extracted from *Taxus brevifolia*. Paclitaxel has a unique chemical structure and a radically distinct mechanism of action against cancer and has been tested successfully in treatment of several cancer types and has been involved in clinical trials. It received US Food and Drug Administration (FDA) approval for the treatment of ovarian cancer in the year 1992–93. (Wani and Horwitz, 2014). Owing to its low solubility in an aqueous medium, however, yields from the natural plant source were low.

11.9 LIMITATIONS

Several challenges and limitations exist to accurately assess the toxicological and epidemiological effects and other activities in the verification of herbal material use. The management of risk factors within ranges, pharmacological and clinical documentation, and an understanding of harmful additives need to be evaluated. The limits with clinical trials, standardization, and safety and efficacy assessments need to be overcome. The identification of novel herbal products has the following six essential steps: identification and characterization of potent molecules, activity of the molecule, identification of any side effects or adverse reaction, its pharmacological activity, and assessment of the toxicity and carcinogenicity in clinical trials. Low yields of the active molecules, lack of adequate research on the development of domestication of the plant source, insufficient techniques to yield product of consistently high quality, lack of good manufacturing practice, poor quality control measures, limited marketing, and lack of proper equipment are the major constraints associated with handling the medicinal plants in alternative approaches to current therapeutic strategies (Rukangira 2000). Another major constraint when dealing with herbal medicine is that the extract contains a mixture of organic substances and it is often difficult to find which molecules have good biological activity. In addition, owing to the complex nature of bioactive molecules, it is difficult to determine the structural and functional features. When determining the concentration of major components, temperature, dissolution, and atmospheric humidity may alter the concentration and sometimes the functions of active ingredients of herbal medicines. Other environmental factors affecting the yield of active ingredients from herbal plants, like pests/diseases, planting density, seeding time, and generic factors may also play an essential role; hence, the collection of plants and the time of harvest are important. Several ways are commonly used for adulteration of herbal plant material by substituting the target plant with inexpensive but readily available local plant relatives (Thillaivanan and Samraj, 2014).

11.10 CONCLUSION

Plant-based immunomodulators are naturally available substances that represent an interesting tool for the handling the immune system within a clinical setting, owing

to their wide range of bioactivities. Medicinal plant products and active compounds are effectively studied and characterized to understand the basic phytochemical constituents with valid analytical methods and extraction protocols. The bioactive components are specifically analyzed and used as active markers to ensure the pharmacological efficacy of the molecule for comparative studies. The purified molecule can then be characterized to understand the beneficial effect of specific components of the molecule. For example, polyphenols are highly involved in the immunomodulatory activity due to polyunsaturated fatty acids (PUFA) -enriched fatty acids. Hence, the identification of major bioactive molecules with clinical evidence for their efficacy and safety is a major task for medicinal plant-induced immunomodulation due to limited studies. Hence, the selection of concentration, experimental protocols, and comparative standard compounds are reported in the preclinical studies (Heinrich et al. 2020; Izzo et al. 2020). Traditional medicinal systems in India provide the major bioactive molecules with multiple pleiotropic activities. Most of the medicinal plants have immunomodulatory effects achieved by an immune booster of the immune system to eradicate the pathogenic microorganisms and exogenous injuries. To control the impaired immune response due to autoimmune disorders, it is influenced by non-immune targets. In this chapter, we emphasize the immunomodulating effect of the traditional medicinal system and its pharmacological effect. In addition, molecular chemistry and the mechanism of action are also discussed. Traditional medicinal plants and their phytoconstituents are used as promising molecules for identification of plant-based drugs, and these molecules act as potential lead compounds for the development of effective, inexpensive immunomodulatory agents.

ACKNOWLEDGEMENT

The authors Chandrabose Selvaraj and Sanjeev Kumar Singh gratefully acknowledge RUSA-Phase 2.0 Policy (TNmulti-Gen), Department of Education, Government of India (Grant No: F.24-51/2014-U). The author Chandrabose Yogeswari gratefully acknowledges Vetri Siddha Medical College Hospital & Research Institute, Thanichayam, Madurai, for providing necessary information on this topic, along with facilities.

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12 Specific Plant Nutrients and Vitamins that Fortify Human Immune System

*Kirubel Teshome Tadele and
Gebeyanesh Worku Zerssa*

CONTENTS

12.1 Introduction	363
12.2 Specific Plant Nutrients and Their Immune System Stimulating Effect.....	365
12.2.1 Garlic	365
12.2.2 Ginger	369
12.2.3 Green Tea.....	370
12.2.4 Echinacea.....	371
12.2.5 Broccoli.....	373
12.2.6 Red Pepper.....	374
12.3 Selected Vitamins Fortifying the Immune System	375
12.3.1 Vitamin C	375
12.3.2 Vitamin D.....	378
12.3.3 Vitamin E.....	380
12.4 Conclusion	382
References.....	382

12.1 INTRODUCTION

From the instant of birth in the process of joining this world, a living organism's body is bombarded by pathogenic microorganisms, the solitary goal of which is living and replicating under favorable conditions based on their natural behaviour and a nutrient-rich environment. Harmful microorganisms reproduce and infect a body by very specialized mechanisms which may even lead to mortality unless managed properly. These microorganisms also use infected bodies as a route for spreading to new hosts (Gombart et al. 2020). Nowadays, the challenging global problems, such as environmental and water pollution, provide extra opportunities for infection by microorganisms, which is facilitated by the technology-aided high mobility of people and commodities around the world. There is no better example than COVID-19 for this, which spread throughout the world within a couple of months after its

outbreak in December 2019 and may be considered to be the most detrimental event of the 21st century.

Nature is not passive, allowing microorganisms to attack and damage living organisms at will. There is an immune system whose main functions are to protect the host's body against infection and damage from the pathogens, removing unwanted damaged tissues, and providing persistent reconnaissance of harmful cells that grow in the body of the host (Wu et al. 2019). The system consists of innate (non-specific) and adaptive (specific) immune systems (Li et al. 2007) as functional branches. Although the immune system has a complicated defensive strategy, orchestrated by specialized tissues, organs, cells, and chemicals (Rondanelli et al. 2018), their organization can be described into three core cooperative clusters, including physical barriers, and innate and adaptive immunity (Calder and Kew 2002; Maggini et al. 2007). The first barrier contains physical barriers with an acidic medium due to the availability of different fatty acids and enzymes, which are able to limit the growth of nearly all bacteria, secreting pathogen-destroying mucus, and enhancing the acidity of the stomach. The second barrier is innate immunity, which contains cells such as natural killer (NK) cells, cytokines, macrophages, and neutrophil granulocytes as elements for its functions (Rondanelli et al. 2018). The innate immune system takes immediate action to distinguish and destroy foreign threats through inflammatory processes, resolving the inflammation, and repairing the damage caused (Murphy and Weaver 2017). Hence, the innate immune system provides the first line of defence against invading pathogens in vertebrates (Narnaware et al. 1994). The problem of the innate immune system is its inability to increase the responding efficacy when there is a repeated pathogenic attack. Then, the additional help needed opens the door for the adaptive (specific) immune system to act subsequently. Antigen-specific cells like T lymphocytes, which play a key role in killing virally-infected cells, as well as B lymphocytes, that are responsible for secretion of antibodies specific to the infecting pathogen after being activated, operate under the adaptive immune system (van Gorkom et al. 2018). Although the adaptive immune system responds more slowly than the innate immune system, it is more efficient in eliminating infections because of the exquisite specificity of antigen recognition by its lymphocytes. But the adaptive immune system is not independent of the innate immune since it interacts with, and relies upon, cells of the innate immune system for many of its functions (Murphy and Weaver 2017).

Innate immunity is strongly influenced by nutrition and the interconnection between nutrition and immunity is considered to be absolute (Mainous and Deitch 1994). Nutrition, taking into account the content and nature of the nutrients as well as the duration of the intake, has a profound impact on human health (Nobs et al. 2020). However, for the immune system to generate an efficient immune response, adequate and balanced nutrition is required to supply it with the necessary components (Marcos et al. 2003). In general, nutrition determines the development of the immune system in infants and their efficiency in adult life (Sima et al. 2016). The enormous influence of nutrition on immune function was confirmed after being studied for several decades and transformed research in the field to a specific discipline called nutritional immunology (Wu et al. 2019). The research findings in this

area greatly emphasize the use of immunity-boosting plant nutrients as one of the most promising methods of controlling diseases (Harikrishnan et al. 2011). Nutrition provides certain micronutrients upon which every stage of an immune response depends (Gombart et al. 2020). Considering the risk of premature death as a result of the persistent infectious diseases globally, the plants containing immune system-boosting nutrients and vitamins are in great demand. The main aim of this chapter is to explore the specific immune system-boosting plant nutrients and vitamins to our current understanding of the field. It also describes some suggested mechanisms by which the nutrients enhance the efficacy of the immune system, although the mechanism is still not fully understood.

12.2 SPECIFIC PLANT NUTRIENTS AND THEIR IMMUNE SYSTEM STIMULATING EFFECT

The great health benefits of functional and nutraceutical foods are making them popular around the world (Suleria et al. 2015). The strong interaction between nutrients and the immune system has been proved and has attracted particular attention to nutrition. Currently, some plants with immune system-boosting specific nutrients, such as garlic, ginger, green tea, echinacea, broccoli, and black pepper are on target to manage the morbidity and mortality due to pathogens causing infectious diseases (Table 12.1).

12.2.1 GARLIC

Garlic (*Allium sativum*) is a bulb-forming annual plant belonging to the genus *Allium* of the Amaryllidaceae family (Lee et al. 2012), native to Central and South Asia (Rouf et al. 2020). The numerous health benefits of garlic make it one of the most used plants in herbal medicine. Garlic has been used to treat as well as to prevent diseases by the Chinese, Greeks, and Romans for centuries. The efficacy of the plant in treating and preventing diseases like cancer, cardiovascular, and obesity is indicated in the literature (Miguel 2011; ia-UI-Haq et al. 2011; Zia-UI-Haq et al. 2013; Khanra et al. 2015). Presently, garlic is cultivated throughout the world, with countries like China, India, South Korea, Egypt, and the USA being among the leaders in garlic production (Medina and Garcia 2007; Rehman et al. 2019). Garlic is an edible crop that has been used as medicine (Gruhlke et al. 2019), a functional food, spice, and seasoning herb (Rehman et al. 2019; Rouf et al. 2020) since ancient times. The plant is among one of those most widely used for its health-giving benefits and it is also used as a flavouring agent, enhancing physical and mental health (Shin and Kim 2004). Garlic is used to treat common viral diseases, such as the common cold, fever, coughs, asthma, and wounds in Asia and Europe (Rehman et al. 2019; Rouf et al. 2020). The oil extracted from garlic has also been used to mitigate the pain of ear infections (Al Abbasi, 2008). In African countries, like Ethiopia and Nigeria, garlic has been used as a traditional remedy for the treatment of several infections, such as sexually transmitted infections, tuberculosis (TB), respiratory system diseases, and wounds due to injuries and damage of different tissues (Gebreyohannes and Mebrahtu 2013; Abiy and Asefaw 2016).

TABLE 12.1
Summary of Major Findings of Immune System Boosting Activity of Some Medicinal Plant Nutrients

Medicinal Plant	Bioactive Compounds	Immune System Stimulating Compounds	Activity	References
Garlic	Organosulphur compounds (G-SAC, alliin, allicin)	Allicin	Activated the release of Zn ²⁺ from proteins S-thioallylated 3S2 proteins of human Jurkat cell proteome	(Grublike et al. 2019)
Ginger	Gingerol, shogaol, zingiberol, zingiberene	Gingerol	Inhibited the gene expression of Th2 cytokines and IFN- γ Stimulated both innate and adaptive immune response mechanisms	(Kawamotoa et al. 2016; Bauter et al. 2014)
Green tea	Catechin flavonoids (EGCG, EGC, EC, ECG, phenolic acid, theobromine, theanine, theophylline, and caffeine)	EGCG	Sustained the levels of CD4 ⁺ and CD8 ⁺ lymphocytes at the required level and increased the secretion of sIgA in BALF mice Prevented skin erythema formation in mice Supported the restoration of T cell activity by mediating PD-L1 inhibition	(Tang et al. 2020; Jung et al. 2019; Rawangkan et al. 2018)
Echinacea (the most potent immuno stimulating)	Polysaccharides, alkaloids, glycoproteins, caffeic acid derivatives, alkylamides, and volatile oils	Polysaccharides Alkamides Glycoproteins	Activated the synthesis of pro-inflammatory cytokine TNF- α in RAW 264.7 macrophage-like cells Enhanced the production and secretion of macrophages	(Balcunaite et al. 2015; Rininger et al. 2000; Todd et al., 2015; Luettig et al. 1989; Roesler et al. 1991)
Broccoli	Glucosinolates, dithiolthiones, indoles, glucoraphanin, S-methyl cysteine sulfoxide, isothiocyanates	Sulphoraphane	Decreased the oozing of pro- inflammatory cytokines	(Aguado et al. 2014; Ruiz- Jimémez et al. 2003; Bessler and Djaldetti, 2018; Busato et al. 2020; Geisel et al. 2014)
Red Pepper	Capsaicin, capsinin, capsantine polyphenol, flavonoids, and flavomols	Capsaicin	Augmented activated macrophages in number as well as phagocytic activity Inhibited IL-12 and IL-23 expression Augmented the immunoglobulin (IgM) levels Elevated the leucocytes cells	(Zaki et al. 2017; Puvaca, 2018; Abdelnour et al. 2018; Abdelnour et al. 2018; Afolabi et al., 2017)

The enormous health benefits of garlic are mainly associated with its organosulphur compounds (Suleria et al. 2015). The organosulphur compound content (1.1–3.5%) content of garlic is much higher than that in other plants, which is the main reason behind its superior health- benefits relative to other plants. Glutamyl-*S*-allyl-L-cysteines (G-SAC) are the principal organosulphur compounds of intact garlic. These compounds hydrolyze and oxidize, forming *S*-allyl-L-cysteine sulphoxides (alliin) when stored (Matsuura and Lachance 1997).

Alliin is highly unstable, being converted to the chief bioactive components, allicin and other thiosulphates, by an enzyme, alliinase, released by crushing, chopping, or chewing of garlic (Amagase 2006).

Allicin is mainly responsible for the medicinal role of garlic (Larry et al. 2018). This bioactive organosulphur compound provides the necessary components for the immune system to defend the host against pathological microorganisms, making garlic the source of numerous health benefits (Gardner et al. 2007). Fresh garlic has a distinctive pleasant flavour, which is also associated with volatile compounds released from the unstable alliin by the help of the enzyme allinase (Krest et al. 2000). About 10 g of edible garlic (one single clove) produces up to 5 mg of allicin (Gruhlke et al. 2019). A diet containing garlic, either raw or crushed, is proved to act as an immune modulator, influencing the expression of immunity in humans (Abdullah 2000; Charron et al. 2015).

Daily consumption of food containing aged garlic extract (AGE) modulates the immune system response of healthy but obese adults by stimulating the immune cells and inflammatory mediators (Xu et al. 2018). Although the mechanism by which the extract plays the role is still in doubt, a hydrogen sulphide (H_2S) -based mechanism is considered to be a potential one. This mechanism deactivates the pathway of NF-kappa-beta signaling, facilitating the production of pro-inflammatory cytokines (Ha et al. 2015; Rios et al. 2015). The bioactive organosulphur compounds in AGE, like *S*-allyl-L-cysteine (SAC), increase the endogenous production of H_2S and act as its mediators (Gu and Zhu 2011; Chulah et al. 2007), driving the suppression of obesity induced-inflammation (Xu et al. 2018). Aging makes garlic nearly odorless by converting its strong organosulphur compounds into hydrophilic compounds, like SAC and *S*-allylmercaptocysteine (SAMC). There are compounds such as lectins and fructooligosaccharides in aged garlic with proven immunomodulating activity (Chandrashekar and Venkatesh 2009; Chandrashekar et al. 2011). Allicin, the main organosulphur compound in garlic, stimulates the immune response by activating the release of Zn^{2+} from proteins to enhance the production of IL-2 in murine EL-4 T cells. It inhibits the activity of enolase, a targeted enzyme in cancer therapy. Allicin also inhibits some selected *S*-thioallylated proteins, which are one of the components of the garlic action mechanism, causing the actin cytoskeleton disruption.

These activities of allicin and other organosulfur compounds of garlic are responsible for modulating the immune system in humans. The strong immunostimulating activity of allicin on mammalian cells at its higher doses is manifested by its ability to achieve *S*-thioallylation of 332 proteins in the human Jurkat cell proteome (Gruhlke et al. 2019).

Identification of garlic or lemon aqueous extracts, as well as their combination, as antiproliferative in mice indicated the good activity of the two, especially when combined. Thus, the garlic and lemon extract combination is a promising option for anti-cancer food and therapy development, although the molecular mechanisms need to be further studied. The combination of garlic and lemon extracts activated the immune system by inhibiting angiogenesis and inducing apoptosis. The combination enhanced the immunity-boosting ability of garlic due to the acidic environment provided by the lemon extract which activates organosulphur compound production (Talib 2017).

It was reported in a randomized crossover garlic-containing meal feeding study that garlic intake up-regulated the nuclear factor of activated T cells (NFAT) activating protein with the immune receptor tyrosine-based activation motif 1 (NFAM1) gene, modulating the immune system (Charron et al. 2015). A study carried out to determine the influence of aged garlic dietary augmentation on the immune system function, targeting the innate immune NK cell and adaptive immune $\gamma\delta$ -T cell functions, revealed a lowering of inflammatory cytokine secretion by the garlic-treated cells. The significantly lower secretion of IFN- γ suggests that the immune system easily destroys the pathogens with a smaller amount of the inflammatory cytokine. The supplementation also reduced cold and flu symptoms, which might be related to lowering in inflammatory cytokine secretion, $\gamma\delta$ -T and NK cell function, and thiol status improvement (Nantz et al. 2012). The modification of the innate immune cells by dietary compounds has been reported (Meadows et al. 1992; Percival et al. 2005; Hanson et al. 2007; Schink et al. 2007). Garlic powder supplemented as natural feed additives for broiler chickens improved their red blood cells (RBC) and haemoglobin content (Hb). It also improved the weight of the liver and immune-related organs, which was due to the bioactive molecules in garlic powder, enhancing the immune system (Ismail et al. 2020).

Garlic, onion lemon, and juice supplementation as natural additives to the diet of buffalo calves increased the digestibility of all nutrients. It also significantly increased blood components GPT and GOT; erythrocytes and leukocytes numbers also increased. Glutamate-pyruvate transaminase (GPT) is highly active glutamate degrading enzyme found in the liver and other tissues, while glutamateoxaloacetic transaminase (GOT) is found in mitochondrial and cytosolic forms, catalyzing amino acid metabolism as well as urea and tricarboxylic acid cycles. Furthermore, the increasing immunity (globulin fractions) was manifested by the elimination of harmful bacteria, avoiding early infections (Ahmed et al. 2009). Post dietary supplementation of garlic and ginger to Sasso broiler chicks modulated their immune system response. The most likely mechanism for this activity included amplification of phagocytosis, increased antifungal activity, and minimization of nitric oxide (NO) synthesis. Phagocytic cells increased, showing 90% engulfing capacity of *Candida albicans* in broiler chicks treated with the two medicinal plant extracts. The antimicrobial activity of garlic which might be associated with its bioactive compounds is reported. The suggested mechanism of the action is *via* hindering the functions of the microbial membrane and the associated membrane proteins (Hafidh et al. 2011). The antibacterial potential of garlic might be attributed to its increased production of TNF- α cytokines and lymphocyte-triggering abilities (Mojani et al. 2016). The extracts have bioactive compounds which interact with innate lymphocytes and

natural killer cells (Percival 2016). It is also reported that the bioactive compounds activate macrophages and B cells, enhance immunoglobulin production, and regulate cytokine secretion (Li et al. 2015). The downregulation of NO production after treatment of the birds with garlic and ginger additives might reduce the pathological damage occurring as a result of excess NO production (Amirghofran et al. 2011).

12.2.2 GINGER

Ginger (*Zingiber officinale*) is a well-known spice and medicinal plant, which has been used throughout the world and is readily accessible in many Asian countries (Bauer et al. 2014; Sheikhi et al. 2015). Tropical Asians, especially in southern China or India, are believed to have been the first to use ginger (Semwal et al. 2015). Ginger rhizome (the actual botanical term for what is referred to as 'ginger root') is used as a spice globally (Kikuzaki and Nakatani 1996). The typical components of a dry ginger root powder are carbohydrates (60–70%), protein (9%), lipid (3–6%), fibre (3–8%), proteases (2–6%), volatile bioactive compounds (1–3%), and vitamins (Murray 1995). Ginger possesses numerous biological activities, such as antidiabetic, anti-inflammatory, and antitumour properties, due to the bioactive compounds such as gingerol, gingerdiol, and gingerdione (Kikuzaki and Nakatani 1996). The bioactive compounds of ginger increase host resistance to infectious diseases by stimulating the immune system response mechanisms of the host (Bauer et al. 2014). It is also reported that cell-mediated immune response, as well as the non-specific proliferation of T lymphocytes, are influenced by ginger oil (Wilasrusmee et al. 2002).

Compounds of phenolic ketone derivatives make ginger a good antioxidant. Gingerol is one of the typical volatile compounds of ginger, which is responsible for the pungent odour and taste of the plant. This compound also increases the palatability of food as well as increasing the secretion of digestive enzymes (Mansour et al. 2012; Jesudoss et al. 2017; Ahmadifar et al. 2019). Ginger has been used to treat gastrointestinal disorders for many centuries (Sheikhi et al. 2015). Ginger is also used as a treatment option for nausea and vomiting (Sharifi-Rad et al. 2017; Tóth et al. 2018). However, it is not recommended for pregnant women since it has mutagenic effects *in vitro* (Nakamura and Yamamoto 1983; Nagabhushan et al. 1987; Srinivasan 2017; Tóth et al. 2018).

Supplementation with ginger powder for patients with active rheumatoid arthritis (RA) decreased the manifestation of the disease by enhancing the expression of FoxP3 genes and declining the expression of ROR γ t and T-bet genes to improve RA symptoms. The anti-inflammatory activity of ginger is indicated by its ability to reduce T-bet. The immunomodulatory effects of ginger were verified by increases in FoxP3 expression in patients who consumed ginger (Aryaeian et al. 2019). The increase in FoxP3 expression activated Tregs function, modulating the immune system (Nazari et al. 2013). The improvement of RA showed the potential of ginger to boost the immune system to prevent the damage caused by autoimmune diseases (Aryaeian et al. 2019).

A range of concentrations of feed supplementation with ginger and organic selenium improved the growth and immune system function of broiler chickens. The improvement was directly related to the increase in secretion of gastrointestinal

enzymes such as disaccharidases, lipase and maltase, which improve digestion and food intake (Zhang et al. 2009). The combined feeding of ginger and selenium improved immune response with no synergistic effect on the performance of broiler chickens (Safiullah et al. 2019).

It was recently reported for the first time that ginger rhizome extract has benefits even for smokers. Ginger consumption increased the concentration of haemoglobin to compensate for its reduction as a result of smoking, a finding which benefits smokers with anaemia. Ginger consumption enhances the thyroid gland activity in smokers as well as in non-smokers. It also enhanced IgM levels of non-smokers for better humoral immunity, antibody response, and defence against infections (Mahassni et al. 2019).

Nanoparticles prepared from compounds isolated from ginger protected mice from alcohol-induced liver damage. It is suggested that the nanoparticles activated nuclear factor erythroid 2-related factor 2 (Nrf2), which plays a key role in the expression of liver detoxifying genes. This also inhibits the production of oxygen free radicals to support the safety of the liver (Zhuang et al. 2015).

An antiallergic effect of ginger is reported, with the major bioactive phenolic compound 6-gingerol suggested to play the role. The potential of 6-gingerol to inhibit the expression of genes encoding Th2 cytokines and IFN- γ was indicated clearly (Kawamotoa et al. 2016). In addition, feeding with ginger prohibited Th2-mediated immune responses and 6-gingerol suppressed eosinophilia in a mouse model (Ahui et al. 2008), so it could be a good option for the prevention of IgE-mediated allergic disorders. 6-Gingerol is a proven immunosuppressing agent (Kawamotoa et al. 2016).

12.2.3 GREEN TEA

After water, tea is the leading beverage to be consumed globally today (Costa et al. 2002; Rietveld and Wiseman 2003). A leaf of *Camellia sinensis* plant is used for the preparation of tea. The plant belongs to the Theaceae family and all types of tea are prepared from its leaf. The beginning of tea usage goes back 5,000 years in Southwest China. In preparing black tea, the basic processes include oxidation, a curing process of maceration and exposure to atmospheric oxygen, and black tea is the preferred form in Western countries (Graham 1992; Langley-Evans 2002). The majority of tea consumed in the USA is black ice tea (Il'yasova et al. 2003). The complex chemical composition of dried green tea contains carbohydrates (7–25%), proteins (15–20%), minerals (5%), flavonoids (25–35%), xanthic bases (3.5%), pigments (0.5–2%) and aromatic organic acids (Graham 1992; Cabrera et al. 2006). Both tea leaves and the tea beverage obtained by processing the leaves are rich in polyphenols (flavonoids), particularly the most biologically active flavanols, the catechins (Crespy and Williamson 2004), and several vitamins (Sato and Miyata 2000; Higdon and Frei 2003). Green tea is rich in catechins and also includes phenolic acid, theobromine, theophylline, theanine, and caffeine (Barbalho et al. 2019).

In the catechins in green tea, epigallocatechin-3-gallate (EGCG) is the most abundant (32–50%), followed by epigallocatechin (EGC) (18–28%), then others

like epicatechin (EC) (6%) and epicatechin-3-gallate (ECG) (8–12%). These bioactive compounds are responsible for the biological activities of the plant, such as its antioxidant and anti-inflammatory properties. These biological activities are very important for the prevention and treatment of numerous diseases such as diabetes, cancer, obesity and cardiovascular diseases (Inoue-Choi et al. 2010; Geetha and Santhy 2013; Najeeb et al. 2016; Cazzola et al. 2018). The immune system stimulating potential of green tea polyphenols has been reported (Shimizu et al. 2010; Kim et al. 2016; Sharma et al. 2017).

It has been reported that tea drinkers showed better immune system stimulation than coffee drinkers through greater $\gamma\delta$ -T-T cell proliferation *in vivo*, which is associated with the presence of the unique amino acid, L-theanine, in tea. L-theanine is converted to glutamic acid, alkylamine and ethylamine *via* hydrolyzation (Kamath et al. 2003). The most abundant bioactive compound, catechin, increased levels of immunoglobulin in the rat model, which demonstrated its potential for stimulating the immune system (Ganeshpurkar and Saluja 2018). The immunomodulating activity of catechins is associated with increasing the level of phagocytic cell production in animals (Banacerraf 1978). Supplementation of feed with green tea by-products showed a positive impact on immune cell proliferation in goats by increasing the proliferation of T and B cells (Ahmed et al. 2015). Anticancer activity of green tea catechins has been reported. EGCG showed immune checkpoint inhibition activity and supported the restoration of T cell activity by mediating PD-L1 inhibition, making T cells kill cancer cells more effectively (Rawangkan et al. 2018). The main polyphenol in green tea, EGCG, restored the immune system disturbed by overdose supplementation of the toxic food contaminant, Perfluorodecanoic acid (PFDA) in mice and significantly reduced their mortality (Wang et al. 2020).

Supplementation with green tea for one week stimulated the function of the skin barrier by modulating skin metabolites and inhibiting metabolome changes in response to UV stress in mice exposed to external UV radiation. It is suggested that this effect prevents the formation of skin erythema (Jung et al. 2019). The components of green tea, such as epigallocatechin gallate, caffeine, and theanine, defend the skin against UV stress by repairing the disturbed immune system caused by UV exposure and by enhancing its functions. (–)-Epigallocatechin-3-gallate (EGCG) enhanced the immune system in mice through maintaining the normal levels of CD4+ and CD8+ lymphocytes and increasing the secretion of sIgA in BALB/c mice and blocked infection by microorganisms in the respiratory tract. However, the activity of the compound was dose-dependent and the risk of immune suppression was reported at overdose levels. In addition, EGCG inhibited the release of the main stress hormones in normal mice, preventing the restraint stress to minimize the liver injury (Tang et al. 2020).

12.2.4 ECHINACEA

Echinacea, commonly known as the purple coneflower, is an herbal medicine that was first recognized by Native Americans in the eighteenth century. Today, the plant is well distributed all over the world and widely found in the USA and Europe.

Echinacea is rich in bioactive metabolites, such as glycoproteins, caffeic acid derivatives, alkaloids, flavonoids, polysaccharides, glycoproteins, and volatile oils (Mirjalili et al. 2006; Göllner et al. 2013; Balciunaite et al. 2015; Moazami et al. 2015). Echinacea and its pharmaceuticals have been used for the treatment of breathing-system-related illnesses like influenza, cough and sore throat, of immunity-related cases like sepsis, and animal-related injuries, such as rabies and snake bites in the developing as well as in the developed world (Hu and Kitts 2000; Binns et al. 2002; Jawad et al. 2012; Rauš et al. 2015; Li et al. 2017). The *Echinacea* genus is in the Asteraceae family and has various species, such as *Echinacea purpurea*, *Echinacea angustifolia*, and *Echinacea pallida* (O'Hara et al. 1998). *E. purpurea* is the most used species and among the most popular medicinal plants worldwide today (Hudson 2012). These species possess several biological activities, such as bactericidal, free radical scavenging, anti-inflammatory, antiproliferative, antihypertensive, and immunomodulation properties (LaLone et al. 2007; Aarland et al. 2017; Chiou et al. 2017). *E. purpurea* is considered to be an efficient medicinal plant due to its low toxicity and few adverse effects.

E. purpurea is rich in numerous bioactive compounds, such as polysaccharides, alkaloids, glycoproteins, caffeic acid derivatives, and alkylamides. The immunomodulatory activities of this plant are also associated with the abundant presence of alkylamides, glycoproteins, and polysaccharides in its roots (Balciunaite et al. 2015). The immunostimulatory activity of *Echinacea* has been reported to be associated with its polysaccharide bioactive compounds (Luettig et al. 1989; Roesler et al. 1991). Although the immunomodulation mechanisms involving plant metabolites are not well understood, it is reported that the immunomodulatory effect of *E. purpurea* is associated with the biochemical changes its phytochemicals cause in immune cells (Todd et al. 2015). The potential of certain standardized *E. purpurea* preparations to treat viral and microbial respiratory infections has been reported (Sharma et al. 2009, 2010).

