Munir Ozturk · Khalid Rehman Hakeem
Editors

Plant and Human Health, Volume 3

Pharmacology and Therapeutic Uses

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Editors
Munir Ozturk
Vice President of the Islamic World
Academy of Sciences
Amann, Jordan

Department of Botany and Centre for
Environmental Studies
Ege University
Izmir, Izmir, Turkey

Khalid Rehman Hakeem
Department of Biological Sciences
Faculty of Science
King Abdulaziz University
Jeddah, Saudi Arabia

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Volume 3 is dedicated to the greatest naturalist and one of the greatest Chinese herbalists and acupuncturists.

Lǐ Shízhēn (1518–1593)

His epic book, the Bencao Gangmu or Compendium of Materia Medica, is a major contribution to medicine. He was interested in the proper classification of herb components.

Foreword

This volume 3 of the book series *Plant and Human Health* is focused on the pharmacological and therapeutic uses of some of the most important medicinal plants. This volume is edited by well-known researchers in the field, Prof. Dr. Munir Ozturk and Dr. Khalid Rehman Hakeem. These competent editors have assembled an impressive group of authors to contribute 16 scholarly written chapters on various medicinal plants and their biological activities.

Medicinal plants have played an important role in human well-being since antiquity. Even today, 25% of the marketed drugs originate from plants and other natural resources. The global business of botanicals exceeds over 100 billion dollars, with ever increasing upward trends. Global interest in natural products, particularly medicinal plants, has led to major scientific research in this field, and it is often difficult to keep track of the tremendous amount of literature published. Therefore, a concise treatise, like the current volume focusing on the health benefits of medicinal plants, is a welcome addition to the literature.

The editors and contributors to this volume are to be congratulated for their excellent efforts in producing such a high-quality and timely text on a topic of wide scientific and public interest. The book should be useful in advanced undergraduate and graduate courses in pharmacognosy, pharmacology, medicinal chemistry, phytotherapy, and phytochemistry. Moreover, specific chapters will serve as helpful contemporary reviews for established and beginning researchers in the therapeutic areas covered.

Iqbal Choudhary
International Center for Chemical and Biological Sciences
University of Karachi
Karachi, Pakistan

Preface

The major diseases of the twenty-first century in the developed countries are reported as age-related and viral diseases, cardiovascular failures, and psychiatriac disorders, whereas in the developing countries, these are listed as infectious, tropical, and nutrition-related diseases. A report published by the journal *Nature* in 2008 says that the side effects of commonly used drugs like aspirin and ibuprofen cause 7000 deaths and over 120,000 hospitalizations every year in the USA alone. Overdose of acetaminophen is a leading cause of acute liver failure, causing 10% of all cases of kidney failure. Similarly medicines like paxil, zoloft, and prozac promote obesity. Nearly 70% of patients with chronic daily headaches suffer from drug-induced headaches. Sleeping pills interfere with normal sleep cycles, produce numerous side effects, and are addictive. In Sweden, one of the highly developed countries, adverse drug reactions are the seventh most common cause of death. Every year, 8 million humans are treated in hospitals due to side effects of the medicines sold with prescriptions. The other side of this story reveals that only 14 of the 1,400 new medicines developed during the last three decades are used for the treatment of diseases of the poor.

Around 1.4 billion people in South Asia alone have no access to modern health care and rely on traditional medicine using native species. On global basis, approximately 50,000–80,000 plants are used medicinally to fight life-threatening diseases like diabetes, asthma, hypertension, HIV, and diarrhea in different countries. For every sort of illness, people have looked for medicines from nature in particular plants. Currently traditional knowledge of herbal medicine is used with the clarity that scientific research can provide. We need information to go back to nature to produce different health curing plants.

Herbal medicine is gaining wide currency and acceptability. Documentation of valuable indigenous knowledge about MAPS is assuming urgent priority, due to recent controversies of illegal biopiracy. Indigenous people and local communities are holders of a rich knowledge about nature and related technical know-how. Precious indigenous knowledge, when supplemented and validated by the latest scientific insights, can offer new holistic models of sustainable development—economically viable, environmentally benign, and socially acceptable. Every lost species means the loss of information hidden in its genes.

Our nature is full of new drugs, and we have endless frontiers waiting for us there. Biodiversity is the outward manifestation of chemical diversity. Developing countries are slowly realizing that they do not have means to provide comprehensive health care to their masses, and they have started to become more interested in traditional medicines. This has lead towards more acceptance of phytotherapy. The demand of plant-based medicines for age-related disease (autoimmune, degenerative diseases) and preventive medicines (antioxidants, edible vaccines, nutritional therapy, etc.) will become very important. In the developing countries, large numbers of the population are unable to afford pharmaceutical drugs, and they continue to use their own systems of indigenous medicine, which are mainly plant based. There is a great need to harness scientific and clinical research in order to investigate the quality, safety, and efficacy of these herbals.

About 2 million taxa of plants and animals have been scientifically named up until now. The estimates are that we possess up to ~10 million. Only 5–15% of plants have been properly studied for biological activity. One in every group of 125 plant taxa contains useful pharmaceuticals. The inventory of 21,000 plants used for medicinal purposes in 91 countries compiled by the WHO depicts that less than 10,000 taxa have been investigated for therapeutic purposes.

The objectives of bioprospecting plants for medical activity include screening of flora in particular plants used ethnobotanically or in traditional indigenous systems of medicine for utilizable therapeutic activity. It must not be forgotten that natural products which result from millennia of biosynthetic pathways modified by evolution have a well-established track record as medicinal agents and present a wide range of structural diversity. Drug development through natural product research is not without its problems, and there is, for example, a need to eliminate common natural products from plant extracts prior to testing. Researchers can play a useful role in this area if they have information available to start with. A key to discovering successful natural remedies is knowing what you are doing and why. Current research in drug discovery from medicinal plants involves a multifaceted approach combining botanical, phytochemical, biological, and molecular techniques.

Izmir, Turkey — Munir Ozturk
Jeddah, Saudi Arabia — Khalid Rehman Hakeem

Contents

Contributors

A. S. Abdulkareim Phytochemistry Research Lab, Department of Pharmacognosy and Phytochemistry, Faculty of Pharmacy, Jamia Hamdard, New Delhi, India

Waseem Mohammed Abdul Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia

Muhammad Afzal Department of Pharmacology, College of Pharmacy, Jouf University, Sakaka, Kingdom of Saudi Arabia

Anas Ahmad Nano-Therapeutics, Institute of Nano Science and Technology, Habitat Centre, Mohali, Punjab, India

Md Faruque Ahmad Department of Clinic Nutrition, College of Applied Medical Sciences, Jazan University, Jizan, Saudi Arabia

Sarfaraz Ahmad Department of Clinical Pharmacy, College of Pharmacy, Jazan University, Jazan, Saudi Arabia

Sayeed Ahmad Department of Pharmacognosy and Phytochemistry, Jamia Hamdard, New Delhi, India

Md Sarfaraz Alam Department of Pharmaceutics, College of Pharmacy, Jazan University, Jizan, Saudi Arabia

Atef M. Al-Attar Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia

Khalid Saad Alharbi Department of Pharmacology, College of Pharmacy, Jouf University, Sakaka, Kingdom of Saudi Arabia

Hassan Ahmad Alhazmi Department of Pharmaceutical Chemistry, College of Pharmacy, Jazan University, Jazan, Saudi Arabia

M. Ali Department of Pharmacognosy, College of Pharmacy, Jazan University, Jizan, Saudi Arabia

Md Sajid Ali Department of Pharmaceutics, College of Pharmacy, Jazan University, Jizan, Saudi Arabia

Saleh Alkarim Department of Biological Science, King Abdulaziz University, Jeddah, Saudi Arabia

Volkan Altay Biology Department, Faculty of Science and Arts, Hatay Mustafa Kemal University, Hatay, Turkey

S. H. Ansari Department of Pharmacognosy and Phytochemistry, Faculty of Pharmacy, Jamia Hamdard, New Delhi, India

Mehri A. Ashiraliyeva State Medical University of Turkmenistan, Ashgabat, Turkmenistan

Babajan Banaganapalli Princess Al-Jawhara Albrahim Center of Excellence in Research of Hereditary Disorders (PACER-HD), King Abdulaziz University, Jeddah, Saudi Arabia

Department of Genetic Medicine, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

Musadiq Hussain Bhat School of Studies in Botany, Jiwaji University, Gwalior, MP, India

Rahil Razzak Bhat Division of Veterinary Biochemistry, Faculty of Veterinary Sciences and Animal Husbandry, Sheri Kashmir University of Agricultural Science and Technology (SKUAST-K), Srinagar, Jammu and Kashmir, India

Z. A. Bhat Depatment of Pharmaceutical Sciences, University of Kashmir, Srinagar, Jammu and Kashmir, India

Damanjit Singh Cannoo Department of Chemistry, Sant Longowal Institute of Engineering and Technology, Sangrur, Punjab, India

Girish Chandran Biochemistry, Department of Lifesciences, Pooja Bhagavat Memorial Mahajana Education Centre, Post Graduate Wing of SBRR Mahajana First Grade College, Metagalli, Mysuru, Karnataka, India

Durgesh Nandini Chauhan Columbia Institute of Pharmacy, Raipur, Chhattisgarh, India

Jyoti Bala Chauhan Biochemistry, Department of Lifesciences, Pooja Bhagavat Memorial Mahajana Education Centre, Post Graduate Wing of SBRR Mahajana First Grade College, Metagalli, Mysuru, Karnataka, India

Nagendra Singh Chauhan Drugs Testing Laboratory Avam Anusandhan Kendra, Raipur, Chhattisgarh, India

Dilfuza Egamberdieva Faculty of Biology and Soil Sciences, National University of Uzbekistan, Tashkent, Uzbekistan

Ayman I. Elkady Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia

Karam A. El-Sharkawy Department of Pharmaceutical Chemistry, College of Pharmacy, Jazan University, Jazan, Saudi Arabia

Mufida Fayaz School of Studies in Botany, Jiwaji University, Gwalior, MP, India

Majid Ahmad Ganaie Department of Pharmacology, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-Kharj, Saudi Arabia

Celal Guven Biophysics Department, Faculty of Medicine, University of Omer Halisdemir, Nigde, Turkey

Khalid Rehman Hakeem Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia

Arshad Hussain Department of Pharmacognosy, King Khalid University, Abha, Saudi Arabia

Faisal Imam College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

Ashok Kumar Jain Institute of Ethnobiology, Jiwaji University, Gwalior, MP, India

Shweta Jain Pharmacy College, Sir Madanlal Group of Institute, Etawah, Uttar Pradesh, India

Salih Tunc Kaya Biology Department, Faculty of Arts and Science, University of Duzce, Duzce, Turkey

Imran Kazmi Glocal School of Pharmacy, Glocal University, Saharanpur, Uttar Pradesh, India

Fazal Khan Department of Genetics and Molecular Medicine, Kamineni Hospital, Hyderabad, India

Rehan Khan Nano-Therapeutics, Institute of Nano Science and Technology, Habitat Centre, Mohali, Punjab, India

Riqaiyah Khan Department of Pharmacology, Siddhartha Institute of Pharmacy, Dehradun, Uttarakhand, India

Shah Alam Khan Department of Pharmacy, Oman Medical College, Muscat, Sultanate of Oman

Amit Kumar Institute of Ethnobiology, Jiwaji University, Gwalior, MP, India

Hassan Madkhali Department of Pharmacology, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-Kharj, Saudi Arabia

Maya A. Mamedova State Medical University of Turkmenistan, Ashgabat, Turkmenistan

Nazim A. Mamedov Medicinal Plants Program, Stockbridge School of Agriculture, University of Massachusetts at Amherst, Amherst, MA, USA

Mubashir Husaain Masoodi Department of Pharmaceutical Sciences, Faculty of Applied Sciences, University of Kashmir, Srinagar, Jammu and Kashmir, India

Muqtadir Baig Mirza Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia

Furkhan Ahmed Mohammed Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia

Kaleemuddin Mohammed Department of Biochemistry, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia

Princess Al-Jawhara Albrahim Center of Excellence in Research of Hereditary Disorders (PACER-HD), King Abdulaziz University, Jeddah, Saudi Arabia

G. Mustafa Herbal Cosmetics and Immunomodulatory Lab, Department of Pharmacognosy and Phytochemistry, Faculty of Pharmacy, Jamia Hamdard, New Delhi, India

G. A. Nayik Department of Food Engineering & Technology, Sant Longowal Institute of Engineering and Technology, Sangrur, Punjab, India

Munir Ozturk Vice President of the Islamic World Academy of Sciences, Amann, Jordan

Department of Botany, Centre for Environmental Studies, Ege University, Izmir, Turkey

Svetlana A. Pleskanovskaya State Medical University of Turkmenistan, Ashgabat, Turkmenistan

Manzoor U. Rahman Mir Division of Veterinary Biochemistry, Faculty of Veterinary Sciences and Animal Husbandry, Sheri Kashmir University of Agricultural Science and Technology (SKUAST-K), Srinagar, Jammu and Kashmir, India

Syed Shoeb Razvi Department of Biochemistry, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia

Muneeb U. Rehman Division of Veterinary Biochemistry, Faculty of Veterinary Sciences and Animal Husbandry, Sheri Kashmir University of Agricultural Science and Technology (SKUAST-K), Srinagar, Jammu and Kashmir, India

Shakir Saleem Glocal School of Pharmacy, Glocal University, Mirzapur Pole, Dist -Saharanpur, UP, India

Department of Pharmacology, Siddhartha Institute of Pharmacy, Dehradun, Uttarakhand, India

Syeda Sanobar Department of Pharmacognosy, College of Pharmacy, Jazan University, Jizan, Saudi Arabia

Ambreen Shabir Faculty of Fisheries, Sheri Kashmir University of Agricultural Science and Technology (SKUAST-K), Srinagar, Jammu and Kashmir, India

Kamal Shah Institute of Pharmaceutical Research, GLA University, Mathura, Uttar Pradesh, India

Noor Ahmad Shaik Princess Al-Jawhara Albrahim Center of Excellence in Research of Hereditary Disorders (PACER-HD), King Abdulaziz University, Jeddah, Saudi Arabia

Department of Genetic Medicine, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

Ajay Sharma Department of Chemistry, Sant Longowal Institute of Engineering and Technology, Sangrur, Punjab, India

Rajbala Singh Siddhartha Institute of Pharmacy, Dehra Dun, Uttarakhand, India

S. R. Smitha Grace Biochemistry, Department of Lifesciences, Pooja Bhagavat Memorial Mahajana Education Centre, Post Graduate Wing of SBRR Mahajana First Grade College, Metagalli, Mysuru, Karnataka, India

Fareeduddin Quadri Syed Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia

Eylem Taskin Physiology Department, Faculty of Medicine, University of Omer Halisdemir, Nigde, Turkey

Ankur Vaidya Pharmacy College, Uttar Pradesh University of Medical Sciences, Etawah, Uttar Pradesh, India

About the Editors

Munir Ozturk, PhD, DSc has served at the Ege University, Izmir, Turkey, for 50 years in different positions. He is currently Vice President of the Islamic World Academy of Sciences. He has received fellowships from Alexander von Humboldt, Japanese Society for the Promotion of Science, and National Science Foundation of the USA. Dr. Ozturk has served as Chairman of the Botany Department and Founding Director of Centre for Environmental Studies, Ege University, Izmir, Turkey; Consultant Fellow at the Faculty of Forestry, Universiti Putra Malaysia, Malaysia; and Distinguished Visiting Scientist at ICCBS, Karachi University, Pakistan. His fields of scientific interest are Plant Ecophysiology, Medicinal and Aromatic Plants, Conservation of Plant Diversity, Biosaline Agriculture and Crops, and Pollution and Biomonitoring. He has published 42 books, 68 book chapters, and 190 papers in international and national journals.

Khalid Rehman Hakeem, PhD is Associate Professor at King Abdulaziz University, Jeddah, Saudi Arabia. After completing his doctorate (Botany; specialization in Plant Eco-physiology and Molecular Biology) from Jamia Hamdard, New Delhi, India, in 2011, he worked as a lecturer at the University of Kashmir, Srinagar, for a short period. Later, he joined Universiti Putra Malaysia, Selangor, Malaysia, and worked there as Post Doctorate Fellow in 2012 and Fellow Researcher (Associate Prof.) from 2013 to 2016. Dr. Hakeem has more than 10 years of teaching

and research experience in plant eco-physiology, biotechnology and molecular biology, medicinal plant research, plant-microbe-soil interactions as well as in environmental studies. He is the recipient of several fellowships at both national and international levels, also he has served as the visiting scientist at Jinan University, Guangzhou, China. Currently, he is involved with a number of international research projects with different government organizations.

So far, Dr. Hakeem has authored and edited more than **35 books** with international publishers, including Springer Nature, Academic Press (Elsevier), and CRC Press. He also has to his credit more than **75 research publications** in peer-reviewed international journals and **50 book chapters** in edited volumes with international publishers.

At present, Dr. Hakeem serves as an editorial board member and reviewer of several high-impact international scientific journals from Elsevier, Springer Nature, Taylor and Francis, Cambridge, and John Wiley Publishers. He is included in the advisory board of Cambridge Scholars Publishing, UK. He is also a fellow of Plantae group of the American Society of Plant Biologists, member of the World Academy of Sciences, member of the International Society for Development and Sustainability, Japan, and member of Asian Federation of Biotechnology, Korea. Dr. Hakeem has been listed in Marquis Who's Who in the World, since 2014–2019.

Currently, Dr. Hakeem is engaged in studying the plant processes at eco-physiological as well as molecular levels.

Phytochemical Constituents and Pharmacological Effects of Licorice: A Review

Nazim A. Mamedov and Dilfuza Egamberdieva

Introduction

Licorice is one of the most widely used and extensively researched medicinal plants of the world (Hoffman 2000; Öztürk et al. 2017). The word liquorice essentially derives from Old Greek glykyrrhiza, glykys means "sweet," and rhiza is "root" (Schulz et al. 1998). One of the main active ingredients is glycyrrhizin, which has a cortisone-like effect. Glycyrrhizin is also 50 times sweeter than sucrose (Brown 1995). Liquorice has several names such as sweetwood, licorice, liquorice radix, reglisse (French), lakritzeholz (German), Gan Cao (Chinese), Meyan or Beyan (Turkish), and Solodka (Russian) (Mills and Bone 2000). Licorice roots have been used worldwide as a medicine and flavor in industry for over 4000 years. Medicinal uses of licorice are recorded in texts such as Assyrian Herbal (2000 BC) and Ebers Papyrus (1600 BC) (Lucas 1976; Reid 2001). Licorice is believed to have originated in Iraq. The most widely distributed species *Glycyrrhiza glabra* is found in Spain, Italy, Turkey, the Caucasus, Central Asia, and the western part of China whereas *Glycyrrhiza uralensis* is distributed form Central Asia to Mongolia and China (Hayash et al. 2003). Various species of licorice are currently grown on commercial scale in Spain, Italy, France, Greece, India, Iran, Iraq, Turkey, Turkmenistan, Uzbekistan, Syria, Afghanistan, Azerbaijan, China, and to a limited extent in England and the United States (Sokolov and Zamotayev 1985; Chevallier 1996).

N. A. Mamedov (✉)
Medicinal Plants Program, Stockbridge School of Agriculture, University of Massachusetts at Amherst, Amherst, MA, USA
e-mail: mamedov@cas.umass.edu

D. Egamberdieva
Faculty of Biology and Soil Sciences, National University of Uzbekistan, Tashkent, Uzbekistan

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Taxonomic Description

The genus *Glycyrrhiza* is in the family *Leguminosae* and about 30 species are accepted up to today including *G. aspera*, *G. bucharica*, *G. echinata*, *G. eurycarpa*, *G. glabra*, *G. iconica*, *G. inflata*, *G. korshinskyi*, *G. lepidota*, *G. macedonica*, *G. pallidiflora*, *G. squamulosa*, *G. triphylla*, *G. uralensis*, and *G. yunnanensis* (Nomura et al. 2002; Fiore et al. 2005).

Botanical Description

Licorice is a perennial herb which grows 1–2 m tall. The plant has a long cylindrical burrowing rootstock that grows to a depth for 1 m. Horizontal stolons grow outwards and typically reach 1.5–1.8 m in length, although they may grow to a length of 7 m. The bark on licorice root is dark reddish, while the inside of the roots is bright yellow. Leaves are alternate, pinnate, with 9–17 ovate, yellow-green leaflets, each 2.5–5 cm long. The spikes of pealike flowers may be white, purple, or yellow. Spikes are usually 10–15 cm long and are born from leaf axils. Seedpods are maroon, 3 cm long, oblong, pointed, and flattened. Licorice roots are harvested 3–4 years after planting (Huxley 1992; Weiss and Fintelmann 2000).

Traditional Uses

Ancient Egyptians, Greeks, and Romans recognized the benefits of licorice in treating coughs, colds, and chills. In the days of Hippocrates, licorice was prescribed for dropsy because of thirst-quenching properties of licorice drugs (Biondi et al. 2005). The use of licorice for stomach and intestinal ulcers goes back at least to the Greek physician Dioscorides in first century AD, although modern clinical use began in about 1930. The ancient Hindus used licorice for improving sexual vigor, and Chinese for strength and endurance and they prepared it most often in tea (Davis and Morris 1991).

In traditional medicine licorice roots have been used against treating chest and lung diseases, pneumonia, bronchitis, arthritis, bronchial asthma, kidney diseases, heart diseases, gastric ulcer, mouth ulcers, coughs, swellings, excessive salivation, fluid retention, low blood pressure, allergies, catarrhs of the upper respiratory tract, liver toxicity, hyperglycemia, Addison's disease, pancreatic disorders, flatulence, sexual debility, skin diseases, leukorrhea, hoarseness, and certain viral infections (Blumenthal et al. 2000; Anon 2005; Armanini et al. 2002; Sharma et al. 2013). Current pharmacopoeias from France, Germany, and Britain are in general agreement on the medicinal application of licorice. In Indian medicine, licorice is used for treatment of influenza, eye diseases, uterine complaints, biliousness, liver

disease, and arthritis (Saxena 2005). In Chinese medicine, licorice is used to treat acne and pimples, nervous disorders such as hysteria, irritability, and epilepsy as well as reduce the toxic or drastic action of other herbs, and to harmonize herbal formulas (Zhu 1998). In earlier studies Kong et al. (1984) showed that root extract of licorice was used to treat diarrhea in mice, whereas Hong et al. (1988) demonstrated strong diuretic activity of licorice in rats. Extract of *G. glabra* was used to treat emotional irritability in adults (Tsuda et al. 1986) and stress (Shirinyan et al. 1988). Licorice extract was also used to treat eczema (Sheehan and Atherton 1992), and allergic dermatitis (Sokolov and Zamotayev 1985).

Pharmacological Activities

Pharmacological studies have confirmed that *Glycyrrhiza* species exhibit a broad range of biological activities. In Table 1 various pharmacological activities of *Glycyrrhiza* species are presented. Many pharmacological activities, such as hypocholesterolemic and hypoglycemic (Sitohy et al. 1991), anxiolytic (Ambawade et al. 2001), antimicrobial (Patil et al. 2009), antiviral (Cinati et al. 2003), preliminary free radical scavenging (Toshio et al. 2003), anti-ulcer (Da Nagao et al. 1996), cytotoxic, antitumor (Hossain et al. 2004), antiallergic (Ram et al. 2006; Kroes et al. 1997), antidiabetic (Isbrucker and Burdock 2006), anticarcinogenic (Satomi et al. 2005), antioxidant (Vaya et al. 1998), anti-inflammatory (Kakegawa et al. 1992; Fujisawa et al. 2000), and hepatoprotective activities (Van Rossum et al. 2001; Wu et al. 2006); skin eruptions; dermatitis; and eczema (Akhtar et al. 2011), have been reported for roots of *Glycyrrhiza* species. The licorice can also be used in the management of impaired learning, dementia, Alzheimer's disease, and other neurodegenerative disorders (Chakravarthi et al. 2012).

Antimicrobial Activity

The antimicrobial activity of plant oils and extracts has been recognized for many years and indicated that it may be attributed to alkaloids, saponins, flavonoids, tannin, glycosides, and phenols (Shinwari et al. 2009). Patil et al. (2009) observed antimicrobial activity of ethanolic extract of *G. glabra* against *Bacillus subtilis* MTCC (121), *Staphylococcus aureus* MTCC (96), *Pseudomonas aeruginosa* MTCC (429), *Escherichia coli* MTCC (443), and one fungal strain *Candida albicans*. *Candida albicans* and *Trichophyton rubrum* growth was also inhibited by ethanolic extracts of *G. glabra* and their fractions (Meghashri 2009), whereas methanolic extracts of *G. glabra* had more fungicidal effect against *Arthrinium sacchari* and *Chaetomium funicola* (Hojo and Sato 2002). In another study Tharkar et al. (2010) also observed antifungal activity of *G. glabra* extracts. In the following study Gupta et al. (2008) reported antimicrobial activity of *G. glabra* against

Table 1. Pharmacological activities of licorice

Species	Pharmacological activity	References
G. glabra *G. uralensis*	Antimicrobial	Hatano et al. (2000), Tanaka et al. (2001), Hojo and Sato (2002), Fukai et al. (2002), Nerya et al. (2003), Statti et al. (2004), Gupta et al. (2008), Fatima et al. (2009), Shinwari et al. (2009), Patil et al. (2009), Nitalikar et al. (2010), Tharkar et al. (2010), Meghashri (2009), Nand et al. (2012), Varsha et al. (2013), Ali (2013)
G. glabra *G. uralensis*	Antiviral	Hattori et al. (1989), Crance et al. (1990), Plyasunova et al. (1992), Van Rossum et al. (1999), Wang et al. (2000), Tandon et al. (2002), Crance et al. (2003), Chen et al. (2004), Orlent et al. (2006), Pellatti et al. (2009), Fiore et al. (2009), Kuo et al. (2009)
	Anti-inflammatory	Matsui et al. (2004), Shin et al. (2008), Vibha et al. (2009), Tokiwa et al. (2004), Furuhashi et al. (2005), Kang et al. (2005)
	Anti-ulcer	Bennett et al. (1980), Van Marle et al. (1981), Da Nagao et al. (1996), Masoomeh and Kiarash (2007), Adel et al. (2005)
G. inflate *G. glabra* *G. uralensis*	Antitumor	Kakegawa et al. (1992), Fukai et al. (1998), Shiota et al. (1999), Liu et al. (1998), Tamir et al. (2000), Nomura et al. (2002), Salvi et al. (2003), Kanazawa et al. (2003), Hsu et al. (2004), Hossain et al. (2004), Jo et al. (2005), Sheela et al. (2006), Yoon et al. (2005), Dong et al. (2007), Rahman and Rashid (2008)
	Antioxidant	Vaya et al. (1997), Hesham and Shgeru (2002), Muralidharan et al. (2009), Singh (2010), Siracusa et al. (2011), Škrovánková et al. (2012), Lateef et al. (2012), Ali (2013)
	Hepatoprotective activity	Subramoniam and Pushpangadan (1999), Van Rossum et al. (2001), Jeong et al. (2002), Curreli et al. (2007), Al-Razzuqi et al. (2012)
	Dermatological effect	Lee et al. (1997), Lee et al. (2005), Akhtar et al. (2011)
	Antidepressant and memory-enhancing activity	Gareri et al. (2004), Dhingra and Sharma (2005, 2006), Zhao et al. (2006), Wang et al. (2008), Chakravarthi et al. (2012)

Mycobacterium tuberculosis. The ethanol, chloroform, and acetone extracts of licorice showed antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* (Nitalikar et al. 2010). *G. glabra* extracts showed high antibacterial activity against *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Propionibacterium acnes* (Nand et al. 2012). Varsha et al. (2013) presented the antibacterial effect of *G. glabra* extract against *Pseudomonas aeruginosa*, *Shigella flexneri, Escherichia coli, Staphylococcus epidermidis, S. aureus,* and *Bacillus subtilis.* The methanolic extract of *G. glabra* showed antimicrobial activity against various strains of *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Micrococcus luteus* ATCC 9622, *Proteus mirabilis* ATCC 29852, *Proteus vulgaris* ATCC 6361, and *Escherichia coli*

ATCC 4350 (Statti et al. 2004). Shinwari et al. (2009) observed antibacterial activity of *G. glabra* extracts against *Pseudomonas aeruginosa* and *B. subtilis*.

The antibacterial activity of secondary metabolites obtained from *Glycyrrhiza* species against upper airway respiratory tract bacteria such as *Streptococcus pyogenes*, *Haemophilus influenza*, and *Moraxella catarrhalis* was studied by Tanaka et al. (2001). The authors observed that licoricidin and coumarin derivatives such as glycyrol, glycyrin, and glycycoumarin exhibited high activity against all tested microorganisms. The compound glabridin, derived from root of *G. glabra*, was found to be active against both yeast and filamentous fungi (Fatima et al. 2009). Glabridin showed various biological activities such as antimicrobial activity against *Helicobacter pylori* (Fukai et al. 2002), *Staphylococcus aureus* (Hatano et al. 2000), and inflammation (Nerya et al. 2003). Essential oils derived from *G. glabra* showed inhibitory effect against *Aspergillus flavus* (Ali 2013).

Antiviral Activity

Licorice and glycyrrhizate compounds have long been used as a potential therapeutic agent for several virus diseases including chronic hepatitis B and C, as well as human acquired immunodeficiency syndrome (AIDS) (Wang et al. 2000; Chen et al. 2004; Orlent et al. 2006; Tandon et al. 2002). There are other several reports indicating antiviral activity of glycyrrhizin and glycyrrhizic acid, where the compounds inhibited growth and cytopathology of hepatitis A and C (Crance et al. 1990: Van Rossum et al. 1999), and immunodeficiency virus (HIV) (Hattori et al. 1989; Plyasunova et al. 1992). Fiore et al. (2009) observed that glycyrrhizin and its derivatives from *Glycyrrhiza glabra* reduced hepatocellular damage in chronic hepatitis B and C and they also showed antiviral activity against HIV-1, SARS-related coronavirus, respiratory syncytial virus, arboviruses, vaccinia virus, and vesicular stomatitis virus.

According to Crance et al. (2003) glycyrrhizin has antiviral effect, through an inhibition of viral particle to cell membrane binding, or through cellular signal transduction mechanisms. 18β-Glycyrrhetinic acid was found to be a promising biological alternative for the topical treatment of persistent vulvovaginal candidiasis (Pellatti et al. 2009). In another study Cinati et al. (2003) observed in vitro antiviral effects for viruses causing respiratory tract infections like influenza virus and the severe acute respiratory syndrome (SARS) corona virus, and human immunodeficiency virus (HIV).

Kuo et al. (2009) studied the potential use of *G. uralensis* for treatment of human infection by enterovirus type 71 (EV71) which can cause life-threatening meningoencephalitis.

Anti-inflammatory

The species of *Glycyrrhiza* has also been used to treat allergies and other inflammatory diseases (Matsui et al. 2004). Shin et al. (2008) studied anti-inflammatory effects of glycyrol (benzofuran coumarin) isolated from *G. uralensis* and found that glycyrols have potential anti-inflammatory effect. In another study Vibha et al. (2009) reported steroid-like anti-inflammatory activity of constituents derived from licorice root, similar to the action of hydrocortisone. They explained this finding due to inhibition of phospholipase A2 activity, an enzyme critical to numerous inflammatory processes.

Matsui et al. (2004) reported that glycyrrhetinic acid (ED 50, 200 mg/kg) showed an inhibitory effect on carrageenan-induced rat paw edema and antiallergic activity. The secondary metabolites of *G. glabra*, namely glycyrrhizic acid, glabridin, and licochalcone A, showed an anti-inflammatory effect (Tokiwa et al. 2004; Furuhashi et al. 2005; Kang et al. 2005).

Anti-ulcer

In earlier work Bennett et al. (1980) demonstrated the anti-ulcer activity of deglycyrrhizinated licorice formulations using a rat model of aspirin-induced gastric mucosal damage. It has been found that the formulation promotes healing by increasing mucus production and blood supply to the damaged stomach mucosa, thereby enhancing mucosal healing (Van Marle et al. 1981; Da Nagao et al. 1996). Masoomeh and Kiarash (2007) reported anti-ulcerogenic effect of carbenoxolone derived from the root of licorice by inhibiting the secretion of gastrin. It has been explained by raising the concentration of prostaglandins in the digestive system by licorice compound that promote mucus secretion from the stomach. Adel et al. (2005) reported on the anti-pepsin effect of secondary metabolites of licorice which prolongs the life span of surface cells in the stomach.

Antitumor

The phytochemical constituents of licorice are reported to demonstrate anticancer effects in in vivo and in vitro studies (Salvi et al. 2003). For example they inhibit tumor formation and growth in breast (Tamir et al. 2000), liver (Shiota et al. 1999), and skin cancer (Liu et al. 1998). In earlier studies Fukai et al. (1998) reported the inhibitory activity of phenolic compounds such as isoliquiritigenin, semilicoisoflavone B, gancaonin C licoisoflavone B, and licoisoflavanone for the growth of both *B. subtilis* H17 (wild type) and M45 (recombinationless mutant cells). In another study Sheela et al. (2006) observed that the extract of *G. glabra* inhibited

proliferation of tumor cells and inhibited angiogenesis in in vivo assay. Jo et al. (2005) observed that the ethanol extract of *G. uralensis* root induced apoptosis and G1 cell cycle arrest in MCF-7 human breast cancer cells. The ethanolic extract and glycyrrhizin display antiproliferative effects against the MCF-7 in a dose-dependent manner (Dong et al. 2007). Similar results were observed by Jo et al. (2005) where the ethanol extract of *G. uralensis* root induced apoptosis and G1 cell cycle arrest in MCF-7 human breast cancer cells. Yoon et al. (2005) found that licochalcone E from the roots of *G. inflate* exhibited the most potent cytotoxic effect compared with the known antitumor agents, licochalcone A and isoliquiritigenin. In the studies of Nomura et al. (2002) several compounds derived from *G. glabra*, namely glyasperin A, gancaonin P, licochalcone B, topazolin, and gancaonin O, showed relatively higher cytotoxic activity against human oral squamous carcinoma cell line HSC-2. In the following studies Yoon et al. (2005) showed that licochalcone E, a new retrochalcone derived from the *G. inflata*, exhibited the potent cytotoxic effect. Hsu et al. (2004) reported that isoliquiritigenin inhibited proliferation of the human non-small cell lung cancer A549 cell line, inducing apoptosis and locking cell cycle progression in the G1 phase. Similar results were observed by Kanazawa et al. (2003) where isoliquiritigenin inhibited the growth of prostate cancer and suggested the compound as a cancer chemopreventive agent in humans. The results indicate that biologically active compound in the root of licorice might be very useful as antiproliferative and antitumor agents (Rahman and Rashid 2008; Hossain et al. 2004).

Antioxidant

It has been reported that the extract of *G. glabra* leaves has been proved to have antioxidant, anti-genotoxic, and anti-inflammatory activities (Siracusa et al. 2011). Several phytochemical constituents derived from *Glycyrrhiza* roots are considered as a potential source of antioxidants (Singh 2010; Lateef et al. 2012). For example in earlier studies Vaya et al. (1997) reported about significant antioxidant activity of isoflavones glabridin and hispaglabridins A and B. Hesham and Shgeru (2002) have reported that flavonoids like luteolin, rutin, and apigenin derived from the root of *G. glabra* possess antioxidant properties. In the following study phenolic compounds have been reported as the main compound linked to antioxidant activity (Škrovánková et al. 2012).

Muralidharan et al. (2009) have found that the ethanol extract of *G. glabra* possesses a cerebroprotective effect in hypoxic rats, which may be mediated by its antioxidant effects. Essential oil of *G. glabra* exhibited DPPH radical scavenging activity (85.2%) at a dose of 400 μg/mL (Ali 2013), whereas methanolic extract exhibited 91.3% scavenging activity at a dose of 62.5 μg (Lateef et al. 2012). Franceschelli et al. (2011) observed that licochalcone C has antioxidant properties since it reduces the production of superoxide radicals and consequently reduces the activity of inducible nitric oxide synthase (iNOS).

Hepatoprotective Activity

In traditional medicine *G. glabra* were used to treat various liver diseases (Subramoniam and Pushpangadan 1999). Later modern medicinal studies showed that secondary metabolites derived from licorice were found to lower serum liver enzyme levels and improve tissue pathology in hepatitis patients (Van Rossum et al. 2001).

Glycyrrhizic acid induced a significant reduction in serum aminotransferases and improved the liver histology (Curreli et al. 2007). In recent studies Al-Razzuqi et al. (2012) demonstrated that the aqueous extract of *G. glabra* showed a significant effect in ameliorating liver functions in acute liver diseases when it was given in a single dose per day of 2 mg/kg body weight. In another study the protective effects of glycyrrhetinic acid against the carbon tetrachloride-induced hepatotoxicity and retrorsine-induced liver damage were reported (Jeong et al. 2002).

Dermatological Effect

The bioactive compounds derived from *Glycyrrhiza* roots have also showed skin-whitening, depigmenting, antiaging, anti-acne, and anti-erythemic properties (Lee et al. 1997). In recent studies Akhtar et al. (2011) found significant decrease in skin melanin by formulation of *G. glabra* extracts. Lee et al. (2005) explained that glycyrrhizin derived from the root of *G. glabra* induced melanin formation that may be mediated via the activation of a tyrosinase gene expression.

Antidepressant and Memory-Enhancing Activity

Licorice has also been found to have a memory-enhancing activity in passive avoidance paradigm (Dhingra and Sharma 2005) and antidepressant-like activity in mouse immobility tests (Dhingra and Sharma 2006). Several secondary metabolites derived from *G. uralensis*, e.g., liquiritin, demonstrated an antidepressant effect on chronic stress-depressed rats (Zhao et al. 2006). In the following studies Wang et al. (2008) also reported antidepressant-like activity of liquiritin and isoliquiritin in two classic animal behavior despair tests—the Forced Swimming Test (FST) and the Tail Suspension Test (TST) in mice. The authors explained the mechanism of action of those compounds which may be due to increased 5-hydroxytryptamine and norepinephrine in the mouse hippocampus, hypothalamus, and cortex. The other compound carbenoxolone also found in licorice demonstrated sedative and muscle-relaxant activities in mice and in genetically epilepsy-prone rats (GEPRs) (Gareri et al. 2004).

Chakravarthi et al. (2012) studied the impact of root extract of *G. glabra* on learning and memory in 1-month-old male Wistar albino rats and they found that

150 and 225 mg/kg doses have shown a significant enhancement in learning and memory which is comparable to control. They explained that such improvement is due to antioxidant and anti-inflammatory action of plant extract where susceptible brain cells get exposed to less oxidative stress resulting in reduced brain damage and improved neuronal function.

Other Effects

There are also many studies reporting on the various pharmacological activities of licorice extract and biologically active compounds. For example the secondary metabolites liquiritigenin and isoliquiritigenin derived from the root of *G. glabra* showed dose-related antiallergic activities (Kakegawa et al. 1992).

Mishra et al. (2011) evaluated the anti-arthritic activity of *G. glabra* by significant reduction of paw edema volume and its capacity to stabilize lysosomal enzyme activity such as ACP significantly. The results justified the benefit of *G. glabra* in the treatment of inflammation-associated diseases like arthritis. Asgary et al. (2007) investigated the effect of *G. glabra* extract on blood lipids and atherosclerosis in rabbits fed with high-cholesterol diet. The authors found that *G. glabra* extract significantly decreased total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) levels and increased high-density lipoprotein cholesterol (HDL-C) and lessened atherosclerotic lesion in aorta. Similar results were observed by Fuhrman et al. (2002) where *G. glabra* extract decreased TC, TG, and LDL cholesterol and increased HDL cholesterol in hypercholesterolemic patients. Won et al. (2007) reported the use of licorice as food ingredients for obesity. They observed that licochalcone A derived from *G. uralensis* reduced the lipase activity as a new inhibitor of pancreatic lipase.

Phytochemistry

Biologically active compounds are primarily secondary metabolites and their derivatives such as alkaloids (Sarker and Nahar 2007; Varsha et al. 2013), glycosides (Firn 2010), flavonoids (Kar 2007; Varsha et al. 2013), phenolics (Cai et al. 2004; Puupponen-Pimiä et al. 2001), saponins (Sarker and Nahar 2007; Vashist and Sharma 2013), tannins (Kar 2007; Varsha et al. 2013), terpenes (Martinez et al. 2008), anthraquinones (Maurya et al. 2008; Vashist and Sharma 2013), essential oils (Martinez et al. 2008; Vashist and Sharma 2013), and steroids (Madziga et al. 2010; Varsha et al. 2013).

Licorice extract contains sugars, starch, bitters, resins, essential oils, tannins, inorganic salts, and low levels of nitrogenous constituents such as proteins, individual amino acids, and nucleic acids (Hoffmann 1990; Isbrucker and Burdock 2006). According to Zhang and Ye (2009) more than 400 compounds have been

isolated from *Glycyrrhiza* species, where triterpene saponins and flavonoids are the main constituents which showed broad biological activity.

Flavonoids

It has been reported that more than 300 flavonoids have been found in various species of *Glycyrrhiza* (Herz et al. 1998; Li et al. 2000). Among them the commonly used flavonoid types are flavanones, chalcones, isoflavanes, isoflavenes, flavones, and isoflavones (Lou and Qin 1995; Xing et al. 2003). *G. glabra* has yellow color due to the flavonoids, e.g., liquiritin and isoliquiritin (Yamamura et al. 1992). A number of licorice flavonoids were identified: liquiritin, liquiritigenin, rhamnolliuiritin, liquiritin apioside, gralbranin, glabrol, licoflavanone, isoliquiritigenin, neoisoliquiritin, licuraside, licochalcone A and B, licoricidin, 7-methillicoricidin, hispaglabridin A and B, liocflavone A and B, liocflavanol, glyzaglabrin, licoisoflavanone, glabroisoflavanone, glabrone, licoricone, and gancaonin (Zhang and Ye 2009).

Hatano et al. (1998) isolated flavonoid glycosides with feruloyl or coumaroyl groups and with an indole conjugate. Ma et al. (2005) isolated and identified bioactive flavonoid compounds, liquiritigenin and isoliquiritigenin, from the crude extract of *G. uralensis* Risch. Franceschelli et al. (2011) identified licochalcone C, the structural isomer of licochalcone A. Other flavonoids such as licoagrodin, licoagrochalcones, glyinflanin B, and glycyrdione A were also reported by several studies (Asl and Hosseinzadeh 2008; Christensen and Kharazmi 2001; Li et al. 2000). Gupta et al. (2008) identified glabridin and hispaglabridin B from ethanolic extract of the roots of *G. glabra*.

Manfredi et al. (2001) isolated and identified bioactive compounds glepidotin B and glepidotin A from the extract of *G. lepidota*. Williamson (2003) isolated and identified isoflavonoid derivatives, namely glabridin, galbrene, glabrone, shinpterocarpin, licoisoflavones A and B, formononetin, glyzarin, and kumatakenin. In other studies hispaglabridin A, hispaglabridin B, 4′-*O*-methylglabridin, and 3′-hydroxy-4′-*O*-methylglabridin were identified from Glycyrrhiza species. Won et al. (2007) isolated and identified licochalcone A from the ethyl acetate extract of the roots of *G. uralensis*. Kinoshita et al. (2005) identified several compounds from the root of *G. glabra*, namely glabridin, galbrene, glabrone, shinpterocarpin, licoisoflavones A and B, formononetin, glyzarin, kumatakenin, hispaglabridin A, hispaglabridin B, glabroisoflavanone A and B, and glabroisoflavanone B.

Saponins

The root of *Glycyrrhiza* contains triterpenoid saponins (glycyrrhizin, glycyrrhizic acid), which are the major characteristic constituents of liquorice, and they are responsible for the sweet taste (Blumenthal et al. 2000). Glycyrrhizic acid is the major triterpenoid saponin in licorice root and the main sweetener of the herb which is 50 times sweeter than sugar (Nomura et al. 2002). Glycyrrhizin and the aglycone of glycyrrhizin are believed to speed the healing of gastric ulcers (Amirova 1993; Blumenthal et al. 2000). Glycyrrhetic acid has shown anti-inflammatory and anti-arthritic activities in animal studies (Amirova 1993). Isbrucker and Burdock (2006) described other triterpenes, namely liquiritic acid, glycyrretol, glabrolide, isoglaborlide, and licorice acid.

Fenwick et al. (1990) described two aglycone forms of glycyrrhizic acid 18β-glycyrrhetinic acid and 18α-glycyrrhetinic acid. Vashist and Sharma (2013) reported about the presence of ammonium glycyrrhizinate (3.4%) and calcium glycyrrhizinate (4%) in the ethanolic extract of *G. glabra*. Zhang and Ye (2009) described several saponins derived from *Glycyrrhiza* species, namely licorice-saponin A3, 22β-actoxylglycyrrhizin, uralsaponin B, apioglycyrrhizin, araboglycyrrhizin, and icorice-saponin E2.

Phenolic Compounds

There are many reports on the phenolic constituents of *Glycyrrhiza* species (Nomura and Fukai 1998). The main phenols include liquiritin, isoliquiritin, liquiritin apioside, and isoprenoid-substituted flavonoids, chromenes, coumarins, and dihydrostilbenes. Nomura et al. (2002) studied phenolic compounds from various *Glycyrrhiza* species, and found isoprenoid-substituted flavonoid (pyranoisoflavan, glabridin) (*G. glabra*), isoflavans (*G. uralensis*), licochalcone A (*G. inflate, G. eurycarpa*), licoricidin (6), and licorisoflavan A (*G. aspera*). For example isobavachin is observed in *G. pallidiflora*, sigmoidin B in *G. uralensis*, and liquiritigenin in *Glycyrrhiza* species (Nomura and Fukai 1998).

Zhang and Ye (2009) described several phenolic compounds derived from *Glycyrrhiza* species including glycycoumarin, glabrocoumarin, glycyrin, inflacoumarin A, licopyranocoumarin, isoglycerol, neoglycerol, licobenzofuran, licocoumarone, glabrocoumarone, gancaonin, and kanzonol. In another study Ammar et al. (2012) isolated phenolic compounds, namely liquiriteginin, liquiritin apioside, neoliquiritin apioside, isoliquiritin, isoliquritin apioside, licuraside2-(5-*P*-coumaryl apiosyl), and isoliquiritin from the total polar extract of *G. glabra* utilizing different chromatographic techniques.

Isolation and identification of isoliquiritigenin from licorice grown in China have been reported by Chin et al. (2007) and liquiritin by Huang et al. (2010).

Zhu et al. (2008) studied biologically active compounds of *G. uralensis* collected in Mongolia and found three flavanone constituents (liquiritin apioside, liquiritin, and liquiritigenin) and three chalcones (isoliquiritin apioside, isoliquiritin, and isoliquiritigenin). Similar observation was reported by Williamson (2003) who identified liquiritin, liquiritigenin, rhamnoliquiritin, neoliquiritin, chalcones isoliquiritin and isoliquiritigenin, neoisoliquiritin, licuraside, glabrolide, and licoflavonol.

Coumarins

Several coumarins were identified from *G. glabra* including liqcoumarin, glabrocoumarone A and B, herniarin, umbelliferone, and glycyrin (Williamson 2003). Kinoshita et al. (2005) studied coumarins from the *Glycyrrhiza* plants and identified liqcoumarin, glabrocoumarone A and B, herniarin, umbelliferone, glycocoumarin, licofuranocoumarin, licopyranocoumarin, and glabrocoumarin. In recent studies Qiao et al. (2014) identified glycerol, glycycoumarin, and dehydroglyasperin from the root extract of *G. uralensis*. De Simone et al. (2001) described two coumarins of *G. glabra*, glycocoumarin and licopyranocoumarin, which were able to inhibit giant cell formation in HIV-infected cell cultures.

Essential Oils and Other Compounds

Other secondary metabolites such as fatty acids, phenol, guaiacol, asparagines, glucose, sucrose, starch, polysaccharides, and sterols (β-sitosterol, dihydrostigmasterol) have also been found and reported by Näf and Jaquier (2006).

Ali (2013) studied essential oil composition of *G. glabra* and found compounds such as α-pinene, β-pinene, octanol, γ-terpinene, stragole, isofenchon, β-caryophyllene, citronellyl acetate, caryophyllene oxide, and geranyl hexanolate. Among those compounds geranyl hexanolate represents higher percentage (34%) whereas β-pinene was the lowest (1.7%). Khalaf et al. (2010) studied phytoestrogens from roots of *G. glabra* from Syria and identified daidzein, daidzin, genistin, ononin, glycitein, genistein, and coumestrol. Sultana et al. (2010) described dihydrostilbenes from the root extract of *G. glabra* grown in Sicily.

Side Effects and Toxicity

The potentially toxic compounds in licorice are unconfirmed, although deglycyrrhinized licorice (DGL) is reported to be free of adverse effects. The toxic effects of licorice are well documented. Large amounts of licorice may result in severe

Table 2. Summary of contradictions and drug interactions of licorice

Contradictions	Drug interactions
Kidney insufficiency	Cardiac glycosides
High blood pressure	Laxatives
Low blood pressure	Diuretics
Cardiac disease	Thiazides
Prolonged use	Corticoid treatment
Pregnancy	Hydrocortisone
Cirrhosis	Insulin
Chronic hepatitis	
Ex-alcoholics	
Obesity	
Diabetes	

hypertension, hypokalemia, and other signs of mineralocorticoid excess (Asl and Hosseinzadeh 2008).

Large doses (more then ten times the standard dose) taken over a long period of time can lead to a number of dangerous conditions (McGuffin et al. 1997). The use of licorice is contradicted in persons with high blood pressure due to hypertension caused by overuse of licorice (Olukoga and Donaldson 2000). This is thought to be due to the effect of licorice on the aldosterone system (Sharma and Agrawal 2013). Al-Qarawi et al. (2002) report the treatment with licorice extract resulted in dose-dependent increases in plasma renin and sodium with concomitant decreases in plasma cortisol, adrenocorticotropic hormone (ACTH), aldosterone, and potassium levels.

Prolonged use of licorice could result in hypertension, hypokalemia, and edema (DeSmet et al. 1997; Asl and Hosseinzadeh 2008). It is also speculated that since insulin-dependent diabetics appear to be predisposed to hypokalemia and sodium retention, licorice use is contradicted by diabetes (McGuffin et al. 1997; Isbrucker and Burdock 2006).

Licorice should not be used with stimulant laxatives or hypotensive diuretics (such as thiazides) because of the potassium loss associated with the laxatives and diuretics (DeSmet et al. 1997; Asl and Hosseinzadeh 2008). In earlier studies glycyrrhizin has been shown to interfere with 5β-reductase breakdown of corticosteroids, thus prolonging the biological half-life of these steroids. The licorice constituent glycyrrhizin or the aglycone, glycyrrhetinic acid, may increase the effect of corticoid treatment (Brinker 1997) (Table 2).

Conclusion

Licorice (Glycyrrhiza) a leguminous plant and the roots have been used worldwide as a medicine and flavor in industry. It is estimated that more than 400 compounds have been isolated from *Glycyrrhiza* species, where triterpene saponins and flavonoids are the main constituents which showed broad biological activity. The

triterpenoid saponins (glycyrrhizin, glycyrrhizic acid), which are the major characteristic constituents of liquorice, are responsible for the sweet taste. The main phenols include liquiritin, isoliquiritin, and coumarins including liqcoumarin and glabrocoumarone A and B. Pharmacological studies have confirmed that plant extracts and individual biologically active compounds exhibit a broad range of biological activities such as antimicrobial, antiviral, anti-ulcer, antitumor, antioxidant, antiallergic, neuroprotective, anti-inflammatory, hepatoprotective, and dermatological activities. The Glycyrrhiza plant can also be used in the management of impaired learning, dementia, and Alzheimer's disease. The potentially toxic compounds in licorice are unconfirmed, whereas the toxic effects of licorice plant are well documented. Large doses taken over a long period of time can lead to a number of severe disorders. From these data and reports it can be concluded that licorice can be used as a therapeutic drug in low doses for major body ailments and presents no concern for safe use.