It has also been reported that ethanolic extracts of *E. purpurea* showed a dual effect on immune system function: activation of production of the pro-inflammatory cytokine TNF- α in RAW 264.7 macrophage-like cells to fortify the immune system response in one way and it suppresses the generation of TNF- α in response to LPS exposure (Todd et al. 2015). Both of the activities are vital for regulation of the host immune response.

Children treated with combined Echinacea and Azithromycin showed a low frequency of tonsillitis recurrence, with reduced symptoms (Awad 2020). Echinacea has immunostimulating properties, for which alkamides are thought to be responsible among the bioactive constituents of the plant (Rininger et al. 2000). The plant can also reduce the severity of symptoms in early infections of the common cold and flu, which is believed to be one of the outcomes of its stimulatory effect on the immune system (Barrett 2003). *Echinacea purpurea* supplementations decreased the death rates of chickens infected with *Escherichia coli* bacteria, which might be due to the enhancement of immune response by the medicinal plant (Hashem et al. 2020). The immunostimulatory potential of *Echinacea purpurea* is believed to increase the resistance of the birds against infection (Gharieb and Youssef 2014).

The addition of 2% *E. purpurea* extracts in the drinking water for broiler chickens increased their immune response (Hassan and Sobhan 2017). *E. purpurea* is the most potent immune system stimulator because it has a high potential to increasing the non-specific immune system.

The immune system stimulating effect of tetraploid (CPE4) wolfberry fruit and diploid (CPE2) *Echinacea purpurea* polysaccharide was compared and reported. The immunoregulatory effect of tetraploid (CPE4) polysaccharide is found to be double that of the diploid (CPE2) polysaccharide, a finding which is clearly related to chromosome doubling (Yang et al. 2018). Polyploidization of this bioactive component (polysaccharide) of the plant enhanced their biological activities (Shi and Liu, 1998). Several studies indicated a direct influence of *E. purpurea* on the immune system function (Cech et al. 2010; King et al. 2014). Cellular immunity was promoted in young Wistar rats treated with *E. purpurea* extract, a finding which was confirmed by a level of immunoregulatory cytokines and immunoglobulins comparable with those in adult rats (Wang et al. 2017).

12.2.5 BROCCOLI

Broccoli (*Brassica oleracea* var. *italica*) is an edible vegetable plant belonging to the family Brassicaceae (Vallejo et al. 2004; Eberhardt et al. 2005). It is indigenous to the eastern Mediterranean and Asia Minor, and was distributed to England and the USA in the eighteenth century. This fast-growing leafy vegetable has attracted much interest recently due to its high value in terms of nutrition and health care (Axelsson et al. 2017). Broccoli has been one of the top research targets (Jones et al. 2010) due to health benefits attributed to phytochemicals such as glucosinolates, glucoraphanin, dithiolthiones, isothiocyanates, indoles and its derivatives, and *S*-methyl cysteine sulfoxide (Ruiz-Jiménez et al. 2003; Aguado et al. 2014).

A common and bioactive compound in cruciferous vegetables, including broccoli, sulphoraphane is an isothiocyanate formed by glucoraphanin hydrolysis (Fahey et al. 2002; Ares et al. 2014; Bricker et al. 2014; Baenas et al. 2015). Sulphoraphane is an important bioactive compound which possesses various biological activities including immunomodulatory activity (Thejass and Kuttan 2007).

Pectin FB extracted from broccoli modulated the immune system of mice *in vivo* in a concentration-dependent way *via* increasing the number of activated macrophages and phagocytic activity. The reported ability of this polysaccharide to modulate the immune system makes it a potential contributor to immunomodulating drug development (Busato et al. 2020).

Sulphoraphane decreased the secretion of pro-inflammatory cytokines in a dose-dependent manner. This compound is reported to have the potential of enhancing the response of the immune system (Bessler and Djaldetti 2018).

Sulphoraphane is a successful therapy in mice against a T cell-mediated autoimmune disease through a suggested inhibition of IL-12 and IL-23 expression (Geisel et al. 2014). ESAT-6 protein, obtained from genetically modified broccoli, enhanced the humoral immune response in mice against *Mycobacterium tuberculosis* (Saba et al. 2020). The concentration of the ESAT-6 antigen derived from this plant is

higher than that obtained from other edible plants (Uvarova et al. 2013; Permyakova et al. 2015), showing its potential for the development of an edible plant-based vaccine against tuberculosis.

Dietary supplementation of broccoli in lower concentrations improved response in ligand-sensitive Ahrb/b mice and improved the resistance of the intestine to the chemical through host-microbiome alteration. This effect of broccoli consumption is partly associated with heightened AHR activity. It also significantly modulated the expression of numerous genes, like the up-regulation of the expression of cyclin and cell cycle regulatory genes. The potential of broccoli to play a therapeutic role in intestinal homeostasis is also suggested (Hubbard et al. 2017).

The water-soluble polysaccharides of broccoli, whose structure has been elucidated for the first time, showed good anticancer activity against HepG2 liver, MDA-MB-231 cell line, and SiHacervical carcinoma cells. One of the three mechanisms by which natural polysaccharides act as an anticancer agent is by regulating the immune system to increase resistance against the cancer (Zong et al. 2012), which might be the mechanism by which the polysaccharides acted here. However, confirmation of the mechanism requires further investigation (Xu et al. 2015).

Dietary supplementation of young broccoli sprout homogenates for smokers decreased viral infection and a similar effect was manifested in a cohort of healthy nonsmokers. The observed effect was related to viral replication minimization due to oxidative stress reduction in nasal cells. This further emphasizes how much the immune system function is influenced by nutritional factors and the broccoli sprout homogenates supplied might alter specific host defense responses (Noah et al. 2014).

12.2.6 RED PEPPER

Red chilli pepper (*Capsicum annuum*) is a plant species from the Solanaceae family which is indigenous to central America. The plant is edible and grown for its fruit which can be consumed either fresh or cooked. The fruit can also be processed to be used as spices (Jancso et al. 1997). At present, hot red peppers are the most important spices in human nutrition globally. However, strong care is needed especially regarding its dose since it is recognized to cause pain to the mucous membranes when consumed in surplus (Nwaopara et al. 2004, 2007). They are well known medicinal plants with several biological activities (Johann et al. 2010; Freires et al. 2013) which are related to their main bioactive component capsaicin (Abdelnour et al. 2018; Puvaca 2018). There are also other bioactive phytochemicals in this herbal plant such as capsaisin and capsantine. The plant has chemopreventive and chemotherapeutic effects, which are due to these bioactive compounds (Al-Kassie et al. 2012). Jancso et al. (1997) reported that red pepper exclusively produces the alkaloids known as the capsaicinoids, about 50% of which is represented by capsaicin. The pungent and irritating effect of hot red pepper is due to capsaicin. The spicy feature of hot pepper is also associated with capsaicin (Govindarajan and Sathyanarayana 1991). The capsaicinoids and capsaicin of hot red pepper increases metabolism in terms of body temperature, oxygen consumption, and energy promotion in humans (Ohnuki et al. 2001). There are subclass compounds of capsaicin, such as dihydrocapsaicin,

nordihydrocapsaicin, homodihydrocapsaicin, and homocapsaicin (Fattori et al. 2016), which also contribute to the medicinal role of the plant. Vitamin C is also abundantly found in hot red pepper as well as pro-vitamin A, which contributes to the antioxidant and anti-stressor activities of the plant (Lee et al. 2005; Puvaca 2018; Puvaca et al. 2019). Hot red pepper has potential to decrease cholesterol and fat deposition which helps the vascular system through participating in the lowering of triglyceride levels (Al-Kassie et al. 2012). Hot red pepper powder supplementation as a feed additive for broiler chicks increased their bacterial inhibitory potential and villi length, improving their performance. The improved bacterial defense might be due to morphological modification of the small intestine *via* a reduction in the growth of pathogenic or nonpathogenic microorganisms in the intestine. This may cause a reduction in the inflammatory reactions at the intestinal mucosa, which directs the increasing villus area to improve secretion, digestion, and nutrient absorption functions. However, it did not affect the weight of the immune organ, the spleen (Soliman and Al-Afifi 2020).

The improvement of immunity parameters, like immunoglobulin G (IgG), by feeding hot red pepper to rabbits has been reported. The improvement of immune system function is linked with increase in the immunoglobulin (IgM) levels (Abdelnour et al. 2018). Moradi et al. (2016) also reported that supplementation with red pepper as a feed additive stimulated the immune system function of broiler chicks, suggesting that the bioactive components of the plant controls microbial growth *via* influencing biological processes of the key microflora like protein synthesis. The bioactive compounds in red pepper further inhibited the multiplication of *Methanobacterium* and *Escherichia coli* (Ghaedi et al. 2014). Afolabi et al. (2017) reported that addition of dried hot red pepper as feed additives for broilers enhanced their performance by stimulating their immune system, elevating the leucocyte cell numbers.

12.3 SELECTED VITAMINS FORTIFYING THE IMMUNE SYSTEM

Vitamins are micronutrients with various roles in the biological system. Several vitamins, including vitamins A, C, D, and E, are essential for effective immune system functioning (Maggini et al. 2007) (Table 12.2).

12.3.1 VITAMIN C

Vitamin C (ascorbic acid) is the most crucial vitamin which humans and other primates must obtain from fruits and vegetables since they cannot synthesize it (Kumar et al. 2013). Any compound carrying out the biological property of L-ascorbic acid is categorized under vitamin C (Kumar et al. 2013). The vitamin is also added widely to food as a scurvy-preventing food factor (Tee et al. 1988; Rasanu et al. 2005). The chemical composition of ascorbic acid is rich in hydroxyl groups which makes it polar and water soluble. The most important reaction of vitamin C is its oxidation that converts the diol group to a diketo group (Tee et al. 1988). Various critical functions of ascorbic acid in the human body make it an essential micronutrient for humans. Scurvy is a potentially fatal disease caused by a severe deficiency of

TABLE 12.2
Summary of Major Findings of Immune System Boosting Activity of Some Vitamins

Vitamins	Dietary sources for human	Bioactive form	Activity	References
Vitamin C	Fruits and vegetables	Ascorbic acid	Enhanced chemotaxis and phagocytosis of phagocytes Contributes to the maturation of T cells Decreased the heterophil count and heterophil: lymphocyte ratio Reduced antibody levels in viral infections Decreased the inflammatory markers and FiO_2 requirements in high-risk COVID-19 patients Augmented the levels of immunoglobulin A and the stimulation index of T lymphocytes	(van Gorkom et al. 2018; Nosrati et al. 2017; Mikirova and Hunninghake, 2014; Hiedra et al. 2020; Gan et al. 2020)
Vitamin D	Skin exposure to sunlight	1, 25(OH) $_2$ D	Decreased the inflammatory cytokines IFN_γ , $\text{TNF-}\alpha$, and IL12p70 levels Decreased pro-inflammatory cytokines and high secretion of interleukin-10 (IL-10) Modulated the percentages and functions of peripheral blood lymphocyte subsets Suppressed the increased production of B cells and $\text{TNF-}\alpha$	(Sharifi et al. 2019; Giraldo et al. 2018; Chen et al. 2016)
Vitamin E	Vegetable oils and nut oils	α -tocopherol	Enhanced humoral immune responses in several animal species Decreased $\text{IFN-}\gamma$ expression Increased the levels of CD55 and CD47 of pneumonia patients	(Lee and Han, 2018; Awadin et al. 2019; Shen and Zhan, 2020)

vitamin C (Sauberlich 1997), leading to several metabolic disorders, such as collagenous structure weakening, delayed recovery from injury recovery, and weakened immunity. People suffering from scurvy are easily exposed to dangerous and potentially lethal diseases like pneumonia. The level of vitamin C in the host determines the degree of infection since deficiency causes inflammation in the biological system (Hemila 2017).

A small amount (~10 mg/day) of vitamin C is enough to combat scurvy (Krebs 1953), but higher dietary intakes (100–200 mg/day) are recommended since storage of vitamin C in the body is low because of its water solubility (Levine et al. 1995; Carr and Frei 1999). The essential nature of the vitamin is apparent in high dietary intakes of vitamin C, which are much higher than those of other vitamins. Vitamin C is a very strong free radical scavenger (antioxidant) and is involved as a cofactor in fifteen mammalian enzyme-catalyzed metabolic reactions *via* iron-, copper- and 2-oxoglutarate-dependent oxidoreductase enzymes. Most mammals synthesize ascorbic acid in their liver using gulono-gamma-lactone oxidase, a vital ascorbate biosynthesizing enzyme. But many primates and humans depend on dietary sources to fulfill their need for ascorbic acid.

Vitamin C has proved to play an extensive role in the immune system (Carr and Maggini 2017). Ascorbic acid promotes microbial killing by enhancing chemotaxis and phagocytosis of phagocytes, although its role in a diverse subclass of lymphocytes is less evident (van Gorkom et al. 2018). However, it is suggested that vitamin C has a crucial function in lymphocytic cells since these cells obtain vitamin C through either its sodium-dependent or -independent transporter (Wilson 2005), having intracellular ascorbic acid concentrations higher than plasma levels (Evans et al. 1982; Omaye et al. 1987). van Gorkom et al. (2018) reported that ascorbic acid contributes to the maturation of T cells. Furthermore, ascorbic acid stimulates Th2 to Th1 shifting of immune responses, which is confirmed by increasing the interferon (IFN)- γ /interleukin (IL)-5 cytokines secretion ratio percentage in broncho-alveolar lavage fluid after ascorbic acid supplementation in mice (Chang et al. 2009). Although the mechanism of the effect is still in doubt, dendritic cell mediation has been suggested. The secretion of more IL-12 and production of more IFN- and less IL-5 dendritic cells (DCs) after treatment of dendritic cells with ascorbic acid is an indication of this (Jeong et al. 2011).

Supplementation of vitamin C in drinking water for broiler chicks significantly augmented the level of lymphocytes and decreased the number of heterophils as well as increasing the lymphocyte/heterophil ratio, which indicated the improvement in their immune response (Nosrati et al. 2017).

It is reported that even an elevated dose of this vitamin has an encouraging outcome on Epstein-Barr Virus (EBV)-caused infectious disease as long-term intravenous (IV) infusions of vitamin C reduced EBV EA IgG and EBV VCA IgM antibody levels (Mikirova and Hunninghake 2014). The mechanism suggested for this is higher cellular glucose uptake rates due to viral infection, leading to increased oxidative stress (Yongjun et al. 2011), which enhances the assimilation rate of ascorbic acid as the vitamin enters cells in the form of dehydroascorbate through the same glucose transporters (Rose 1988; Vera et al. 1993; Vera et al. 1995).

Rondanelli et al. (2018) reported that both the duration and severity of the common cold is reduced by regular supplementation of vitamin C with about a two-fold higher positive effect in children than in adults. The level of vitamin C in SARS-CoV-2 patients was analyzed and the level was found to be undetectable in most of the patients. The reduced level of the vitamin might be associated to its higher metabolic consumption due to the virus (Chiscano-Camón et al. 2020). Therefore, increasing the dose of vitamin C consumption may compensate for the reduced level and help the immune system to efficiently fight the virus, minimizing the severity of the disease and the need for hospitalization of the patients.

It has been reported that treating high-risk COVID-19 patients of advanced age and with multiple comorbidities with IV vitamin C showed a positive effect. The treatment significantly decreased the inflammatory markers and FiO_2 requirements (Hiedra et al. 2020). This emphasizes that regular consumption of vitamin C might be a potential preventive route for viral infection and a higher dose might be required for patients.

Dietary supplementation of vitamin C for broilers challenged with the bacterium *Salmonella enteritidis* improved the microbial population structure and intestinal morphology of the birds. The crucial outcome of the vitamin supplementation was the improvement of the immune response. The effect enhanced the intestinal health of the birds and increased their productivity, while minimizing their death rate (Gan et al. 2020).

12.3.2 VITAMIN D

Vitamin D refers to a cluster of fat-soluble secosteroids that play a key role in boosting assimilation of micronutrients such as zinc, calcium, iron, magnesium, and phosphate (Holick 2007). Humans obtain vitamin D either from skin exposure to sunlight (80–100%) and/or from the food they eat, either as a daily diet or from supplements. The two most important compounds from fat-soluble secosteroid groups in humans are vitamin D₃ and vitamin D₂. Particularly, the body can synthesize the former one in the skin from a cholesterol-inadequate sunlight UVB-supplying environment, unlike other fat- or water-soluble vitamins. Although it is suggested that sunlight UVB exposure for vitamin D synthesis is regulated by a negative feedback loop to avoid toxicity, the doubt over cancer development due to prolonged sunlight exposure has remained a problem when setting the quantity of sunlight exposure needed to fulfill vitamin D requirements by national bodies. The adequate synthesis of vitamin D by many mammals including humans *via* sunlight exposure means that it should not be considered strictly as a vitamin. Rather, it is a vital nutrient required in limited amounts and may be considered a hormone after hydroxylation in the body to 1, 25(OH)₂D since its production and application take place in different sites (He et al. 2016). Vitamin D was discovered and its chemical structure elucidated by Adolf Windaus, who was awarded the Nobel Prize for Chemistry in 1928 for his key contributions (Wolf 2004). The biologically active form, 1, 25(OH)₂D, is obtained by two-time hydroxylation of the inert vitamin D by the 25-hydroxylase enzyme. The main storage form, as well as the chief circulating metabolite of the vitamin, is 25(OH)D, and muscles and adipose tissue are its storage sites (Baeke et al. 2010).

The important effect of the vitamin on the functioning of both innate and adaptive immune systems (He et al. 2016) was confirmed after the discovery of its receptor in almost all immune cells (Baeke et al. 2010), which have the potential to change 25(OH)D to 1, 25(OH)2D by expressing the mitochondrial vitamin D-activating enzyme. The conversion is regulated by the major circulating metabolite of vitamin D, 25(OH)D (Bikle 2009). It is interesting that vitamin D often prominently up-regulates immune system-related genes although genes involved in cellular metabolism are less sensitive to the nuclear hormone (Neme et al. 2017). Thus, vitamin D deficiency affects the immune system function (Holick 2007) in addition to the bone disorders ('rickets') it causes (Carlberg 2014).

The occurrence of the initial COVID-19 outbreak in winter and the declining of cases in the southern Hemisphere about the end of the summer, when there is the highest quantity of 25-hydroxyvitamin D (25(OH)D) in the cell showed that higher vitamin D3 doses might be useful to treat COVID-19-infected people. It has also been suggested that raising the concentration of 25(OH)D *via* vitamin D supplementation in winter might help in influenza prevention (Grant et al. 2020). Supplementation of magnesium is recommended along with vitamin D supplementation since it activates the vitamin for better regulation of calcium and phosphate homeostasis. Magnesium is required by all vitamin D-metabolizing enzymes, acting as a cofactor for enzymatic reactions in the liver and kidneys (Uwitonze and Razzaque 2018).

A long-term high-dose supplementation of vitamin D resulted in hypercalcaemia, rendering T cells more prone to pro-inflammatory activation which can promote the worsening of CNS demyelinating disease. It also stimulated the activation as well as the division of both myeloid antigen-presenting cells (APC) and T cells in mice (Häusler et al. 2019). This novel finding is not in agreement with the previous reports suggesting that the moderate dose of the vitamin is safe in short-term supplementation (Sotirchos et al. 2016). However, the longer-term supplementation of high-dose vitamin D in the novel finding might make it more efficient and recommended as it broadly activated the immune system cells. It is finally suggested that the moderate level may cause an immediate regulatory influence, whereas the continuous high-dosage supplementation might activate multiple sclerosis disease activity by enhancing mean levels of T cell excitatory calcium (Häusler et al. 2019).

Treatment of ulcerative colitis patients with vitamin D3 decreased the inflammatory cytokines (TNF- α , IFN- γ , and IL12p70) levels without affecting the circulatory amount of IL-4 and IL-10. This highlighted the inhibition potential of vitamin D toward Th1 immune responses but not Th2 responses, suggesting the therapeutic immunomodulatory potential of vitamin D (Sharifi et al. 2019).

Addition of vitamin D as a food supplement significantly decreased the level of pro-inflammatory cytokines and the elevated production of interleukin-10 (IL-10), enhancing the resistance of healthy individuals to DENV-2 infection. The dose-dependent inhibitory effect of the vitamin against DENV infection indicated its influence on the immune response and its ability to act as an immunity modulator (Giraldo et al. 2018). Chen et al. (2016) reported that 1,25(OH)2D supplementation might regulate the cellular immune response abnormalities caused due to deficiency

of vitamin D in patients with recurrent miscarriage (RM). The deficiency of vitamin D observed in most of the patients indicated the key role of the vitamin in the modulation of blood lymphocyte subsets.

12.3.3 VITAMIN E

Vitamin E comprises eight fat-soluble compounds divided into tocopherols (α -, β -, γ -, and δ -tocopherol) and tocotrienols (α -, β -, γ -, and δ -tocotrienol) (Traber 2006). Although all members of vitamin E are bioactive, α -tocopherol (α -TOH) is the most biologically active in mammals (Hosomi et al. 1997; Traber 2006), which is related to the absence of interconversion between these forms. As a result, the only vitamin E form meeting the human requirement is α -tocopherol (Traber, 2007). The tocopherols and tocotrienols have a common chromanol ring and their differences lie in their tails: a phytol tail for tocopherols, but an unsaturated tail for tocotrienols. The α -, β -, γ -, and δ - forms differ in the quantity and attachments of methyl groups on the ring. There is also a difference in stereochemistry between natural and synthetic tocopherols: natural tocopherols have a single (RRR) stereochemistry, while the synthetic groups are a mixture of eight stereoisomers (Lee and Han 2018).

Vegetable oils and oils from sources such as cottonseed, soybean, wheat germ, corn, walnut, sunflower, palm (Sheppard et al. 1980; Lee and Han, 2018), avocados (Dreher and Davenport 2013), olives (Piroddi et al. 2017), and legumes (Soba et al. 2020) are well-known dietary sources of vitamin E. There is no toxic accumulation level of vitamin E in the liver unlike other fat-soluble vitamins since its metabolism increases with its intake, resulting in the removal of its catabolic products from biological system *via* urine and faeces. The most likely three compartments in the liver for the metabolism of the vitamin E (mainly α -TOH) are the endoplasmic reticulum, peroxisomes, and mitochondria (Sontag and Parker 2002).

The molecular structure of vitamin E has three functionally distinct units: the first (I) is a functional unit, the second (II) is a signalling unit, and the third (III) is a hydrophobic domain which determines the properties of the vitamin (Wallert et al. 2020).

The biological activity, especially the free radical scavenging potential, of vitamin E is reported (Olcott and Mattill 1931). The most potent form of vitamin E, in terms of the above-mentioned activity and ensuring fertility, α -tocopherol has a biological activity as a result of units I and II (Neuzil et al. 2002). These units possess phenolic groups which are good free radical scavengers and the antioxidant potential of the vitamin is directly related to this group. The third unit is responsible for the hydrophobicity of the vitamin which facilitates the integration into lipoproteins and membranes (Neuzil et al. 2002).

The immunomodulating property of vitamin E in animals, including humans, is reported in which dendritic cells are suggested to play the role in initiating adaptive immune responses by connecting innate and specific immune systems. It is also well reported that dietary supplementation with the vitamin enhances humoral immune responses in several types of animals *via* increasing lymphocytic proliferation, the level of immunoglobulins, the degree of antibody responses, the activity of NK cells,

and interleukin IL-2 production. The increased lymphocytic proliferation in humans due to high-dose (above the recommended levels) supplementation of vitamin E enhanced delayed-type hypersensitivity (DTH) response, increased IL-2 production, and decreased IL-6 production (Lee and Han 2018). Vitamin E greatly supports defence against pathogens due to its immunostimulatory activity with a reported mechanisms of increased macrophage activity and antibody (Ab) production for *Streptococcus pneumoniae* type 1 (Heinzerling 1974), and higher NK activity and Th1 response to the influenza virus (Hayek et al. 1997; Han et al. 2000). Thus, the deficiency of vitamin E vastly contributes to the oxidation of unsaturated fatty acids to increase oxidative stress which could also happen in the elderly, potentially reducing the immune system function (Fukui et al. 2001; Muller 2010; Wu and Meydani 2014; Lee and Ulatowski 2019; Lewis et al. 2019). Furthermore, vitamin E deficiency causes abnormal functioning of the central nervous system and the reproductive system (Saito et al. 2020).

The immune-system-stimulating potential of vitamin E in chickens has been reported. Supplementation of the vitamin with Fetomune Plus® for experimentally AIV H9N2-infected chickens improved their immunological and pathological effects through decreasing IFN-gamma expression. The improvement of immune system response was further indicated by a significantly reduced mortality rate of the chickens (Awadin et al. 2019). Supplementation of vitamin E as a feed additive stimulated the immune system function of goats and increased their resistance to epsilon toxin D of *Clostridium perfringens* (Khan et al. 2019).

Treatment of patients with stroke-associated pneumonia with vitamin E increased resistance to the disease due to an auxiliary therapeutic effect of the vitamin which increased the levels of CD55 and CD47. The effect was dose dependent in which the high-dose vitamin E group showed better resistance and shorter duration of hospitalization (Shen and Zhan 2020). The potential of vitamin E in inhibiting PMN apoptosis was reported in which the enhancement of CD55 and GPI binding stability is suggested as a potential mechanism (Witt et al. 2000). Polymorphonuclear neutrophil (PMN) are the most abundant circulating immune cells.

Dietary supplementation with vitamin E improved the immune response by increasing the total antioxidant capacity in pigs. However, the effect was insignificant in pigs fed with peroxidized lipids since the concentration of vitamin E was not adequately increased as the vitamin was consumed by peroxidized lipids to save cells from oxidative damage caused as a result of oxidative stress by the oxidants. However, addition of peroxidized lipids canceled the immune system stimulation by the vitamin and no improvement in immune response was recorded (Silva-Guillen et al. 2020).

Dietary supplementation of 30 IU vitamin E/kg for *Salmonella enteritidis*-challenged laying hens improved their immunity response by alleviating the oxidative and immune stress due to the challenge, decreasing the mortality rate of the birds (Liu et al. 2019). Dalia et al. (2018) reported that the combination of vitamin E with bacterial organic selenium as a feed additive (ADS18-Se) improved the immune system in broiler chickens by regulating some cytokine expression levels and immunoglobulin levels. The immune system-stimulating activity of the two combined was better than that of the bacterial organic selenium alone.

12.4 CONCLUSION

The immune system is one of the critical parts of a biological system, with its key roles including protection against infection and the removal of damaged tissues. However, the system greatly depends on nutrients and vitamins to efficiently perform its activities. Although specific bioactive compounds of some medicinal plants show immune system strengthening activities, there is still a need to identify the mechanism by which they operate in order to improve the use of plants as immune system enhancers to cope with the problems caused by infectious diseases and drug resistance of pathogenic microorganisms.

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13 Role of Specific Spices in Fortifying the Human Immune System

*Yashdeep Srivastava, Swati Upadhyay,
Mohd Ahmad, Deepak Kumar Verma,
and Vinod Kumar Mishra*

CONTENTS

13.1 Introduction	397
13.2 Specific Spices for a Strong Immune System.....	398
13.2.1 Turmeric (<i>Curcuma longa</i> L., family Zingiberaceae).....	398
13.2.1.1 Curcumin	399
13.2.2 Cinnamon (<i>Cinnamomum zeylanicum</i> and <i>Cinnamomum cassia</i>)	399
13.2.3 Black Pepper (<i>Piper nigrum</i>)	399
13.2.4 Star Anise (<i>Illicium verum</i>)	400
13.2.5 Clove (<i>Syzygium aromaticum</i>)	400
13.2.6 Fenugreek (<i>Trigonella foenum-graecum</i>)	401
13.2.7 Black Cumin (<i>Nigella sativa</i>).....	402
13.2.8 Garlic (<i>Allium sativum</i>).....	402
13.2.9 Ginger (<i>Zingiber officinale</i>).....	403
13.2.10 Capsicum.....	403
13.2.11 Omum (<i>Trachyspermum ammi</i>).....	404
13.2.12 Asafoetida (<i>Ferula assafoetida</i>)	404
13.2.13 Saffron (<i>Crocus sativus</i>)	404
13.3 Conclusion and Future Perspectives	405
References.....	405

13.1 INTRODUCTION

Since ancient times, spices have been known for their medicinal properties and health benefits, as well as their culinary impact. In the wake of the COVID-19 outbreak, there is a growing concern in strengthening our immune system in order to protect our bodies from infectious diseases. The immune system is a network of biological processes that protects an organism against disease. It involves many types

of cells, tissues, and organs. Immunity is the key mechanism for the protection of the host against infectious agents. A very important role in the immune system is played by the cytokines, which are a broad group of low-molecular-weight glycoproteins, secreted by specific immune system cells and categorized as signalling messengers that mediate and regulate immunity, inflammation, and haematopoiesis. Basically, immunity is of two types, namely innate immunity, which is the first line of protection, in which phagocytic cells and macrophages play an important role, and adaptive immunity, which is capable of specifically recognizing and selectively removing various foreign microorganisms and molecules. In addition, the processing and presentation of antigens is also a complex process mediated by the Major Histocompatibility Complex (MHC), which is categorized as either Class-I or Class-II MHC. An endogenous antigen can be processed and presented by class-I MHC to antigen-presenting cells (APCs), where it can be recognized by CD8⁺ cells. An exogenous antigen can be processed and presented by class-II MHC to APCs, where it can be recognized by CD4⁺ T cells. Although the immune system does a remarkable job of defending our body against disease-causing microorganisms, if it is weakened, pathogens will invade successfully and may lead to disease. Is it possible to intervene in this process and boost our immune system?

Recently, many studies have shown the conclusive role of food-derived substances in modulation of immune function, such as nutrients (Field et al. 2002; Amati et al. 2003), amino acids (Takegoshi et al. 1998), fatty acids (Kaminogawa and Nanno 2004), vitamins (Meydani et al. 1990; Coutsoudis et al. 1992), minerals (Sempertegui et al. 1996), nucleotides (Nagafuchi et al. 2000), and probiotics (Arak et al. 1999; Hatakka et al. 2001).