References

Adel M, Alousi LA, Salem HA (2005) Licorice: a possible anti-inflammatory and anti-ulcer drug. AAPS PharmSciTech 6:74–82

Akhtar N, Khan MS, Iqbal A, Khan BA, Bashir S (2011) *Glycyrrhiza glabra* extract cream: effect on skin pigment melanin. In: Proceeding book of international conference on bioscience, biochemistry and bioinformatics IPCBEE. IACSIT Press, Singapore

Ali EM (2013) Phytochemical composition, antifungal, antiaflatoxigenic, antioxidant, and anticancer activities of *Glycyrrhiza glabra* L. and *Matricaria chamomilla* L. essential oils. J Med Plants Res 7(29):2197–2207

Al-Qarawi AA, Abdel-Rahman HA, Ali BH, El Mougy SA (2002) Liquorice (*Glycyrrhiza glabra*) and the adrenal-kidney-pituitary axis in rats. Food Chem Toxicol 40(10):1525–1527

Al-Razzuqi RAM, Al-Jawad FH, Al-Hussaini JA, Al-Jeboori AA (2012) Hepatoprotective effect of *Glycyrrhiza glabra* in carbon tetrachloride-induced model of acute liver injury. J Phys Pharm Adv 2(7):259–263

Ambawade S, Kasture VS, Kasturi SB (2001) Anxiolytic activity of *Glycyrrhiza glabra* Linn. J Nat Remedies 2:130–134

Amirova GS (1993) Licorice in Azerbaijan (in Russian). Elm, Baku 104 pp

Anon (2005) *Glycyrrhiza glabra*. Altern Med Rev 10:230–237

Armanini D, Fiore C, Mattarello MJ, Bielenberg J, Palermo M (2002) History of the endocrine effects of licorice. Exp Clin Endocrinol Diabetes 110:257–261

Asgary S, Jafari Dinani N, Madani H, Mahzoni P, Nader G (2007) Effect of *Glycyrrhiza glabra* extract on aorta wall atherosclerotic lesion in hypercholesterolemic rabbits. Pak J Nutr 6(4):313–317

Asl MN, Hosseinzadeh H (2008) Review of pharmacological effects of *Glycyrrhiza* sp. and its bioactive compounds. Phytother Res 22:709–724

Bennett A, Clark-Wibberley T, Stamford IF, Wright JE (1980) Aspirin-induced gastric mucosal damage in rats: cimetidine and deglycyrrhizinated liquorice together give greater protection than low doses of either drug alone. J Pharm Pharmacol 32:151

Biondi DM, Rocco C, Ruberto G (2005) Dihydrostilbene derivatives from *Glycyrrhiza glabra* leaves. J Nat Prod 68:1099–1102

Blumenthal M, Goldberg A, Brinckmann J (2000) Herbal medicine: expanded commission E monographs. Integrative Medicine Communications, Newton, MA

Brinker F (1997) Herb contradictions and drug interactions. Eclectic Medical Publications, Sandy, Portland, OR

Brown K (1995) Medicinal plants, indigenous medicine and conservation of biodiversity in Ghana. In: Swanson T (ed) Intellectual property rights and biodiversity conservation. Cambridge University Press, Cambridge, pp 201–231

Cai Y, Luo Q, Sun M, Corke HA (2004) Antioxidant activity and phenolic compounds of 112 traditional Chinese medicinal plants associated with anticancer. Life Sci 74:2157–2184

Chakravarthi KK, Vadhani RA, Narayan RS (2012) Effect of *Glycyrrhiza glabra* root extract on learning and memory in wistar albino rats. Int J Biol Med Res 3(3):2059–2064

Chen F, Chan KH, Jiang Y, Kao RYT, Lu HT, Fan KW, Cheng VCC, Tsui WHW, Hung IFN, Lee TSW, Guan Y, Peiris JSM, Yuen KY (2004) In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol 31:69–75

Chevallier A (1996) Encyclopedia of medicinal plants. Dorling Kindersley Pty Limited, St Leonards

Chin YW, Jung HA, Liu Y, Su BN, John A, Castoro WJ, Keller MA, Douglas K (2007) Anti oxidant constituents of the roots and stolons of licorice (Glyc*yrrhiza glabra)*. J Agric Food Chem 55(1):4691–4696

Christensen SB, Kharazmi A (2001) Antimalarial natural products. In: Tringali C (ed) Bioactive compounds from natural sources: isolation, characterization and biological properties. Taylor & Francis, New York, pp 379–432

Cinati J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW (2003) Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. Lancet 361:2045–2046

Crance JM, Biziagos E, Passagot J, Van Cuyuck-Gandré H, Deloince DR (1990) Inhibition of hepatitis A virus replication in vitro by antiviral compounds. J Med Virol 31:155–160

Crance JM, Scaramozzino N, Jouan A, Garin D (2003) Interferon, ribavirin, 6-azarridine and glycyrrhizin: antiviral compounds active against pathogenic flaviviruses. Antiviral Res 58:73–79

Curreli F, Friedman K, Alvin E, Flore O (2007) Protective mechanism of glycyrrhizin on acute liver injury induced by carbon tetrachloride in mice. Biol Pharm Bull 30(10):1898–1904

Da Nagao Y, Sata M, Suzuki H, Tanikawa K, Itoh K, Kameyama T (1996) Effectiveness of glycyrrhizin for oral lichen planus in patients with chronic HCV infection. J Gastroenterol 31:691–695

Davis EA, Morris DJ (1991) Medicinal uses of licorice through the millennia: the good and plenty of it. Mol Cell Endocrinol 78:1–6

DeSmet PAGM, Keller K, Hansel R, Chandler RF (1997) Adverse effects of herbal drugs, vol 2–3. Springer, Berlin

Dhingra D, Sharma A (2005) Evaluation of antidepressant-like activity of glycyrrhizin in mice. Indian J Pharmacol 37:390–394

Dhingra D, Sharma A (2006) Antidepressant-like activity of *Glycyrrhiza glabra* L. in mouse models of immobility tests. Prog Neuropsychopharmacol Biol Psychiatry 30:449–454

Dong S, Inoue A, Zhu Y, Tanji M, Kiyama R (2007) Activation of rapid signaling pathways and the subsequent transcriptional regulation of breast cancer MCF-7 by the treatment with an extract of *Glycyrrhiza glabra* root. Food Chem Toxicol 45:2470–2478

Fatima A, Gupt VK, Luqman S, Negi AS, Kumar JK, Shanker K, Saikia D, Srivastava S, Darokar MP, Khanuja SPS (2009) Antifungal activity of *Glycyrrhiza glabra* extracts and its constituent glabridin. Phytother Res 23:1990–1993

Fenwick GR, Lutomski J, Nieman C (1990) Liquorice, *Glycyrrhiza glabra* L. composition, uses and analysis. Food Chem 38:119–143

Fiore C, Eisenhut M, Ragazzi E, Zanchin G, Armanini D (2005) A history of the therapeutic use of liquorice in Europe. J Ethnopharmacol 99:317–324

Fiore C, Eisenhut M, Krausse R, Ragazzi E, Pellati D, Armanini D, Bielenberg J (2009) Antiviral effects of *Glycyrrhiza* species. Am J Chin Med 37(2):383–394

Firn R (2010) Nature's chemicals: the natural products that shaped our world. Oxford University Press, Oxford, pp 74–75

Franceschelli S, Pesce M, Vinciguerra I, Ferrone A, Riccioni G, Patruno A, Grilli A, Felaco M, Speranza L (2011) Licocalchone-C extracted from Glycyrrhiza glabra inhibits lipopolysaccharide-interferon-gamma inflammation by improving antioxidant conditions and regulating inducible nitric oxide synthase expression. Molecules 16:5720–5734

Fuhrman B, Volkova N, Kaplan M, Presser D, Attias J, Hayek T, Aviram M (2002) Antiatherosclerotic effect of licorice extract supplementation on hypercholestrolomic patients. Nutr., 18:268–273

Fujisawa Y, Sakamoto M, Matsushita M, Fujita T, Nishioka K (2000) Glycyrrhizin inhibits the lytic pathway of complement—possible mechanism of its anti-inflammatory effect on liver cells in viral hepatitis. Microbiol Immunol 44(9):799–804

Fukai T, Cai BS, Maruno K, Miyakawa Y, Konishi M, Nomura T (1998) An isoprenylated flavanone from *Glycyrrhiza glabra* and rec-assay of licorice phenols. Phytochemistry 49(7):2005–2013

Fukai T, Ali M, Kaitou K, Kanda T, Terada S, Nomura T (2002) Anti-*Helicobacter pylori* flavonoids from licorice extract. Life Sci 71:1449–1463

Furuhashi I, Iwata S, Shibata S, Sato T, Inoue H (2005) Inhibition by licochalcone A, a novel flavonoid isolated from liquorice root, of IL-1β-induced PGE2 production in human skin fibroblasts. J Pharm Pharmacol 57:1661–1666

Gareri P, Condorelli D, Belluardo N, Russo E, Loiacono A, Barresi V, Trovato-Salinaro A, Mirone MB, Ferreri Ibbadu G, De Sarro G (2004) Anticonvulsant effects of carbenoxolone in genetically epilepsy prone rats (GEPRs). Neuropharmacology 47(8):1205–1216

Gupta VK, Fatima A, Faridi U, Negi AS, Shanker K, Kumar JK, Rahuja N, Luqman S, Sisodia BS, Saikia DS, Darokar MP, Khanuja SPS (2008) Antimicrobial potential of *Glycyrrhiza glabra* roots. J Ethnopharmacol 116:377–380

Hatano T, Takagi M, Ito H, Yoshida T (1998) Acylated flavonoid glycosides and accompanying phenolics from licorice. Phytochemistry 47:287–293

Hatano T, Shintani Y, Aga Y, Shiota S, Tsuchiya T, Yoshida T (2000) Phenolic constituents of licorice. VIII. Structures of glicophenone and glicoisoflavanone, and effects of licorice phenolics on methicillin resistant *Staphylococcus aureus*. Chem Pharm Bull 48:1286–1292

Hattori T, Ikematsu S, Koito A, Matsushita S, Maeda Y, Hada M, Fujimaki M, Takatsuki K (1989) Preliminary evidence for inhibitory effect of glycyrrhizin on HIV replication in patients with AIDS. Antiviral Res 11:255–261

Hayash H, Hattori S, Inoue K, Khodzhimatov O, Ashurmetov O, Ito M, Honda G (2003) Field survey of *Glycyrrhiza* plants in Central Asia: chemical characterization of *G. glabra* collected in Uzbekistan. Chem Pharm Bull 51(11):1338–1340

Herz W, Kirby GW, Moore RE, Steglich W, Tamm C (1998) Fortschritte der Chemie Organischer Naturstoffe, vol 73. Springer, New York

Hesham RE, Shgeru N (2002) Chemistry of bioflavonoids. Indian J Pharm Educ 36:191–194

Hoffman D (2000) Easy breathing: natural treatments for asthma, colds, flu, coughs, allergies, sinusitis. Storey Books, Pownal, VT

Hoffmann D (1990) The new holistic herbal, 2nd edn. Element, Shaftesbury

Hojo H, Sato J (2002) Antifungal activity of licorice (*Glycyrrhiza glabra*) and potential applications in beverage. Foods Food Ingred J 203:27–33

Hong ND, Koo BH, Joo SM, Lee SK (1988) Studies on the efficacy of combined preparation of crude drugs. Effects of sipmidojuksan on the central nervous and cardiovascular systems. Korean J Pharmacol 19(2):141

Hossain MS, Hossain MA, Islam R, Alam AH, Zahan K, Sarkar S, Farooque MA (2004) Antimicrobial and cytotoxic activities of 2-aminobenzoic acid and 2-aminophenol and their coordination complexes with magnesium (Mg-II). Pak J Biol Sci 7:25–27

Hsu YL, Kuo PL, Chiang LC, Lin CC (2004) Isoliquiritigenin inhibits the proliferation and induces the apoptosis of human non-small cell lung cancer A549 cells. Clin Exp Pharmacol Physiol 31(7):414–418

Huang M, Wang W, Wei S (2010) Investigation on medicinal plant resources of Glycyrrhiza uralensis in China and chemical assessment of its underground part. J Nat Med 63(2):137–146

Huxley A (1992) Dictionary of gardening. Stockton Press, New York

Isbrucker RA, Burdock GA (2006) Risk and safety assessment on the consumption of licorice root (*Glycyrrhiza* sp.), its extract and powder as a food ingredient, with emphasis on the pharmacology and toxicology of glycyrrhizin. Regul Toxicol Pharmacol 46:167–192

Jeong HG, You HJ, Park SJ, Moon AR, Chung YC, Kang SK, Chun HK (2002) Hepatoprotective effects of 18β-glycyrrhetinic acid on carbon tetrachloride-induced liver injury: inhibition of cytochrome P450 2E1 expression. Pharm Res 46:221–227

Jo EH, Kim SH, Ra JC, Kim SR, Cho SD, Jung JW, Yang SR, Park JS, Hwang JW, Aruoma OI, Kim TY, Lee YS, Kang KS (2005) Chemopreventive properties of the ethanol extract of Chinese licorice (*Glycyrrhiza uralensis*) root: induction of apoptosis and G1 cell cycle arrest in MCF-7 human breast cancer cells. Cancer Lett 230:239–247

Kakegawa H, Matsumoto H, Satoh T (1992) Inhibitory effects of some natural products on the activation of hyaluronidase and their anti-allergic actions. Chem Pharm Bull 40:1439–1442

Kanazawa M, Satomi Y, Mizutani Y, Ukimura O, Kawauchi A, Sakai T, Baba M, Okuyama T, Nishino H, Miki T (2003) Isoliquiritigenin inhibits the growth of prostate cancer. Eur Urol 43(5):580–586

Kang JS, Yoon YD, Cho IJ, Han MH, Lee CW, Park SK, Kim HM (2005) Glabridin, an isoflavan from licorice root, inhibits inducible nitric-oxide synthase expression and improves survival of mice in experimental model of septic shock. J Pharmacol Exp Ther 312(3):1187–1194

Kar A (2007) Pharmacognosy and pharmacobiotechnology. New Age International Ltd Publishers, New Delhi, pp 332–600

Khalaf I, Vlase L, Lazăr D, Corciovă A, Ivănescu B, Lazăr MI (2010) Hplc-Ms study of phytoestrogens from *Glycyrrhiza glabra*. Farmacia 58(1):89–94

Kinoshita T, Tamura Y, Mizutani K (2005) The isolation and structure elucidation of minor isoflavonoids from licorice of *Glycyrrhiza glabra* origin. Chem Pharm Bull 53:847–849

Kong ND, Chang IK, Lee SI, Kim NJ (1984) Studies on the efficacy of combined preparation of crude drugs: effects of "Bojungikgi-tang" on the digestive system, blood pressure and diuretic actions. Korean J Pharmacog 15(3):121–127

Kroes BH, Beukelman CJ, van den Berg AJ, Wolbink GJ, van Dijk H, Labadie RP (1997) Inhibition of human complement by beta-glycyrrhetinic acid. Immunology 90(1):115–120

Kuo KK, Chang JS, Wang KC, Chiang LC (2009) Water extract of *Glycyrrhiza uralensis* inhibited enterovirus 71 in a human foreskin fibroblast cell line. Am J Chin Med 37(2):383–394

Lateef M, Iqba L, Fatima N, Siddiqui K, Afza N, Zia-ul-Haq M, Ahmad M (2012) Evaluation of antioxidant and urease inhibition activities of roots of Glycyrrhiza glabra. Pak J Pharm Sci 25:99–102

Lee KT, Kim BJ, Kim HJ, Heo MY, Kim HP (1997) Biological screening of 100 plant extracts for cosmetic use (I): inhibitory activities of tyrosinase and DOPA auto-oxidation. Int J Cosmet Sci 19:291–298

Lee J, Jung E, Park J, Jung K, Park J, Kim J, Hong S, Park J, Park S, Lee S, Park D (2005) Glycyrrhizin induces melanogenesis by elevating a camp level in b16 melanoma cells. J Invest Dermatol 124:405–411

Li W, Asada Y, Yoshikawa T (2000) Flavonoid constituents from *Glycyrrhiza glabra* hairy root cultures. Phytochemistry 55:447–456

Liu W, Kato M, Akhand A, Hayakawa A, Takemura M, Yoshida S, Suzuki H, Nakashima I (1998) The herbal medicine Sho-saiko-to inhibits the growth of malignant melanoma cells by up-regulating Fas mediated apoptosis and arresting cell cycle through down regulation of cyclin dependent kinases. Int J Oncol 12:1321–1326

Lou ZC, Qin B (1995) Species systematization and quality evaluation of commonly used Chinese traditional drugs. North ed, vol 1–3. Beijing Medical University Press and Peking Union Medical College Press, Beijing, p 19

Lucas (1976) Nature's medicines. Melvin Powers, Wilshire Book Company, Hollywood, CA

Ma CJ, Li GS, Zhang DL, Liu K, Fan X (2005) One step isolation and purification of liquiritigenin and isoliquiritigenin from *Glycyrrhiza uralensis* Risch. using high-speed counter-current chromatography. J Chromatogr 1078:188–192

Madziga HA, Sanni S, Sandabe UK (2010) Phytochemical and elemental analysis of *Acalypha wilkesiana* leaf. J Am Sci 6(11):510–514
Manfredi KP, Vallurupalli V, Demidova M, Kindscher K, Pannell LK (2001) Isolation of an anti-HIV diprenylated bibenzyl from *Glycyrrhiza lepidota*. Phytochemistry 58:153–157
Martinez MJA, Lazaro RM, del Olmo LMB, Benito PB (2008) Anti-infectious activity in the Anthemideae tribe. Stud Nat Prod Chem 35:445–516
Masoomeh MJ, Kiarash G (2007) In vitro susceptibility of *Helicobacter pylori* to licorice extract. Iran J Pharm Res 6:69–72
Matsui S, Matsumoto H, Sonoda Y, Ando K, Aizu-Yokota E, Sato T, Kasahara T (2004) Glycyrrhizin and related compounds down-regulate production of inflammatory chemokines IL-8 and eotaxin 1 in a human lung fibroblast cell line. Int Immunopharmacol 4(13):1633–1644
Maurya R, Singh G, Yadav PP (2008) Antiosteoporotic agents from natural sources. Stud Nat Prod Chem 35:517–545
McGuffin M, Hobbs C, Upton R, Goldberg A (1997) Botanical safety handbook. CRC Press, Boca Raton, FL
Meghashri SG (2009) In vitro antifungal and antibacterial activities of root extract of *Glycyrrhiza glabra*. J Appl Sci Res 5:1436–1439
Mills SY, Bone K (2000) Principles and practice of phytotherapy: modern herbal medicine. Churchill Livingstone, London
Mishra NK, Bstia S, Mishra G, Chowdary KA, Patra S (2011) Anti-arthritic activity of *Glycyrrhiza glabra*, *Boswellia serrata* and their synergistic activity in combined formulation studied in Freund's adjuvant induced arthritic rats. J Pharm Educ Res 2:92–98
Muralidharan P, Balamurugan G, Babu V (2009) Cerebroprotective effect of *Glycyrrhiza glabra* Linn. root extract on hypoxic rats. Bangladesh J Pharmacol 4:60–64
Näf R, Jaquier A (2006) New lactones in liquorice (*Glycyrrhiza glabra* L.). Flavour Fragr J 21:193–197
Nand P, Drabu S, Gupta R (2012) Phytochemical and antimicrobial screening of medicinal plants for the treatment of acne. Indian J Nat Prod Res 3(1):28–32
Nerya O, Vaya J, Musa R, Izrael S, Ben-Arie R, Tamir S (2003) Glabrene and isoliquiritigenin as tyrosinase inhibitors from liquorice roots. J Agric Food Chem 51(5):1201–1207
Nitalikar MM, Munde KC, Dhore BV, Shikalgar SN (2010) Studies of antibacterial activities of *Glycyrrhiza glabra* root extract. Int J PharmTech Res 2(1):899–901
Nomura T, Fukai T (1998) Phenolic constituents of licorice (*Glycyrrhiza* species). In: Herz W, Kirby GW, Moore RE, Steglich W, Ch T (eds) Progress in the chemistry of organic natural products. Springer, Wien, pp 1–140
Nomura T, Fukai T, Akiyama T (2002) Chemistry of phenolic compounds of licorice (*Glycyrrhiza* species) and their estrogenic and cytotoxic activities. Pure Appl Chem 74(7):1199–1206
Olukoga A, Donaldson D (2000) Liquorice and its health implications. J R Soc Promot Health 120:83–89
Orlent H, Hansen BE, Willems M, Brouwer JT, Huber R, Kullak-Ublick GA, Gerken G, Zeuzem S, Nevens F, Tielemans WSM, Zondervan PE, Lagging M, Westin J, Schalme SM (2006) Biochemical and histological effects of 26 weeks of glycyrrhizin treatment in chronic hepatitis C: a randomized phase II trial. J Hepatol 45(4):539–546
Öztürk M, Altay V, Hakem KR, Akçiçek E (2017) Liquorice—from botany to phytochemistry, Springer briefs in plant sciences. Springer Nature, Basel, 139 pp. https://doi.org/10.1007/978-3-319-74240-3
Patil SM, Patil MB, Sapkale GN (2009) Antimicrobial activity of *Glycyrrhiza glabra* Linn. Roots. Int J Chem Sci 7(1):585–591
Pellatti D, Fiore C, Armanini D, Rassu M, Bertoloni G (2009) In vitro effects of glycyrrhetinic acid on the growth of clinical isolates of *Candida albicans*. Phytother Res 23:572–574
Plyasunova OA, Egoricheva IN, Fedyuk NV, Pokrovsky AG, Baltina LA, Murinov YI, Tolstikov GA (1992) Antiviral activity of licorice. Voprosy Virusologii 37:235–238

Puupponen-Pimiä R, Nohynek L, Meier C, Kähkönen M, Heinonen M, Hopia A, Oksman-Caldentey KM (2001) Antimicrobial properties of phenolic compounds from berries. J Appl Microbiol 90:494–507

Qiao X, Liu CF, Ji S, Lin XH, Guo DA, Ye M (2014) Simultaneous determination of five minor coumarins and flavonoids in *Glycyrrhiza uralensis* by solid-phase extraction and high-performance liquid chromatography/electrospray ionization tandem mass spectrometry. Planta Med 80(2-3):237–242

Rahman MS, Rashid MA (2008) Antimicrobial activity and cytotoxicity of Eclipta prostrata. Oriental Pharm Exp Med 8:47–52

Ram A, Mabalirajan U, Das M, Bhattacharya I, Dinda AK, Gangal SV, Ghosh B (2006) Glycyrrhizin alleviates experimental allergic asthma in mice. Int Immunopharm 6(9):1468–1477

Reid D (2001) A handbook of Chinese healing herbs. Periplus, Singapore

Salvi M, Fiore C, Armanini D, Toninello A (2003) Glycyrrhetinic acid-induced permeability transition in rat liver mitochondria. Biochem Pharmacol 66:2375–2379

Sarker SD, Nahar L (2007) Chemistry for pharmacy students: general, organic and natural product chemistry. Wiley, London

Satomi Y, Nishino H, Shibata S (2005) Glycyrrhetinic acid and related compounds induce G1 arrest and apoptosis in human hepatocellular carcinoma HepG2. Anticancer Res 25(6):4043–4047

Saxena S (2005) *Glycyrrhiza glabra*: medicine over the millennium. Nat Prod Radiance 4(5):358–367

Schulz V, Hänsel R, Tyler VE (1998) Rational phytotherapy. A physicians' guide to herbal medicine. Springer, Berlin, pp 160–187

Sharma V, Agrawal RC (2013) Glycyrrhiza glabra-a plant for the future. J. Pharm Med Scien 2(3):15–20

Sharma V, Agrawal RC, Pandey S (2013) Phytochemical screening and determination of antibacterial and anti-oxidant potential of *Glycyrrhiza glabra* root extracts. J Environ Res Dev 7(4):1552–1558

Sheehan MP, Atherton DJ (1992) A controlled trial of traditional Chinese medicinal plants in widespread non-exudative atopic eczema. Br J Dermatol 126(2):179–184

Sheela ML, Ramakrishna MK, Salimath BP (2006) Angiogenic and proliferative effects of the cytokine VEGF in Ehrlich ascites tumor cells is inhibited by *Glycyrrhiza glabra*. Int Immunopharmacol 6:494–498

Shin EM, Zhou HY, Guo LY, Kim JA, Lee SH, Merfort I, Kang SS, Kim SM, Kim S, Kim YS (2008) Anti-inflammatory effects of glycyrol isolated from *Glycyrrhiza uralensis* in LPS-stimulated RAW264.7 macrophages. Int Immunopharmacol 8:1524–1532

Shinwari ZK, Khan I, Naz S, Hussain A (2009) Assessment of antibacterial activity of three plants used in Pakistan to cure respiratory diseases. Afr J Biotechnol 8(24):7082–7086

Shiota G, Harada K, Ishida M, Tomie Y, Okubo M, Katayama S, Ito H, Kawasaki H (1999) Inhibition of hepatocellular carcinoma by glycyrrhizin in diethylnitrosamine-treated mice. Carcinogenesis 20:59–63

Shirinyan E, Panosyan A, Barikyan M, Avakyan O (1988) New antistressor compounds from licorice. Izv Akad Nauk USSR 6:932–936 (in Russian)

Singh M (2010) Comparative phytochemical and antioxidant study of aqueous extracts of *Glycyrrhiza glabra* (mulethi) and *Piper longum* (long pepper). Int J Drug Res Technol 2:203–207

Siracusa L, Saija A, Cristani M, Cimino F, D'Arrigo M, Trombetta D, Rao F, Ruberto G (2011) Phytocomplexes from liquorice (*Glycyrrhiza glabra* L.) leaves—chemical characterization and evaluation of their antioxidant, anti-genotoxic and anti-inflammatory activity. Fitoterapia 82(4):546–556

Sitohy MZ, El-Massry RA, El-Saadany SS, Labib SM (1991) Metabolic effect of licorice roots (*Glycyrrhiza glabra*) on lipid distribution pattern, liver and renal functions of albino rats. Nahrung 35:799–806

Škrovánková S, Mišurcová L, Machů L (2012) Chapter 3—Antioxidant activity and protecting health effects of common medicinal plants. Adv Food Nutr Res 67:75–139

Sokolov S, Zamotayev I (1985) Directory of medicinal plants. Medicina, Moscow (in Russian)

Statti GA, Tundis R, Sacchetti G, Muzzoli M, Bianchi A, Menichini F (2004) Variability in the content of active constituents and biological activity of *Glycyrrhiza glabra*. Fitoterapia 75:371–374

Subramoniam A, Pushpangadan P (1999) Development of phytomedicines for liver diseases. Indian J Pharmacol 31:166–175

Sultana S, Haque A, Hamid K, Urmi KF, Roy S (2010) Antimicrobial, cytotoxic and antioxidant activity of methanolic extract of *Glycyrrhiza glabra*. Agric Biol J North Am 1(5):957–960

Tamir S, Eizenberg M, Somjen D, Stern N, Shelach R, Kaye A, Vaya J (2000) Estrogenic and antiproliferative properties of glabridin from licorice in human breast cancer cells. Cancer Res 60:5704–5709

Tanaka Y, Kikuzaki H, Fukuda S, Nakatani N (2001) Antibacterial compounds of licorice against upper airway respiratory tract pathogens. J Nutr Sci Vitaminol 47:270–273

Tandon A, Tandon BN, Bhujwala RA (2002) Clinical spectrum of acute sporadic hepatitis E and possible benefit of glycyrrhizin therapy. Hepatol Res 23:55–61

Tharkar PR, Tatiya AU, Shinde PR, Surana SJ, Patil UK (2010) Antifungal activity of *Glycyrrhiza glabra* Linn. and *Emblica officinalis* Gaertn. by direct bioautography method. Int J Pharm Res 2:1547–1549

Tokiwa T, Harada K, Matsumura T, Tukiyama T (2004) Oriental medicinal herb, *Periploca sepium*, extract inhibits growth and IL-6 production of human synovial fibroblast-like cells. Pharm Bull 27:1691–1693

Toshio F, Kazue S, Taro N (2003) Preliminary evaluation of anti nephritis and radical scavenging activities of glabridin from *Glycyrrhiza glabra* Linn. Fitotherapia 74:624–629

Tsuda T, Kubota K, Yasuda K, Nishikava S, Sugaya A, Sugaya E (1986) Effects of Chinese herbal medicine "Kanbalu-Taiso-To" on transmembrane ionic currents and its local anesthetic action. J Ethnopharmacol 17(3):257–261

Van Marle J, Aarsen PN, Lind A, van Weeren Kramer J (1981) Deglycyrrhizinised liquorice (DGL) and the renewal of rat stomach epithelium. Eur J Pharmacol 72:219–225

Van Rossum TG, Vulto AG, Hop WC, Schalm SW (1999) Pharmacokinetics of intravenous glycyrrhizin after single and multiple doses in patients with chronic hepatitis C infection. Clin Ther 21:2080–2090

Van Rossum TG, Vulto AG, Hop WC, Schalm SW (2001) Glycyrrhizin-induced reduction of ALT in European patients with chronic hepatitis C. Am J Gastroenterol 96:2432–2437

Varsha S, Agrawal RC, Sonam P (2013) Phytochemical screening and determination of antibacterial and anti-oxidant potential of *Glycyrrhiza glabra* root extracts. J Environ Res Dev 7(4):1552–1558

Vashist H, Sharma D (2013) Pharmacognostical aspects of *Glycyrrhiza glabra*. Asian J Pharm Clin Res 6(4):55–59

Vaya J, Belinky PA, Aviram M (1997) Antioxidant constituents from licorice roots: isolation, structure elucidation and antioxidative capacity toward LDL oxidation. Free Radic Biol Med 23:302–313

Vaya J, Belinky PA, Aviram M (1998) Structural aspects of the inhibitory effect of glabridin on LDL oxidation. Free Radic Biol Med 24:1419–1429

Vibha JB, Choudhary K, Singh M, Rathore MS, Shekhawat NS (2009) A Study on pharmacokinetics and therapeutic efficacy of *Glycyrrhiza glabra*: a miracle medicinal herb. Bot Res Int 2(3):157–163

Wang ZY, Athar M, Bickers DR (2000) Licorice in foods and herbal drugs: chemistry, pharmacology, toxicology and uses. In: Mazza G, Oomah BD (eds) Herbs, botanicals and teas. Technomic Publishing Co., Lancaster, PA, pp 321–335

Wang W, Hu X, Zhao Z, Liu P, Hu Y, Zhou J, Zhou D, Wang Z, Guo D, Guo H (2008) Antidepressant-like effects of liquiritin and isoliquiritin from *Glycyrrhiza uralensis* in the forced swimming test and tail suspension test in mice. Prog Neuropsychopharmacol Biol Psychiatry 32:1179–1184

Weiss RF, Fintelmann V (2000) Herbal medicine. Georg Thieme Verlag, Stuttgart

Williamson EM (2003) Potter's cyclopedia of herbal medicine. C.W. Daniel, Saffron Walden, pp 269–271

Won SR, Kim SK, Kim YM, Lee PH, Ryu JH, Kim JW, Rhee HI (2007) Licochalcone A: a lipase inhibitor from the roots of *Glycyrrhiza uralensis*. Food Res Int 40:1046–1050

Wu YT, Shen C, Yin J, Yu JP, Meng Q (2006) Azathioprine hepatotoxicity and the protective effect of liquorice and glycyrrhizic acid. Phytother Res 20(8):640–645

Xing GX, Li N, Wang T, Yang MY (2003) Advances in studies on flavonoids of licorice. China J Chin Mater Med 28(7):593–597

Yamamura Y, Kawakami J, Santa T, Kotaki H, Uchino K, Sawada Y, Tanaka N, Iga T (1992) Pharmacokinetic profile of glycyrrhizin in healthy volunteers by a new high-performance liquid chromatographic method. J Pharm Sci 81(10):1042–1046

Yoon G, Jung YD, Cheon SH (2005) Cytotoxic allylretrochalcone from the roots of *Glycyrrhiza inflate*. Chem Pharm Bull 53:694–695

Zhang Q, Ye M (2009) Chemical analysis of the Chinese herbal medicine Gan-Cao (licorice). J Chromatogr 1216(11):1954–1969

Zhao ZY, Wang WX, Guo HZ, Guan ZQ, Zhou DF (2006) Anti-depressive effect of liquiritin on chronic stress depression in rats. Chin J Clin Rehabil 27:69–72

Zhu YP (1998) Chinese materia medica: chemistry, pharmacology and applications. Harwood Academic Publishers, Amsterdam

Zhu S, Sugiyama R, Batkhuu J, Sanchir C, Zou K, Komatsu K (2008) Survey of Glycyrrhizae Radix resources in Mongolia: chemical assessment of the underground part of *Glycyrrhiza uralensis* and comparison with Chinese *Glycyrrhizae Radix*. Phytother Res 22(2):141–148

Glycyrrhiza glabra (Licorice) in Turkmenistan: Medicinal and Biological Aspects

Svetlana A. Pleskanovskaya, Maya A. Mamedova, Mehri A. Ashiraliyeva, Volkan Altay, and Munir Ozturk

Introduction

Turkmenistan (Fig. 1) is spread over a vast area of deserts of Turan, Karakum, Caspian, and Sundukli on the right bank of Amu Darya river. In the north lie Kopetdag-Khorasan mountains, and low ranges of Paropamisus and Gissar Mountains. Almost all territory of the country is located in the dry subtropical desert and semidesert zones (Kurganova 1966), experiencing a sharp continental and drought-dominated climate. The flora is quite peculiar and distinctive due to physiographic conditions which influence its formation, but also because of the characteristics of interrelation with contiguous floras of Western Asia (Iran) and other regions of Central Asia.

There are four floristic (botanical-geographical) regions (Muravyeva 1991):

1. Kopetdag-Khorasan mountainous province: Great Balkan, Minor Balkan, Kopetdag-North-Western Kopetdag, South-Western Kopetdag, Eastern Kopetdag.
2. Transitional territory (foothills and low mountains) of Karabil-Badkhyz.
3. Central-Asian mountainous province: Kugitang and hills west to Kugitang.
4. Turan desert province: Karakums, Sundukli, Capian deserts, and Ustyurt Plateau.

S. A. Pleskanovskaya · M. A. Mamedova · M. A. Ashiraliyeva
State Medical University of Turkmenistan, Ashgabat, Turkmenistan

V. Altay
Biology Department, Faculty of Science and Arts, Hatay Mustafa Kemal University, Hatay, Türkiye

M. Ozturk (✉)
Vice President of the Islamic World Academy of Sciences, Amann, Jordan

Department of Botany, Centre for Environmental Studies, Ege University, Izmir, Turkey

M. Ozturk, K. R. Hakeem (eds.), *Plant and Human Health, Volume 3*,
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Fig. 1 Map showing the study area (www.uyduharita.org/turkmenistan)

The flora is represented by more than 2650 species, some of which are rare ones. Kopetdag Mountain's flora is particularly rich where one can find more than 1700 species of wild plants, 332 of which are endemics. Systematic research on Turkmenistan's flora started 150 years ago. A total of 7 volumes entitled "Flora of Turkmenistan" have been published during 1928–1960. In 1988 the book "Determination of Plants of Turkmenistan" was published, which describes 2800 species from 133 families, all arranged in accordance with A. Engler's system of classification (Obuchov 1934; Nikitin and Geldichanov 1988).

One of the important plants in Turkmenistan flora is licorice. Licorice is known as "buyan" in Turkmen language. It belongs to the family Fabaceae. The plant species included in the genus *Glycyrrhiza* are well known from ancient times. Mountains of Central Asia are reported to be the center of origin of this genus. The first official mentioning of this plant appears in the work of Theophrastus, written more than 2300 years ago. In the third century BC he has commented on the taste of different

roots such as sweet Scythian root which grows around the lake Maeotis (Sea of Azov), which is good for asthma, dry cough, and all pectoral diseases. Licorice root has been used in ancient Chinese, Indian, and Tibetan medicine as well as in West Asia as well as Mediterranean countries. It has made its way to the European medicine around twelfth century (Ozturk et al. 2017a). *Glycyrrhiza* is divided into two groups—first group combines the species that contain glycyrrhizic acid (glycyrrhizin) and the second group lacks it. The genus of *Glycyrrhiza* includes 11 species. The first group includes *G. glabra, G. uralensis, G. korshinskyi, G. aspera,* and *G. inflata*, whereas the second group includes *G. echinata, G. pallidiflora, G. foetida, G. lepidota, G. acanthocarpa,* and *G. astragalina. Glycyrrhiza glabra* belongs to the first group (Obuchov 1934; Nikitin and Geldichanov 1988).

The perennial, herbaceous *G. glabra* (Fig. 2) is widespread in Turkmenistan and has vigorous roots brown from outside and rhizomes. The underground part consists of a vertical tap root, often with several branches, and horizontal rhizomes or stolons, thrown off from the root below the ground, which attain a length of several meters. These runners are furnished with leaf buds and produce stems in the second year. The perennial roots as well as the long horizontal stolons are equally preserved for use. The stem is branching and upright, 0.5–2.0 m tall with small glandular prickles. Stipules are lanceolate often deciduous during the flowering. The plant has light, spreading, pinnate foliage, consisting of 9–10 pairs of leaflets. The leaflets are oblong, ovate with dotted glands. The corolla is violet, or light violet, and calyx is puberulent. In *G. glabra* the pods are smooth, curved, and oblong with 1–8 rounded seeds (Altay et al. 2016; Ozturk et al. 2017a). It is found in the Caspian region, Dashoguz province, Kyurendag, Sumbar, Murgab, Kopetdag, Tejen, and few other places. It generally grows alongside the river valleys, banks, and moist places, and rarely on the dry hills (Ozturk et al. 2017a).

Fig. 2 *Glycyrrhiza glabra* (photo: Greg Kenicer, Royal Botanic Garden Edinburgh—www.powo.science.kew.org)

G. aspera is also found in Turkmenistan. It grows on dry steppes and semideserts, on the foothills and plains, and can survive in various ecological environments including deserts. It is not valuable for industries because of small amounts of glycyrrhizin. It easily becomes a weed due to its ability to quickly propagate with the help of multiple buds on thin rootstocks. It generally grows in Mary province and Kugitang area. *G. aspera* is also a perennial plant, with thin roots and rhizomes. The underground part consists of a vertical root and stolons. The stem is branching and upright, standing up to 0.1–1.5 m tall with small prickles. In the type specimen the pods are spiny. The systematic observation of *Glycyrrhiza* proves that both *G. aspera* and *G. glabra* are found in Turkmenistan (Gladishev 1990). In earlier taxonomical studies *G. glabra* is reported to include three varieties (var. *glandulifera*, var. *pulescens*, and var. *grandiglandulosus*) and one hybrid form. *G. glabra* var. *grandiglandulosus* is reported to be distributed only in Central Kopetdag, on the banks of river next to Kelyata canyon. This plant is described as perennial and grassy with alternate leaves having short hairy and spiny petioles. The stem is upright, hairy, up to 0.6–0.8 m tall. Leaflets are paired, oblong, prickly, and adhesive. In the type specimen glabra, the pods are smooth. This form of licorice is distinctive from other kinds by its larger fruits and heavily covered by glandules. Their morphological features depend on ecological conditions of the place where they grow. Intraspecific variety of licorice is not as big based on its widespread distribution. The reason is that it is grown only by vegetative propagation and we have to deal with clones that are different by form and size of leaves and fruits (Gladishev 1990; Gladishev 1991a, b).

Medicinal Value of Licorice (*G. glabra*)

The root of licorice is known all over the world as a medicinal herb. In olden days Tibetans, Indians, and Arabs prepared drugs from this plant to cure several diseases (Ozturk et al. 2017a, b). The roots from the coast of Amu Darya had a particular place in the old prescriptions. The roots from Kunyaurgench and Termez too were highly valued due to their medicinal properties (Lager 1988). This root has been used by the Greeks in ancient times in the treatment of cough and asthma. Almost all books mention about this right from the Middle Ages (Kurganova 1966; Ozturk et al. 2017a). Avicenna too has recommended the use of licorice roots in the treatment of cutaneous ulcers, kidney and urinary bladder diseases, gastritis, fever, lung disorders like bronchial asthma and chronic bronchitis, as well as heart diseases (Ozturk et al. 2017a). In Central Asia it has been used in the treatment of gastric and duodenal ulcers, against hemorrhoid, tumors, dryness, and spasms in the throat, and as an appetite stimulant and expectorant in the catarrh of the upper respiratory tract. This root is considered to be as important as ginseng in the Chinese medicine and is used as antifebrile, analgesic, and expectorant, as a mild purgative and against eczema (Karriyev 1996; Ozturk et al. 2017a).

Medicinal features of licorice root are due to the high glycyrrhizin acid and presence of a considerable number of flavonoids. In 1933 the Japanese chemists Shinoda and Uyeda first time extracted a flavonoid from these roots. These are derived from flavone NB (flavonon) and chalcone. The main one among these is liquiritigenin and its glycosides: monosides like liquiritin and neoliquiritin and biosides such as globoside and uraloside (Muravyeva 1991). In some of the upper parts of the plant flavonoids C-glycosides such as vitexin and its isomer saponaretin as well as foleroside have been extracted. The plant contains coumarins like umellipheron and gernisarin and such oxybrown acids as ferulic and siponic. Much work has been done in this connection till to date (Ozturk et al. 2017a). Some work has also been carried out on the triterpenic compounds being similar in structure to adrenal gland hormones. The glycyrrhizin acid is reported to metabolize in the organism forming substances affecting corticosteroids. Drugs received on the glycyrrhizin and glycyrric acid basis are used in the treatment of Addison's disease and few other disorders (Ozturk et al. 2017a). Flavonoid preparations such as liquriton and flacarbin have spasmolytic effect (Obuchov 1934; Muravyeva 1991; Socolov and Zamotayev 1990).

Several medicinal preparations like dry and liquid forms from the roots, syrup, powder, and crushed roots are used. All these enter into the composition of various herb mixtures and teas used against respiratory defects, as expectorant, antitussive, and diuretic. These are reported to regulate the water-salt metabolism and are useful in treating gastric ulcers and gastritis (Nikitin and Geldichanov 1988; Ozturk et al. 2017a). Recently the tablets of dry extract of *G. glabra* have been developed with the following composition: dry extract of *G. glabra*, calcium stearate, magnesium subcarbonate, and potato starch (Nepesov et al. 1995). The experimental studies have shown that these tablets dissolve in water and stimulate the production of the mucus, and increase the cell mitotic activity, as well as the number of cells in the main gland and in the pit of the white rat stomach. The functional activity of the specialized cells of the stomach increases and due to this regenerative process is activated in the mucus of stomach. Our contention is that *G. glabra* extract tablets are effective in the stomach due to their hyperfunction in the glandular system diseases (Gladishev 1991a; Khodjageldiyev et al. 1995; Khalmedov et al. 1999).

The root extract tablets were given to the patients as clinical trial in the treatment of gastric ulcerative diseases as a therapy at the "Hospital of Turkmen State Medical Institute" (Gladishev 1991a, b). Another tablet form "*Liquiritin*" containing up to 55% of flavonoids was used in the patients as anti-inflammatory, antispastic, and antacidic agent in hyperacidic gastritis and gastric and duodenal ulcers (Lager 1988; Muravyeva 1991).

The technology used lately in the preparation of emulsion ointments with thick extract of licorice has been developed and introduced (Sakhatov et al. 1997). The ointment has the optimal dehydrogenating activity not less than well-known "*Levomecol*" and "*Vishnevskiy*" ointments. In the treatment of purulent wounds its high healing effect was experimentally observed (Sakhatov et al. 1996; Khudaybergenov et al. 1996). The morphological control over the regeneration process showed that licorice ointment stimulated the appearance of early granulations

containing a large number of lymphocytes and plasmatic cells. Authors consider that the high wound-healing ability of the ointment gives rise to the activation of immune component of inflammation (Nepesov et al. 1995; Karimov and Garadjayev 1997).

The glycyrrhizin acid too enters into the composition of aerosolic ointment "*Epigen*" (*Heminova International S.A.*). This preparation is used successfully in the treatment of vaginosis and cervical erosion. In the treatment of vaginal candidiasis "*Epigen*" is not less effective than well-known "Diflukan" (Annamuradova et al. 1999, 2001). The study of toxicity and chemical properties of the ointment with thick extract of *G. glabra* has shown its well absorption, harmlessness, and ability to hold optimal pH (Socolov and Zamotayev 1990; Shukurova et al. 1995; Shukurova and Avdeenko 1997). Application of thick extract of licorice root to the skin of experimental animals has revealed that there is loss of hair during 5–10 days of administration. Considerable changes in the epithelial cell ultrastructure develop simultaneously. The prolonged use of this extract leads to the epidermal atrophy, hyperkeratosis, dystrophy, and sclerosis of the derma fibrillar structures. These changes are reversed after stopping the use of extract (Nepesov et al. 1995; Kakadjanova and Karimov 1999). In the National Turkmenistan Institute of Medicines in Ashgabat, new medicinal forms of licorice are being evaluated. Gelatinous capsules with 100% dry licorice root extract and powder without auxiliary agents or preservatives are also studied. Active preparations of the glycyrrhizin acid (not less than 25%), flavonoids, trace and macroelements (Ca, Mg, Na), and mucosal substances are under investigation at present; these are effective against *St. aureus, Sh. flexneri, Candida* spp., and *E. coli* (Khalmedov et al. 1999; Khodjageldiyev et al. 1995; Cocanov and Spiridonova 2005).

The decoction of licorice has not lost the importance even today. The root decoction or water solution of its thick extract in combination with other medicinal herbs is used in the monotherapy traditional treatment of pneumonia patients (Sakhatov et al. 1997; Chorekliyev et al. 2003). The effectivity of treatment in the chronic bronchitis patients has increased in the cases of intrabronchial administration of 3.0–5.0 mL of licorice thick extract water solution. In a short period the clinical (Sakhatov et al. 1996; Toychiyev and Hudayberdiyeva 2001) and immune hematological (Khudaybergenov et al. 1996; Rakhmanova et al. 2002) rehabilitation of patients has been achieved. The thick extract water solution is used well in gastroenterology, in particular chronic gastritis and ulcerative diseases of the stomach and the duodenum (Khodjageldiyev et al. 1995; Karimov and Garadjayev 1997) treatment, and stomach surgery (Annamuradova et al. 1999; Chalmedov and Karimov 1995). The water extract protects the mucosal membrane of the stomach from ulcerogenes. The defects of the mucous membrane were found to have recovered in the rabbits in the erosive and ulcerative gastritis after 10–15 days (Annamuradova et al. 2001). The tablets of *G. glabra* have successfully prevented the development of glucous ulcers of the stomach in rats (Shukurova et al. 1995; Chalmedov 1997). The preparations of root on oil basis such as "Licorice oil" "Oil of the *Glycyrrhiza*," and "Shukur mai" have been recommended in the treatment of ulcerative disease of stomach and duodenum associated with *Helicobacter pylori* (Shukurova and

Avdeenko 1997; Kalandiya et al. 2005). Ergeshov et al. (1999) have reported high bactericidal properties of licorice root.

To cleanse the sutural material Turkmen silk with alcoholic or water solution of thick extract of *G. glabra* promotes long-term preservation of silk sterility and prevents the surgical wound from being infected (Kakadjanova and Karimov 1999; Ergeshov et al. 1999). The high efficiency of 5% water solution of the thick extract of *G. glabra* was observed in the treatment of patients with rheumatoid arthritis. Under the traditional treatment the patients were administered 100 mL of 5% water solution of thick extract of *G. glabra* as empty stomach once a day for 4 weeks; not only clinical but also immunological rehabilitations were observed in short term and of great degree. The concentration of Gig decreased in the serum of patients; the tendency to decrease in Riga and IBM was marked when compared to the patients who received only the traditional medical treatment. These data were considered to show immunomodulating features of licorice root decoction (Cocanov and Spiridonova 2005; Kheshiyeva et al. 1996).

Results of our studies have confirmed the immunomodulating activity of preparations of licorice root. The white nonlinear mice were immunized with the erythrocytes of sheep under the administration of 1% water solution of thick extract of *G. glabra*; the number of rosette-forming lymphocytes increased in the spleen of animals sharply in comparison with mice which didn't take preparation (Khmelewskaya and Pleskanowskaya 2000). The ability of licorice to stimulate the immune response of mice to the thymus-dependent antigen was found (Chorekliyev et al. 2003).

In vitro studies with the water solution of thick extract of *G. glabra* have shown that it increases the ability of lymphocytes for the rosula formation with the erythrocytes of sheep (T-rosette formation) in healthy persons. In this case the ability of lymphocytes for the rosette formation with the erythrocytes of mouse (B-rosette formation) and for the double (simultaneously) rosula formation with the erythrocytes of sheep and the erythrocytes of mouse (D-rosula formation) did not change. The triterpenic glycyrrhizin acid given as its monosubstituted ammonium salt-glycyram was stimulative and didn't change T- and B-rosula formation of lymphocytes. The flavonoid component liquiritin stimulated T- and D- but oppressed B-rosula formation (Toychiyev and Hudayberdiyeva 2001; Mavlanov et al. 1991). The data obtained allowed to recommend the water solution of the thick extract of *G. glabra* and its components as an immunomodulator.

The phenomenon of the rosula formation is known to be related to the membranous receptors of lymphocytes and to depend on a degree of expression of letters (Rakhmanova et al. 2002). Therefore, the water solution of thick extract of *G. glabra* as a whole and its main components—the glycyrrhizin acid and liquiritin—modulate the expression of membranous receptors of the lymphocytes of human blood in vitro (Brondz and Rochlin 1978). The quick and complete rehabilitation of immune status in the patient with pneumonia and chronic bronchitis (Khudaybergenov et al. 1996; Toychiyev and Hudayberdiyeva 2001; Rakhmanova et al. 2002) is likely to be affiliated with this exact property of licorice both in the conservative and the surgical treatment. The chronic tonsillitis is known to be one of the manifestations of the deficiency of the immune system in humans (Kalandiya et al. 2005; Mavlanov

et al. 1991; Khmelewskaya et al. 2003). Quick and complete rehabilitation of the immune status is manifested by the increase of number of T-lymphocytes and the decrease of IgG concentration in patients with chronic tonsillitis, when they take licorice decoction approved by the high immunomodulating activity of the drug (Chalmedov and Karimov 1995).

The thick extract of *G. glabra* produces immunocorrigating as well as antitoxic and hepatoprotective effect including the stimulatory effect on the regeneration in the experimental pesticide magnesium chlorate poisoning of animals. Used intragastrically for pesticide poisoning in rabbits the licorice decoction protects the liver tissue from narcosis. The albuminous structure of the liver is restored in 15 days; the cellular infiltration of the interstitial tissue disappears; glycogen, DNA, and RNA are recovered in hepatocytes (Ergeshov et al. 1999; Karimov and Lipchenko 1991). The water solution of the thick extract of *G. glabra* possesses high adaptogenic properties. Under heat stroke the considerable oppression of granulocytopoiesis is observed in rats (Khmelevskaya and Pleskanovskaya 1995). The administration of 1% solution intragastrically 10 days before the heat stroke protects animals from death. Besides, the functional activity of the granulocytopoiesis is preserved (Kheshiyeva et al. 1996). It is likely that it is due to the antioxidative properties of the water solution of the thick licorice extract. The extract decreases the concentration of malondialdehyde in the blood serum, in the liver, and in the spleen of rats under the physiologic stress (Khmelewskaya and Pleskanowskaya 2000; Gurbanova et al. 2000; Gurbanowa and Konstantinowa 2002).

Douglas (2000) has fully stressed the actuality of this issue for medicine and biology. At present the chemical composition of a cell (and/or its organelles) is a starting point for the individual selection of a phytopreparation; that is, cytotoxicity, antibacterial, antiviral, immunostimulating, and anticancerogenic properties as well the insecticide activity of a cell are determined in vitro. However, even then many-sided approaches do not solve a problem of individual sensitivity of a subject to the exact preparation under just that very pathology (Mavlanov et al. 1991; Douglas 2000).

In the Turkmen State Medical Institute the immunology method for the individual selection of medicinal herbs has been developed to treat a range of diseases of internal organs (Brondz and Rochlin 1978; Ovezova and Pleskanovskaya 2002). Medical herbs have been found to be able to modulate in vitro migrational activity of blood leukocytes in healthy volunteers as well as in patients with very different diseases of kidneys, heart, thyroid glands, prostate, and pancreas. The phytopreparation was selected on this basis to treat pathologies in patients. It was determined that 1% water solution of the thick extract or 5% decoction of licorice root is able to modulate considerably the immune response of leukocytes to tissue antigens in vitro depending on the nature of pathology and the degree of sensitivity of a patient to the phytopreparation—either to stimulate the immune response or to inhibit bringing it to a full stop. More than 4000 researches carried out studies to determine the individual sensitivity of patients against 12 medicinal plants including licorice.

The results showed that licorice root decoction is an effective phytopreparation and it was recommended for 83% of patients with pathology of lungs, 64% with

diseases of gallbladder, 54.6% with diseases of cornea, 50% with pathology of kidneys, 50% with pathology of prostate, 30% with pathology of ovaries, 33% with pathology of pancreas, and 20% with autoimmune thyroiditis. The maximal effect of licorice root decoction was observed in patients with pathology of lungs, and the minimal effect was in patients with autoimmune thyroiditis. The individual approach to the administration of phytopreparation increased the efficiency in the treatment of patients with organs indicated (unpublished data). We consider that it is necessary to administer the licorice root decoction very carefully to patients with pathology of thyroid gland and pancreas as far as in 66–67% of cases the preparation in vitro oppresses sharply the immune response of leukocytes to antigens of tissues mentioned and it can provoke the oppression of the functional activity of these organs in vitro.

The preparations of *G. glabra* are of great medicinal and biological significance. They are used widely in the treatment of lungs, gastrointestinal tract, and female genital infections. The properties of licorice studied reveal its efficiency in the treatment of kidneys and cornea due to immunomodulating and antioxidating activity. It can be a preparation of choice in solving the problems on controlled immunocorrection, increasing the organism adaptation possibility (Ozturk et al. 2017a).

Industrial Aspects

Glycyrrhiza plants are known since ancient times (Altay et al. 2016; Karahan et al. 2016; Ozturk et al. 2017a, b). It is said that these plants appeared before olygocen (Kurganova 1966; Ozturk et al. 2017a). However, its trade is said to have started from Azerbaijan in particular from Kura-Araksin lowland. The British-American firm "Mack Andrius" laid the foundation of the industrial purchase of licorice root in the valley of Amu Darya river in the environs of Chardzhou (modern Turkmenabat) in 1906. The licorice root purchased from the valley of Amu Darya is of high quality and valued all over the world. The underground biomass of licorice root of this region is high together with its size (Obuchov 1934).

Since 1923 the Bukhara State Trade purchases the root produced in Turkmenistan. Before 1990s Turkmenistan was the sole leader in purchasing and exporting licorice root. The annual purchase of licorice root by "Soyuzlakrisa" was 21,0022 tons including 14,658 tons delivered by Turkmenistan while Tadzhikistan delivered 164 tons. Currently the region of licorice root takes the area equal to almost 900 km along the right and left banks of Amu Darya valley (Atayev 2004).

To increase purchase of root sovkhozes were established in the republics of Central Asia and Kazakhstan for cultivating licorice. In Turkmenistan its cultivation started in Karabekaul on an area of about 5000 ha. To grow licorice as a crop is more difficult than to exploit its natural thickets. The Botany Institute of Turkmenistan worked out the practical recommendations for cultivation of licorice on the flood lands and sands of the Middle Amu Darya oasis. The intensive cultivation of licorice root gives fruits on the third year of its growth. Normally the first industrial

harvesting of licorice root is carried out in 4–5 years; some quantity of roots (up to 25%) are left in the ground for the renewal of plantation (Gladishev and Kerbabyev 1969). It is cultivated in the pre-oasis sandy tracts of the area which is equal to 8900 ha (Keldjayev 1986). In contrast to the licorice cultivated in the floodlands of the Amy Darya those growing in pre-oasis sands (for instance, in Karabekaul district of Chardzhou region named Turkmenabat velayat today) make partial shrubs from the axil buds of the horizontal roots in the first year (Gladishev and Kerbabyev 1969).

Conclusions

Under the Research Program of the experimental station "Ylym" of Agroindustrial complex "Buyan" named after S.A. Niyazov and Research-industrial amalgamation "Turkmen derman" of the Ministry of Health and Medical Industry of Turkmenistan, the researchers aim at improving the state of licorice thickets and turn it into an industrial crop. The work is going on for the last 20 years. Data on ecological and biological features of this agrocenoses, its development under the conversion of licorice into an industrial crop, as well as the complete botanic characteristics of introduced forms together with recommendations for improving the natural herbage of this plant are presented in this chapter. It is shown that not only licorice root but also its surface part have good fodder properties and can be used in agriculture widely. At present licorice hay makes 90% of all coarse fodder and its thickets serve as all-the-year-round pastures. The hay is ascertained to be the fine fodder to gain fat, as its estrogens are considered to be stimulators for the growth of animals (Gladishev and Kerbabyev 1969; Goryachev 1966; Rizayeva et al. 1969). The results of the long-term experiment on surface and radical improvement of the state of natural licorice thickets and its crop and the analysis of cases reducing the unique natural habitat of the plant are given in a range of monographs and articles by Turkmen scientists (Kurganova 1966; Gladishev 1990, 1991a; Gladishev and Kerbabyev 1969; Kerbabayev and Gladishev 1971; Kerbabayev et al. 1969).

The licorice root is purchased from the valley of Middle Amu Darya (Turkmenabat velayat). It has exceptional trade qualities and is exported from Turkmenistan. The specialized branches of industry for processing of licorice root have been set up in Europe, the USA, and Japan. The exclusive medicinal properties of this unique plant and its rich and peculiar chemical composition point that licorice is a plant of the future.

References

Altay V, Karahan F, Ozturk M, Hakeem KR, Ilhan E, Erayman M (2016) Molecular and ecological investigations on the wild populations of *Glycyrrhiza* L. taxa distributed in the East Mediterranean Area of Turkey. J Plant Res 129(6):1021–1032

Annamuradova AD, Palvanova BB, Jumakuliyeva GP, Choliyev RCh (1999) Licorice root's effectivity in the endocervicoses treatment. In: Proc. annual 59th scient. conf. Turkmen gos. Med. Inst., Ashgabat, Turkmenistan, p 78 (Russian)

Annamuradova AD, Seyradowa BM, Otuzowa GT, Gulliyewa OG, Kakageldiyewa MA (2001) Aýal jyns organlarynyň suwuklama kesellerinde "Epigen" bilen buýan köüiniň şirasiniň bejergi täsirini öwrenmek. In: Proc. annual scient. conf. Turkmen state. Med. Inst., Ashgabat, Turkmenistan, p 328 (Turkmen)

Atayev A (2004) Biological and ecological funds of Turkmenistan licorice agrocenosis' usage. Ilim, Ashgabat, p 287 (Russian)

Brondz BD, Rochlin OV (1978) Molecular and cellular basis of the immunological recognition. Nauka, Moscow, p 304 (Russian)

Chalmedov BS (1997) The experimental study of the tabletted form of the licorice thick extract usage in the stomach' ulcer prophylactics. In: Proc. annual 57th scient. conf. Turkmen gos. Med. Inst., Ashgabat, Turkmenistan, p 95 (Russian)

Chalmedov BS, Karimov ShA (1995) On the possibility of the licorice thick extract usage on the surgical treatment of stomach diseases. In: Annual 55th scient. conf. Turkmen gos. Med. Inst. Devot., 8th anniver. Independ. Ashgabat, Turkmenistan, p 95 (Russian)

Chorekliyev TB, Allaberdiyew AA, Atajanowa MA (2003) Buýanyň, borjagyň we goşadiş ösümliklerinden edilen erginiň ötüşen pnewmoniýaly näsaglara täsiri. In: Proc. annual scient. conf. Turkmen state. Med. Inst., Ashgabat, Turkmenistan, p 194 (Turkmen)

Cocanov A, Spiridonova N (2005) The new native medicine forms of licorice. In: International scientific and practical conference dedicated to the 10th anniversary of State Programme of President of Turkmenistan Saparmurat Turkmenbashy The Grate "Health", Ashkhabad, Turkmenistan, p 575 (Turkmen)

Douglas KA (2000) Biological activity of plants. In: XIII Bitkisel ilaç hammaddeleri Toplantisi, Marmara Universiti Eczacilik Fakultesi Bildiri Özetleri, Istanbul

Ergeshov MB, Amanov GA, Byashimov KU, Berdichanova AB, Kurbanova OP, Chalilov MK (1999) Processing of the silk surgical thread by the licorice solutions. In: Proc. annual 59th scient. conf. Turkmen gos. Med. Inst., Ashgabat, Turkmenistan, p 214 (Russian)

Gladishev AI (1990) Licorice—the valuable medicine technical plant. Edit. Society "Znaniye", Ashkhabad, p 4 (Russian)

Gladishev AI (1991a) Some peculiarity of licorice (*Glycyrrhiza glabra*) ontogenesis in spate its' cultivation. Izvestiya AN TSSR, Ser Biol Scien 1:43–47

Gladishev AI (1991b) The finding of unique example of *Glycyrrhiza glabra* L. root in Amu Darya river poem. Veget Resour 1:74–77

Gladishev AI, Kerbabyev BB (1969) On the licorice culture in the Amu Darya river poem. In: Proc. symp. stud. usage of licorice in the nation. Econ. SSSR. Ilim, Ashkhabad, Turkmenistan, pp 68–74 (Russian)

Goryachev VS (1966) Some purposes of the licorice' fodder usage in SSSR. Nauka, Moscow, pp 171–175 (Russian)

Gurbanova JD, Konstantinova TG, Pleskanovskaya SA, Khmelevskaya TM (2000) Malonic dialdehyde concentration in the licorice root extract treated white mouse internal organs and blood. In: Proc. annual scient. conf. Turkmen state. Med. Inst., Ashgabat, Turkmenistan, p 39 (Turkmen)

Gurbanowa JT, Konstantinowa TG (2002) Eksperimental fisiologik stress seritlerinde buýan köküniň ekstraktynyň antioksidant täsiri. In: Proc. annual scient. conf. Turkmen state. Med. Inst. Devot., 10th cel. Independ. Ashgabat, Turkmenistan, p 171 (Turkmen)

Kakadjanova AG, Karimov ShA (1999) Structural—functional changes of the skin treated by the licorice thick extract. In: Annual 57th scient. conf. Turkmen gos. Med. Inst. Devot., 10th anniver. Independ. Turkmenistan, Ashgabat, Turkmenistan, p 61 (Russian)

Kalandiya I, Kanturinova A, Aldiyarova N, Kuzdenbayeva R (2005) The perspective of the "Licorice oil" and "Shukur may" preparations on the ulcer diseases of stomach and duodenum. In: International scientific and practical conference dedicated to the 10th anniversary of State Programme of President of Turkmenistan Saparmurat Turkmenbashy The Grate "Health", Ashkhabad, Turkmenistane, p 577

Karahan F, Avsar C, Ozyigit II, Berber I (2016) Antimicrobial and antioxidant activities of medicinal plant *Glycyrrhiza glabra* var. *glandulifera* from different habitats. Biotechnol Biotechnol Equip 30(4):797–804

Karimov ShA, Garadjayev BCh (1997) Morphological basis of the on the water prepared licorice thick extract' ointment usage in the fester wounds' treatment. In: Proc. annual 57th scient. conf. Turkmen gos. Med. Inst. Devot, 9th anniver. Independ. Ashgabat, Turkmenistan, p 98 (Russian)

Karimov ShM, Lipchenko MYu (1991) Immune disorders of poisoning magnesium chloratum experimental animals by licorice roots' extract. In: Proc. actual. pupr. immunol. allergol, Ashkhabad, Turkmenistan, pp 92–93 (Russian)

Karriyev MO (1996) Medicine plants of Turkmenistan, Ashgabat, Turkmenistan, pp 195–198 (Russian)

Keldjayev PS (1986) Cultivation of licorice on the preoasis sands, vol 24. TurkmenNIINTI, Ashkhabad, p 17 (Russian)

Kerbabayev BB, Gladishev AI (1971) Turkmen licorice root. Ilim, Ashkhabad, p 94 (Russian)

Kerbabayev BB, Gladishev AI, Kazakov IF (1969) Industrial stocks of the licorice roots in Turkmen SSR. In: Proc. symp. stud. usage of licorice in the nation. Econ. SSSR. Ilim, Ashkhabad, Turkmenistan, pp 17–18 (Russian)

Khalmedov BS, Kurbanov MA, Byashimov KU (1999) Morphological show of the stomach mucosal of the intact animals' treated by the tablets form of the licorice thick extract. In: Proc. annual 58th scient. conf. Turkmen gos. Med. Inst. Devot., 8th anniver. Independ. Ashgabat, Turkmenistan, p 74 (Russian)

Kheshiyeva MB, Seitnepesov KN, Annanepesova OCh, Sergeeva LA, Grigoryan VG (1996) The rheumatoid arthritis patients' receiving the complex treating with licorice roots' solution humoral immunity changes. In: Proc. annual 56th scient. conf. Turkmen gos. Med. Inst., Ashgabat, Turkmenistan, pp 48–49 (Russian)

Khmelevskaya TM, Pleskanovskaya SA (1995) Thick licorice root's extract on the rat's peripheral blood cytosis under the heat shock condition. In: Proc. annual 55th scient. conf. Turkmen gos. Med. Inst. Devot., 8th anniver. Independ. Ashgabat, Turkmenistan, p 75 (Russian)

Khmelewskaya TM, Pleskanowskaya SA (2000) Suňk ýigilindäki rozetka emele getirýan limfositleriň goýy ekstraktynyň tasiri barada. In: Proc. annual scient. conf. Turkmen state. Med. Inst., Ashgabat, Turkmenistan, p 40 (Turkmen)

Khmelewskaya TM, Garayew TA, Pleskanowskaya SA, Nazarowa GA, Kuliyewa B, Soltanow GS (2003) Tonsillektomiýaniň esasynda döreýän stress ýagdaýalarda limfositleriň derman otlara duýujylygy. In: Proc. annual scient. conf. Turkmen state. Med. Inst., Ashgabat, Turkmenistan, p 103 (Turkmen)

Khodjageldiyev TG, Ovvadov DO, Allaberdiyev AA, Muradgeldiyeva D (1995) The effectivity of some medicinal herb of Turkmenistan in gastroenterology. In: Annual 55th scient. conf. Turkmen gos. Med. Inst. Devot., 8th anniver. Independ. Turkmenistan, Ashgabat, Turkmenistan, p 180 (Russian)

Khudaybergenov GS, Garadjayev BCh, Beynar LS, Shukurova GCh, Nepesov GA (1996) Study of antimicrobial activity of prepared on the emulsion basis licorice thick extract' ointment on the experimental fester wound model. In: Proc. annual 56th scient. conf. Turkmen gos. Med. Inst. Devot., 8th anniver. Independ. Ashgabat, Turkmenistan, pp 164–165 (Russian)

Kurganova EA (1966) On the systematic and geographer of the *Glycyrrhiza glabra* L. genus. Pupr. stud. usage licorice in nation. Econ. SSSR. Nauka, Moscow, pp 19–26 (Russian)

Lager AA (1988) Phitoterapiya. Edit. Krasnoyarsky Univ., Krasnoyarsk, p 268 (Russian)
Mavlanov K, Konstantinova TG, Arutyunova TN (1991) The licorice root's extract influence on the hypertension disease patients' cell immunity properties. In: Actual purposes of the immunology and allergology in the Aride zone, Ashgabat, Turkmenistan, p 98 (Russian)
Muravyeva DA (1991) Pharmacognosiya. Medisina, Moscow, pp 485–486 (Russian)
Nepesov GA, Sachatov ES, Kurbanov MA (1995) The study of the technological properties of tablets prepared from the thick licorice extract. In: Annual 55th scient. conf. Turkmen gos. Med. Inst. Devot., 8th anniver. Independ. Turkmenistan, Ashgabat, Turkmenistan, p 77 (Russian)
Nikitin VV, Geldichanov AM (1988) Turkmenistan plants definitor. Nauka, Leningrad, p 60 (Russian)
Obuchov AN (1934) Licorice root and its' storage, work and sale. Nauka, Moscow, p 96 (Russian)
Ovezova GK, Pleskanovskaya SA (2002) The effective using in the internal organs diseases' treatment phytopreparation individual selection immunological determination test. Patent of Turkmenistan state reestr no. 274 from 04.07.2002, Ashgabat, Turkmenistan (Russian)
Ozturk M, Altay V, Hakeem KR, Akçiçek E (2017a) Liquorice from botany to phytochemistry, SpringerBriefs in plant science. Springer Nature, Basel, 139 pp. https://doi.org/10.1007/978-3-319-74240-3
Ozturk M, Altay V, Karahan F (2017b) Studies on trace elements distributed in *Glycyrrhiza* taxa in Hatay-Turkey. Int J Plant Environ 3(2):1–7
Rakhmanova M, Pleskanovskaya SA, Mamedkulieva A, Karajaeva O (2002) Immunohematological criteria of chronic obstructive bronchitis treatment tactics determination Toraks Dernegi 5 Yillik Kongresi, 24–27 Nisan, 2002, Antalya, Turkey, p 23 (English)
Rizayeva ChSh, Tovmasyan DA, Shimanov VG (1969) *Glycyrrhiza glabra* estrogens influence on the male animals sperm genesis. In: Proc. symp. stud. usage of licorice in the nation. Econ. SSSR. Ilim, Ashkhabad, Turkmenistan, pp 76–77 (Russian)
Sakhatov ES, Nepesov GA, Shukurova GCh, Kulamova NA (1996) Investigation of osmotics properties of the licorice thick extract' ointment. In: Proc. annual 56th scient. conf. Turkmen gos. Med. Inst., Ashgabat, Turkmenistan, p 82 (Russian)
Sakhatov ES, Shukurova GCh, Nepesov GA (1997) Determination of the optimal parameters of the technological process of the licorice thick extract' ointment reception. In: Proc. annual 57th scient. conf. Turkmen gos. Med. Inst. Devot., 8th anniver. Independ. Ashgabat, Turkmenistan, p 102 (Russian)
Shukurova GCh, Avdeenko YuS (1997) The study of the rheological properties of the licorice thick extract's ointment. In: Proc. annual 57th scient. conf. Turkmen gos. Med. Inst. Devot., 9th anniver. Independ. Turkmenistan, Ashgabat, Turkmenistan, p 105 (Russian)
Shukurova GCh, Nepesov GA, Garadjayev BCh (1995) Investigation of the acute toxicity and chemical physician properties of the licorice thick extract' ointment. In: Proc. annual 55th scient. conf. Turkmen gos. Med. Inst. Devot., 8th anniver. Independ. Ashgabat, Turkmenistan, p 183 (Russian)
Socolov CZ, Zamotayev IP (1990) Reference book on the medicinal herbs. Metallurgiya, Moscow, p 427 (Russian)
Toychiyev GK, Hudayberdiyeva JP (2001) Hroniki bronhitli näsaglarda buýan köküniň ekstraktynyň netijeliligi. In: Proc. annual scient. conf. Turkmen state. Med. Inst., Ashgabat, Turkmenistan, p 171 (Turkmen)

Chemical Composition and Biological Uses of *Artemisia absinthium* (Wormwood)

Rahil Razzak Bhat, Muneeb U. Rehman, Ambreen Shabir, Manzoor U. Rahman Mir, Anas Ahmad, Rehan Khan, Mubashir Husaain Masoodi, Hassan Madkhali, and Majid Ahmad Ganaie

Introduction

Artemisia absinthium (synonym: grand wormwood, wormwood).

Artemisia absinthium (*A. absinthium*) is a woody herbaceous perennial undershrub plant with fibrous roots native to Central Europe, southern Siberia, North America, and Asia where it is used as herbal medicine (Nin 2001). *Absinthium* is the name originally given to the plant. It is believed to come from the Greek word "absinthium" meaning "undrinkable," a reflection of its very bitter taste (Brunton et al. 2005). Artemisia: named for Artemis, the Greek goddess of chastity and childbirth. The plant was used to promote menstruation and the name may result from its ability to, therefore, demonstrate chastity.

The root is perennial, and from it arise branched, firm, leafy stems, sometimes almost woody at the base. The flowering stem is 2–2½ ft high and whitish, being

R. R. Bhat · M. U. Rehman (✉) · M. U. Rahman Mir
Division of Veterinary Biochemistry, Faculty of Veterinary Sciences and Animal Husbandry, Sheri Kashmir University of Agricultural Science and Technology (SKUAST-K), Srinagar, Jammu and Kashmir, India

A. Shabir
Faculty of Fisheries, Sheri Kashmir University of Agricultural Science and Technology (SKUAST-K), Srinagar, Jammu and Kashmir, India

A. Ahmad · R. Khan
Nano-Therapeutics, Institute of Nano Science and Technology, Habitat Centre, Mohali, Punjab, India

M. H. Masoodi
Department of Pharmaceutical Sciences, Faculty of Applied Sciences, University of Kashmir, Srinagar, Jammu and Kashmir, India

H. Madkhali · M. A. Ganaie
Department of Pharmacology, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-Kharj, Saudi Arabia

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closely covered with fine, silky hairs. The leaves, which are also whitish on both sides from the same reason, are about 3 in. long by 1½ in. broad, cut into deeply and repeatedly, the segments being narrow and blunt. The leafstalks are slightly winged at the margin. The small, nearly globular flower heads are arranged in an erect, leafy panicle, the leaves on the flower stalks being reduced to three or even one linear segment, and the little flowers themselves being pendulous and of a greenish-yellow tint. The ripe fruits are not crowned by a tuft of hairs as in the majority of the Compositae family. The leaves and flowers are very bitter, with a characteristic odor, resembling that of thujone. The root has a warm and aromatic taste. Flowers of wormwood plant are pale yellow, tubular, and clustered in spherical bent-down heads (capitula), which are in turn clustered in leafy and branched panicles (Chu et al. 2017). Season of flowering starts from early summer to early autumn and possesses anemophilous type of pollination. The fruit is a small achene; seed dispersal is by gravity.

It grows naturally on uncultivated, arid ground, on rocky slopes, and at the edge of footpaths and field (Masoudi and Saiedi 2017). Artemisia species are grown for their silvery-green foliage and for their aromatic, culinary, and medicinal properties. They have alternate, sometimes deeply divided, grey or silver leaves. Flowers are not showy. These plants are a good choice for rock gardens and other sunny, dry-landscape sites. Flowering occurs in midsummer; pale yellow, tubular flowers develop in drooping heads in the axils of the leaves. The word wormwood is based on its use as an antihelminthic, which dates back to the ancient Egyptians. It was later used to treat almost any complaint imaginable. In 2013, Artemisia Research Project at the Centre for Novel Agricultural products (CNAP) has successfully developed new hybrid varieties of the medicinal plant *Artemisia annua*, which serves as the primary source of the leading antimalarial drug artemisinin.

Historical Background of Artemisia absinthium

There is interesting historical importance of extracts of wormwood. Artemisia was the wife and sister of the Persian King Mausolus. The genus Artemisia was named after her and includes over 400 plants. Artemisia was a botanist and medical researcher (Goud and Swamy 2015). Extracts of this plant are described as being of great antiquity in Pliny's Historia Naturalis, from the first century AD Dioscorides describes wormwood and its uses in his 65 AD work De Materia Medica. This work served as the pharmacopoeia for over 1500 years after its completion. Wormwood, in the context of its bitter taste, is mentioned several times in the bible (Deu 29:18; Pro 5:4; Jer 9:15; Amo 5:7; Rev 8:11; Lam 3:15). The Greek word **apsinthion**, meaning "undrinkable," is likely the ancestor of the word absinthe, which is used in French for the plant species as well as for the alcoholic beverage (Padosch et al. 2006). The Greek mathematician and philosopher, Pythagoras of Samos (569–475 BC), recommended wine-soaked wormwood leaves to alleviate labor pains; Hippocrates (~460–377 BC) used wormwood extracts for the treatment of

menstrual pain and rheumatism (Baker 2001). In the middle ages, wormwood was used as a purge and vermifuge, and it developed towards a "general remedy for all diseases." Internal parasite-expelling activity of **wormwood** was mentioned in an Egyptian scroll that is 3600 years old.

Medicinal Importance of Artemisia absinthium

Wormwood was known earlier for repelling cloth moths and other pests such as bookworms, bedbugs, and even rats. **Essential oils (EOs)** of the plant generally have a broad spectrum of bioactivity, owing to the presence of several active ingredients that work through various modes of action. From the ethno-pharmacological point of view, EOs of the *Artemisia absinthium* (*A. absinthium*) plant have traditionally been used and they have several medicinal properties such as hepatoprotective, antidepressant, carminative (gas reliever), cholagogue (promotes bile flow), emmenagogue (promotes menstrual flow), diuretic, choleretic, hypnotic, preservative, stimulant, tonic, balsamic and depurative antihelminthic, anti-inflammatory, antiseptic, antispasmodic, antitumor, neuroprotective, antifungal, antimicrobial insecticidal, acaricidal, antimalarial, or antiprotozoal effects against *Leishmania aethiopica* and *Leishmania donovani* (Msaada et al. 2015).

The composition and biological effects of the EOs of *A. absinthium* have been widely studied. EOs of *A. absinthium* possess abundant concentration of **thujone**, which have been shown to have acaricidal (Chiasson et al. 2001), insecticidal, and fungicidal effects (Umpiérrez et al. 2012) and **myrtenol-rich oils** of *A. absinthium*, repel fleas, flies, mosquitoes (Erichsen Brown 1979), and ticks (Jaenson et al. 2005).

A. absinthium is grown as an ornamental plant and is used as an ingredient in the "**spirit absinthe**" as well as some other alcoholic drinks. Absinthe is regarded as a strong notorious spirit drink which contains extracts of the plant. and was referred to as "a herb of Mars" for its main medical powers (Padosch et al. 2006).

A banned spirit drink commonly known as absinthe is made from *A. absinthium*. Absinthe, a strong liquor, containing wormwood extract, reached its peak popularity in the late 1800s and early 1900s; it acquired a reputation for triggering psychotic events called **absinthism** (Riahi et al. 2013). The oil composition of the plant is regarded as a key factor for distinguishing absinthe from other strong liquor. The most plausible hypothesis today is that absinthism was just misdiagnosed alcoholism, as ethanol alone can explain all of absinthe's alleged effects (Padosch et al. 2006). Absinthe originated in the canton of Neuchâtel in Switzerland in the late eighteenth century. It rose to great popularity as an alcoholic drink in late nineteenth and early twentieth centuries particularly among Parisian artists and writers. The high consumption of absinthe, along with the acute and chronic effects of **absinthe**, led most countries to ban the drink containing wormwood. As early as 1872, the French National Assembly attempted to control absinthe production and sales, without success (Vogt and Montagne 1982). Side effects from consumption of wormwood include renal failure, convulsions, involuntary evacuations, abnormal

respiration, and foaming at the mouth though it is argued that these effects are seen only as a result of consuming oil of wormwood. In the nineteenth century, people were believed to become addicted to absinthe and some doctors described a condition which they called "**absinthe epilepsy**." Recently, the idea that absinthe was any more harmful than other alcohol products has been challenged.

At the beginning of the twentieth century, the spirit was banned in most of the countries. In 1908, Switzerland banned absinthe, followed shortly by the United States, with France following suit in 1915 as it was supposed to be **hallucinogenic. By 1915, absinthe** had been banned in the United States and in much of Europe (Arnold 1989). An important chemical which is present in the essential oil of wormwood was **thujone**. It was responsible for the hallucinogenic action. But in early 2000s the ban on this spirit was repealed. Switzerland was the first country who repealed its ban in 2005, making it legal once again. In 2007, two brands of this spirit were considered legal and sold in the United States (Hussain et al. 2017). By the early twenty-first century, nearly 200 brands of absinthe were being produced in a dozen countries, most notably in France, Switzerland, Australia, Spain, and the Czech Republic.

The 2015 Nobel Prize in Physiology or Medicine was awarded to Professor Youyou Tu for her key contributions to the discovery of artemisinin which has antimalarial property derived from *Artemisia annua* plant. Discovery of artemisinin led a paradigm shift in antimalarial drug development. Artemisinin has saved millions of lives and represents one of the significant contributions to global health (Su and Miller 2015).

Taxonomy

Binomial Name: *Artemisia absinthium* Linn.

There are almost 500 species of Artemisia. Among them, *Artemisia absinthium* (*A. absinthium*) which is commonly known as wormwood is a well-known herb. It is mentioned in almost all the herbal medicinal books of the Eastern as well as Western world. The genus Artemisia is characterized by a wide range of morphological and phytochemical variability, which is associated with different geographical origins of the samples. The genus displays a huge ecological plasticity, with species occurring from sea level to high mountains and from arid zones to wetlands. Additionally, polyploidy is notably common and reported **cytotypes** differ in external morphology, anatomy, fertility, and phytochemical cytogenetically (Vallès et al. 2011).

The accepted scientific name for **absinth wormwood** is *Artemisia absinthium* Linn. (Boivin 1972). Artemisia is a genus of small herbs and shrubs found in northern temperate regions. It belongs to the important family Compositae (Asteraceae), one of the most numerous plant groupings, which comprises about 1000 genera and over 20,000 species (Abad et al. 2012). Within this family, Artemisia is included in the tribe Anthemideae and comprises over 500 species, which are mainly found in

Table 1 Taxonomic hierarchy of *Artemisia absinthium* plant (Riahi et al. 2013)

Taxonomic hierarchy	
Rank	Scientific name and common name
Kingdom	Plantae—plants
Subkingdom	Viridiplantae
Infrakingdom	Streptophyta—land plants
Superdivision	Embryophyta—seed plants
Division	Tracheophyta
Subdivision	Spermatophytina
Class	Magnoliopsida
Superorder	Asteranae
Order	Asterales
Family	Asteraceae—sunflowers, tournesols
Genus	*Artemisia* L.—sagebrush, wormwood, sagewort
Species	*Artemisia absinthium* L.—absinthium, absinth wormwood, absinth sagewort, common sagewort

Fig. 1 Leaves of *Artemisia absinthium*

Asia, Europe, and North America (Bora and Sharma 2011a). They are mostly perennial herbs dominating the vast steppe communities of Asia. Asia has the greatest concentration of species, with 150 accessions for China, 174 in the ex-USSR, about 50 reported for Japan, and 35 species of the genus found in Iran (Abad et al. 2012) (Table 1 and Fig. 1).

Phytochemistry of *Artemisia absinthium*

Exhaustive literature survey on phytochemical reports of *A. absinthium* reveals that they comprise mainly terpenoids, flavonoids, coumarins, polyphenolics, caffeoylquinic acids, sterols, and acetylenes. Preliminary phytochemical screening of *Artemisia annua* is achieved by using standard screening method. The Molisch's

test and the Fehling's test are carried out for carbohydrate, foam test for saponins, Salkowski test and Liebermann Burchard test for phytosterol, sodium hydroxide test, concentrated sulfuric acid test and Shinoda's test for flavonoids, biuret test, ninhydrin test, and million's test for proteins and amino acid (Trease and Evans 1983). It was later demonstrated for the first time the presence of methyl hinokiate in the essential oil of *A. absinthium* (Joshi 2017).

Phytochemical constituents of *A. absinthium* are as follows:

Absinthin: Sesqueterpines lactones, sesqueterpinoids, α-**thujone**, β-**thujone**, and chrysanthenyl acetate **thujone**

Artabsin: Sesqueterpines lactones, sesqueterpinoids, α-**thujone**, β-**thujone**, and chrysanthenyl acetate **thujone**

Essential oil
Anabsinthin
Anabsin
Matricin
Organic acids
Lactones and resins

Flavonoids: rutin, quercetin, and other flavonoid glycosides including quercitin-3-*O*-D-glucoside, isoquercitrin, quercitin-3-*O*-rhamnoglucoside, isorhamnetin-3-glucoside, isorhamnetin-3-*O*-rhamnoglucoside.

Phenolic acids including syringic, chlorogenic, caffeic acid, ferulic acid, sinapic acid, *p*-hydroxyphenol acidic acid, vanillic acid, salicylic acid, and *p*-coumaric acid that are responsible for some therapeutic effects and possibly involved in the mechanism of free radical scavenging: These pharmacophores exhibit effective free radical scavenging, anti-inflammatory activity, and antioxidant potential (Masoudi and Saiedi 2017).

Chemically key constituents in *A. absinthium* are trans-sabinylacetate, myrcene, and trans-thujones. Thujone, a $GABA_A$ receptor antagonist that can cause epileptic-like convulsion, is considered as the most important component. Thujone is less soluble in water as compared to ethanol; only 8% of thujone is recovered in water as compared to extraction in 90% ethanol.

Active Constituents

Volatile oil: including **α-thujone, β-thujone**
Sesquiterpene lactones: absinthin, artemetin, matricin, isoabsinthin, and artemolin
Acetylenes
Flavonoids
Phenolic acids
Ligans: diayangmbin and epiyangambin (Hoffmann 2003)

Thujone is the major active constituent of wormwood oil (*Artemisia absinthium*). Thujone is bicyclic ketone terpene that has gained notoriety over the years. In the banned period of *Absinthe* liquor, thujone was blamed for the alleged misbehavior and hallucinogenic character of absinthe drinkers. Thujone is one of the principal active ingredients in wormwood which was used to make absinthe; however, it was discovered by analysis that there was not enough of the thujone in absinthe to cause the hallucinations and brain damage suffered by its regular drinkers (Dettling et al. 2004). It was more likely the excess of the alcohol that did the damage. It has been proved that thujone is not inherently dangerous, psychically or physically, except in extremely high doses (Ashok and Upadhyaya 2013) (Tables 2 and 3).

The characteristic bitterness of wormwood is due to the presence of sesquiterpene lactones such as absinthin, the main bitter constituent, anabsin, ketopelenolide-b, and anabsinthin. Among the major components reported in its essential oils are α- and β-thujene (Carnat et al. 1992), *Z*-epoxyocimene and chrysanthenyl acetate, and sabinyl acetate, depending on the origin of plant. All of the studied essential oil components show antioxidant activity except camphor and 1,8-cineole (Kordali et al. 2005a) (Figs. 2 and 3).

The essential oils from shade-dried leaves contain α-thujene, α-pinene, camphene, *p*-cymene, 1,8-cineol, methyl heptenone, β-phellandrene, caryophyllene oxide, α-terpineol, thujyl alcohol, geraniol, thujyl acetate, caryophyllene, α-himachalene, α-cardinene, and elemol. While studying the preliminary pharmacognostical standardization of aerial parts of *Artemisia absinthium* Linn. it was revealed that phytochemical screening of the *A. absinthium* contains polyphenolic compounds, flavonoids, and steroid glycosides in hot methanolic extracts (Javed 2012) (Tables 4 and 5).

Techniques commonly used for isolation of the essential oils of *A. absinthium*

- Hydrodistillation (HD)
- Solvent-free microwave extraction (SFME)
- Gas chromatography (GC)
- Gas chromatography-mass spectrometry (GC/MS)

Table 2 Quantitative estimation of physicochemical parameters of *A. absinthium*

S. no.	Parameters	Range (%)	Mean (%)	S.D.
1	Moisture content (w/w)	19.8–16.1	17.2	±0.8124
2	Foreign matters (w/w)	0.2–0.8	0.5	±0.0702
3	Total ash (w/w)	2.42–2.52	2.50	±0.1714
4	Acid molecule ash (w/w)	0.22–0.27	0.25	±0.3762
5	Water-soluble ash (w/w)	0.35–0.44	0.39	±0.0327
6	Alcohol-soluble extractive (w/w)	11.37–13.59	12.67	±0.2731
7	Water-soluble extractive (w/w)	10.60–11.57	10.98	±0.3521
8	Starch	11.55–11.73	11.66	±0.1622
9	Sugar	6.15–6.43	6.38	±0.0023
10	Tannin	0.20–0.21	0.20	±0.0132
11	Total phenolic	2.75–2.86	2.78	±0.0520

Table 3 Phytoconstituents of *A. absinthium*

Group	Phytoconstituents
Essential oil	Chamazulene, nuciferol butanoate, nuciferol propionate, caryophyllene oxide, phellandrene, pinene, azulene. [10]-thujone, [9]-thujone, myrcene, trans-sabinyl acetate cis- and trans-epoxyocymenes, chrysanthenyl acetate, thujyl alcohol, nerol, isothujyl acetate. Prochamazulenogen. ß-pinene, hydrocarbon monoterpenes, sabinene, 1,8-cineole, *Artemisia* ketone, linalool, trans-verbenol, carvone, curcumene, neryl butyrate, neryl 2-methylbutanoate, neryl 3-methylbutanoate.
Sesquiterpene lactones	Arabsin, artabin, ketopelenolide, santonin-related lactones
Tannins	
Carotenoids	
Lignan	
Glucosides	Absinthin, anabsinthin
Phenolic compounds	
Flavonoid	5,6,3′,5′-Tetramethoxy, 7,4′-hydroxyflavone, 5-hydroxy-3,3′,4′,6,7-pentamethoxyflavone, artemitin, rutin, glycosides of quercetin, chlorogenic, caffeic acids
Bitter principles	Artamarin, artamaridin, artamaridinin, artamarinin quebrachitol, artemitin, rutin, glycosides of quercetin, 24-zeta-ethylcholesta-7,22-dien-3-ß-ol

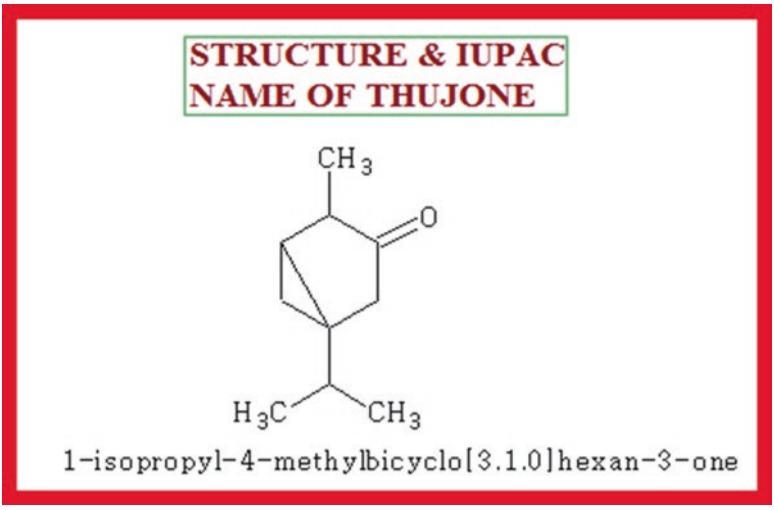

Fig. 2 A schematic diagram representing the IUPAC name and chemical structure of thujone

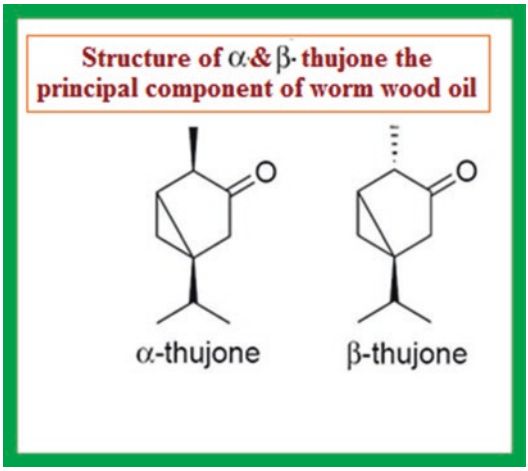

Fig. 3 Schematic diagram representing the anomeric forms of thujone

Table 4. Chemical composition of the essential oil of *A. absinthium*

Compound	Ri[a]	Ri[b]	%[a]	%[b]
Tricyclene	932	1014	0.7	0.5
a-Thujene	937	1084	0.3	0.2
a-Pinene	943	1021	0.4	0.3
Camphene	957	1052	1.8	2.1
Thuja-2,4(10)-diene	960	1145	0.5	0.3
b-Pinene	985	1124	1.1	1.0
a-Terpinene	1022	1131	0.5	0.7
p-Cymene	1030	1242	0.4	0.6
Limonene	1036	1165	1.6	1.3
1,8-Cineole	1139	1175	1.3	1.9
[9]-b-Ocimene	1058	1195	3.5	2.9
g-Terpinene	1065	1195	0.8	0.5
cis-Sabinene hydrate	1073	1461	0.3	0.9
Terpinolene	1092	1258	0.7	0.5
Linalool	1105	1563	0.4	0.7
cis-2-Menthenol	1129	1581	0.3	0.2
Camphor	1150	1541	2.9	2.3
b-Pinene oxide	1163	1942	0.9	1.3
Pinocarvone	1170	2156	1.1	1.2
Borneol	1073	1744	18.7	16.7
Terpinen-4-ol	1181	1656	2.8	2.5
cis-Pinocarveol	1189	1693	1.4	1.4
a-Terpineol	1193	1736	0.6	0.5
Myrtenol	1199	1718	1.0	0.8
trans-Piperitol	1213	1788	1.0	1.2
[10]-Ocimenone	1240	1901	1.2	1.5
Cumin aldehyde	1249	1832	1.6	1.3
Piperitone	1258	1782	0.7	0.5

(continued)

Table 4. (continued)

Compound	Ri[a]	Ri[b]	%[a]	%[b]
Perilla aldehyde	1279	1845	2.1	2.7
Isobornyl acetate	1293	1605	4.0	4.7
Thymol	1295	2225	1.7	1.4
Carvacrol	1304	2252	0.6	0.8
6-Hydroxycarvotanacetone	1311	1796	t	0.1
Eugenol	1361	2217	t	t
Cyclosativene	1379	1454	0.3	0.5
b-Cubebene	1393	1499	t	t
Cyperene	1407	1545	0.3	0.1
a-Gurjunene	1416	1552	0.2	0.1
b-Caryophyllene	1426	1627	0.1	0.3
b-Gurjunene	1441	1532	3.8	4.4
a-Humulene	1457	1710	0.3	0.5
Seychellene	1468	1661	0.5	0.2
g-Gurjunene	1479	1618	0.7	0.6
g-Curcumene	1488	1725	0.4	0.1
Germacrene D	1493	1760	0.1	0.2
ar-Curcumene	1491	1817	0.4	0.6
b-Selinene	1493	1766	0.2	0.1
cis-b-Guaiene	1499	1575	0.7	0.9
epi-Cubenol	1506	1939	1.1	0.9
Bicyclogermacrene	1507	1672	0.9	0.7
a-Muurolene	1504	1753	0.5	0.3
d-Cadinene	1533	1802	0.4	0.5
b-Vetivenene	1533	–	0.9	–
6,11-oxido-Acor-4-ene	1539	1918	0.1	t
a-Calacorene	1545	1961	0.4	0.3
b-Calacorene	1571	1975	0.2	0.6
Germacrene-D-4-ol	1583	2103	0.6	0.5
Caryophyllene oxide	1589	2049	3.7	4.3
Guaiol	1612	2137	0.6	0.2
Cubenol	1652	1993	1.9	2.8
a-Muurolol	1658	2230	0.6	0.1
b-Eudesmol	1661	2274	0.4	0.1
a-Cadinol	1666	2240	2.6	2.8
Methyl hinokiate	1714	2354	11.9	12.9
Total identified			*91.7*	*90.1*
Monoterpene hydrocarbons			12.3	10.2
Oxygenated monoterpenes			39.7	41.1
Sesquiterpene hydrocarbons			11.3	10.7
Oxygenated sesquiterpenes			23.5	24.6
Phenyl derivatives			3.9	3.5

t trace (50.1%)

[a]CP Sil-8-CB (30 m × 0.25 mm i.d., 0.25 mm film thickness) column

[b]BP 21 (60 m × 0.25 mm i.d., 0.25 mm film thickness) column

Table 5. Reported major constituents of essential oil of *A. absinthium* from different countries

Country	Major constituents
Belgium	Sabinene (9.3%), myrcene (5.4%), sabinyl acetate (18.6%) (Orav et al. 2006)
Canada	Myrcene (10.8%), trans-thujone (10.1%), and trans-sabinyl acetate (26.4%) (Lopes-Lutz et al. 2008)
Cuba	Bornyl acetate (23.0%) (Pino et al. 1997)
Egypt	a-Phellandrene (50.5%) and terpinen-4-ol (12.0%) (Aboutabl et al. 1998)
Estonia	Epoxyocimenes (59.7%) (Orav et al. 2006)
Ethiopia	Camphor (27.4%), dehydrocostus lactone (41.8%) (Tariku et al. 2011)
France	cis-Chrysanthenol (69.0%) (Carnat et al. 1992); cis-epoxyocimene (49.7%) and cis-chrysanthenyl acetate (36.7%) (Juteau et al. 2003)
Germany	1,8-Cineol (3.4%), curcumeme structures (8.9%), neryl-3-methyl butanoate (3.8%) (Orav et al. 2006)
Greece	Caryophyllene oxide (23.3%), *p*-cymene (16.8%), 1,8-cineole (18.9%), and lanceol acetate (7.3%) b-thujone (38.7%) (Orav et al. 2006)
Hungry	Sabinene (18.1%), myrcene (17.7%) (Orav et al. 2006)
India	b-Phellandrene (10.0%), thujone (9.22%), a-himachalene (7.0%) and b-caryophyllene (5.0%) (Kaul et al. 1979)
Iran	b-Pinene (34.0%), *p*-cymene (14.6%), a-pinene (8.3%), a-thujone (6.9%) thujone (5.1%) (Sefidkin et al. 2003); b-pinene (23.8%) and trans-thujone (18.6%) (Rezaeinodehi and Khangholi 2008)
Italy	Epoxyocimenes (23.1–56.6%) (Orav et al. 2006)
Latvia	Trans-verbenol (9.2%), sabinyl acetate (23.6%), curcumene structures (9.0%) (Orav et al. 2006)
Lithuania	Trans-verbenol (11.7%), sabinyl acetate (13.7%), curcumene structures (6.3%) (Orav et al. 2006); thujones (cis þ trans, 10.2–36.3%), trans-sabinyl acetate (9.8–39.2%), myrcene (5.1–9.2%), b-pinene (5.4–10.4%), linalool (4.7%), trans-sabinol (6.4%), and 1,8-cineole (5.2–7.1%) (Judzentiene et al. 2009)
Morocco	Thujone (Derwich et al. 2009)
Russia	Epoxyocimenes (22.1%), sabinene (9.3%) (Orav et al. 2006); myrcene (35.0%), a-pinene (6.0%), and nerol (3.0%) (Goraev et al. 1962)
Scotland	Sabinene (30.1%), myrcene (18.0%) (Orav et al. 2006)
Serbia and Montenegro	b-Thujone (19.8–63.4%), cis-b-epoxyocimene (10.7%), trans-sabinyl acetate (8.8–15.5%), linalyl 3-methylbutanoate (7.5–12.5%), geranyl 3-methylbutanoate (4.0–12.9%) (Blagojević et al. 2006)
Spain	cis-Epoxyocimene (76.3–39.9%), cis-chrysanthenyl acetate (33.4%) (Ariño et al. 1999), 1,8-cineole (18.0%), carvone (18.5%), thymol (10.8%), and carvacrol (9.7%), b- (6.2%) (Orav et al. 2006)
Turkey	Chamazulene (17.8%), nuciferyl butyrate (8.2%), and propionate (5.1%) (Kordali et al. 2005b)
USA	Trans-thujone (33.1%) and cis-sabinyl acetate (32.8%) (Tucker et al. 1993)

Antimicrobial Activity of *Artemisia absinthium*

Medicinal plants have considerable antimicrobial activities that can be used for preventing or inhibiting growth of infectious microorganisms and degeneration factors. High interest in replacing chemical materials with natural ones caused performing thousands of studies on natural resource researches on different plant extracts that

resulted in discovery of suitable natural substances of treatment of various diseases (Weinstein 2001). The therapeutic properties of extracts and essential oils against microbial and nonmicrobial diseases have been known from many years ago and many positive effects have been reported from different plant species against microorganisms (Arrieta et al. 2001). In recent decades, antimicrobial properties of herbal products have attracted many researchers because of a rapid increase in antibiotic resistance to microorganisms (Guangrong et al. 2008). Many members of the genus *Artemisia* are important medicinal plants.

Artemisia absinthium (**Wormwood**) is one of the important medicinal plants with antimicrobial properties. Wormwood is effective against both bacteria and fungi. Essential oil distilled from the aerial parts of *Artemisia absinthium* inhibited the growth of a very broad spectrum of tested fungi. The antifungal activities of essential oils (which include chamazulene, nuciferol propionate, nuciferol butanoate, caryophyllene oxide, borneol, alpha-terpineol, spathulenol, cubenol, beta-eudesmol, and terpinen-4-ol) were tested against 11 plant fungi and were compared with those of a commercial antifungal reagent, benomyl (Kordali et al. 2005a). The results of this study showed that all of the oils have potent inhibitory effects at very broad spectrum against all of the tested fungi. Pure camphor and 1,8-cineole, which are the major components of the oils, are able to show antifungal activity against only some of the fungal species. Another study published in *Planta Medica* showed that *A. absinthium* oil inhibited the growth of *Candida albicans* (Juteau et al. 2003). This is the most common type of yeast infection found in the mouth, intestinal tract, and vagina, and it may affect skin and other mucous membranes. *Candida albicans* can cause all kinds of common yet highly unwanted *Candida albicans* symptoms like hormonal imbalance, skin and nail fungal infections, brain fog, intestinal distress, sinus infections, oral thrush, recurring vaginal and urinary tract infections (UTI), mood disorders, and chronic fatigue. In vitro studies have shown that the essential oils of wormwood have antimicrobial activity. Research published showed that wormwood oil showed a broad spectrum of antimicrobial activity against several bacterial strains, including *E. coli* and *Salmonella* (Blagojević et al. 2006). Every year, *Salmonella* bacterial genus is estimated to cause 1 million foodborne illnesses in the United States. *E. coli* bacteria constitute another concerning type of bacteria that can cause a range of issues from diarrhea to urinary tract infections to pneumonia and other illnesses.

Habibipour and Rajabi (2015) investigated the antibacterial activity of hydroalcoholic extracts of *A. lappa* and *Artemesia absinthium* on *P. aeruginosa, H. influenza, B. subtilis, B. cereus, Klebsiella pneumonia*, and *Staphylococcus aureus* in laboratory conditions. Extract of *A. absinthium* showed more inhibitory effect on *B. subtilis*. The extracts of *A. lappa* and *A. absinthium* had inhibitory effects on *H. influenza* and *P. aeruginosa.* Among antibiotics, only ofloxacin and ciprofloxacin had effects on *H. influenza*. Extract of *A. lappa* showed flimsy effect on *K. pneumonia*, while extract of *A. absinthium* had no effect on this bacterium. The higher effect on *H. influenza* was obtained by extract of *A. absinthium*. Extract of *A. lappa* had effect on this bacterium similar to ofloxacin, while *A. absinthium* was better than **ofloxacin**. Joshi (2017) revealed from his study that the essential oil possesses anti-

microbial activity against bacteria and fungi that could attribute the traditional use of the plant as an antiseptic.

Adaptogenic and Nootropic Activity of *Artemisia absinthium*

According to naturopath Edward Wallace, an adaptogen doesn't have a specific action; it helps you respond to any influence or stressor, normalizing your physiological functions. Adaptogens are a unique class of healing plants: they help balance, restore, and protect the body.

The term of adaptogenic herbs or substances was first recorded in 1947 by N.V. Lazarev, a Russian scientist, who used it to describe this nonspecific effect that increases the body's resistance to stress. Defined by two other Russian research scientists in 1958, adaptogens "must be innocuous and cause minimal disorders in the physiological functions of an organism, must have a nonspecific action, and usually (Sánchez-Chávez and Salceda 2001) a normalizing action irrespective of the direction of the pathological state." This effect has been observed in animal studies, finding that various adaptogens have the ability to create this generally increased tolerance to stress (Panossian et al. 2010).

In 2009, Mohmoudi et al. investigated the antidepressant activity of *A. absinthium* by forced swimming test (FST) and tail suspension test (TST) models of depression. *A. absinthium* significantly reduced the immobility period in both FST and TST. The extract also exhibited good but different levels of antioxidant activity in some models studied. Many different plants in the genus *Artemisia* are used as medicine. Some aspects of them are similar while others are different. All *Artemisia* species are antimicrobial and stimulate digestion to some degree. They vary more widely in that some are distinctly nootropic (enhance memory and cognitive function) and inflammation modulating. All species are also emmenagogue to some extent. This means that they should be avoided in women trying to get pregnant, or who already are, but may be useful as part of preventing implantation of a recently fertilized ovum. *Artemisia absinthium* L. has long been used as traditional herbal medicine for the treatment of gastric pain, cardiac stimulation, to improve memory and for the restoration of declining mental function. The brain oxidative stress and damage and behavioral deficits were significantly attenuated by pretreatment with the methanol extract of *Artemisia absinthium* (100 and 200 mg/kg, p.o.) (Bora and Sharma 2010).

Nootropic drugs used as a memory enhancer can improve thinking, memory, and alertness in people with Alzheimer's disease and other diseases that affect the mind. Memory is perhaps the most vital of all aspects that differentiates human beings from other animals. However, memory can become faulty due to several reasons, and in that case the person is not able to make full use of his or her potentials. Since ages, drugs and natural remedies have been prescribed to enhance memories in people (Desai et al. 2010).

A. absinthium L. (wormwood) is an aromatic bitter herb known to possess many ethnomedical and biological properties (Mahmoudi et al. 2009). Its antioxidant activity has been reported recently. There is published scientific data available for antidepressant activity of this plant. Numerous study showed that *A. absinthium* (total crude extract) has good antidepressant activity. Because of high amount of polyphenolic compounds in this plant polyphenolic fraction of *A. absinthium* is commonly selected for evaluation of the antidepressant activity. The antidepressant activity is determined by forced swimming test (FST) and tail suspension test (TST) in order to understand the importance of polyphenolic fraction of *A. absinthium*.

Forced Swimming Test (FST)

The forced swimming test (FST) was developed by Porsolt and colleagues in the rat and subsequently in the mouse (Anjaneyulu et al. 2003). The test involves a lab animal/experimental common mice. The experimental animal is dropped into a glass cylinder (20 cm in height and 12 cm in diameter) containing 8 cm deep water at 24–25 °C and left there for 6 min. The duration of mobility is recorded for a period of 5 min (Ebrahimzadeh et al. 2009). Control group is also taken which is subjected with solvent. The other groups of experimental animals receive an intraperitoneal (i.p.) injection of extracts (300, 400, and 500 mg/kg) in Tween 80 plus 0.9% (w/v) saline solution and imipramine (15 mg/kg), 1 h before the experiment. Imipramine is utilized as positive control of the test. The swimming test has been extensively employed to evaluate the effect of various agents on the central nervous system, such as antidepressants, sedative-hypnotics, psychostimulants, euphorics, nootropics, and adaptogens (Mahmoudi et al. 2009).

Tail Suspension Test

Experimental animals, well acquitted with the laboratory environment, are selected. Animals are treated with given concentrations of plant extract by intraperitoneal injection 30 min prior to testing. For the test, the animals are suspended on the edge of a shelf, 58 cm above a tabletop by adhesive tape placed approximately 1 cm from the tip of the tail. The duration of mobility is recorded for a period of 5 min. Experimental animals are considered immobile when they hang passively and completely motionless for at least 1 min. Imipramine (15 mg/kg) is commonly used as positive control of the test. TST detects the anti-immobility effects of a wide array of antidepressants, including tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI), monoamine oxidase inhibitors (MAOI), electroconvulsive shock (ECS), and even atypical antidepressants (Ebrahimzadeh et al. 2010).

According to recent researches, it is now renowned fact that polyphenolic compounds such as flavonoids have antidepressant activity (Lei et al. 2007). Because of

high polyphenol and flavonoid contents of *A. absinthium*, its polyphenol fraction is selected for an assay of antidepressant activity. Behavioral despair was proposed as a model to test for antidepressant activity. This test is the most widely used tool for assessing antidepressant activity preclinically (Cryan et al. 2002). The swimming test has been extensively employed to evaluate the effect of various agents on the central nervous system, such as antidepressants, sedative-hypnotics, psychostimulants, euphorics, nootropics, and adaptogens (Mahmoudi et al. 2009). It was suggested that mice or rats forced to swim in a restricted space from which they cannot escape are induced to a characteristic behavior of immobility. This behavior reflects a state of despair which can be reduced by several agents which are therapeutically effective in human depression. The investigations carried out by Ahangar et al. (2011) suggest the weak antidepressant activity of *A. absinthium* polyphenol fraction in both FST and TST models of depression.

Antidiabetes Effects of *Artemisia absinthium*

Over the last century, human lifestyle and food habits have drastically changed which led to various chronic diseases. Diabetes is a ceaseless issue of uncontrolled body metabolism of carbohydrate, fat, and protein. Diabetes just got a little more complicated, or clearer, depending on your perspective. Researchers in Scandinavia have proposed classifying diabetes as five types of disease, rather than two types, according to a new study. "This is the first step towards personalized treatment of diabetes," said senior author **Leif Groop**, an endocrinologist at Lund University in Sweden, adding that the new classification is a "paradigm shift" in how the disease is viewed (Ahlqvist et al. 2018).

Diabetes mellitus (Lei et al. 2007) is a lifelong condition caused by deficiency or diminished effectiveness of endogenous insulin hormone that can be either inherited or acquired (Kumar et al. 2013). Diabetic symptoms include increased urine output (polyuria), excessive thirst (polydipsia), excessive hunger (polyphagia), and fatigue (Hakim et al. 1997). It is characterized by acute complications like hyperglycemia (high blood sugar), hypoglycemia (low blood sugar), and chronic complications like indelible damage, debilitation, and failure of various organs, notably the kidneys, eyes, heart, nerves, and blood vessels due to hyperglycemia. Allopathic drugs are not much effective in handling the disease and its complications. Hence focus has been turned towards the traditional system of medicine. Medicinal plants play an important role in the management of diabetes mellitus. Since the year 2000 until April 2017, numerous studies were conducted and the blood glucose data obtained from these studies clearly showed that both the aqueous and alcoholic extracts of species of *Artemisia* produced significant hypoglycemic effects in induced diabetic animals and diabetic humans with different mechanisms of action as compared to standard antidiabetic medications.

Diabetes has been linked with an expanded peril of developing early on atherosclerosis due to increase in triglycerides (TG) and low-density lipid (LDL) levels

and decrease in high-density lipid (HDL) levels. Many published studies have reported decline in the activity of acetylcholine esterase enzyme in brain and RBC membrane in diabetic condition (Sánchez-Chávez and Salceda 2001). Decrease in the levels of acetylcholinesterase acts as an indicator for **diabetic neuropathy**.

Goud and Swamy (2015) investigated the effect of the methanolic leaf extract of *Artemisia absinthium* (MLEAA) on the activity of acetylcholinesterase, levels of acetylcholine, and lipid profile in the brain tissue of Streptozotocin (STZ)-induced diabetic Wistar rats and concluded that constructive chattel of MLEAA is anticipating in counteracting against hypertriglyceridemia and is helpful in maintaining normal levels of Ach, AChE, and lipids (phospholipids, glycolipids, and cholesterol) (Mohamed et al. 2010).

Artemisia absinthium was found to produce significant hypoglycemic activity in both normal and diabetic animals, which could be compared to 10 mg/kg. *Artemisia absinthium*-treated diabetic rat show increased food intake and body weight. The elevated triglycerides, total cholesterol, ALT, AST, urea, and creatinine levels have been found to reduce significantly and high-density lipoprotein (HDL) levels increase in diabetic rat after *Artemisia absinthium* treatment. The liver glycogen levels also show significant increase (Shafi and Tabassum 2013).

Li et al. (2015) also studied the antidiabetic effect of *Artemisia absinthium* where they concluded that the plant possesses good antidiabetic features; however these herbal products had no significant effect on lipid profiles of the diabetic human which is contrary to abovementioned research work done by Goud and Swamy (2016). Similar findings were also found by Daradka et al. (2014), where the different doses of ethanolic extraction of *A. absinthium* produced a significant reduction in blood glucose level in a dose-dependent manner in alloxan-induced diabetic rats.

Anticancer Activity of *Artemisia absinthium*

Cancer is a dreadful disease which arises due to uncontrolled cell proliferation, and tissue invasion/metastasis. Unregulated cell growth without invasion is known as benign tumor/neoplasms or new growths while if they are capable to invade tissue or basement membrane it is known as malignant tumors. The malignant form of cancer often requires mutations in several different genes that regulate cell proliferation, survival, DNA repair, motility, invasion, and angiogenesis. Cancer-causing mutations often activate signal transduction pathways leading to aberrant cell proliferation and perturbations of tissue-specific differentiation programs. The normal cell has protective mechanisms that lead to the repair of DNA damage that occurs during DNA synthesis and mitosis and in response to environmental mutagens; these repair pathways are often abnormal in cancer cells. Cancers of epithelial tissues are called carcinomas; cancers of non-epithelial (mesenchymal) tissues are called sarcomas. Cancers arising from hematopoietic or lymphoid cells are called leukemias or lymphomas.

Natural products have become increasingly important in pharmaceutical discoveries, and traditional herbalism has been a pioneering specialty in biomedical science. The search for effective plant-derived anticancer agents has continued to gain momentum in recent years.

Besides antimalarial activity, *Artemisia absinthium* is also suspected to have anticancer activity so far its anticancer research data is concerned. There is enormous work going on in the world on this medicinal plant to explore its anticancer drug potential. Dr. Robert Jay R. Rowen published his article entitled as "Chinese herb cures cancer" in 2002 May issue. Dr. Rowen's work was based on the research findings of Drs. Henry Lai and Narenda Singh (bioengineering professors at the University of Washington) that indicated that the herb "might provide a safe, nontoxic, and inexpensive alternative for cancer patients particularly in breast cancer and leukemia patients." According to Lai, it is believed to work because when artemisinin or any of its derivatives come into contact with iron, a chemical reaction ensues, spawning charged atoms that chemists call free radicals. Cells need iron to replicate DNA when they divide, and since cancer is characterized by out-of-control cell division, cancer cells have much higher iron concentrations than do normal cells. What Lai did was to pump up cancer cells with even more iron and then introduce artemisinin to selectively kill them. Lai theorizes that more aggressive cancers such as pancreatic and acute leukemia—which are characterized by more rapid cell division and thus higher iron concentrations—may respond even better. Dr. Rowen also reported in an article in a major cancer journal demonstrating significant artemisinin anticancer activity in a wide variety of laboratory-cultured cancer cells. Cancers resistant to common chemotherapy drugs showed no resistance to artemisinin (Efferth et al. 2001).

This treatment is said to be nontoxic, so you can continue taking it indefinitely with no expected side effects, though it does depend on the form of *Artemesia* one uses. There are three common Artemesia derivatives: Artesunate is water soluble and may be the most active and the least toxic, but it has the shortest life within the body. Artemether is oil or lipid soluble and has the longest half-life. It also has the most toxicity (but this is related to rather high dosages, which are not necessary). Its big advantage is that it can cross the blood-brain barrier to reach cancers in the nervous system. Artemisinin is the active parent compound of the plant. It has an intermediate half-life, is very safe, and also can cross the blood-brain barrier. The first two are slightly altered semisynthetic derivatives of artemisinin, the concentrated and purified active agent (http://www.cancure.org/12-links-page/43-artemesia).

Shafi et al. (2012) conducted a study in order to explore anticancer potential of crude extracts of the aerial parts of *Artemisia absinthium* crude extract on two breast cancer cell lines—estrogenic-unresponsive cell line, MDA-MB-231, and an estrogenic-responsive cell line, MCF-7. This study suggested that *Artemisia absinthium* induced antiproliferative effects on human breast cancer cells possibly by triggering apoptosis in both cell lines through the modulation of Bcl-2 family proteins and the MEK/ERK pathway.

Artemisinin (Tucker et al. 1993) and its analogues, such as **dihydroartesunate** (Msaada et al. 2015) and **artesunate** (Ahlqvist et al. 2018), are sesquiterpene lac-

tones with anticancer activities (Firestone and Sundar 2009). In order to improve the target delivery and the anticancer activity of ARTs, Yang et al. (2014) performed a study by **fabricated adducts of transferrin** (Nassiri-Asl et al. 2013) with ART, DHA, or ATS by simply combining ART, DHA, or ATS with Tf. The increased antitumor effects of these adducts were observed on cancer cells (HepG2 and A549). Meanwhile, only a low level of toxic effect was observed on normal human liver cells (HL-7702). Improved cellular uptake of ATS-Tf adduct compared to ATS alone was confirmed by HPLC analysis. UV–vis, fluorescence spectroscopy, and docking study further confirmed the formation of adducts with relatively high binding constants at neutral pH in cancerous cells (Yang et al. 2014). Such type of adducts of ART and its analogues, ATS and DHA, are therefore promising potential novel anticancer agents.

Gastrointestinal Effects of *Artemisia absinthium*

A number of plant extracts including that of *Artemisia absinthium* have been tested for their effects on induced hyperperistalsis in rats. It is shown by Fernando et al. that in a dose of 300 mg/kg, the extract of Artemisia showed moderate inhibitory activity and that too comparable to loperamide drug used as control (Calzada et al. 2010). Also Artemisia shows some other effects in terms of promoting gut health such as aiding the fat digestion, stimulating the appetite, and enhancing the absorption of nutrients. It also restores the necessary amount of stomach juice to normalize the digestive and stomach functions (Taquechel 2018).

Antioxidant Activity of *Artemisia absinthium*

A. absinthium extracts have both in vitro and in vivo free radical scavenging activity. The *A. absinthium* extract exhibited neuroprotection as it is evident from the reduction of infarct volume and lipid peroxidation, and restoration of endogenous antioxidants. Focal cerebral ischemia was induced by middle cerebral artery occlusion (MCAO) for 90 min followed by reperfusion for 24 h. It is well documented that transient focal MCAO causes neurological abnormality. The focal MCAO-induced increase in lipid peroxidation and administration of *A. absinthium* before focal cerebral ischemia markedly decreased ischemia and reperfusion-induced increase in the level of thiobarbituric acid-reactive substances (Jivad and Rabiei 2015).

A. absinthium contains flavonoids such as quercetin, rutin, and other flavonoid glycosides such as isoquercitrin, quercitin-3-*O*-D-glucoside, quercitin-3-*O*-rhamnoglucoside, isorhamnetin-3-*O*-rhamnoglucoside, isorhamnetin-3-glucoside, and phenolic acids such as chlorogenic, syringic, coumaric, salicylic, and vanillic acids that are probably involved in the mechanism of oxidative damage (Kordali et al. 2005b). Several researches have shown *A. absinthium* to possess potent anti-

oxidant, free radical scavenging, and anti-inflammatory activity (Canadanovic-Brunet et al. 2005).

Wormwood have a high content of nutrients and phytochemicals such as total phenolic compounds and total flavonoids, suggesting that these compounds contribute to the antioxidative activity (Canadanovic-Brunet et al. 2005). Phenolic substances such as flavonols, cinnamic acids, coumarins, and caffeic acids or chlorogenic acids are believed to have antioxidant properties, which may play an important role in protecting cells and any organ from oxidative degeneration (Wiseman et al. 2000). Oxidative stress is defined as the imbalance between reactive oxygen species production and natural antioxidants in biological systems, which leads to the damage of macromolecules such as lipids, proteins, carbohydrates, RNA, and DNA. It has been demonstrated that the pretreatment with aqueous extract of *Artemisia absinthium* (AEAA) significantly ($P < 0.05$) reduced the lipid peroxidation in the liver tissue and restored activities of defense antioxidant enzymes superoxide dismutase (SOD) and *glutathione* (Sun et al. 2012) towards normal levels. In the BCG/LPS model, increase of the levels of important pro-inflammatory mediators TNF-α and IL-1 was significantly ($P < 0.01$) suppressed by AEAA pretreatment. Histopathology of the liver tissue showed that AEAA attenuated the hepatocellular necrosis and led to reduction of inflammatory cells infiltration. It has got a protective effect against acute liver injury which may be attributed to its antioxidative and/or immunomodulatory activity, and thereby scientifically supports its traditional use. The ability of wormwood extract to restore membrane-bound enzymes like Na^+-K^+-ATPase, Ca^{2+}-ATPase, Mg^{2+}-ATPase, and oxidative damage induced by lead was investigated by Kharoubi et al. (2008).

Lead (Pb) is a ubiquitous environmental toxin. Exposure to lead has been shown to disrupt many processes in the liver and kidney. Several molecular mechanisms that result in damage to cellular membrane lipids leading to membrane fragility and permeability are thought to exist. One possibility is the disruption of the pro-oxidant/antioxidant balance, which can lead to liver and kidney injury. Lead is also reported to release free radicals (hydroxyl), thereby stimulating the process of lipid peroxidation. The assumption of oxidative stress as a mechanism in lead toxicity suggests that antioxidants might play an important role in therapy. Lead is reported to have an inhibitory action on the membrane-bound enzymes such as Na^+-K^+-ATPase, Ca^{2+}-ATPase, and Mg^{2+}-ATPase in various vital organs.

Wormwood (*Artemisia absinthium* L.) extract has high contents of total phenolic compounds and total flavonoids, suggesting that these compounds contribute to the antioxidative activity; phenolic substances are believed to have antioxidant properties, which may play an important role in protecting cells and any organ from oxidative degeneration. It has been shown that the treatment with aqueous extract of *Artemisia absinthium* in animals exposed to lead reduced thiobarbituric acid-reactive substances (TBARS) and carbonyl levels in liver and kidney and restored the levels of membrane-bound enzymes and lipid levels to near normal. These results indicate that aqueous wormwood extract had a significant antioxidant activity and protects liver and kidney from the lead-induced toxicity.

Bora and Sharma (2011b) designed a study to evaluate the methanol extract of *Artemisia absinthium* Linn. (*Asteraceae*; MAB) for its in vitro free radical scavenging effects using different classical assays, and in vivo antioxidant activity using global cerebral ischemia and reperfusion (I/R)-induced oxidative stress in mice. The study revealed that in the in vitro assays, methanol extract of *A. absinthium* showed significant ($P < 0.05$) superoxide anion, hydrogen peroxide, hydroxyl and nitric oxide radical scavenging activities, and significant reducing power. Furthermore, in the in vivo studies, oral administration of MAB (100 or 200 mg/kg) inhibited cerebral I/R-induced oxidative stress by decreasing TBARS, and restoring levels of SOD and GSH, which leads to conclusion that *A. absinthium* possess potent antioxidant properties, and may be used as a protective agent against disorders associated with oxidative stress.