Correlation study data from 163 countries between COVID-19 incidence and spice consumption has revealed the potential of spices to fight COVID-19 (Elsayed and Khan 2020). Recently, there has been growing interest in inexpensive natural immunomodulatory molecules, derived from spices, for strengthening and boosting immune response. It has been reported that coumarins and flavonoids from some spices exhibited immunomodulatory activity, i.e., directly enhancing lymphocyte activation and/or secretion of the multipotent cytokine, interferon gamma (IFN- γ) (Cherng et al. 2008). Curcumin, a polyphenol derived from the spice turmeric, is reported to activate the host innate immunity (Catanzaro et al. 2018). Given the proven immunomodulatory properties of some spices, the aim of this chapter was to research the immune booster properties of spices, such as Turmeric (*Curcuma longa*), Cinnamon (*Cinnamomum zeylanicum* and *Cinnamomum cassia*), Black pepper (*Piper nigrum*), Star Anise (*Illicium verum*), Clove (*Syzygium aromaticum*), Fenugreek (*Trigonella foenum-graecum*), Black Cumin (*Nigella sativa*), Garlic (*Allium sativum*), Ginger (*Zingiber officinale*), *Capsicum* sp. and *Omum* (*Trachyspermum ammi*).

13.2 SPECIFIC SPICES FOR A STRONG IMMUNE SYSTEM

13.2.1 TURMERIC (*CURCUMA LONGA* L., FAMILY ZINGIBERACEAE)

The use of turmeric has been known in India since the Vedic period, for almost 4,000 years. In food, it is used as a colouring agent and is often referred to as “Indian

saffron” and also “the golden spice”. In the traditional system of medicine, it has been widely used for treatment of various ailments, such as respiratory illness (e.g., asthma, bronchial hyperactivity, and allergy), liver disorders, anorexia, rheumatism, diabetic wounds, sprain, and swelling. Modern interest in turmeric started in the 1970s when researchers found that the spice may possess biological anti-inflammatory and antioxidant properties and may prove effective in hepatobiliary diseases (Hu et al. 2017). Health benefits of turmeric are attributed to curcumin, obtained from the rhizome (Nelson et al. 2017).

13.2.1.1 Curcumin

The transcription factor, nuclear factor-kappa B (NF- κ B) has been reported to be constitutively active in many types of cancer (Giuliani et al. 2018). Curcumin down-regulates the constitutive activity of NF- κ B and induces apoptosis in novel mouse melanoma cells (Marín et al. 2007). Tumour necrosis factor- α (TNF- α) is an inflammatory cytokine produced by macrophages/monocytes during acute inflammation and the reduction of its concentration is a therapeutic target in several inflammatory diseases. The results of several preclinical studies on the effect of curcumin on TNF- α have shown that it effectively blocked TNF- α (Sahebkar et al. 2016). Studies showed that inhibition of the JAK/STAT pathway by curcumin is involved in reduced migration and invasion of cancer cells (Ashrafizadeh et al. 2020). Curcumin exerts anti-diabetic, renoprotective, and neuroprotective impacts by normalizing the expression of the JAK/STAT signalling pathway (Ashrafizadeh et al. 2020). Several studies have demonstrated immunomodulatory properties of curcumin on immune cells and mediators, such as various T lymphocytes, dendritic cells, NK cells, monocytes and macrophages, B cells, neutrophils, eosinophils, mast cells, and different inflammatory cytokines (Srivastava et al., 2011; Momtazi-Borojeni et al. 2018).

13.2.2 CINNAMON (*CINNAMOMUM ZEYLANICUM* AND *CINNAMOMUM CASSIA*)

The bark of various cinnamon species is used worldwide for cooking and also in traditional and modern medicines. Cinnamaldehyde is one of the major constituents of cinnamon essential oil, which is known to possess anti-inflammatory properties. It was found that cinnamaldehyde inhibits TNF- α -induced inflammation through suppression of NF- κ B activation (Liao et al. 2008) and TLR4, and NLRP3 signalling pathways (Lee et al. 2015).

13.2.3 BLACK PEPPER (*PIPER NIGRUM*)

Black pepper has long been used in many cuisines and it holds a very valuable place among herbal medicinal plants. Piperine exhibits a strong anti-inflammatory function. Clinical studies have demonstrated remarkable immunomodulatory potential of piperine, together with antioxidant, antitumour, and drug availability-enhancing properties. It possesses the potential to treat lipopolysaccharide (LPS)-induced inflammation. Results indicated that piperine inhibited LPS-induced expression of IRF-1 and IRF-7 mRNAs, inhibited phosphorylation of IRF-3, type1 IFN mRNA, and down-regulation of STAT-1 activity (Bae et al. 2010). Similarly, Wang-Sheng

et al. (2016) reported that piperine inhibited LPS-induced TNF- α , IL-6, IL-1 β , and prostaglandin E2 (PGE-2) production in BV2 microglial cells. It found to inhibit the production of IL-2, and IFN- γ in activated human peripheral blood mononuclear cells (PBMCs) (Chuchawankul et al. 2012). Also, piperine reduced the level of proinflammatory cytokines IL-1 β , IL-6, and TNF- α , and lowered the expression of COX-2, NOS-2, and NF- κ B in cerebral ischaemia in rats (Vaibhav et al. 2012).

13.2.4 STAR ANISE (*ILICIMUM VERUM*)

Star anise (*Illicium verum*) is an important medicinal plant in traditional Chinese medicine and is widely known for its antiviral properties. It is source of shikimic acid, which is used in the manufacture of oseltamivir (Tamiflu[®]), an antiviral medication for influenza A and influenza B (Patra et al. 2020). *Staphylococcus aureus* cultures treated with *trans*-anethole (a terpenoid from anise or from star anise essential oils) have shown human neutrophil phagocytic activity as well as IL-8 production, suggesting an innate immune response (Kwiatkowski et al. 2020). An extract from this plant was found to reduce expression of IL-4, IL-6, TNF- α , TARC, RANTES, ICAM-1, and VCAM-1, but not IFN- γ in atopic dermatitis in a mouse model (Sung et al. 2012a). The extract inhibited TNF- α /IFN- γ -induced chemokines, proinflammatory cytokines, and adhesion molecules *via* blockade of NF- κ B, STAT1, MAPK, and Akt activation (Sung et al. 2012b), indicating therapeutic properties of *Illicium verum* extract against inflammatory skin diseases like atopic dermatitis.

13.2.5 CLOVE (*SYZYGIUM AROMATICUM*)

Clove (*Syzygium aromaticum*, from the plant family Myrtaceae) is an aromatic flower bud which is native to the small islands of Maluku in Indonesia, also known as the “Spice Islands”. Recently, the application of natural spices as immunomodulators has attracted increasing attention. Clove shows great potential as an immunostimulant (Halder et al. 2011). Eugenol is the major constituent of *Syzygium aromaticum*. The immunomodulatory effect of *S. aromaticum* essential oil has been attributed to an augmentation of humoral and cell-mediated immune responses (Halder et al. 2011). Islamuddin et al. (2016) demonstrated antileishmanial activity of a eugenol emulsion through potentiating Th1 immunostimulation without adverse side effects, and may help to alleviate the depressed cell-mediated immunity and hence complement the antileishmanial activity. Inflammation is known as adaptive immunity response of the body. Eugenol possesses anti-inflammatory potential, with *in-vitro* studies revealing that clove oil polyphenol inhibits nuclear factor- κ B (NF- κ B) activation in lipopolysaccharide-initiated macrophages induced by inactivated cyclooxygenase activity (COX-2) and tumour necrosis factor (TNF- α) (Kim et al. 2003). Thus, eugenol may serve as a plausible lead candidate for developing the COX-2 inhibitor as an anti-inflammatory or anticancer chemopreventive agent. Eugenol reduced levels of TNF- α and neutrophils in the mouse during pulmonary inflammation. It also protected against nicotine-induced dysfunction of murine macrophages through down-regulating the Th1 cytokines (TNF- α , IL-12) with concurrent activation of

Th2 responses (IL-10, TGF- β) (Kim et al. 2003). Studies on collagen-induced arthritis in the murine model showed the anti-arthritic property of eugenol. It inhibits mononuclear cell infiltration into the knee joints of arthritic mice and also decreases the levels of cytokines, such as tumour necrosis factor (TNF- α), interferon (IFN γ), and tumour growth factor (TGF- β) within the ankle joints (Grespan et al., 2012). The eugenol shows significant potential against dermatitis as an anti-inflammatory molecule which inhibited the release of myeloperoxidase (MPO) in degranulation of PMA-stimulated neutrophils (Lopes et al. 2018). It is reported that MPO displays cytokine-like properties that can activate leukocytes in an inflammatory response (Lau et al. 2005). It prevents neutrophil degranulation and can be used as an anti-inflammatory compound against dermatitis disease (Sheppard et al. 2005). Han et al. (2017) reported significant inhibitory effects of eugenol in human dermal fibroblasts that exhibited antiproliferative activity and also significantly decreased the levels of inflammatory biomarkers, such as vascular cell adhesion molecule-1 (VCAM-1), interferon gamma-induced protein 10 (IP-10), interferon-inducible T-cell α chemoattractant (I-TAC), and monokine induced by gamma interferon (MIG).

13.2.6 FENUGREEK (*TRIGONELLA FOENUM-GRAECUM*)

Fenugreek (*T. foenum-graecum*) is an important species of the Fabaceae family. It is an annual herb that has been used widely in the Indian (Ayurvedic) system of medicine. Medicinal properties of this herb are due to the presence of alkaloids, saponins, and flavonoids (Yadav et al. 2011). Apart from its traditional medicinal uses, fenugreek is found to have many pharmacological properties, such as antidiabetic, antinociceptive, anticarcinogenic, antioxidant, anti-inflammatory, and hypocholesterolaemic activities (Goyal et al. 2016). Several studies have shown that seeds of fenugreek possess significant immunomodulatory functions. The dietary administration of fenugreek enhances the humoral immune response and the expression of immune-associated genes, particularly IgM gene expression in fish (Bahi et al. 2017). An extract of this plant elicited a significant increase in phagocytic index and phagocytic capacity of macrophages and showed a stimulatory effect on immune functions in mice (Bin-Hafeez et al. 2003). Fenugreek extract cured Th2-induced allergic skin inflammation by enhancing Th1 differentiation and may prove to be a useful therapeutic agent for treatment of allergic inflammatory diseases according to traditional use, as well as Th2-mediated allergic response (Bae et al. 2012). The seeds of this plant also exhibit anti-inflammatory activity by suppressing the production of pro-inflammatory cytokines and IgE-mediated immune response. It also regulates the balance between helper T (T_H) cells (Piao et al. 2017). The administration of *T. foenum-graecum* extract improved metabolic features, and corrected inflammatory alterations associated with ovariectomy and helped in reducing the metabolic and inflammatory alternations associated with menopause (Abedinzade et al. 2015a). Fenugreek seed has been shown to affect immunological responses in piglets after weaning. The addition of fenugreek increased the relative concentration of the $\gamma\delta$ T cell population (TCR1+CD8 α -) in the blood with a simultaneous reduction of antigen-presenting cells (MHCII+CD5-) (Zentek et al. 2013).

13.2.7 BLACK CUMIN (*NIGELLA SATIVA*)

Nigella sativa (black cumin) is a medicinal belonging to the Ranunculaceae family and is native to Southwest Asia, southern Europe, and North Africa, but it is cultivated and used in different parts of the world (Gholamnezhad et al. 2015). Mainly, the seeds of this plant are found to possess immunomodulatory functions along with other medicinal properties, such as antidiabetic, anticancer, analgesic, antimicrobial, anti-inflammatory, gastroprotective, hepatoprotective, and antioxidant properties (Abel-Salam, 2012). Phytochemical analyses of *N. sativa* displayed the presence of alkaloids, saponins, sterols, and essential oil (Ghahramanloo et al. 2017).

Thymoquinone (TQ) is one of the main active components of the volatile oil of *N. sativa* seeds and most effects and actions of *N. sativa* are mainly related to TQ concentration (Samarghandian et al. 2018). The oil and extracts of this plant were found to suppress humoral immune response while alleviating the cell-mediated response (Majdalawieh and Fayyad, 2015). The oil of *N. sativa*, combined with artemether (ART) and praziquantel (PZQ), was used to check the immune and inflammatory response of mice infected with *Schistosoma mansoni*. Immunity of host was improved after administration of *N. sativa* oil, and levels of cytokines and IgG in the blood significantly increased (Sheir et al. 2015). Due to its ability to suppress the inflammatory mediators, *N. sativa* oil was also reported to enhance cell-mediated immunity in immuno-suppressed male rabbits (Salem, 2005). Another study revealed the immunostimulatory effect of *N. sativa* seeds on non-phytohaemagglutinin (PHA)-stimulated proliferation of human peripheral blood mononuclear cells (PBMCs). PHA was used to trigger B and T lymphocyte proliferation by interaction between active components of extracts and cell surface molecules or growth factors involved in non-PHA activation. *N. sativa* was reported to have chemopreventive or anticancer activities as a result of immunostimulatory activity (Alshatwi, 2014). Elmowalid et al. (2013) reported that an extract of this plant showed prominent increases in the microbicidal activity of monocyte-derived macrophages against yeast or bacteria, enhancing the activity of macrophages (innate immunity) and also regulating adaptive immunity to infectious diseases (Elmowalid et al. 2013). Recently, it was also observed that *N. sativa* has potential antiviral activity against COVID-19. The seeds and oil of *N. sativa* can be considered to be a first aid kit as a preventive measure against COVID-19. The bioactive compounds, thymoquinone, α -hederin, or nigellidine, could be promising alternative herbal drugs with which to combat COVID-19 (Islam et al. 2021). *In-silico* studies proved that the bioactive constituents of this plant can bind with the ACE2 receptors, while the bioactive phytoconstituents are involved in molecular pathways like HIF1, VEGF, IL-17, AGE-RAGE, chemokine and calcium signalling pathways, which can be particularly helpful in combating hypoxia and inflammation caused by a compromised immune system and oxidative stress (Jakhmola et al. 2020).

13.2.8 GARLIC (*ALLIUM SATIVUM*)

Garlic (*A. sativum*; Amaryllidaceae) originates from Central Asia and has been used as a medicinal plant for thousands of years. It contains organosulphur compounds,

such as ajoene, allicin, alliin, allixin, γ glutamyl-S-2-propenyl cysteine, diallyl disulphide, methyl allyl disulphide, S-allyl-cysteine, and 1,2-vinyldiithin (Martin et al. 2016). Allicin inhibited TNF- α -induced secretion of IL-1 β , IL-8, IP-10, and IFN- γ and also achieved suppression of the degradation of the NF- κ B inhibitory protein I κ B in intestinal epithelial cells (Lang et al. 2004). Thus, allicin may have the potential to attenuate intestinal inflammation. Garlic appears to enhance the functioning of the immune system by stimulating certain cell types, such as macrophages, lymphocytes, natural killer (NK) cells, dendritic cells, and eosinophils *via* modulation of cytokine secretion, immunoglobulin production, phagocytosis, and macrophage activation (Arreola et al. 2015). Several garlic associated compounds, such as ajoene, allicin, allyl, methyl thiosulphinate, and methyl allyl thiosulphinate, have been found to possess high viricidal activity (Mikaili et al. 2013).

13.2.9 GINGER (*ZINGIBER OFFICINALE*)

Ginger (*Z. officinale*; family Zingiberaceae) is widely used in folk medicine and as a spice. The bioactive molecules present in ginger include α -zingiberene, α -farnesene, β -bisabolene, α -curcumene, [6]-gingerol and [6]-shogaol, paradol, zingerones, and allied derivatives (Zhan et al., 2008). Ginger is consumed in many cultures as an immune booster (Kannappan et al., 2011). Ginger extracts have been reported to have anti-inflammatory, anti-oxidant, and anti-cancer effects. 6-Shogaol is one of the most bioactive components of ginger rhizomes and possesses neuroprotective, neurotrphic, and anti-inflammatory properties. It was shown to suppress the release of pro-inflammatory cytokines and decreased the level of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and phospho-NF- κ B in LPS-treated astrocytes, as well as up-regulated histone H3 acetylation and suppressed histone deacetylase (HDAC)1 expression (Shim et al. 2011). [6]-Gingerol inhibits COX-2 expression by blocking the activation of p38 MAP kinase and NF- κ B in phorbol ester-stimulated mouse skin (Kim et al. 2005). Ginger ameliorated allergic asthma by reducing inflammation of the allergic airway and suppressed Th2-mediated immune responses in mice with ovalbumin-induced allergic asthma (Khan et al. 2015). An *in-vitro* study indicated that 6-gingerol could alleviate allergic rhinitis by reducing cytokine production for T cell activation and inhibiting the activation of B cells and mast cells (Kawamoto et al. 2016).

13.2.10 CAPSICUM

Capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide) is the principal component of hot peppers, in the genus *Capsicum*. It has been employed in pain relief, weight loss, and cancer prevention (Luo et al. 2011). Capsaicin from juice of *Capsicum baccatum* exhibited an anti-inflammatory effect by inhibition of the production of pro-inflammatory cytokines (TNF-alpha and IL-1-beta) at the inflammatory site in mouse inflammatory immune peritonitis. Furthermore, capsaicin was able to inhibit the neutrophil migration towards the inflammatory site (Spiller et al. 2008). Capsaicin has been shown to suppress cell proliferation and to trigger apoptosis of Multiple Myeloma (MM) cells, by reducing STAT3 phosphorylation and activation

(Bhutani et al. 2007). Cytotoxic anticancer therapeutics induce immunogenic cell death (ICD), inducing tumour cells to undergo apoptosis while eliciting the emission of a spatiotemporally defined combination of damage-associated molecular patterns (DAMPs) which is decoded by the immune system to activate antitumour immunity for long-term therapeutic success. The neurotoxin capsaicin (CPS) can induce both cancer cell apoptosis and immune-mediated tumour regression (D'Eliseo et al., 2013). It has been reported that capsaicin reduced the Mcl-1 expression level, leading to the capsaicin-mediated cell death and autophagy induction (Granato et al. 2015).

13.2.11 OMUM (*TRACHYSPERMUM AMMI*)

Omum (*T. ammi*), commonly known as ajwain, ajowan, caraway, Bishop's weed, or carom, is an annual herb of the family Apiaceae (previously, the Umbelliferae). It has been used in food preparation and also as a traditional medicine in Ayurveda. Although a number of pharmacological activities have been attributed to ajowan, its role in immunomodulation is not known. Ajowan glycoprotein (Agp) showed effective mitogenic activity towards splenocytes, induced proliferation of B cell-enriched murine splenocytes and activated macrophages to release NO, promoted phagocytosis, and produced pro-inflammatory cytokines (IL-12, TNF- α and IFN- γ) (Shruthi et al. 2017). Seed extracts of *T. ammi* exhibited an immunomodulatory effect on cell-mediated immunity through the delayed-type hypersensitivity assay skin thickness method (Siddiqui et al. 2019). The carvacrol present in ajwain oil showed an inhibitory effect on TNF- α , IL-1 β , and TGF- β (Liu et al. 2012). Carvacrol also inhibited secretion of TNF- α and IL-1 β in porcine alveolar macrophages (Liu 2011).

13.2.12 ASAFOETIDA (*FERULA ASSAFOETIDA*)

Asafoetida (known as Heeng in India), an oleo-gum-resin obtained from the roots of *Ferula assafoetida*, is used in different countries for various purposes. This oleo-gum-resin has been known to possess antifungal, antidiabetic, anti-inflammatory, antimutagenic, and antiviral activities (Iranshahi and Iranshahi 2010). The oleogum-resin, ferulic acid, and the essential oil of *F. assafoetida* has shown cytotoxic effect on 4T1 breast cancer cells (Bagheri et al. 2017).

13.2.13 SAFFRON (*CROCUS SATIVUS*)

The dark red stigma of *C. sativus* has a very long history as a food colouring and flavouring agent. The main bioactive metabolites of the saffron spice are the carotenoids (Poma et al. 2012; Hosseini et al. 2018). Saffron has an inhibitory effect on production of the inflammatory cytokines, IL-1 β , IL-4, IL-5, IL-6, IL-8, IL-13, tumour necrosis factor alpha (TNF- α), interferon gamma (IFN- γ), TGF- β , and VEGF (Umigai et al. 2012; Zeinali et al. 2019). Saffron down-regulates the key pro-inflammatory enzymes such as myeloperoxidase (MPO), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), phospholipase A2, and prostanoids (Zeinali et al. 2019).

13.3 CONCLUSION AND FUTURE PERSPECTIVES

An ancient Indian text says, ‘aushadham ucchyathe sarvam’, which implies that food is the absolute cure and healer. Ayurveda promotes a number of herbs and spices for boosting immunity. However, scientific exploration of diet–health linkages is a significant area of research. Spices and their active ingredients possess immunomodulatory properties acting through activation/or suppression of immune systems *via* interfering with several pathways, culminating in improved immune responses. In addition, some of these spices possess antioxidant properties which are important for their anti-inflammatory and anticancer activities. Evidence from *in-vitro* and *in-vivo* studies into the active constituents of spices indicate that many of the active phytochemicals from various spices may reduce the risk or severity of disease by boosting immunity. However, before the therapeutic use of spices as immune booster, this must be thoroughly investigated and information must be disseminated to the various stakeholders with respect to the efficacies and health benefit claims associated with the respective spices.

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14 Specific Fruits and Berries for a Strong Human Immune System

Rakesh Kumar

CONTENTS

14.1 Introduction	411
14.2 Structure of the Immune System.....	412
14.3 Immunity: Types and Mechanisms	413
14.4 Effects of Nutrition on the Immune System.....	413
14.5 Role of Fruits and Berries on Health and Immunity	415
14.6 Roles of Fruits and Berries in Disease Prevention and Immunity	419
14.7 Possible Mechanism of Action of Fruits in Immunity and Disease Prevention.....	420
14.8 Conclusion	421
Bibliography	421

14.1 INTRODUCTION

The immune system consists of organs, tissues, cells, and some proteins which collaborate to defend the body against attacks by foreign agents. These agents can be infectious microbes, such as bacteria, viruses, fungi, and parasites. Many microbes and pathogens find our bodies very favourable for their growth, so, they try to enter into our body to achieve multiplication but our immune system tries to check their entry and destroy them. If the immune system fails to check the entry and multiplication of a pathogen, our body becomes infected. The immune system is able to kill each and every pathogen, by recognizing and remembering each different pathogen. Several cells and chemicals take part in this mechanism. These cells work in a collaborative manner to secrete and move powerful chemicals from one site to another. The system automatically upgrades its defences as it is attacked by a new enemy.

Immunity is a complex mechanism which achieves resistance against foreign agents by either inbuilt ('innate immunity') or acquired means ('adaptive immunity'), functioning in a collaborative manner. Nutrition plays an important role in developing natural resistance. Poor nutrition or, worse, malnutrition badly affects our immune system and suppress its function (Coico and Sunshine 2009). Our

immune system can be boosted by balanced nutrition, so diet can be very important for improving the efficiency of immune system. Immunity functions can be damaged by a low-nutrient diet deficient in either macronutrients or micronutrients. The strength of body defence can be enhanced or improved if a balanced diet or proper nutrition are provided. Reports indicate that a balanced diet is important to carry out the vital role supporting the immune system (Chandra 1997). Negative mental state, anxiety, or traumas lead to malfunctioning of the immune system and decrease body resistance by destruction of proteins. Malnutrition during childhood causes infections and its complications compromise immunity, leading to illness and premature mortality (Chandra 1997, 2003). This book chapter highlights the structure of the immune system and the role of nutrition on immune function. It also describes the effect of the intake of specific fruits and berries on immune function.

14.2 STRUCTURE OF THE IMMUNE SYSTEM

The defence system in our bodies that protects us against harmful substances or pathogens is called the immune system. It consists of many physical (e.g., skin) and biochemical barriers for self-defence (Karacabey 2012). Macrophages and neutrophils are non-specific cells that can enhance the defence competency of phagocytes and stimulate the immune system. The production of many substances, like interferons, interleukins, and other sophisticated compounds, is stimulated when these substances are added onto the surfaces of phagocytes and lymphocyte cells, so that the immune system is activated (Karacabey 2012).

A healthy immune system has the capability to identify and distinguish the body's own cells and foreign cells. The body's own cells and foreign cells are known as 'self' cells and 'non-self' cells, respectively. The defence system behaves in a friendly and peaceful manner with cells that are identified as self cells, but it quickly launches an attack against non-self or foreign cells. This type of response of immune system is called an autoimmune reaction (Basoglu and Turnagol 2004; Akalin and Unal 2005; Coskun 2005; Karacabey 2005; Saygin et al. 2006; Palmer 2011; Cantorna et al. 2012). Technically, an antigen is an element that can trigger the immune response. An antigen can be any foreign element, like a bacterium, virus, or any other microbe or even a part of it. Tissue or cells from of a different genotype also act as antigens. Such behaviour of the immune system explains how the body rejects transplanted tissues or organs. But, during abnormal behaviour, sometimes, the defence system can make a mistake in distinguishing self and non-self cells and can harm self cells; this type of behaviour of body is called an *autoimmune disorder* or disease. Sometimes, in special cases, the defence system reacts against comparatively harmless substances like pollen, identifying them as antigens, and this type of antigen may be termed an allergen.

Our defence or immune system consists of various parts like the lymphoid organs, thymus, spleen, lymphoid nodes, and several cell types located throughout the body. As soon as pathogenic substances enter into the body, the immune system starts

working against invaders; this type of act of immune system is known as the *immune response* (Keith and Jeejeebhoy 1997; Coico and Sunshine 2009; Bistrrian 2011).

14.3 IMMUNITY: TYPES AND MECHANISMS

The immunity has been conceptually divided into two types, namely innate and adaptive immunity. Innate immunity is inbuilt. Basically, it is the first line of defence in the form of physical and biochemical barriers and is represented by some specialized cells. It activates instantly when the body comes into contact with a foreign agent (Medzhitov and Janeway 2000). The mechanism of innate immunity is composed of various specialized cells, like macrophages, neutrophils, dendritic cells, and natural killer cells. Its mechanism depends upon the process of phagocytosis, the release of inflammatory mediators, activation of proteins of the complement system, and synthesis of acute phase proteins (Medzhitov et al. 1997). During the process of phagocytosis, the pathogen attaches to surface receptors on the phagocyte, which then starts internalizing into vesicles. These vesicles are called phagosomes, which later fuse to form a lysosome, and subsequently digestion of the pathogen starts (Abbas and Lichtman 2003).

The acquired or adaptive immune response is different from the innate response. The acquired immune response basically depends on lymphocyte activation and on the production of soluble molecules. The main features of the acquired response are specificity and diversity of recognition, memory, specialized response, self-restraint, and tolerance of self components of the organism. In the mechanism of acquired immune response, antigen-presenting cells play a key role in the activation of lymphocytes, and presenting antigens are associated with molecules of the major histocompatibility complex (MHC) to the T lymphocytes (Delves and Roitt 2000). The outline of immunity, the various types and its components is depicted in Figure 14.1.

14.4 EFFECTS OF NUTRITION ON THE IMMUNE SYSTEM

Malnutrition is a very serious problem in the world, especially in developing countries. According to estimates, approximately 6 million children of the world die due to infection because of breakdown of the immune system caused by malnutrition. Therefore, our diet must be balanced and rich in adequate proteins to keep our immune system strong (Chandra 2003). Vitamins, mineral nutrients, and beta-carotene are also very important components of our daily diet, which are thought to contribute to our first line of defence against free radicals. Our body requires free radicals for smooth metabolic functioning but, when present in excessive quantities, they become dangerous ('reactive oxygen species', ROS). Compounds which provide protection against free radicals, and the oxidation and subsequent damage of substances such as membrane fats are called antioxidants. Antioxidants trap or quench ROS and prevent the oxidation of substances like fats (Greiner 2011).