Immunomodulatory Effect of *Artemisia absinthium*

In recent years immunomodulation has attracted the interests of scientists all over the world in view of growing awareness regarding the need to modulate the immune system for achieving the objective of preventing infection rather than treating it at an advanced stage. Hence the concept of "Prohost therapy" has been introduced, which aims to prevent infections. Medicinal plants are known to have good immunomodulatory property (Pandey 2011). They act by stimulating both forms of immunity—innate and acquired. These plants may promote host resistance against infection by reestablishing the body equilibrium and conditioning the body tissue. *Artemisia absinthium* L. is regarded as one of the plants with immunomodulatory activity due to presence of various biomolecules such as sesquiterpene lactones, flavonoids, phenolic acids, and tannins (Pandey 2011).

Sesquiterpene lactones, flavonoids, phenolic acids, and tannins which are contained in aqueous extract of *Artemisia absinthium* L. (AEAA) have got a protective effect against acute liver injury which may be attributed to their antioxidative and/or immunomodulatory activity. In vivo hepatoprotective property of the aqueous extract of *Artemisia absinthium* L. was assessed. The results of this study strongly indicate the protective effect of AEAA against acute liver injury which may be attributed to its antioxidative and/or immunomodulatory activity, and thereby scientifically support its traditional usage (Adams and Garcia 2006). Habibi et al. (2016) studied the effects of different levels of essential oils (EOs) of wormwood (*Artemisia absinthium*) and cumin (*Cuminum cyminum*) on growth performance, carcass characteristics, and immune system in broiler chicks. Results showed that cumin and wormwood EO supplementation to the diets had no significant effects on growth performance and carcass characteristics ($P > 0.05$) of broiler chicks. EO infusions significantly ($P < 0.05$) increased the relative weight of immune organ such as *bursa of fabricius*. The results of this experiment suggest that inclusion wormwood and cumin EOs to the diets tended to increase growth performance and improve immune system of broiler chickens.

Artemisia absinthium is a rich source of terpenes, antioxidant phenolics, flavonoids, and other biologically active compounds (Mohamed et al. 2010). In modern medicine, these compounds have been investigated for their anthelmintic and antioxidant activities in parasitized animals by neutralizing the free radicals and toxins formed in their blood, boosting their immune system and helping fight gastrointestinal parasites (Pillay et al. 2008).

Amat et al. (2010) performed a study to evaluate in vivo hepatoprotective activity of the aqueous extract of *Artemisia absinthium* L. (AEAA), which has been used for the treatment of liver disorders. Obtained results demonstrated that the pretreatment with AEAA significantly ($P < 0.001$) and dose-dependently prevented chemically or immunologically induced increase in serum levels of hepatic enzymes. Furthermore, AEAA significantly ($P < 0.05$) reduced the lipid peroxidation in the liver tissue and restored activities of defense antioxidant enzymes SOD and GPx towards normal levels. The results of this study strongly indicated the protective effect of AEAA against acute liver injury which may be attributed to its antioxidative and/or immunomodulatory activity.

Central Nervous System and Epileptic Effects of *Artemisia absinthium*

Many herbs are known to affect the central nervous system, some with sedative effects (kava, valerian, passion flower, and chamomile) and others stimulating CNS function (ephedra and the caffeine-containing herbs coffee, tea, cocoa, cola, mate, and guarana) (Spinella 2001). The most famous example of herb-induced seizures is that of the artist Vincent van Gogh, who during the last 2 years of his life suffered from hallucinatory convulsions. Many believe that his seizures were the result of the toxic effects of wormwood (*Artemesia absinthium*), a herb used to distill alcohol, which contains the proconvulsant compound terpene thujene (Remy 1988).

Wormwood is a central nervous system stimulant and nervine tonic. Wormwood oil contains **thujone** phytochemical, which influences central nervous system. It can also excite the nervous system and cause seizers and convulsions. It also improves blood circulation due to cardiac-stimulant properties. Due to these reasons, it can also help in paralytic disorders. It can improve sensation and movement of paralytic parts of the body. Its leaf decoction is used in paralysis. In Ayurveda, internal use of leaves is also suggested for epilepsy and hysteria. However, it may be beneficial in lower dosage (less than 500 mg/day). Larger amounts of leaves powder can also excite the central nervous system and can cause more seizures, so unwise use of wormwood leaves can result in severe side effects. The second thing to remember is that wormwood extract should not be preferred than crude wormwood powder. Administrations of wormwood extract can enhance the activity of AchE on low dosage. Wormwood extract can maintain acetylcholine levels in the brain and improve cognitive ability (Auclair et al. 2004).

Zeng et al. (2015) evaluated the anti-neuroinflammatory effects of natural sesquiterpene dimer caruifolin D from *Artemisia absinthium* L., which is an edible vegetable or traditional medicinal food in East Asia due to its various health good and ill effects like anti-asthma, antipruritic effects, and sedation. The study reported that caruifolin D significantly inhibited the productions of various neuroinflammatory mediators from microglia in response to bacterial lipopolysaccharide stimulation. Moreover, anti-inflammatory mechanism study showed that caruifolin D markedly suppressed the production of intracellular reactive oxygen species, which is an important player involved in neuroinflammation, leading to inhibitory effects on the activations of protein kinase C (PKC) and c-Jun N-terminal kinase (JNK), which are two major neuroinflammatory signaling pathways in the brains. Furthermore, caruifolin D protected neurons against microglia-mediated neuronal inflammatory damages by upregulating neuronal viability and maintaining healthy neuronal morphology. Taken together, these results revealed the anti-neuroinflammatory and neuroprotective mechanism of *Artemisia absinthium* L., and also suggested that caruifolin D is a major anti-inflammatory component from *Artemisia absinthium* L., which might be developed as a drug candidate for neuroinflammation-related diseases.

α-Thujone generally is considered to be the principal active ingredient of wormwood oil and toxic principle in absinthe (Arnold 1989). The content of β-thujone often exceeds that of α-thujone depending on the plant source, but the β-diastereomer is generally of lower toxicity. α-Thujone also is reported to have antinociceptive activity in mice (Rice and Wilson 1976). This monoterpenoid occurs in many plants, including *Artemesia* species, sage, and the Thuja tree (Arnold 1989).

Höld et al. (2000) established from his study that a-thujone acts at the noncompetitive blocker site of the $GABA_A$ receptor and is rapidly detoxified, thereby providing a reasonable explanation for some of the actions of absinthe other than those caused by ethanol, and allowing more meaningful evaluation of risks involved in the continued use of herbal medicines containing a-thujone. α-Thujone is a competitive inhibitor of (3H)EBOB (ethynylbicycloorthobenzoate or 49-ethynyl-4-*n*-propylbicycloorthobenzoate) binding, i.e., of the noncompetitive blocker site of the GABA-gated chloride channel (Cole and Casida 1992). Most importantly, electrophysiological studies establish that in dorsal root ganglion neurons a-thujone is a reversible modulator of the $GABA_A$ receptor. Absinthe and wormwood oil contain not only α-thujone as their purported active ingredient but also many other candidate toxicants, including b-thujone and ethanol in the case of absinthe. b-Thujone is less toxic than a-thujone to mice (Rice and Wilson 1976) and *Drosophila* and in addition is 2.3-fold less potent in the (^{3}H)EBOB assay (Höld et al. 2000).

Thujone can cause the following side effects: seizures, nausea and vomiting, restlessness, dizziness, tremors, numbness, thirst, paralysis, and insomnia.

Anti-obesity Effects of *Artemisia absinthium*

Obesity is a condition in which a person has an abnormally high and unhealthy proportion of body fat. Obesity is a major risk factor for many metabolic disorders, including hyperlipidemia, diabetes mellitus, atherosclerosis, hypertension, and

cardiovascular disease (Lei et al. 2007). Physiologically, obesity is associated with increased levels of adipocytes and an increase in adipocyte volume. Natural anti-obesity products are increasingly common in the global market, providing an alternative to currently available chemical treatments or medical interventions (e.g., bariatric surgery). These natural alternatives are mainly found in the realm of food supplements, given that dietary changes are closely linked to preventing and fighting obesity. Products that generally support metabolic activity and provide a feeling of satiety are also associated with anti-obesity treatment. The plant world offers options of interest for this indication. Herbal medicinal products, on the other hand, are not relevant for this indication, as there are no licenses within herbal medicinal products for the treatment of obesity and little documentation to support its use (apart from exceptions such as dandelion as an appetite suppressant).

Kim et al. (2015) invented the anti-obesity herbal mixture that comprises extract of *Melissa*, extract of *Artemisia*, and extract of *Mori Folium* as active ingredients in order to suppress the obesity. The term *Artemisia* may comprise any kind of *Artemisia* species *including Artemisia capillaris, Artemisia iwayomogi, Artemisia princeps, Artemisia annua, Artemisia abrotanum, Artemisia absinthium, Artemisia japonica, Artemisia cina*, etc.

Antifertility Effects *of Artemisia absinthium*

Artemisia absinthium is used together with other plants as fertility regulators by the French and Spanish New Mexicans (emmenagogue) and in Madeira and this use is ancient (Lans 2006). *Artemisia absinthium* is also used across Europe for reproductive purposes and these uses are ancient (Pieroni 2000). *Artemisia absinthium* is used together with other plants as fertility regulators in western Panama and Paraguay and this use is ancient (Adams and Garcia 2006). Smith (2010) conducted a study in mice subjected to heat stress, to explore the potential of *Artemisia* absinthium on potency in mice. Based on his results, the use of the herb *Artemisia absinthium* has the potential to decrease the negative effects of heat stress on fertility.

Toxicity and Interaction *of Artemisia absinthium*

Insufficient available evidence suggests that *Artemisia absinthium* should be avoided during pregnancy and in children under the age of 18 (Armstrong et al. 2014). The World Health Organization strongly discourages the use of the herb as sole treatment for malaria, due to the potential for malarial parasite to develop resistance to it (Armstrong et al. 2014). It is not listed in the US FDA generally recognized as safe list and is not recommended for oral administration (Armstrong et al. 2014). There have been adverse reactions recorded with *Artemisia absinthium* in individuals with cardiovascular conditions, gastrointestinal disorders, musculoskeletal disorders, neurological conditions, and renal dysfunction (Armstrong et al.

2014). *Artemisia absinthium* has reported to have a negative interaction with alcohol, antiangiogenic drugs, and antiarrhythmic agents (Armstrong et al. 2014).

References

Abad MJ et al (2012) The Artemisia L. genus: a review of bioactive essential oils. Molecules 17(3):2542–2566

Aboutabl E, El Azzouny A, El Dahmy S (1998) Constituents of the essential oil of Artemisia absinthium grown in Egypt. J Essent Oil Bear Plants 1:82–86

Adams JD, Garcia C (2006) Women's health among the Chumash. Evid Based Complement Alternat Med 3(1):125–131

Ahamad J, Mir SR, Naquvi KJ (2012) Preliminary pharmacognostical standardization of aerial parts of A. absinthium Linn. Int Res J Pharm 3:218–220

Ahangar N, Mirfetros S, Ebrahimzadeh M (2011) Antidepressant activity of polyphenol fraction of Artemisia absinthium L. Pharmacologyonline 1:825–832

Ahlqvist E et al (2018) Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. Lancet Diabetes Endocrinol 6:P361–P369

Amat N, Upur H, Blažeković B (2010) In vivo hepatoprotective activity of the aqueous extract of Artemisia absinthium L. against chemically and immunologically induced liver injuries in mice. J Ethnopharmacol 131(2):478–484

Anjaneyulu M, Chopra K, Kaur I (2003) Antidepressant activity of quercetin, a bioflavonoid, in streptozotocin-induced diabetic mice. J Med Food 6(4):391–395

Ariño A et al (1999) Essential oil of Artemisia absinthium L. from the Spanish Pyrenees. J Essent Oil Res 11(2):182–184

Armstrong E et al (2014) Wormwood (Artemisia absinthium). Natural standard monograph

Arnold WN (1989) Absinthe. Sci Am 260(6):112–117

Arrieta J et al (2001) Amoebicidal and giardicidal compounds from the leaves of Zanthoxylum liebmannianun. Fitoterapia 72(3):295–297

Ashok PK, Upadhyaya K (2013) Preliminary phytochemical screening and physico-chemical parameters of Artemisia absinthium and Artemisia annua. J Pharmacogn Phytochem 1(6):229–235

Auclair A et al (2004) 5-HT2A and α1b-adrenergic receptors entirely mediate dopamine release, locomotor response and behavioural sensitization to opiates and psychostimulants. Eur J Neurosci 20(11):3073–3084

Baker P (2001) The book of absinthe: a cultural history. Grove Press, New York

Blagojević P et al (2006) Chemical composition of the essential oils of Serbian wild-growing Artemisia absinthium and Artemisia vulgaris. J Agric Food Chem 54(13):4780–4789

Boivin B (1972) Flora of the Prairie provinces. III. Connatae. Phytologia 22:315–398

Bora KS, Sharma A (2010) Neuroprotective effect of Artemisia absinthium L. on focal ischemia and reperfusion-induced cerebral injury. J Ethnopharmacol 129(3):403–409

Bora KS, Sharma A (2011a) The genus Artemisia: a comprehensive review. Pharm Biol 49(1):101–109

Bora KS, Sharma A (2011b) Evaluation of antioxidant and free-radical scavenging potential of Artemisia absinthium. Pharm Biol 49(12):1216–1223

Brunton L, Lazo J, Parker K (2005) Goodman's and Gilman's the pharmacological basic of therapeutics. 11th ed. McGraw Hill Companies, New York

Calzada F, Arista R, Pérez H (2010) Effect of plants used in Mexico to treat gastrointestinal disorders on charcoal–gum acacia-induced hyperperistalsis in rats. J Ethnopharmacol 128(1):49–51

Canadanovic-Brunet JM et al (2005) Free-radical scavenging activity of wormwood (Artemisia absinthium L.) extracts. J Sci Food Agric 85(2):265–272

Carnat A-P et al (1992) cis-Chrysanthenol, a main component in essential oil of Artemisia absinthium L. growing in Auvergne (Massif Central), France. J Essent Oil Res 4(5):487–490
Chiasson H et al (2001) Acaricidal properties of Artemisia absinthium and Tanacetum vulgare (Asteraceae) essential oils obtained by three methods of extraction. J Econ Entomol 94(1):167–171
Chu W et al (2017) Composition and morphology of cuticular wax in blueberry (Vaccinium spp.) fruits. Food Chem 219:436–442
Cole LM, Casida JE (1992) GABA-gated chloride channel: binding site for 4′-ethynyl-4-n-[2, 3-3H2] propylbicycloorthobenzoate ([3H] EBOB) in vertebrate brain and insect head. Pestic Biochem Physiol 44(1):1–8
Cryan JF, Markou A, Lucki I (2002) Assessing antidepressant activity in rodents: recent developments and future needs. Trends Pharmacol Sci 23(5):238–245
Daradka HM et al (2014) Antidiabetic effect of Artemisia absinthium extracts on alloxan-induced diabetic rats. Comp Clin Pathol 23(6):1733–1742
Derwich E, Benziane Z, Boukir A (2009) Chemical compositions and insecticidal activity of essential oils of three plants Artemisia sp.: Artemisia herba-alba, Artemisia absinthium and Artemisia pontica (Morocco). Electron J Environ Agric Food Chem 8(12):1202–1211
Desai PB et al (2010) Oxidative stress and enzymatic antioxidant status in rheumatoid arthritis: a case control study. Eur Rev Med Pharmacol Sci 14(11):959–967
Dettling A et al (2004) Absinthe: attention performance and mood under the influence of thujone. J Stud Alcohol 65(5):573–581
Ebrahimzadeh M et al (2009) Antioxidant and antidepressant effects of four novel Bupropion analogues. Pharmacologyonline 2:317–322
Ebrahimzadeh M et al (2010) Biological and pharmacological effects of Delphinium elbursense. Afr J Biotechnol 9(34):5542–5549
Efferth T et al (2001) The anti-malarial artesunate is also active against cancer. Int J Oncol 18(4):767–773
Erichsen Brown C (1979) Use of plants for the past 500 years. Breezy Creeks Press, Aurora, ON, p xxii, 512p.-illus. En Icones. General (KR, 198100065)
Firestone GL, Sundar SN (2009) Anticancer activities of artemisinin and its bioactive derivatives. Expert Rev Mol Med 11:e32
Goraev M, Bazalitskaya U, Lishtvanova L (1962) The terpene portion of the essential oil of Artemisia absinthium. Zeitschrift fur Naturforschung 35:2799–2802
Goud BJ, Swamy B (2015) A review on history, controversy, traditional use, ethnobotany, phytochemistry and pharmacology of Artemisia absinthium Linn. Int J Adv Res Eng Appl Sci 4(5):77–107
Goud BJ, Swamy BC (2016) Effect of Artemisia absinthium on the neurochemical profile of streptozotocin induced diabetic rat brain. Int J Pharm Res Health Sci 4:1150–1159
Guangrong H, Jiaxin J, Dehui D (2008) Antioxidative and antibacterial activity of the methanol extract of Artemisia anomala S. Moore. Afr J Biotechnol 7(9):1335–1338
Habibi R et al (2016) Effect of Different levels of essential oils of Wormwood (Artemisia absinthium) and Cumin (Cuminum cyminum) on growth performance carcass characteristics and immune system in broiler chicks. Iran J Appl Anim Sci 6(2):395–400
Habibipour R, Rajabi M (2015) Antibacterial effects of Arctium lappa and Artemesia absinthium extracts in laboratory conditions. J Herbmed Pharmacol 4:133–137
Hakim ZS, Patel BK, Goyal RK (1997) Effects of chronic ramipril treatment in streptozotocin-induced diabetic rats. Indian J Physiol Pharmacol 41:353–360
Hoffmann D (2003) Medical herbalism: the science and practice of herbal medicine. Simon and Schuster, New York
Höld KM et al (2000) α-Thujone (the active component of absinthe): γ-aminobutyric acid type A receptor modulation and metabolic detoxification. Proc Natl Acad Sci 97(8):3826–3831
Hussain M et al (2017) A status review on the pharmacological implications of Artemisia absinthium&58; a critically endangered plant. Asian Pac J Trop Dis 7(3):185–192

Jaenson TG, Pålsson K, Borg-Karlson AK (2005) Evaluation of extracts and oils of tick-repellent plants from Sweden. Med Vet Entomol 19(4):345–352
Jivad N, Rabiei Z (2015) Review on herbal medicine on brain ischemia and reperfusion. Asian Pac J Trop Biomed 5(10):789–795
Joshi RK (2017) A perspective on the phytopharmaceuticals responsible for the therapeutic applications. In: Keservani RK, Sharma AK, Kesharwani RK (eds) Recent advances in drug delivery technology. IGI Global, Delhi, pp 229–262
Judzentiene A, Tomi F, Casanova J (2009) Analysis of essential oils of Artemisia absinthium L. from Lithuania by CC, GC (RI), GC-MS and 13C NMR. Nat Prod Commun 4(8):1113–1118
Juteau F et al (2003) Composition and antimicrobial activity of the essential oil of Artemisia absinthium from Croatia and France. Planta Med 69(02):158–161
Kaul V, Nigam S, Banerjee A (1979) Thin layer and gas chromatographic studies of the essential oil of Artemisia absinthium Linn. Indian Perfum 23:1–7
Kharoubi O et al (2008) Prophylactic effects of Wormwood on lipid peroxidation in an animal model of lead intoxication. Indian J Nephrol 18(2):51
Kim M-Y et al (2015) Antiobesity composition. Google Patents
Kordali S et al (2005a) Determination of the chemical composition and antioxidant activity of the essential oil of Artemisia dracunculus and of the antifungal and antibacterial activities of Turkish Artemisia absinthium, A. dracunculus, Artemisia santonicum, and Artemisia spicigera essential oils. J Agric Food Chem 53(24):9452–9458
Kordali S et al (2005b) Screening of chemical composition and antifungal and antioxidant activities of the essential oils from three Turkish Artemisia species. J Agric Food Chem 53(5):1408–1416
Kumar A et al (2013) India towards diabetes control: key issues. Australas Med J 6(10):524
Lans C (2006) Creole remedies of Trinidad and Tobago book self-published on Lulu.com
Lei F et al (2007) Evidence of anti-obesity effects of the pomegranate leaf extract in high-fat diet induced obese mice. Int J Obes 31(6):1023
Li Y et al (2015) Effect of Gymnema sylvestre, citrullus colocynthis and Artemisia absinthium on blood glucose and lipid profile in diabetic human. Acta Pol Pharm 72:981–985
Lopes-Lutz D et al (2008) Screening of chemical composition, antimicrobial and antioxidant activities of Artemisia essential oils. Phytochemistry 69(8):1732–1738
Mahmoudi M et al (2009) Antidepressant and antioxidant activities of Artemisia absinthium L. at flowering stage. Afr J Biotechnol 8(24):7170–7175
Masoudi M, Saiedi M (2017) A review study of ethnopharmacology, phytochemistry, and anti-inflammatory, antioxidant, and anti-microbial effect of Artemisia absinthium. Der Pharmacia Lettre 9:155–162
Mohamed AE-HH et al (2010) Chemical constituents and biological activities of Artemisia herba-alba. Rec Nat Prod 4(1):1
Msaada K et al (2015) Chemical composition and antioxidant and antimicrobial activities of wormwood (Artemisia absinthium L.) essential oils and phenolics. J Chem 2015:804658
Nassiri-Asl M et al (2013) Effects of rutin on oxidative stress in mice with kainic acid-induced seizure. J Integr Med 11(5):337–342
Nin S, Bennici A (2001) Transgenic Artemisia (Wormwood). In: Bajaj YPS (ed) Transgenic crops III. Biotechnology in agriculture and forestry. Springer, Berlin
Orav A et al (2006) Composition of the essential oil of Artemisia absinthium L. of different geographical origin. In: Proceedings-Estonian Academy of Sciences Chemistry. TRUEKITUD OU
Padosch SA, Lachenmeier DW, Kröner LU (2006) Absinthism: a fictitious 19th century syndrome with present impact. Subst Abuse Treat Prev Policy 1(1):14
Pandey G (2011) Medicinal plants against liver diseases. Int Res J Pharm 2:115–123
Panossian A, Wikman G, Sarris J (2010) Rosenroot (Rhodiola rosea): traditional use, chemical composition, pharmacology and clinical efficacy. Phytomedicine 17(7):481–493
Pieroni A (2000) Medicinal plants and food medicines in the folk traditions of the upper Lucca Province, Italy. J Ethnopharmacol 70(3):235–273
Pillay P, Maharaj VJ, Smith PJ (2008) Investigating South African plants as a source of new antimalarial drugs. J Ethnopharmacol 119(3):438–454

Pino JA, Rosado A, Fuentes V (1997) Chemical composition of the essential oil of Artemisia absinthium L. from Cuba. J Essent Oil Res 9(1):87–89
Remy S (1988) Vincent van Gogh and the thujone connection. JAMA 260:3042–3044
Rezaeinodehi A, Khangholi S (2008) Chemical composition of the essential oil of Artemisia absinthium growing wild in Iran. Pak J Biol Sci 11(6):946–949
Riahi L et al (2013) Variations in Tunisian wormwood essential oil profiles and phenolic contents between leaves and flowers and their effects on antioxidant activities. Ind Crop Prod 46:290–296
Rice KC, Wilson RS (1976) (−)-3-Isothujone, a small nonnitrogenous molecule with antinociceptive activity in mice. J Med Chem 19(8):1054–1057
Sánchez-Chávez G, Salceda R (2001) Acetyl- and butyrylcholinesterase in normal and diabetic rat retina. Neurochem Res 26(2):153–159
Sefidkin F et al (2003) Chemical composition of the essential oil of five Artemisia species from Iran. J Essent Oil Bear Plants 6(1):41–45
Shafi S, Tabassum N (2013) Survey on anti-diabetic plants in Kashmir [India]. J Adv Pharm Educ Res 3(4):306–318
Shafi G et al (2012) Artemisia absinthium (AA): a novel potential complementary and alternative medicine for breast cancer. Mol Biol Rep 39(7):7373–7379
Smith HM (2010) Effects of Artemisia afra and Artemisia absinthium on fertility of male mice exposed to increased ambient temperatures for 24 hours. University of Missouri, Columbia, MO
Spinella M (2001) Herbal medicines and epilepsy: the potential for benefit and adverse effects. Epilepsy Behav 2(6):524–532
Su X-Z, Miller LH (2015) The discovery of artemisinin and the Nobel Prize in physiology or medicine. Sci China Life Sci 58(11):1175–1179
Sun H et al (2012) Dexamethasone and vitamin B12 synergistically promote peripheral nerve regeneration in rats by upregulating the expression of brain-derived neurotrophic factor. Arch Med Sci 8(5):924
Taquechel M (2018) Artemisia—an intensely bitter herb with fantastic gut health, and anti diabetic properties
Tariku Y et al (2011) In vitro evaluation of antileishmanial activity and toxicity of essential oils of Artemisia absinthium and Echinops kebericho. Chem Biodivers 8(4):614–623
Trease G, Evans W (1983) Textbook of pharmacognosy (Balliere). Tindall, London, pp 57–59
Tucker AO, Maciarello MJ, Sturtz G (1993) The essential oils of Artemisia 'Powis Castle' and its putative parents, A. absinthium and A. arborescens. J Essent Oil Res 5(3):239–242
Umpiérrez ML et al (2012) Essential oils from Asteraceae as potential biocontrol tools for tomato pests and diseases. Phytochem Rev 11(4):339–350
Vallès J et al (2011) Biology, genome evolution, biotechnological issues and research including applied perspectives in Artemisia (Asteraceae). In: Kader J-C, Delseny M (eds) Advances in Botanical Research. Elsevier, London, pp 349–419
Vogt DD, Montagne M (1982) Absinthe: behind the emerald mask. Int J Addict 17(6):1015–1029
Weinstein RA (2001) Controlling antimicrobial resistance in hospitals: infection control and use of antibiotics. Emerg Infect Dis 7(2):188
Wiseman H et al (2000) Isoflavone phytoestrogens consumed in soy decrease F2-isoprostane concentrations and increase resistance of low-density lipoprotein to oxidation in humans. Am J Clin Nutr 72(2):395–400
Yang Y et al (2014) Enhanced delivery of artemisinin and its analogues to cancer cells by their adducts with human serum transferrin. Int J Pharm 467(1–2):113–122
Zeng K-W et al (2015) Caruifolin D from Artemisia absinthium L. inhibits neuroinflammation via reactive oxygen species-dependent c-jun N-terminal kinase and protein kinase c/NF-κB signaling pathways. Eur J Pharmacol 767:82–93

Dietary Phytochemicals and Their Potential Effects on Diabetes Mellitus 2

Rajbala Singh, Imran Kazmi, Muhammad Afzal, and Faisal Imam, Khalid Saad Alharbi

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most important contemporary medical problems; currently the number of people with diabetes exceeds 200 million worldwide, most of them being patients with T2DM. T2DM causes increased risks of cardiovascular disease, kidney failure, blindness, neuropathy, and peripheral circulatory disease. Type 2 diabetes mellitus was formerly called as non-insulin-dependent diabetes mellitus, obesity-related diabetes, or adult-onset diabetes. T2DM is a metabolic disorder that is primarily characterized by insulin resistance, relative insulin deficiency, and hyperglycemia (Dilmec et al. 2010). The loss of traditional dietary habits, increasing consumption of energy-dense foods, and increasing portion sizes, together with less physical activity at work and/or during leisure time, are strongly associated with the explosive increase of these diseases (Heidemann et al. 2005; Montonen et al. 2005). The prevalence of diabetes is rapidly rising all over the globe at an alarming rate (Huizinga and Rothman 2006). The global prevalence of diabetes mellitus has

R. Singh
Siddhartha Institute of Pharmacy, Dehra Dun, Uttarakhand, India

I. Kazmi (✉)
Glocal School of Pharmacy, Glocal University, Saharanpur, Uttar Pradesh, India

M. Afzal (✉) · K. S. Alharbi
Department of Pharmacology College of Pharmacy, Jouf University, Sakaka, Kingdom of Saudi Arabia

F. Imam
College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

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Table 1 List of top ten countries with diabetes (Wild et al. 2004)

Rank	Country	People with T2DM (million) (year 2000)	Rank	Country	People with T2DM (million) (year 2030)
1	India	31.7	1	India	79.4
2	China	20.8	2	China	42.3
3	USA	17.7	3	USA	30.3
4	Indonesia	8.4	4	Indonesia	21.3
5	Japan	6.8	5	Japan	13.9
6	Pakistan	5.2	6	Pakistan	11.3
7	Russia Fed	4.6	7	Russia Fed	11.1
8	Brazil	4.6	8	Brazil	8.9
9	Italy	4.3	9	Italy	7.8
10	Ukraine	3.2	10	Ukraine	6.7

been estimated at 171 million people and is projected to more than double, to 366 million people, by 2030 (Wild et al. 2004). See Table 1.

The third National Health and Nutrition Examination Study carried out in the USA gives peak prevalence rates of diabetes for men as 21.1% in the 75-plus age group. The peak prevalence for women is 17.8%, which occurs in the 60–74 age range. These data suggest that diabetes is more common in females than males (Harris et al. 1998). In Europe rates are 3–10%, while some Arab, Asian-Indian, and Hispanic-American populations have rates of 14–20%. However in South Africa it is 7.1%. The neighboring country Oman has reported that the prevalence of diabetes mellitus is 13.1% (King and Rewers 1993). In Saudi Arabia, it has been observed as 11.8% and 12.8% for males and females, respectively (Al-Nuaim et al. 1997). The highest rates were found in natives of Nauru, a Pacific Island, and the Pima Indians in the USA that had prevalence rates as high as 50% (King and Rewers 1993). Urbanization is associated with lifestyle changes, which expose individuals to various risk factors that can lead to noncommunicable diseases (WHO and IDF 2006; Richard et al. 2006). Obesity is a key risk factor for T2DM. The association between increasing body mass index (BMI) and greater weight gain increases the risk of diabetes. Genome-wide association studies have catalogued around 20 gene variants, e.g., the chromosome 12q24 in HNF-1α gene, I27L/exon1 (Reynisdottir et al. 2003), rs7903146 in TCF7L2, E23 K in KCNJ11, P12A in PPAR-c (Grant et al. 2006; Gloyn et al. 2003), CRP locus APCS and CRPP1 genes, SNP 133552, and SLC30A8 (Wolford et al. 2003).

Pathogenesis

Insulin resistance is a major risk factor for the pathogenesis of type 2 diabetes and the insulin resistance syndrome (Reaven et al. 1995). Abnormalities in both insulin action and insulin secretion occur early in the pathogenesis of T2DM (Ferrannini

1998; Iwasaki 2001). Primary defects in pancreatic ß-cells have been recognized in maturity-onset diabetes of the young (MODY), a rare form of diabetes resulting from gene mutation; different types of MODY genes have been identified that encode the glycolytic enzyme glucokinase (GCK) and transcription factors include hepatocyte nuclear factor (HNF)-4a/MODY1, glucokinase/MODY2, HNF-I a/MODY3, insulin promoter factor (IPF)-1/MODY4, HNF-1 IMODY5, neurogenic differentiation (NeuroD1)/MODY6, and Islet (Isl)-1/MODY7 (Bell and Polonsky 2001). The HNF-la mutation causes a progressive defect that alters β-cell insulin secretion rather than the sensing of glucose (Pearson et al. 2001). Currently many literature discusses that diabetes has concomitant increased free radical production and depletion of cellular antioxidant defense systems. It is well established that alloxan- and streptozotocin-induced diabetic animals become hyperglycemic as the result of destruction of ß-cells of the pancreas by free radicals (Oberley 1988). Pancreatic β-cells are especially vulnerable to oxidative stress, probably because of their low free radical scavenging enzyme capacity reflected in low superoxide dismutase (SOD), catalase, and glutathione peroxide activities. The reduction of insulin-dependent 2-deoxyglucose uptake was consequently accompanied by decreased P13 kinase activity and GLUT4 translocation and defective insulin-mediated glucose uptake. The imbalance of free radicals and antioxidants is an important pathogenic factor affecting insulin-signaling pathways (Ceriello et al. 2000).

The development of diabetic nephropathy has been reported to correlate with levels of aldose reductase mRNA (Shah et al. 1998). Recent studies have indicated that ROS plays a key role in the development of diabetic nephropathy. High glucose level directly increases hydrogen peroxide production by mesangial cells and lipid peroxidation of glomerular mesangial cells. Hyperglycemia-induced secondary mediator's activation such as protein kinase C (PKC), mitogen-activated protein (MAP) kinases and cytokine production is also responsible for oxidative stress-induced renal injury in the diabetic condition (Anjaneyulu and Chopra 2004). Diabetic dyslipidemia is associated with insulin resistance, visceral obesity, and liver fat content. Islet amyloidal polypeptide (IAPP)-derived amyloid deposition increases along with the duration of type 2 diabetes mellitus; hence hypersecretion of IAPP may be involved in the progression of this disease (Haruhiko 2004). Approximately 20–40% of adults with type 2 diabetes have some signs of retinopathy, and nearly about 8% have more severe vision-threatening retinopathy. Diabetic retinopathy is classified into an earlier stage called nonproliferative diabetic retinopathy (NPDR) and a later, more advanced stage called proliferative diabetic retinopathy (PDR). In NPDR, microaneurysms, hemorrhages, hard exudates, cotton wool spots, intraretinal microvascular abnormalities, and venous beading are common ophthalmoscopic features. PDR is characterized by the presence of new abnormal blood vessels, vitreous hemorrhage, and fibrous scarring. An additional complication of NPDR is the development of macular edema, characterized by swelling and hard exudate deposition near the central macula (Kempen et al. 2004). Diabetic cataract is a major complication of diabetes mellitus, and is primarily

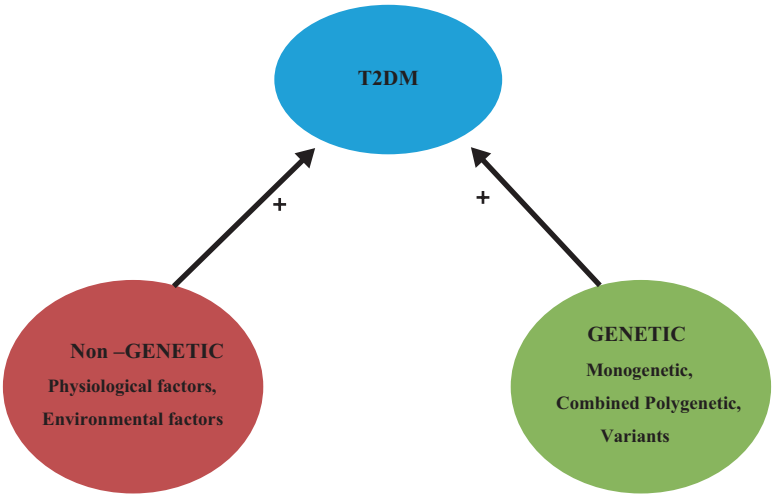

Fig. 1 Factor responsible for type 2 diabetes mellitus (T2DM)

caused by polyol accumulation and glycation within lens fibers and epithelium (Chung et al. 2005), Fig. 1.

Diabetic foot problems result from complex interactions between peripheral neuropathy (including autonomic dysfunction), peripheral arterial disease, and poor foot hygiene (Malone et al. 1989). The mechanism by which hyperglycemia causes neural degeneration is via the increased oxidative stress that accompanies diabetes. Metabolic and oxidative insults often cause rapid changes in glial cells. Key indicators of this response are increased synthesis of glial fibrillary acidic protein (GFAP) and S100B, both astrocytic markers (Baydas et al. 2003). Diabetic foot ulcers are typically found due to neuropathy, peripheral arterial disease, or poor foot hygiene, and are frequently precipitated by inappropriate footwear. Neuropathic ulcers are usually seen at sites of repetitive pressure. Furthermore also erectile dysfunction as a diabetic complication remains incompletely understood. Diabetes has a known pathologic effect on peripheral tissue innervation and vascularization, both of which are critical for erectile function. Oxidative stress to cavernous tissue may be an important contributory factor to erectile dysfunction in diabetics (Ryu et al. 2005). One of the major complications of diabetes is cardiovascular disease. The established risk factors such as dyslipidemia, hypertension, and smoking cannot explain this increased prevalence of macrovascular disease in diabetes. Oxidative stress plays a crucial role in atherogenesis and causes oxidation of low-density lipoprotein. Increased concentrations of autoantibodies to both oxidized and glycated LDL and glyco-Ox-LDL have been documented in diabetes suggesting that in type 2 diabetes enhanced oxidative stress occurs in vivo (Jialal et al. 2002; Kedziora et al. 2000).

Dietary Phytochemicals

Polyphenols

Polyphenols, including their functional derivatives esters and glycosides, have one to various phenol groups with one hydroxyl-substituted aromatic ring (Dey and Harborne 1998). According to their structure number of phenol rings and the type and number of structural elements binding polyphenols are grouped into different classes:

1. Simple phenolic acids, e.g., ferulic, caffeic, *p*-coumaric, vanillic, gallic, ellagic, *p*-hydroxybenzoic, chlorogenic acids.
2. Stilbenes, e.g., resveratrol.
3. Curcuminoids, e.g., curcumin.
4. Chalcones, e.g., phlorizin, naringenin chalcone.
5. Lignans, e.g., matairesinol, secoisolariciresinol.
6. Flavonoids, composed of seven subclasses: (a) flavonols, e.g., quercetin; (b) flavanols (monomeric, e.g., catechin, epicatechin, oligomeric, and polymeric compounds, e.g., proanthocyanidins, also called condensed tannins); (c) anthocyanins, e.g., cyaniding; (d) flavones, e.g., luteolin, apigenin; (e) flavanones, e.g., naringenin; (f) flavanonols, e.g., taxifolin, (g) isoflavones, e.g., genistein (Bravo 1998; Harborne and Baxter 1999; Williams et al. 2004)

Simple phenolic acids are non-flavonoid phenolic compounds conjugated with other natural chemicals such as flavonoids, alcohols, hydroxy fatty acids, sterols, and glucosides (Nobili et al. 2009; Soobrattee et al. 2005).

Anthocyanins have been shown to act as antioxidants and can regulate adipocytokine gene expression to ameliorate adipocyte function; thus the dietary intake of polyphenol-rich food might be beneficial in preventing the onset of type 2 diabetes mellitus (Clifford 2000).

Cyanidin is the most common anthocyanidin in foods. Its food contents are generally proportional to color intensity and reach values up to 2–4 g/kg fresh wt in blackberries. Wine contains 200–350 mg anthocyanins/L (Clifford 2000). These flavonoids have been shown to have anti-inflammatory activity in obese adipose tissues, which is mediated by PPAR-γ-independent mechanisms (Tsuda 2008). Moreover, cyanidin 3-glucoside (C3G) downregulates the RBP4, which is known to ameliorate insulin sensitivity in the adipose tissue of diabetic mice (Sasaki et al. 2007).

Ferulic acid (FA) is a natural polyphenol which is extracted from the rice bran (Atsuyo et al. 2008), vegetables, fruits such as sweet corn, tomatoes (Chiu-Mei et al. 2010), and most abundant hydroxycinnamic acid in cell wall polysaccharides; it is widely distributed in higher plants, and has antioxidative, hypotensive, and anti-inflammatory, diabetic nephropathy activities. FA is thought to act via the suppression of mesangial cell activation, which is a critical process in diabetic nephropathy, as the suppression of TGF-b1 mRNA expression was observed (Estelle et al. 2002).

Ferulic acid (FA) to the diabetic rats (induced with streptozotocin) resulted in a decrease in the levels of glucose, thiobarbituric acid-reactive substances (TBARS), hydroperoxides, and FFA; increase in reduced glutathione (GSH); increased activities of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx); and expansion of pancreatic islets (Sri Balasubashini et al. 2004).

Resveratrol (3,5,40-trihydroxy-trans-stilbene; RV) is a member of the stilbene family of phenolic compounds (Fernández et al. 2012) and was identified in 1963 as the active constituent of the dried roots of *Polygonum cuspidatum*, also called Ko-jo-kon in Japanese, and used in traditional Asian medicine. It is commonly found in many plants as peanut and its derivatives, pistachio, berries, dark chocolate, and grapes as well as their derivatives; red wine is the most notable dietary source of resveratrol than white wine (Philipp et al. 2008). Electrophysiological measurements allowed demonstrating that resveratrol binds to sulfonylurea receptor (SUR) and is a blocker of pancreatic ATP-sensitive K^+ channels. It was also observed that resveratrol displaced binding of glibenclamide, a sulfonylurea drug that blocks ATP-sensitive K^+ channels in β-cells and is applied in type 2 diabetes mellitus to enhance insulin secretion (Hambrock et al. 2007). ATP-sensitive K^+ channels are normally blocked as a result of the increase in the ATP/ADP ratio resulting from metabolism of glucose or other fuel secretagogues. The rise in the ATP/ADP ratio induces depolarization of the plasma membrane and triggers secretion of insulin (Henquin 2000). The effects of resveratrol on blood insulin concentrations in diabetes were investigated using two experimental animal models: a model of diabetes which is similar to type 1 diabetes in humans (streptozotocin-induced diabetic rats) and a model which is similar to type 2 diabetes in humans (streptozotocin–nicotinamide diabetic rats). In the short-term experiment on streptozotocin–nicotinamide diabetic rats, a considerable hyperinsulinemic effect of resveratrol was shown (Chi et al. 2007). It is also known that resveratrol may influence secretion and blood concentrations of some adipokines (Szkudelska et al. 2009; Rivera et al. 2009). Hydroxytyrosol is a phenyl ethyl alcohol, 2-(3,4-dihydroxyphenyl) ethanol (3,4-DHPEA), and the diet is virgin olive oil, being present, mainly as secoiridoid derivatives or as acetate and free form. Hydroxytyrosol and its derivatives arise from oleuropein (ester of hydroxytyrosol and elenolic acid) present in olives during extraction of olive oil (Fernández et al. 2012). Fiber, phytosterols, polyphenolics, and a high unsaturated to saturated fat ratio may be accountable for the hypocholesterolemic effect of almonds. Almonds may be cardioprotective because they are excellent sources of monounsaturated fats, α-tocopherol, dietary fiber, copper, magnesium, arginine, plant sterols, and polyphenols. Most almond studies in the literature have illustrated the hypolipidemic effect of almonds in healthy subjects or hypercholesterolemic patients (Sing et al. 2011).

Beta-sitosterol, stigmasterol evaluated in *Liriope spicata*: It is a Chinese medicinal plant, which belongs to Liliaceae family. Extract of *Liriope spicata* did not have any appreciable effect on fasting blood glucose level in normal mice, but it caused a marked decrease of fasting blood glucose level and a significant improvement on glucose tolerance and insulin resistance in STZ-induced type 2 diabetic mice. Chalcone compounds naturally found in plants or of synthetic origin are known to

exhibit several biological activities and have been involved in glucose metabolism. It is isolated from plants and have improved the glucose uptake in adipocytes and potentiated insulin-stimulated glucose uptake in adipocytes. Furthermore, chalcone derivatives from aryloxypropanolamines have shown potential anti-hyperglycemic effect when administered in hyperglycemic rats (Rosangela et al. 2009). Lignans are a group of phytoestrogen formed of two phenylpropane units. The most important sources of lignans are flaxseed and grain. Flaxseed (linseed) is the richest dietary source of lignans that contains secoisolariciresinol (>3.7 g/kg dry weight) and low quantities of matairesinol (Adlercreutz 2007). Other lignans have been identified in rye, e.g., pinoresinol, lariciresinol, isolariciresinol, and syringaresinol (Hallmans et al. 2003). Other sources of lignans are soya, sesame seed, berries, nuts, broccoli, tea, wine, and a variety of edible plants including algae, leguminous, cereals, vegetables (garlic, asparagus, carrots), and fruits (pears, prunes) (Adlercreutz 2007). Secoisolariciresinol diglucoside was shown to reduce total serum cholesterol and atherosclerosis in rabbits (Prasad 1999); it has antihypertensive effects (Prasad 2004) and reduces the incidence of diabetes in several animal models (Prasad 2000). In several human intervention studies, flaxseed reduces total and LDL cholesterol, without an influence on HDL or total TG (Bloedon and Szapary 2004; Prasad 2001).

Curcumin was a yellow spice and pigment in food system, and well known for its antioxidant, anti-inflammatory, antidiabetic, anticancer, and anti-HIV integrase activity (Nurfina et al. 1997). *Curcuma longa* Linn. or turmeric (Zingiberaceae) was a medicinal plant widely cultivated in tropical regions of Asia. The extract from *C. longa*, commonly called curcuminoids, was mainly composed of curcumin (75–90%) and together with a small amount of demethoxycurcumin and bisdemethoxycurcumin (Jayaprakasha et al. 2002) *C. longa* was recommended to use in Chinese traditional medical prescriptions against the diabetic complications. The plant extract of *C. longa* could inhibit the activity of α-glucosidase resulting in lowering the high blood sugar. The interesting discovery of the α-glucosidase inhibitory activity of phenolic compounds like curcuminoids prompted us to study a series of curcumin analogs. Curcuminoids have the ability to scavenge free radicals in vivo, especially peroxyl radicals of the form ROO, where R is an alkyl group. The possible mechanism of curcumin action in cerebellum may be by lowering the blood glucose level which results in rendering the anti-apoptotic property (Zhaoa et al. 2008). The increased blood glucose level and decreased body weight, observed during diabetes, are similar with previous reports as a result of the marked destruction of insulin-secreting pancreatic β-cells by STZ (Junod et al. 1969). Previous reports showed that curcumin has the potential to protect pancreatic islet cells against streptozotocin-induced death dysfunction (Meghana et al. 2007) and increase plasma insulin level in diabetic mice (Seo et al. 2008). Curcumin also inhibited superoxide anion generation in xanthine-xanthine oxidase system to an extent of 40% at the concentration of 75 mM and the generation of hydroxyl radicals (OH) to 76% as measured by deoxyribose degradation. The spice principle also prevented the oxidation of Fe^{2+} in Fenton reaction which generates OH radicals. Curcumin (5–50 mM) inhibited ascorbate/Fe^{2+}-induced lipid peroxidation in a dose-dependent manner in rat liver microsomes. Feeding 0.5% curcumin diet to STZ diabetic rats partially

reversed the abnormalities in plasma albumin, urea, creatine, and inorganic phosphorous. It also lowered lipid peroxidation in plasma and urine despite no effect on hyperglycemic status or body weights. The underlying mechanism involved was believed to be on account of its hypocholesterolemic influence, antioxidant nature, and free radical scavenging property (Geetanjali et al. 2010).

Luteolin exhibits anti-lipase activity (17.3%) and enhanced insulin sensitivity via activation of PPAR gamma-transcriptional activity in adipocytes (Zheng et al. 2010) and it inhibits proliferation of human leukemia cells and plays an important role as a promoter of carbohydrate metabolism (Xavier et al. 2009). Green tea polyphenols especially epigallocatechin gallate injected IP into rats significantly reduced food intake, body weight, blood levels of insulin, glucose, cholesterol, and triglyceride.

Epicatechin gallate showed the highest inhibition of glucose uptake by human intestinal epithelial Caco-2-cells suggesting that tea catechins could play a role in controlling the dietary glucose uptake at the intestinal tract and possibly contribute to blood glucose homeostasis.

A polyphenol extract from red wine (200 mg/kg) administered for 6 weeks reduced glycemia and decreased food intake and body growth in STZ diabetic and nondiabetic animals. Ethanol (1 mL/kg) administered alone or in combination with polyphenols corrected the diabetic state.

Dietary gallate esters of tea catechins (epigallocatechin gallate and epicatechin gallate) fed to rats at 1% level for 23 days reduced the activities of enzymes related to hepatic fatty acid synthesis, thereby causing reduction of hepatic triacylglycerol and possibly of visceral fat deposition (Li et al. 2004).

Flavonoid, kakonein, was experimentally identified to be effective to lower the blood glucose level of alloxan- or adrenalin-induced diabetic mice. 7-(6-*O*-malonyl-D-glucopyranosyloxy)-3-(4-hydroxyphenyl)-4*H*-1-benzopyran-4-one is the constituent proved to be useful for treatment of diabetes complications such as cataract, retinopathy, neuropathy, and kidney disorders. Pueraria flavonoid (PF) is a useful preparation for patients with diabetes complicated by hyperlipidemia. Tectorigenin and kaikasaponin III, isolated from the flowers of *Pueraria thunbergiana* (same genus as *Pueraria lobata*), showed potent hypoglycemic and hypolipidemic effects in the streptozotocin-induced diabetic rats. The antioxidant action of tectorigenin and kaikasaponin III may alleviate the streptozotocin-induced toxicity and contribute hypoglycemic and hypolipidemic effects. There is experimental result to show that glycosylation of human serum albumin (HSA) and rat lens protein was effectively inhibited by the ethanol extract of Radix Puerariae, which indicated that the extract can be used in treating diabetic complications (Li et al. 2004). The flavanones, exclusively found in citrus fruit and tomato predominantly as glycosides, undergo similar metabolic routes to flavonols (Andreas et al. 2002). These are benzo-y-pyrone derivatives which resemble coumarin and are ubiquitous in photosynthesizing cells. It occurs as aglycons, glycosides, and methylated derivatives. The flavonoid aglycons all consist of a benzene ring (A) condensed with a

six-member ring (C) which in the 2-position carries a phenyl ring (B) as a substituent (Havsteen 1983). Observational and intervention studies have investigated the effect of flavonols on cardiovascular risk factors, including blood pressure, serum lipids, diabetes mellitus, and obesity (Perez and Duarte 2010). In *Artemisia herba-alba* sesquiterpene lactones were found in the aerial parts and a total of eight flavonoids *O*- and *C*-glycoside were isolated and identified. It is a popular folk remedy, used in the treatment of diabetes mellitus. The aqueous extract of the aerial parts of *A. herba-alba* caused a significant fall in plasma glucose levels in both normoglycemic and alloxanized rabbits (Abou et al. 2010). *Combretum micranthum* is a medicinal plant used for treating diabetes in Northwestern Nigeria. The aqueous leaf extract of *Combretum micranthum* has potential antidiabetic property for both type 1 and type 2 diabetes mellitus. Flavonoid of *Parinari excelsa* shows the hypoglycemic effect and the ability to induce insulin secretion in diabetic animal models. The hypoglycemic effect of *Parinari excelsa* was similar to that of glibenclamide and is already observed with some other plant extracts.

The methanolic extract and ethyl acetate-soluble portions of the leaves of *Myrcia multiflora* DC showed an inhibitory activity on aldose reductase and alpha-glucosidase. The plant also inhibited the increase of serum glucose level in sucrose-loaded rats and in alloxan-induced diabetic mice. New flavanone glucosides (myrciacitrins I and II) and new acetophenone glucosides (myrciaphenones A and B) were identified (Mohamed et al. 2006).

Elatoside E was isolated from the root cortex of *Aralia elata* Seem. (Japanese angelica). It was shown to affect the elevation of plasma glucose levels in an oral sugar tolerance test in rats. The hypoglycemic activity of oleanolic acid and nine oleanolic acid glycosides isolated from the root cortex of this plant were tested. Five new saponins named elatosides G, H, I, J, and K were isolated from a garnish foodstuff "Taranome" which is the young root shoot of *A. elata* Seem. Elatosides G, H, and I were found to exhibit potent hypoglycemic activity in the oral glucose tolerance test in rats. Nine oleanolic acid oligoglycosides were isolated from the cortex of *A. elata* (Mohamed et al. 2006).

The stem bark of *Kalopanax pictus Nakai* and seven kinds of chemical constituents including hederagenin glycosides and phenolic glycosides were isolated. The antidiabetic evaluation of these isolates in streptozotocin-induced diabetic rats showed that kalopanax saponin A has a potent antidiabetic activity in contrast to a mild activity of hederagenin. To investigate the relationship between the intestinal bacterial metabolism of kalopanaxsaponin B and H from *K. pictus*, and their antidiabetic effect, kalopanaxsaponin B and H were metabolized by human intestinal microflora and the antidiabetic activity of their metabolites was measured. The main metabolites of kalopanaxsaponin B were kalopanaxsaponin A and hederagenin. The main metabolites of kalopanax H were kalopanaxsaponin I and hederagenin. Among kalopanaxsaponin B, H, and their metabolites, kalopanaxsaponin A showed the most potent antidiabetic activity, followed by hederagenin (Mohamed et al. 2006).

Amino Acid

4-Hydroxyisoleucine, a novel amino acid, has been extracted and purified from fenugreek seeds. It increased glucose-induced insulin release (ranging from 100 to 1 mmol/L) through a direct effect on the isolated islets of Langerhans in both rats and humans (Li et al. 2004). The insulinotropic effect of *Citrullus colocynthis Schrad.* fruits: Different extracts were obtained from the seeds of this plant: RN II (crude extract), RN VI (aqueous alcoholic extract), RN X (purified extract), and RN XVII (beta-pyrazol-1-ylalanine, the major free amino acid derivative present in the seeds) (Mohamed et al. 2006).

S-allyl cysteine sulfoxide (SACS), a sulfur-containing amino acid of *Allium sativum* L. (garlic) that is the precursor of allicin and garlic oil, has been found to show significant antidiabetic effects in alloxan diabetic rats. Administration of a dose of 200 mg/kg significantly decreased the concentration of serum lipids, blood glucose, and activities of serum enzymes like alkaline phosphatase, acid phosphatase, and lactate dehydrogenase and liver glucose-6-phosphatase. SACS significantly stimulated in vitro insulin secretion from β-cells isolated from healthy rats. Hence it can be surmised that the beneficial effects of SACS could be due to both its antioxidant and its secretagogue actions (Mohamed et al. 2006).

Oral administration of *Allium cepa* L. (onion) *S*-methyl cysteine sulfoxide (SMCS) daily at a dose of 200 mg/kg body weight for a period of 45 days to alloxan diabetic rats controlled the blood glucose and lipids in serum and tissues and altered the activities of liver hexokinase, glucose 6-phosphatase, and HMG CoA reductase towards normal values (Mohamed et al. 2006).

Saponins

Saponins such as ginsenoside Rb1, Rg1Re, Rg3, CEG, Rb2, CY, and DPG-3-2 were isolated roots and rhizomes of *Panax ginseng* C.A. Mey, family *Araliaceae*. Ginseng lowers hyperglycemia and raises hypoglycemia, not to influence normal blood glucose. The mechanism of action of these saponins is to regulate the activity of enzymes related to glucose metabolism directly and/or indirectly, inhibit the renal disorder, and promote insulin secretion (Li et al. 2004). Saponin isolated from the leaves of *Acanthopanax senticosus* injected to mice (100, 200 mg/kg, i.p.) decreased experimental hyperglycemia induced by injection of adrenaline, glucose, and alloxan, without affecting the levels of blood sugar in untreated mice (Mohamed et al. 2006).

Litchi water extract improved the metabolic profile of rats, characterized by decreased body weight, fasting blood glucose, total cholesterol, triglycerides, free fatty acid (FFA), leptin, and fasting insulin levels. The water extract of litchi has been found to have the antidiabetic potential and also enhances basal prostaglandin E2 (PGE2) production in a macrophage cell line (RAW264.7). *Psidium guajava*

(guava) in the type 2 diabetic and fatty liver disease phenotype in Lep db/db mice: Extract of *P. guajava* (10 mg/kg body weight) significantly decreased blood glucose levels and accumulation of fat droplets in liver tissues of Lep db/db mice. This effect was mediated through the inhibition of protein tyrosine phosphatase 1B (a negative regulator of insulin signaling). The combination of pomegranate seed oil (PSO) and brown marine algae fucoxanthin (xanthigen) significantly reduced the occurrence of fatty liver disease in human subjects. The findings were characterized by significantly decreased body weight, waist circumference, hepatic fat content, and triglyceride and improved liver function tests. The mechanism of xanthigen for these beneficial effects was through increased whole-body energy expenditure that was characterized by increased resting energy expenditure in xanthigen-fed subjects (Samir et al. 2011).

In Korea, there are several traditional fermented soybean products, the most commonly used being chungkookjang, doenjang, kochujang, and soy sauce. The isoflavonoid aglycons act though PPAR-gamma; it is the central regulator of insulin and glucose metabolism and helps improve insulin sensitivity in type 2 diabetic patients and in diabetic rodent models. PPAR-g agonists are well-characterized insulin sensitizers. The components of isoflavonoids and peptides were changed according to the fermentation periods and these changes altered antidiabetic actions as evidenced by their effects on insulin sensitivity and insulin and GLP-1 secretion. Daidzein enhanced PPAR-gamma activity to increase insulin-stimulated glucose uptake in 3T3-L1 adipocytes, whereas genistein potentiated insulinotropic actions in Min6 cells and GLP-1 secretion in NCI-H716 cells (Dae et al. 2011).

Terpenoids (Isoprenoids)

Terpenoids (isoprenoids) constitute one of the largest families of natural products, accounting for more than 40,000 compounds of both primary and secondary metabolisms (Goto et al. 2010). The simplest unifying feature present in the structure of all terpenoids is the isoprene unit ($CH_2C(CH_3)$–$CHCH_2$). Based on the number of carbon atoms, terpenoids can be classified into further groups: hemiterpenoid (C5), monoterpenoids (C10), sesquiterpenoids (C15), diterpenoid (C20), sesterterpenoid (C25), triterpenoids (C30), tetraterpenoid (C40), and polyterpenoid (C>40). Most of the terpenoids are of plant origin and are present in vegetables and fruits. Geranylgeraniol, farnesol, and geraniol terpenoids are ligands with potential to activate PPAR-gamma, dietary lipid sensors that control energy homeostasis and lipid and carbohydrate disorders (Goto et al. 2010; Takahashi et al. 2002). *Lantana camara* L. is regarded as a notorious weed; extract of this plant is used in folk medicine for the treatment of cancers, chicken pox, measles, asthma, ulcers, swellings, eczema, tumors, high blood pressure, bilious fevers, catarrhal infections, tetanus, rheumatism, malaria, and ataxy of abdominal viscera, and for its anticonvulsant, termicidal, wound healing, anticancer, antiulcer, antioxidant, antidiabetic, analgesic, anti-inflammatory, anti-motility, anti-feedant, larval mortality/repellency,

antifungal, and antibacterial activities. The presence of new triterpenoid glycoside ester urs-12-en-3β-ol-28-oic acid 3β-D-glucopyranosyl-4′-octadecanoate in *Lantana camara* was evaluated for its antidiabetic action (Kazmi et al. 2012).

Abscisic Acid (ABA)

This significantly improved glucose tolerance, or the glucose-normalizing ability; decreased fasting blood glucose concentrations; reduced TNF-a mRNA and the number of macrophages; reduced average adipocyte size; increased adipocyte differentiation and adipogenesis; and increased the expression of PPAR-gamma and its responsive genes (i.e., adiponectin, aP2, and CD36), which are involved in lipid metabolism in white adipose tissue. ABA supplementation was also associated with significant improvements in hepatic steatosis and plasma triglyceride levels (Guri et al. 2007, 2008).

Lycopene and b-Carotene

Two kinds of important fat-soluble carotenoids are essential nutrients in human diet mainly found in tomatoes, red peppers, and some fruits including watermelon and pink grapefruits; its fat solubility and heating process make it more easily absorbed (Stahl and Sies 2005). It is a powerful antioxidant with a strong ability to scavenge free radicals and, because of its high number of conjugated dienes, is the most potent singlet oxygen quencher among the natural carotenoids (Arab and Steck 2000). Recent studies have demonstrated that mechanisms other than the antioxidant ones are responsible for the biological activities of lycopene. Examples include intercellular gap junction communication, hormonal and immune system modulation, induction of phase II enzymes, suppression of insulin-like growth factor-1-stimulated cell proliferation, antiangiogenesis and inhibition of cell proliferation; and induction of apoptosis (Kun et al. 2006).

Vitamin D levels are inversely related to body mass index (BMI), waistline, and HbA1c. In addition, there are seasonal variations of HbA1c levels and incidental type 2 DM. The supplementation of calcium and vitamin D at 800 IU daily, instead of the prior recommendation of 400 IU, decreased the risk of type 2 DM by 33%. Human subjects obtain vitamin D from sunlight exposure, diet, or dietary supplements. UVB radiation, wavelength from 290 to 315 nm, penetrates the skin and converts 7-dehydrocholesterol to pre-vitamin D, which is converted to 25-hydroxycholecalciferol vitamin D3 (25(OH)D). The hydroxylation of 25(OH)D to its active form 1a,25$(OH)_2$ vitamin D3 (1,25(OH_2)D) takes place in different parts of the body, such as the endothelium, the pancreas, but mainly in the kidney. Thus, an inverse relationship exists between vitamin D levels and the frequency of type 2 DM (Pelle et al. 2010).

Alcohol consumption light to moderate seems to reduce the risk of type 2 diabetes by 30%, while heavy drinkers have the same or higher risk than total abstainers. Alcohol should, however, be restricted in type 2 diabetic patients who are overweight, suffering from hypertension or hypertriglyceridemia. Alcohol abstention is advised in patients with advanced neuropathy and erectile dysfunction and total abstention is recommended to pregnant women and to people with a history of former alcohol abuse or pancreatitis (Pietraszek and Hermansen 2010).

Oxyphytosterol

Dietary 5-campestenone (24-methylcholest-5-en-3-one) was recently shown to activate enzymes responsible for b-oxidation and to suppress enzymes responsible for fatty acid synthesis in rats. It activated peroxisome proliferator-activated receptor (PPAR) in a specific ligand assay. PPAR regulates the mRNA expression of enzymes involved in b-oxidation. When 0.3% 5-campestenone was added to the diet of obese type 2 diabetes C57BL/KsJ-db/db mice, blood and urinary glucose, as well as plasma free fatty acid, were reduced (Konno et al. 2005).

5-Campestenone was shown to decrease serum triacylglycerols in rodents (Ikeda et al. 2006; Suzuki et al. 2002; Konno et al. 2005). Similar results were obtained with 24-ethylcholest-4-en-3-one. In line with the observed decrease in serum triglycerides, the concentration of liver triacylglycerols was reduced (Ikeda et al. 2006).

Organosulfur compounds are particularly abundant in Allium vegetables including garlic, onion, scallion, chive, shallot, and leek that contain bioactive substances such as allicin, allixin, and allyl sulfides (Sahu 2002). These molecules account for the distinctive flavor and aroma as well as the many purported medicinal effects of these vegetables. Organosulfurs provide glucosinolates, which are converted in the human body in thiosulfonates, indoles (indole-3-carbinol), and isothiocyanates (Cartea and Velasco 2008).

Phytosterols/Stanols

Phytosterols/stanols reduce serum low-density lipoprotein cholesterol levels, and food products containing these plant compounds are widely used as a therapeutic dietary option to reduce hypercholesterolemia and atherosclerotic risk (NCEP EP 2001). Aloe vera-derived phytosterols ameliorated hyperglycemia in treated db/db type 2 diabetic mice (Tanaka et al. 2006). Also a phytostanol mixture induced improvement in glucose tolerance in fat Zucker rats (Wasan et al. 2003). Two stigmasterol-derived compounds extracted from the cashew plant produced a significant reduction in blood glucose levels when intravenously administered to dogs (Alexander et al. 2004). Furthermore, changes in intestinal cholesterol absorption

could correlate with insulin sensitivity, as type 2 diabetic patients present increased cholesterol synthesis but decreased absorption (Simonen et al. 2000).

Legumes are low in fat, and rich in proteins, complex hydrocarbons, and minerals, exhibiting lower glycemic index compared to other starchy foods. It contains a rich variety of phytochemicals, including phytosterols, natural antioxidants, and bioactive carbohydrates (Amarowicz and Pegg 2008; Rochfort and Panozzo 2007). Legumes contain antinutritional factors, such as trypsin inhibitors, phytic acid, a-galactosides, and phenolics, that can diminish protein digestibility and mineral bioavailability; thus they have to be appropriately treated prior to consumption (Chung et al. 1998; Sendberg 2002; Vidal et al. 2002).

Flax seeds (*Linum usitatissimum* L., member of Linaceae family) and pumpkin seeds (*Cucurbita pepo* L., member of Cucurbitaceae family) contain high levels of Omega-3 fatty acid (Burdge and Calder 2005), fiber components, and phytochemicals such as lignans (Vijaimohan et al. 2006). The high linoleic acid contributes to antioxidant properties (Simopoulos 1991) against various diseases, including atherosclerosis, diabetes, and hypertension, and anti-inflammatory and anticarcinogenic effects (Simopoulos 1991; Fukuda et al. 1985).

Omega-6 fatty acids have a number of biological applications. In addition to anti-inflammatory and hypolipidemic effects, they also have significant antioxidant activity (Suresh and Das 2003). DAG and conventional edible oil containing triacylglycerol (TAG) are almost identical in terms of digestibility and caloric value. DAG reduces postprandial levels of serum TAG (Taguchi et al. 2000, 2001; Tada et al. 2001). It also reduces body fat in obese/overweight Japanese and American adults as well as Japanese children (Takase et al. 2005; Nagao et al. 2000; Takahashi et al. 2002). DAG oil has a beneficial effect for type 2 DM patients in relation to body weight, BMI, waist circumference, HOMA-IR, blood levels of insulin, glucose, and leptin (Duo et al. 2008).

The stevioside, diterpene glycoside isolated from *Stevia rebaudiana* (Bertoni), exhibits a direct insulin tropic action in both isolated mouse islets and the clonal β-cell lines (INS-1) and possesses insulin tropic, glucagon static, and antihyperglycemic effects in diabetic animals. Stevioside caused only the decrease of adrenalin-induced hyperglycemia. BBCr product prevented the onset of experimental diabetes in mice caused by alloxan. Based on these results it can be concluded that BBCr has its role in the prevention and treatment of hyperglycemia in mice (Jeppesen et al. 1996, 2000).

Berberine is a plant alkaloid found in *Hydrastis canadensis* (goldenseal), *Coptis chinensis* (Coptis or goldenthread), *Berberis aquifolium* (Oregon grape), *Berberis vulgaris* (barberry), and *Berberisaristata* (tree turmeric). Berberine has been found to act on glucose metabolism through several mechanisms: mimicking insulin action; improving insulin action by activating AMPK; reducing insulin resistance through protein kinase C-dependent upregulation of insulin receptor expression; inducing glycolysis; promoting GLP-1 secretion and modulating its release; and inhibiting DPP-4 (Sterti 2010).

Charantin which is composed of sitosteryl glucoside and stigmasteryl glucoside can potentially replace treatment by insulin. Another compound, polypeptide p

(plant insulin) found in seeds and fruits of *Momordica charantia* [bitter melon], is similar to insulin in composition; bitter melon alkaloids have also been noted to have a blood sugar-lowering effect. Compounds known as oleanolic acid glycosides have been found to improve glucose tolerance in type 2 diabetes (Ibraheem et al. 2012). *M. charantin* markedly reduced the STZ-induced lipid peroxidation in the pancreas of mice, RIN cells (rat insulinoma cell line), and islets. Ethanolic extract of *M. charantia* (250 mg/kg dose orally) significantly lowered blood sugar in fasted as well as glucose-loaded nondiabetic rats. *M. charantia* may cause hypoglycemia via an increase in glucose oxidation through the activation of glucose metabolism and/or the inhibition of glucose absorption in the gut. There is an increase in the levels of intestinal Na^+/glucose cotransporters (SGLT1) in STZ-induced diabetes resulting in increased glucose uptake in the gut of these animals. The increase of Na^+- and K^+-dependent glucose uptake by small intestine brush border membrane (BBM) vesicles in STZ-induced diabetes has been demonstrated recently (Celia et al. 2003). Gymnemic acid found in *Gymnema sylvestre* (leaf extract) which is said to inhibit the adenohypophyseal stress response, and the hyperglycemic response to adrenaline and growth hormone. It may also help by increasing peripheral utilization of glucose.

Tinospora cordifolia also increases peripheral utilization of glucose, and inhibits hepatic glucose release caused by adrenaline. *Pterocarpus marsupium* has been reported to block glucose absorption from gut. Pterocarpus extract has been reported to promote β-cell regeneration in pancreas. Shilajeet has anabolic and pancreatotrophic effects (Anturlikar et al. 1995).

Fagomine increased plasma insulin levels in diabetic mice and potentiated the 8.3 mM glucose-induced insulin release from the rat isolated perfused pancreas. The fagomine-induced potentiation of insulin release may contribute in part to its antihyperglycemic action. Seven polysaccharides and peptidoglycans obtained from the seeds of *Malva verticillata* were tested for hypoglycemic activity. Neutral polysaccharide especially exhibited promising hypoglycemic effects in non-insulin-dependent diabetes mellitus.

The hypoglycemic activity of the extract of jamun pulp from the fruit of *Eugenia jambolana* Lam. (Gambol) *Syzygium cumini* Skeels (Jamun) was seen after 30 min, while the seeds of the same fruit required 24 h to produce the same effect. These results were confirmed in streptozotocin-induced diabetic animals. The oral administration of the extract resulted in the enhancement of insulinemia in normoglycemic and diabetic rats. The incubation of isolated pancreatic islet cells of normal and diabetic animals with this plant extract resulted in increased insulin secretion. A new tetrahydropyran was isolated from the methanolic extract of roots from *Acrocomia mexicana* Karw. The extract was hypoglycemic in healthy and alloxan-induced diabetic mice (2.5–40 mg/kg i.p.). Masoprocol (nordihydroguaiaretic acid, a lipoxygenase inhibitor) is a pure compound isolated from *Larrea tridentata* (Creosote bush). The oral administration of masoprocol produced a fall in the plasma glucose concentrations in two mouse models of type 2 diabetes, without any change in plasma insulin concentrations. In addition, oral glucose tolerance improved and the ability of insulin to lower plasma glucose concentrations was accentuated in masoprocol-treated db/db mice (Mohamed et al. 2006), Fig. 2.

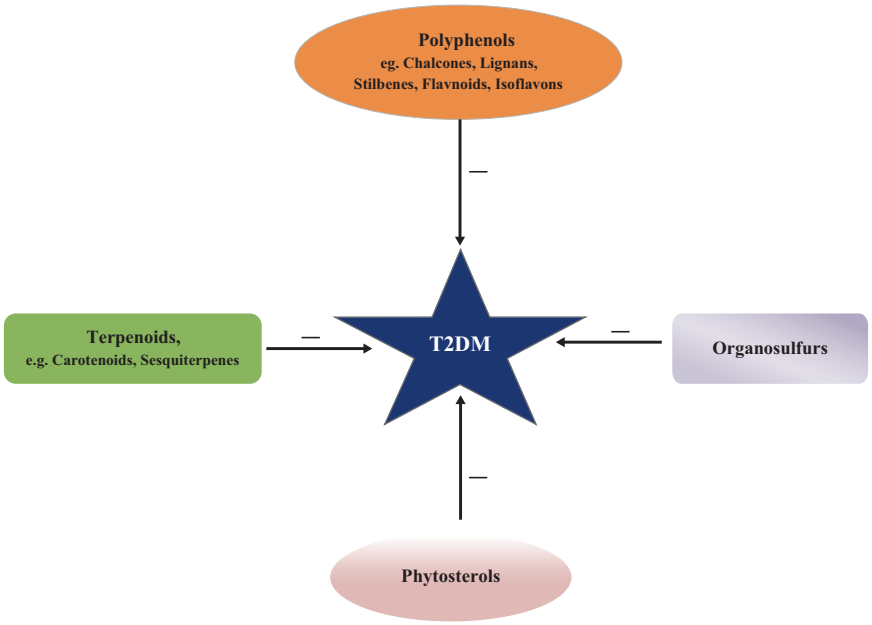

Fig. 2 Dietary fibers which are helpful in the treatment of type 2 diabetes mellitus (T2DM)

Conclusion

It was concluded that phytochemicals present in various dietary fibers can be helpful in the treatment of type 2 diabetes mellitus.

Future Consideration

More diabetes research and studies should be considered on the dietary phytochemicals, so that it can be beneficial for the patients having type 2 diabetes mellitus.

References

Abou EM, Magdi HA, El-Sayed M, Hegazy E, Soleiman EH, Abeer ME, Naglaa SM (2010) Chemical constituents and biological activities of Artemisia herba-alba. Rec Nat Prod 4(1):1–25

Adlercreutz H (2007) Lignans and human health. Crit Rev Clin Lab Sci 44(5–6):483–525

Alexander LRL, Morrison EY, Nair MG (2004) Hypoglycaemic effect of stigmast-4-en-3-one and its corresponding alcohol from the bark of Anacardium occidentale (cashew). Phytother Res 18:403–407

Al-Nuaim A, Al-Rubeaan K, Al-Mazrou Y (1997) National chronic metabolic diseases survey 1995. Ministry of Health and King Saud University, Riyadh, pp 23–54
Amarowicz R, Pegg RB (2008) Legumes as a source of natural antioxidants. Eur J Lipid Sci Technol 110:865–878
Andreas RR, Kuhnle G, Paul B, Gary P, Hubbard KP, Moore C, Rice E (2002) The metabolic fate of dietary polyphenols in humans. Free Radic Biol Med 33(2):220–235
Anjaneyulu M, Chopra K (2004) Nordihydroguaiaretic acid, a lignin, prevents oxidative stress and the development of diabetic nephropathy in rats. Pharmacology 72:42–50
Anturlikar SD, Gopumadhavan S, Chauhan BL, Mitra SK (1995) Effect of D-400, a herbal formulation, on blood sugar of normal and alloxan-induced diabetic rats. Indian J Physiol Pharmacol 39(2):95–100
Arab L, Steck S (2000) Lycopene and cardiovascular disease. Am J Clin Nutr 71:1691–1695
Atsuyo F, Hideyuki S, Asako D, Kunihisa O, Shohei M, Hiroto F, Masahiro N, Taisei N, Takuo T, Hisaji T, Kishio N (2008) Ferulic acid prevents pathological and functional abnormalities of the kidney in Otsuka Long-Evans Tokushima Fatty diabetic rats. Diabetes Res Clin Pract 79:11–17
Baydas G, Reiter RJ, Yaser A, Tuzcu M, Akdemir I, Nedzvetskii V (2003) Melatonin produces glial reactivity in the hippocampus, cortex, and cerebellum of streptozocin-induced diabetic rats. Free Radic Biol Med 35(7):797–804
Bell GI, Polonsky SK (2001) Diabetes mellitus and genetically programmed defects in ß-cell function. Nature 414:788–791
Bloedon LT, Szapary PO (2004) Flaxseed and cardiovascular risk. Nutr Rev 62(1):18–27
Bravo L (1998) Polyphenols: chemistry, dietary sources, metabolism and nutritional significance. Nutr Rev 56:317–333
Burdge GC, Calder PC (2005) α-Linoleic acid metabolism in adult humans: the effect of gender and age on conversion to longer chain polyunsaturated fatty acids. Eur J Lipid Sci Technol 107:426–439
Cartea ME, Velasco P (2008) Glucosinolates is Brassica foods: bioavailability in food and significance for human health. Phytochem Rev 7(2):213–229
Celia G, Cummings E, Phoenix DA, Singh J (2003) Beneficial effect and mechanism of action of Momordica charantia in the treatment of diabetes mellitus: a mini review. Int J Diabetes Metab 11:46–55
Ceriello A, Morocutti A, Mercuri F, Quagliaro L, Moro M, Damante G, Viberti GC (2000) Defective intracellular antioxidant enzyme production in type I diabetic patients with nephropathy. Diabetes 49:2170–2177
Chi TC, Chen WP, Chi TL, Kuo TF, Lee SS, Cheng JT, Su MJ (2007) Phosphatidylinositol-3-kinase is involved in the antihyperglycemic effect induced by resveratrol in streptozotocin-induced diabetic rats. Life Sci 80:1713–1720
Chiu-Mei L, Jen-Hwey C, Wu IH, Wang BW, Chun-Ming P, Yen-Hsu C (2010) Ferulic acid augments angiogenesis via VEGF, PDGF and HIF-1α. J Nutr Biochem 21:627–633
Chung K, Wong TY, Wei C, Huang YW, Lin Y (1998) Tannins and human health: a review. Crit Rev Food Sci Nutr 38:421–464
Chung YS, Choi YH, Lee SJ, Choi S, Lee JH, Kimb H, Honga EK (2005) Water extract of Aralia elata prevents cataractogenesis in vitro and in vivo. J Ethnopharmacol 101:49–54
Clifford MN (2000) Anthocyanins-nature, occurrence and dietary burden. J Sci Food Agr 80:1063–1072
Dae YK, Sang M, Hong MS, Sung Ahn MS, Min Jung Kim MS (2011) Isoflavonoids and peptides from meju, long-term fermented soybeans, increase insulin sensitivity and exert insulinotropic effects in vitro. Nutrition 27:244–252
Dey PM, Harborne JB (1998) Diabetes mellitus: problems and prospectus. Endocr Rev 19:477–490
Dilmec F, Uzer E, Akkafa F, Kose E, van Kuilenburg AB (2010) Detection of VDR gene ApaI and TaqI polymorphisms in patients with type 2 diabetes mellitus using PCR-RFLP method in a Turkish population. J Diabetes Complications 24:186–191

Duo L, Tongcheng X, Hideto T, Ichiro T, Pianhong Z, Qingqing W, Xiaomei Y, Aizhen Z (2008) Diacylglycerol-induced improvement of whole-body insulin sensitivity in type 2 diabetes mellitus: a long-term randomized, double-blind controlled study. Clin Nutr 27:203–211

Estelle B, Luc S, Magali B, Cécile M, Laurence LM, Marcel A, Jean-François T (2002) Release of ferulic acid from agroindustrial by-products by the cell wall-degrading enzymes produced by Aspergillus niger I-1472. Enzym Microb Technol 31:1000–1005

Fernández MIM, Mateos R, García-Parrilla MC, Puertas B, Cantos VE (2012) Bioactive compounds in wine: resveratrol, hydroxytyrosol and melatonin: a review. Food Chem 130:797–813

Ferrannini E (1998) Insulin resistance versus insulin deficiency in non-insulin-dependent diabetes mellitus: problems and prospects. Endocr Rev 19:477–490

Fukuda Y, Osawa T, Namiki M, Ozaki T (1985) Studies on antioxidative substances in sesame seed. Agric Biol Chem 49:301–306

Geetanjali K, Santosh S, Rakesh KK, Naik SN (2010) Commonly consumed Indian plant food materials in the management of diabetes mellitus. Diabetes Metab Syndr Clin Res Rev 4:21–40

Gloyn AL, Weedon MN, Owen KR, Turner MJ, Knight BA, Hitman G (2003) Large-scale association studies of variants in genes encoding the pancreatic beta-cell K-ATP channel subunits Kir6.2 (KCNJ11) and SUR1 (ABCC8) confirm that the KCNJ11 E23K variant is associated with type 2 diabetes. Diabetes 52:568–572

Goto T, Takahashi N, Hirai S, Kawada T (2010) Various terpenoids derived from herbal and dietary plants function as PPAR modulators and regulate carbohydrate and lipid metabolism. PPAR Res 2010:9

Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J (2006) Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat Genet 38:320–323

Guri AJ, Hontecillas R, Si H, Liu D, Bassaganya RJ (2007) Dietary abscisic acid ameliorates glucose tolerance and obesity-related inflammation in db/db mice fed high-fat diets. Clin Nutr 26(1):107–116

Guri AJ, Hontecillas R, Ferrer G, Casagran O, Wankhade I, Noble AM (2008) Loss of PPARg in immune cells impairs the ability of abscisic acid to improve insulin sensitivity by suppressing monocyte chemoattractant protein-1 expression and macrophage infiltration into white adipose tissue. J Nutr Biochem 19:216–228

Hallmans G, Zhang J, Lundin E, Stattin P, Johansson A (2003) Rye, lignans and human health. Proc Nutr Soc 62:193–199

Hambrock A, de Oliveira Franz CB, Hiller S, Grenz A, Ackermann S, Schulze DU, Drews G, Osswald H (2007) Resveratrol binds to the sulfonylurea receptor (SUR) and induces apoptosis in a SUR subtype-specific manner. J Biol Chem 282:3347–3356

Harborne JB, Baxter H (1999) The handbook of natural flavonoids, US Department of Agriculture. USDA Database for the Flavonoid Content of Selected Foods—2003, vol 2. Wiley, West Sussex

Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR (1998) Prevalence of diabetes, impaired fasting glucose and impaired glucose tolerance in US adults, the third National health and Nutrition examination survey, 1988–1994. Diabetes Care 21:518–524

Haruhiko OAK (2004) Islet amyloid polypeptide-derived amyloid deposition increases along with the duration of type 2 diabetes mellitus. Available online 22 Apr

Havsteen B (1983) flavonoids, a class of natural products of high pharmacological potency. Biochem Pharmacol 32(7):1141–1148

Heidemann C, Hoffmann K, Spranger J, Klipstein GK, Mohlig M, Pfeiffer AF (2005) A dietary pattern protective against type 2 diabetes in the European prospective investigation into cancer and nutrition (EPIC)—potsdam study cohort. Diabetologia 48(6):1126–1134

Henquin JC (2000) Triggering and amplifying pathways of regulation of insulin secretion by glucose. Diabetes 49:1751–1760

Huizinga MM, Rothman RL (2006) Addressing the diabetes pandemic: a comprehensive approach. Indian J Med Res 124:481–484

Ibraheem M, Samah E, Sanaa M, Madeha E (2012) An evaluation of anti-diabetic and anti-lipidemic properties of Momordica charantia (Bitter Melon) fruit extract in experimentally induced diabetes. Life Sci J 9(2):363–374

Ikeda I, Konno R, Shimizu T, Ide T, Takahashi N, Kawada T (2006) Campest-5-en-3-one, an oxidized derivative of campesterol, activates PPAR-alpha, promotes energy consumption and reduces visceral fat deposition in rats. Biochim Biophys Acta 1760:800–807

Iwasaki N (2001) Diabetes mellitus. Rinsho Byori 49(2):161–164

Jayaprakasha GK, Rao LJM, Sakariah KK (2002) Improved HPLC method for the determination of curcumin, demethoxycurcumin, and bisdemethoxycurcumin. J Agric Food Chem 50:3668–3672

Jeppesen PB, Gregersen S, Hermansen K (1996) Stevioside and steviol stimulate insulin secretion from isolated mouse islets. Diabetologia 125:472

Jeppesen PB, Gregersen S, Poulsen CR, Hermansen K (2000) Stevioside acts directly on pancreatic beta cells to secrete insulin: actions independent of cyclic adenosine monophosphate and adenosine triphosphate-sensitive K+-channel activity. Metabolism 49:208–214

Jialal I, Devaraj S, Venugopal SK (2002) Oxidative stress, inflammation, and diabetic vasculopathies: the role of alpha tocopherol therapy. Free Radic Res 36(12):1331–1336

Junod A, Lambert AE, Staufferacher W, Renold AE (1969) Diabetogenic action of streptozotocin relationship of dose to metabolic response. J Clin Investig 48(11):2129–2139

Kazmi I, Mahfoozur R, Muhammad A, Gaurav G, Shakir S, Obaid A, Md. Adil S, Ujjwal N, Sayeed A, Firoz A (2012) Anti-diabetic potential of ursolic acid stearoyl glucoside: a new triterpenic glycosidic ester from Lantana camara. Fitoterapia 83:142–146

Kedziora KKZ, Luciak M, Paszkowski J (2000) Lipid peroxidation and activities of antioxidant enzymes in the diabetic kidney: effect of treatment with angiotensin convertase inhibitors. IUBMB Life 49:303–307

Kempen JH, Colmain BJO, Leske MC (2004) Eye Diseases Prevalence Research Group. The prevalence of diabetic retinopathy among adults in the United States. Arch Ophthalmol 122:552–563

King H, Rewers M (1993) Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults. Diabetes Care 16:157–177

Konno R, Kaneko Y, Suzuki K, Matsui Y (2005) Effect of 5-campestenone (24-methylcholest-5-en-3-one) on Zucker diabetic fatty rats as a type 2 diabetes mellitus model. Horm Metab Res 37:79–83

Kun Y, Lule US, Xiao LD (2006) Lycopene: its properties and relationship to human health. Food Rev Int 22(4):309–333

Laakso M, Kesaniemi YA, Kervinen K, Jauhiainen M, Pyorala K (1991) Relationship of coronary heart disease and apolipoprotein E phenotype in patients with non-insulin-dependent diabetes. BMJ 303:1159–1162

Li WL, Zheng HC, Bukuru J, Kimpe ND (2004) Natural medicines used in the traditional Chinese medical system for therapy of diabetes mellitus. J Ethnopharmacol 92:1–21

Malone JM, Snyder M, Anderson G (1989) Prevention of amputation by diabetic education. Am J Surg 158:520–524

Meghana K, Sanjeev G, Ramesh B (2007) Curcumin prevents streptozotocin-induced islet damage by scavenging free radicals: a prophylactic and protective role. Eur J Pharmacol 577(1–3):183–191

Mohamed B, Abderrahim Z, Hassane M, Abdelhafid T, Abdelkhaleq L (2006) Medicinal plants with potential antidiabetic activity—a review of ten years of herbal medicine research (1990–2000). Int J Diabetes Metab 14:1–25

Montonen J, Knekt P, Harkanen T, Jarvinen R, Heliovaara M, Aromaa A (2005) Dietary patterns and the incidence of type 2 diabetes. Am J Epidemiol 161(3):219–227

Nagao T, Watanabe H, Goto N (2000) Dietary diacylglycerol suppresses accumulation of body fat compared to triacylglycerol in men in a double-blind controlled trial. J Nutr 130:792–798

NCEP EP (2001) Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 285:2486–2497

Nobili S, Lippi D, Witort E, Donnini M, Bausi L (2009) Natural compounds for cancer treatment and prevention. Pharmacol Res 59(6):365–378

Nurfina AN, Reksohadiprodjo MS, Timmerman H, Jenie UA, Sugiyanto D, van der Goot H (1997) Synthesis of some symmetrical curcumin derivatives and their anti-inflammatory activity. Eur J Med Chem 32:321–328

Oberley L (1988) Free radicals and diabetes. Free Radic Biol Med 5:113–124

Pearson ER, Velho G, Clark P, Stride A, Shepherd M, Frayling TM, Bulman PM, Ellard S, Fronguel P, Hattersley T (2001) ß-Cell genes and diabetes: quantitative and qualitative differences in the pathophysiology of hepatic nuclear factor-1 and glucokinase mutations. Diabetes 50:5101–5107

Pelle GL, Olsson HK, Mona LO (2010) Are active sun exposure habits related to lowering risk of type 2 diabetes mellitus in women, a prospective cohort study? Diabetes Res Clin Pract 90:109–114

Perez VF, Duarte J (2010) Phytochemicals and cardiovascular protection: flavonols and cardiovascular disease. Mol Asp Med 31(6):478–494

Philipp S, Akos S, Walter J, Thomas S (2008) Resveratrol and its analogs: defense against cancer, coronary disease and neurodegenerative maladies or just a fad? Mutat Res 658:68–94

Pietraszek AG, Hermansen SK (2010) Alcohol and type 2 diabetes, a review. Nutr Metab Cardiovasc Dis 20:366–375

Prasad K (1999) Reduction of serum cholesterol and hypercholesterolemic atherosclerosis in rabbits by secoisolariciresinol diglucoside isolated from flaxseed. Circulation 99(10):1355–1362

Prasad K (2000) Antioxidant activity of secoisolariciresinol diglucoside-derived metabolites, secoisolariciresinol, enterodiol, and enterolactone. Int J Angiol 9:220–225

Prasad K (2001) Secoisolariciresinol diglucoside from flaxseed delays the development of type 2 diabetes in Zucker rat. J Lab Clin Med 138:32–39

Prasad K (2004) Antihypertensive activity of secoisolariciresinol diglucoside (SDG) isolated from flaxseed: role of guanylate cyclase. Int J Angiol 13:7–14

Reaven PD, Herlod DA, Barnet J, Edelman S (1995) Effects on vitamin E on susceptibility of low density lipoprotein subfraction to oxidation and protein glycation in NIDDM. Diabetes Care 18:807–816

Reynisdottir G, Thorleifsson R, Benediktsson G, Sigurdsson VE, Einarsdottir AS (2003) Localization of a susceptibility gene for type 2 diabetes to chromosome 5q34–q35. 2. Am J Hum Genet 73:323–335

Richard S, Shaw J, Zimmet P (2006) Prevalence and projections. In: Gan D (ed) International Diabetes Atlas, 3rd edn. Brussels, International Diabetes Federation, pp 15–104

Rivera L, Morón R, Zarzuelo A, Galisteo M (2009) Long-term resveratrol administration reduces metabolic disturbances and lowers blood pressure in obese Zucker rats. Biochem Pharmacol 77:1053–1063

Rochfort S, Panozzo J (2007) Phytochemicals for health, the role of pulses. J Agric Food Chem 55:7981–7994

Rosangela GD, Zanatta AP, Cazarolli LH, Alessandra M, Louise DC, Ricardo JN, Rosendo AY, Fatima RM, Barreto S (2009) Nitrochalcones: potential in vivo insulin secretagogues. Biochimie 91:1493–1498

Ryu JK, Lee T, Kim DJ (2005) Free radical scavenging activity of Korean red ginseng for erectile dysfunction in non insulin dependent diabetes mellitus rats. Urology 65:611–615

Sahu SC (2002) Dual role of organosulfur compounds in foods: a review. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev 20:61–76

Samir D, Shalini J, Hariom Y (2011) Exotic fruits as therapeutic complements for diabetes, obesity and metabolic syndrome. Food Res Int 44:1856–1865

Sasaki R, Nishimura N, Hoshino H, Isa Y, Kadowaki M (2007) Cyanidin 3-glucoside ameliorates hyperglycemia and insulin sensitivity due to down regulation of retinol binding protein 4 expression in diabetic mice. Biochem Pharmacol 74(11):1619–1627

Sendberg AS (2002) Bioavailability of minerals in legumes. Br J Nutr 88:281–285

Seo K, Choi MS, Jung UJ, Kim HJ, Yeo J, Jeon SM, Lee MK (2008) Effect of curcumin supplementation on blood glucose, plasma insulin, and glucose homeostasis related enzyme activities in diabetic db/db mice. Mol Nutr Food Res 52(9):995–1004

Shah VO, Scavini M, Nikolic J, Sun Y, Vai S, Griffith KJ (1998) Z-2 microsatellite allele is linked to increased expression of the aldose reductase gene in diabetic nephropathy. J Clin Endocrinol Metab 83:2886–2891

Simonen P, Gylling H, Howard AN, Miettinen TA (2000) Introducing a new component of the metabolic syndrome: low cholesterol absorption. Am J Clin Nutr 72:82–88

Simopoulos AP (1991) Omega-3 fatty acids in health and disease and in growth and development. Am J Clin Nutr 54:438–463

Sing CL, Yen HL, Jen FL, Wen HC, Chiao MC, Chen CYO (2011) Almond consumption improved glycemic control and lipid profiles in patients with type 2 diabetes mellitus. Metab Clin Exp 60:474–479

Soobrattee MA, Neergheen VS, Luximon RA, Aruoma OIB (2005) Phenolics as potential antioxidant therapeutic agents: mechanism and actions. Mutat Res 579:200–213

Sri Balasubashini M, Rukkumani R, Viswanathan P, Venugopal PM (2004) Ferulic acid alleviates lipid peroxidation in diabetic rats. Phytother Res 18(4):310–314

Stahl W, Sies H (2005) Bioactivity and protective effects of natural carotenoids. BBA—Mol Basis Dis 1740(2):101–117

Sterti R (2010) Berberine for diabetes mellitus type 2. Nat Med J 2(10):5–6

Suresh Y, Das UN (2003) Long-chain polyunsaturated fatty acids and chemically induced diabetes mellitus: effect of ω-6 fatty acids. Nutrition 19:93–114

Suzuki K, Tanaka M, Konno R, Kaneko Y (2002) Effects of 5-campestenone (24-methylcholest-5-en-3-one) on the type 2 diabetes mellitus model animal C57BL/KsJ-db/db mice. Horm Metab Res 34:121–126

Szkudelska K, Nogowski L, Szkudelski T (2009) The inhibitory effect of resveratrol on leptin secretion from rat adipocytes. Eur J Clin Investig 39:899–905

Tada N, Watanabe H, Matsuo N, Tokimitsu I, Okazaki M (2001) Dynamics of postprandial remnant-like lipoprotein particles in serum after loading of diacylglycerols. Clin Chim Acta 311:109–117

Taguchi H, Watanabe H, Onizawa K (2000) Double-blind controlled study on the effects of dietary diacylglycerol on postprandial serum and chylomicron triacylglycerol responses in healthy humans. J Am Coll Nutr 19:789–796

Taguchi H, Nagao T, Watanabe H (2001) Energy value and digestibility of dietary oil containing mainly 1,3-diacylglycerol are similar to those of triacylglycerol. Lipids 36:379–382

Takahashi N, Kawada T, Goto T, Yamamoto T, Taimatsu A (2002) Dual action of isoprenols from herbal medicines on both PPAR and PPAR-gamma in 3T3-L1 adipocytes and HepG2 hepatocytes. FEBS Lett 514(2–3):315–322

Takase H, Shoji K, Hase T, Tokimitsu I (2005) Effect of diacylglycerol on postprandial lipid metabolism in non-diabetic subjects with and without insulin resistance. Atherosclerosis 180:197–204

Tanaka M, Misawa E, Ito Y, Habara N, Nomaguchi K, Yamada M (2006) Identification of five phytosterols from Aloe vera gel as antidiabetic compounds. Biol Pharm Bull 29:1418–1422

Tsuda T (2008) Regulation of adipocyte function by anthocyanins; possibility of preventing the metabolic syndrome. J Agric Food Chem 56(3):642–646

Ubels FL, Links TP, Sluiter WJ, Reitsma WD, Smit AJ (1999) Walking training for intermittent claudification in diabetes. Diabetes Care 22:198–201

Vidal VC, Frías J, Sierra I, Blazquez I, Lambien F, Kuo YH (2002) New functional legume food by germination. Effect on the nutritive value of beans, lentils and peas. Eur Food Res Technol 215:472–476

Vijaimohan K, Jainu M, Sabitha KE, Subramaniyam S, Anandhan C, Shyamala DCS (2006) Beneficial effects of alpha linolenic acid rich flaxseed oil on growth performance and hepatic cholesterol metabolism in high fat diet fed rats. Life Sci 79:448–454

Wasan KM, Zamfir C, Pritchard PH, Pederson RA (2003) Influence of phytostanol phosphoryl ascorbate (FM-VP4) on insulin resistance, hyperglycemia, plasma lipid levels, and gastrointestinal absorption of exogenous cholesterol in Zucker (fa/fa) fatty and lean rats. J Pharm Sci 92:281–288

WHO, IDF (2006) Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: 2006. World Health Organization, Geneva

Wild S, Roglic G, Green A, Sicree R, King H (2004) Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 27:1047–1053

Williams RJ, Spencer JP, Rice EC (2004) Flavonoids: antioxidants or signaling molecules. Free Radic Biol Med 36:838–849

Wolford JK, Gruber JD, Ossowski VM, Vozarova B, Antonio Tataranni P, Bogardus C, Hanson RL (2003) A C-reactive protein promoter polymorphism is associated with type 2 diabetes mellitus in Pima Indians. Mol Genet Metab 78:136–144

Xavier CPR, Lima CF, Preto A, Seruca R, Fernandes FM, Pereira WC (2009) Luteolin, quercetin and ursolic acid are potent inhibitors of proliferation and inducers of apoptosis in both KRAS and BRAF mutated human colorectal cancer cells. Cancer Lett 281(2):162–170

Zhaoa J, Zhaob Y, Zhenga W, Lub Y, Fengb G, Yub S (2008) Neuroprotective effect of curcumin on transient focal cerebral ischemia in rats. Brain Res 1229:224–232

Zheng CD, Duan YQ, Gao JM, Ruan ZG (2010) Screening for anti-lipase properties of 37 traditional Chinese medicinal herbs. J Chin Med Assoc 73(6):319–324

Antianxiety Activities Associated with Herbal Drugs: A Review

G. Mustafa, S. H. Ansari, Z. A. Bhat, and A. S. Abdulkareim

Introduction

Anxiety is a complex progressive behavioral and physiological alteration of the organism characterized by restlessness, easy fatigability, difficulty in concentration, irritability, muscle tension, and sleep disorders which ultimately leads to a wide variety of CNS disorders if remains untreated. Anxiety disorders are often associated with autonomic symptoms, including heart palpitations, sweating, elevation of body temperature, and alterations of gastrointestinal motility. In addition to individual genetic factors also external influences, such as nutrition, smoking, alcohol, socioeconomic status, and environmental conditions, can strongly contribute to its anticipated appearance. During the whole life a human being is confronted with social, psychological, and emotional stress. Chronic social stress is one of the most important factors responsible for precipitation of depressive disorder in humans. In recent years, the impact of social stress on the development of psychopathologies has been thoroughly investigated in preclinical animal studies.

There are many anxiolytics used in clinical practice but most of them are associated with one or the other undesirable effect, which ranges from psychological dependence to severe withdrawal symptoms. The effective anxiolytic agents should reduce anxiety symptoms, and exert calming effect with little or no effect on motor or mental function (Katzung 2001).

G. Mustafa (✉) · S. H. Ansari
Herbal Cosmetics and Immunomodulatory Lab, Department of Pharmacognosy and Phytochemistry, Faculty of Pharmacy, Jamia Hamdard, New Delhi, India

Z. A. Bhat
Depatment of Pharmaceutical Sciences, University of Kashmir, Srinagar, Jammu and Kashmir, India

A. S. Abdulkareim
Phytochemistry Research Lab, Department of Pharmacognosy and Phytochemistry, Faculty of Pharmacy, Jamia Hamdard, New Delhi, India

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Allopathic Anxiolytic Agents, Pharmacodynamics, and Disadvantages

Benzodiazepines like diazepam, lorazepam, and oxazepam are the common allopathic treatment for anxiety. Other class of compounds called barbiturates are used and are superior to benzodiazepine. Miscellaneous agents, e.g., Buspirone which is non-gabanergic antianxiety agent, are free from benzodiazepine side effect (CNS depression, tolerance, dependency).

Pharmacodynamic: The benzodiazepines and barbiturates act by binding to $GABA_A$ receptors present in the neural membrane of the CNS. (GABA) is the major inhibitory neurotransmitter in the CNS. The benzodiazepines bind to their binding site in the $GABA_A$ receptors. The other miscellaneous agents produce their effect by different mechanism (partial agonist effect on the brain $5\text{-}HT_{1A}$ receptors), e.g., Buspirone—non-gabanergic antianxiety agent.

Disadvantages and drawback: Tendency to produce psychological dependency (not related to the blood serum concentration) known as withdrawal symptoms characterized by restlessness, tremor, agitation and sleep disorder, amnesic effect, synergetic depressive effect with alcohol and other CNS depressants (alcohol, antidepressant agents), tolerance (decrease in response with repeated exposure), and barbiturates have narrow therapeutic index, hangover effect, and physiological dependency (Katzung 2001).

The significances of studying the herbal medicines of anxiety: In addition to their intolerance to side effects, the action of herbal formulation has been found comparable with the allopathic anxiolytic agents as a result of many studies done in this area. Wide range of safety has been ascribed to the herbal anxiolytic agents compared with the severe side effect of the allopathic agents in case of long exposure (tolerance, physiological, and psychological dependency), severe toxicity with over dose (CNS depression, respiratory and cardiovascular system depression), in addition to the psychosocial problems associated (hangover, job impairment, depression of the locomotor activity). 54% of anxiety and depression disorder patients use alternative/complementary medicines out of which 38% use herbal medicines (Brown and Gerbarg 2001).

Mechanism of action of herbal anxiolytic preparations: Inhibition of 5-HT, DA, NE reuptake, participate in 5-HT receptors downregulation, agonist the GABA, BZ, 5-HT and glutaminergic NMDA-type receptor, block Na channels (Conner and Davidson 2002).

Plants Having Anxiolytic Effects

Ashwagandha

Biological name: *Withania somnifera*, *family*: *Solanaceae*, *part used*: Root powder, decoction, and leaves, *active constituents responsible for the anxiolytic effect*: glycowithanolides.

Mechanism of action: GABA mimetic activity. Researchers from George Washington University School of Medicine and Health Sciences, the adult Psychopharmacology program at National Institute of Mental Health, and the San Antonio Cochrane Center reviewed all the traditional literature concerning this Ayurvedic herb. They put this herb on clinical trials to determine its safety and it was found to have anxiolytic and antidepressant activity. Toxicity studies didn't reveal any significant adverse effects (www.holistic.com, herb for anxiety). It induced an anxiolytic effect, comparable to that produced by lorazepam, in the elevated plus maze, social interaction, and feeding latency in an unfamiliar environment (Bhattacharya et al. 2000). Another study at Dept. of Pharmacology, University of Texas, found GABA-like activity in *Withania somnifera*. These results suggest that the *W. somnifera* extract contains an ingredient which has a GABA-mimetic activity. This activity was correlated with anti-anxiolytic effect (Mehta et al. 1991). Dosage: 150–300 mg of root extract as mentioned by the American pharmaceutical association, 2–3 g of root powder thrice daily, and capsule of 2–5 mg of withanoloides (Duke 2002).

Kava

Biological name: *Piper methysticum*, *family*: *Piperaceae*, *part used*: root, *active constituents responsible for the anxiolytic effect*: Kava pyrone. *Mechanism of action*: Binds to GABA receptors at benzodiazepine site (Julien 2004). Inhibits glutamate. Blocks sodium channels, 5-HT agonist (Conner et al. 2002). A study was carried out to compare the anxiolytic potential of Kava-Kava extract with diazepam. Acute effects of diazepam and a Kava-Kava preparation, compared to their respective controls, were examined in Wistar rats using the elevated plus maze (X-maze). The time spent on open arms, percentage of open-arm visits, and parameters describing the risk assessment were evaluated. Kava-Kava extract (120–240 mg/kg p.o.) affected the behavior measured in the X-maze test, inducing an anxiolytic-like behavior similar to diazepam (15 mg/kg p.o.). These data support the use of Kava-Kava in the treatment of anxiety (Rex et al. 2002). *Dosage*: As revealed by many studies the range of dose is 70–240 mg/kg of kava pyrone. The use of kava extract is contraindicated with other CNS depressant (benzodiazepine, L-dopa, mood-changing drugs) (Fetroro and Avila 2000).

St. John's-Wort

Biological name: *Hypericum perforatum*; *family*: *Clusiaceae*; *part used*: flower and upper stem leaves; *active constituents responsible for the anxiolytic effect*: hypericin.

Mechanism of action: Participates in 5-HT receptor downregulation (Davidson and Conner 2001). Active at GABA, benzodiazepine, and glutaminergic NMDA-type receptors, 5-HT, DA, and NE reuptake inhibitor (Julien 2004). St. John's-wort extract as sublingual cap. Containing 300–500 mg has been standardized to contain 0.3% hypericin, and 250 mg capsule standardized to 0.14% hypericin (Fetroro and Avila 2000). In a reported case study it was found that St. John's-wort not only alleviated GAD symptoms, buy it also helped the ability to cope with daily stresses and difficult social interactions. In case using (900 mg bid) for 4 weeks the result is improvements in sleep, ability to relax, worry, and coping with daily stress and premenstrual stress with no side effects or relapse.

When used as 900 mg bid for 2 weeks the result is improvements in sleep and ability to cope with family stresses. The same dose for 4 weeks resulted in 50% improvement reduction in nervousness, worry, and irritability.

At an increased dose level of 1500 mg/day, dry mouth was the only side effect (Davidson and Conner 2001).

Brahmi

Biological name: *Bacopa monnieri*; *family name*: *Scrophulariaceae*; *part used*: whole plant; *active constituents responsible for the anxiolytic effect*: bacopasides.

Mechanism of action: Increases enzyme level of EROD and PROD (prophylactic). In this study on rats, *B. monnieri* showed the potential to be effective in stress. The response had been better in the group that was pretreated for 1 week with 20–40 mg/kg/daily of it even before exposing to stress stimuli. The level of Hsp70 increases in brain as a response to stress. After giving *B. monnieri* for 7 days, and then giving stress to animals, the Hsp70 was found in lower concentration in animals pretreated with Bacopa. EROD and PROD enzyme levels in pretreated rats were found more even before exposure to stress. Thus *B. monnieri* primed the brain for stress by stockpiling these useful enzymes even before stressful conditions. Using this medicinal herb could lower our susceptibility to stress (www.holistic.com, herb for anxiety) (Chowdhuri et al. 2002). Research on rats as models of clinical anxiety showed the anxiolytic activity of its extracts with 25% bacopasides as comparable to lorazepam. Plus there were no side effects of lorazepam, like amnesia. Rather there was memory-enhancing effect. Another 1-month study on diagnosed anxiety neurosis patients, with syrup of this medicinal herb equivalent to 12 g of crude powder, found significant reduction in anxiety symptoms, level of disability, and fatigue. There was additional increase in immediate memory, decreased respiratory rate, and decreased SBP or systolic blood pressure (www.holistic.com, herb for anxiety).

Dosage: Standardized fluid extract: 1:2 fluid extract should be taken in 4–12 ml for adults and 2–4 ml for children within 6–12 years of age. Standardized 20% extract (both bacopasides A and B): 200–400 mg/day in two or three divided dosages for adults and 100–200 mg/day in two or three divided dosages for children within 6–12 years of age (www.holistic.com, herb for anxiety).

Passionflower

Biological name: *Passiflora incarnata*; *family name*: *Passifloraceae*; *part used*: whole herb, aerial part; *active constituents responsible for the anxiolytic effect*: suggested to be benzo-flavonoids (methanol extract).

Mechanism of action: Unrevealed. A pilot double-blind randomized control trial with oxazepam found the Passiflora extract to be an effective herb for the management of generalized anxiety disorder. It has the added side benefit of having low chances of job impairment found with the use of oxazepam due to morning after side effects (Akhondzadeh et al. 2001).

A fraction derived from the methanol extract of *P. incarnata* has been observed to exhibit significant anxiolytic activity at a dose of 10 mg/kg in mice using elevated plus maze model of anxiety. This fraction comprises mainly two components that are visible as blue- and turquoise-colored fluorescent spots at 366 nm of the UV light. The possibility of a phytoconstituent having benzoflavone nucleus as the basic moiety being responsible for the bioactivity of *P. incarnata* is highly anticipated (Dhawan et al. 2001a).

The petroleum ether, chloroform, methanol, and water extracts of *Passiflora incarnata* whole plant and sorted-out plant parts have been evaluated for their anxiolytic activity using the elevated plus maze model in mice. The methanol extracts of leaves, stems, flowers, and whole plant exhibited anxiolytic effects at 100, 125, 200, and 300 mg/kg, respectively. *The roots were practically devoid of anxiolytic effects*. These results show that roots and flowers of *P. incarnata* act as natural adulterants by causing a significant increase in the anxiolytic dose. Therefore, separation of these parts is recommended prior to any pharmacological, phytochemical, and standardization studies on *P. incarnata* (Dhawan et al. 2001b).

It works best in thin, nervous, and easily stressed persons. *Passiflora incarnata* got the official approval of Commission E (1985) in Germany for its role in anxiety and insomnia. Kava and valerian have quick action but the effect of *Passiflora incarnata* builds up in about a month (www.holistic.com, herb for anxiety).

Dosage: Capsule—300–450 mg twice or thrice a day. Fluid extract (1:1 in 25% alcohol)—10–30 drops three times a day. Hot infusion or tea—pour one teaspoon (2–5 g) of herb powder with 150 ml hot water. Strain after 10 min and use it. It can be taken twice or thrice a day, and the last dose one or 2 h before bedtime. Tincture (1:5 in 45% alcohols). 10–60 drops twice or thrice daily. Passionflower and the herbal compounds containing it are standardized to contain not less than 0.8% flavonoids to meet the standards of German, French, and Swiss Pharmacopoeias. Low levels of serotonin have been identified that is used to explain its effects as a natural calming agent, as an aid to concentration, and to elevate the mood. Maltol, another compound, is also found to have mild sedative properties (www.holistic.com, herb for anxiety).

To ensure uniformity and consistency of the biologic effects exhibited by plant-derived phytopharmaceuticals, uniform standards are required globally. The monographs on *P. incarnata* mention standardization of the plant using any known flavonoid as the chemical marker and the marker compound was not the one respon-

sible for the plant's multifarious biologic effects. The recent report of a trisubstituted benzoflavone compound (BZF) as the main bioactive phytoconstituent of *P. incarnata* made it feasible to resort to biologic standardization of this plant using BZF as the biomarker compound. The biologic standardization would ensure bioequivalence of the medicinal preparations of *P. incarnata*. These studies also recommend the incorporation of leaf constants, ash values, extractive values, thin-layer chromatography profile (vital "fingerprints" specific for a plant), and quantitative assay by determining the bioactive BZF moiety in pharmacopoeias in order to ensure uniform biologic results and standards of *P. incarnata* because the plant currently has tremendous usefulness (Dhawan et al. 2002).

Siberian Ginseng

Biological name: *Eleutherococcus senticosus*; *family*: *Araliaceae*; *Part used*: root; *active constituents responsible for the anxiolytic effect*: eleutherosides and sennosides; *mechanism of action*: unrevealed.

Dosage range: 100–200 mg but the common is 200 mg (standardized extract), 2–3 times daily. A regimen of 4 weeks on 2 weeks off is recommended for maximum benefits.

Standardization: The most current available medical and scientific literature indicates that this dietary supplement should be standardized to 0.8% eleutherosides B and E per dose.

Star Flower

Biological name: *Echium amoenum*; *family*: *Boraginaceae*; *part used*: flower; *active constituents responsible for the anxiolytic effect*: ethanol extract of flower (50 mg/kg).

Mechanism of action: Unrevealed. Study reveals that the ethanol extract of *Echium amoenum* flowers at the dose of 50 mg/kg increased the percentage of time spent and the percentage of arm entries in the open arms of the elevated plus maze (EPM) and decreased the percentage of time spent in the closed arms of EPM. Also, the locomotor activity was affected but not to the same extent as observed for diazepam. These results suggested that the extract of *E. amoenum* seems to possess anxiolytic effect with lower sedative activity than that of diazepam (Rabbani et al. 2004).

Ginseng

Biological name: *Panax ginseng*; *family*: *Araliaceae*; *part used*: root; *active constituents responsible for the anxiolytic effect*: ginsenoside Rb1.

Mechanism of action: Unrevealed. There has been investigation of the anxiolytic-like effects of red ginseng (RG, steamed raw ginseng at 98–100 °C) and sun ginseng (SG, heat-processed ginseng at higher temperature) in mice using the elevated plus maze model. Furthermore, the anxiolytic-like effects of RG and SG were compared to a known active anxiolytic drug (diazepam). The RG butanol fraction (100 mg/kg) significantly increased the number of open-arm entries and the time spent on the open arm (indicators of anxiolytic-like effects) compared with that of the saline group. However, lower doses of the SG total extract (50 mg/kg) and the SG butanol fraction (25 and 50 mg/kg) significantly increased the number of open-arm entries and the time spent on the open arms. The RG total extract (100 mg/kg) and the SG total extract at a lower dose (25 mg/kg) did not increase the number of open-arm entries or the time spent on the open arm. These data indicate that ginseng has anxiolytic-like effects, and the anxiolytic potential of SG is stronger than that of RG in the elevated plus maze model. Ginseng saponins have been suggested to play an important role in the anxiolytic effects of ginseng (Park et al. 2005).

Pharmacological identification of the active constituents which give the anxiolytic effect has been performed on albino mice using elevated plus maze as indicator, using the following, drug diazepam (0.5, 1, 1.5 mg/kg – p.o), red ginseng crude powder (300,600 and 1200 mg/kg p.o), crude saponin and non-saponin ginseng fraction (50, 100 and 200 mg/kg ip), and pure ginsenoside rb1 rg1 ro (2.5, 5, and 10 mg/kg ip), and it is found that the ginseng powder and the crude saponin increase the frequency and duration of open-arm entries, but only the Rb1 shows this effect among the ginsenoside pure fraction (Carr et al. 2006).

Salvia reuterana

Biological name: *Salvia reuterana*; *family*: *Boiss*; *part used*: whole plant; *active constituents responsible for the anxiolytic effect*: hydroalcoholic extract (100 mg/kg). *Mechanism of action*: Unrevealed. The anxiolytic and sedative effects of hydroalcoholic extract (HE) of *Salvia reuterana* (*Boiss*) was evaluated in mice. The HE of *Salvia reuterana* (100 mg/kg) increased the percentage of time spent and the percentage of arm entries in the open arms of the elevated plus maze. Spontaneous locomotor activity count measured in 15 min of the test was significantly decreased in animals pretreated with diazepam and 100 mg/kg of *Salvia reuterana* extract.

Ginkgo

Biological name: Ginkgo biloba; *family*: *Ginkgoaceae*; *part used*: leaf; *active constituents responsible for the anxiolytic effect*: ginkgolide-A (1–2 mg/kg).

Mechanism of action: Unrevealed.

The anxiolytic-like effects of *Ginkgo biloba* extract (GBE) and its four terpenoid components (ginkgolide-A, ginkgolide-B, ginkgolide-C, and bilobalide) were assessed using the elevated plus maze test in mice. Administration of GBE as a single oral dose (0.5 or 1 g/kg, po) caused a state of suppressed motor activity and, thus, shortened the time spent in the open-sided arms. However, when GBE (0.063–1 g/kg, po) was administered daily for 7 days and the plus maze test was carried out 24 h after the final administration, the time spent in the open-sided arms was prolonged, with the peak anxiolytic-like effect at 0.125 g/kg. A combination of 7-day administration of GBE (0.125 g/kg) and a single dose of diazepam (1 mg/kg, po, and 10 min before testing) enhanced the anxiolytic-like effect. Flumazenil (0.3 mg/kg, ip, and 10 min before testing) blocked the effect of diazepam, but not of GBE. Daily administration of ginkgolide-A (1 or 2 mg/kg, po) resulted in an anxiolytic-like effect by the third treatment, with the maximal effect observed after the fifth administration. Neither ginkgolide-B, ginkgolide-C, nor bilobalide produced any anxiolytic-like effects. At doses higher than 0.5 g/kg, GBE not only inhibited motor activity but also suppressed active avoidance behavior, reduced caffeine-induced stimulation, and enhanced pentobarbital-induced sleep, while ginkgolide-A (up to 20 mg/kg) did not exhibit these effects. Diazepam (1 mg/kg) is known to enhance pentobarbital-induced sleep. These results suggest that GBE produces a significant anxiolytic-like effect following repeated administration and that ginkgolide-A is most likely responsible for this effect. There are also indications that although GBE exerts a sedative effect at comparatively higher doses, ginkgolide-A has a relatively weak tendency to produce benzodiazepine-like side effects (Kuribara et al. 2003).

American Skullcap

Biological name: *Scutellaria lateriflora*; *family*: *Lamiaceae*; *part used*: whole plant; *active constituents responsible for the anxiolytic effect*: baicalin, baicalein, GABA, and glutamine.

Mechanism of action: $GABA_A$ agonist.

The phytochemistry and biological activity of *Scutellaria lateriflora* L. (American skullcap) which has been traditionally used as a sedative and to treat various nervous disorders such as anxiety were studied. In vivo animal behavior trials were performed to test anxiolytic effects in rats orally administered with *S. lateriflora* extracts. Significant increases in the number of entries into the center of an "open-field arena," number of unprotected head dips, number of entries, and length of time spent on the open arms of the elevated plus maze were found. The identification and quantification of the flavonoid baicalin in a 50% EtOH extract (40 mg/g) and its aglycone baicalein in a 95% EtOH extract (33 mg/g), as well as the amino acids GABA in H_2O and EtOH extracts (approximately 1.6 mg/g) and glutamine in an aqueous extract (31 mg/g), were performed using HPLC. These compounds may play a role in anxiolytic activity since baicalin and baicalein are known to bind to

the benzodiazepine site of the $GABA_A$ receptor and since GABA is the main inhibitory neurotransmitter (Awad et al. 2003). The aqueous extract of American skullcap (*Scutellaria lateriflora* L. (*S. lateriflora*) (*Lamiaceae*)) has been traditionally used by North American Indians as a nerve tonic and for its sedative and diuretic properties. Recent reports stated that flavonoids and possibly amino acids are responsible for the anxiolytic activity. As a part of search for environmentally friendly solvents to extract the active components from medicinal plants, in a comparison of accelerated solvent extraction (ASE) using water, and supercritical fluid extraction (SFE) using CO_2 and 10% EtOH as modifier, at different temperatures, flavonoids and amino acids were quantified by HPLC-UV and HPLC-MS, respectively. The flavonoid content was compared with conventional extraction methods (hot water extraction and 70% ethanol). The use of ASE at 85 Cingrate with water as solvent gave the best results for flavonoid glycosides and amino acids, whereas SFE gave higher yields of flavonoid aglycones. However, the results obtained for total flavonoids were not significantly superior to hot water extraction or 70% aqueous EtOH extract (Bergeron et al. 2005).