It has been very well reviewed and documented by various researchers and authors that micronutrients (vitamins and minerals) play a very important role in boosting

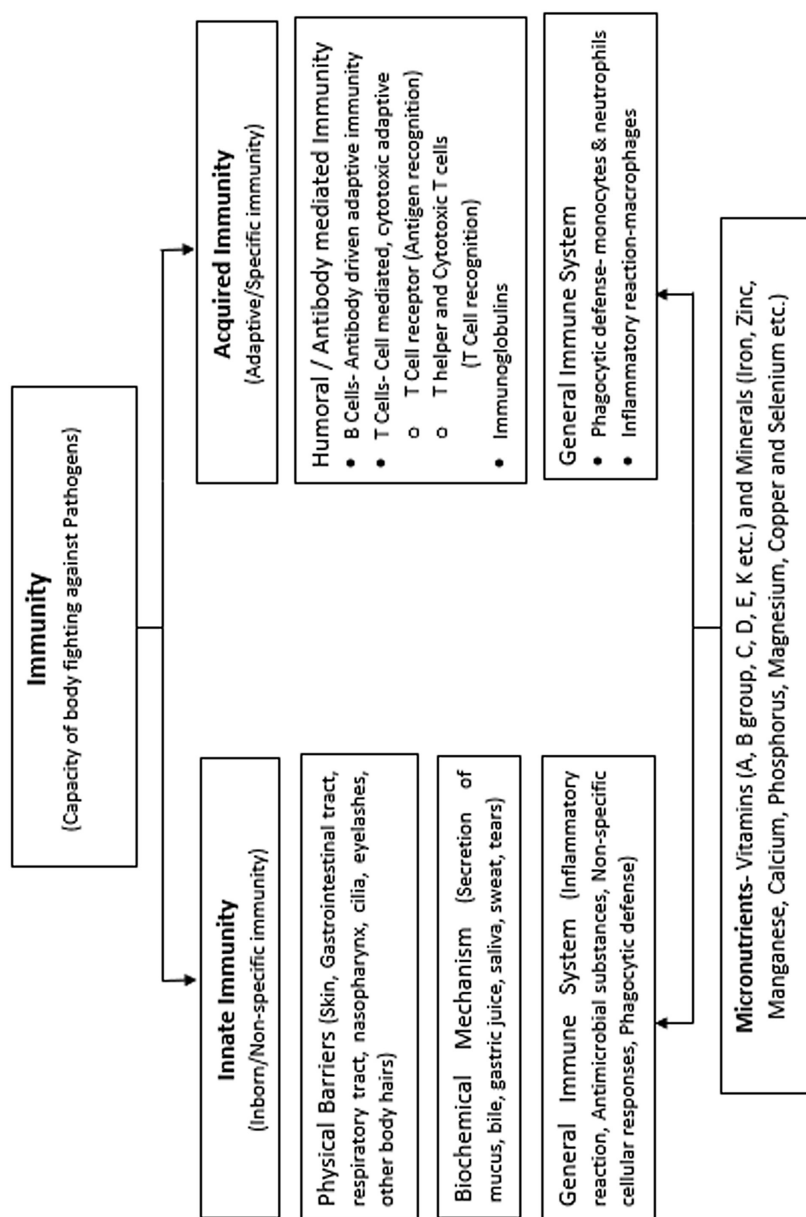


FIGURE 14.1 Outline of the immune system of our body and the role of micronutrients.

the immune system. Various vitamins and minerals has been reported to maintain the structural and functional integrity of physical barriers, such as the skin, digestive tract, and respiratory tract (Clairmont et al. 1996; Gniadecki et al. 1997; Palmer et al. 2001; Chew and Park 2004; Gombart 2009; Yin et al. 2011; Haryanto et al. 2015; Sirisinha 2015; Biesalski 2016; Clark and Mach 2016; Levy 2016; Carr and Maggini 2017; Lin et al. 2017; Mihajlovic et al. 2017; Yoshii et al. 2019); to allow differentiation, proliferation, movement, and functioning of innate immune cells (Tanaka et al. 1991; Sly et al. 2001; WHO 2006; Maggini et al. 2008, 2018; Sheikh et al. 2010; Wu and Meydani 2014; Haryanto et al. 2015; Saeed et al. 2016; Carr and Maggini 2017; Wishart 2017; Agoro et al. 2018; Gao et al. 2018; Bozonet and Carr 2019; Wu et al. 2019; MIC 2020); antimicrobial activity (Matsui et al. 1986; Reichel et al. 1987; Rigby et al. 1987; Inoue et al. 1998; Wang et al. 2004; Gombart et al. 2005; Weber and Heilborn 2005; Haryanto et al. 2015; Carr and Maggini 2017; Wu et al. 2019; MIC 2020); inflammation and antioxidant activity (Tanaka et al. 1991; Sly et al. 2001; Topilski et al. 2004; Wintergerst et al. 2006; Maggini et al. 2008; Sakakeeny et al. 2012; Zhang et al. 2012; Haryanto et al. 2015; Lin and Li 2016; Saeed et al. 2016; Carr and Maggini 2017; Jarosz et al. 2017; Ueland et al. 2017; Wishart 2017; Wu et al. 2019; MIC 2020); differentiation, proliferation, and normal functioning of T cells (Penna et al. 2000; Piemonti et al. 2000; Wintergerst et al. 2006; Maggini et al. 2008; Ross 2012; Haryanto et al. 2015; Bscheider and Butcher 2016; Saeed et al. 2016; Carr and Maggini 2017; Sassi et al. 2018; Wu et al. 2019; MIC 2020); antibody production and development (Maggini et al. 2008; Haryanto et al. 2015; Saeed et al. 2016; Carr and Maggini 2017; MIC 2020); and in antibody response to an antigen (Han et al. 2004; Maggini et al. 2008; Saeed et al. 2016; Wu et al. 2019).

Lack of micronutrients represses immune system by weakening individual immune functions. Malnutrition weakens the immunity functions by suppressing the immune system. Recently, increased cases of repressive immune systems have been reported (Palmer 2011). Basoglu and Turnagol (2004) reported that of the factors related to diet, particularly energy intake, macro- and micronutrients are the main effects of malfunction on the immune system.

14.5 ROLE OF FRUITS AND BERRIES ON HEALTH AND IMMUNITY

In botanical terminology, berries are fruits developed from a single flower containing a single ovary, which contain large numbers of seeds. Examples of berry fruits are tomatoes, banana, and grapes, but common ‘berries’ in the literature, like strawberries, blackberries, blueberries, cranberries, and raspberries, are not included as botanical berries (Figure 14.2). For the present chapter, both types of fruits, i.e., botanical berries and common (but non-botanical) berries are considered. Furthermore, the health effects of some common berry fruits, like grapes, have already been reviewed extensively by several authors (Yang and Xiao 2013; Georgiev et al. 2014; Singh et al. 2015a). Kolouchova-Hanzlikova et al. (2004) reported the presence of a key phytochemical, resveratrol, in grapes, which has been found to be beneficial with respect to improved health in terms of diseases like cancer and cardiovascular disease. Similar results have also been reported by various research groups (Pagliaro et al. 2015;

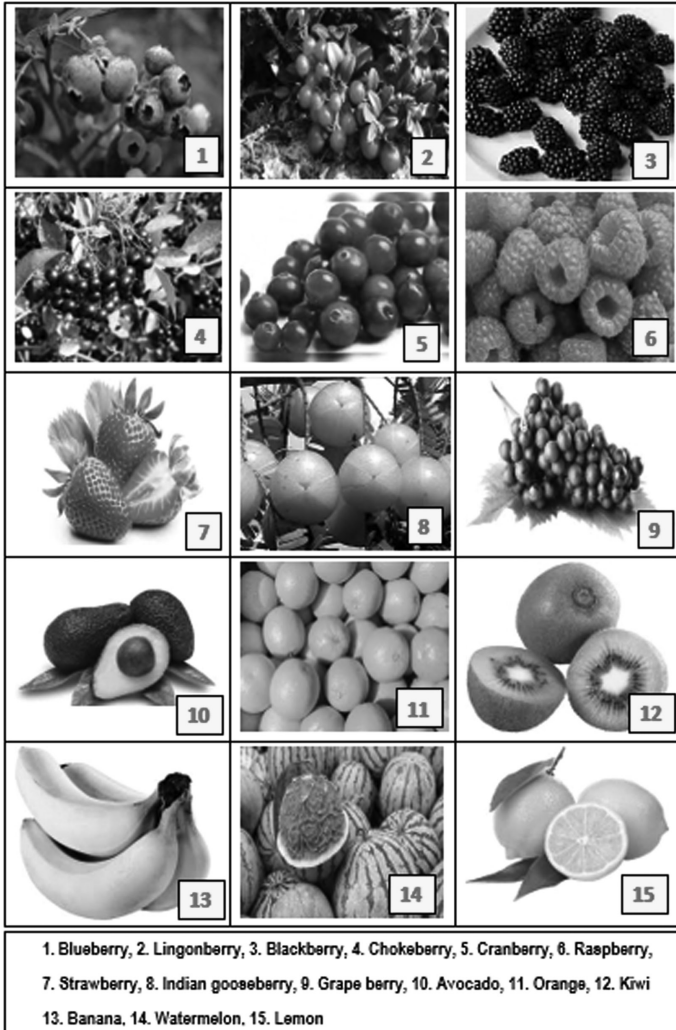


FIGURE 14.2 Immunomodulator fruits and berries.

Singh et al. 2015b; Zulueta et al. 2015; Kursvietiene et al. 2016). Due to the synergistic potential of various berry components, whole berry consumption has shown a clear advantage over consumption of phytochemical supplementation of the diet. Our digestive system also supports consumption of raw fruits in our diet because bioactive compounds (vitamins, minerals, and antioxidants) and beneficial phytochemicals are generally readily extracted by the enzymes, microbiota, and epithelium of the gut.

Several researchers have described and reviewed the beneficial effects of berry fruits due to their bioactive components in relation to various health conditions and diseases like diabetes and obesity (Tsuda 2016), cardiovascular diseases (Basu et al. 2010),

cancer development (Kristo et al. 2016), and metabolic syndrome (Vendrame et al. 2016). Comparatively little research has been performed on the potential health benefits of berries on the digestive system but *in vivo* studies have demonstrated that intake of berry fruits had direct, positive effects on the health of the digestive tract, i.e., mouth, oesophagus, stomach, intestine, microbiota and, ultimately, on the immune system. As mentioned in the literature, berries support the function of the digestive system, immune cells, and cellular repair of damage due to cancer. It has been reported that immune cells educated in the gut migrated throughout the body and resulted in suppression of lung carcinoma (Hong et al. 2004). It is very well proved that specific illnesses can be cured by alterations of immune responses, with nutrition playing an important role in developing immunity. So, a comprehensive understanding of these alterations and applications of certain bioactive phytochemicals found in specific berries and fruits can help in improving the immunity of the body.

Fruits, especially berries, have been reported to contain phytochemicals and biochemicals showing antioxidant properties (Jia et al. 2012). The biochemical analysis of fruits shows that berries are excellent source of bioactive compounds like flavonoids, phenolics, and tannins, which, individually or in combination, may be helpful against chronic diseases such as cardiovascular disease, diabetes, cancer, and obesity (Wu et al. 2010). Slavin et al. (2012) and other workers have reviewed and described the relationship between fruit intake and the risk of disease development. Fruits, especially berries, have been reported for their high concentrations of phytochemicals, micronutrients, sugars, etc. (Table 14.1). Phytochemicals are bioactive substances, responsible for colour, aroma, defence, etc. of plants. More than 5,000 phytochemicals have been identified to date in plants. These may be classified into alkaloids, phenolics, nitrogen-containing components, organosulphur components, carotenoids, and phytosterols (Liu 2004). Research findings highlight the use of phytochemicals in the treatment of diseases, such as cancer metastases (Kim et al. 2016; Shankar et al. 2016), inflammatory bowel disease (Kaulmann and Bohn 2016), and obesity-induced insulin resistance (Younus and Anwar 2016), as well as their role in stimulating weight loss (Rupasinghe et al. 2016). Furthermore, studies are being conducted to determine the relationship between fruits and immunity and the mechanisms responsible for any such association.

The health effects of berries have been analysed in *in-vivo* and *in-vitro* studies conducted in animal and human systems. Both types of study have their own merits and demerits, with *in-vitro* studies being mostly conducted for screening and studying the mechanism of action, whereas *in-vivo* studies can be helpful to analyse the beneficial and harmful effects of berry fruit components. Research findings of *in-vivo* studies recommend consumption of whole berries for better results due to their high concentration of phytochemicals and their increased bioavailability and activity in the presence of other components. The phytochemical concentrations of various berries have been identified and listed by the United States Department of Agriculture (USDA) database. Several research groups (Wada and Ou, 2002; Rimando et al. 2004; Ehala et al. 2005; Mertz et al. 2007; Abe et al. 2012; Rodriguez-Mateos et al. 2012) have contributed to the USDA information regarding the consumption of berries.

TABLE 14.1**Various Fruits and Berries and Their Phytochemical and Micronutrient Components (adapted and modified from Giancarlo et al. (2011))**

Common Name	Botanical Name	Phytochemicals and Micronutrients
Cornelian cherry	<i>Cornus mas</i>	Vitamin C, fructose, minerals and tannins
Red raspberry	<i>Rubus idaeus</i>	Phenols, flavonols, such as kaempferol, myricetin, and quercetin
Bilberry	<i>Vaccinium myrtillus</i>	Vitamin C, minerals (calcium and iron), fibre, and some antioxidant compounds such as anthocyanins and proanthocyanidins
Sea buckthorn	<i>Hippophaë rhamnoides</i>	Vitamins (A, C, E, F, K, and B group), flavonols, and mineral elements such as iron, calcium, magnesium, and copper.
Wild rose	<i>Rosa canina</i>	Vitamin C, flavonols, proanthocyanidins, polyphenols, and antioxidants
Elderberry	<i>Sambucus nigra</i>	Vitamins A, C, anthocyanins, cyanogenic glucosides
Barbados cherry	<i>Malpighia glabra</i>	Vitamins (C, A, B ₁ , B ₆), flavonoids, and minerals (calcium, phosphorus, iron, potassium, and magnesium).
Guava	<i>Psidium guajava</i>	Vitamin C, tannins, polyphenols, terpenes, flavonoids, fibre, fatty acids, and minerals (calcium, phosphorus, iron, and manganese).
Pomegranate	<i>Punica granatum</i>	Polyphenols, particularly ellagitannins, and antioxidants
Tamarind	<i>Tamarindus indica</i>	Vitamin C, phenolics, and antioxidants
Grape	<i>Vitis vinifera</i>	Vitamins C, E, A, K, minerals (calcium, iron, phosphorus, zinc, manganese)
Indian gooseberry	<i>Phyllanthus emblica</i>	Vitamin C, tannins, and polyphenols
Blueberry	<i>Vaccinium corymbosum</i>	Vitamins C, K, micronutrients, and anthocyanins
Lingonberry	<i>Vaccinium vitis-idaea</i>	Vitamin C, A, B, minerals (potassium, calcium, magnesium, and phosphorus), and anthocyanins
Blackberry	<i>Rubus fruticosus</i>	Vitamins C, K, folic acid, minerals (e.g., manganese), and anthocyanins
Blackcurrant	<i>Ribes nigrum</i>	Vitamins C, E, fatty acids, polyphenols, and anthocyanins
Chokeberry	<i>Aronia</i> spp.	Vitamin C and polyphenols
Cranberry	<i>Vaccinium macrocarpon</i>	Vitamin C, manganese, and polyphenols
Raspberry	<i>Rubus</i> spp.	Vitamin A, thiamine, riboflavin, vitamin B ₆ , calcium, zinc, and anthocyanins
Strawberry	<i>Fragaria × ananassa</i>	Vitamin C, manganese, and polyphenols

14.6 ROLES OF FRUITS AND BERRIES IN DISEASE PREVENTION AND IMMUNITY

Various research reports have proved that our diet, with adequate fruits and vegetables, makes our immune system stronger and protects us against various chronic diseases, like cardiovascular disease, eye disease, and cancer of the digestive tract, pancreas, and urinary bladder (Crawford et al. 1994; Van Duyn and Pivonka 2000). It is also observed that the habit of mothers of regular fruit consumption has a positive impact on the health and food habits of their children. Studies show that requirement for consuming fruits and vegetables of males and females is different (Wardle et al. 2000; Wang et al. 2002).

Fruits and vegetables are rich source of micronutrients and provide various essential vitamins and elements, such as vitamin C, thiamine, niacin, riboflavin, folic acid, pyridoxine, calcium, potassium, zinc, phosphorus, and dietary fibre. The phytochemicals and bioactive substances present in fruits are powerful antioxidants, which activate metabolism and detoxify carcinogens from our body (Wargovich 2000). Several research groups have reported the value of fruits and berries in supporting and boosting the immune system (Kushi et al. 2012; Sinha et al. 2012; Calder 2013). The antioxidant capacity of various fruits and vegetables can vary greatly (Kalt 2002), so it is advisable to take a combination of various fruits and vegetables in our daily diet. Reports showed that the benefits of consumption of carotenoid-rich fruits has been found to be superior over carotenoid dietary supplements in increasing resistance to low-density lipoprotein (LDL) oxidation, and improving repair of our body cells and DNA (Southon 2000; Seifried et al. 2003). Normally, consumption of fruits like orange, mango, melon, pineapples, grapes, etc. is recommended for a better immune system.

The findings of several studies have shown that intake of fibre from fruit and vegetables is inversely proportional to the incidence of coronary heart disease. Meta-analyses of studies showed that cardiovascular events decreased, when intake of fruits was increased, meaning that consumption of fruits has a positive impact on cardiac health (Dauchet et al. 2005; He et al. 2006). Clinical and biological investigations also support the protective effect of fruit and vegetable intake against coronary heart disease (CHD), diabetes, dyslipidaemia, and hypertension (Appel et al. 1997; Ness and Powles 1997; Van Duyn et al. 2000; Ford and Mokdad 2001; Bazzano et al. 2003; Alonso et al. 2004; He et al. 2006). Similarly, different population studies have also observed a negative correlation between intake of adequate fruits and incidence rates of CHD. Lock et al. (2005), for example, noted a lower risk of cardiac arrest in persons who consumed adequate quantities of fruits.

Studies conducted by Block et al. (1992) and Steinmetz and Potter (1996) have indicated that a diet rich in fruits and vegetables can prevent different types of cancer, of the digestive tract (oropharynx, oesophagus, stomach, colon, and rectum); similarly, Galeone et al. (2007) reported that a high dietary intake of fruits and vegetables can reduce the risk of lung cancer in smokers as well as in non-smokers. Furthermore, adequate intake of fruits and vegetables was shown to reduce the

risk of developing cancer by 19% (Van't Veer et al. 2000). It has been reported that dietary supplementation with berry fruits and vegetables is beneficial in arresting old-age-related problems in rats (Joseph et al. 1999). A diet rich in carotenoids, like lutein and zeaxanthin, can be beneficial in preventing damage to the retina caused by light or oxidants (Mares-Perlman et al. 2002). It has been found that these carotenoids are helpful to reduce the risk of age-related macular degeneration (Seddon et al. 1994; Snellen et al. 2002).

Romieu and Trenga (2001) reported that fruit and vegetable consumption is beneficial in reducing the risk of chronic obstructive pulmonary disease. The consumption of apple fruits has also been reported to be associated with better lung function by Tabak et al. (2001) and Butland et al. (2000). Although the actual reason for the beneficial effects of fruit intake in reducing the risk of chronic obstructive pulmonary disease is not known, it is suggested that antioxidants like vitamin C or flavonoids must be playing an important role in reducing the risk of the disease. Some other studies have also demonstrated that a diet rich in antioxidants is found to be beneficial in reducing the risk of developing Alzheimer's disease. This may be due to the fact that fresh fruit juice is rich in micronutrients (minerals and vitamins) which catalyze metabolic reactions occurring in the body. Fruits rich in vitamin C and antioxidants, like citrus fruits, pineapple, grapes, and tomatoes, are helpful in detoxifying the body (Cuthbertson 2002). According to the Department of Health, South Africa (2001), fruits are an important integral part of a healthy diet as they are rich source of vitamins, minerals and other substances that could be useful in boosting the immune function.

14.7 POSSIBLE MECHANISM OF ACTION OF FRUITS IN IMMUNITY AND DISEASE PREVENTION

According to biological concepts, cells are constantly exposed to a range of oxidizing agents. These oxidants may be produced by metabolic activities or food, air, or water may be sources of these agents. However, to sustain optimal physiological conditions, it is important to maintain the balance between oxidants and antioxidants. If the number of oxidants is large in comparison with antioxidants, it can lead to oxidative stress (Ames et al. 1993; Adom et al. 2003). This oxidative stress is responsible for oxidative damage to macromolecules such as lipids, proteins, and DNA, that consequently lead to increased risk of developing chronic diseases like cancer and cardiovascular disease (Ames et al. 1993; Liu et al. 1995). To reduce oxidative stress or improve the oxidant/antioxidant balance, a high concentration of antioxidants is needed. In order to fulfil the demand for sufficient quantities of antioxidants, adequate amounts of fruits rich in antioxidants, such as carotenoids and phenolics, need to be consumed. These antioxidant compounds may help to reduce the risk of developing chronic diseases by protecting cellular systems from oxidative damage (Wang et al. 1996; Vinson et al. 2001; Adom et al. 2003).

Phenolics are secondary plant metabolites of the utmost importance for both plants and humans. In plants, they provide support of reproductive functions and protection

from enemies like pathogens, parasites, and predators, whereas, in humans, where they need to be supplied in our diet, phenolics are associated with reduced risk of chronic diseases (Sun et al. 2002). Different species of fruits and vegetables contain different phytochemicals in different quantities (Adom and Liu 2002; Adom et al. 2003). Fruits such as apple, orange, blueberry, and grapes contain diverse types of phytochemicals in various quantities, so, in combinations, different fruits show synergistic effects with respect to antioxidant activity.

Oxidative damage is linked to several mechanisms of tumour formation that lead to carcinogenesis (Ames et al. 1993; Liu et al. 1995). Oxidative stress induced by free radicals causes DNA damage, gene mutations, or chromosomal aberrations (Ames et al. 1993). Recent studies have demonstrated that phytochemicals in fruits and berries can have complementary and overlapping mechanisms of action. They have antioxidant activity and hence carry out the scavenging of free radicals, as well as the regulation of gene expression in determining cell functions. They protect cells from abnormal growth and development and boost the immune functions of cells (Ames et al. 1993; Liu et al. 1995; Adom and Liu 2002). Fruits and vegetables produce precursors to bicarbonate ions which form acidic buffers, which help to neutralize acids consumed in the diet and maintain the normal pH (New 2002).

14.8 CONCLUSION

The function of our immune system depends upon various factors like age, gender, food and dietary habits, genetics, and the physiology of the host. The nutrition level of the host plays an important role in boosting the immune system. Fruits, specifically berries, are generally considered to be beneficial in improving the health of our digestive tract and microbiome due to their phytochemical and micronutrient content. The studies show that efficiency of our immune system can be improved by consuming specific fruits and berries. But an extensive body of research is still needed to understand the functioning of our immune system in relation to the dietary intake of various fruits and berries. The studies have shown that phytochemicals supplied as whole fruits are relatively more beneficial than those in fruit juice or in the form of a dietary supplement. Fruits lose their nutrition level after prolonged storage, so it is advised to consume seasonal fresh fruits without any additives to strengthen the immune system.

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15 Natural Immunity Boosters and Anticancer Medicinal Plants

*Swati Agarwal, Sonu Kumari,
and Amrendra Kumar*

CONTENTS

15.1	Introduction	432
15.2	Medicinal Plants: Immune Boosters.....	433
15.3	Anticancer Medicinal Plants	433
15.3.1	<i>Allium sativum</i>	433
15.3.2	<i>Annona muricata</i>	437
15.3.3	<i>Astragalus cytosus</i>	437
15.3.4	<i>Boswellia serrata</i>	437
15.3.5	<i>Camellia sinensis</i>	438
15.3.6	<i>Centella asiatica</i>	438
15.3.7	<i>Curcuma longa</i>	438
15.3.8	<i>Phyllanthus amarus</i>	439
15.3.9	<i>Withania somnifera</i>	439
15.3.10	<i>Zingiber officinale</i>	439
15.4	Phytochemicals Used for Cancer Treatment	439
15.4.1	Apigenin.....	439
15.4.2	Curcumin	440
15.4.3	Crocetin.....	440
15.4.4	Cyanidins	442
15.4.5	Diindolylmethane.....	442
15.4.6	Fisetin.....	443
15.4.7	Genistein	443
15.4.8	Kaempferol.....	443
15.4.9	Resveratrol	444
15.4.10	Rosmarinic Acid	444
15.5	Phytochemical Preparation.....	445
15.5.1	Phytochemical Extraction	445
15.5.2	Phytochemical Purification.....	445

15.5.3	Phytochemical Identification	446
15.5.4	Clinical Trials	447
15.6	Mechanism of Action of Phytochemicals on Cancerous Cells.....	447
15.7	Conclusion and Future Prospects	447
	References.....	448

15.1 INTRODUCTION

Cancer is a disease which leads to uncontrolled cell growth and division, with the potential to spread and invade other parts of the body. It is one of the foremost causes of death worldwide. It mainly occurs because of genomic alterations in the DNA and it starts with a natural cell change, leading to abnormal growth (Krishnamurthi 2007). The number of cases of cancer is continuously rising and expected to reach 21 million by 2030 (Siegel et al. 2019). Almost 1,762,450 new cancer sufferers and 606,880 deaths were estimated in the United States alone in the year 2019. In 2014, the world cancer report released the data for year 2003, where around 4.7 million women and 5.3 million men were reported to develop a malignant growth annually, with 6.2 million people dying of cancer (McGuire 2016).

Nowadays, several methods are used to treat cancers. Some methods are conventional, like surgery, chemotherapy, radiotherapy, stem cell transplants, etc., but they all have one major side effect, which is non selectivity between the healthy and diseased cells (Sersa et al. 2003). On the other hand, some modern techniques are more specific for small populations of abnormal cells, such as proton therapy, robot-assisted surgery, stereotactic radiosurgery, etc. To avoid the harm to healthy cells during these treatments, research is now shifting towards more natural therapies and the use of phytochemicals. Phytochemicals are plant-derived chemicals. This process requires screening raw extracts of plants for potential anticancer phytochemicals, and then carrying out their purification, identification, characterization, and activity towards different cancerous cells.

The immune system can easily be improved through the use of medicinal plants as these have high concentrations and diversity of flavonoids, as well as vitamin C. These phytochemicals can behave as agents with anti-inflammatory and immunostimulant properties. Therefore, it can increase the action of lymphocytes, enhance phagocytosis, and stimulate interferon development. For instance, *Allium sativum* (garlic) acts mainly as an immune system booster. Several other plant species act as immune system stimulators, which achieve an immune-potentiating outcome by exciting usual killer cell action (Khodadadi 2015).

Medicinal plants are significant for cancer management because of the various chemical complexes present in the preparations (Ji et al. 2009). These compounds are known as secondary plant metabolites which are useful but not essential to the plant. Some important secondary plant metabolite classes are alkaloids, polyphenols, terpenoids, pigments, tannins, flavonoids, etc. These compounds have several curative properties on the human body, like anti-inflammatory, contraceptive, anti-cancer, antiseptic etc. Several secondary plant metabolites have been reported for the management of cancer. The method for treating cancer is by suppressing the cancer

stimulating enzymes, inducing the production of anticancer enzymes, repairing the DNA, increasing the immunity of the body, and inducing antioxidant activity, etc. (Efferth 2010).

In this chapter, we will attempt to describe some of the more effective anticancer medicinal plants including their phytochemicals, herbal preparation, and their mechanism of action in cancer treatment.

15.2 MEDICINAL PLANTS: IMMUNE BOOSTERS

During the infection period, viruses, bacteria, and fungi are attacked by the body's immune system. It identifies the foreign body in the system through the action of particular receptors to generate an instant reaction through immune cell activation, and the production of cytokines and chemokines (Kumar et al. 2011). Plants with medicinal properties play important roles in the prevention of infection from a range of disease-causing microorganisms. Globally, several medicinal plants have been reported to act as immune boosters. Some medicinal plants are suggested to improve the patient's physical condition and to sustain natural resistance against illness through re-establishing body stability (Das et al. 2014). It is appealing to consider that the curative and tonic influences of these herbal medications may be because of their direct effect on the human immune system. There are number of medicinal plants which have been proposed to improve the natural resistance to various infections.

Certain therapeutic plants are particularly effective immune system boosters. Immunomodulator plants are considered to be most effective for the nervous and hormonal systems of the body, whereas other medicinal plants have antioxidant, antiviral, or anticancer properties, which decrease the ageing effects as well as improving immunity. In plant-based medications, preparation of single plant species as well as compound formulations of different species have been approved to treat illness (Saklani and Kutty 2008).

15.3 ANTICANCER MEDICINAL PLANTS

Medicinal plants are exploited by extracting their phytochemicals and other compounds, which are in addition to the conventional drugs synthesized to treat tumours and other cancerous growths (Desai et al. 2008). Approximately 35,000 plant species were selected by the National Cancer Institute (NCI) for their possible anticancer actions. Of them, about 3,000 plant species showed activity against cancer cell lines (Douros and Suffness 1980).

Some medicinal plants (Figure 15.1) and bioactive compounds derived from them have curative properties against cancers and immunity boosting abilities and are reported in detail in the next sections of this chapter, with others being presented in Table 15.1.

15.3.1 *ALLIUM SATIVUM*

Allium sativum (garlic) is a member of the Amaryllidaceae family. *A. sativum* is a native of northern Iran and central Asia. It has been used for several centuries for

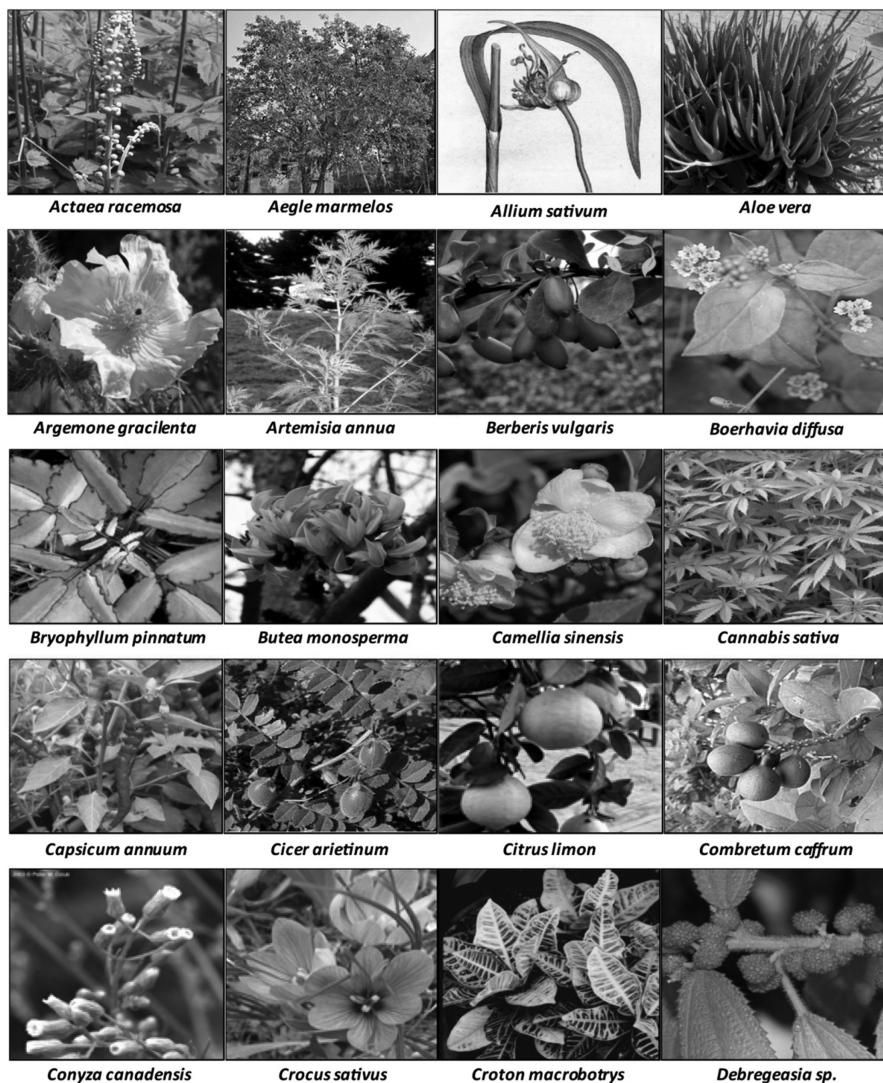


FIGURE 15.1 Some important medicinal plants used in the treatment of cancer.

food flavouring and medicinal purposes. Traditionally, garlic is recognized as a noteworthy immune booster. Matured garlic extract shows higher immunomodulatory results than raw garlic. Extracts of garlic contain high concentration of organosulphur compounds, which helps in prevention of cancer of the bladder, breast, colon, lung, skin, throat, and larynx.