Valerian

Biological name: *Valeriana officinalis*; *family*: *valerianaceae*; *part used*: root; *active constituents responsible for the anxiolytic effect*: valerenic acid and valepotriates. *Mechanism of action*: $GABA_A$ agonist.

Valerian has anxiolytic, tranquilizing, and sleep-inducing effects that have been demonstrated in both animal studies and clinical trials. Valerian or its constituents could induce these effects by interacting with central gamma-amino butyric acid (GABA) receptors. Early in vitro studies testing the binding of valerian extract to GABA receptors showed that the agonist muscimol was displaced, suggesting valerian binding to these receptors.

Pretreatment with valerian extract or valerenic acid decreased the brainstem inhibitory effects produced by muscimol (both P _ 0.05), suggesting that these compounds play an important role in the regulation of GABAminergic activity. Data from study suggest that the pharmacological effects of valerian extract and valerenic acid are mediated through modulation of $GABA_A$ receptor function. Thus, valerian may potentiate the sedative effects of anesthetics and other medications that act on GABA receptors, and presurgical valerian use may cause a valerian-anesthetic interaction. Treatment with valerian extract or valerenic acid caused an inhibitory effect on muscimol-sensitive NTS neurons in an in vitro brainstem preparation. It was also observed that the inhibitory activity of both valerian extract and valerenic acid was induced via $GABA_A$, but not $GABA_B$, receptors. The GABA agonistic activity of valerian and its positive modulation of $GABA_A$ receptors could partly explain valerian's antianxiety and sedative effects (Yuan et al. n.d.).

Damiana

Biological name: *Turnera aphrodisiaca*; *family*: *Turneraceae*; *part used*: whole plant; *active constituents responsible for the anxiolytic effect*: mother tincture of the plant. *Mechanism of action*: Not revealed.

Turnera aphrodisiaca Ward (synonym *Turnera diffusa*) Family (*Turneraceae*) is commonly known as "Damiana." The leaves of *T. aphrodisiaca* have been used traditionally as a stimulant, aphrodisiac, tonic, diuretic, nerve tonic, and laxative, and in kidney, menstrual, and pregnancy disorders. British Herbal Pharmacopoeia lists specific indications for Damiana as anxiety neurosis associated with impotency.

Phytochemical reports on *T. aphrodisiaca* indicate that the plant contains tetraphyllin B (a cyanoglycoside); gonzalitosin I (a flavonoid); arbutin (a phenolic glycoside); damianin; tricosan-2-one, hexacosanol (hydrocarbons); a volatile oil containing pinene, *p*-cymene, and 1,8-cineole; and -sitosterol (a phytosterol) (Kumar and Sharma 2005).

Nees

Biological name: *Aniba riparia*; *Family*: *Lauraceae*; *part used*: unripe fruit; *active constituents responsible for the anxiolytic effect*: riparin III.

Mechanism of action: Not revealed.

The anxiolytic effect of riparin III from the plant *Aniba riparia* on mice was tested using the elevated plus maze which has shown antianxiety effect at an oral dose of 25–50 mg/kg and both doses show no effect on the locomotor activity (Anonymous n.d.-a).

Safed Musli

Biological name: *Chlorophytum borivilianum*; *part used*: root; *active constituents responsible for the anxiolytic effect*: butanolic fraction of alcoholic extract.

Mechanism of action: Not revealed. The acute toxicity effect studies carried out on albino mice found that the alcoholic extract and the butanolic fraction were evaluated for in vivo antistress activity using cold stress model on albino rats at a dose of 500 mg/kg. The alcoholic extract exhibited moderate activity (Anonymous n.d.-b).

Griseb

Biological name: *Aloysia polystachya*; *family*: *Verbenaceae*; *part used*: aerial part; *active constituents responsible for the anxiolytic effect*: hydroethanolic extract of the aerial part. *Mechanism of action*: Not revealed.

The hydroethanolic extract of the aerial part of the plant was tested on male mice and found that it does not show any change on the locomotive activity and motor coordination body temperature (advantage) at a dose 1.0, 10.0, and 100 mg/kg. The percentage of both number of entries and time spent in the open arm of the EPZ test was significantly increased with a dose range of 10–100 mg/kg (Hellión 2006).

Clary

Biological name: *Salvia sclarea*; *family name*: *Lamiaceae*; *part used*: flowering top; *active constituents responsible for the anxiolytic effect*: clary (aromatic essential oil). *Mechanism of action*: Not revealed.

The active constituents of the aromatic oil (clary) are obtained by steam distillation of the flowering top. The dose for anxiety disorder, depression, and mental fatigue is two drops of the essential oil to be inhaled. Side effects: drowsiness, headache, increases the menstrual bleeding and euphoria. Contraindicated with estrogen-sensitive cancer, pregnancy, and breastfeeding (Fetoro and Avila 2000).

Mugwort

Biological name: *Artemisia vulgaris*; *Family name*: *Compositae*; *part used*: root; *active constituents responsible for the anxiolytic effect*: root tincture.

Mechanism of action: Not revealed. The dose used to produce the antianxiety effect is 5 ml of root tincture orally 30 min before bedtime. Side effects: skin inflammation, wheezing, itching, and rash. Contraindicated with pregnancy, bleeding disorder, and acid reflux (Fetoro and Avila 2000).

Magnoliaceae

Biological name: Magnolia obovata; *family*: *Magnoliaceae*; *part used*: stem bark; *active constituents responsible for the anxiolytic effect*: honokiol.

Honokiol (3′, 5-di-2-propenyl-1, 1′-biphenyl-2, 4′-diol) is an isomer of neolignans isolated and identified from the stem bark of Magnoliaceous plants (*Magnolia obovata*). The magnolia bark has been utilized as an herbal remedy for the treatment

of a wide variety of clinical disorders. Honokiol and magnolol (an isomer of honokiol) were recently identified as anxiolytic agents in the extracts of Saiboku-to, an oriental herbal Chinese medicine (Kampo). Behavioral evaluation through an elevated plus maze test demonstrated that honokiol, 0.2–2 mg/kg, p.o., for 7 days, was at least 5000 times more potent than Saiboku-to. Honokiol has a comparatively lower risk of causing benzodiazepine-like side effects, such as central depression, muscle relaxation, amnesia, or physical dependence (Maruyama and Kuribara 2000).

Comparison of Anxiolytic Activity of Herbal Plant Against Allopathic Formulations

- It's found that the anxiolytic effect of ashwagandha (*Withania somnifera*) is comparable with lorazepam using EPM and social interaction as the evaluation parameter.
- A study on rats showed that Bacopa extract showed prophylactic property if it is used for 1 week (20–40 mg/kg/day) before exposing to stress factors.
- It is also revealed that the extract of Bacopa containing not less than 25% bacosides is comparable to lorazepam but have the advantages of absence of lorazepam side effect.
- Kava root extract (120–240 mg/kg p.o) is found to be equally effective as diazepam (15 mg/kg p.o) without many of their side effects.
- In a pilot double-blind randomized controlled trial it was found that passionflower (*Passiflora incarnata*) is effective in the treatment of general anxiety disorder compared with oxazepam, with advantages of absence of chances of job impairment.
- Anxiolytic effect of (*Salvia reuterana*) hydroalcoholic extract of the plant (100 mg/kg) has been found comparable to diazepam 15 mg/kg.
- The daily administration of ginkgolide-A (1–2 mg/kg p.o) (*Ginkgo biloba*) active constituents to mice is equally active as the combination of Ginkgo extract (125 mg/kg) and diazepam (1 mg/kg p.o).

Conclusion

Although evidence of the efficacy of herbal preparations in treating anxiety conditions is growing, translating the results of efficacy studies into effective treatments for patients is hampered by the chemical complexity of the products, lack of standardization of commonly available preparations, and paucity of well-controlled studies revealing the exact mechanism of actions and safety study on human.

References

Akhondzadeh S et al (2001) Passionflower in the treatment of generalized anxiety: a pilot double-blind randomized controlled trial with oxazepam. J Clin Pharm Ther 5(26):363–367

Anonymous (n.d.-a) Medicinal aromatic plant abstract. Vol 28 No

Anonymous (n.d.-b) J Indian Drug 43(11):878–880

Awad R, Arnason JT, Trudeau V, Bergeron C, Budzinski JW, Foster BC, Merali Z (2003) Phytochemical and biological analysis of skullcap (Scutellaria lateriflora L.): a medicinal plant with anxiolytic properties. Phytomedicine 10(8):640–649

Bergeron C, Gafner S, Clausen E, Carrier DJ (2005) Comparison of the chemical composition of extracts from Scutellaria lateriflora using accelerated solvent extraction and supercritical fluid extraction versus standard hot water or 70% ethanol extraction. J Agric Food Chem 53(8):3076–3080

Bhattacharya SK, Bhattacharya A, Sairam K, Ghosal S (2000) Anxiolytic antidepressant activity of *Withania somnifera* glycolwithanolides, experimental study. Phytomedicine 7:463–469

Brown RP, Gerbarg PL (2001) Herbs and nutrients in the treatment of depression, anxiety, insomnia, migraine, and obesity. J Psychiatr Pract 7(2):75

Carr MN, Bekku N, Yoshimura H (2006) Identification of anxiolytic agents in ginseng root. Eur J Pharmacol 531(1–3):160–165

Chowdhuri DK, Pannar D, Kakkar P et al (2002) Antistress effects of bacopasides of B. monnieri: modulation of Hsp70 expression, superoxide dismutase and cytochrome P450 activity in rat brain. Phytother Res 16:639–645

Conner KM, Davidson JRT (2002) Homeopathy, kava, and other herbal treatments for anxiety. Nat Med Psychiatr Disord 125–131:236

Davidson JRT, Conner KM (2001) St. John's wort in generalized anxiety disorder: three case reports. J Clin Psychopharmacol 21(6):635–636

Dhawan K, Kumar S, Sharma A (2001a) Anti-anxiety studies on extracts of Passiflora incarnata Linneaus. J Ethnopharmacol 78(2–3):165–170

Dhawan K, Kumar S, Sharma A (2001b) Anxiolytic activity of aerial and underground parts of Passiflora incarnata. Fitoterapia 72:922–926

Dhawan K, Kumar S, Sharma A (2002) Comparative anxiolytic activity profile of various preparations of *Passiflora incarnata* Linneaus: a comment on medicinal plants' standardization. J Altern Complement Med 8(3):283–291

Duke JA (2002) Handbook of medicinal herbs, 2nd edn. CRC Press LLC, New York

Fetoro CW, Avila JR (2000) The complete guide to herbal medicines. Spring House, Montgomery County

Fetroro CW, Avila JR (2000) The complete guide to herbal medicines. Pocket Books, New York

Hellión-Ibarrola MC (2006) The anxiolytic-like effects of Aloysia polystachya (Griseb.) Moldenke (Verbenaceae) in mice. J Ethnopharmacol 105(3):400–407

Julien RM (2004) The primer of drug action: a concise, nontechnical guide to the actions, uses and side effects of psychoactive drugs. Worth Publishers, New York, NY

Katzung BG (2001) Basic & clinical pharmacology, 8th edn. McGraw-Hill, New York, p 364

Kumar S, Sharma A (2005) Anti-anxiety activity studies on homoeopathic formulations of Turnera aphrodisiaca Ward. J Oxf Univ 2(1):117–119

Kuribara H, Weintraub ST, Yoshihama T, Maruyama Y (2003) An anxiolytic-like effect of Ginkgo biloba extract and its constituent, ginkgolide-a, in mice. J Nat Prod 66(10):1333–1337

Maruyama Y, Kuribara H (2000) Overview of the pharmacological features of Honokiol. J CNS Drug Rev 6(1):35

Mehta AK, Binkley P, Gandhi SS, Ticku MK (1991) Pharmacological effects of *W. somnifera* root extract on $GABA_A$ receptors complex. Indian J Med Res 94:312–315

Park JH, Cha HY, Seo JJ, Hong JT, Han K, Oh KW (2005) Anxiolytic-like effects of ginseng in the elevated plus-maze model: comparison of red ginseng and sun ginseng. Prog Neuro-Psychopharmacol Biol Psychiatry 29(6):895–900

Rabbani M, Sajjadi SE, Vaseghi G, Jafarian A (2004) Anxiolytic effects of *Echium amoenum* on the elevated plus-maze model of anxiety in mice. Fitoterapia 75(5):457–464

Rex A, Morgenstern E, Fink H (2002) Anxiolytic-like effects of kava-kava in the elevated plus maze test – a comparison with diazepam. J Prog Neuropsychopharmacol Biol Psychiatry 26(5):855–860

Yuan C-S, Mehendale S, Xiao Y, Aung HH, Xie J-T, Ang-Lee MK (2004), The gamma-aminobutyric acidergic effects of valerian and valerenic acid on rat brainstem neuronal activity. Int Anesth Res Soc 98(2):353–8

Medicinal Plants in the Treatment of Arthritis

Shakir Saleem, Riqaiyah Khan, Imran Kazmi, and Muhammad Afzal

Introduction

Arthritis is the umbrella of two Greek words "arthron" and "ites" which together mean inflammation of joint. Arthritis can be defined as a chronic, inflammatory, and systemic autoimmune disorder branded by pain, swelling, and stiffness of the synovial joints. Rheumatoid arthritis (RA) is a chronic autoimmune disease of unknown etiology characterized by persistent synovitis, systemic inflammation, and progressive cartilage and bone destruction resulting in gradual immobility of the victim and autoantibodies specifically for rheumatoid factor and citrullinated peptide.

RA was diagnosed for the first time in early Native American population several centuries ago but it occurred in Europe after the seventeenth century (Firestein 2003). RA generally affects 20% of total Indian population and approximately 1% of the general population in Western countries and is two–three-fold more common in females than in males (Majithia and Geraci 2007).

S. Saleem
Glocal School of Pharmacy, Glocal University, Mirzapur Pole, Dist -Saharanpur, UP, India

Department of Pharmacology, Siddhartha Institute of Pharmacy,
Dehradun, Uttarakhand, India

R. Khan
Department of Pharmacology, Siddhartha Institute of Pharmacy,
Dehradun, Uttarakhand, India

I. Kazmi (✉)
Glocal School of Pharmacy, Glocal University, Mirzapur Pole, Dist -Saharanpur, UP, India

M. Afzal (✉)
Department of Pharmacology, College of Pharmacy, Jouf Univeristy,
Sakaka, Kingdom of Saudi Arabia

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Causes

Cartilages are meant to protect the joints and facilitate its smooth movement (A.D.A.M. Medical Encyclopedia 2011). Arthritic condition develops an inflammatory response of the synovial secondary to hyperplasia of synovial cells, excess synovial fluid, and development of panes in the synovial. The exact cause of RA is not known; however autoimmunity has a key role in its progression and chronicity and is hence considered a systemic autoimmune disease. The crippling disability in RA is caused by multiple pro-inflammatory molecules liberated by macrophages which also include reactive oxygen species and eicosanoids like prostaglandins, leukotrienes, and cytokines (Shin 2003). The complex process of RA which includes the proliferation and fibrosis of synovial cell, pannus formation, and erosion of bone and cartilage is mediated by a symbiotic network of cytokines, prostanoids, and proteolytic enzymes (Kore and Shete 2011).

Epidemiology

Arthritis is one of the most frequent chronic health disorders and is a prime reason for disability. It affected 43 million people of the United States in 2002 and it is expected to cross 60 million limit by 2020 (Lemke and Williams 2008). The frequency of its occurrence is more in smokers than nonsmokers, particularly in men, and also in those who are rheumatoid factor positive (Agarwal and Malavia 2005).

Need for Herbal Drugs for the Management of RA

Conventional allopathic treatment of RA poses a threat in terms of safety and efficacy (Lee et al. 2004). With an eye on the side effects of synthetic drugs, patients are now reconsidering their line of treatment and are pursuing complementary and alternative medicine options to cope up with this debilitating disease. List of medicinal plants traditionally used in the treatment of arthritis is summarized in Table 1.

Medicinal Plants with Antiarthritic Potential

Botanical name: *Althaea officinalis L.*
Common name: Marshmallow
Family: Malvaceae

Table 1 Medicinal plants traditionally used in the treatment of arthritis

S.No.	Botanical name	Common name	Family	Major phytoconstituents	Uses
1	*Althaea officinalis* L.	Marshmallow	*Malvaceae*	Scopoletin	Respiratory diseases, colitis and joint pains, anti-inflammatory
2	*Arctium lappa* L.	Greater Burdock, Gobo, Lappa	*Asteraceae*	Arctigenin	Rheumatoid arthritis, chronic inflammatory bowel disease, anti-inflammatory and anti-arthritic drug
3	*Artemisia absinthium* L.	Wormwood Plant	*Asteraceae*	Scoparone, scopoletin, scopolin, and esculetin	Neuralgia, rheumatoid disorders, rheumatoid arthritis
4	*Cassia angustifolia* M. Vahl	Seena, Indian Seena, Tinnervelly Senna	*Fabaceae*	Sennosides A, B, C, and D	Rheumatoid arthritis, purgative, and laxative
5	*Citrus medica* L.	Citron	*Rutaceae*	Limonene, citropten, and γ-terpinene	Antioxidant, anti-inflammatory, hepatitis, arthritis
6	*Clematis ochroleuca* Aiton	Curly heads	*Ranunculaceae*	*Rich in saponins*	Rheumatoid arthritis, anti-inflammatory, anti-arthritic
7	*Colchicum autumnale* L.	Autumn Crocus, Naked Lady	*Colchicaceae*	*Colchicine*	Hemorrhoid, gout, hepatitis, and rheumatoid arthritis, anti-inflammatory
8	*Cuscuta epithymum* L.	Dodder	*Convolvulaceae*	*Quercetin*	Anti-inflammatory
9	*Ferula asafoetida* L.	Asafoetida, Hing	*Apiaceae*	Ferutinin and teferdin	Anti-inflammatory, osteoprotective
10	*Nigella sativa* L.	Kalonji, Black caraway	*Ranunculaceae*	*Thymoquinone*	Anti-inflammatory, antioxidant, neuroprotective and anticancer, anti-arthritic, rheumatoid arthritis
11	*Rheum palmatum* L.	Rhubarb	*Polygonaceae*	*Emodin*	Anti-inflammatory, rheumatoid arthritis
12	*Smilax china* L. *and S. glabra* Roxb.	China root	*Smilacaceae*	*Seiboldogenin*	Anti-inflammatory especially chronic pelvic inflammation, anticancer and anti-nociceptive, gastric tonic, gout, hemorrhoid, rheumatoid arthritis

(continued)

Table 1 (continued)

S.No.	Botanical name	Common name	Family	Major phytoconstituents	Uses
13	*Strychnos nux-vomica* L.	Poison nut, and quaker buttons	*Loganiaceae*	*Strychnine and Brucine*	Anti-inflammatory, rheumatoid arthritis, analgesic
14	*Pongamia pinnata* (L.) Pierre	Karanja	*Fabaceae*	Pongone, galbone, pongalabol, pongagallon A and B	Anti-inflammatory, anti-ulcer, anti-diarrheal, antioxidant, anti-plasmodium, anti-hypoglycemic, antiviral, antibacterial, anti-inflammatory activities, and anti-arthritic activity
15	*Boerhaavia diffusa* L.	Punarnava	*Nyctaginaceae*	Punarnavoside, boeravinone G, and boeravinone H	Blood purifier, tonic, expectorant and carminative, lumbago, scabies, antibacterial, hypoglycemic, antiproliferative, antistress, antiestrogenic, immunomodulatory activity, and hepatoprotective
16	*Terminalia chebula* Retz.	Haritaki	*Combretaceae*	Arjunglucoside I, arjungenin, and chebulosides I and II	Gastrointestinal disorders, inflammatory diseases, for the improvement of immunity, sinusitis, allergy, hemorrhoids, constipation, high level of cholesterol, rheumatism, blood purifier, antibacterial, and an anticonvulsant agent
17	*Persea americana* Mill.	Avocado	*Lauraceae*	Isorhamnetin, luteolin, rutin, quercetin, and apigenin	Antihypertensive, exfoliative, vasorelaxation, analgesia, anti-inflammatory activity, anticonvulsant activity, antiviral, wound healing, hepatoprotective, antioxidant, and hypoglycemic
18	*Uncaria tomentosa* Willd.	Cat's Claw, Una de Gato	*Rubiaceae*	Oxindole alkaloid, quinovic acid, glycosides, plant sterol, and catechins	Intestinal disorders, wounds, fever, ulcers, anticancer, antidiabetic, anti-inflammatory, allergic conditions, acne, chronic fatigue, menstrual disorders, hormonal imbalance, viral infection, and even depression
19	*Cayaponia tayuya* (Vell.) Cogn.	Tayuya	*Cucurbitaceae*	Flavones, glycosides, cucurbitacin, and terpenes	Analgesic, epilepsy, backache, sciatic pain, headaches, gout, neuralgia, constipation, anemia, cholera, dyspepsia, stomach problems and fatigue, antioxidant, anti-inflammatory, analgesic, and anticancer agent

20	*Maytenuskrukovii*	Chuchuhuasi	*Celastraceae*	Alkaloids: Mayteine andmaytansine Triterpernes: Dammarane and friedelane	Antimutagenic, antioxidant, antimicrobial, analgesic, anti-inflammatory, hypotensive, and anti-arthritic
21	*Bidens pilosa*Linn.	Carrapicho	*Asteraceae*	Chalcone kanin and ethyl caffeate	Diabetes, hypertension, inflammation, immunosuppression, cancer and malaria, anti-arthritic
22	*Mikania guaco* Humb. & Bonpl.	Guaco	*Asteraceae*	Caffeoylquinic acid, amyrins, Steroids: campesterol, stigmasterol and β-sitosterol	Cough, asthma, pain, infections and inflammation, anti-arthritic, anti-inflammatory
23	*Boswellia serrata* Linn.	Shallaki/Indian Frankincense	*Burseraceae*	*β-Boswellic acid*	Anti-inflammatory, anti-atherosclerotic and anti-arthritic activities apart from an astringent, stimulant, expectorant, antiseptic, antiatherosclerotic, analgesic, and sedative
24	*Smilax officinalis* Griseb	Sarsaparilla	*Liliaceae*	*Smilagenin, sarsasapogenin, and sarsaponin*	Diuresis, immunomodulation, antibacterial and blood purification, anti-inflammatory, analgesic, and antipyretic activity
25	*Aloe barbadensis*	Curacao aloe, Lily of the desert	*Liliaceae*	Anthraquinone, anthracene, cinnamic acid, and anthranilic acid	Bruises, insect stings, mild cuts, poison ivy, eczema, itching and as a moisturizer and skin softener, antibacterial and antifungal properties, blood purifier, diuretic, uterine tonic, spermatogenic, laxative, purgative, antipyretic, anti-inflammatory, and anti-arthritic
26	*Withania somnifera* Linn.	Winter cherry, withania root and ashwagandha	*Solanaceae*	Withanine, pseudo-withanine, tropine, pseudo-tropine, somniferine, somnine, and steroidal lactones	Aphrodisiac, liver tonic, anti-inflammatory agent, asthma, ulcers, insomnia, senile dementia, anxiety, neurological disorders, anti-arthritic, anti-inflammatory, and Parkinson's disease

(continued)

Table 1 (continued)

S.No.	Botanical name	Common name	Family	Major phytoconstituents	Uses
27	*Piper nigrum* Linn.	Pepper	*Piperaceae*	Piperine, piperidine	Stimulant, stomachic, carminative, aromatic, anti-arthritic
28	*Actaea racemose* Linn.	Black snakeroot, bugwort	*Ranunculaceae*	Acteina, cimigoside, steroidal terpenes, and 27-deoxyactein	Arthritis, diarrhea, dieresis, dyspepsia, kidney problems, malaria, snake bite and as an insect repellant, menopause, anti-inflammatory
29	*Zingiber officinale*	Ginger root	*Zingiberaceae*	Zingerone, zingiberene, shogaols, and gingerols	Antioxidant, anti-inflammatory, antiseptic, anticarcinogenic, antifungal, antimicrobial, nausea, vomiting and diarrhea, anti-arthritic
30	*Curcuma longa* Linn.	Turmeric root, Indian saffron	*Zingiberaceae*	Curcumin, curcuminoids	Antispasmodic, antimicrobial, hepatoprotective, neuroprotective, anticancer
31	*Calotropis procera* Linn.	Giant Swallow Wort, Milkweed	*Asclepiadaceae*	Amyrins, sterols, ursolic acid, calotropin, calotoxin, calactin, and uscharin	Anti-inflammatory activity along with analgesic, antioxidant, and antifungal activity
32	*Camellia sinensis* Linn.	Green tea extract, Chinese tea	*Theaceae*	Epigallocatechin and caffeine	Antioxidant, anti-inflammatory, anti-hyperlipidemic.
33	*Ficusben galensis* Linn.	Banyan tree, Bargad	*Moraceae*	Leucopelargonidin,β-sitosterol, α-L-rhamnoside, leucocynidin 3-O-α-D-galactosylcellobioside, and β-glucoside	Dysentery, diarrhea, diabetes, leucorrhoea, menorrhagia, nervous disorders, tonic, astringent, hemostatic, antiseptic, anti-inflammatory, antioxidant, anticancer agent, and anti-arthritic
34	*Ammannia baccifera* Linn.	Acrid weed, Monarch red stem, tooth cup	*Lythraceae*	Sterols, glycosides, alkaloids, triterpenoids, and saponin	Hypothermia, urolithiasis, bacterial infections, seminal weakness, fever, flatulence, CNS depression, anti-inflammatory, and anti-arthritic
35	*Cedrus deodara*	Deodar, devadaru, cedar	*Pinaceae*	Alkaloids, flavonoids, glycosides, phenolic compounds, saponin, and proteins	Anti-inflammatory and anti-rheumatic
36	*Barringtonia racemose* Linn.	Powder-puff tree	*Lecythidaceae*	3, 3′-Dimethoxy ellagic acid, dihydromyticetin, gallic acid, bartogenic acid, and stigmasterol	Antimicrobial, antioxidant activity, anti-inflammatory activity, and anti-rheumatic

37	*Mangifera indica* Linn.	Anbah, Manga, and Aam	*Anacardiaceae*	Polyphenols, flavonoids, triterpenoids, mangiferin, isomangiferin, tannin, and derivatives of gallic acid	Antidiabetic, antioxidant, antifungal, antimicrobial, anti-inflammatory, antiviral, hepatoprotective, hypoglycemic, anti-allergic, and anticancer
38	*Tinospora cordifolia* Linn.	Guduchi	*Menispermaceae*	Tinosporine, tinosporaside, cordifolide, cordifol, heptacosanol, tinosporidine, columbin, and b-sitosterol	Immunity booster, antispasmodic, anti-inflammatory, and antipyretic agent
39	*Nyctanthes arbor tristis* Linn.	Coral jasmine	*Oleaceae*	Mannitol, b-amyrin, b-sitosterol, and nycthanic acid	Laxative, diuretic, diaphoretic, expel roundworm and threadworm, anti-inflammatory, and anti-arthritic
40	*Vitex negundo* Linn.	Huang Ping, Huang Ching, Man Ching	*Verbenaceae*	Polyphenolic compounds, terpenoids, glycosidic iridoids, and alkaloids	Angina, cold, cough and bacterial infections, limb pain, weakness and paralysis, expectorant, febrifuge, and tonic
41	*Cissampelos pareira* Linn.	Velvet leaf, Barbasco	*Menispermaceae*	Alkaloids, flavonoids, and saponins	Antibacterial, anti-inflammatory, anti-histaminic, antioxidant, antispasmodic, diuretic, hypotensive, muscle relaxant, uterine relaxant, antiseptic, aphrodisiac, analgesic, anti-hemorrhagic, cardiotonic, diaphoretic, expectorant, febrifuge, hepatoprotective, stimulant, tonic, dyspepsia, diarrhea, dropsy, cough, dysuria, dysentery, asthma, and heart diseases
42	*Justicia gendarussa* Linn.	Gandarusa, water willow	*Acanthaceae*	β-Sitosterol, β-sitosterol-b-D-glycoside and aromadendrin, vitexin, apigenin flavone glucoside	Anti-inflammatory and anti-arthritic
43	*Terminalia paniculata* Roxb.	Kindal, Kinjal	*Combretaceae*	Alkaloids, triterpenes, flavonoids, saponin, and tannins	Cough, bronchitis, cardiac debility, diabetes, wound, and skin disorders

The flowers of *Althaea officinalis* have been used since ages for relieving chronic pain and treatment of inflammatory diseases. This traditional remedy also inherits a vivid therapeutic indication like respiratory diseases, colitis, and joint pains. The extract of its flowers has anti-inflammatory potential and also reduces the permeability of blood capillaries by inhibiting the release of PGE from inflammatory tissue (Lee et al. 2004; Tirkey and Tiwari 2012).

The leaves of *A. officinalis* contain scopoletin, as one of the main constituents, which can recuperate the manifestations of RA by limiting the release of the pro-inflammatory cytokines PGE2, TNF-α, IL-1 b, and IL-6 and conversely by quelling the expression of COX-2 (Wilder 1999; Kleinau and Erlandsson 1991).

The survey of scientific literature reveals the activation of a transcription factor, called as nuclear factor (NF). This NF binds to the DNA factors that are existent on the promoter of specific genes; this binding leads to the expression of pro-inflammatory cytokines. The transcription factor RELA [v-rel avian reticuloendotheliosis viral oncogene homolog A] (p65) is a subfamily of NF-κB, present in the nucleus of human mast cell line. It is also known through studies that NF-κB is activated due to the phosphorylation and degradation of inhibitor of NF-κB, resulting in the nuclear migration of NF-κB binding to DNA, and consequently stimulates the expression of cytokine genes. Silencing of I-jB, a process of phosphorylation and degradation in the cytoplasm of human mast cell, carried out by scopoletin is pivotal for anti-inflammatory activity of this established natural remedy (Wilder 1988).

Similarly, scopoletin recuperates the histological architecture of arthritic joints. Moreover, it restricts the hyperplasic cells in synovial tissue and counters angiogenesis within the tissue. It manages to defend cell erosions and diminishes osteoclast mechanism in the bone and cartilage. Scopoletin stimulates the macrophages of synovial tissue to produce an abundant amount of vascular endothelial growth factor (VEGF), responsible for vascular permeability, into the joint cavity which binds to specific receptors on local endothelium that results in increased angiogenesis and migration (Paola 2008).

The disease pathogenesis of RA has been closely associated with the mismanaged countenance of VEGF. Thus, this finding creates the interest of many researchers towards the phenomenon of angiogenesis as a therapeutic approach for countering the accelerated rate of VEGF secretion and related growth factors for successful protection and treatment of RA. A high dose of scopoletin limits the excess secretion of VEGF, basic fibroblast growth factor (bFGF)-2, and IL-6 in the synovial tissues of animals which are known to causes arthritis. In a nutshell, it is clear that this remarkable natural component has the capability to reduce the symptoms and provide therapeutic relief in RA through alteration in angiogenesis and manage the normal vascular architecture mediated by inhibiting IL-6, VEGF, and FGF-2 overexpression (Cui-Ping and Xin 2014; Chen-Jian 2014).

Arctium lappa

Botanical name: *Arctium lappa* L.

Common name: Greater Burdock, Gobō, Edible Burdock, Lappa

Family: Asteraceae

Arctium are available in a variety of species and most of them are popular as folk therapy in the management of inflammatory disorders like RA and chronic inflammatory bowel disease. The secondary metabolites possessed by the plant specifically arctigenin (lignan compound) are the main constituents of *Arctium lappa* seeds responsible for the activity. In RA, inflammatory response is mediated by increased expression of VEGF and macrophages that releases inflammatory cytokines and nitric oxide. Scientific literature suggests the anti-inflammatory activity of arctigenin and its glycoside arctin via declining various interleukins like IL-1b, IL-6, IL-4, and IL-5 and TNF-α. This compound is also shown to inhibit the release of inducible NO synthase (i-NOS) that naturally alleviates the expression of NO in the inflamed tissue. In addition to that on a cellular level this compound arctigenin which is attributed as anti-inflammatory and anti-arthritic drug completely blocks the nuclear signaling pathway (NF-jB) and mitogen-activated protein kinase (MAPK) phosphorylation. Between the two, the major signaling pathway that receives attention as a therapeutic approach is MAPK as it increases the expression of all ranges of pro-inflammatory mediators. The a-isoform is important to the intracellular signaling pathway for the generation of TNF-α or IL-1b. It also regulates the expression of COX-2, the enzyme that regulates PGE2 in inflammation (Zhang 2014).

Arctigenin being the inhibitor of MAPK limits the synthesis and expression of TNF-α and IL-1b in monocytes and in synovial tissue of arthritic animals (Prashikanti 2014; Bhangale and Acharya 2014); same like that, the leaf of *A. minus* (Hill) Bernh shows anti-inflammatory potential depicted in animal model of carrageenan-induced paw edema (Baroroh et al. 2014).

Artemisia absinthium L.

Botanical name: *Artemisia absinthium* L.

Common name: Common wormwood plant

Family: Asteraceae

Since archaic age, the aerial part of *Artemisia absinthium* is well known of its medicinal properties against neuralgia, rheumatoid disorders, as well as inflammatory disease in Persian medicines. Scoparone, being the active secondary metabolite of *A. capillaris Thunb*., revealed to amputate several inflammatory cascades that are produced by macrophages significantly in IFN-c- and LPS-stimulated RAW 264.7 cell. The mechanism includes the direct inhibition of the release of NO and pro-inflammatory compound PGE-2 (Mamatha et al. 2014).

The reduction in the level of nitric oxide is due to the ability of active moiety scoparone to directly hinder the synthesis and release of adjuvant nitric oxide synthase and confine its expression on the inflammatory site. Moreover, scoparone also limits the availability of COX-2, which is responsible for the generation of many cytokines and inflammatory mediators (Mamatha et al. 2014).

Cellular expression of COX-2 and synthesis of various cytokines and inflammatory mediators, such as TNF-α, IL-1b, IL-6, and IL-8, in rheumatoid disorders are governed by nuclear signaling pathway which is again checked by the active constituent of the plant significantly (Kumbhar 2014).

The aerial part of the plants *A. sylvatica* Maxim. and *A. douglasiana* Besser. has also been reported to reduce the nuclear signaling pathway (NF-jB), which were accountable to synthesize COX and cytokines. Thus they play a significant role in the improvement of RA symptoms (Mamatha et al. 2014; Ijeoma et al. 2014).

Phytochemical screening of the plants reveals the presence of some active moieties which are tremendously beneficial agents against inflammatory disorders both in acute and chronic conditions like arthritis, chronic bowel disease, and RA. Secondary metabolites with anti-inflammatory potential include artemisolide, 3-methoxytanapartholide, deacetyllaurenobiolide, moxartenolide, arteminolides, dehydroleucodine, scopoletin, scopolin, and esculetin (Mamatha et al. 2014; Karnati 2013; Lu-Ping and Hong 2013).

Senna

Botanical name: *Cassia angustifolia M. Vahl*

Common name: Seena, Seenay, Indian Seena, Tinnervelly Senna

Family: Fabaceae

Cassia angustifolia is one of the important traditional remedies used for clinical symptoms of RA. Senna constitutes anthraquinones including dianthrone glycosides, sennosides A and B (rhein dianthrones), and sennosides C and D (rhein aloeemodin heterodianthrones). There is no scientific evidence on the efficacy of this species in managing rheumatoid disorders. However, the leaf of *C. alata* L. improves RA symptoms, including swelling, and cartilage degradation, and inhibits leucocyte infiltration into synovial fluid of rat knee joint (Lewis and Levy 2011).

Citrus medica L.

Botanical name: *Citrus medica* L.

Common name: Citron

Family: Rutaceae

Citrus medica commonly known as citron is cultivated worldwide, and the peel, leaves, and root have been used in folk medicine of Asian nations particularly India

and Iran. In traditional medicine, this natural drug is suggested to be useful for the treatment of rheumatism, hepatitis, and arthritis. It has been confirmed that the fruits possess antioxidant and anti-inflammatory activity. The peels of *C. medica* and fruits of *C. unshiu* (Swingle) Marcow suppress inflammatory response in rheumatoid condition. These natural remedies execute anti-inflammatory activity in terms of suppressing inflammatory cytokines such as TNF-a, PGE2, IL-1 b, as well as IL-6, which regulate different vascular and intercellular cell adhesion agents, leading to the recruitment of leucocytes to sites of inflammation.

Citrus fruits also inhibit the release of NO via suppressing the expression of i-NOS enzyme. Limonene as one of the active agents of *C. medica* is effective in inhibiting the production of NO and decreases the expression of i-NOS and COX-2 proteins. It also decreases the expression of TNF-a, IL-1 b, and IL-6 (Bosca 2005; Kim 2013; Murakami 2000).

Limonene and γ-terpinene are the major phytoconstituents obtained by hydrodistillation and cold-pressing (CP), whereas citropten is isolated by supercritical carbon dioxide extraction (Menichini et al. 2011).

The inhibitory effect of this medicinal plant on pro-inflammatory cytokines and mediators is mediated by suppressing the nuclear signaling pathway (Kim 2013). MAPK pathway is considered as one of the most broadly investigated cellular signal transduction pathways regulating inflammatory process in arthritic condition. In vitro investigations have shown that this transduction pathway possesses a crucial role in modulating i-NOS and COX-2 enzyme expression, as well as stimulating the production of RA-associated cytokines in macrophages and synovial cells. In addition, TNF-α, IL-1, and IL-6 are the major inducers of extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinase (JNK), and p-38 MAPK activation in cultured human synovial cells. Citrus constituents possess therapeutic effects on RA-associated inflammation via reducing the phosphorylation of MAPK subsets, JNK, and ERK (Kim 2013; Schett 2000).

Clematis ochroleuca

Botanical name: *Clematis ochroleuca* A.

Common name: Curly heads

Family: Ranunculaceae

Clematis ochroleuca is a very popular traditional drug among various tribes worldwide that is being widely used for symptomatic relief in various rheumatic disorders. Saponin-enriched extracts from the root of *C. chinensis Osbeck* comprises a significant therapeutic potential for LPS-stimulated acute inflammatory arthritis in rabbit. This natural herb can markedly enhance the levels of matrix collagen II in the immune histochemical assay in various in vivo screening models in animals. In the similar manner, the saponin fraction comprises prophylactic effects on the arthritis induced in animals by monosodium iodoacetate. Macrophages present in the synovial tissue stimulate the matrix metalloproteinase-3 (MMP)-3-

associated damage of cartilage. The saponin compounds displayed inhibitory effects against overexpression of MMP-3 and MMP-13 stimulated by LPS, thus establishing its beneficent activity against the joint degradation associated with inflammation. Wen et al. proved that liposome cream from this medicinal plant relieved complications related to the arthritic condition and also improved the levels of IL-1b and TNF-α in the synovial fluid of rabbits induced with arthritic condition and stimulated by intra-articular injections of papain. The therapeutic potential of this drug has been confirmed by positron-emission tomography (PET) imaging in animal model of RA. It significantly diminishes 2,18-F-fluoro-2-deoxy-d-glucose (18-F-FDG) acceptance in terms of standard uptake value assessed by PET in the animal with arthritic joints. The diminution in the levels of PGE2 in primary human chondrocytes occurs due to cessation of COX-2 expression, and therefore it is the major contributor in anti-arthritic potential (Park 2006; Hsieh 2011; Wen 2008).

The roots of *C. mandshurica Rupr.* have significant anti-inflammatory activity. The roots markedly reduce LPS- and IFN-c-stimulated PGE2 and NO production in peritoneal macrophages of mouse model and lessen IL-2 and IFN-c in Con A-activated splenocytes (Park 2006; Hsieh 2011). Moreover, triterpene saponins like C-glycosylflavon and 40-O-coumaroyl-isovi-texine are impressive anti-arthritic agents of Clematis spp. (Yesilada and Kupeli 2007; Peng 2012).

Colchicum autumnale

Botanical name: *Colchicum autumnale* L.

Common name: Autumn Crocus, Meadow Saffron, or Naked Lady

Family: Colchicaceae

The corn of *Colchicum autumnale* is one the most significant and efficacious drugs occurring in the nature with ancient use as an anti-inflammatory agent for several inflammatory disorders like hemorrhoid, gout, hepatitis, and rheumatoid arthritis. Baker et al. identified the astonishing potential of the hydroalcoholic extract obtained from the corm of *C. luteum* in treating arthritis induced by formaldehyde in animal model. Baker also reported its superiority to indomethacin in mitigating the joint swelling during the period of observation.

Similarly, the extract obtained from the corm also exhibited convincing therapeutic effect in treating the arthritis induced by complete Freund's adjuvant (CFA). CFA-induced arthritis is strikingly similar to human RA in respect to pathological and immunological features. The mechanism of action involved in this anti-arthritic activity is due to the inhibition of the production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1b as well as the expression ofTNF-R1 in the synovium. Many scientific studies have demonstrated the involvement of TNF-R1 in pathophysiological effects of TNF-α which consequently leads to arthritic conditions (Nair 2011, 2012).

Colchicine, the active phytochemical constituent found in *C. luteum*, has been reported to suppress pro-inflammatory cells like macrophages by interacting with

cellular tubulin protein, validating that this medicinal plant obviously recuperates the rat paw edema symptoms including the formation of granuloma mediated by suppressing the inflammatory cytokines TNF-α, IL-6, and IL-1b in inflamed tissues (Nair 2011, 2012).

Cuscuta epithymum

Botanical name: *Cuscuta epithymum* L.
Common name: Dodder
Family: Convolvulaceae

Cuscuta epithymum is one of the traditionally used medicinal plants, which has been commonly used by the physicians of Persia for a wide range of diseases. Methanolic extract obtained from the seeds of *C. campestris* yuncker, when subjected to in vitro assessment, was found to lower the nitrite production in activated macrophages. Quercetin is one of the major active constituents present in the seeds of *C. campestris*. It potentially contributes to the anti-inflammatory action of this plant. Lee et al. observed in their study that the processed seeds of *C. campestris* have higher concentration of quercetin which subsequently enhances the inhibition of inflammatory reaction in RAW264.7 cells (Lee 2011). Similarly, *C. reflexa* Roxb. also inhibits the binding of NF-κBto to its complementary motif and subsequent initiation of the transcription process, which consequently leads to the regulation of several inflammatory signaling pathways. It has also been established that down-regulation of cytokines, COX-2 and TNF-α, involved in inflammatory arthritis, is caused by the suppression of NF-κB expression which is mediated by this natural agent (Suresh 2011; Lee 2011).

Asafoetida

Botanical name: *Ferula asafoetida* L.
Common name: Asafoetida, Hing
Family: Apiaceae

The oleo-gum resin obtained from *F. asafoetida* and *F. persica* is one of the important remedies of traditional Persian medicine, which has been used for several disorders particularly inflammatory illnesses. According to a research, the active phytoconstituents, ferutinin and teferdin, play a key role in alleviating the inflammatory response (Geroushi 2010).

Ferutinin is a compound with phytoestrogen, present in abundance in Ferula genus. It has significant osteoprotective activity. It has been found that daily administration of ferutinin for 2 consecutive months prevents osteoporosis caused by the deficiency of estrogen in ovariectomized rats. The histomorphometrical investigation of trabecular and cortical bone from lumbar vertebrae and femur confirmed that

this natural molecule is a better anti-osteoporotic agent than estradiol benzoate on bony mass (Palumbo 2009).

The molecular compounds, methyl-3,5-O-dicaffeoylquinate and 3,5-O-dicaffeoylquinic acid obtained from the flowers of *F. lutea* Poir, inhibit 5-LOX enzyme, which subsequently catalyzes the deoxygenation of polyunsaturated fatty acids to produce hydroperoxyeicosatetraenoic acids and hydroxyleicosatetraenoic acids (Znati 2014b, pp 2733–2747; Znati 2014a, pp 16959–16975). Thus, the precursors of inflammatory responses are inhibited, which ultimately placates the diseased condition.

The crude extract of *F. persica* and other isolated active ingredients such as persicasulfide and umbelliprenin, inhibit the MMP-2 and MMP-9, a family of endopeptidase which regulates the obliteration of extracellular matrix and is a participant of inflammatory arthritis (Shahverdi 2006).

Black Caraway

Botanical name: *Nigella sativa* L.

Common name: Kalonji, Black caraway

Family: Ranunculaceae

The black seeds of *Nigella sativa* are commonly called as black caraway or cumin. It grows in south Asia and south-west Asia, where the seeds have been traditionally used by the ancient physicians for remedial therapy of several diseases. Gheita and Kenawy et al. reported that the administration of oil of *N. sativa* alleviated the symptoms of RA including the inflammation of joints and disease activity score of the patients (Gheita and Kenawy 2012).

It has also been found in other research studies that the extracts obtained from the seeds of *N. sativa* resolved the ear and paw edema in animal models (Ghannadi 2005).

Thymoquinone is the major active constituent obtained from *N. sativa*. It is a bioflavonoid with potential anti-inflammatory, antioxidant, neuroprotective, and anticancer activity. Several in vivo studies have demonstrated the ability of thymoquinone in the treatment of inflammatory diseases; anti-arthritic effects were observed on the administration of thymoquinone for consecutive 21 days in Wistar strain rats with collagen-induced arthritis. Thymoquinone produces anti-arthritic effects by reducing articular elastase and myeloperoxidase (MPO) activity.

In the arthritic condition of joints, MPO is released from the stimulated granulocytes within the inflamed region and is associated with the activity and accumulation of leucocytes. Thymoquinone is also responsible for hindering the expression of pro-inflammatory cytokines including IL-1b, TNF-α, IL-10, IFN-c, PGE-2, and IL-6; these factors are dominantly expressed in the rheumatoid joint and thus play a key role in the pathogenesis of RA. Moreover, *Nigella sativa* also has a significant property of repairing the cellular impairment caused due to the antioxidants by increasing the activity of antioxidant enzymes as well as by impeding the products

of lipid peroxidation and NO (Laughton 1991; Ghannadi 2005; Umar 2012; Vaillancourt 2011).

Rhubarb Root

Botanical name: *Rheum palmatum* L.

Common name: Chinese rhubarb, ornamental rhubarb, Turkish rhubarb, Turkey rhubarb, Indian rhubarb, Russian rhubarb, or rhubarb root

Family: Polygonaceae

It has been found during several animal studies that the roots of *R. palmatum* exhibit sturdy anti-inflammatory potential. Emodin (1,3,8-trihydroxy-6-methyl-anthraquinone) is a derivative of anthraquinone obtained from the rhizomes and roots of *R. palmatum*; it has very significant potential to inhibit the overexpression of inflammatory factors such as TNF-α, iNOS, and IL-10 as well as NF-κB and p65.

Emodin can reduce the proliferation of RA synoviocytes significantly, which are revoked by IL-1b as well as LPS under hypoxic condition. Hypoxic conditions elucidate transcription factor, hypoxia-inducible factor 1 (HIF-1), and also VEGF. Many research studies have reported the elevation of VEGF in the RA synovial fluid, and it has been found to have a key role in the angiogenesis of RA.

Strong anti-inflammatory activity in roots of *R. palmatum* has been investigated and reported in preclinical studies. Emodin has the potential ability to seize the expression of inflammatory agents like TNF-α, iNOS, and IL-10 as well as NF-jB p65. Moreover, this compound also inhibits the abundant production of RA synoviocytes, which are persuaded by IL-1 b and LPS. Hypoxia is demarcated as a pathological condition where tissue is been deprived of oxygen that results in the stimulating transcription factor hypoxia-inducible factor 1 (HIF-1) and also VEGF. According to the available literature source, there is stimulation and abundant availability seen in the RA synovial fluid. They also demonstrate that VEGF has a specific role in the angiogenesis of rheumatoid joints. Emodin potentially muffle the RA due to hypoxic condition through declining the overexpression of HIF-1 and VEGF. Likewise, this compound suppresses the availability of pro-inflammatory cytokines like TNF-a, IL-6, IL-8, and PGE2, which is arbitrated by inhibiting the activity of COX-2 in the rheumatoid condition, which clearly demonstrates the therapeutic action on RA progress (Li 2005; Ha 2011).

Literature evidences also reveal that MMPs discharged from synoviocytes are responsible for the joint obliteration in rheumatoid pathogenesis. Involvement with both IL-1 band LPS has obviously accelerated the over-regulation and overexpression of MP-1 and MMP-13 in synoviocytes; fortunately it is suppressed by emodin significantly. Scientists adhered and declared to the fact that the intracellular signaling pathways, p38 MAPK and NF-jB, are the main participants involved in the transcriptional activation of MMP expression. However, the potential of emodin in reducing MMP-1 and MMP-13 is distinctive to MAPK and NF- jB pathways (Li 2005; Ha 2011).

Histone deacetylases (HDACs) comprehend a class of enzymes which have modulatory effect on inflammatory cascade and MMP function in synoviocytes. It has been established that the mitigation of HDAC activity—particularly HDAC1—is actually the main contrivance of emodin in managing IL-1b- and LPS-induced RA in oxygen-deprived situation (Li 2005; Ha 2011).

China Root

Botanical name: *Smilax china* L. and *S. glabra* Roxb.

Common name: China root

Family: Smilacaceae

The rhizome of *S. china* and *S. glabra* enjoys quite large antiquity and fame in Persian medicines for being used as an inflammatory agent; along with that it serves better as a gastric tonic, and for gout, hemorrhoid, as well as joint disorders. Several pharmacological studies have also depicted the anti-inflammatory, anticancer, and anti-nociceptive activity of this plant. Chinese medicine reveals the traditional use of these plants of having remedy for different therapeutic effects, particularly chronic pelvic inflammation. In inflammatory models, the animals used demonstrated and established the anti-inflammatory potential of this natural drug, which is regulated by decreasing the abundant expression of pro-inflammatory mediators such as TNF-α, NO, and IL-2. In addition, modulation of nuclear signaling NF-jB is the possible mechanism revealed off its anti-arthritic effect. T lymphocyte has a distinct role in immunological events of pathological processes in RA. In vitro studies have revealed that this remedy can significantly attenuate the proliferation of T lymphocyte (Jiang and Xu 2003; Galhena 2012).

Moreover, *S. glabra* has depicted various progresses in RA symptoms by checking and reducing the migration of activated macrophages in vivo (Galhena 2012; Jiang and Xu 2003; Khan 2009).

A steroidal saponin called seiboldogenin is obtained from ethyl acetate fraction of the *S. china* and *S. glabra* crude extract. Literature established that seiboldogenin possesses modulatory influence on biphasic inflammatory reactions including early phase of the inflammation via attenuating the release of histamine and serotonin as well as later phase of inflammatory response interceded by activity of kinin-like agents, proteases, and PGs, in animal models (Akkol 2008).

Another evidence that exhibits and confirms the ability of this drug to improve inflammatory condition is that it can inhibit the LOX which is one of the major factors for inflammatory responses. Inhibitory potential of this molecule on LOX indicates its ability to manage inflammatory conditions as RA (Jiang and Xu 2003; Khan 2009).

Nux Vomica

Botanical name: *Strychnos nux-vomica* L.

Common name: Strychnine tree, nux vomica, poison nut, semen strychnos, and quaker buttons

Family: Loganiaceae

One of the natural drugs, which have traditionally been used for inflammatory disorders, especially rheumatoid condition, is *S. nux-vomica*. In traditional medicine, this plant is assumed to have palliative effect on rheumatic pain. Experimental investigations have shown that the seeds of *S. nux-vomica* possess anti-inflammatory activity in terms of suppressing PGE2 and decreasing vascular permeability. Brucine and brucine N-oxide are two natural alkaloids, which are isolated from the seeds of *S. nux-vomica* (Yin 2003) (Chaurasia 2009).

Many experimental models tested the analgesic activity of the alkaloidal moiety of the plant like hot plate and writhing test; the alkaloids of *S. nux-vomica* have been found to be shielding on thermic and chemical stimuli. Their analgesic activity has been long lasting when compared to pethidine. Similarly, these alkaloids have revealed the inhibitory effect on carrageenan-induced rat paw edema (Oliva 2002).

5-Hydroxytryptamine (5-HT) is the neurotransmitter expressed in large amount in the excited sensory neurons at the inflammatory sites. It is also an initiator for the pain sensation in arthritic joints. The compounds brucine and brucine N-oxide work by decreasing the levels of 6-keto-PGF1a. They have been shown to significantly reduce the levels of 5-HT in CFA-induced arthritis rat's blood plasma and had elevated 5-hydroxytryindole-3-acetic acid, the main metabolite of degradation of 5-HT by MAO, clearly suggesting the role of MAO activity in regulating 5-HT pathway by these natural agents (Oliva 2002; Yin 2003). Brucine and brucine N-oxide seize the synthesis and release of PGE-2 at the site of inflammation and tend to suppress the levels of 6-keto-PGF1a in blood plasma. It does not interfere with the activity of thromboxane-B2 so the level of thromboxane is found to be same. This evidence suggests that these compounds share the same mechanism of action as NAIDS (Yin 2003).

Astragalus arbusculinus Bornm, Gauba (Fabaceae), *Convolvulus arvensis* L. (Convolvulaceae), *Dolichos lablab* L. (Fabaceae), *Dorema ammoniacum* D. Don. (Apiaceae), *Narcissus tazzeta* L. (Amaryllidaceae), *Nepeta menthoides* Boiss. & Buhse (Lamiaceae), *Opopanax chironium* W.D.J Koch (Apiaceae), and *Peganum harmala* L. (Nitrariaceae) have been recorded in various books for their immense use as anti-inflammatory drugs widely used traditionally. However, there are no scientific evidences recorded to clearly establish the mechanism of action of these drugs. Cellular and preclinical studies for scientific evaluation of the efficacy of these drugs are needed to be prerequisite.

Karanja

Botanical name: *Pongamia pinnata* (L.) Pierre
Common name: Karanja
Family: Fabaceae

The perennial plant is inhabitant to the regions of Southeast Asia and Australia widely used by the folks for the medicinal properties. The plant is of medium size, and glabrous, and has nitrogen-fixing ability (Sangwan et al. 2010). The parts possessing therapeutic values are mostly seeds, roots, flowers, bark, and leaves, which contain many phytochemicals like sterol and its derivatives; leaves and stem contain flavone and chalcone derivatives such as pongone, galbone, pongalabol, and pongagallon A and B (Yadav et al. 2011; Bansod et al. 2010). As a crude drug, whole of this plant is traditionally used in folk medicines to treat tumors, piles, skin diseases, wounds, and ulcers (Sangwan et al. 2010). To elaborate more on the molecular level, scientists evaluated the drug for its anti-ulcer, anti-diarrheal, antioxidant, anti-plasmodium, anti-hypoglycemic, antiviral, antibacterial, and anti-inflammatory activities, and anti-arthritic activity (Bansod et al. 2010; Yadav et al. 2011; Nadagouda et al. 2010).

Punarnava

Botanical name: *Boerhaavia diffusa* L.
Common name: Punarnava
Family: Nyctaginaceae

This creeping plant of nearly a height of 1 m has ascending weed. It is localized in many regions of the world including Australia, China, Egypt, Pakistan, Sudan, Sri Lanka, South Africa, the USA, and other countries of the Middle East (Awasthi and Verma 2006; Chaudhary and Dantu 2011; Agrawal et al. 2011). The plant grows in all seasons and leaves; seeds and root of the plant are widely used for various medicinal purposes (Chaudhary and Dantu 2011). Punarnava includes various phytochemical constituents including prominent ones like punarnavoside, boeravinone G, and boeravinone H (Chaudhary and Dantu 2011; Agrawal et al. 2011).

In the indigenous system of medicine like Ayurveda and Unani, roots of punarnava are used for the treatment of conditions like dyspepsia, jaundice, abdominal pain, splenomegaly, and stress. However, its roots are employed as blood purifier, tonic, expectorant, and carminative, and also have additional remedial action in lumbago and scabies (Awasthi and Verma 2006; Chaudhary and Dantu 2011). The alcoholic extract of the punarnava has shown several beneficial pharmacological actions like antibacterial, hypoglycemic, antiproliferative, anti-stress, anti-estrogenic, and immunomodulatory activity whereas the aqueous extract has been evaluated for its hepato-protective activity (Murti et al. 2010). Punarnava has also been identified as a scavenger of free radical and nitric oxide scavenging activity. Moreover, punarnava has potential anti-inflammatory activity and is therefore used in placating the inflammatory response of arthritic condition (Agrawal et al. 2011).

Haritaki

Botanical name: *Terminalia chebula* Retz.

Common name: Haritaki

Family: Combretaceae

Terminalia chebula, also known as Haritaki, is a medium to large deciduous tree with a height of 30 m approximately and is mainly found in the Indian subcontinent. Its fruits are used in different traditional medicines employed in the treatment of gastrointestinal disorders and inflammatory diseases and for the improvement of immunity (Maheshwar et al. 2010). The fruits of *Terminalia chebula* include tannins, alkaloids, flavonoids, terpenoids, steroids, carbohydrates, proteins, and saponins (Jayalakshmi et al. 2011). Few major phytoconstituents obtained are glycosides including the triterpenes arjunglucoside I, arjungenin, and chebulosides I and II. Haritaki is a part of popular Ayurvedic formulation "Triphala" which is a churna (powder form of preparation), and is used as a remedy for sinusitis, allergy, hemorrhoids, constipation, high level of cholesterol, and rheumatism and as a tonic for blood purification and malabsorption (Takauji et al. 2016). Haritaki has also been found to be an antibacterial and an anticonvulsant agent (Jayalakshmi et al. 2011; Maheshwar et al. 2010) besides being salubrious for arthritic condition in Freund's adjuvant-induced arthritis model (Nair et al. 2010).