Numerous papers have verified the therapeutic property of *A. sativum* extract and its essential oil. The major compounds in *A. sativum* extract are alliin, allylmercaptocysteine, allicin, and S-allyl-mercapto-L-cysteine. One additional organosulphur

TABLE 15.1
List of Some Important Medicinal Plants and Their Phytochemicals against Specific Types of Cancer

Plant Name	Common name	Plant Part extract	Phytochemicals	Specific Cancer	References
<i>Actaea racemosa</i>	Black cohosh	Rhizome	Actein	Liver, breast, gland	Wuttke et al. (2014)
<i>Aegle marmelos</i>	Bael fruit	Fruit	Lupeol, skimmianine	Leukaemia, breast, liver	Baliga et al. (2013a)
<i>Allium sativum</i>	Garlic	Fruit	Alliin, allylmercaptocysteine, allicin	Breast, colon, gland	Capasso (2013)
<i>Aloe vera</i>	Indian aloe	Leaf	Aloesin, emodin, alexin	Lymphoma, cervix	
<i>Argemone gracilentia</i>	Prickly poppy	Complete plant	Argemone, berberine	Anti-angiogenic activity, stomach, head, neck, leukaemia	Ahmadi (2012)
<i>Artemisia annua</i>	Wormwood	Arial parts	Artemisinin	B cell lymphoma, leukemia	Iqbal et al. (2017)
<i>Berberis vulgaris</i>	Barberry	Fruit	Berberine, canmabisin	Liver and breast	Efferth (2017)
<i>Boerhavia diffusa</i>	Punarnava	Roots	Punarnavine	Breast, colon, liver, prostate	Hoshyar et al. (2016)
<i>Bryophyllum pinnatum</i>	Goethe plant	Leaf	Bryophyllin	Malignant melanoma	Khan et al. (2013)
<i>Butea monosperma</i>	Flame-of-the-forest	Flower	Butrin	Cervical	Mahata et al. (2012)
<i>Camellia sinensis</i>	Tea plant	Leaf	Theabrownin, epigallocatechin gallate	Liver	Choedon et al. (2010)
<i>Cannabis sativa</i>	Hemp	Flower and leaf	Cannabinoid	Lung, brain, prostate, cervical, bladder	Luo et al. (2014)
<i>Capsicum annuum</i>	Peppers	Fruit	Luteolin, capsaicin	Lung, pancreas, prostate, breast, colorectal	Hall et al. (2005)
<i>Cicer arietinum</i>	Chickpea	Seeds	Bowman-Birk type protease inhibitor	Colorectal	Chapa-Oliver and Mejia-Teniente (2016)
<i>Citrus limon</i>	Lemon	Fruit	5-hydroxy-6,7,8,30,40-pentamethoxyflavone	Prostate, breast	Magee et al. (2012)
<i>Combretum caffrum</i>	Bushwillow tree	Fruit and bark	Combretastatins A1, A4, B1	Colon, colorectal, buccal	Raimondo et al. (2015)
				Cervical, lung, colon	Ley et al. (2007)

(Continued)

TABLE 15.1 (CONTINUED)
List of Some Important Medicinal Plants and Their Phytochemicals against Specific Types of Cancer

Plant Name	Common name	Plant Part extract	Phytochemicals	Specific Cancer	References
<i>Conyza canadensis</i>	Horseweed	Roots	Conyzapyranone A, B, 3-β-Erythrodiol	Gastric	Liu et al. (2016)
<i>Crocus sativus</i>	Saffron	Stigma	Crocins, crocetin	Colorectal, lung	Samarghandian et al. (2010)
<i>Croton macrobotrys</i>	Rushfoil	Leaves	Corydine, salutaridin	Leukaemia, lung	Jain et al. (2016)
<i>Debregeasia longifolia</i>	Orange wild rhea	Fruit	Epicatchin, apigenin	Breast	Bo et al. (2003)
<i>Ginkgo biloba</i>	Maidenhair	Leaves	Kaempferol, gink	Pancreatic, breast, prostate	Zhang et al. (2008)
<i>Glycine max</i>	Soybean	Seeds	Genistein, Bowman-Birk Inhibitor IBB1, IBBD2	Colorectal, breast, prostate	Clemente et al. (2010)
<i>Hibiscus mutabilis</i>	Confederate rose	Seeds	Lectins	Breast, hepatoma	Lam and Ng (2009)
<i>Linum usitatissimum</i>	Flax	Roots, leaf	Cyanogenic glycosides	Breast	Szewczyk et al. (2014)
<i>Moringa oleifera</i>	Drumstick tree	Leaf, bark, seed	Eugenol, isopropyl isothiocyanate, D-allose	Breast, pancreatic	Al-Asmari et al. (2015)
<i>Ocimum sanctum</i>	Basil	Leaf, aerial parts	Camphor, linalool	Lung, cervical, fibrosarcoma	Baliga et al. (2013b)
<i>Paeonia suffruticosa</i>	Moutan	Seeds	<i>Cis</i> -, trans-gnetin H	Gastric, breast, lung	Gao et al. (2015)
<i>Peganum harmala</i>	Syrian rue	Seeds	Harmine, harmaline	Leukaemia, breast	Zaker et al. (2007)
<i>Pisum sativum</i>	Garden pea	Seeds	Protease inhibitors rT11B, rT12B	Colorectal, colon	Clemente et al. (2012)
<i>Podophyllum hexandrum</i>	Mayapple	Rhizome, roots	Podophyllotoxin	Leukaemia, ovarian	Giri and Narasu (2000)
<i>Maltus domestica</i>	Apple	Bark, fruit	Quercetin, catechin	Lung, colon, breast	Madhuri and Pandey (2009)
<i>Solanum lycopersicum</i>	Tomato	Fruit	Alpha-solanine, lycopen	Breast	Mohsemikia et al. (2013)
<i>Tylophora indica</i>	Indian ipecac	Leaf	Tylophorin, cryptopleurine	Breast	Saraswati et al. (2013)
<i>Vaccinium macrocarpon</i>	American cranberry	Fruit	Proanthocyanidins	Prostate	MacLean et al. (2011)
<i>Vitis vinifera</i>	Grape	Seed	Proanthocyanidins, procyanidins	Oral squamous	Aghbali et al. (2013)
<i>Ziziphus jujuba</i>	Chinese date	Fruit, seeds	<i>p</i> -Coumaroyl/maslinic acid	Breast	Plastina et al. (2012)

compound derived from *A. sativum* is S-allylcysteine, which has been found to reduce the growth of tumours. In other research, allicin showed its antitumour characteristics against breast and prostate cancer, inducing programmed death (apoptosis) of cancer cells (Madhuri and Pandey 2008). Ajoene (E and Z isomers) is another important anticancer compound derived from *A. sativum* that works against leukaemia (Kaschula et al. 2011).

15.3.2 *ANNONA MURICATA*

The common name of *Annona muricata* is the soursop fruit. It is mostly found in tropical regions of South America, the Caribbean and Southeast Asia (Yajid et al. 2018). *A. muricata* belongs to the family Annonaceae (Mishra et al. 2013). The important plant parts that are commonly used as a therapeutic agent in cancer treatment are its leaf, root, bark, and fruits.

The plant parts of *A. muricata* contain several phytochemicals, such as acetogenins 1, 2, 2-hexenoic acid esters, 2-octenoic acid, β -caryophyllene, cineole, linalool, terpineol, and bullatacin, which have antitumour properties (Pieme et al. 2014). Rieser and his co-workers (1991) showed the activity of *A. muricata* seed extract, with acetogenin 1 active against the human pancreatic tumour and human lung carcinoma, whereas acetogenin 2 was active against human hepatoma carcinoma (Rieser et al. 1991).

15.3.3 *ASTRAGALUS CYTOSUS*

Commonly known as milkvetch, *A. cytosus* belongs to the family Fabaceae. A recent studies explains the effect of the related *Astragalus mongolicus* extract against COVID-19 due to the presence of phytosterols, triterpenes, saponins, isoflavonoids, etc. (Boone et al. 2020). Other studies showed the effect of *A. cytosus* extract on human lung epithelial carcinoma cell A549, mammary tumour, colon cancer, gastric cancer, and urological tumour (Tin et al. 2007).

15.3.4 *BOSWELLIA SERRATA*

The common name of *Boswellia serrata* is Indian frankincense, and it is found mostly in Asia and Africa. The exuded gum is produced from *B. serrata* plants via incisions made on the trunk. The gum appears like a milky resin and has several medicinal and immune modulator properties (Khajuria et al. 2008).

According to research conducted by Winking and co-workers, the resin of *Boswellia* species possesses anticancer activity, exhibiting an anti-pro-apoptotic nature in rat astrocytoma cell lines (Winking et al. 2000). Further studies showed the effect of *B. serrata* resin constituents on two important cancerous cell lines, HepG2 and HCT 116. Furthermore, there are some reports showing the effect of *Boswellia* resins on brain oedema and brain tumours. The main active constituents of *Boswellia* resin are boswellic acids, which are mainly used in cancer treatment (Roy et al. 2016).

15.3.5 *CAMELLIA SINENSIS*

It is an evergreen shrub, generally recognized as the tea plant with the leaves of *C. sinensis* being utilized to produce tea. After water, the next most consumed liquid on the planet is the leaf extract of *C. sinensis* (Sharangi 2009). *C. sinensis* is a very good source of the alkaloids theophylline, theanine, caffeine, and other antioxidants. According to the National Cancer Institute, the leaves of *C. sinensis* contain highly effective antioxidants, which can ward off several types of cancer (Sharangi 2009).

C. sinensis extract also contains epigallocatechin, epicatechin, epigallocatechin-3, and epigallocatechin, which have various therapeutic effects against bacterial/viral infections and against cancer-causing cells (Sultan et al. 2014). These polyphenols play a significant function in cancer prevention through decreasing oxidative DNA injury in the host cells. In one of the studies conducted by Setiawan and colleagues, they found that the regular habit of drinking green tea decreased the risk of developing gastric cancer (Setiawan et al. 2001).

15.3.6 *CENTELLA ASIATICA*

Centella asiatica, commonly known as pennywort, is native to the Indian subcontinent. It belongs to the family Apiaceae. The leaves or sometimes the whole plant are used for various medicinal purposes and as an immunomodulatory agent. The leaf extract of *C. asiatica* contains several flavonoids including hyperin and its various glycosides (Babu et al. 1995).

The purified extract of *C. asiatica* demonstrated action against Ehrlich tumour cell lines and Dalton's lymphoma ascites cells. Direct inhibition of DNA synthesis is the key mechanism underlying the anticancer activity of the *C. asiatica* extract. The oral consumption of *C. asiatica* leaves also provides protection against oxidative damage (Gupta and Flora, 2006).

15.3.7 *CURCUMA LONGA*

Curcuma longa is popularly known as turmeric (Yue et al. 2010). The rhizome is the most important part of this plant and the main active ingredient present in it is known as curcumin (diferuloylmethane), a polyphenol. Other than curcumin, *C. longa* contains one other group of important constituents known as sesquiterpenoids, which also possess some important biological properties.

Curcumin has anticancer properties. It is utilized to prevent different cancers, such as blood, ovarian, gastrointestinal tract, lung, liver, skin, prostate, breast, bladder, and pancreatic cancers as well as lymphomas (Luthra and Lal 2016). Down-regulating the expression of genes (encoding lysyl oxidase, NF-kappa β , epidermal growth receptors, inducible nitric oxide synthase (iNOS), cyclooxygenase, tumour necrosis factor, and matrix metalloproteinase) is the key mechanism behind the anticancer activity of curcumin.

15.3.8 *PHYLLANTHUS AMARUS*

P. amarus is generally identified as bhui-aamla and it belongs to the family Phyllanthaceae. The complete plant, as well as parts, such as root, shoots, and leaves, has medicinal properties. The anticancer property of *P. amarus* is due to the presence of various flavanoids, lignins, and tannins. The major phytochemicals found are gallotannins (corilagin, amariin, phyllanthusiin D, geraniin) and the lignans (phyllanthin and hypophyllanthin) (Sripanidkulchai et al. 2002).

The extract of this plant has a significant effect on reducing the tumour size in mice having Dalton's lymphoma (Rajeshkumar et al. 2002). The mechanism behind the anticancer property of *P. amarus* extract involves its ability to stimulate cell cycle arrest or by inhibiting metabolic activation of carcinogenic compounds.

15.3.9 *WITHANIA SOMNIFERA*

Popularly known as ashwagandha or poison gooseberry, *W. somnifera* belongs to the family Solanaceae. It is a small, perennial shrub, mainly cultivated in drier regions of India and is also found in China, Yemen, and Nepal. The roots and leaves of this plant have been traditionally used to cure and prevent several diseases (Jayaprakasam et al. 2003).

The root extract of this plant has several bioactive phytochemicals (withanolide A, withaferin A) which help in inducing apoptosis in cancerous cells. However, the synthesis or isolation of withanolides from *W. somnifera* extract is a serious limitation to their effective use in the medical field (Malik et al. 2007).

15.3.10 *ZINGIBER OFFICINALE*

This plant is widely known as ginger and is a member of the family Zingiberaceae. It is a herbaceous plant, commonly found in hot and humid regions of India. Traditionally, *Z. officinale* is used as medicine for the cure of a number of diseases, such as inflammatory diseases (Afzal et al. 2001). *Z. officinale* includes several bioactive phytochemicals, such as phenolic compounds (gingerol, paradol, and shogaol). These polyphenolic compounds have anti-cancer properties.

Extract of *Z. officinale* down-regulates transcriptional factors involved in the cellular proliferation of ovarian cancer cells (Nonn et al. 2007). One of the studies reported the rhizome extract of *Z. officinale* as being effective at chemosensitizing certain neoplastic cells.

15.4 PHYTOCHEMICALS USED FOR CANCER TREATMENT

15.4.1 APIGENIN

Apigenin (4',5,7-trihydroxyflavone) is a flavone compound available mainly from *Moringa peregrina* and some other vegetables and herbs, such as chamomile, celery, and parsley. It is a yellow crystalline solid used in several therapeutic products

(Patel et al. 2007). Apigenin has specific effects in normal *versus* cancer cells in comparison with other structurally related compounds. The chemical configuration of apigenin is given below (Figure 15.2a).

Apigenin is effective against almost every form of cancer, like breast, colon, cervical, leukaemia, ovarian, prostate, skin, thyroid, neuroblastoma, and lung cancer (Patel et al. 2007). Different action mechanisms of apigenin have been identified which include anti-proliferative activity, oestrogenic/anti-oestrogenic activity, apoptosis, induction of detoxification enzymes, prevention of oxidation, and regulation of the host immune system. It has been shown to have anticancer action on human breast cancer cell lines. Apigenin showed growth inhibitory activity against breast cancer cells HER2/neu by inducing apoptosis through the phosphatidylinositol 3-kinase pathway (Way et al. 2004).

15.4.2 CURCUMIN

Curcumin (1*E*, 6*E*)-1,7-Bis (4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione) is the major phytochemical of the popular Indian spice turmeric, *Curcuma longa*. Curcumin down-regulates different pro-inflammatory cytokines, like chemokines, tumour necrosis factor (TNF- α), interleukins (IL-1, IL-2, IL-6, IL-8, IL-12), etc. (Zhou et al. 2011). The chemical structure of curcumin is illustrated in Figure 15.2b.

Curcumin has proved to be a potential curative agent against cancer due to its property of inducing apoptosis in cancer cells without affecting normal ones. Numerous clinical trials have been completed to test its activity on tumorous cells. Kuttan and his co-workers in 1987 conducted a clinical trial and observed the reduced size of oral cancer and leukoplakia after treatment with curcumin (Kuttan et al. 1987). Curcumin also shows activity against different types of cancer, such as breast, oral, prostate, lung, multiple myeloma, colorectal, pancreatic, and neck and head squamous cell carcinoma (Gupta et al. 2013).

15.4.3 CROCETIN

Crocetin is a natural carotenoid, found in the flower of the Saffron crocus and in dehydrated stigmas of *Crocus sativus* (Gutheil et al. 2012). The structure of crocetin has 20 carbon atoms with conjugated double bonds and containing two carboxylic acid groups (Fig. 15.2c). Crocetin is a potential agent against skin carcinoma, hepatocellular carcinoma, colorectal cancer cells, a pancreatic cancer cell line, lung cancer, and breast cancer.

The action mechanism of crocetin includes inhibiting the synthesis of nucleic acid, enhancing the antioxidative system, which induces apoptosis and inhibits the growth factor signalling pathways (Figure 15.3). In 2013, Bathaie and his co-workers demonstrated the positive effects of crocetin on gastric adenocarcinoma and gastric cancer in rats (Bathaie et al. 2013).

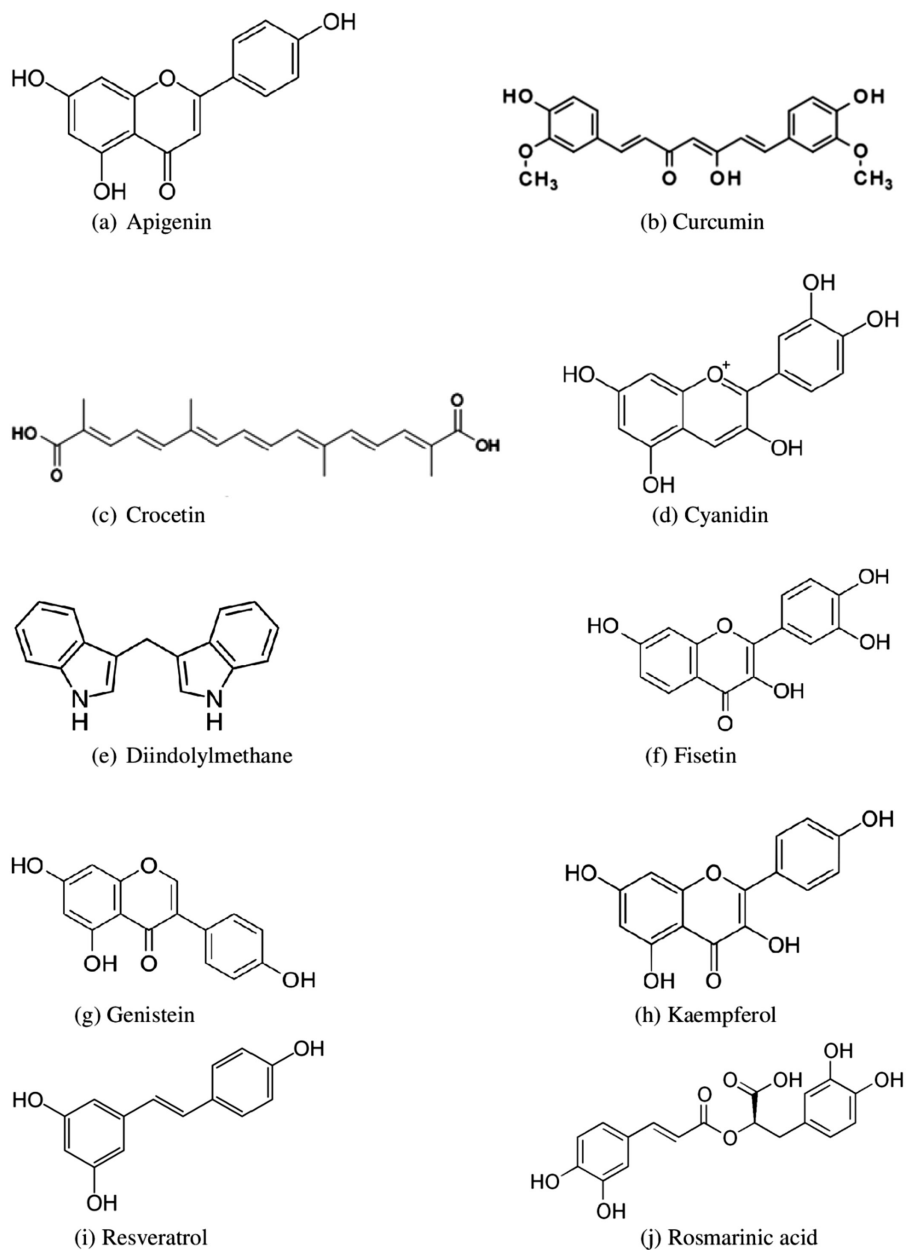


FIGURE 15.2 Chemical structures of some important phytochemicals used against specific type of cancer.

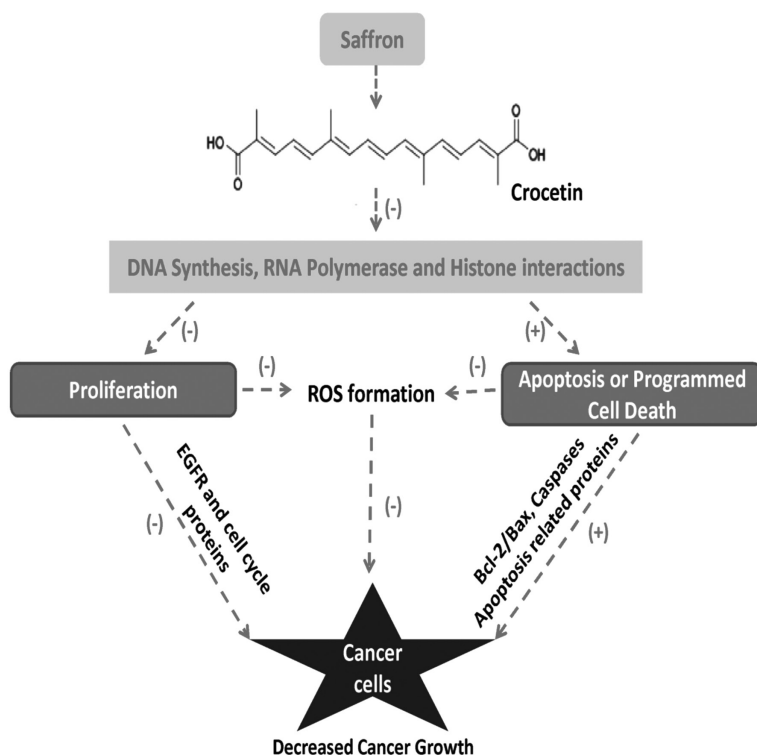


FIGURE 15.3 Possible chemopreventive mechanisms of crocetin against cancer cells.

15.4.4 CYANIDINS

Cyanidins are a group of pigments extracted from red berries, red onion, apples, plums, grapes, raspberry, blackberry, red cabbage, and cranberry. Cyanidin is a natural organic compound (an anthocyanidin) possessing radical-scavenging and anti-oxidant effects on cancer cells. The chemical structure of cyanidin is illustrated in Figure 15.2d.

Cyanidin shows activity against several cancers, such as colorectal, colon, lung, breast, leukaemia, etc. In 2010, a group of researchers concluded in their study that the cyanidin preferentially kills cancer cells with highly malignant characteristics (Cvorovic et al. 2010). Other research has demonstrated the inhibitory effect of the cyanidin glycosides (examples of anthocyanins) cyanidin-3-rutinoside and cyanidin-3-glucoside on human lung carcinoma cells.

15.4.5 DIINDOLYLMETHANE

Diindolylmethane (3,3'-methanediylbis) is a glucosinolate, produced by plant species limited to the 'cruciferous' vegetables (Brassicaceae family) such as cabbage, kale, Brussels sprouts, cauliflower, and broccoli (Hong et al. 2002). It is an analogue of indole-3-carbinol

which is formed *via* condensation in the acidic medium after digestion in the stomach. Indole-3-carbinol and diindolylmethane are extremely effective in terms of anticancer effects against hormone-responsive cancers like prostate, ovarian, and breast cancers. The chemical structure of diindolylmethane is shown in (Figure 15.2e).

Some studies showed the action of diindolylmethane in human cancer cells to be by activation of the human protein p53 which results in inducing apoptosis (Ge et al. 1996). One of the other studies (Beaver et al., 2012) showed that diindolylmethane transduced signalling *via* activating transcription factors like NF- κ B, Wnt, Akt, mTOR, etc. They also concluded that diindolylmethane and indole-3-carbinol had a more efficient activity to cancer at the early phases of prostate cancer.

15.4.6 Fisetin

Fisetin (2-(3,4-dihydroxyphenyl)-3,7-dihydroxychromen-4-one) is a polyphenol from the flavonoid fraction. It is mostly found in fruits and vegetables such as onion, tomato, cucumber, apple, kiwi, peach, strawberries, grape, and persimmon (Lall et al. 2015). Fisetin showed effectiveness against different cancers, such as prostate, lung, skin, colorectal, bladder, breast, leukemia, and cervical cancers. The chemical structure of fisetin is shown in Figure 15.2f.

15.4.7 GENISTEIN

Genistein (5,7-dihydroxy-3-(4-hydroxyphenyl)chromen-4-one) is an isoflavone reported from several plants such as fava beans, psoralea, lupin, kudzu, soybeans (all members of the Fabaceae), and coffee. It has been reported to have anti-angiogenic effects and may inhibit the uncontrolled cell growth associated with cancer (Yu et al. 2012). Genistein acts as a tyrosine kinase inhibitor, with a function of inhibiting DNA topoisomerase II. The chemical structure of genistein is shown in Figure 15.2g.

According to a study conducted by a group of researchers in 2008, genistein inhibits the activation of different transcription factors, such as NF- κ B, STAT-3, and Akt. These transcription factors are used to sustain a homeostatic equilibrium between its cell cycle and apoptosis (Banerjee et al. 2008). Genistein also showed activity against mammary cancer treatment. In 1995, Lamartiniere and his coworkers perform an experiment on female Sprague-Dawley rat (which had been chemically induced to express breast cancer) by pre-treating them with genistein (Lamartiniere et al. 1995). The experiment resulted in a decreased number of terminal ends and an increased number of lobular structures. Genistein was reported to be an efficient inhibitor against RTK (Receptor Tyrosine Kinase) together with EGFR (Epidermal Growth Factor Receptor)(Figure 15.4).

15.4.8 KAEMPFEROL

Kaempferol (3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one) is a natural polyphenol of the flavonol type isolated from a variety of fruits and vegetables, such as tomato, grapes, apples, grapefruit, tea, squash, broccoli, potato, onions, and Brussels

medicinal herbs, such as rosemary, thyme, lemon balm, oregano, peppermint, and sage. Extract of rosemary plays an important role in anti-inflammation, antitumour, and antiproliferation in various *in-vitro* and *in-vivo* studies (Yesil-Celiktas et al. 2010). The chemical structure of rosmarinic acid is shown in (Figure 15.2j).

Rosmarinic acid has been shown to reduce tumour necrosis factor (TNF- α) in induced human dermal fibroblasts. It was found that treatment with rosmarinic acid considerably sensitized TNF- α and stimulated apoptosis in human leukaemia cells through repression of the nuclear transcription factor (κ - γ - β). Some studies reported the successful treatment of human colon carcinoma using rosmarinic acid (Xu et al. 2010).

15.5 PHYTOCHEMICAL PREPARATION

The prospective of medicinal plants as curative agents depends upon the quality and quantity of the active phytochemicals in the herbal preparation. Certain phytochemicals have been established for their anti-cancer activities. They were extracted from different plant parts using several extraction techniques. The effectiveness of phytochemicals depends upon their successful extraction and purification. A detailed scheme of phytochemical extraction, characterization, identification, and clinical trials as a cancer therapeutic agent is shown in Figure 15.5.

15.5.1 PHYTOCHEMICAL EXTRACTION

The extraction of phytochemicals from medicinal plants is the most important step in the preparation of pharmaceutical products. The extraction of phytochemicals can be done using fresh, dried, or frozen plant samples. The first step of extraction is grinding of the plant sample. Grinding is usually performed after air-drying of the plant sample and then milling and homogenization (Abascal et al. 2005).

Solvent extractions are the most frequently utilized method for isolation of plant materials due to its easy procedure, wide applicability, and high efficiency. Solvent selection is a crucial step for phytochemical extraction, because different phytochemicals have different solubility efficiencies in various solvents (Xu and Chang 2007). Solvents, such as ethyl acetate, methanol, ether, ethanol, and acetone, alone or in combination, have been used for the extraction of phytochemicals.

15.5.2 PHYTOCHEMICAL PURIFICATION

The crude extracts of plants contain a number of impurities, usually carbohydrates or lipids, which can result in very low concentrations of phenolics in the crude plant extract. To concentrate and obtain phytochemical-rich fractions before analysis, purification approaches are required. Purification can be done by several methods, such as centrifugation, filtration, chromatographic separation (column chromatography), and some other methods (solid-phase extraction, liquid-liquid partitioning, sequential extraction). In general, for the removal of lipid impurities, the crude extract is washed with non-polar solvents (Ramirez-Coronel et al. 2004), such as chloroform

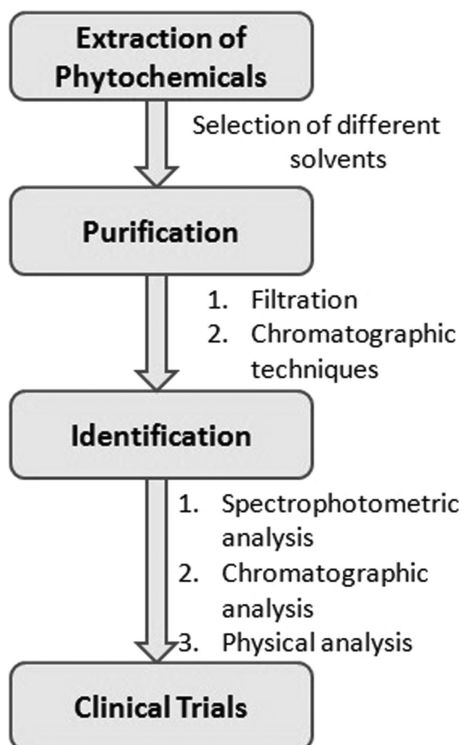


FIGURE 15.5 Detailed scheme of phytochemical preparation.

or dichloromethane (Neergheen et al. 2006), whereas, for the removal of polar non-phenolic compounds, such as organic acids and sugars, solid-phase extraction is used.

Column chromatography has been also used for the extraction of phytochemicals. Even though this process is time consuming and requires large volumes of solvent, it provides generally pure phytochemicals. Different columns used for the fractionation of phytochemicals include RP-C18 (Queiroz et al. 2005), Toyopearl (Kandil et al. 2002), LH-20 (Pedreschi and Cisneros-Zevallos, 2006) and, to a less extent, polyamide resin (Ranilla et al. 2007). Eluents used for separation include ethanol, acetone, water, or methanol, or combinations thereof. In some cases, preparative-scale HPLC or classical liquid–liquid extraction has also been utilized in plant extract purification (Ek et al. 2006). As a substitute for liquid chromatography, countercurrent chromatography has also been developed for fractionation of various classes of phytochemicals. The main advantage of using countercurrent chromatography is the absence of a solid matrix (Berthod et al. 1999).

15.5.3 PHYTOCHEMICAL IDENTIFICATION

The process of phytochemical identification begins with the confirmation test for biological activity of the natural extract. Then, suitable matrices are employed for

the fractionation of the active extracts. Bioactivity tests are performed using several analytical techniques, such as chromatographic analysis (absorption, ion exchange, affinity, partition, High Pressure Liquid Chromatography (HPLC) and Gas Chromatography (GC), paper, etc.) (Dai and Mumper, 2010), spectrophotometric analysis (UV-Vis, MS) (Jac et al. 2006) or physical structural analysis (Fourier-transform infrared spectroscopy (FTIR), X-ray diffraction analysis (XRD), Nuclear magnetic resonance (NMR)) (Pawlowska et al. 2008) etc. These are used for the identification and separation of active fractions.

15.5.4 CLINICAL TRIALS

After identification of these phytomolecules, they must be studied to determine *in-vitro* or *in-vivo* anticancer behaviour. If an improved anticancer efficiency is achieved by the molecules, then other aspects, like pharmacokinetics, pharmacodynamics, immunogenicity, metabolic fate, biosafety and side effects, drug interactions, dose concentration, etc. must be considered for future drug design and administration.

15.6 MECHANISM OF ACTION OF PHYTOCHEMICALS ON CANCEROUS CELLS

The mechanism of action involved in cancer treatment using polyphenols is categorized in different sections. Some phytochemicals, like quercetin and resveratrol, are used for the antioxidant-mediated cancer therapy mechanism. This mechanism involves scavenging free radicals and reducing oxidative stress in cancerous cells (Childers et al. 1995). The second mechanism engaged in cancer treatment is inhibition of activity by phytochemicals. The inhibition mechanism involves reduction of cell proliferation, oncogene expression, and signal transduction pathways (Singh et al. 2006). Next is induction activity exhibited by plant extracts, such as cranberry extract in breast cancer, glutathione in colon cancer (Odom et al. 2009), quercetin in cervical cancer, etc.

Cancer therapy using phytochemicals can also be achieved by enzyme inhibition and enzyme induction mechanisms. The enzyme inhibition mechanism involves phase I enzyme, cyclooxygenase-2 inhibition, inducible nitric oxide synthase inhibition, or xanthine oxidase inhibition (Rajendran et al. 2011). The enzyme induction mechanism involves phase II enzyme induction, glutathione peroxidase induction, catalase induction, and superoxide dismutase induction (Hayes et al. 2008).

Finally, some phytochemicals show different regulation activity to treat cancerous cells. Regulation activity involves regulation of steroid hormone metabolism (Mandlekar et al. 2006), regulation of oestrogen metabolism (Clarke et al. 1996), microRNA (miRNA) regulation (Tilghman et al. 2013), or regulation of activator signal transduction pathway (Frigo et al. 2002).

15.7 CONCLUSION AND FUTURE PROSPECTS

Several conventional treatments are available for cancer therapy, but they all come with severe side effects and symptoms (kidney failure, anaemia, fertility issues,

gastrointestinal disorders, etc.). The current major challenges are the increasing incidence of cancer cases, the high expense of conventional treatments, a number of limitations to the traditional remedy, and the high toxicity of current anticancer medicines. Therefore, the immediate objective is to propose and develop a substitute, eco-friendly, biocompatible and more affordable approach through a greener route. Phytochemicals obtained from medicinal plants provide a capable and valuable research field with much promise. Anticancer medicinal plants act as natural immune boosters, modulating the immune response in several disease treatments. The more eco-friendly and biocompatible nature of phytochemicals have elevated the effectiveness of these phytochemicals in cancer management. However, detailed studies are still required to gain more insights into these phytochemicals to estimate their potential functions, and their toxicological and particular genotoxic profiles against different categories of cancer.

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16 Potential of Medicinal Plants as Immunity Booster against COVID-19

Saumya Pandey

CONTENTS

16.1 Introduction	455
16.2 SARS-CoV-2: Structural Assembly and Mechanism of Action in Human Host Cell	456
16.3 Medicinal Plants as Immunity Boosters Against COVID-19.....	457
16.3.1 <i>Ocimum sanctum</i> L. (Tulsi, Holy Basil).....	459
16.3.2 <i>Piper nigrum</i> L. (Kaali Mirch, Black Pepper).....	462
16.3.3 <i>Zingiber officinale</i> Roscoe (Sunthi, Ginger).....	462
16.3.4 <i>Cinnamomum verum</i> J. Presl (Dalchini, Cinnamon)	463
16.3.5 <i>Tinospora cordifolia</i> (Willd.) Miers (Moonseed, Giloe).....	463
16.3.6 <i>Panax quinquefolius</i> L. (Ginseng).....	464
16.3.7 <i>Glycyrrhiza glabra</i> L. (Licorice, Sweet Wood).....	464
16.3.8 <i>Curcuma longa</i> L. (Haldi, Turmeric)	465
16.4 Immunological Responses Associated with Interaction Between Medicinal Plants and SARS-CoV-2.....	465
16.5 Conclusion	467
References.....	467

16.1 INTRODUCTION

Over the past twenty years, the world has witnessed several pandemic/epidemic viral diseases, such as Ebola virus in 2014–16, Middle East Respiratory Syndrome (MERS) in 2012, Severe Acute Respiratory Syndrome (SARS-CoV) in 2002–2003, and many more, which have represented serious issues to public health. The new contagious virus, named SARS-CoV-2 virus by ICTV (International Committee on Taxonomy of Viruses), was first reported on December 31, 2019 to the World Health Organization (WHO) office in China and was later declared as pandemic when the

number of COVID-19 cases outside China had increased 13-fold, involving more than 114 countries, on March 11, 2020 (Cascella et al. 2020).

According to WHO, COVID-19 has caused over one million deaths globally, with the maximum number reported from the USA(55%), followed by Europe (23%) (Sousa et al. 2020). Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is an infectious disease transmitted by direct contact, droplet, airborne, fomite, faecal-oral, bloodborne, mother-to-child, and animal-to-human (Lei et al. 2020). Since, its first appearance in late December 2019 in Wuhan (China), this disease has disrupted the living standard of billions of people, caused economic losses, and deaths globally. This disease leads to mild to severe pneumonia, septic shock, dyspnea, and multiple organ dysfunctions (MOD)/failure (Zaim et al. 2020). The fatality rates were reported to be higher among the elderly patients and the patients with pre-existing comorbidities, for example, chronic respiratory disease, hypertension, oncological disease, cardiovascular disease, and diabetes (Casmella et al. 2020).

Until now, precautionary measures to prevent community transmission and some therapeutic approaches for the treatment of infected patients such as nucleoside analogues, remdesivir, anti-inflammatory drugs, or lopinavir/ritonavir, are the best available weapons to fight against this fatal disease (Vellingiri et al. 2020). WHO has suggested several precautionary measures, such as practising social distancing, respiratory etiquettes, and hand hygiene, identification and isolation of patients at an early stage, environmental cleaning and disinfection, and conveying correct information to the public to prevent transmission of disease (WHO 2020).

Several reports suggest a higher mortality rate among patients who are immunocompromised and those with preexisting comorbidities; the factors that aid in boosting the immunity could therefore help to combat severe symptoms of COVID-19 infection (Zheng et al. 2018; Felsenstein et al. 2020). Medicinal plants have been used by mankind for thousands of years, either in a pure form or as crude extracts, to boost immunity and treat various diseases. Around 45,000 species of plants have been used in traditional medicine systems in India. The various studies have suggested that the immune-stimulating properties of medicinal plants are mainly due to the presence of a wide range of phytochemicals, such as flavonoids, lignans, terpenoids, polyphenols, carotenoids, curcumins, sulphides, phthalides, plants sterols, and saponins (Kumar et al. 2012; Benarba and Pandiella 2020). The broad range of medicinal plants possess antiviral and immune booster properties and hence can be potentially exploited for the prevention and treatment of COVID-19 infection. Recently, the Ministry of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homoeopathy) of the Government of India has recommended the combined use of Kadha and Golden Milk herbal preparations for boosting the immune system against severe COVID-19 infection (Khanal et al. 2020).

16.2 SARS-CoV-2: STRUCTURAL ASSEMBLY AND MECHANISM OF ACTION IN HUMAN HOST CELL

The SARS-CoV-2, a member of family Coronaviridae, is an enveloped single-stranded RNA (ssRNA) virus containing a positive-sense RNA genome (27–32 Kb)

with poly-A tail and cap structure at 3'- and 5'- ends, respectively (Chen 2020). SARS-CoV-2 is made up of four important structural proteins, namely nucleocapsid protein (N), membrane protein (M), envelope protein (E), and spike protein (S) necessary for the regulation of its structure and function (Schoeman and Fielding 2019). Based on sequence analysis, SARS-CoV-2 is classified in the genus β -coronavirus of CoVs (Cascella et al. 2020). The genome sequence of SARS-CoV-2 has shown 82% similarity with the genome of human SARS-CoV (Chan et al. 2020).

As SARS-CoV and SARS-CoV-2 share similarities between sequences of the receptor-binding domain (RBD) and the receptor-binding motif (RBM), they probably have similar mechanisms for viral infection of the human cell (Yin and Wunderink 2018; Tai et al. 2020; Zhang et al. 2020). The receptor-binding motif of SARS-CoV-2 causes the viral S protein to attach to and fuse with the ACE2 receptor of the human cell, especially in the respiratory epithelium and alveoli of the lungs (Liu et al. 2020). Attachment to the receptor subsequently activates proteases that act on the viral S protein and cleave it into two domains, S1 and S2. The S1 domain remains attached to the ACE2 receptor of the host cell whereas the S2 domain undergoes a conformational change and internalizes the membrane, followed by membrane fusion between the ACE2 receptor and the viral subunit leading to viral RNA entry into the host cell. The entry into the host cell is followed by RNA replication and cleaving and shedding of ACE2 into the extramembrane space by ADAM17 (Vellingiri et al. 2020). ACE2 shedding is possibly responsible for the increased pulmonary vascular permeability and alveolar injury observed during viral infection (Le and Clercq 2020).

16.3 MEDICINAL PLANTS AS IMMUNITY BOOSTERS AGAINST COVID-19

Medicinal plants have played a significant role in addressing global healthcare demands from ancient times because of the presence of a diverse range of secondary plant metabolites with the ability to prevent and treat infectious diseases. The traditional system of medicines, such as the Indian traditional medicinal systems (including Ayurveda, Siddha, Unani, Yoga, Naturopathy, and Homoeopathy), the traditional Chinese medicinal system, and Kampo (the traditional Japanese medicinal system), is primarily dependent upon plant, animal, and mineral products, and has been practised for centuries, if not millenia, to cure different ailments in humans (Vaidya et al. 2007; Mukherjee et al. 2017). The precise application of plant resources for particular conditions requires traditional knowledge about plants and their usage (Petrovska 2012). According to a recent WHO report, nearly 80% of the populations from underdeveloped countries still rely on traditional medicines (WHO 2019). Out of 21,000 medicinal plants listed by the WHO as having therapeutic potential, 2,500 species of plants have been reported from India (Pundarikakshudu and Kanaki 2019; Shukla et al. 2019). Despite extensive therapeutic potential, medicinal plants are still overlooked by researchers for the development of modern drugs (Yuan et al. 2016). The desired pharmacological effect needed to cure or prevent specific diseases can be obtained from phytochemicals purified as single constituents or in combination with other phytochemical compounds, as a herbal preparation (Parasuraman et al. 2014) derived from one or several plant species.

The plant-based medicines have been proved to be effective in controlling the adverse effects of infection in the case of the earlier SARS pandemic caused by SARS-CoV (Wen et al. 2011; Verma et al. 2020). As SARS-CoV2 (Coronavirus) shares homology with SARS-CoV, the medicinal plants can be recommended as a potential source to address the existing health crises (Aanouz et al. 2020; Wahedi et al. 2020). The medicinal plants have proved to be efficient in controlling and curing viral respiratory infections because they can manage the immune system by modulating inflammation and stimulating immunity.

Presently, in the absence of an established regimen against COVID-19, the whole world is facing immense uncertainty in the management of this pandemic disease. The therapeutic strategies which can be used globally against COVID-19 include: (1) an allopathic system: presently broad-spectrum antibiotics, including hydroxychloroquine, lopinavir, retinovir, and remdesivir, are used but they pose many adverse side effects; (2) vaccination: nearly 13 different vaccines (For Example: Pfizer/BioNtech, SII/Covishield, Janssen/Ad26.COVS.2.S, AstraZeneca/Oxford) have been administered to large number of peoples through mass vaccination programme; (3) herd immunity: can be achieved either by vaccinating a large number of people against the disease or when a high proportion of the population contracts the disease and develops natural immunity; (4) immunity boosting: enhancing the internal power of the immune system to minimize symptoms of COVID-19 infections (Ponnam and Akondi 2020). Several natural remedies have been suggested as immune boosters from the ancient medicine systems, most importantly the use of natural herbs to strengthen the natural immunity of the individual.

Considering the present pandemic situation, the Ministry of AYUSH, India, has recommended a holistic approach for the treatment and prevention of COVID-19 that includes dietary management, symptom management, lifestyle management, and prophylactic measures to boost immunity. The cost-effective decoction known as 'Ayush Kwath', 'Ayush Kudineer', or 'Ayush Joshanda' has been recommended by AYUSH, and it comprises of five medicinal herbs, namely *Ocimum tenuiflorum*, *Cinnamomum verum*, *Piper nigrum*, *Zingiber officinale*, and *Vitis vinifera* (AYUSH 2020).

Traditional Chinese medicine system practitioners have also developed several formulae containing combinations of natural herbs based on the symptoms of COVID-19 infections (Zhao et al. 2020). Among various Chinese formulation, lung cleansing and detoxifying decoction (LCDD) is one of the clinically proven and most commonly consumed formulations, comprising twenty-one medicinal herbs, namely *Ephedra sinica*, *Cinnamomum cassia*, *Alisma plantago-aquatica*, *Atractylodes macrocephala*, *Bupleurum chinense*, *Scutellaria baicalensis*, *Pinellia ternata*, *Aster tataricus*, *Tussilago farfara*, *Iris domestica*, *Wolfiporia extensa*, and the mushroom *Polyporus umbellatus*, as well as wild ginger, Chinese yam, Korean mint, bitter orange, licorice, ansu apricot, ginger, and orange peel. The clinical trial with LCDD treatment in 1262 COVID-19 patients showed a 99.28% recovery rate; furthermore, the severity of infection did not increase in those patients with mild symptoms of infection when the treatment started (Weng 2020).

Similarly, the Government of Tamil Nadu has taken initiatives to supply the Nilavembu Kudineer Chooranam (NKC) decoction to healthcare centers to control

morbidity levels during an outbreak of viral infectious diseases (Ramanathan et al., 2019). NKC is comprised of nine medicinal plants: *Andrographis paniculata*, *Vetiveria zizanioides*, *Plectranthus vettiveroides*, *Santalum album*, *Trichosanthes dioica*, *Cyperus rotundus*, *Zingiber officinale*, *Piper nigrum*, and *Mollugo cerviana*. NKC has shown antiviral, antipyretic, antibacterial, anti-ulcer, antioxidant, and analgesic properties, etc. (Kavinilavan et al. 2017; Jain et al. 2020). NKC also acts as an immunostimulator and an immunomodulator, thus playing important role in preventing infection symptoms by enhancing the immune system and modulating the defense response of the host (Nakkeeran et al. 2016; Kamalarajan et al. 2019).

El-Alami et al. (2020) has reported *Allium sativum*, *Olea europaea*, *Allium cepa*, *Zingiber officinale*, *Thymus maroccanus*, *Eucalyptus globulus*, *Foeniculum vulgare*, *Curcuma xanthorrhiza*, *Phoenix dactylifera*, *Rosmarinus officinalis*, *Thymus satureioides*, *Mentha pulegium*, and *Pimpinella anisum* to be the most widely used medicinal plants for the prevention of COVID-19 infection in Morocco. The presence of a diverse range of bioactive compounds, such as flavonoids, tannins, glycosides, lignans, carotenoids, essential oils, etc., results in positive effects on respiratory and circulatory functions. The efficiency of some selected medicinal plants in boosting the immune response of the human body to prevent COVID-19 infection is given in Table 16.1.

16.3.1 *OCIMUM SANCTUM* L. (TULSI, HOLY BASIL)

Tulsi is known as the ‘Elixir of Life’ and plays a significant role in boosting immunity and thus helps the human body to fight against a wide range of bacteria and viruses. It has been widely used in treating various health ailments, such as bronchitis, pyrexia, asthma, genito-urinary disorders, fever, microbial and parasitic infections, rheumatism, and anxiety because of its analgesic, antidiarrhoeal, antimicrobial, renoprotective, hepatoprotective, antipyretic, cardioprotective, antioxidant, immunomodulatory, and anti-inflammatory properties (Vasudevan et al. 1999; Cohen, 2014).

The immune-boosting property of this herb is due to the presence of various bioactive compounds, such as eugenol, cirsilineol, carnosol, ursolic acid, rosmarinic acid, apigenin, and cirsimaritin, which play a significant role in major defence mechanisms, such as suppressing NF- κ B classical pathways, down-regulating interleukin-1 beta (IL-1 β) and antigen-specific antibodies, up-regulating interleukin 2 (IL-2), interferon gamma (IFN- γ) and tumour necrosis factor alpha (TNF- α), enhancing Sheep Red Blood Cells agglutinin titres and haemoglobin concentration, and decreasing cyclooxygenase-2 and lipoxigenase-5 enzyme activities (Lo et al. 2002). Also, tulsi acts as an efficient immunomodulator as it aids in increasing the percentage of T helper and natural killer (NK) cells and enhances the phagocytic index and antibody titre (Mondal 2010). Mondal et al. (2011) reported an increase in the percentage of T helper cells and NK cells after four weeks in twenty-four healthy subjects given 300 mg ethanolic extract of tulsi. Also, the role of seven bioactive compounds present in tulsi has been shown to inhibit SARS-CoV replication by a molecular docking study. As SARS-CoV shares several clinical and genetic

TABLE 16.1
List of Medicinal Plants Commonly Used as Immunity Boosters to Prevent COVID-19 Infection

Common Name	Scientific Name	Parts Used	Phytoconstituents	Pharmacological Activities	References
Amla	<i>Embllica officinalis</i> Gaertn.	Fruit	Galic acid, ellagic acid, emblicanin A, B, phyllembin, quercetin, and ascorbic acid	Anti-inflammatory, antimutagenic, immunomodulatory, analgesic, antitussive, nephron- and neuroprotective, chemopreventive, anticancer, antioxidant	Suja et al. 2009
Baheda	<i>Terminalia bellirica</i> (Gaertn.) Roxb.	Dried fruit	Tain, terminalignan, thammilignan, arjungenin, belleric acid, bellericoside, camnogeno	Antiviral, anti-inflammatory, antibacterial, antifungal, antidiarrhoeal, analgesic, antimalarial, antioxidant, anticancer	Cock 2015
Bala	<i>Sida cordifolia</i> L.	Leaves	Asparagine, quinazoline, ephedrine, choline, betaine, rutin, β -sitosterol, hypaphorine, vasicinone, vasicinol	Analgesic, antispasmodic, anti-inflammatory, hypoglycaemic, hepatoprotective	Sivapalan 2015
Chandrasoor	<i>Lepidium sativum</i> L.	Leaves	Sinapic acid, sinapin, lepidine	Anti-asthmatic, anti-inflammatory, haemagglutinating	Mali et al. 2007
Clove	<i>Syzygium aromaticum</i> (L.) Merr. & L.M. Perry	Flower bud	Eugenol, thymol, caryophyllene	Anti-inflammatory, antiviral, antitumour, antibacterial, antifungal	Bowmik et al. 2012
Draksa	<i>Vitis vinifera</i> L.	Fruits	flavonoids, polyphenols, anthocyanins, proanthocyanidins, procyanidines, esveratrol.	antioxidative, anti-inflammatory, antimicrobial, cardioprotective, hepatoprotective, neuroprotective	Nassiri-Asl and Hosseinzadeh 2009
Fenugreek	<i>Trigonella foenum-graecum</i> L.	Seeds and leaves	trigonolline, cholin, gentianine, diosgenin, gitogenin, yamogenin	Anti-inflammatory, antimicrobial, antidiabetic, antihyperlipidaemic, anti-obesity, anticancer, antioxidant	Yadav and Baquer 2014

(Continued)

TABLE 16.1 (CONTINUED)
List of Medicinal Plants Commonly Used as Immunity Boosters to Prevent COVID-19 Infection

Common Name	Scientific Name	Parts Used	Phytoconstituents	Pharmacological Activities	References
Kalmegh	<i>Andrographis paniculata</i> (Burm. F.) Nees.	Leaves	andrographolide, neoandrographolide, deoxyandrographolide	Immunomodulatory, antiviral, immune enhancement, antioxidant, hepatoprotective, anti-HIV	Verma et al. 2019
Kalonji	<i>Nigella sativa</i> L.	Seed	Nigellicine, nigellimine, pinene, <i>p</i> -cymene, carvene	Immunopotentiating, immunomodulatory, hypoglycaemic, anticancer, antimicrobial, anti-inflammatory, anti-ulcer	Kooti et al. 2016
Nagkesar	<i>Mesua ferrea</i> L.	Bark and root	Mesulol, mesuagin, mameisin, 4-alkylcoumarins feruols A and B, guttiferol, ferraxanthone, β -sitosterol.	Anti-inflammatory, immunostimulant, antioxidant, analgesic, hepatoprotective	Chahar et al. 2013
Nutmeg	<i>Myristica fragrans</i> Houtt.	Seeds	Trimyristin, myristic acid, myristicin, safrole, elimicin	Anti-inflammatory, antioxidant, anticonvulsant, analgesic, antidiabetic, antibacterial, antifungal	Asgarpanah and Kazemivash 2012
Paan	<i>Piper betle</i> L.	Leaves	Hydroxychavicol, chavibetol, estragole, eugenol, caryophyllene	Anti-inflammatory, antimicrobial, antioxidant, anticancer, antidiabetic	Madhumita et al. 2020
Sandalwood	<i>Santalum album</i> L.	Oil	α -, β -santalol, bergamotols, curcumenes, β -bisabolene	Anti-inflammatory, antiviral, antifungal, antibacterial, hepatoprotective, antipyretic, cardioprotective	Kumar et al. 2015
Satavari	<i>Asparagus racemosus</i> Willd.	Dried root	Shatavarin, aspariginins, curillins, asparosides, curillosides	Anti-inflammatory, cardioprotective, antistress, antidepressant activity	Hasan et al. 2016
Wild Carrot	<i>Daucus maritimus</i> Lam.	Seeds	Daucucarotol, β -bisabolene, <i>trans</i> - β -caryophyllene, <i>trans</i> - α -asarone, β -selinene, β -bisabolene, bicyclogermacrene	Antiviral, anti-inflammatory, antidiabetic, nephroprotective, hepatoprotective, antioxidant	Al-Snafi 2017

similarities with SARS-CoV2, these bioactive compounds could significantly inhibit SARS-CoV-2 replication by blocking ACE-2 receptors (Khaerunnisa et al. 2020).

16.3.2 *PIPER NIGRUM* L. (KAALI MIRCH, BLACK PEPPER)

Also known as the 'King of Spices', *P. nigrum* contains more than 600 different bioactive compounds, such as lignans, terpenes, alkaloids, neolignans, etc. (Damanhour et al. 2014). Due to the presence of such a vast range of phytoconstituents, it has antioxidant, analgesic, antiplatelet, immunomodulatory, antipyretic, antihypertensive, anti-asthmatic, anticarcinogenic, antispasmodic, antimicrobial, antimutagenic, anti-thyroid, anti-ulcer, antidepressant, hepatoprotective, and antidiarrhoeal properties (Nahak et al. 2011; Srivastava et al. 2017). The key alkaloid components, like piperine and piperamides, enhance the defence mechanism of the human body by regulating the balance between cytokines and T cells, inhibiting the expressions of GATA3, IL-4, IL-6, IL β , I-17A, TNF- α , ROR γ T, and increasing the activation of macrophages and the proliferation of T and B cells (Damanhour et al. 2014; Balkrishna et al. 2020). Furthermore, it can also inhibit mast cell activation and allergic responses, alleviate fibrotic scarring and inflammatory cell infiltration, suppress the release of histamine and antibodies IgE, anti-OVA IgG1 in serum, inhibit P glycoprotein and CYP3A4 functions, and inhibit NF-kB, CREB, ATF-2, c-Fos and PKCa/ERK pathways (Zhai et al. 2016; Bui et al. 2019).

16.3.3 *ZINGIBER OFFICINALE* ROSCOE (SUNTHI, GINGER)

Ginger belongs to the family Zingiberaceae and has potential immune-boosting and anti-inflammatory characteristics that enhance the immune responses and metabolic activities of the human body and thus provide a shield against infectious diseases. Its chemical constituents include gingerdione, 6-gingediol, germacrene, zingiberene, 6-shogaol, methyl-6-shogaol, β -sitosterol, nevirapine, etc., which play roles in the inhibition of viral replication, with β -sitosterol as the most potent inhibitor of the reverse transcriptase enzyme (Kharisma et al. 2018). Moreover, the main bioactive components of ginger, like the gingerols and shogaols, enhance fibrinolysis, inhibit pro-inflammatory cytokines (IL-1, TNF- α , IL-8), inhibit leukotriene and prostaglandin biosynthesis, and inhibit cyclooxygenase and lipoxygenase activities. A ginger preparation also inhibits the anti-influenza cytokine TNF- α , inhibits platelet aggregation and thromboxane synthetase, down-regulates expression of iNOS and COX-2 genes, and reduces the production of age-related oxidative stress markers (Habib et al. 2008; Mahluji et al. 2013).

Mahassni et al. (2019) has studied the efficacy of ginger extract in enhancing humoral immunity among male smokers and non-smokers and reported a significant increase in the IgM concentration and eosinophil count in non-smokers as compared with smokers, whereas the lymphocyte count and haemoglobin concentration in smokers were found to be higher than in non-smokers. Thus, ginger has greater potential to enhance humoral immunity in non-smokers than in smokers. Also, fresh ginger has greater effectiveness in reducing viral infection as compared with dried

ginger. Bhat et al. (2010) showed that both the alcoholic extract as well as the crude extract of ginger can increase the immune response. The alcoholic extract of ginger has caused increased phagocytic activity by macrophages, whereas treatment with the crude extract has shown enhanced humoral and cell-mediated immunity in mice. The inhibitory potential of fresh ginger against the human respiratory syncytical virus was reported to be higher than that of dried ginger. Fresh ginger inhibits viral binding and internalization processes as well as stimulating mucosal cells to secrete IFN- β , thus promoting a reduction in viral infection (Srivastava et al. 2020).

16.3.4 CINNAMOMUM VERUM J. PRESL (DALCHINI, CINNAMON)

Cinnamon belongs to the family Lauraceae and contains various bioactive compounds, such as benzaldehyde, cuminaldehyde, cinnamaldehyde, and terpenes (Valizadeh et al. 2015). Because of its immunomodulatory and immune-boosting effects, it has been used in preventing and curing various ailments. A study showed that both high (100 mg/kg bodyweight) and low doses (10 mg/kg) can enhance the immune response, whereas the low dose increased only humoral immunity while the high dose enhances both cell-mediated as well as humoral immunity (Niphade et al. 2009). Kim et al. (2010) have demonstrated that cinnamaldehyde can inhibit the expression of phosphoinositide 3-kinase (PI3K), phosphoinositide-dependent-kinase-1 (PDK1), and nuclear factor kappa β (NF- κ β) and alleviates the host innate immune responses. Further, cinnamaldehyde brings about activation of CD29 and CD43 which, in turn, block cell migration and induce cell–cell adhesion apart from cell–fibronectin adhesion. Also, cinnamaldehyde suppresses the production of NO (nitric oxide) as well as up-regulating the pattern recognition receptors (PRRs) TLR2 and CR3 and levels of co-stimulatory molecules CD69 and CD80 expressed on the surface of cells. Chemicals such as cinnamaldehyde, cinnamophilin, etc. found in cinnamon bark have shown anti-atherosclerotic, anticoagulative, and thromboxane A2 receptor antagonist properties, preventing unnecessary platelet clumping and atherosclerotic cardiovascular diseases (Tsui et al. 2018).

The potency of cinnamon bark as an immunomodulator has been shown by its ability to down-regulate the IFN- γ expression in activated T cells with no change in IL-2 production through inhibiting the activation of p38, JNK, ERK1/2, and STAT4, but not I κ Ba degradation or STAT6 (Lee et al. 2011). The use of cinnamon is safe for daily dietary consumption and medicinal use.