Avocado

Botanical name: *Persea americana* Mill.

Common name: Avocado

Family: Lauraceae

Persea americana is commonly called as avocado, and is generally used as a fruit. It is a medium-sized perennial tree with an average height of 15–20 m. It is found globally including but not limited to Americas and Southeast Asia (Ding et al. 2007). The avocado fruit contains several chemical constituents; however the important ones are alkanols, terpenoids, glycosides, furan-containing derivatives, flavonoid, and coumarin. Also the chief constituents obtained from its leaves are isorhamnetin, luteolin, rutin, quercetin, and apigenin (Yasir et al. 2010). The aqueous extract of leaves of avocado tree has been found to possess antihypertensive activity (Ogochukwu et al. 2009), whereas the oils isolated from the seeds of avocado are used as a traditional treatment for skin eruptions. Additionally, the pharmacological responses of avocado also include vasorelaxation, analgesia, anti-inflammatory activity, anticonvulsant activity, antiviral activity, wound healing, hepatoprotective activity, antioxidant activity, and hypoglycemic activity (Yasir et al. 2010).

In different in vivo preclinical studies, it has been observed that the extracts obtained from avocado reduce cartilage breakdown by slowing down the degradation of collagen and hindering chondrocyte hyperplasia as well as its cloning.

Avocado decelerates the synthesis of proteases like MMP-13 in the core of the cartilages (Christelle et al. 2009). In a research report, avocado has been identified as an inhibitor of inducible nitric oxide synthase (i-NOS) enzyme and therefore it has found its use in the treatment of arthritis (Christelle et al. 2009).

Cat's Claw

Botanical name: *Uncaria tomentosa* Willd.
Common name: Cat's Claw, Una de Gato
Family: Rubiaceae

Uncaria tomentosa is commonly called as "cat's claw," due to the appearance of its trident thorns as the claw of a cat. It is primarily found in the tropical Amazon rain forest of Central and South America. It is usually 100 ft. tall and has elliptical leaves with smooth edge (Kuras et al. 2009). The barks and roots of cat's claw are used medicinally by the native people since ages for treating intestinal disorders, wounds, fever, ulcers, etc. (Arya et al. 2011; Sandoval et al. 2002; Williams 2001). The chemical constituents found in this plant are oxindole alkaloid, quinovic acid, glycosides, plant sterol, and catechins (Ibrahim et al. 2009). According to recent research studies, cat's claw has found remedial use in life-endangering diseases like cancer and diabetes. It is also known to possess anti-inflammatory activity besides being a healing agent for allergic conditions, acne, chronic fatigue, menstrual disorders, hormonal imbalance, viral infection, and even depression (Williams 2001).

The cat's claw is found to inhibit the cytokines like interleukins (IL-1β) and TNF-α and thus it elucidates its anti-inflammatory activity in arthritic condition. Additionally, it enhances the repair of cartilage by stimulating the production of insulin-like growth factor (Williams 2001).

Tayuya

Botanical name: *Cayaponia tayuya* (Vell.) Cogn.
Common name: Tayuya
Family: Cucurbitaceae

Cayaponia tayuya is commonly known as Tayuya and is a native of Brazil but it is also found in many parts of the Amazon rain forest (Das 2009). Long tuberous roots are the characteristic features of this plant (Aquila et al. 2009). Since ages, Tayuya has been traditionally used by the local people to relieve pain, epilepsy, backache, sciatic pain, headaches, gout, neuralgia, constipation, anemia, cholera, dyspepsia, stomach problems, and fatigue (Das 2009). Important phytochemicals found in the Tayuya are flavones, glycosides, cucurbitacin, and terpenes. Tayuya has been identified as a potential antioxidant, anti-inflammatory, analgesic, and anticancer agent (Das 2009; Aquila et al. 2009; Escandell et al. 2008).

One of the chemical constituents of Tayuya, dihydrocucurbitacin-β, has an effective role in the synthesis, release, and activity of pro-inflammatory enzymes like elastase, cyclooxygenase, and NO synthase and also in inflammatory mediators like IL-1β and TNF-α (Aquila et al. 2009; Escandell et al. 2008, 2007).

Chuchuhuasi

Botanical name: *Maytenus krukovii*
Common name: Chuchuhuasi
Family: Celastraceae

Maytenus krukovii is also known as Chuchuhuasi, and is generally found in the Amazon rain forest. The tree of Chuchuhuasi is generally 30 m long, and has large leaves, small white flowers, and reddish brown bark which is extremely tough. Its leaves, bark, and roots are used for medicinal purpose. Alcoholic extract of chuchuhuasi has been studied and was evidenced for its antimutagenic, antioxidant, antimicrobial, analgesic, anti-inflammatory, and hypotensive properties. Chuchuhuasi consists of various chemical constituents including triterpeneslike (dammarane and friedelane), flavonols, and sesquiterpene alkaloids (Salazar et al. 2008, 2006; Mota et al. 2008). The alkaloids, mayteine and maytansine, present in the chuchuhuasi are responsible for its anti-arthritic activity, since they inhibit the enzyme, protein kinase-C, which in turn is involved in the pathophysiology of arthritis (Bradshaw et al. 1993). Hence, it is also used in the suppression of inflammatory response due to arthritic condition.

Carrapicho

Botanical name: *Bidens pilosa* Linn.
Common name: Carrapicho
Family: Asteraceae

Bidens pilosa, aka Carrapicho, is a small erect herb which grows perennially. It is usually 1 m in height and is normally found in Amazon rain forest areas like South America, Africa, the Caribbean, and the Philippines. The major phytoconstituents of Carrapicho are phenyl propanoids, glucosides, polyacetylenes, diterpene flavonoids, and flavone glycoside. It also contains chalcone okanin and ethyl caffeate, a hydroxycinnamic acid. The extracts of Carrapicho plants are used in diabetes, hypertension, inflammation, immunosuppression, cancer, and malaria (Deba et al. 2008; Ashafa and Afolayan 2009; Chiang et al. 2004). It is also used as an agent to relieve arthritis because of its free radical scavenging and nitric oxide synthase inhibition activity (Chang et al. 2007).

Guaco

Botanical name: *Mikania guaco* Humb. & Bonpl.
Common name: Guaco
Family: Asteraceae
Mikania guaco, commonly called as Guaco, is found in South America, Brazil, Peru, Venezuela, and Colombia (Herida et al. 2005). Guaco leaves which are heart shaped and bright green in color are its characteristic feature, and are also used medicinally. It has beneficial use in the treatment of cough, asthma, pain, infections, and inflammation (Perez-Amador et al. 2010). The major phytochemicals present in the Guaco are steroids: campesterol, stigmasterol, and β-sitosterol, diterpenes; triterpenes: α-amyrin, β-amyrin, α-amyrinacetate, β-amyrin acetate, lupeol, lupeol acetate, and friedelin; coumarin: scopoletin; and flavonoids: quercetin and caffeoylquinic acid. Caffeoylquinic acid has been identified for its in vitro anti-inflammatory activity and is thus used as an anti-arthritic agent (Alves et al. 2009).

Shallaki

Biological Name: *Boswellia serrata* Linn.
Common Name: Shallaki/Indian Frankincense
Family: Burseraceae
Boswellia serrata is commonly known as Shallaki, and is a moderate to large branching tree distributed mainly in the regions of North Africa, Middle East, and India including the states of Bihar, Madhya Pradesh, and Gujarat. Gummy oleo-resins are obtained from the tree of *Boswellia serrata*, which contains β-boswellic acid. This acid has revealed anti-inflammatory, anti-atherosclerotic, and anti-arthritic activities apart from being an astringent, stimulant, expectorant, antiseptic, anti-atherosclerotic, analgesic, and sedative. It also helps in recovery of the integrity of the vessels surrounding the joints from spasm or impairment. Other constituents of the gummy oleo-resins are volatile oil, terpenoids, and sugars. Extracts of Shallaki have been found to decrease the degradation of glycosaminoglycan (Kokate et al. 2007; Sumantran et al. 2011).

Sarasaparilla

Botanical name: *Smilax officinalis* Griseb
Common name: Sarasaparilla
Family: Liliaceae
Smilax officinalis is commonly called as Sarasaparilla, and is native to South America, Jamaica, the Caribbean, Mexico, and West Indies. Roots of Sarasaparilla

are used for medicinal purpose. It has many chemical constituents like flavonol, steroidal glycoside, saponins, phenyl propanoids, and phenolic compounds (Sautour et al. 2006). There were two isomeric genin compounds extracted named as smilagenin and sarsasapogenin and a crystalline glycoside, sarsaponin. Its therapeutic indication includes diuresis, immunomodulation, antibacterial, and blood purification. Aqueous extract of sarasaparilla has been observed to possess anti-inflammatory, analgesic, and antipyretic activity (Sautour et al. 2006; Shao et al. 2007). It also diminishes the inflammation in Freund's adjuvant-induced arthritis in rats (Jiang and Xu 2003).

Aloe Plant

Biological Name: *Aloe barbadensis*

Common Name: Curacao aloe, Lily of the desert

Family: Liliaceae

Aloe barbadensis is mainly grown in Europe and various parts of India, including the Himalayan region. It has been one of the major plants used in the traditional medicine. The phytochemical ingredients of this plant include anthraquinone, anthracene, cinnamic acid, and anthranilic acid. Aloe vera is one of the most significant plants employed in the healing of skin ailments, namely bruises, insect stings, mild cuts, poison ivy, eczema, and itching and as a moisturizer and skin softener. It has also been observed to have antibacterial and antifungal properties apart from being a blood purifier, diuretic, uterine tonic, spermatogenic, laxative, purgative, antipyretic, and an anti-inflammatory agent. The anti-arthritic property of this plant is because of anthraquinone, a chemical constituent chiefly found in aloe vera. The extracts of aloe vera when applied topically reduce the inflammation in Freund's adjuvant-induced arthritis in Sprague-Dawley rats (Davis et al. 1986a, b; Joshph and Raj 2010).

Ashwagandha

Biological Name: *Withania somnifera* Linn.

Common Name: Winter cherry, withania root, and ashwagandha

Family: Solanaceae

Ashwagandha, commonly known as Indian ginseng, is one of the significant plants of ancient India. It is mainly found in the subtropical regions like Rajasthan, Punjab, Haryana, Uttar Pradesh, Gujarat, Maharashtra, and Madhya Pradesh. Roots of ashwagandha are used as drug in the Unani and Ayurveda system of medicine. The pharmacological activity is concealed in the phytochemical ingredients of its root; the major ones are alkaloids including withanine, pseudo-withanine, tropine, pseudo-tropine, somniferine, somnine, and steroidal lactones. Two acyl glucosides,

viz. sitoindoside-7 and sitoindoside-8, have been isolated from ashwagandha roots. This herbal drug is used as an aphrodisiac, liver tonic, and anti-inflammatory agent, and more recently it has been therapeutically engaged for asthma, ulcers, insomnia, and senile dementia. Through various clinical trials and preclinical research it has been observed that ashwagandha is also helpful in alleviating anxiety, neurological disorders, inflammation, and Parkinson's disease. In a preclinical study, Freund's adjuvant-induced arthritis rats were administered with powdered roots of ashwagandha, and significant improvement in the arthritic condition was noticed (Patwardhan et al. 2010; Mirjalili et al. 2009).

Black Pepper

Biological Name: *Piper nigrum* Linn.

Common Name: Pepper

Family: Piperaceae

Black pepper is one of the most common spices used all across the globe; it is indigenous and cultivated in southern part of India, being its major producer. Pepper farming is also very common in Indonesia, Brazil, Malaysia, and Sri Lanka. The phytochemical ingredients of pepper are alkaloids: piperine, piperidine, volatile oils, pungent resins, and starch. It has been used as stimulant, stomachic, and carminative and for aroma. It has been found that it promotes the secretion of gastric juices and also increases the bioavailability of a few drugs. In a preclinical setup, it has been noticed that piperine, isolated from pepper, when administered for a fortnight in a dose of 20 and 100 mg/kg everyday reduces the inflammation due to acute paw arthritis caused by carrageenan (Aggarwal and Paridhavi 2012).

Black Cohosh

Biological Name: *Actaea racemosa* Linn.

Common Name: Black snakeroot, Bugwort

Family: Ranunculaceae

Actaea racemosa is also known as bugwort or black cohosh. It is mainly found in eastern North America from extreme south of Ontario to central Georgia, and west to Missouri and Arkansas. Its roots and rhizomes have been used in traditional medicine since ages. The major chemical constituents isolated from black cohosh are acteina, cimigoside, steroidal terpenes, and 27-deoxyactein. Others include tannins, salicylic acid, and an isoflavone and formononetin. The drug has multipurpose use such as for arthritis, diarrhea, dieresis, dyspepsia, kidney problems, malaria, and snake bite and as an insect repellant. Black cohosh has been used for treating several female health problems, particularly menopause. It has also been observed that black cohosh reduces the inflammation caused due to arthritis (Mayo 1998; Johnson 2002).

Ginger

Biological Name: *Zingiber officinale*
Common Name: Ginger root
Family: Zingiberaceae

Ginger is one of the most commonly used spice ingredients in every household across the world. It originated from Southeast Asia, but is now cultivated in several regions like Caribbean island, Africa, Australia, Mauritius, Taiwan, and India. India alone contributes to more than 30% of the entire production of ginger around the world. Ginger comprises volatile oils, starch, fat, fibers, inorganic material, and residual moisture. Ginger oil includes monoterpene, hydrocarbons, sesquiterpene hydrocarbons, and oxygenated mono- and sesquiterpenes as its major constituents. It is used as stomachic, aromatic, carminative, stimulant, and flavoring agent. Ginger has been customized as various therapeutic agents such as antioxidant, anti-inflammatory, antiseptic, anti-carcinogenic, antifungal, and antimicrobial besides being used for day-to-day problems of nausea, vomiting, and diarrhea. Ginger extract is also beneficial in normalizing the arthritic joint pain. The key constituents are zingerone, shogaols and gingerols, and sesquiterpenoids, with (−) zingiberene and sesquiterpene lactones which are actually responsible for its anti-inflammatory response (Rehman et al. 2011; Zakeri et al. 2011; Feng et al. 2011).

Turmeric

Biological name: *Curcuma longa* Linn.
Common Name: Turmeric root, Indian saffron
Plant family: Zingiberaceae

Curcuma longa, commonly called as turmeric, is cultivated in India, China, Sri Lanka, Indonesia, Jamaica, and Peru. Turmeric has volatile oils, resins, starch, and curcuminoids specially curcumin as the chief components. Curcumin is a natural compound present in the rhizomes of the *Curcuma longa* plant and has significant anti-inflammatory activity (Kohli et al. 2005).

It is traditionally used as antispasmodic, antimicrobial, hepatoprotective, neuroprotective, and also an anticancer agent. It has been observed in a study that when lower dose of 4 mg/kg purified curcuminoids was administered to arthritic patients every day, the inflammatory responses in both acute as well as chronic phases of arthritis began to subside (Funk et al. 2006; Curcuma longa n.d.; Vaidya 2006).

Milkweed

Biological Name: *Calotropis procera* Linn.
Common name: Giant Swallow Wort, Milkweed
Family: Asclepiadaceae

Calotropis procera Linn. is commonly known as milkweed, and is a native of North Africa, tropical Africa, western Asia, South Asia, and Indochinese region. Different parts of milkweed have been found to possess anti-inflammatory activity along with analgesic, antioxidant, and antifungal activity. Its leaf comprises amyrins, sterols, ursolic acid, calotropin, and calotropagenin. The latex of this plant has specific anti-inflammatory potential in various models of animal study (Raghavendra and Mahadevan 2011). Its latex contains caoutchouc, calotropin, calotoxin, calactin, and uscharin, which were found to inhibit the inflammatory cell influx and edema formation induced by various inflammagens. In a study it was found that these factors also alleviate locomotion in experimentally induced monoarthritis in rats. Roots of milkweed, at doses of 180 mg/kg (methanol extract) and 200 mg/kg (other extracts), exhibit anti-inflammatory activity in cotton pellet-induced granuloma and carrageenan-induced paw edema model (Kumar and Roy 2007; Mossa et al. 1991; Babu and Karki 2011).

Green Tea

Biological Name: *Camellia sinensis* Linn.

Common Name: Green tea extract, Chinese tea

Family: Theaceae

Camellia sinensis, aka green tea, is a small evergreen shrub, mainly found in China and South and Southeast Asia but is now also grown in tropical and subtropical regions across the globe. The major phytoconstituents present in the green tea are polyphenols (catechins and flavonols), caffeine, and essential oils. Epigallocatechin (−) is the most significant catechin in the green tea, and is also a potent antioxidant. It was found in a study that the incidence of collagen-induced arthritis and its severity were reduced in the mice fed with green tea extract. It is reasoned that the observed results were possibly due to the inhibition of inflammatory mediators COX-2, IFN-γ, and TNF-α. In parallel to these mediators the levels of total immunoglobulins (IgG) and type II collagen-specific IgG were observed to be suppressed in the serum and arthritic joints of green tea-fed mice (Ahmed 2010; Akroum et al. 2009; Chopade et al. 2008).

Banyan Tree

Biological Name: *Ficus benghalensis* Linn.

Common name: Banyan tree or Bargad

Family: Moraceae

Banyan tree is one of the most sacred trees for the Hindus living in the Indian subcontinent. It is usually a large tree and is characterized by aerial prop roots. The major constituents of banyan tree are namely α-L-rhamnoside, leucocyanidin 3-O-

α-D galactosyl cellobioside, β-glucoside, pentatriacontan-5-one, and β-sitosterol α-D-glucose. The extracts obtained from banyan tree are found to be effective in the remedial therapy of dysentery, diarrhea, diabetes, leukorrhea, menorrhagia, and nervous disorders. The extracts obtained from its bark, leaves, and fruits are employed as tonic, astringent, hemostatic, antiseptic, anti-inflammatory, antioxidant, and anticancer agent. Leucopelargonidin, a glycoside extracted from the barks of banyan tree, has considerable antidiabetic activity. A study involving the evaluation of antirheumatic activity of the methanolic extract obtained from the bark of *Ficus benghalensis* was carried out using three different models of arthritis, namely formalin-induced arthritis model, agar-induced arthritis model, and Freund's complete adjuvant-induced arthritis model. The methanolic extract significantly reduced the edema especially on secondary immunological arthritis and produced graded inhibition of both phases of formalin-induced pain. The methanolic extract of banyan tree contains various phytochemicals like tannins, saponin, alkaloids, glycosides, flavonoids, and steroids, which may contribute to its antirheumatic activity as well as modify the autoimmune system (Manocha et al. 2011; Patil and Patil 2010; Joseph and Raj 2011).

Aginbuti

Biological Name: *Ammania baccifera* Linn.

Common name: Acrid weed, Monarch red stem, Tooth cup

Family: Lythraceae.

Aginbuti is found in the tropical regions of Asia, America, and Africa. It is annual and herbaceous, and can be spotted in marshes, swamps, rice fields, and water courses at low elevations throughout India. It has sterols, glycosides, alkaloids, triterpenoids, and saponin as its chief phytoconstituents. Aginbuti has been observed for remediation of conditions like hypothermia, urolithiasis, bacterial infections, seminal weakness, fever, flatulence, and CNS depression. The aerial parts of this herb possess significant anti-inflammatory and anti-arthritic activity in arthritic models of rats. Alcoholic extract of *Ammannia baccifera* inhibits inflammation in cotton pallet granuloma test and adjuvant arthritis models (Tripathy et al. 2010; Correa and Antonio 2012).

Deodar

Biological Name: *Cedrus deodara.*

Common name: Deodar, Devadaru, Cedar

Family: Pinaceae

Deodar cedar is mainly found in the western Himalayas in eastern Afghanistan, northern Pakistan, north-central India, southwest Tibet, and western Nepal. Deodar is an ancient tree and has been used since ages in Ayurvedic system of medicine for treating inflammations and RA (Kirtikar and Basu 1933). The key phytoconstituents present in this wooden tree are alkaloids, flavonoids, glycosides, phenolic compounds, saponin, and proteins. The extracts obtained from deodar constrained the phase of polyarthritis as evaluated by the paw edema on the injected limbs of rats with complete adjuvant-induced arthritis (Chandur et al. 2011; Singh et al. 2008).

Barringtonia

Biological Name: *Barringtonia racemosa* Linn.

Common Name: Powder-puff tree

Family: Lecythidaceae

Barringtonia racemose is commonly known as powder-puff tree and is found in coastal swamp forests and on the edges of estuaries in the countries like India, Sri Lanka, Malaysia, Thailand, Laos, southern China, northern Australia, Ryukyu Islands, and many Polynesian islands. The chemical constituents found in powder-puff tree are 3,3′-dimethoxy ellagic acid, dihydromyticetin, gallic acid, bartogenic acid, and stigmasterol. Powder-puff tree has different pharmacological activities like antimicrobial, antioxidant, and anti-inflammatory activities. It is used in alleviating the symptoms of RA and it is assumed that bartogenic acid is responsible for this activity. It has also been established through preclinical studies that bartogenic acid prevents against the primary and secondary arthritic lesions, and hematological disruptions induced by complete Freund's adjuvant (Sun et al. 2006; Behbahani et al. 2007; Patil et al. 2011).

Mango

Biological Name: *Mangifera indica* Linn.

Common name: Anbah, Manga and Aam

Plant family: Anacardiaceae

Mangifera indica is one of the most popular fruits in India and is one of the species of mango. It is now commercially cultivated throughout tropical and subtropical regions. The key phytoconstituents of mango are polyphenols, flavonoids, triterpenoids, mangiferin, isomangiferin, tannin, and the derivatives of gallic acid. High concentration of mangiferin is isolated from the young leaves, bark, and old leaves . Mangiferin has high antioxidant potential and various other pharmacological effects such as antidiabetic, antioxidant, antifungal, antimicrobial, anti-inflammatory, antiviral, hepatoprotective, hypoglycemic, anti-allergic, and anticancer activity. Its methanolic extract has anti-inflammatory activity as observed in a study, in which this extract plummeted the arthritic index, paw edema, and rheumatoid factor (Barbara et al. 2010; Garrido et al. 2001, 2004).

Tinospora gulancha

Biological Name: *Tinospora cordifolia* Linn.
Common name: Guduchi
Family: Menispermaceae

Tinospora cordifolia, also known as guduchi, is found mainly in the tropical Indian subcontinent and China. The major constituents present in guduchi are tinosporine, tinosporide, tinosporaside, cordifolide, cordifol, heptacosanol, clerodane-furano-diterpene, diterpenoid-furanolactone tinosporidine, columbin, and b-sitosterol. This plant has been used since ages for the improvement of immune system and body's resistance to infections. It has been identified as antispasmodic, anti-inflammatory, and antipyretic agent. It is also used in the remedial treatment of RA. In a study report, it has been inferred that the extract of guduchi at the dose of 100 mg/kg has been found to normalize the paw edema volume in a collagen-induced arthritic rat models (Paval et al. 2011; Singh et al. 2003).

Night Jasmine

Biological Name: *Nyctanthes arbor tristis* Linn.
Common name: Coral Jasmine
Plant family: Oleaceae

Nyctanthes arbor tristis, commonly known as night jasmine, is a small shrub found in southern Asia from northern Pakistan, Nepal, and northern Indian states. The major phyto-ingredients are mannitol, b-amyrin, b-sitosterol, and nycthanic acid. It has been used as laxative, diuretic, and diaphoretic. Coral jasmine has been employed to expel roundworm and threadworm in children. It also relieves cough and RA. Extracts obtained from the leaves of jasmine have been found to stall the acute inflammatory edema caused by different phlogistic agents like carrageenan, formalin, histamine, 5-hydroxytryptamine, and hyaluronidase in the hind paw of rats. It also works well in significantly restricting the acute and chronic phases of formaldehyde-induced arthritis. Night jasmine also obstructs the inflammatory response provoked by Freund's adjuvant-induced arthritis (Bhalerao et al. 2011; Sandhar et al. 2011).

Chaste Tree

Biological Name: *Vitex negundo* Linn.
Common name: Huang Ping, Huang Ching, Man Ching
Family: Verbenaceae

Vitex negundo is a large aromatic shrub native to south and Southeast Asia. Its key ingredients are polyphenolic compounds, terpenoids, glycosidic iridoids, and alkaloids. It has been found beneficial in the treatment of angina, cold, cough, and bacterial infections. A tincture prepared by pounding the fresh berries relieves limb pain, weakness, and paralysis. The root is used as an expectorant, febrifuge, and tonic. Petroleum-ether extract of chaste tree has been found to inhibit the paw edema in 4 h in a dose-dependent manner in carrageenan-induced hind paw edema (Vishwanathan and Basavaraju 2010; Subramanai et al. 2009).

Abuta

Biological Name: *Cissampelos pareira* Linn.

Common name: Velvet Leaf, Barbasco

Family: Menispermaceae

Cissampelos pareira is a flowering plant, commonly known as abuta or velvet leaf. It constitutes alkaloids, flavonoids, and saponins. It has dynamic use such as antibacterial, anti-inflammatory, anti-histaminic, antioxidant, antispasmodic, diuretic, hypotensive, muscle relaxant, uterine relaxant, antiseptic, aphrodisiac, analgesic, antihemorrhagic, cardiotonic, diaphoretic, expectorant, febrifuge, hepatoprotective, stimulant, and tonic. The extracts of roots of abuta are used as a remedy for dyspepsia, diarrhea, dropsy, cough, dysuria, dysentery, asthma, and heart diseases. The ethanolic extract of the roots of abuta has significant protective effect against complete Freund's adjuvant-induced arthritis in dose-dependent manner (Amresh et al. 2007; Singh et al. 2010; Arya et al. 2011).

Black Adusa

Biological Name: *Justicia gendarussa* Linn.

Common name: Gandarusa, Water willow

Family: Acanthaceae

Black adusa is an evergreen plant which grows in moist and shady places. It is supposed to be of Chinese origin; however it can be easily found across India, Sri Lanka, and Malaysia. The major phytoconstituents found in black adusa are alkaloids, flavonoids, carbohydrates, and tannins. The aerial parts of black adusa have been chemically investigated and it was found to contain β-sitosterol, β-sitosterol-b-D-glucoside, and aromadendrin. Vitexin, apigenin flavone glucoside, isolated from the ethanolic extract obtained from the leaves of *Justicia gendarussa* Linn., has significant remedial effect against inflammation and RA. This extract showed anti-arthritic activity in equivalence to that of aspirin against Freund's adjuvant-induced and collagen-induced arthritic rat models (Baccheti et al. 2011; Paval et al. 2009a, b).

Kindal Tree

Biological Name: *Terminalia paniculata* Roxb.
Common name: Kindal, Kinjal
Family: Combretaceae

Terminalia paniculata, aka Kindal tree, is a native of southwest India. It has been found to contain alkaloids, triterpenes, flavonoids, saponin, and tannins. Kindal tree has been used for curing cough, bronchitis, cardiac debility, diabetes, wound, and skin disorders. Antirheumatic activity of the aqueous extract obtained from the bark of Kindal tree was noted at the dose of 200 mg/kg in complete Freund's adjuvant-induced arthritis (Maridass 2010; Talwar et al. 2011).

Conclusion

Medicinal plants are a prime source of highly effective conventional drugs for the treatment of many forms of arthritis. From the above review it should be evident that there are many medicinal plants which exert anti-arthritic activity at a particular dose. This review makes an attempt to give scientific account of use of valuable medicinal plant extracts in arthritis.

Conclusion and Future Prospect

Large number of medicinal plants are in use in various areas of the world for the treatment and prevention of arthritis in various conventional ways for generations to generations. Use of phytoconstituents in the treatment of arthritis is increasing rapidly and promising. Scientific work with biologically bioactive chemical compounds along with their detailed anti-arthritic activity with specific mechanism of action on human body and clinical trials might be an interesting subject of extensive research on cancer. This chapter summarized short details of plants used in the treatment of arthritis with their possible mechanism of action.

References

ADAM Medical Encyclopedia (2011) U.S. National Library of Medicine
Agarwal V, Malavia AN (2005) Cytokine network and its manipulation in rheumatoid arthritis. J Indian Rheumatol Assoc 13:86–95
Aggarwal S, Paridhavi M (2012) Herbal drug technology, 2nd edn. Orient Blackswan Private Limited, New Delhi

Agrawal B, Das S, Pandey A (2011) Boerhaavia diffusa Linn.: a review on its phytochemical and pharmacological profile. Asian J Appl Sci 4(7):663–684
Ahmed S (2010) Green tea polyphenol epigallocatechin 3-gallate in arthritis: progress and promise. Arthritis Res Ther 12(2):1–9
Akkol EK (2008) In vivo anti-inflammatory and anti-nociceptive actions of some Lamium species. J Ethnopharmacol 19:166–172
Akroum S, Satta D, Lalaoui K (2009) Antimicrobial, antioxidant, cytotoxic activities and phytochemical screening of some Algerian plants. Eur J Sci Res 31(2):289–295
Alves CF, de Assis IP, Uber-Bucek E, Dal-Secco D, Napimoga MH (2009) Anti-inflammatory activity and possible mechanism of extract from Mikania laevigata in carrageenan-induced peritonitis. J Pharm Pharmacol 61:1097–1104
Amresh G, Singh PN, Rao CV (2007) Antinociceptive and antiarthritic activity of Cissampelos pareira roots. J Ethnopharmacol 111(3):531–536
Aquila S, Giner RM, Recio MC, Speqqzzini EP, Rios JL (2009) Anti-inflammatory activity of flavonoids from Cayaponia tayuya roots. J Ethnopharmacol 121:333–337
Arya V, Gupta VK, Kaur R (2011) A review on plants having anti-arthritic potential. Int J Pharm Sci Rev Res 7(2):131–136
Ashafa OT, Afolayan AJ (2009) Screening the root extracts from Bidens pilosa Linn. var. radiata (Asteraceae) for antimicrobial potentials. J Med Plants Res 3(8):568–572
Awasthi LP, Verma HN (2006) Boerhaavia diffusa - A wild herb with potent biological and antimicrobial properties. Asian Agric Hist 10(1):55–68
Babu SA, Karki SS (2011) Anti-inflammatory activity of various extracts of roots of Calotropis procera against different inflammation models. Int J Pharm Pharm Sci 3(3):191–194
Baccheti RK, Pandey DP, Joshi A, Rana V (2011) Chemical analysis of aerial parts of Justicia gendarussa. Int J Chem Tech Res 3(1):244–247
Bansod MS, Virendra GK, Somkuwar AD (2010) Evaluation of analgesics and anti-inflammatory activity of a poly-herbal formulation. Int J Pharm Tech Res 2(2):1520–1527
Barbara BG, Garrido G, Delgado R, Bosch F, Rabi MD (2010) A Mangifera indica L. extract could be used to treat neuropathic pain and implication of Mangiferin. Molecules 15(12):9035–9045
Baroroh HN, Iskandar S, Rachmani EPN, Hertiani T, Ikawati Z (2014) Jatropha curcas Linn. leaves exert anti-arthritic activity on adjuvant induced arthritis in rats. Universamedicina 33:3–10
Behbahani M, Ali AM, Muse R, Mohd NB (2007) Anti-oxidant and anti-inflammatory activities of leaves of Barringtonia racemosa. J Med Plants Res 1(5):95–102
Bhalerao AR, Desai SK, Serathia BR, Vartak KM, Doshi GM (2011) Anti-arthritic studies on Nyctanthes arbor tristis and Maharasnadi ghan. Sch Res Libr 3(4):101–110
Bhangale J, Acharya S (2014) Anti-arthritic activity of Cynodon dactylon L. Pers. Indian J Exp Biol 52:215–222
Bosca L (2005) Nitric oxide and cell viability in inflammatory cells: a role for NO in macrophage function and fate. Toxicology 208:249–258
Bradshaw D, Hill CH, Nixon JS, Wilkinson SE (1993) Therapeutic potential of protein kinase C inhibitors. Agents Actions 38:135–147
Chandur U, Shadhidhar S, Chandrasekar SB, Rao NM (2011) Studies of preliminary phytochemical and anti-arthritic activity of heart wood of Cedrus deodar (Roxb.). Res J Pharm, Biol Chem Sci 2(3):654–660
Chang SL, Chiang YM, Chang CL, Yeh HH, Shyur LF, Kuo YH, Yang WC (2007) Flavonoids, centaurein and centaureidin from Bidens pilosa, stimulate IFN-expression. J Ethnopharmacol 112:232–236
Chaudhary G, Dantu PK (2011) Morphological, phytochemical and pharmacological studies on Boerhaavia diffusa L. J Med Plants Res 5(11):2125–2130
Chaurasia S (2009) Anti-inflammatory and antioxidant activity of Strychnos nux-vomica Linn. Am Eurasian J Sustain Agric 3:244–252
Chen-Jian Z (2014) Therapeutic effects of standardized Vitex negundo Linn. seeds extract on complete Freund's adjuvant induced arthritis in rats. Phytomedicine 21:838–846

Chiang YM, Chuang DY, Wang SY, Kuo YH, Shyur LF (2004) Metabolite profiling and chemopreventive bioactivity of plant extracts from Bidens pilos. J Ethnopharmacol 95:409–419
Chopade VV, Phatak AA, Upaganlawar AB (2008) Green tea (Camellia sinensis), Chemistry, traditional, medicinal uses and its pharmacological activities - a review. Pharmacogn Rev 2(3):157–162
Christelle B, Johanne MP, Judith C, Philippe M, Georges BG, Caroline B, Jean-Pierrre P (2009) Protective effects of total fraction of avocado/soya bean unsaponifiables on the structural changes in experimental dog osteoarthritis: inhibition of nitric oxide synthase and matrix metalloproteinase-13. Arthritis Res Ther 11(2):1–9
Correa GM, Antonio FD (2012) Alcantara chemical constituents and biological activities of species of Justicia - a review. Rev Bras 1(3):2011
Cui-Ping J, Xin H (2014) Anti-rheumatoid arthritic activity of flavonoids from Daphne genkwa Linn. Phytomedicine 21:830–837
Curcuma longa (n.d.) Alternative medicine review monographs. pp 119–125
Das K (2009) Medicinal plants for snake bite treatment-future focus. Ethnobot Leaflet 13:508–521
Davis RH, Agnew PS, Shapiro E (1986a) Antiarthritic activity of anthraquinones found in aloe vera for podiatric medicine. J Am Podiatric Med Assoc 76(2):1–8
Davis RH, Agnew PS, Shapiro E (1986b) Anti arthritic activity of anthraquinones found in aloe for podiatric medicine. J Am Podiatric Med Assoc 76(2):61–66
Deba F, Xuan TD, Yasuda M, Tawata S (2008) Chemical composition and antioxidant, antibacterial and antifungal activities of the essential oils from Bidens pilosa Linn. Var. radiata. Food Control 19:346–352
Ding H, Chin YW, Kinghorn AD, D'Ambrosio SM (2007) Chemo preventive characteristics of avocado fruit. Semin Cancer Biol 17:386–394
Escandell JM, Recio MC, Manez S, Ginger RM, Cerda NM, Gil-Bensor RJL (2007) Dihydrocucurbitacin B inhibits delayed type hypersensitivity reactions by suppressing lymphocyte proliferation. J Pharmacol Expl Therapeut 322(3):1261–1268
Escandell JM, Keller P, Recio MC, Sazaqzuki T, Shirasawa S, Augenlicht L, Rios JL (2008) Activated kRas protects colon cancer cells from cucurbitacin-induced apoptosis: the role of p53 and p21. Biochem Pharmacol 76:198–207
Feng T, Su J, Ding ZH, Zheng YT, Li Y, Leng Y, Liu JK (2011) Chemical constituents and their bioactivities of "Tongling White Ginger" (Zingiber officinale). J Agric Food Chem 9(21):11690–11695
Firestein G (2003) Evolving concepts of rheumatoid arthritis. Nature 423:356–361
Funk JL, Oyarzo JN, Frye JB, Chen G, Lantz RC, Jolad SD (2006) Turmeric extracts containing curcuminoids prevents experimental rheumatoid arthritis. NIH Public Access 69(3):351–355
Galhena PB (2012) Anti-inflammatory activity is a possible mechanism by which the polyherbal formulation comprised of Nigella sativa (seeds), Hemidesmus indicus (root), and Smilax glabra (rhizome) mediates its anti hepatocarcinogenic effects. Evid Based Complement Alternat Med 2012:108626
Garrido G, Delporte B, Quintero JNSA (2001) Analgesic and anti-inflammatory effects of Mangifera indica L. extract (Vimang). Molecules 15(1):18–21
Garrido G, Lemus G, Lodeiro Q (2004) In vivo and in vitro anti-inflammatory activity of Mangifera indica L. extract. Molecules 50(2):143–149
Geroushi A (2010) Antinociceptive and anti-inflammatory activity of Ferula hermonis root oil in experimental animals. Lat Am J Pharm 29:1436–1439
Ghannadi A (2005) An investigation of the analgesic and anti-inflammatory effects of Nigella sativa seed polyphenols. J Med Food 8:488–493
Gheita T, Kenawy S (2012) Effectiveness of Nigella sativa oil in the management of rheumatoid arthritis patients: a placebo controlled study. Phytother Res 26:1246–1248
Ha MK (2011) Emodin inhibits proinflammatory responses and inactivates histone deacetylase 1 in hypoxic rheumatoid synoviocytes. Bio Pharm Bull 34:1432–1437

Herida RN, Salgado FF, Roncari FD, Moreira RRD (2005) Antidiarrhoeal effects of Mikania glomerata Spreng. (Asteraceae) leaf extracts in mice. Braz J Pharmacogn 15(3):205–208
Hsieh MS (2011) Using 18F-FDG microPET imaging to measure the inhibitory effects of Clematis chinensis Osbeck on the pro-inflammatory and degradative mediators associated with inflammatory arthritis. J Ethnopharmacol 136:511–517
Ibrahim KE, Al-Ashban RM, El-Sammani SA (2009) A study of the toxicity study of the Cat's claw herbal medicine. Res J Pharmacol 3(3):52–57
Ijeoma UR, Onyebuchi NC, Ositadimma US (2014) Evaluation of the anti-arthritic effect of Sterculia tragacantha (Lindl) leaf extract in rats. Am J Pharmacol Toxicol 9(2):107–113
Jayalakshmi B, Raveesha KA, Amruthesh KA (2011) Phytochemical investigations and antibacterial activity of some medicinal plants against pathogenic bacteria. J Appl Pharm Sci 1(5):124–128
Jiang J, Xu Q (2003) Immunomodulatory activity of the aqueous extract from rhizome of Smilax glabra in the later phase of adjuvant-induced arthritis in rats. J Ethnopharmacol 85(1):53–59
Johnson PL (2002) Pocket guide to herbal remedies. Blackwell Science Ltd., Oxford
Joseph B, Raj SJ (2011) An overview- Ficus benghalensis Linn. Int J Pharm Sci Rev Res 6(1):21–24
Joshph B, Raj SJ (2010) Pharmacognostic and pharmacology properties of Aloe vera. Int J Pharm Sci Rev Res 4(2):106–109
Karnati M (2013) Arthritic activity of root bark of Oroxylum indicum (L) vent against adjuvant induced arthritis. Pharm Res 5(2):121–128
Khan I (2009) Anti-inflammatory activities of Sieboldogenin from Smilax china Linn: experimental and computational studies. Ethnopharmacol Comm 121:175–177
Kim KN (2013) Anti-inflammatory effect of essential oil and its constituents from fingered citron (Citrus medica L. var sarcodactylis) through blocking JNK, ERK and NF-kB signalling pathways in LPS-activated RAW 2647 cells. Food Chem Toxicol 57:126–131
Kirtikar KR, Basu BD (1933) Indian medicinal plants, 2nd edn. Bishen Singh, New Delhi
Kleinau S, Erlandsson H (1991) Adjuvant oils induce arthritis in the DA rat I. Characterization of the disease and evidence for an immunological involvement. J Autoimmune 4:871–880
Kohli K, Ali J, Ansari MJ, Raheman Z (2005) Curcumin: a natural anti-inflammatory agent. Indian J Pharmacol 37(3):141–147
Kokate CK, Purohit AP, Gokhale SB (2007) Text book of pharmacognosy, 39th edn. Nirali Prakashan, Pune
Kore KJ, Shete RV (2011) Anti-arthritic activity of hydro alcoholic extract of Lawsonia inermis against adjuvant arthritis. Int J Drug Dev Res 3(4):217–224
Kumar VL, Roy S (2007) Calotropis procera latex extract affords protection against inflammation and oxidative stress in Freund's complete adjuvant-induced monoarthritis in rats. Mediat Inflamm 2007:47523
Kumbhar CM (2014) Prophylactic effect of hydroalcoholic extract of Colocasia esculenta Linn. leaves in CFA and formaldehyde induced arthritic rats. Asian J Pharm Res Dev 2(1):52–59
Kuras M, Radoslaw P, Julita N, Alicja Z, Krzysztof B, Justyna A, Krzysztof G (2009) Effect of alkaloid-free and alkaloid-rich preparations from Uncaria tomentosa bark on mitotic activity and chromosome morphology evaluated by Allium test. J Ethnopharmacol 121:140–147
Laughton MJ (1991) Inhibition of mammalian 5-lipoxygenase and cyclooxygenase by flavonoids and phenolic dietary additives relationship to antioxidant activity and to iron ion-reducing ability. Biochem Pharmacol 42:1673–1681
Lee MS (2011) Quercetin is increased in heat-processed Cuscuta campestris seeds, which enhances the seed's anti-inflammatory and anti-proliferative activities. Process Biochem 46:2248–2254
Lee J, Kim S, Kim T (2004) Anti-inflammatory effect of Bee venom on type II collagen-induced arthritis. Am J Chin Med 32(3):361–367
Lemke TL, Williams DA (2008) Foye's principles of medicinal chemistry, 6th edn. Lippincott Williams & Wilkins, Philadelphia
Lewis A, Levy A (2011) Anti-inflammatory activities of Cassia alata leaf extract in complete Freund's adjuvant arthritis in rats. West Indian Med J 60:615–621

Li HL (2005) Regulatory effects of emodin on NF-kB activation and inflammatory cytokine expression in RAW 2647 macrophages. Int J Mol Med 16:41–47
Lu-Ping Q, Hong Z (2013) Inhibitory effect of the root extract of Litsea cubeba (lourI) pers. on adjuvant arthritis in rat. J Ethnopharmacol 147:327–334
Maheshwar GH, Deshpande SV, Pramod HJ (2010) Anticonvulsant activity of fruits of Terminalia chebula Retz. against MES and PTZ induced seizures in rats. J Herb Med Toxicol 4(2):123–126
Majithia V, Geraci SA (2007) Rheumatoid arthritis: diagnosis and management. Am J Med 120(11):936–939
Mamatha GC, Prabhakar T, Madhuri V, Neelima T, Venkatanagaraju E, Chandrasekar SB (2014) Antiarthritic activity of euphorbia thymifolia Linn. World J Pharm Pharm Sci 3(2):1323–1331
Manocha N, Samanta KC, Sharma V (2011) Evaluation of anti-rheumatic activity of extract of stem bark of Ficus benghalensis. J Global Pharma Technol 3(3):31–37
Maridass M (2010) Survey of phytochemical diversity of secondary metabolism in selected wild medicinal plants. Ethnobot Leaflets 1(4):616–625
Mayo JL (1998) Facog Black Cohosh and Chaste berry: herbs valued by women for centuries. Clin Nutr Insights 6(15):1–3
Menichini F, Tundis R, Bonesi M, de Cindio B, Loizzo MR, Conforti F, Statti GA, Menabeni R, Bettini R (2011) Chemical composition and bioactivity of Citrus medica L. cv. Diamante essential oil obtained by hydrodistillation, cold-pressing and supercritical carbon dioxide extraction. Nat Prod Res 25(8):789–799
Mirjalili MH, Moyano E, Bonfill M, Cusido RM, Palajon J (2009) Steroidal Lactones from Withania Somnifera, an ancient plant for novel medicines. Molecules 14:2373–2393
Mossa JS, Tariq M, Mohsin A, Ageel AM, Yahya AI, Said AI, Rafatullah S (1991) Pharmacological studies on aerial parts of Calotropis procera. Am J Chin Med XIX(3–4):223–231
Mota KS, Pita J, Estevam E, Medeiros V, Tavares J, Agra M, Batist L (2008) Evaluation of the toxicity and antiulcerogenic activity of the ethanol extract of Maytenus obtusifolia Mart. leaves. Braz J Pharmac 18(3):441–446
Murakami A (2000) Inhibitory effect of citrus nobiletin on phorbol ester-induced skin inflammation, oxidative stress and tumor promotion in mice. Cancer Res 60:5059–5066
Murti K, Mayank A, Panchal VL (2010) Pharmacological properties of Boerhaavia diffusa - a review. Int J Pharm Sci Rev Res 5(2):107–110
Nadagouda SG, Karigar AA, Sikarwar MS, Geetanjali SS (2010) Anti-inflammatory activity of Pongamia pinnata stem bark in rats. J Pharm Res 3(4):828–830
Nair V (2011) Evaluation of the disease modifying activity of Colchicum luteum Baker in experimental arthritis. J Ethnopharmacol 133:303–307
Nair V (2012) Investigation into the anti-inflammatory and anti-granuloma activity of Cochicum luteum Baker in experimental models. Inflammation 35:881–888
Nair V, Singh S, Gupta YK (2010) Anti-arthritic and disease modifying activity of Terminalia chebula Retz. experimental models. J Pharm Pharmacol 62(12):1801–1806
Ogochukwu NA, Raymond IO, Stephen O (2009) Effect of the aqueous seed extract of Persea Americana Mill. (Lauraceae) on the blood pressure of Sprague-Dawley rats. Afr J Pharm Pharmacol 3(10):485–490
Oliva P (2002) The anti-nociceptive effect of tramadol in the formalin test is mediated by the serotonergic component. Eur J Pharmacol 445:179–185
Palumbo C (2009) Influence of fertinin on bone metabolism in ovariectomized rats I: role in preventing osteoporosis. J Bone Miner Metab 27:538–545
Paola RD (2008) Autoimmunity of animal model of arthritis. Autoimmun Rev 8:73–75
Park EK (2006) Anti-inflammatory effects of an ethanolic extract from Clematis mandshurica Rupr. J Ethnopharmacol 108:142–147
Patil VV, Patil VR (2010) Ficus benghalensis Linn. - an overview. Int J Pharm Bio Sci 2:1–11
Patil KR, Patil CR, Jadhav RB, Mahajan VK, Raosaheb P, Gaikwad PS (2011) Anti-arthritic activity of bartogenic acid isolated from fruits of Barringtonia racemosa Roxb. (Lecythidaceae). Evid Based Complement Alternat Med 2011:785245

Patwardhan SK, Bodas KS, Gundewar SS (2010) Coping with arthritis using safer herbal options. Int J Pharm Pharm Sci 2(1):6–7

Paval J, Kaitheri SK, Potu BK, Govindan S, Kumar RS (2009a) Anti-arthritic potential of the plant Justicia gendarussa Burm F. Clinics 64(4):357–362

Paval J, Kaitheri SK, Potu BK, Govindan S, Kumar RS, Narayanan SN, Moorkoth S (2009b) Comparing the anti-arthritic activities of the plants Justicia gendarussa Burm F. and Withania somnifera Linn. Int J Green Pharm 3(4):281–284

Paval J, Kaitheri SK, Kumar A, Govindan S, Mohammed CA, Kumar RS (2011) Anti-arthritic activity of the plant Tinospora cordifolia Willd. J Herb Med Toxicol 5(1):11–16

Peng C (2012) Anti-inflammatory effects of Clematis chinensis Osbeck extract (AR-6) may be associated with NF-kB, TNF-a and COX-2 in collagen induced arthritis in rat. Rheumatol Int 32:3119–3125

Perez-Amador MC, Ocotero BR, Jimenez FG (2010) Phytochemical and pharmacological studies on Mikania micrantha H.B.K. (Asteraceae). Int J Exp Bot 79:77–80

Prashikanti G (2014) Anti arthritic activity of ethanolic extract from the leaves of commiphora caudata Linn in complete Freund's adjuvant induced arthritis. Niger J Exp Clin Biosci 2(1):42–48

Raghavendra R, Mahadevan GD (2011) In vitro antimicrobial activity of various plant latex against resistant human pathogens. Int J Pharm Pharm Sci 3(4):70–72

Rehman R, Akram M, Akhtar N, Jabeen Q, Saeed T, SS A (2011) Zingiber officinale Roscoe (pharmacological activity). J Med Plants Res 5(3):344–348

Salazar A, Santa MJ, Zimic C, Salinas I, Sanchez L, Arrambide J, Benjamin C (2006) Evaluation of anti-nociceptive effect of chchuhuasi methanolic extract in a model of visceral pain in mice. Horiz Med J 6(2):135–140

Salazar A, Gemez J, Paravic T (2008) Evaluation of the hypotensive activity of Maytenus Krukovii (Chuchuhuasi) in conscious rat. Horiz Med J 8(2):41–47

Sandhar HK, Kaur M, Kumar B, Prasher S (2011) An update on Nyctanthes arbor tristis Linn. Int Pharmaceuticasciencia 1(1):77–86

Sandoval M, Okuhama NN, Zhang XJ, Condezo LA, Lao J, Angeles FM, Miller MJ (2002) Anti-inflammatory and anti-oxidant properties of Cat's Claw (Uncaria tomentosa and Uncaria guinensis) are independent of their alkaloid content. Phytomedicine 9:325–337

Sangwan S, Rao DV, Sharma RA (2010) A review on Pongamia pinnata (Linn.) Pierre: a great versatile leguminous plant. Nat Sci 8(11):130–139

Sautour M, Miyamoto T, Lacaille-Duboi MA (2006) Bioactive steroidal saponins from Smilax medica. Planta Med 72(7):667–670

Schett G (2000) Activation, differential localization, and regulation of the stress-activated protein kinases, extra-cellular signal-regulated kinase, c-JUN N-terminal kinase, and p38 mitogen-activated protein kinase, in synovial tissue and cells in rheumatoid arthritis. Arthritis Rheum 43:2501–2512

Shahverdi AR (2006) Two matrix metalloproteinases inhibitors from Ferula persica var persica. Phytomedicine 13:712–717

Shao B, Guo H, Cui Y, Ye M, Han J, Guo DS (2007) Steroidal saponins from Smilax china and their anti-inflammatory activities. Phytochemistry 68(5):623–630

Shin HY (2003) Jeong-tang inhibits the stem cell factor-induced migration and inflammatory cytokines secretion in mast cells. J Ethnopharmacol 85:157–161

Singh SS, Pandey SC, Srivastava S, Gupta VS, Patro B, Ghosh AC (2003) Chemistry and medicinal properties of Tinospora cordifolia. Indian J Pharmacol 35:83–91

Singh A, Malhotra S, Subban R (2008) Anti-inflammatory and analgesic agents from Indian medicinal plants. Int J Integr Biol 3(1):57–72

Singh A, Duggal S, Singh J, Katekhaye S (2010) An inside preview of ethnopharmacology of cissampelos pareira Linn. Int J Biol Technol 1(1):114–120

Subramanai J, Damodaran A, Kanniappan M, Mathuram LN (2009) Anti-inflammatory effect of petroleum ether extract of Vitex negundo leaves in rat models of acute and subacute inflammation. Pharm Biol 47(4):335–339

Sumantran VN, Joshi AK, Boddul S, Koppikar SJ, Warude D, Patwardhan B, Chopra A, Chandwaskar R, Wagh UV (2011) Antiarthritic activity of a standardized, multiherbal, Ayurvedic formulation containing Boswellia serrata: in vitro studies on knee cartilage from osteoarthritis patients. Phytother Res 25(9):1375–1380

Sun HY, Long LJ, Wu J (2006) Chemical constituents of mangrove plant Barringtonia racemosa. J Chin Med Mater 29(7):671–672

Suresh V (2011) In vitro anti-inflammatory and anti-cancer activities of Cuscuta reflex Roxb. J Ethnopharmacol 134:872–877

Talwar S, Nandakumar K, Nayak PG, Bansal P, Mudgal J, Mor V (2011) Anti-inflammatory activity of Terminalia paniculata bark extract against acute and chronic inflammation in rats. J Ethnopharmacol 134(2):323–328

Tirkey R, Tiwari P (2012) Effect of Cocculus hirsutus leaves extract on Freund's complete adjuvant and formaldehyde induced arthritis. Int Res J Pharm 3(2):267–270

Tripathy S, Pradhan D, Anjana M (2010) Anti-inflammatory and antiarthritic potential of Ammania baccifera Linn. Int J Pharm Bio Sci 1(3):1–7

Takauji Y, Miki K, Mita J, Hossain MN, Yamauchi M, Kioi M, Ayusawa D, Fujii M (2016) Triphala, a formulation of traditional Ayurvedic medicine, shows protective effect against X-radiation in HeLa cells. J Biosci 41(4):569–575

Umar S (2012) Modulation of the oxidative stress and inflammatory cytokine response by thymoquinone in the collagen induced arthritis in Wistar rats. Chem Biol Interact 197:40–46

Vaidya AD (2006) Reverse pharmacological correlates of ayurvedic drug action. Indian J Pharmacol 38(5):311–315

Vaillancourt F (2011) Elucidation of molecular mechanisms underlying the protective effects of thymoquinone against rheumatoid arthritis. J Cell Biochem 112:107–117

Vishwanathan S, Basavaraju R (2010) A review on vitex negundo L. - a medicinally important plant. Eur J Biol Sci 3(1):30–42

Wen XY (2008) The effects of Radix Clematidis liposome on knee joints in osteoarthritis rabbits. J Tradit Chin Orthoped Trauma 10:19–21

Wilder RL (1988) Streptococcal cell-wall-induced arthritis in rats: an overview. Int J Tissue React 10:1–5

Wilder RL (1999) Genetic factors regulating experimental arthritis in mice and rats. Curr Dir Autoimmun 1:121–165

Williams JE (2001) Review of anti-viral and immunomodulating properties of plants of the Peruvian rainforest with a particular emphasis on Una de Gato and Sangre de Grado. Altern Med Rev 6(6):567–579

Yadav RD, Jain SK, Alok S, Prajapati SK, Verma A (2011) Pongamia pinnata: an overview. Int J Pharm Sci Res 2(3):494–500

Yasir M, Das S, Kharya MD (2010) The phytochemical and pharmacological profile of Persea americana Mill. Pharmacogn Rev 4(7):77–84

Yesilada E, Kupeli E (2007) Clematis vitalba L aerial part exhibits potent anti-inflammatory, anti-nociceptive and anti-pyretic effect. J Ethnopharmacol 110:504–515

Yin W (2003) Analgesic and anti-inflammatory properties of brucine and brucine N-oxide extracted from seeds of Strychnos nux-vomica. J Ethnopharmacol 88:205–214

Zakeri Z, Izadi S, Bari Z, Soltani F, Narouie B, Rad MG (2011) Evaluating the effects of ginger extract on knee pain, stiffness and difficulty in patients with knee osteoarthritis. J Med Plants Res 5(15):3375–3379

Zhang CF (2014) Antioxidant effects of Genkwa flos Linn flavonoids on Freund's adjuvant-induced rheumatoid arthritis rats. J Ethnopharmacol 153:793–803

Znati M (2014a) Chemical composition, biological and cytotoxic activities of plant extracts and compounds isolated from Ferula lutea. Molecules 19:16959–16975

Znati M (2014b) Chemical composition, biological and cytotoxic activities of plant extracts and compounds isolated from Ferula lutea. Molecules 19:2733–2747

Herbal Medicine in Diabetes Mellitus with Cardiovascular Diseases

Salih Tunc Kaya, Celal Guven, and Eylem Taskin

Introduction

The largest global health problem in the twenty-first century is considered to be diabetes mellitus (referred to as diabetes). The prevalence of diabetes cases has increased day by day across the globe. It is critically announced that 642 million people will face diabetes by the year 2040 (IDF 2016). There is a close relationship between diabetes and cardiovascular dysfunctions, including coronary artery diseases, ischemic heart diseases, hypertension, acute myocardial ischemia/reperfusion (I/R) injury, etc. Several experimental and clinical studies reveal that diabetes is a crucial risk factor for cardiovascular disorders and is one of the main reasons of mortality and morbidity in diabetic people (Brindisi et al. 2010; Whittington et al. 2012). It was reported that approximately 5.0 million people died probably from diabetes, especially due to diabetes-related cardiovascular disorders in 2015 (IDF 2016).

Although great efforts have been given to search for a cure, diabetes remains a critical medical problem for human beings. There are several classes of drugs for diabetic patients to manage hyperglycemia: insulin, sulfonylureas, biguanides, alpha-glucosidase inhibitors, thiazolidinediones, glucagon-like peptide analogues, dipeptidyl peptidase IV inhibitors, and meglitinides. However, these drugs have undesired side effects such as weight gain or loss, headache, gastrointestinal disorders, and significantly increased risk of myocardial infarction (Stein et al. 2013). That is why it is important to find an effective cure to either prevent diabetes

S. T. Kaya (✉)
Biology Department, Faculty of Arts and Science, University of Duzce, Duzce, Turkey

C. Guven
Biophysics Department, Faculty of Medicine, University of Omer Halisdemir, Nigde, Turkey

E. Taskin
Physiology Department, Faculty of Medicine, University of Omer Halisdemir, Nigde, Turkey

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or decrease cardiovascular complications in the diabetic patients, and thereby declining mortality rate and/or increasing quality of diabetic patient's life. Herbal compounds can be given as an alternative way to prevent or treat diabetes and its complications. Within this context, herbal products have drawn attention. They may be regularly used in our daily life as a dietary regime before development of diabetes alone or may be used with the antidiabetic drugs as a combination treatment to increase the resistance against cardiovascular disorders in diabetic patients by enhancing the efficiency of desired drugs in the management of high blood glucose level or decreasing unexpected side effects. Among them, resveratrol, berberine, ginseng, curcumin, and ginkgo are of great interest because of their antihyperglycemic and cardioprotective effects. In this chapter, their potential therapeutic effects in the management of both hyperglycemia and cardiovascular dysfunctions associated with diabetes have been reviewed depending on the current evidences from experimental and clinical studies. Additionally, the interaction of antidiabetic agents such as insulin, glibenclamide, and metformin with herbal products mentioned in diabetic hearts from literature is summarized. The underlying mechanisms involved in the cardiovascular effects are also emphasized to design new drugs from herbal plants, to improve new therapeutic approaches, and to open a new perspective for future studies. To sum up, this chapter underlines resveratrol, berberine, ginseng, curcumin, and ginkgo for the therapeutic usage in the management of diabetes as well as either preventing or decreasing the vulnerability of diabetic patients to cardiovascular diseases with the focus on underlying mechanisms of their actions.