16.3.5 TINOSPORA CORDIFOLIA (WILLD.) MIERS (MOONSEED, GILOE)

Giloe belongs to the family Menispermaceae and has been used in many traditional Ayurvedic medicines for therapies against several diseases, such as allergy, urinary disorder, rheumatism, leprosy, diabetes, etc. (Sonkamble and Kamble 2015). Several important bioactive compounds have been reported from parts of *Tinospora*, including steroids, glycosides, alkaloids, aliphatics, phenolics, diterpenoids, sesquiterpenoids, and flavonoids, which act as immunomodulators and support the immune system by increasing resistance of the body against various

infections (Singh et al. 2003). Giloe shows antitoxic, anti-osporotic, anti-HIV, wound healing, antimicrobial, anti-allergic, antioxidant, anti-inflammatory, and antidiabetic properties (Saha and Ghosh 2012; Sharma et al. 2019). An *in-silico* study, performed using molecular docking, has demonstrated that, among the phytochemicals in *Tinospora cordifolia*, berberine can serve as a potential inhibitor in regulating 3CL^{pro} protein function, subsequently controlling viral replication (Chowdhary 2020). The herbal formulations containing a combination of giloe, tulsi, ginger, and kali mirch has been proven effective for preventing and curing COVID-19 symptoms (Srivastava et al. 2020).

16.3.6 *PANAX QUINQUEFOLIUS* L. (GINSENG)

Ginseng belongs to the family Araliaceae and has shown a broad range of biological activities including antimicrobial, antidiabetic, anti-inflammatory, anticardiovascular, antioxidative, T cell-mediated immune reaction, and anticancer properties. It also serves as an immunomodulator by playing an important role in activating natural killer cells, antagonistic reactions for immunosuppressive mediators, and triggering innate immunity (Im et al. 2016; Ratan et al. 2020). It is a source of various bioactive compounds, such as ginsenosides, polysaccharides, polyacetylenes, phytosterols, and essential oils (Wang et al. 2015). Several studies have shown the therapeutic potential of ginseng in treating diverse diseases, such as immune system disorder, neuronal disease, microbial infections, cancer, and cardiovascular disease. Ginseng has also been shown to possess protective activities against different viral infections, such as the human herpes virus, immune deficiency virus, rhinovirus, influenza virus, enterovirus, rotavirus, coxsackievirus, and norovirus (Iqbal and Rhee 2020). The pharmacological activities and stability of heat-processed ginseng have been reported to be higher than those of fresh ginseng (Im et al. 2016). The consumption of milk enriched with ginseng (150–300 ml) has been suggested because of its potential health benefit in boosting the immunity of the body (Lee et al. 2014).

16.3.7 *GLYCYRRHIZA GLABRA* L. (LICORICE, SWEET WOOD)

Licorice belongs to the family Fabaceae and exhibits a broad range of biological properties, including antimicrobial, anti-inflammatory, antioxidant anti-ulcer, antidiuretic, antidiabetic and antitussive activities (Sharma et al. 2018). Various bioactive compounds, such as glycyrrhizin, glabrin A and B, isoflavones, and glycyrrhetic acid, are present, that have shown various pharmacological activities (Ozturk et al. 2017). Several studies have suggested the use of glycyrrhizin for the treatment of SARS infection because of its antiviral properties (Bailly et al. 2020; Chen et al. 2020).

Cinatl et al. (2003) has reported on the clinical trials of various chemical compounds present in *Glycyrrhiza* against two clinical coronavirus isolates; out of all the compounds tested, glycyrrhizin was found to be most effective in inhibiting virus replication, and was found to be effective against various viruses, including hepatitis A, B, C, varicella-zoster, HIV, herpes simplex type-1, and cytomegalovirus (Asl and

Hosseinzadeh 2008). Furthermore, the bioactive compounds glyasperin A and glycyrrhizic acid have been used to produce nanomembranes by electrospinning which can be used as wound dressing materials, masks, gloves and against skin infection. Glycyrrhizic acid binds to the pocket of the spike glycoprotein and prohibits the entry of the virus into the host cell, whereas glyasperin A showed higher affinity with Nsp15 endoribonuclease and affects coronavirus infection (Sinha et al. 2020).

16.3.8 *CURCUMA LONGA L.* (HALDI, TURMERIC)

Turmeric belongs to the family Zingiberaceae and its rhizome is used for medicinal purposes to treat a number of severe diseases. Turmeric has been used as a natural cleanser of the respiratory tract and has been employed for curing congestion, cough, throat infection, and bronchial asthma. It has anti-inflammatory, antiviral, antifungal, and antibacterial properties, and helps to boost the immune system to fight against infection (Zorofchian et al. 2014; Praditya et al. 2019). Curcumin, ar-turmerone, and zingiberene are the main bioactive constituents that show antiviral activities against a diverse range of viruses, such as dengue virus, hepatitis B virus, Zika virus (ZIKV), and chikungunya virus (Hesari et al. 2018; Nabila et al. 2020). Also, the consumption of golden milk containing one-half of a teaspoon of turmeric in 150 ml hot milk has been recommended by the Ministry of AYUSH to boost the immune system (AYUSH 2020).

16.4 IMMUNOLOGICAL RESPONSES ASSOCIATED WITH INTERACTION BETWEEN MEDICINAL PLANTS AND SARS-CoV-2

SARS-CoV-2 interacts with immune cells and subsequently affects the patient's immune system. Thus, to develop immunotherapies for COVID-19, the most crucial prerequisite is to build up a better understanding of the immunopathology of chronic lung conditions in the infected person. The immunological abnormalities evident in patients infected with COVID-19 consist of neutrophilia, increased levels of inflammatory markers in the serum, monocyte/macrophage dysfunction, and lymphopaenia, which affect CD4+ T cells, CD8+ T cells, natural killer cells, and B cells (Figure 16.1). Yang et al. (2005) reported that the ectopic expression of the SARS-CoV E protein induces T cell apoptosis and contributes to SARS-CoV-induced lymphopaenia. The interaction between BH3-like regions (Bcl-2 homology domain 3) located in the C-terminal cytosolic domain of the SARS-CoV E protein and the cellular oncogene Bcl-xL (anti-apoptotic protein) primarily causes apoptosis of T cell lymphocytes. Similar to the SARS-CoV envelope protein, conserved Bcl-2 Homology 3 (BH3)-like motifs in the C-terminal region, necessary for binding to Bcl-xL, protein has been reported in the SARS-CoV-2 envelope (E) protein (Navratil et al. 2020).

The symptoms of the disease may be associated with the functional characteristics of IgG antibodies against glycoproteins of the virus envelope. These functional

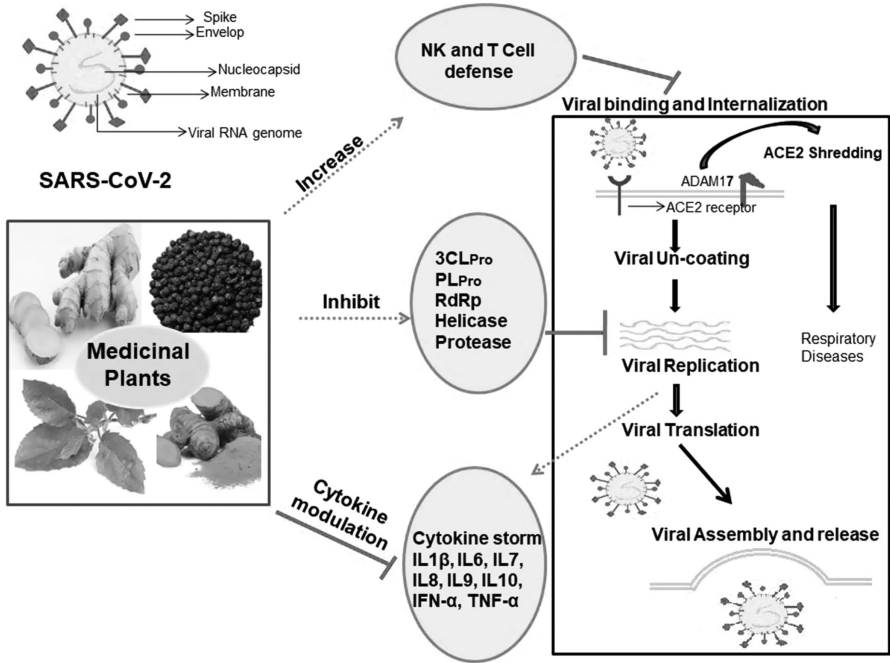


FIGURE 16.1 Immunity-boosting potential of medicinal plants against SARS-CoV-2 pathogenesis.

characteristics of IgG antibodies leads not only to neutralization of the virus and other antibody defensive functions but might also augment the immune cell infection. A study on dengue virus suggests that the undesirable action of IgG antibodies is associated with the alteration in glycosylation profile of the Fc region of IgG, leading to antibody-dependent enhancement (ADE) of virus uptake *via* macrophages, eventually causing greater secretion of pro-inflammatory cytokines and chemokines (Bournazos et al. 2020). Kruse (2020) reported that the ACE2 protein combines with the Fc domain of IgG antibodies and thus might play an important role in the treatment of COVID-19.

Several studies on medicinal plants have suggested their role in enhancing natural killer (NK) cell activity, increasing the secretions of IL-10 and INF- γ , inhibition of ATF-2, IL-4, IL-6, GATA3, down-regulation of Th-17 and Th2-related cytokines, etc. Hoffmann et al. (2020) established that the SARS-CoV-2 enters human cells *via* the ACE2 receptor. Various medicinal plants, such as *Berberis integerrima*, *Crataegus laevigata*, *Onopordum acanthium*, and *Quercus infectoria*, have shown ACE2 inhibition, of which *Quercus infectoria* was found to be the most active (94%) in terms of inhibition owing to its higher phenolic content and increased antioxidant potential (Sharifi et al. 2013).

Khanal et al. (2020) studied the AYUSH herbal preparation ‘Kwath’ and reported that bioactive compounds present in the formulation boost the immune system by

modulating several signaling pathways such as HIF-1, p53, PI3K-Akt, MAPK, cAMP, Ras, Wnt, NF-kappa- β , IL-17, TNF, and cGMP-PKG. Similarly, *Andrographis paniculata* has been reported to suppress the enhanced level of NLRP3, CASP-1, and IL-1 β molecules that play a significant role in the pathogenicity of SARS-CoV as well as in SARS-CoV-2 (Liu et al. 2020). In another study, the medicinal plant *Salacia oblonga* was found to significantly suppress the angiotensin II receptor type 1 (AT1) signal that is associated with lung damage (He et al. 2011). Thus, the immune-boosting and immunomodulatory efficacies of the medicinal plants in 'Kwath' facilitate the prevention of infection as well as ameliorating the symptoms of COVID-19 by increasing the innate immunity of an individual.

16.5 CONCLUSION

Medicinal plants with different pharmacological activities have been used for ages as herbal preparations for the treatment of viral infection and enhancement of host immune response. The outbreak of the COVID-19 disease has caused a severe threat to public health and the global economy. As the SARS-CoV-2 can escape innate immune response, an individual with weak immunity can develop a severe infection. Also, the unavailability of approved medication to date has intensified the pandemic situation. Precautionary measures against virus infection, such as social distancing, self-quarantine, respiratory etiquettes, etc., have been recommended by WHO to avoid human contact and thus minimize the risk of transmission and infection. Appropriate medicinal plants can be used as a promising resource for managing this pandemic situation owing to their capacity to boost the immune response of the human body and fight against viral infection. This pandemic situation has raised concern about the healthcare system and greater investment in research into infectious diseases is needed to avoid such pandemic situations in the future. As the pathways involved in decreasing infection load by bioactive compounds from medicinal plants are still not clearly understood, further investigation is required for effective utilization of medicinal plants in the treatment of such diseases.

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Index

Note: Locators in *italics* represent figures and **bold** indicate tables in the text.

- Abelmoschus sp.
 - A. manihot*, 32
 - A. moschatus*, 29
- Abroma augustum*, 29
- Abrus precatorius*, 344
- Abutilon sp.
 - A. angulatum*, 28
 - A. indicum*, 40
- Acacia sp.
 - A. concinna*, 344
 - A. eriloba*, 28
 - A. farnesiana*, 29
 - A. nilotica*, 350
 - A. xanthophloea*, 31
- Acalypha sp.
 - A. fimbriata*, 18, 30
 - A. hispida*, 29
 - A. indica*, 31
- Acanthus montanus*, 18, 30
- ACE2 receptors, *see* Angiotensin-converting enzyme 2 receptors
- Achillea millefolium*, 18, 20, 107, 234
- Achyranthes sp.
 - A. aspera*, 29, 31
 - A. bidentata*, 32
- Acinetobacter baumannii*, 15
- Aconitum gammiei*, 32
- Actinidia eriantha*, 232–234
- ADE, *see* Antibody-dependent enhancement
- Adenia sp.
 - A. gummifera*, 29
 - A. venenata*, 31
- Adhatoda vasica*, 20, 31
- Aegle marmelos*, 20, 29, 60, 274, 274
- Aethiopinone, structure of, 38
- African locust bean, 204
- African medicinal plants for strong immune system, 17–18, 173
 - commercial formulations, 186
 - immunomodulatory agents from plants, 174–175
 - mechanisms of action of, 175
 - medicinal plants, 175, **176–185**, 186
- Agave sp.
 - A. americana*, 31
 - A. sisalana*, 29
- Aged garlic extract (AGE), 367
- Agrimonia pilosa*, 59
- Albizia anthelmintica*, 166
- Alchornea cordifolia*, 30
- Alisma plantago-aquatica*, 458
- Alkaloids, 4, 35, 41
 - structure of, 36
- Allicin, 348–349, 367
- Allium sp.
 - A. cepa*, 3, 31, 459
 - A. fistulosum*, 65
 - A. giganteum*, 40
 - A. sativum*, 3, 30, 31, 230, 308, 346, 365–369, 402–403, 432–437, 459
- Allyl-L-cysteine sulphoxides, 348
- Aloe sp.
 - A. barbadensis*, 306
 - A. vera*, 31
- α -tocopherol (α -TOH), 380
- Alstonia boonei*, 32
- Alternanthera sessilis*, 29
- Alzheimer's disease, 420
- Amalaki, 79
- Amaranthus spinosus*, 29
- Ambrosia maritima*, 31
- Amelanchier alnifolia*, 59
- AMR, *see* Antimicrobial resistance
- Amyris balsamifera*, 30
- Anacardium occidentale*, 204
- Andrographis paniculata*, 60, 107, 308, 346, 459
- Andrographolide, 92
- Angiotensin-converting enzyme 2 (ACE2)
 - receptors, 57
- Angiotensin II receptor type 1 (AT1)
 - signal, 467
- Anjeer, 261, 269
 - evidence-based research, 270
- Annona muricata*, 437
- Anredera cordifolia*, 29
- Ansu apricot, 458
- Anthraquinones, 34
- Antibacterial properties of medicinal plants, 13
 - common bacterial diseases and their pathogenesis, 16, **17**
 - ethnobotanical data, **21–27**
 - future perspective, 40–41
 - mechanism and mode of action of plant-based antibacterial drugs, 33–37
 - medicinal plant-based antibacterial chemicals, 37–39

- natural sources, significance of antibacterial drugs from, 32–33
- origin-based classification of medicinal plants
- African medicinal plants, 17–18
 - Chinese medicinal plants, 19
 - European medicinal plants, 20
 - Indian medicinal plants, 19–20
 - medicinal plants from the Americas, 18–19
- plant-based nanoparticles for antibacterial activity, 39–40
- recent progress in bacterial activities
- bacterial meningitis, 30
 - bacterial pneumonia, 28
 - cholera, 28–29
 - diphtheria, 29
 - gonorrhoea, 29
 - Lyme disease, 30
 - syphilis, 30–31
 - tetanus, 31
 - tuberculosis (TB), 31–32
 - typhoid, 32
- Antibiotics, 3
- Antibody-dependent enhancement (ADE), 466
- Anticancer agents, 4
- Anticancer medicinal plants, 433
- Allium sativum*, 433–437
 - Annona muricata*, 437
 - Astragalus cytosus*, 437
 - Boswellia serrata*, 437
 - Camellia sinensis*, 438
 - Centella asiatica*, 438
 - Curcuma longa*, 438
 - Phyllanthus amarus*, 439
 - Withania somnifera*, 439
 - Zingiber officinale*, 439
- Antigen-presenting cells (APCs), 398
- Antimicrobial activity of plants, 15
- Antimicrobial resistance (AMR), 32
- Antioxidants, 420
- Antiretroviral (ARV) program, 124
- Antiviral activity of medicinal plants, 55
- challenges and future perspectives, 67–68
 - clinical rationale, 67
 - common human viral diseases and their pathogenesis, 57–58
 - origin-based classification, 58
 - Americas, 59–60
 - Chinese, 59
 - European, 58–59
 - Indian Ayurvedic plants, 60 - recent insights, 61
 - herpes simplex virus (HSV), 65
 - influenza virus, 65–66
 - SARS-CoV, 66
 - viral hepatitis, 61–65
 - significance of antiviral drugs from natural sources, 66–67
- Antiviral agent/drug, 56
- APCs, *see* Antigen-presenting cells
- Apigenin, 102, 439–440
- chemical structure of, 441
- Apocynins, 92
- Apple, 420
- Arachis hypogaea*, 29
- Areca catechu* L., 274, 280
- Arisaema tortuosum*, 60
- Aristolochia* sp.
- A. esperanzae*, 31
 - A. trilobata*, 18
- Ark, 106
- Artemisia* sp.
- A. annua*, 106
 - A. dracunculus*, 234
- Artemether (ART), 402
- Artemisia* sp., 66
- A. absinthium*, 30
 - A. afra*, 29, 31, 186
 - A. annua*, 213, 344
 - A. dracunculus*, 234
- Artemisinin, 103
- Arthritis, 106
- ARV program, *see* Antiretroviral program
- Asafoetida, 404
- Ascorbic acid, 2, 7
- Ashok, 274, 278
- evidence-based research, 278
- Ashwagandha, 79, 106, 344, 439
- Asparagus racemosus*, 29, 32
- Aspidosperma ramiflorum*, 18
- Astavarga plants, 212
- Aster tataricus*, 458
- Astragalus* sp.
- A. cytosus*, 437
 - A. membranaceus*, 3, 230, 235, 308
- Astridia velutina*, 29
- AT1 signal, *see* Angiotensin II receptor type 1 signal
- Atharva Veda, 77
- Atherosclerosis, 16
- Atractylodes macrocephala*, 458
- Atreya Sampradaya, 304
- Autoimmune disorder, 412
- Autoimmune reaction, 1
- AYMS, *see* Ayurvedic medicinal system
- Ayurveda, 60, 104, 304–305
- Ayurvedic medicinal system (AYMS), 77
- Ayush Joshanda, 458
- Ayush Kudineer, 458
- Ayush Kwath, 458
- Azadirachta indica*, 18, 30, 32, 39, 60, 106, 275–276, 306

- Baccharis* sp.
B. teindalensis, 59
B. trinervis, 60
- Bacillus* sp.
B. anthracis, 34
B. cereus, 14, 37
B. subtilis, 20
- Bacterial activities, of medicinal plants
bacterial meningitis, 30
bacterial pneumonia, 28
cholera, 28–29
diphtheria, 29
gonorrhoea, 29
lyme disease, 30
syphilis, 30–31
tetanus, 31
tuberculosis (TB), 31–32
typhoid, 32
- Bacterial diseases and their pathogenesis, 16, **17**
- Bacterial meningitis, medicinal plants for treating, 30
- Bacterial pneumonia, medicinal plants for treating, 28
- Bael, 274, 274
evidence-based research, 275
- Bala, 79
- Banana–yoghurt combination, 7
- Bauhinia* sp.
B. petersiana, 31
B. variegata, 18, 30
- Begonia picta*, 32
- Beilschmiedia roxburghiana*, 38
- Benincasa hispida*, 29, 31
- Benzophenanthridine, 36
- Ber, 261, 271
evidence-based research, 271–272
- Berberine, 92, 464
- Berberis vulgaris*, 14, 41
- Berchemia discolor*, 31
- Berlinia grandiflora*, 18, 30
- Berries, *see* Fruits and berries for strong human immune system
- Bersama engleriana*, 29
- 5-Beta cholanic acid, 344
- Beta vulgaris*, 20
- Bhagavad Gita, 257
- Bhava Prakasha, 77
- Bible, medicinal value mentioned in, 259–260
- Bidens pilosa*, 32, 65, 234
- Biological response modifiers, 174
- Bitter orange, 458
- Black cumin, 402
- Black grapes, 5
- Black pepper, 399–400, 462
- Black tea, 370
- Blumea laciniata*, 59
- Boerhavia diffusa*, 29, 106, 232, 235, 346
- Borrelia* sp.
B. afzelii, 30
B. burgdorferi, 16, 30
B. garinii, 30
- Boswellia serrata*, 437
- Brahmi, 106
- Brassica oleracea* var *italica*, 5
- Brazil, immunomodulatory properties of medicinal plants in, 203–206
- Brazilian flora, 200
ethnobotanical aspects, 201–202
- Brazilian health system, medicinal plants within the scope of, 202–203
- Brazilian plants, native and exotic, **201**
immunomodulatory activities of herbaceous, shrub, and tree plants of, **205–206**
- Breynia retusa*, 39
- Bridelia micrantha*, 31
- Broccoli, 5, 373–374
- Bupleurum chinense*, 458
- Burkholderia pseudomallei*, 34
- Burkina Faso, 18
- Bursera simaruba*, 18
- Caesalpinia bonducella*, 29
- Callitris glaucophylla*, 15
- Calophyllum inophyllum*, 29
- Calotropis procera*, 106
- Camellia sinensis*, 28, 65, 344, 346, 370, 438
- Cancer, 432
medicinal plants used in the treatment of, 434, **435–436**
- Cancerous cells, mechanism of action of phytochemicals on, 447
- Cancer therapy, 447
- Cancer treatment, phytochemicals used for, 439
apigenin, 439–440, 441
crocetin, 440, 441
curcumin, 440, 441
cyanidins, 441, 442
diindolylmethane, 441, 442–443
fisetin, 441, 443
genistein, 441, 443
kaempferol, 441, 443–444
resveratrol, 441, 444
rosmarinic acid, 441, 444–445
- Candida albicans*, 368
- Cannabis sativa*, 274, 277–278, 343
- Cantuarea pseudosinaica*, 66
- Capsaicin, 92
- Capsicum, 403–404
- Capsicum* sp.
C. annuum, 4, 374–375
C. frutescens, 31
- Cardamine angulata*, 59

- Carica papaya*, 18, 30, 32
Carissa edulis, 29
Carpobrotus edulis, 29
Carum carvi, 234
 Carvacrol, structure of, 38
Carya alba, 38
 Cashew nut, 204
Cassia sp.
 C. alata, 60
 C. auriculata, 19
 C. didymobotrya, 31
 C. floribunda, 31
 C. italica, 34
 C. petersiana, 31
 C. tora, 32
Cassine papillosa, 31
Cassipourea flanaganii, 125
 CCR5, 57
 CD4+ T cells, 57, 174, 465
 CD8+ T cells, 262, 465
 CD47, 381
 CD55, 381
 CD69, 463
 CD80, 463
 Celastrol, 103
Centaurea perrottetii, 31
Centella sp.
 C. asiatica, 18, 28, 29, 235, 438
 C. coriacea, 29
Chaetachme aristata, 31
 Charaka Samhita, 77, 106
 Chelerythrine, 92
Chelidonium majus, 19
 Chinese medicinal plants, 19
 with antiviral activity, 59
 Chinese yam, 458
Chlamydia pneumoniae, 16
 Cholera, 16
 medicinal plants for treating, 28–29
Chrysopogon zizanioides, 30
 Cinnamaldehyde, 399
Cinnamomum sp.
 C. camphora, 28, 261, 267–268
 C. cassia, 399, 458
 C. verum, 37, 458, 463
 C. zeylanicum, 399
 Cinnamon, 399, 463
 Cirsimaritin, 66
Cistus incanus, 65
Citrus sp.
 C. grandis, 4
 C. sinensis, 38
Clausena anisata, 15
Clerodendrum sp.
 C. glabrum, 31
 C. inerme, 60
Clitoria ternatea, 60
Clostridium perfringens, 16, 381
 Clove, 400–401
 CMS, *see* Conventional herbal medical system
 Colchicine, 92, 213
 Column chromatography, 446
Combretum micranthum, 18
Combretum sp.
 C. molle, 31
 C. platypetalum, 28
 Commercial formulations, of African medicinal plants, 186
 Commercially available products, derived from traditional medicinal plants, **108–112**
Commiphora sp., 213
 C. myrrha, 18, 30
 Concanavalin-A (ConA), 304
Conocephalum conicum, 59
 Conventional herbal medical system (CMS), 212
 Conventional medicinal plants, 75
 conventional medicinal systems, importance of, 79–92
 history of medicinal systems, 76
 Ayurvedic medicinal system (AYMS), 77
 traditional Chinese medicinal (TCM) system, 77–79
 immunity enhancer, local medicinal plants as, 99
 immuno-adjuvants, 100
 immunostimulants, 99–100
 immunosuppressants, 100
 immunity-enhancing plant-derived drugs, 92–99
 pharmacology, 104–107
 phytochemistry, 102
 flavonoids, 102–103
 organosulphur compounds, 104
 terpenoids, 103–104
 and their constituent properties, **80–91**
Conyza scabrida, 31
Copaifera langsdorffii, 31
Corynebacterium diphtheriae, 29
 Coronavirus disease 2019, *see* COVID-19
 Coronaviruses, 66
Cortex phellodendri, 37
Corymbia citriodora, 28
Corynebacterium sp.
 C. diphtheriae, 20
 C. pseudodiphthericum, 34
 COVID-19, 398, 402
 medicinal plants as immunity booster against, 455, **460–461**
 Cinnamomum verum J. Presl, 463
 Curcuma longa L., 465
 Glycyrrhiza glabra L., 464–465
 immunological responses, 465–467

- Ocimum sanctum* L., 459–462
Panax quinquefolius L., 464
Piper nigrum L., 462
 SARS-CoV-2, 456–457
Tinospora cordifolia (Willd.) Miers, 463–464
Zingiber officinale Roscoe, 462–463
 COX, *see* Cyclooxygenase
 COX-2, *see* Cyclooxygenase-2
Crinum purpurascens, 32
 Crocetin, 440
 chemical structure of, 441
Crocus sativus, 37, 404, 440
Crossostephium chinense, 66
 Crude drug, 229
Cryptocarya latifolia, 31
Cuminum cyminum, 30, 306
Curculigo orchioides, 29
Curcuma sp.
 C. longa, 3, 20, 28, 344, 398, 438, 465
 C. xanthorrhiza, 459
 Curcumin, 92, 344, 398–399, 440
 chemical structure of, 441
 Cyanidins, 442
 chemical structure of, 441
 Cyclooxygenase (COX), 106
 Cyclooxygenase-2 (COX-2), 102, 400, 447
Cymbopogon citratus, 15, 32
Cynodon dactylon, 31, 60
Cyperus rotundus, 459
 Cytokines, 175, 307

Dacryodes edulis, 18
 Dalchini, 463
 Dalton's lymphoma, 439
 Damage-associated molecular patterns (DAMPs), 404
 DAMPs, *see* Damage-associated molecular patterns
Datura sp.
 D. metel, 30
 D. stramonium, 14, 41
 Delayed Type Hypersensitivity (DTH) test, 272
Dendrobium nobile, 343
 Deoxyelephantopin, 103
 Dermatological and immune significance, ethnomedicinal plants of, **128–164**
 Dermatological significance, plant species of, 165
 D-glucarolactone, 5
 Dhanvantari Sampradaya, 304
 Dihydrocapsaicin, 374
 5,7-Dihydroxy-3-(4-hydroxyphenyl)chromen-4-one, 443
 2-(3,4-Dihydroxyphenyl)-3,7-dihydroxychromen-4-one, 443
 (2*R*)-3-(3,4-Dihydroxyphenyl)-2-[[*(2E*)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxy]propanoic acid, 444
 Diindolylmethane, 442–443
 chemical structure of, 441
 Diphtheria, medicinal plants for treating, 29
 Diterpenoid essential oils, 37
 Docosahexaenoic acid, 7
Dodonaea viscosa, 28, 29
Dorstenia sp., 14
Dracocephalum heterophyllum, 234
Dryopteris crassirhizoma, 59
 DTH test, *see* Delayed Type Hypersensitivity test

 EBV, *see* Epstein-Barr Virus
 EC, *see* Epicatechin
 ECG, *see* Epicatechin-3-gallate
Echinacea sp.
 E. angustifolia, 372
 E. pallida, 372
 E. purpurea, 347, 372
 EGC, *see* Epigallocatechin
 EGCG, *see* Epigallocatechin-3-gallate
 Eicosapentaenoic acid, 7
 Elephantopin derivatives, 103
Elephantopus scaber, 28, 59, 103
Embelia ribes, 60, 61
Emblca officinalis, 5, 79
 Endemic Brazilian plants, 200
 EOs, *see* Essential oils
Ephedra sinica, 19, 458
 Ephedrine, 213
 Epicatechin (EC), 371
 Epicatechin-3-gallate (ECG), 371
 Epigallocatechin (EGC), 370
 structure of, 35
 Epigallocatechin-3-gallate (EGCG), 5, 370
 Epstein-Barr Virus (EBV), 377
Eriosema salignum, 186
Escherichia coli, 41, 372
 Essential oils (EOs), 15, 37, 92
Eucalyptus sp., 15
 E. cinerea, 38
 E. citriodora, 30
 E. globulus, 29, 459
 E. odorata, 38
Eugenia jambolana, 20
 Eugenol, 400
 structure of, 38
Eupatorium sp.
 E. articulatum, 59
 E. glutinosum, 59
Euphorbia sp.
 E. abyssinica, 18
 E. hirta, 18

- European medicinal plants, 20
with antiviral activity, 58–59
- False black pepper, *see Embelia ribes*
- Fenugreek, 401
- Ferula* sp.
F. assafoetida, 404
F. jaeskiana, 234
- Ficus* sp.
F. carica, 29, 261, 269–270
F. fistulosa, 61
F. religiosa L., 273–274, 274
- Filipendula ulmaria*, 76
- Fisetin, 443
chemical structure of, 441
- Flavaglines, 59
- Flavanols, 92
- Flavones, 92
- Flavonoids, 4, 7, 92, 102–103
- Flavonols, 92
- Foeniculum vulgare*, 459
- Foful, 274, 281
evidence-based research, 281
- Fresh fruit juice, 420
- Fritillaria roylei*, 212
- Fruits and berries for strong human immune system, 411, 416
in disease prevention, 419–420
effects of nutrition, 413–415
on health, 415–417
immunity, types and mechanisms of, 413
in immunity and disease prevention, 420–421
structure of immune system, 412–413
and their phytochemical and micronutrient components, **418**
- Fumaria parviflora*, 31
- Gallic acid, 344
- Gallium pauciflorum*, 234
- Gardenia jasminoides*, 103
- Garlic, 7, 308, 346, 365–369, 402–403
- Gelselegine, 92
- Genistein, 92, 443
chemical structure of, 441
- Genopsida, 103
- Geranium sanguineum*, 65
- Giloe, 463–464
- Ginger, 20, 106, 344, 349, 369–370, 403, 458, 462–463
- Gingerol, 349, 369
- Ginkgo biloba*, 19
- Ginseng, 304, 464
- Gladiolus sericeovillosus*, 186
- Glochidion lanceolarium*, 39
- Gloriosa superba*, 29
- γ -glutamyl-allyl-L-cysteines, 348
- Glutamyl-S-allyl-L-cysteines (G-SAC), 367
- γ -glutamyl-S-allyl-L-cysteines, 349
- Glycoproteins, 4
- Glycosides, 308
- Glycyrrhiza glabra*, 28, 66, 464–465
- Glycyrrhizin, 66, 344
- Gokhru, 106
- Gonorrhoea, 16
medicinal plants for treating, 29
- Gram-negative bacteria, 37, 39
- Gram-positive bacteria, 37, 39
- Grape seed proanthocyanidins (GSPs), 264
- Green leafy vegetables and lemon, combination of, 7
- Green tea, 5, 7, 344, 370–371
- Grewia* sp.
G. occidentalis var. *occidentalis*, 186
G. subinaequalis, 29
- Grindelia argentina*, 66
- G-SAC, *see* Glutamyl-S-allyl-L-cysteines
- GSPs, *see* Grape seed proanthocyanidins
- Guazuma ulmifolia*, 18
- Guduchi, 79, 231
- Guiera senegalensis*, 29
- Gymnema sylvestre*, 107
- HA, *see* Haemagglutination Antibody
- Habenaria* sp.
H. edgeworthii, 212
H. intermedia, 212
- Haemagglutination Antibody (HA), 272
- Haldi, 465
- Hamelia patens*, 18
- HBV, *see* Hepatitis B virus
- Hedychium spicatum*, 30
- Heisteria acuminata*, 59
- Helianthus annuus*, 106
- Helichrysum* sp.
H. bracteatum, 66
H. litoreum, 65
- Helicobacter pylori*, 34, 37
- Hepatitis B virus (HBV), 61
- Heracleum pinnatum*, 234
- Herbs/herbal products, 3
- Herpes simplex virus (HSV), 65
- Hieracium pilosella*, 18
- Himalayan medicinal plants, traditional, 211, 215–229
background, 213–215
comparison of, **216–228**
ethanopharmacology, 234–235
recent advances in immunomodulatory research, 235–236
roles of Himalayan medicinal flora in disease treatment, 229
Actinidia eriantha, 232–234

- Allium sativum*, 230
Astragalus membranaceus, 230
Boerhaavia diffusa, 232
Panax ginseng, 231
Picrorhiza scrophulariiflora, 232
Rhus toxicodendron, 234
Tinospora cordifolia, 231–232
Tylophora asthmatica, 230–231
Withania somnifera, 231
 and their decline, 236
 Hindu mythology, medicinal plants mentioned in, 256–257, 259
Hippophaë rhamnoides, 234
 Hispidulin, 66
 History of medicinal systems, 76
 Ayurvedic medicinal system (AYMS), 77
 traditional Chinese medicinal (TCM) system, 77–79
Holarrhena sp., 213
 H. antidysenterica, 28
 Holy basil, 459–462
 Homocapsaicin, 375
 Homodihydrocapsaicin, 375
 Honey, 7
 HSV, *see* Herpes simplex virus
 Human viral diseases and their pathogenesis, 57–58
 3-Hydroxy caruillignan C (3-HCL-C), 61
 Hydroxychloroquine, 458
Hymenocardia acida, 31
 Hypaphorine, 344
Hypericum perforatum, 4
Hyptis suaveolens, 30
Hyssopus officinalis L., 274, 279–280

 ICAM, *see* Intracellular adhesion molecule
 ICD, *see* Immunogenic cell death
 IFN- γ , *see* Interferon gamma
 IgM gene, 401
 IHMs, *see* Indian herbal medicines
Illicium verum, 59, 400
 Immune boosters, medicinal plants as, 344–346
 Immune system, structure of, 412–413
 Immunity enhancer, local medicinal plants as, 99
 immuno-adjuvants, 100
 immunostimulants, 99–100
 immunosuppressants, 100
 Immunity-enhancing plant-derived drugs, 92–99
 Immunoadjuvants, 100, 174, 308
 Immunoaugmentors, 174
 Immunogenic cell death (ICD), 404
 Immunomodulation, 4
 mechanisms, 107
 medicinal plants used in African traditional medicine for, 175, **176–185**, 186
 Immunomodulators, 2, 99, 174, 308
 types of, **309–342**
 Immunomodulatory agents from plants, 174–175
 mechanisms of action of, 175
 Immunomodulatory phytochemicals and associated responses, 4–5
 Immunorestoratives, 174
 Immunostimulants, 99–100, 174, 308
 Immunosuppressants, 100, 174
 Immunosuppressive effect, major bioactive compounds with, 345
 Immunotolerance, 5
 India, 256
 Indian Ayurvedic plants with antiviral activity, 60
 Indian herbal medicines (IHMs), 77
 Indian medicinal plants, 19–20
Indigofera tinctoria, 60
 Indole-3-carbinol, 443
 Indolizidine, structure of, 36
 Inducible nitric oxide synthase (iNOS), 102
 Inflammatory eicosanoids, 7
 Influenza virus, medicinal plants for treating, 65–66
 Innate immune system, 364
 iNOS, *see* Inducible nitric oxide synthase
 Interferon gamma (IFN- γ), 398
 Interferons, 307
 Intracellular adhesion molecule (ICAM), 102
Inula racemosa, 234, 235
 Inulins, 7
Ipomoea pandurata, 18
Ipomopsis aggregata, 59
 IRI, *see* Ischaemia–reperfusion injury
Iris domestica, 32, 458
 Ischaemia–reperfusion injury (IRI), 7
 Islam, medicinal plants mentioned in, 256–259
 Isodeoxyephantopin, 103
 Isoflavones, 92
 Isoquinolines, 36

Jacaranda mimosifolia, 29
Jasminum floribundum, 18
 Jensenone, 66
Juglans regia, 38, 39
 Jurkat cell, 367
Justicia adhatoda, 28

 Kaali mirch, 462
 Kaempferol, 443–444
 chemical structure of, 441
 Kafoor, 261, 267
 evidence-based research, 268
 Kalonji, 261, 265
 evidence-based research, 266–267
 Khajoor, 260, 261
 evidence-based research, 261–262

- Khaya senegalensis*, 18
Klebsiella pneumoniae, 16
 Korean mint, 458
 Koumine, 92

Lactococcus lactis, 19
Laggera pterodonta, 59
Lantana camara, 29, 31, 60
 LCDD, *see* Lung cleansing and detoxifying decoction
Leishmania donovani, 249
 Lemon juice, 7
 Leonurine, 92
Leucas aspera, 60
 Licorice, 458, 464–465
Lilium polyphyllum, 212
Limonium brasiliense, 59
 Lipid nanoparticles (LNPs), 40
 Lipid polysaccharide (LPS), 103
 Lipikyure, 8
 Lipopolysaccharide (LPS), 263, 304, 399
 Lipoxigenase (LOX), 106
Lippia alba, 30
Litsea cubeba, 30
 LNPs, *see* Lipid nanoparticles
Lomatium dissectum, 59
Lonicera japonica, 103
 Lopinavir, 458
 LOX, *see* Lipoxigenase
 LPS, *see* Lipid polysaccharide;
 Lipopolysaccharide
 L-theanine, 371
 Lung cleansing and detoxifying decoction
 (LCDD), 458
 Luteolin, 103
 Lycopene, 5
 Lycorine, 92
 Lyme disease, 16
 medicinal plants for treating, 30
Lysichiton americanum, 59

 Madin–Darby canine kidney (MDCK) cells,
 65–66
 Major histocompatibility complex (MHC), 398,
 413
Malaxis sp.
 M. acuminata, 212
 M. muscifera, 212
 Malnutrition, 413
Mangifera indica, 32
Manilkara hexandra, 19
 Matrine, 92
 Mauz, 270
 evidence-based research, 270–271
 Maweez, 263
 evidence-based research, 264

Maytenus buchananii, 28
 MDCK cells, *see* Madin–Darby canine kidney
 cells
 MDR pathogens, *see* Multidrug-resistant
 pathogens
 Medicinal plant-based antibacterial chemicals,
 37–39
 Medicinal plants from the Americas, 18–19
 with antiviral activity, 59–60
Melaleuca alternifolia, 15
Melanolepis multiglandulosa, 61
Melicope latifolia, 61
Mentha sp.
 M. longifolia, 29, 234
 M. pulegium, 459
Mesua ferrea, 19
 3,3'-Methanediylbis, 442–443
 MHC, *see* Major histocompatibility complex
Micotea debilis, 66
Micrococcus sp., 41
 Micronutrients, role of, 414
 Microorganisms, 363–364
 MicroRNA (miRNA) regulation, 447
Mikania micrantha, 38
 Milkvetch, 437
 Miller, 204
 miR-122, 57
 MM cells, *see* Multiple Myeloma cells
 Modern medicine, role of medicinal plants in,
 303
Mollugo cerviana, 459
Momordica charantia, 32, 60
 Mongolian milkvetch, 3
 Moonseed, 463–464
Morella cerifera, 38
Moringa oleifera, 30
Morus alba, 59
 MPO, *see* Myeloperoxidase
Mucuna pruriens, 213
 Multidrug-resistant (MDR) pathogens, 14
 Multiple Myeloma (MM) cells, 403
Murraya koenigii, 30
Musa × paradisiaca L., 270–271
Mussaenda sp.
 M. frondosa, 32
 M. pubescens, 59
Mycobacterium tuberculosis, 31, 32, 373
 Myeloperoxidase (MPO), 401
 Myricetin, structure of, 35
Myristica fragrans, 32

Nardostachys jatamansi (D. Don) DC, 274,
 279–280
 Naringenin, structure of, 35
 Natural immunity boosters, 431, 433
 anticancer medicinal plants, 433

- Allium sativum*, 433–437
Annona muricata, 437
Astragalus cytosus, 437
Boswellia serrata, 437
Camellia sinensis, 438
Centella asiatica, 438
Curcuma longa, 438
Phyllanthus amarus, 439
Withania somnifera, 439
Zingiber officinale, 439
cancerous cells, mechanism of action of phytochemicals on, 447
future prospects, 447–448
phytochemical preparation, 445
 clinical trials, 447
 phytochemical extraction, 445
 phytochemical identification, 446–447
 phytochemical purification, 445–446
phytochemicals used for cancer treatment, 439
 apigenin, 439–440, 441
 crocetin, 440, 441
 curcumin, 440, 441
 cyanidins, 441, 442
 diindolylmethane, 441, 442–443
 fisetin, 441, 443
 genistein, 441, 443
 kaempferol, 441, 443–444
 resveratrol, 441, 444
 rosmarinic acid, 441, 444–445
Natural killer (NK) cell, 459, 465, 466
Natural sources
 significance of antibacterial drugs from, 32–33
 significance of antiviral drugs from, 66–67
Neem, 106, 275
 evidence-based research, 276
Neisseria gonorrhoeae, 16, 29
Neopicrorhiza scrophulariiflora, 32
Nepeta podostachys, 234
NFAT activating protein, *see* Nuclear factor of activated T cells activating protein
NF- κ B, *see* Nuclear factor-kappa B
Nicotiana tabacum, 31
Nigella sativa L., 261, 265–266, 402
Nilavembu Kudineer Chooranam (NKC)
 decoction, 458–459
Nilofar, 274, 281
 evidence-based research, 282
NIM-76, 276
NKC decoction, *see* Nilavembu Kudineer Chooranam decoction
NK cell, *see* Natural killer cell
Nocardia brasiliensis, 343
Noni (*Morinda citrifolia*), 204
Nordihydrocapsaicin, 375
Nuclear factor-kappa B (NF- κ B), 399, 400
Nuclear factor of activated T cells (NFAT) activating protein, 368
Nutraceuticals, 1
 applications of, 2
 examples of plants commonly used as, 6
 immunomodulatory phytochemicals and associated responses, 4–5
 major plant-based nutraceuticals, 4
 synergistic effect of herbal and other plant products, 5–8
Nutrition, 3
 on immune system, 413–415
Nymphaea alba L., 274, 281–282
Ocimum sp.
 O. gratissimum, 20, 29
 O. sanctum, 20, 79, 104, 107, 261, 272–273, 459–462
 O. tenuiflorum, 458
Oils, 3, 380
Olea europaea, 5, 29, 261, 262–263, 459
Olive oil, 5, 263
Omega-3 fatty acids, 3
Omum, 404
Oncosiphon suffruticosum, 28
Onion (*Allium cepa*), 106
Ophiocordyceps sinensis, 235
Opuntia sp.
 O. streptacantha, 65
 O. stricta, 29
Orange peel, 458
Organosulphur compounds, 104, 349, 367
Origanum vulgare, 234
Origin-based classification, of medicinal plants
 African medicinal plants, 17–18
 Chinese medicinal plants, 19
 European medicinal plants, 20
 Indian medicinal plants, 19–20
 medicinal plants from the Americas, 18–19
Overeating, 1
Overweight, 1
Oxidants, 420
Oxidative damage, 421
Oxidative stress, 7, 421
Paclitaxel, 351
Panax sp.
 P. ginseng, 3, 4, 19, 231, 235, 304
 P. quinquefolius L. (ginseng), 464
Papaver somniferum, 213
Parachlamydia acanthamoebae, 16
Paris polyphylla, 343
Parkia biglobosa, 204
Parthenium integrifolium, 113
PBMCs, *see* Peripheral blood mononuclear cells

- Pectin FB, 373
Pedaliium murex, 29
 Peepal, 273, 274
 evidence-based research, 273–274
Peganum harmala, 234
Pelargonium sidoides, 28, 65, 187
 Pelvic inflammatory disease (PID), 16
 Pennywort, 438
 Peperine, 92
 Peppermint (*Mentha × piperita*), 3
Pereskia aculeata, 204
 Pergularinine, structure of, 36
 Peripheral blood mononuclear cells (PBMCs), 402
 Permeabilization, 37
 PFC, *see* Plaque-forming cells
 Pharmacology, 104–107
 Pharmacology and toxicity, of medicinal plants, 350
 Phenolics, 4, 420
 Phloroglucinols, 92
Phoenix dactylifera L., 260–262, 261, 459
Phyllanthus sp., 61
 P. amarus, 60, 306, 439
 P. emblica, 106, 306
 P. fraternus, 29
 P. niruri, 59, 61
 Phytochemical compounds, **93–98**
 Phytochemical extraction, 445
 Phytochemical identification, 446–447
 Phytochemical purification, 445–446
 Phytochemicals, 3–5, 33, 250, 348
 Phytochemicals, cancer treatment, 439
 apigenin, 439–440
 crocetin, 440
 curcumin, 440
 cyanidins, 442
 diindolylmethane, 442–443
 fisetin, 443
 genistein, 443
 kaempferol, 443–444
 resveratrol, 444
 rosmarinic acid, 444–445
 Phytochemistry, 102
 flavonoids, 102–103
 organosulphur compounds, 104
 terpenoids, 103–104
 Phytoconstituents, molecular chemistry of, 348–349
Picrorhiza scrophulariiflora, 232, 308
 PID, *see* Pelvic inflammatory disease
Pimenta officinalis, 30
Pimpinella anisum, 459
Pinellia ternata, 458
 Piperine, 5, 7
Piper nigrum, 14, 41, 399–400, 458, 459, 462
Pithecellobium clypearia, 59
Pittosporum viridiflorum, 66
 PLA, *see* Polylactic acid
Plantago major, 204, 235
 Plant-based nanoparticles, for antibacterial activity, 39–40
 Plant-derived immunity boosters, molecular chemistry of, 346–348
 Plant nutrients and their immune system stimulating effect, 365, **366**
 broccoli, 373–374
 Echinacea, 371–373
 garlic, 365–369
 ginger, 369–370
 green tea, 370–371
 red pepper, 374–375
 Plaque-forming cells (PFC), 232
Plectranthus vetiveroides, 459
Plumbago indica, 30
 Podophyllotoxin, 65
Podophyllum peltatum, 65
 Poison gooseberry, 439
Polygonatum sp.
 P. cirrhifolium, 212
 P. verticillatum, 212
 Polylactic acid (PLA), 40
 Polyphenols, 347
Polypodium glycyrrhiza, 59
Polyporus umbellatus, 458
 Polysaccharides, 4, 204, 235, 304
 Polyunsaturated fatty acids (PUFA), 7
 Potential herbal products, molecular features of, 301
 current developments in immunomodulator research, 350–351
 immune boosters, medicinal plants as, 344–346
 limitations, 351
 medicinal plants and immunological regulation, 307
 immunomodulator agents, 308, 343
 immunosuppressive agents, 343–344
 mechanism of action of immunomodulators, 343
 pharmacology and toxicity, 350
 phytoconstituents, molecular chemistry of, 348–349
 plant-derived immunity boosters, molecular chemistry of, 346–348
 roles of medicinal plants, 303
 in Ayurveda, 304–305
 in modern medicine, 303
 in regional medicinal systems, 307
 in Siddha, 305–307
 in traditional Chinese medicine, 303–304
Potentilla arguta, 59

- Pouzolzia zeylanica*, 29
 Praziquantel (PZQ), 402
Premna arborea, 29
Prosopis juliflora, 40
 Protein–energy malnutrition, 3
Proteus vulgaris, 34
 Protoberberine, 36
 structure of, 36
Prunus sp.
 P. persica, 165
 P. serotina, 29
 Pseudocoptisine, 92
Pseudomonas sp., 350
 P. aeruginosa, 34
Psidium guajava, 32, 59
 Psoriasis, 106
Pterocarpus erinaceus, 18
 PUFA, *see* Polyunsaturated fatty acids
 Punarnava, 106
 Punarnavine, 232
Punica granatum, 28, 32, 59, 60, 261, 264–265
 Purple coneflower, *see* *Echinacea* sp.
 PZQ, *see* Praziquantel
- Qinnab, 274, 277
 evidence-based research, 278
 Quercetin, 4, 34, 92
 structure of, 35
Quercus infectoria, 466
 Quinones, 92
 Qur'an, medicinal plants mentioned in, 256–259
- RA, *see* Rheumatoid arthritis
Rapanea melanophloeos, 66, 186
 Rasayana, 212
Rauwolfia serpentina, 213
 RBD, *see* Receptor-binding domain
 RBM, *see* Receptor-binding motif
 Reactive oxygen species (ROS), 7, 413
 Receptor-binding domain (RBD), 457
 Receptor-binding motif (RBM), 457
 Red pepper, 374–375
 Regional medicinal systems, role of medicinal plants in, 307
 Rehan, 261, 272
 evidence-based research, 272–273
 Remsedivir, 458
 Respiratory syncytial virus (RSV), 59
 Resveratrol, 444
 chemical structure of, 441
Retama raetam, 14
 Retinovir, 458
Rhamnus sp.
 R. prinoides, 28
 R. purshiana, 14
 Rheumatism, 106
 Rheumatoid arthritis (RA), 266
Rhizoma coptidis, 36
 Rhizome, 349
Rhodiola sp.
 R. heterodonta, 234
 R. imbricata, 234, 235
 R. rosea, 29
Rhus sp.
 R. parviflora, 234
 R. toxicodendron, 234
 Rhynchophylline, 92
Rhynchosia caribaea, 28
 Rituximab, 174
 Robinetin, structure of, 35
 ROS, *see* Reactive oxygen species
Rosa sp.
 R. macrophylla, 234
 R. nulkana, 59
 R. webbiana, 234
 Rosmarinic acid, 444–445
 chemical structure of, 441
Rosmarinus officinalis, 103, 459
 RSV, *see* Respiratory syncytial virus
Rubia cordifolia, 234
Rubus ellipticus, 32
 Rumman, 261, 264
 evidence-based research, 265
- SAC, *see* S-allyl-L-cysteine
 Sacred medicinal plants and their use by
 indigenous people, 255
 future perspectives, 282–286
 medicinal activities of, **283–285**
 in sacred books, 257
 Anjeer, 261, 269–270
 Ashok, 274, 278
 Bael, 274, 274–275
 Ber, 261, 271–272
 Foful, 274, 281
 Kafoor, 261, 267–268
 Kalonji, 261, 265–267
 Khajoor, 260–262, 261
 Mauz, 270–271
 Maweez, 263–264
 Neem, 275–276
 Nilofar, 274, 281–282
 Peepal, 273–274, 274
 Qinnab, 274, 277–278
 Rehan, 261, 272–273
 Rumman, 261, 264–265
 Sandal, 274, 276–277
 Sumbul-ut Teeb, 274, 279
 Zaitoon, 261, 262–263
 Zanjabeel, 261, 268–269
 Zoofa, 274, 279–280
 Sacred plants, 256, 259

- Saffron, 404
Salacia oblonga, 467
 S-allylcysteine, 437
 S-allyl-L-cysteine (SAC), 349, 367
 S-allylmercaptocysteine (SAMC), 367
Salmonella enteritidis, 378, 381
Salvadora persica, 39
Salvia sp.
 S. miltiorrhiza, 103
 S. officinalis, 19, 28, 66
 S. palaestina, 66
 S. rosmarinus, 28
 S. sclarea, 37
 Salvipisone, structure of, 38
Sambucus sp.
 S. nigra, 58, 65
 S. racemosa, 59
 SAMC, *see* S-allylmercaptocysteine
 Sandal, 274, 276–277
 evidence-based research, 277
Santalum album, 274, 276, 459
 Saponins, 4
Saraca asoca L., 274, 278
Sarcophy tepiriei, 18
 SARS-CoV, medicinal plants for treating, 66
 SARS-CoV-2, structural assembly and
 mechanism of action in human host
 cell, 456–457
Sassafras albidum, 38, 39
Schefflera octophylla, 59
Schisandra chinensis, 350
Schistosoma mansoni, 402
Scoparia dulcis, 29
Scorparia centaurea, 66
 Scurvy, 375
Scutellaria sp.
 S. baicalensis, 59, 458
 S. indica, 59
 Selenium, 2
Semecarpus anacardium, 39
Senna sp.
 S. didymobotrya, 29
 S. podocarpa, 29
 Sesquiterpene lactones, 103
 Shahakusan, 65
Sida sp.
 S. acuta, 18
 S. cordifolia, 350
 Siddha, role of medicinal plants in, 305–307
 SIDS, *see* Sudden Infant Death Syndrome
 Sindbis virus, 58
 Single-stranded RNA (ssRNA) virus, 456
 Sinomenine, 92
 Skin beauty, South African plants for use in,
 127–165
 Skin care/therapy, 123
 Skin diseases, classification of, 126–127, **126**
Solanum sp.
 S. aethiopicum, 4
 S. lycopersicum, 5, 32
 S. mauritianum, 29
 S. trilobatum, 306
Solidago canadensis, 18
 Sophocarpine, 92
 Sophoraflavanone G, structure of, 35
Sophora sp.
 S. flavescens, 59
 S. japonica, 4
Sorghum bicolor, 18
 South Africa, medicinal plants in, 123
 common methods of preparation, 166
 dermatological and immune significance,
 ethnomedicinal plants of, **128–164**
 dermatological significance, plant species
 of, 165
 literature survey of plants of dermatological
 significance, 127
 skin diseases, classification of, 126–127, **126**
 sustainable utilization and conservation of
 plants for skin therapy, 166–168
 for use in skin beauty, 127–165
 South Indian herbal plants, 245, 246
 and immune system, 246–247
 medicinal value of herbal plants, 249–250
 and their healing properties, **248–249**
Sphaeranthus indicus, 60
 Spices, for strong immune system, 397
 asafoetida (*Ferula assafoetida*), 404
 black cumin (*Nigella sativa*), 402
 black pepper (*Piper nigrum*), 399–400
 capsicum, 403–404
 cinnamon (*Cinnamomum zeylanicum* and
 Cinnamomum cassia), 399
 clove (*Syzygium aromaticum*), 400–401
 fenugreek (*Trigonella foenum-graecum*), 401
 future perspectives, 405
 garlic (*Allium sativum*), 402–403
 ginger (*Zingiber officinale*), 403
 omum (*Trachyspermum ammi*), 404
 saffron (*Crocus sativus*), 404
 star anise (*Illicium verum*), 400
 turmeric (*Curcuma longa* L., family
 Zingiberaceae), 398–399
 Squalene, 344
 ssRNA virus, *see* Single-stranded RNA virus
Stachytarpheta jamaicensis, 32
Staphylococcus sp., 350
 S. aureus, 15, 19, 20, 186, 281
 Star anise, 400
Streblus asper, 30
Streptococcus sp.
 S. agalactiae, 37

- S. mutans*, 18
S. pneumoniae type 1, 381
 Sudden Infant Death Syndrome (SIDS), 16
 Sulphoraphane, 5, 373
 Sumbul-ut Teeb, 274, 279
 evidence-based research, 279
 Sunflower, 106
 Sunthi, 462–463
 SUS care, 203
 Sushruta Samhita, 77
 Sweet wood, 464–465
Swertia chirata, 60
Swietenia macrophylla, 61
 Synergistic effect, of herbal and other plant products, 5–8
Syngonium podophyllum, 18
 Syphilis, medicinal plants for treating, 30–31
Syzygium aromaticum, 28, 30, 39, 400–401

Tabernaemontana stapfiana, 31
Tagetes pusilla, 59
Tamarindus indica, 186
Tanacetum gracile, 234
 Tannins, 5
 Tanshinone IIA, 103
Taraxacum officinale, 31
 Taxol, 4
Taxus brevifolia, 103, 351
 TB, *see* Tuberculosis
 TCM system, *see* Traditional Chinese medicinal system
 Tea, 370
Terminalia sp.
 T. bellirica, 5
 T. chebula, 5
 T. macroptera, 29
 T. sericea, 28
 Terpenoids, 92, 103–104
 Terpenoid steroidal saponins, 4
 Tetanus, medicinal plants for treating, 31
 Tetrandrine, 92
Teucrium trifidum, 17
 T helper cell, 459
Thespesia lampas, 350
 Thiosulphinates, 349
Thryptomene calycina, 15
 Thymol, structure of, 38
 Thymoquinone (TQ), 267, 402
Thymus sp.
 T. maroccanus, 459
 T. praecox, 28
 T. satureioides, 459
 T. vulgaris, 30
Tinospora cordifolia, 79, 104, 231–232, 235, 463–464
 TLR, *see* Toll-like receptors

 T lymphocytes, 204, 369
 TNF- α , *see* Tumour necrosis factor- α
 Toll-like receptors (TLR), 100
 Tomatoes, 5
Toona sureni, 61
 TQ, *see* Thymoquinone
 Trace elements, 3
Trachyspermum ammi, 404
 Traditional Chinese medicinal (TCM) system,
 19, 77–79
 role of medicinal plants in, 303–304
Tragia meyeriana, 186
Treponema pallidum, 30
Tribulus terrestris, 20, 106
Trichilia emetica, 28
Trichosanthes dioica, 459
Trigonella foenum-graecum, 401
 4',5,7-Trihydroxyflavone, 439–440
 3,5,7-Trihydroxy-2-(4-hydroxyphenyl)-4H-
 chromen-4-one, 443–444
 3,5,4'-Trihydroxy-trans-stilbene, 444
 Triphala, 5
 Tuberculosis (TB), 31–32
 Tulsi, 79, 459–462
 Tumour necrosis factor- α (TNF- α), 264, 399,
 400, 445
 Turmeric, 344, 398–399, 438, 465
Tussilago farfara, 19, 458
Tylophora asthmatica, 230–231
 Tylophorinidine, structure of, 36
 Typhoid, medicinal plants for treating, 32

uMakhonya[®], 186
 Undernourishment, 1
 Ursolic acid, 103
Utrica hyperborea, 234

 Vascular cell adhesion molecule (VCAM), 102
 VCAM, *see* Vascular cell adhesion molecule
 Vedas, medicinal plants mentioned in, 256–257
 VEE, *see* Venezuelan equine encephalitis virus
 Vegetable oils, 380
 Venezuelan equine encephalitis virus (VEE), 58
Verbascum thapsus, 59, 60
Veronica persica, 58
Vetiveria zizanioides, 459
Vibrio cholerae, 16, 18
Vicia faba, 38
 Vinblastine, 4
 Vincristine, 4
 Viral diseases, medicinal plants used against,
 62–64
 Viral hepatitis, medicinal plants for treatment
 of, 61–65
 Vitamin A, 3
 Vitamin C, 2, 7, 375–378

- Vitamin D, 1, 3, 378–380
vitamin E, 380–381
Vitamins, 3
 fortifying immune system, 375, **376**
Vitex sp.
 V. doniana, 32
 V. trifolia, 60
Vitis vinifera, 29, 263, 458
Vyadhibala, 77
Vyadhi-ksamatva, 77

WHV, *see* Woodchuck hepatitis virus
Wild ginger, 458
Willow tree bark, 99
Withania somnifera, 79, 106, 231, 306,
 344, 350, 439
Wolfiporia extensa, 458
Woodchuck hepatitis virus (WHV), 61
Woodfordia fruticosa, 19

Xanthomonas sp., 350

Yajurveda, 77
Yellow turmeric powder, 3
Yoghurt, 7
Yucca schidigera (Mojave yucca), 4

Zaitoon, 261, 262
 evidence-based research, 263
Zanjabeel, 261, 268
 evidence-based research, 268–269
Zanthoxylum sp.
 Z. armatum, 38, 39
 Z. capense, 186
Zinc oxide NPs (ZnONPs), 40
Zingiber officinale, 306
Zingibain, 349
Zingiber officinale, 3, 20, 106, 261, 268–269, 344,
 369–370, 403, 439, 458, 459, 462–463
Ziziphus mauritiana (Lamk.), 261, 271–272
Zoofa, 274, 279–280
 evidence-based research, 280
Zoonotic viruses, 57