Diabetes Mellitus

Diabetes is defined as a metabolic disorder associated with high blood glucose level. Blood glucose level is not controlled in diabetes due to insulin deficiency, insulin resistance, or both. There are three main types of diabetes defined so far which are type I diabetes, type II diabetes, and gestational diabetes (American Diabetes Association 2010).

Type I diabetes, well known as insulin-dependent diabetes, is resulted from immune-mediated destruction of beta (β)-cells of pancreatic islets. Insulin usage is inevitable for type I diabetic patients to survive. The exact reasons for diabetes are sophisticated. The physiopathology of type I diabetes has been reported to participate several components, including genetic and environmental factors leading to diabetes (Szablewski 2014). Moreover, the roles of these factors in the development of diabetes are recently well reviewed (Atkinson et al. 2014). Generally, the symptoms of type I diabetes include lack of energy, hungry, weight loss, polyuria, polydipsia, and dry mouth.

The second type of diabetes is named as type II diabetes that is the most prevalent type of diabetes. It is also called as insulin-independent diabetes associated with relative insulin insufficiency and increased peripheral insulin resistance or

decreased insulin sensitivity (Atkinson et al. 2014). The exact pathophysiological mechanism in type II diabetes is still a mystery. However, excess body weight, sedentary life, and wrong feeding habits may be given as examples for some factors to induce type II diabetes. The symptoms of type II diabetes may be similar to those of type I diabetes but less obvious than type I diabetes. The other difference of type II from type I is that patients do not have to use insulin for decreasing blood glucose level. On the other hand, patients with type II diabetes need to take oral antihyperglycemic agents such as sulfonylureas, biguanides, alpha-glucosidase inhibitors, thiazolidinediones, glucagon-like peptide analogues, dipeptidyl peptidase IV inhibitors, and meglitinides for restoration of blood glucose level.

Third type of diabetes is gestational diabetes. This type is observed during pregnancy, which is also called as diabetes mellitus in pregnancy. Gestational diabetes is predicted to be observed in 2–5% of pregnant women (McCowen and Smith 2013). Several factors are involved in the development of gestational diabetes, including alternation of growth hormone, cortisol secretion, human placental lactogen secretion, insulinase (an enzyme-inactivating insulin) secretion, estrogen, progesterone, and elevation of food consumption, but decreasing exercise (Gilmartin et al. 2008).

The Experimental Models of Diabetes

Animal models of diabetes are frequently used to understand diabetes-related complications and to find effective cure to modulate or prevent diabetes and comorbid complications. That is why there are plenty of studies available on animal research in the literature. There are several techniques present to induce diabetes in experimental animals such as chemical, surgical, genetic, or modified diets (King 2012). In literature, streptozotocin (STZ) and alloxan are two main chemicals to induce diabetes in the experimental model. Administration of these chemicals destroys β-cells of pancreas, resulting in decline or no production of insulin (Kumar et al. 2012). A low-dose injection of STZ and feeding high-fat diet (HFD) give rise to induce type II diabetes although a single injection of STZ causes to develop type I diabetes in experimental animals. However, there is a dilemma that STZ utilization could mimic type I or type II diabetes in human beings. The effect of STZ on β-cells is in a dose-dependent manner. It was indicated that lower than 50 mg/kg of STZ induces reversible diabetes although higher than 50 mg/kg causes rapid and irreversible diabetes (Ar'Rajab and Ahren 1993). Accordingly, STZ-induced diabetes for type I diabetes mellitus, STZ/HFD- or STZ/nicotinamide (NA)-induced diabetes for type II diabetes mellitus, and a specific name for genetically modified diabetic animals are preferred throughout the chapter.

Herbal Medicine and Diabetic Hearts

Diabetic patients face various complications due to mainly hyperglycemia. The complications can be examined under two categorizes: microvascular and macrovascular alterations (Forbes and Cooper 2013). Microvascular complications, e.g., retinopathy, nephropathy, and neuropathy, result from damage to small blood vessels, whereas macrovascular complications including cardiovascular diseases and cerebrovascular diseases occur due to damage to the arteries. This chapter focuses on cardiovascular diseases associated with diabetes and the underlying mechanisms involved.

The cardiovascular diseases such as hypertension, ischemic heart disease, cerebrovascular disease, peripheral vascular diseases, or heart failure are one class of diseases affecting the heart and circulation (Balakumar et al. 2016). Diabetes leads to increased risk of cardiovascular diseases. Cardiovascular disease is, therefore, one of the major causes of morbidity and mortality in diabetic patients. Approximately, 80% of diabetic patients died due to cardiovascular diseases (Hayat et al. 2004). In addition, diabetic hearts are more vulnerable to myocardial I/R injury, including myocardial infarction and cardiac arrhythmias. For example, experimental and clinical studies indicate that the diabetic hearts exert less resistance to myocardial I/R injury, resulting in an increase in the incidence of arrhythmias and myocardial infarction (Nakou et al. 2012; Bhatt and Veeranjaneyulu 2014). The underlying mechanisms and signaling pathways in the increased susceptibility of diabetic heart to cardiac dysfunctions are miscellaneous. The exact causes are not well known. However, several studies are present to elucidate molecular, biochemical, and ion channel changes in the diabetic myocardium (Fig. 1) (Takeda 2010; Balakumar and Sharma 2012; Yildirim et al. 2013; Costantino et al. 2016; Chen et al. 2012; Fancher et al. 2013). Some of these alterations as a target for the herbal products are discussed in detail later within this chapter.

The treatment of a specific class of antidiabetic agents in diabetic patients with heart failure could increase the hospitalization risk. For example, glibenclamide has been reported to increase the mortality rate, myocardial ischemic area, and possibility of malignant arrhythmias in diabetic patients (Monami et al. 2006; Xianghua et al. 2010). Also, saxagliptin is indicated to increase the hospitalization risk of diabetic patients due to heart failure without affecting the rate of ischemic heart events (Scirica et al. 2013; Monami et al. 2014). Taken into account, there is a need to develop a specific drug therapy for diabetic patients. As more researches regarding the safety and efficiency of the herbal product usage alone or with other antidiabetic agents in treating diabetes as well as decreasing the risk for cardiovascular diseases are conducted to explain exact signaling pathways for the physiological actions in the manner of acute and chronic application, the prevalence of and interest in using herbal products will largely be increased. Table 1 summarizes the cardiovascular effects of resveratrol, berberine, ginseng, curcumin, and gingko in diabetes. In this chapter, the relationship of phytotherapy for diabetes with cardiovascular disease and microRNAs has been discussed after every herbal product as well.

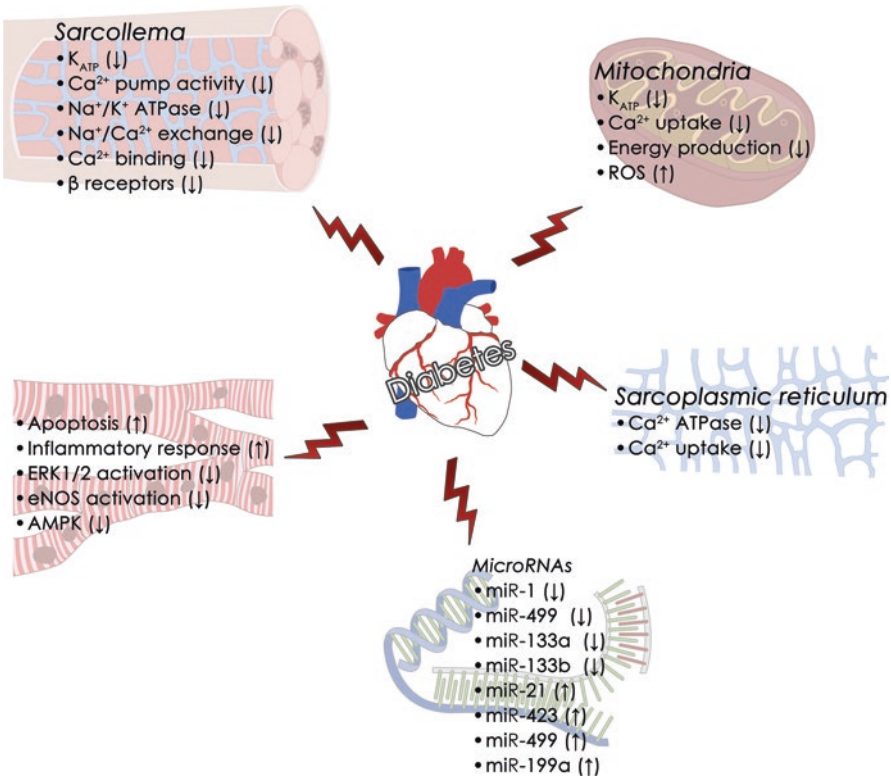

Fig. 1 The possible changes in the diabetic hearts. *Abbreviations:* (↓), decrease; (↑), increase; K_{ATP} ATP-dependent potassium channel; *AMPK* adenosine monophosphate-activated protein kinase; *eNOS* endothelial nitric oxide synthase; *ERK* extracellular signal-regulated kinase; *ROS* reactive oxygen species. The figure is modified from Takeda (2010) and Balakumar and Sharma (2012)

The Role of MicroRNAs in Diabetic Herbal Medicine

MicroRNAs (miRNAs) are small noncoding RNA molecules about 22 nucleotides in the length, which regulate posttranscriptionally gene regulation through inhibiting messenger RNA (mRNA) translation or degrading the mRNA molecules by binding to 3′-untranslated region. miRNAs are implicated in numerous physiological and pathological processes such as cardiovascular dysfunctions, diabetes, and its associated complications (Pan et al. 2010; Sethupathy 2016). For example, several miRNAs including miR-103/107, miR-24, and miR-29 have altered diabetes and related dysfunctions such as obesity and hyperlipidemia, which was well summarized in a previous review (Sethupathy 2016). In addition, miR-21 inhibition is effective in the management of blood glucose level in the diabetic patients (Sekar et al. 2016). Another example is that upregulations of miR-1, 106b, and 222 are reported to alleviate hyperglycemia by promoting β-cell proliferation (Tsukita et al. 2017). In

Table 1 The cardiovascular effects of resveratrol, berberine, ginseng, curcumin, and gingko in diabetes

Active ingredient	Dose, Route, Time	Diabetes	Myocardial injury	Effects with mechanism(s)	References
Resveratrol	2.5 mg/kg, OG, 15 days	Rat, 65 mg/kg STZ, IP, 15 days	In vitro, 30 min global isch and 2 h rep	Decrease myocardial infarct size, myocardial apoptosis; improve left ventricular functions; by upregulating Trx-1, NO/HO-1, and VEGF as well as increasing MnSOD activity	Thirunavukkarasu et al. (2007)
	0.1 and 1 mg/kg, OG, 5 days	Rat 65 mg/kg STZ, IV, 2 weeks	In vivo, 1 h isch and 3 h reperfusion, LMCA	No change in myocardial infarct size, duration of VF, VT, and the incidence of VPC; improve MAP, CO, SV, EF, SW, ESV, EDV; reduce mortality rate; by inhibiting iNOS/nitrotyrosine/superoxide anion overexpression	Huang et al. (2010)
	A diet with resveratrol at 0.067%, 4 and 12 weeks	Mice, 150 mg/kg STZ, IP, 12 weeks	—	Improve survival rate and cardiac functions such as systolic, diastolic diameter and fractional shortening; reduce myofibrosis; by restoring SERCA2a expression via activating SIRT1-dependent mechanisms	Sulaiman et al. (2010)
	20 mg/kg, OG, 4 weeks	Homozygous type 2 diabetic mice ($Lepr^{db}$)	—	Increase the left ventricular diastolic peak filling rate; by suppressing oxidative/nitrative stress and enhancing NO availability	Zhang et al. (2010a)
	1.0 mg/kg, OG, 30 days	Rat, 60 mg/kg STZ, IP, 30 days	—	Improve cardiac energy metabolism and oxidative stress as evidenced by increasing pyruvate dehydrogenase activity, reduced glutathione and the glutathione reductase activity as well as decreasing myocardial β-hydroxyacyl coenzyme-A dehydrogenase and citrate synthase activity	Carolo dos Santos et al. (2014)
	25 mg/kg and 10 mg/kg, 8 weeks	Rat, 50 mg/kg STZ, IP or STZ/high fructose diet, 8 weeks	—	Modulate cardiac atrophy in STZ-induced diabetic heart and cardiac hypertrophy in STZ/HFD-induced diabetic heart; by improving the alteration in SIRT1 in STZ/HFD-induced diabetic hearts and SIRT1, 2, 3, and SIRT5 in STZ-induced diabetic heart	Bagul et al. (2015)
	80 mg/kg, OG, 12 weeks	Rat, 40 mg/kg STZ, IV, 12 weeks	—	Attenuate pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β; improve cardiac hemodynamic parameters including LVSP, LVEDP, $-dP/dt_{max}$, and $+dP/dt_{max}$; by downregulating AT1R-ERK/p38 MAPK signaling pathway	Gao et al. (2016)

Berberine	30 mg/kg, OG, 6 weeks	Rat, 30 mg/kg STZ/HSFD, 12 weeks	—	Improve SV, CO, LVSP, LVEDP, $-dP/dt_{max}$, $+dP/dt_{max}$; by inducing glucose transport and attenuating lipid deposition in myocardium, as evidenced by upregulation of GLUT4 and PPARγ at protein and gene levels as well as downregulation of PPARα at protein level	Dong et al. (2011)
	180 mg/kg, OG, 14 days after the isch	Rat, 55 mg/kg, STZ/HFD, IP, 2 weeks	In vivo, 24 h isch, LAD	Decrease the score of arrhythmia and the incidence of arrhythmias; by improving depressed Kir2.1 protein expression and K^+ current	Wang et al. (2011)
	100 mg/kg, OG, 7 days before isch	Rat, 40 mg/kg, STZ/HFD, IP, 8 weeks	In vivo, 12 h isch, LAD	No effect on HR; attenuate arrhythmia score and the duration of arrhythmia; via improving the transient outward K^+ current and L-type Ca^{2+} current	Wang et al. (2012)
	200 mg/kg, OG, 4 weeks	Rat, 30 mg/kg STZ/HFD, IP, 12 weeks	In vivo, 30 min isch and 3 h rep, LAD	No effect on HR; improve left ventricular functions following reperfusion; attenuate myocardial apoptosis; via activating AMPK and PI3K–Akt–eNOS signaling pathways	Chen et al. (2014)
	100 mg/kg, OG, 16 weeks	Rat, 30 mg/kg, STZ/HFD, IP, 25 weeks	—	Improve cardiac functions; decrease cardiac fibrosis and hypertrophy; by enhancing activation of AMPK and AKT and reducing GSK3β activity	Chang et al. (2015)
	100 mg/kg, OG, 7 days before isch	Rat, 30 mg/kg, STZ/HFD, IP, 12 weeks	In vivo, 30 min isch and 3 h rep, LAD	No effect on HR during ischemia and reperfusion; reduce infarct size and the duration of VT and VF; by activating AMPK, AKT and inhibiting GSK3β in the nonischemic myocardium	Chang et al. (2016)
	100 mg/kg, OG, 30 days	Rat, 45 mg/kg, STZ, IP, 30 days	Isoproterenol-induced myocardial infarction	Reduce the degree of myocardial inflammation, necrosis, edema as well as CK-MB	Suman et al. (2016)

(continued)

Table 1 (continued)

Active ingredient	Dose, Route, Time	Diabetes	Myocardial injury	Effects with mechanism(s)	References
Ginseng	Ginsenoside Rb1 40 mg/kg, IV, 10 min before ischemia	Rat, 65 mg/kg STZ, IP, 8 weeks	30 min isch and 2 h rep, LAD	Increase MAP; attenuate the level of LDH and CK-MB; decrease myocardial infarct size, apoptosis, and caspase-3 activity; via activating PI3K/Akt pathway	Wu et al. (2011)
	Alcoholic ginseng root extract, 200 mg/kg, OG, 2 and 4 months	C57BL/6 mice, $Lepr^{db}$ mice, 50 mg/kg STZ, IP, 2 and 4 months	—	Increase SV, EF, CO, LVDP, and LVSP; decrease ANP, BNP; attenuate superoxide anion accumulation and HO-1 expression	Sen et al. (2013)
	Ginseng powder, 150 mg/kg, OG, 7 days	Rat, 60 mg/kg STZ, IV, 10 weeks	—	Decrease HR; increase CO, SBP, DBP; by enhancing the expression of PPARδ and TnI phosphorylation	Tsai et al. (2014)

Curcumin	100 mg/kg/day, orally, 8 weeks	Rat, 55 mg/kg STZ, IP, 11 weeks	—	Attenuate cardiomyocyte hypertrophy, myocardial fibrosis, and left ventricular dysfunctions; by inhibiting PKC-α and -β2-MAPK pathway and reducing oxidative stress	Soetikno et al. (2012)
	100 or 200 mg/kg, orally, 16 weeks	Rat, 40 mg/kg STZ/HFD, IP, 17 weeks	—	Improve myocardial dysfunction, cardiac fibrosis, AGEs accumulation, oxidative stress, inflammation, and apoptosis; via Akt/GSK3β signaling pathway	Yu et al. (2012)
	A novel water soluble curcumin derivative, 20 mg/kg, orally, 45 days	Rat, 50 mg/kg STZ, IP, 45 days	—	Improve left ventricular functions such as increasing HR, LVDP, LV and decreasing SBP; by preventing the upregulation of ANP, MEF2A, MEF2C, p300, and HO-1 expression in diabetic heart	Aziz et al. (2013)
	200 mg/kg, orally, 6 weeks	Rat, 55 mg/kg STZ, IP, 6 weeks	—	Increase cardiac antioxidant enzymes (SOD, CAT, glutathione-S-transferase) and decrease inflammatory cytokines (IL-6 and TNF-α)	Abo-Salem et al. (2014)
	200 mg/kg, OG 4 weeks	Insulin/estrogen-depleted hypertensive mRen2.Lewis rats, 4 weeks	—	Attenuated cardiac systolic and diastolic dysfunction; by reducing Ang II signaling pathway	VonCannon et al. (2014)

(continued)

Table 1 (continued)

Active ingredient	Dose, Route, Time	Diabetes	Myocardial injury	Effects with mechanism(s)	References
Gingko	25 or 50 mg/kg, EGb 761, orally, 10 days	Rat, 55 mg/kg STZ, IV, 8 weeks	In vitro, 30 min *global* isch and 30 min rep, preconditioning	Decrease the incidence of reperfusion-induced VF, VT; improve aortic flow and left ventricular pressure; by attenuating free radical formation	Tosaki et al. (1996)
	100 mg/kg, EGb 761, in drinking water, 3 months	Rat, 60 mg/kg STZ, IP, 4 months	Acute respiratory hypoxia	Improve hypoxia-induced myocardial ultrastructural changes such as sarcoplasm, t-tubules, mitochondria, cytoplasmic vacuoles; increase SOD and malondialdehyde in diabetic myocardium	Fitzl et al. (2000)
	100 mg/kg, EGb 761, in drinking water, 3 months	BioBreeding/ Ottawa Karlsburg rats, 6 months	—	Improve autonomic nerve fibers and related Schwann cells; restore alterations in the presynaptic nerve terminals and the postsynaptic β1-AR-AC coupling system in diabetic heart	Schneider et al. (2010)
	100 or 200 mg/kg, OG, EGb761, 6 weeks	Otsuka Long-Evans Tokushima Fatty rats	Carotid artery injury	Decrease intima-media ratio, proliferation and migration of VSMCs; increase apoptosis, caspase-3 activity, and DNA fragmentation; protective against atherosclerosis	Lim et al. (2011)
	50 mg/kg, EGb761, IP, 3 weeks	Rat, 50 mg/kg STZ, IP, 8 weeks	—	Improve cardiovascular dysfunctions such as decreased left ventricular collagen content, protein content, serum LDH level; attenuate oxidative and nitrosative stress; improve antioxidant enzyme (reduced glutathione); by inhibiting the opening of mPTP	Saini et al. (2014)

AGEs advanced glycation end products, *Akt* protein kinase B, *Ang II* angiotensin II, *ANP* atrial natriuretic peptide, *AT1R* angiotensin II type 1 receptors, *BNP* brain natriuretic peptide, *CAT* catalase, *CK-MB* creatine kinase-MB, *CO* cardiac output, *DBP* diastolic blood pressure, $-dP/dt_{max}$ maximum rate of fall of left ventricle pressure, $+dP/dt_{max}$ maximum rate of rise of left ventricle pressure, *EDV* end-diastolic volume, *EF* ejection fraction, *eNOS* endothelial nitric oxide synthase, *ERK1/2* extracellular signal-regulated kinases, *ESV* end-systolic volume, *GSK3β* glycogen synthase kinase 3 beta, *HFD* high-fat diet, *HO-1* heme oxygenase-1, *HR* heart rate, *HSFD* high-sucrose/fat diet, *IL-1β* interleukin 1 beta, *IL-6* interleukin 6, *iNOS* inducible nitric oxide synthase, *IP* intraperitoneal, *Isch* ischemia, *IV* intravenous, *LAD* left anterior descending coronary artery, *LDH* lactate dehydrogenase, *LMCA* left main coronary artery, *LVDP* left ventricular diastolic pressure, *LVEDP* left ventricular end-diastolic pressure, *LVSP* left ventricular systolic pressure, *MAP* mean arterial pressure, *MAPK* mitogen-activated protein kinase, *MEF2A* myocyte enhancer factor 2 A, *MEF2C* myocyte enhancer factor 2 C, *MnSOD* manganese superoxide dismutase, *mPTP* mitochondrial transition pore, *NO* nitric oxide, *OG* oral gavage, *PI3K* phosphatidylinositol-3-kinase, *PKC-α* protein kinase C alpha, *PPARα* peroxisome proliferator-activated receptor alpha, *PPARδ* peroxisome proliferator-activated receptor delta, *Rep* reperfusion, *SBP* systolic blood pressure, *SERCA2a* sarcoplasmic calcium ATPase, *SIRT* sirtuin, *SOD* superoxide dismutase, *STZ* streptozotocin, *SV* stroke volume, *SW* stroke work, *TNF-α* tumor necrosis factor alpha, *TnI* troponın I, *Trx-1* thioredoxin-1, *VEGF* vascular endothelial growth factor, *VF* ventricular fibrillation, *VPC* ventricular premature contraction, *VSMCs* vascular smooth muscle cells, *VT* ventricular tachycardia, *β1-AR/AC* beta 1-adrenergic receptor/adenylate cyclase

case of diabetic heart disease, the role of miRNAs remains to be clarified. However, a recent review describes the potential changes of some particular miRNAs such as miR-133, miR-1, miR-208, miR-499, miR-126, and miR-132 that play a major role in the cardiovascular systems in diabetic heart disease as well as circulating miRNAs in diabetic patients (Rawal et al. 2014). Importantly, diabetes might induce long-term changes in miRNA profile of diabetic hearts. Therefore, even if hyperglycemia could be controlled, diabetes-related cardiovascular dysfunctions might progress due to sustained alteration of some miRNAs inducing apoptosis, fibrosis, oxidative stress, and heart failure, e.g., miR-320b, miR-150, miR-155, and miR-423 (Costantino et al. 2016). Moreover, Yildirim et al. (2013) reported that STZ-induced diabetes resulted in downregulation of miR-1, miR-499, miR-133a, and miR-133b and upregulation of miR-21 in the heart. Another important result of this study was that administration of an antioxidant molecule, *N*-acetylcysteine, improved the expression of these miRNAs. It means that antioxidant molecules such as resveratrol, berberine, ginseng, gingko, and curcumin may be protective against cardiovascular dysfunctions in the diabetic hearts via modulating miRNA profile due to their antioxidant features. However, a functional link between herbal products and miRNAs in the pathogenesis of diabetes and cardiovascular dysfunctions associated with diabetes remains to be elucidated. As more evidence is obtained on the underlying mechanisms in the physiological actions of herbal products at gene and protein levels, the use of herbal products in the treatment and/or reduction of diseases as an alternative treatment will be of more interest. Now, we know that herbal products or natural components play an important role in many biological processes via modulating miRNAs (Blade et al. 2014). Along with advances in technology and science, scientist's interest on miRNAs is increasing day by day. By this way, it is possible to develop innovative and promising therapies targeting miRNAs for several diseases in near future. For this, it is needed to focus on such relations in future investigations. Therefore, this section is also focusing on the possible role of miRNAs in the physiological effects of herbal products mentioned through the chapter in diabetes-induced cardiovascular dysfunctions.

Resveratrol

Resveratrol (3,5,4′ trihydroxystilbene) is a most studied phytoalexin that belongs to subclass, stilbenes. Resveratrol was first identified in *Veratrum grandiflorum* (white hellebore). It is also found in a variety of plants, including *Vaccinium myrtillus* (blueberry), *Vitis vinifera* (grapes), *Gnetum montanum* (Gnetum), *Arachis hypogea* (Peanut), *Morus rubra* (Mulberry), etc. (Shakibaei et al. 2009). Plants against environmental stresses such as fundal attack, ultraviolet radiation, and cold temperature produce naturally resveratrol (Soleas et al. 1997). In addition, resveratrol can be chemically produced and sold as a nutritional supplement. Two isoforms are present for resveratrol: *cis*- and *trans*-resveratrol. *Trans*-resveratrol is biologically a more active form than the other. Until the discovery of "French

paradox," little attention was given to resveratrol. Later on, the greater interest by scientist has been paid to examine the biological roles of resveratrol in both in vivo and in vitro studies.

The Antidiabetic Effects of Resveratrol

Several studies indicate that resveratrol has antihyperglycemic actions in the experimental model of diabetes via multifaceted mechanisms such as increasing blood insulin levels, peripheral glucose utilization, suppressing hepatic glucose output, and increasing insulin sensitivity (Szkudelski and Szkudelska 2015). Resveratrol exerts antihyperglycemic effects in both STZ- and STZ/NA-induced diabetic rats with a different underlying mechanism. Increased insulin secretion seems to be involved in its actions in STZ/NA-induced diabetic rats. However, enhanced peripheral glucose utilization via activating phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt) pathways and upregulation of skeletal muscle glucose transporter type 4 (GLUT-4) expression as well as downregulation of phosphoenolpyruvate carboxykinase (PEPCK) expression in the liver without a significant effect on insulin levels are related to mechanisms mediated by resveratrol in STZ-induced diabetic rats (Chi et al. 2007). In addition, resveratrol (20 mg/kg for 8 weeks) decreased blood glucose level by improving the expression of GLUT-4, vistafin, and sirtuin-1 (SIRT1) in the skeletal muscle and by enhancing the expression of GLUT-2 and insulin A expression in the pancreas of STZ-induced diabetic rats (Gencoglu et al. 2015). These results suggested that resveratrol revealed its hypoglycemic effects via increasing glucose utilization and insulin action on extrahepatic tissues and the pancreas. The anti-apoptotic features of resveratrol have also an important role in the prevention of diabetes. The pretreatment of STZ-induced diabetic rats with resveratrol (30 mg/kg for 1 week) prevented the development of diabetes by inhibiting β-cell apoptosis and cleavage of poly (ADP-ribose) polymerase (Ku et al. 2012). Resveratrol may also modulate the liver key enzymes in the control of blood glucose level. An experimental study indicated that resveratrol (5 mg/kg for 3 weeks) exerted its antihyperglycemic effect by possibly increasing hexokinase, pyruvate kinase levels, and glucose 6 phosphate dehydrogenase activity as well as decreasing fructose 1,6 bisphosphatase and glucose 6 phosphatase (G6Pase) activity (Yazgan et al. 2015). In compared to antidiabetic drugs, resveratrol has been shown to be as effective as antidiabetic drugs such as glibenclamide, metformin, insulin, and gliclazide in the management of hyperglycemia (Chi et al. 2007; Palsamy and Subramanian 2008; Frendo-Cumbo et al. 2016; Yonamine et al. 2016). It was reported that the combination of resveratrol (100 mg/kg) with metformin (250 mg/kg) for 4 weeks improved the glucose and insulin tolerance in diet-induced insulin-resistant mice through enhancing insulin signaling in adipose tissue and muscle (Frendo-Cumbo et al. 2016). Another experimental study showed that the treatment of STZ-induced diabetic rats with the combination of resveratrol (10 mg/kg) and insulin (5 U/day) for 30 days resulted in the improvement of glycemic control as

indicated by an additional reduction in glycosuria and fructosamine concentration when compared to insulin treatment alone (Yonamine et al. 2016). The mechanisms involved were purposed to be associated with downregulations of solute carrier family 2 member 2 (Slc2a2), phosphoenolpyruvate carboxykinase (Pck1), and glucose-6-phosphatase catalytic subunit (G6pc) and GLUT-2, and to be related with upregulation of SIRT1 nuclear protein content in liver. Therefore, resveratrol could reduce glucose production and efflux. It is also important to state that resveratrol may be effective in the management of gestational diabetes. A recent study indicates that resveratrol has a potential therapeutic in attenuating symptoms of gestational diabetes such as hyperglycemia, insulin resistance, and decreased fetal survival via possibly increasing the activation of adenosine monophosphate-activated protein kinase (AMPK) in genetically modified pregnant mouse model (Yao et al. 2015b). On the other hand, it should be stated that there are experimental studies demonstrating that resveratrol failed to decrease blood glucose level in diabetic rats. For example, treatment of diabetic rats with resveratrol (10 mg/kg for 6 weeks) did not change blood glucose level in STZ-induced diabetic rats in comparison to non-treated diabetic rats (Ates et al. 2007). Consistent with this finding, resveratrol (10 mg/kg or 20 mg/kg for 30 days) did not show antihyperglycemic effect (Schmatz et al. 2009; Schmatz et al. 2012). A recent study also indicated that resveratrol (2.5 mg/kg for 8 weeks) failed to control fasting glucose level in STZ-induced diabetic rats (Yan et al. 2016). The exact reasons for these discrepancies remain unknown; however, the differences in the dose, application interval, and model of diabetes may account for these inconsistent results.

In consistent with experimental studies, clinical data also show contradictory results about the effect of resveratrol on hyperglycemia in the diabetic patients. Resveratrol (10 mg/day for 4 weeks) was indicated to increase insulin sensitivity, which might be mediated via decreasing oxidative stress and activating Akt pathway in type II diabetic patients (Brasnyo et al. 2011). Another study also reported that resveratrol (250 mg/day for 3 months) administration to type II diabetic patients receiving oral hypoglycemic agents such as metformin, glibenclamide, or both decreased glycated hemoglobin (HbA1c) level, total cholesterol, total protein, and systolic blood pressure (SBP). However, resveratrol did not change high-density lipoprotein (HDL) and low-density lipoprotein (LDL) when compared to patients using only hypoglycemic agents (Bhatt et al. 2012). Furthermore, treatment of type II diabetic patients with resveratrol (1 g/day for 45 days) in addition to antidiabetic agents such as glibenclamide, metformin, insulin, or combinations with metformin was revealed to decrease fasting blood glucose level, insulin resistance, HbA1c level, and SBP and to increase HDL compared to baseline values (Movahed et al. 2013). Controversially, it has been recently demonstrated that resveratrol (500 and 40 mg/kg for 6 months) does not change SBP and diastolic blood pressure (DBP), fasting glucose, HbA1c, insulin, C-peptide, free fatty acids, liver transaminases, uric acid, adiponectin, interleukin-6 (IL-6), and C-reactive-protein (CRP) concentration in type II diabetic patients when compared to placebo (Bo et al. 2016). Another recent clinical study on diet-controlled type II diabetic patients has illustrated that resveratrol (1 g/day for 5 weeks) does not have a significant effect on

glucagon-like peptide 1 (GLP-1) secretion, fasting blood glucose, HbA1c, body weight, energy intake, and gastric emptying compared to placebo as well (Thazhath et al. 2016). In addition, resveratrol (150 mg/day for 30 days) does not significantly affect hepatic and peripheral insulin sensitivity as well as phosphorylated AMPK expression in type II diabetic patients receiving the metformin, suggesting that resveratrol might fail to activate further AMPK in the patients, given as a reason for the ineffectiveness of resveratrol on insulin sensitivity (Timmers et al. 2016). In the mentioned study, it is also emphasized that metformin usage in the patients influences metabolite levels of the resveratrol, which is presented as an underlying cause for the failure of resveratrol to modify insulin levels. So, more clinical studies about resveratrol's effect on diabetic patients are needed to clarify this dilemma.

The Cardiovascular Effects of Resveratrol

The protective effects of resveratrol on cardiovascular diseases and its potential mechanisms have been extensively investigated in nondiabetic hearts (Bonnefont-Rousselot 2016). Nonetheless, there are limited studies regarding the effect of resveratrol on the diabetic hearts. Resveratrol (2.5 mg/kg for 15 days) decreased myocardial infarct size and apoptosis and improved left ventricular function during reperfusion period in an in vitro model of I/R injury in diabetic rats. The protection was mediated via upregulating the expression of thioredoxin-1 (Trx-1), nitric oxide/heme oxygenase-1 (NO/HO-1), and vascular endothelial growth factor (VEGF) as well as increasing manganese superoxide dismutase (MnSOD) activity (Thirunavukkarasu et al. 2007). Inconsistent with the result of mentioned study, it was shown that resveratrol (1 mg/kg for 5 days) did not affect the arrhythmias severity and myocardial infarct size in an in vivo model of I/R injury; however, resveratrol improved hypotension, bradycardia, and systolic and diastolic dysfunction and reduced mortality rate. The mechanisms involved in the protective effects of resveratrol were suggested to be related to the inhibition of inducible nitric oxide synthase (iNOS)/nitrotyrosine/superoxide anion overexpression (Huang et al. 2010). It is also crucial to state that the beneficial effects of resveratrol were antagonized by insulin (4 U/day) in the diabetic hearts facing acute heart attack in the mentioned study. Similarly, resveratrol (20 mg/kg for 4 weeks) improved cardiac dysfunctions via suppressing oxidative/nitrative stress and enhancing NO. Briefly, inhibition of tumor necrosis factor-alpha (TNF-α)-induced nuclear factor kappa B (NF-κB) activation resulted in inhibition of nicotinamide adenine dinucleotide phosphate-oxidase (NADPH oxidase) and iNOS as well as upregulation of endothelial NO synthase (eNOS) in genetically modified diabetic mice (Zhang et al. 2010a). An in vitro study indicated that resveratrol exerted protection against high-glucose-induced oxidative stress and apoptosis in neonatal cardiomyocytes (Guo et al. 2015). Reactive oxygen species (ROS) generation reduced by decreasing NAPDH oxidase and upregulating endogenous antioxidant systems such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px) activity, and

glutathione (GSH) in resveratrol treatment. In addition, apoptosis of cardiomyocytes reduced via downregulating Bax-2 and upregulating Bcl-2 expression, and AMPK-dependent pathways might be involved in the protective mechanisms of resveratrol in the mentioned study. It is also important to emphasize that possible signaling pathways for the protective effects of resveratrol could be associated with AMPK pathways, as evidenced by the inhibition of AMPK with the inhibitor resulting in loss of the protection of resveratrol. In a recent experimental study, the cardioprotective effects of resveratrol and its underlying mechanisms in both STZ- and STZ/high-fructose diet-induced diabetic rats have been comprehensively investigated (Bagul et al. 2015). Resveratrol modulated cardiac atrophy in STZ-induced diabetic hearts and reduced the cardiac hypertrophy in STZ/high-fructose diet-induced diabetic hearts. Moreover, the underlying cardioprotective mechanisms of resveratrol showed differences depending on the model of diabetes; it increased Akt phosphorylation in STZ-induced diabetic rats whereas it decreased Akt phosphorylation in STZ/HFD-induced diabetic rats. In addition, resveratrol attenuated the reduction of SIRT-1, -2, and -3 and SIRT-5 at mRNA levels, except SIRT-4, SIRT-6, and SIRT-7 in STZ-induced diabetic rats although it increased SIRT-1 and SIRT-2 and decreased the levels of SIRT-3 in STZ/high-fructose diet-induced diabetic rats. It was also indicated that resveratrol resulted in increased antioxidant status in the diabetic heart via increasing GSH levels, activity of GSH-Px, glutathione reductase, and glutathione-S-transferase in both types. Another experimental study showed that feeding resveratrol-enriched diets improved cardiac functions including increased fractional shortening and decreased left ventricular end-diastolic and -systolic diameters as well as myocardial fibrosis by increasing sarcoplasmic calcium ATPase (SERCA2a) expression via activation of SIRT1 in STZ-induced diabetic mice (Sulaiman et al. 2010). A recent experimental study indicated that resveratrol (80 mg/kg for 12 weeks) decreased total cholesterol, triglyceride, LDL, and pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β (Gao et al. 2016). Furthermore, it was indicated in the mentioned study that cardiac hemodynamic parameters including left ventricular systolic pressure (LVSP), left ventricular end-diastolic pressure (LVEDP), maximum rate of fall of left ventricle pressure ($-dP/dt_{max}$), and maximum rate of rise of left ventricle pressure ($+dP/dt_{max}$) improved in the diabetic rats treated with resveratrol. The mechanisms of the improvement of cardiac hemodynamic parameters were suggested to be related to the downregulation of angiotensin II type I receptors—extracellular signal-regulated kinase/mitogen-activated protein kinase (AT1R-ERK/p38 MAPK) signaling pathways. Another recent study showed that resveratrol (2.5 mg/kg for 8 weeks) also protected the diabetic hearts against mitochondrial injury and myocardial apoptosis (Yan et al. 2016). By this way, resveratrol may be effective in improving cardiac functions and in attenuating cardiac fibrosis. In addition, resveratrol (1 mg/kg for 30 days) was indicated to regulate cardiac energy metabolism in the diabetic heart via effecting the activity of key enzymes such as glutathione reductase, pyruvate dehydrogenase, myocardial β-hydroxyacyl coenzyme-A dehydrogenase, and citrate synthase (Carolo dos Santos et al. 2014).

Taken together, further studies are needed to evaluate the effectiveness of resveratrol alone and its combinations with antidiabetic agents in acute I/R injury and pre- and postischemic conditions in the diabetic hearts.

The Relationship of Resveratrol with MicroRNAs

The effects of resveratrol on miRNAs in ischemic nondiabetic heart were reviewed previously (Mukhopadhyay et al. 2011). However, to date, there are no comprehensive investigations on the relationship between resveratrol and miRNAs as a target in the pathogenesis of diabetes and cardiovascular complications in diabetes. A clinical study reported that resveratrol (8 mg for 12 months) reduced the pro-inflammatory cytokines such as C–C motif chemokine ligand 3 (CCL3), IL-1β, and TNF-α by altering several miRNAs including miR-21, miR-181b, miR-663, miR-30c2, miR-155, and miR-34a in type II diabetic hypertensive patients with coronary artery disease (Tome-Carneiro et al. 2013). In addition, it can be speculated that resveratrol might be effective to improve diabetic cardiomyopathy via modulating miR-155. It was demonstrated that miR-155 expression changed in heart, kidney, and aorta of the diabetic rats, suggesting that miR-155 might take a part in diabetes-related dysfunctions although it is unknown whether a causal relationship between miR-155 dysfunction and diabetic complications is present or not (Khamaneh et al. 2015). Recently, resveratrol has been shown to attenuate the severity of cardiac hypertrophy in nondiabetic mice by downregulating miR-155 (Fan et al. 2016). With the light of such knowledge, it is possible that resveratrol will improve diabetic cardiomyopathy by suppressing miR-155, which needs to be investigated. In addition, it is also possible that resveratrol might target miR-21, because inhibition of miR-21 resulted in decreased cardiac fibrosis due to diabetes by blocking phosphorylated p38 MAPK (Wang et al. 2016). Given a previous study showing that the mechanism involved in the cardioprotective effect of resveratrol in the diabetes might be related with the suppression of p38 MAPK (Gao et al. 2016) it yields a question “Does miR-21 take a part in the signaling pathways for such resveratrol effects?” That is why the role of resveratrol in miRNA under both physiological and pathophysiological conditions, especially diabetes-related heart diseases, is needed to elucidate more studies in animals and patients as well.

Berberine

Berberine is an isoquinoline alkaloid that is present as an active component in root, rhizome, and stem of several plants, including *Hydrastis Canadensis*, *Coptis chinensis*, *Berberis vulgaris*, and *Berberis aristata* (Kumar et al. 2015). Berberine has been used in the treatment of several diseases such as Alzheimer’s disease, cancer, obesity, cardiovascular diseases, and diabetes for many years (Yao et al. 2015a; Jin et al. 2016).

The Antidiabetic Effects of Berberine

The antihyperglycemic action of berberine was reported for the first time in China in the year 1986 (Yao et al. 2015a). The multiple mechanisms and signaling pathways may be involved in the antihyperglycemic effects of berberine, which include increasing insulin sensitivity, activating AMPK pathways, inhibiting gluconeogenesis in liver, increasing glucose transporters, stimulating peripheral glucose utilization, and inducing GLP-1 secretion as well as changing miRNAs (Pang et al. 2015a; Chang 2017). For example, berberine (100 and 200 mg/kg for 21 days) exerted antihyperglycemic effects via possibly inducing peripheral glucose utilization instead of stimulating insulin release (Tang et al. 2006). Depending on the type of diabetes, antihyperglycemic effects of berberine show differences. Berberine (100 mg and 200 mg/kg for 15 days) was reported to decrease blood glucose level in KK-Ay mice (type II model), but it failed to change blood glucose level in nonobese diabetic mice (the NOD/LtJ mice, type I model) (Kong et al. 2009). The most important effect of it for decreasing fasting blood glucose level is not emphasized to associate with changing serum insulin levels in STZ/HFD-induced diabetic rats (Xia et al. 2011). On the contrary, a recent study reported that berberine (100 mg/kg for 16 weeks) decreased fasting blood glucose level by increasing insulin level in STZ/HFD-induced diabetic rats (Chang et al. 2015). Moreover, it was shown in another recent study that berberine (300 mg/kg for 12 weeks) reduced plasma glucose level and HbA1c in Zucker diabetic fatty rats (Wu et al. 2016). Berberine was proposed to increase protein kinase C (PKC) activity, which led to increased insulin receptor expression on cell surface and then increased glucose consumption via PI3K pathway as a signaling pathway (Kong et al. 2009). On the other hand, it was indicated that berberine (500 mg/kg for 14 weeks) was shown to decrease serum glucose level (Chueh and Lin 2012b) and to increase islet cell number and serum insulin levels in nonobese diabetic female rats (Chueh and Lin 2011). This protection of berberine on islet cell might probably relate to abolish apoptosis in mouse primary pancreatic islet cells via downregulating Bax/Bcl-2 gene expression ratio in vitro (Chueh and Lin 2012a). The other mechanisms of berberine's effects on diabetes may be relied on the inhibition of mitochondrial activity in liver, resulting in the inhibition of hepatic gluconeogenesis and hepatic lipid deposition. In detail, these may be mediated by downregulating the expression of forkhead transcription factor O1 (Fox O1), sterol regulatory element-binding protein 1c (SREBP1), carbohydrate-responsive element-binding protein (ChREBP) and phosphoenolpyruvate carboxykinase (PEPCK), G6Pase, as well as fatty acid synthase (FAS) at both mRNA and protein levels (Xia et al. 2011). The other possible mechanisms involved in the antidiabetic effects of berberine are also reported as to changes of expression of seven potential target genes in the liver of diabetic rats. These include downregulation of the expression of ras homolog gene family, member A (RHOA), MAPK4 and dihydrolipoamide S-acetyltransferase (DLAT) genes, as well as upregulation of the expression of the uncharacterized serine/threonine-protein kinase SgK494 (SgK494), DOT1-like, histone H3

methyltransferase (DOT1L), SET-domain containing 2 (SETD2), and malic enzyme 3 (ME3) genes (Wu et al. 2016). Its regulation of blood glucose depending on its dose and duration of application should not be ruled out. According to a previous study, short-term berberine (100 mg/kg for 7 days) administration to STZ/HFD-induced diabetic rats was reported to not significantly change the blood glucose level, body weight, and SOD level (Chang et al. 2016).

There are also numerous clinical studies regarding the efficiency of berberine in the management of blood glucose level in the diabetic patients. The studies have been reported to have some healing effect of berberine on diabetes based on differences in its dose and utilization time. One of the pilot clinical studies reported that berberine alone (0.5 g 3 times a day for 3 months) or combination with metformin decreased significantly fasting blood glucose level, HbA1c, and postprandial blood glucose level without altering fasting insulin level in type II diabetic patients (Yin et al. 2008). Berberine (1 g/day for 2 months) decreased fasting blood glucose levels, HbA1c, and serum insulin levels (Zhang et al. 2010b). In the mentioned study, berberine significantly increased the insulin receptor expression on the peripheral blood lymphocytes from the patients and in human cell lines with enhancing insulin sensitivity. In type II diabetic patients with dyslipidemia, berberine (1 g/day for 3 months) decreased fasting plasma glucose, post-load plasma glucose, HbA1c, triglyceride, total cholesterol, and LDL cholesterol without changing fasting serum insulin and post-load serum insulin levels (Gu et al. 2010). According to another result, berberine significantly reduced triglycerides and total cholesterol whereas metformin failed to change, indicating that berberine had a greater efficiency on lipid parameters than metformin (Yin et al. 2008). It should also be stated that gastrointestinal adverse effects of berberine were observed in the mentioned study depending on its dose. Nevertheless, another clinical study indicated that berberine could be effective in the management of blood glucose level in type II diabetic patients as much as metformin and rosiglitazone (Zhang et al. 2010b). Nonetheless, a systemic review and meta-analysis stated that berberine alone was not significantly better than oral hypoglycemic drugs such as rosiglitazone, metformin, or glipizide in the control of blood glucose levels in the diabetic patients; however, its combination with the mentioned agents was more effective in the management of hyperglycemia than oral hypoglycemic agents alone (Dong et al. 2012). In another current meta-analysis study, data from 27 randomized controlled clinical studies with 2569 patients indicated that there were no differences in the management of blood glucose level in type II diabetic patients between berberine and oral hypoglycemic agents. However, berberine was also effective to reduce the fasting plasma glucose and HbA1c when combined with lifestyle intervention in contrast to placebo or lifestyle intervention alone (Lan et al. 2015). In addition, berberine with oral hypotensive drugs or lifestyle intervention was effective to control blood pressure when compared to placebo, hypotensive drugs, or lifestyle intervention without serious adverse effect. On the contrary, a recent clinical study showed that the treatment of hypertensive type II diabetic patients with berberine in addition to hypotensive and hypoglycemic agents for 2 years did not significantly change the fasting plasma glucose, HbA1, SBP, and DBP when compared to control

groups and baseline values (Dai et al. 2015). However, it should be stated that berberine improved renal function, inhibited oxidative stress, and reduced inflammatory response.

The Cardiovascular Effects of Berberine

Data from recent studies reveal that berberine has a promising potential for the protection of diabetic heart. Berberine (30 mg/kg for 6 weeks) prevented lipid deposition and induced glucose transport in the diabetic heart by upregulating GLUT4 and peroxisome proliferator-activated receptor-γ (PPARγ) expression at mRNA and protein levels as well as downregulating PPARα expression at mRNA level (Dong et al. 2011). By this way, berberine improved cardiac functions such as stroke volume (SV), cardiac output (CO), and left ventricular systolic pressure (LVSP) in the diabetic rats. Berberine also reveals anti-arrhythmic effects in the diabetic rats. For example, berberine (180 mg/kg for 14 days after coronary ligation) attenuated the arrhythmia score and the incidence of arrhythmias by recovering resting membrane potential via improving the expression of Kir2.1 subunits of potassium (K^+) channels and the inwardly rectifying K^+ current in STZ/HFD-induced diabetic heart (Wang et al. 2011). Similarly, berberine (100 mg/kg for 7 days before myocardial ischemia) alleviated the arrhythmia score and the duration of arrhythmias at ischemia by ameliorating depressed transient outward K^+ current and L-type Ca^{2+} current, thereby improving the delay of electrical conduction in STZ-induced diabetic heart (Wang et al. 2012). In addition, a recent study indicated that berberine (100 mg/kg for 7 days) decreased myocardial infarct size and duration of VT and VF following myocardial I/R injury in STZ/HFD-induced diabetic rats, and had no significant effect on hemodynamic parameters such as heart rate (HR) during ischemia and reperfusion. The activation of AMPK, Akt, and inhibition of glycogen synthase kinase 3 beta (GSK3β) in the nonischemic myocardium might be involved in the protective effects of berberine (Chang et al. 2016). Berberine has anti-apoptotic effect against I/R injury. Berberine protected the diabetic heart against I/R-induced apoptosis and improved the left ventricular functions. The mechanisms underlying the anti-apoptotic effect of berberine seemed to be related to the activation of AMPK and PI3K–Akt–eNOS signaling pathways (Chen et al. 2014). Furthermore, berberine (100 mg/kg for 16 weeks) attenuated systolic and diastolic dysfunctions as well as cardiac fibrosis and hypertrophy in STZ/HFD-induced diabetic rats, and these cardioprotective effects might be mediated via enhancing activity of AMPK, Akt, and GSK3β activity as shown in vitro as well (Chang et al. 2015). Berberine (100 mg/kg for 30 days) also ameliorated the degree of myocardial inflammation, necrosis, and edema as well as reduced creatine phosphokinase-MB (CK-MB) in the diabetic hearts with isoproterenol-induced myocardial infarction (Suman et al. 2016).

To date, the efficiency of berberine alone or in combination with other antidiabetic drugs in the diabetic patients coexisting with cardiovascular diseases such as

acute myocardial I/R injury, myocardial infarction, hospitalization, and mortality remains to be unknown. In addition to numerous promising experimental studies, further studies are needed to test the effects of berberine on diabetes-induced cardiovascular dysfunction depending on age and gender.

The Relationship of Berberine with MicroRNAs

The relationship between miRNAs and berberine in type II diabetes has been recently reviewed in the concept of antihyperglycemic mechanisms of berberine (Chang 2017). The involvement of miRNAs in the cardioprotective effect of berberine has not been extensively examined in the diabetic hearts. Overexpression of miR-1 was shown to exacerbate arrhythmias in normal and infarcted hearts via depressing *KCNJ2* gene, encoding Kir2.1 subunit of the K^+ channels, and *GJA1* gene, encoding connexin 43 (Yang et al. 2007). Berberine also showed its antiarrhythmic affect in the diabetic heart by improving the repressed Kir2.1 (Wang et al. 2011). These findings may suggest that berberine exerts its cardioprotective actions in the diabetic heart by a possible mechanism that involves the regulation of miR-1 and subsequently recovery of the suppression of Kir 2.1. Although the underlying mechanisms of berberine's antidiabetic and cardioprotective effects have been investigated, there is a still more need to investigate functional interaction between berberine and miRNAs in both diabetic and nondiabetic hearts.

Ginseng

Ginseng is a perennial plant in the genus *Panax* of the family Araliaceae. The English word ginseng means literally "man root" and the genus name *Panax* means the word "panacea" or "all healing" which refers to a cure for all disease as a traditional belief (Park et al. 2012). South Korea, China, Canada, and the USA are the four countries with the largest production of fresh ginseng worldwide (Baeg and So 2013). In China, there are three main species of ginseng produced: *Panax ginseng* C.A. Meyer, *Panax quinquefolius* L., and *Panax notoginseng* Burkill. In South Korea, *Panax ginseng* C.A. Meyer is commonly produced. In Canada and the USA, *Panax quinquefolius* L. is mostly produced (Baeg and So 2013). Among them, *Panax ginseng* C.A. Meyer is a leading species in the production.

Ginseng includes several important compounds, such as amino acids, vitamins, fatty acids, and volatile oils. However, one of them is very valuable in the term of medical, which is ginsenosides. Ginsenosides are triterpene saponins or ginseng saponins that are the active components of ginseng. More than 150 ginsenosides have been identified so far (Kim et al. 2015).

Ginseng has been widely used as an alternative medicine for the treatment of various diseases in China, Korea, and Japanese as well as in Western countries with

an increased sale in North America and Europe (Wee et al. 2011). Anti-atherosclerotic, anti-arrhythmic, anti-myocardial ischemic effects of ginseng as well as its inhibitory effect on ventricular remodeling without focusing on diabetes have been comprehensively examined in a recent review (Sun et al. 2016). Moreover, antihyperglycemic effects of ginseng and its constituents with a possible signaling mechanism have been discussed in detail according to experimental and clinical studies (Yuan et al. 2012; Li and Gong 2015). On the other hand, there is a need to summarize the current data on the effects of ginseng and its constituents in the control of diabetes and diabetic heart diseases.

The Antidiabetic Effects of Ginseng

There are several experimental studies indicating that ginseng has shown hypoglycemic effects on diabetes (Jung et al. 2005). For example, the leaf extract of wild *Panax ginseng* C.A. Meyer (40 mg/kg or 200 mg/kg for 4 weeks) was reported to reduce blood glucose level in STZ-induced diabetic rats (Jung et al. 2005). Ginseng was also reported to be effective in decreasing blood glucose level in both STZ-induced and genetically modified diabetic mice (Sen et al. 2013). In addition, heat-processed American ginseng (100 mg/kg in aqueous solution for 20 days) reduced the serum glucose level in STZ-induced diabetic rats (Kim et al. 2007). Malonyl-ginsenosides extracted from roots of *Panax ginseng* (120 mg/kg for 4 days) were shown to decrease fasting glucose level without changing hepatic glycogen and cholesterol levels in STZ-induced diabetic mice (Liu et al. 2009). Moreover, another study reported that ginseng exerted antihyperglycemic action by decreasing glucose production in liver, insulin resistance in adipocytes and pancreas, and glucose absorption in intestine besides increasing glucose uptake in adipocytes and skeletal muscle (Li and Gong 2015). According to studies, the healing effects of ginseng rely on many pathways. It was also reported that ginseng (400 mg/kg for 6 weeks) improved the blood glucose level via protecting β-cells and increasing insulin secretion in STZ-induced diabetic rats (Karaca et al. 2010). It was indicated in vitro that ginseng might be protective against STZ-induced β-cell damage by downregulating iNOS, cyclooxygenase-2 (COX-2), and TNF-α through blocking NF-κB and MAPK activities (Yuan and Chung 2010). Another study demonstrated that ginseng (300 mg/kg for 8 days) reduced blood glucose level probably due to the mechanisms of improving insulin levels, and restoring hepatic glycogen phosphorylase and hepatic G6Pase levels (Amin et al. 2011). Ginseng (200 mg/kg) decreased HbA1c after 2 months in STZ-induced diabetic mice and 4 months in genetically modified diabetic mice (Sen et al. 2013). Ginseng polysaccharide from the root (50 mg/kg for 10 days) reduced fasting blood glucose and increased serum insulin level in STZ-induced diabetic rats. Its antihyperglycemic effects might be related to antioxidant effect indicated by increased SOD activity and decreased MDA levels as well. (Sun et al. 2014). Similarly, another experimental study demonstrated that wild Korean ginseng (200 mg/kg for 8 weeks) reduced blood glucose and enhanced

insulin level in STZ-induced diabetic rats (Moon et al. 2015). A recent study indicated that compound K from the roots of *P. ginseng* C.A. Meyer improved blood glucose level by suppression of hepatic gluconeogenesis possibly via activation of the AMPK both in vivo and in vitro (Wei et al. 2015). Ginsenoside Rg1 (20 mg/kg for 30 h) was reported to decrease glucose uptake and sodium glucose cotransporter 1 expression via the epidermal growth factor receptor/cAMP response element-binding protein signaling pathways in the intestine of mice as well as in differentiated human intestinal Caco-2 cells (Wang et al. 2015). Black ginseng extract (200 mg/kg for 5 weeks) decreased blood glucose level, reduced β-cell apoptosis, and inhibited inflammatory responses in STZ-induced diabetic mice, suggesting that downregulation of pro-inflammatory cytokine expression and blocking NF-κB activation might involve in the mechanism (Kim et al. 2016a). Ginseng is also used for phytotherapy against diabetes, inflammation, oxidative stress, and apoptotic cell loss. Red ginseng has been indicated to be with anti-apoptotic and anti-inflammation for β-cell at pancreas, resulting in elevation of insulin secretion. The other alternative therapy for diabetes is β-cell transplantation. It was informed that β-cell transplantation is higher when the donor received red ginseng (400 mg/kg for 7 days before transplantation) due to its anti-apoptotic and anti-inflammation properties (Kim et al. 2016b). A recent study showed that the extract of black ginseng increased glucose uptake in C2C12 cell line through AMPK, SIRT1, and PI3-k pathway. In addition, ginseng (300 mg/kg or 900 mg/kg for 5 weeks) decreased blood glucose level, HbA1c, triglyceride, and total cholesterol in STZ-induced diabetic mice (Seo et al. 2016). The mechanisms involved in the antihyperglycemic actions of black ginseng extracts are associated with suppression of expression hepatic genes in gluconeogenesis, glycogenolysis, and glycogenesis in the liver as well as increased expression of the genes related with glucose uptake in muscle. A recent study reported that red ginseng might be important as an adjuvant to invigorate the actions of rosiglitazone, an antidiabetic agent acting as an insulin sensitizer, in the regulation of blood glucose levels in obese mice on HFD (Oh et al. 2017). In addition, the authors suggested that ginseng would be useful in controlling blood glucose levels of the diabetic patients when combined with the mentioned agent. On the other hand, a previous experimental study brings us to ask a question: Could the application period of ginseng be important for its antihyperglycemic actions? Because ginseng (150 mg/kg for 7 days) did not change plasma glucose levels in STZ-induced diabetic rats (Tsai et al. 2014). That is why there is a need for further studies to evaluate the efficiency based on the treatment time or the dose of ginseng on diabetes.

Unlike experimental studies, clinical data on the antihyperglycemic action of ginseng are not too much to support the efficacy of ginseng in the management of hyperglycemia in diabetic patients. In type II diabetic patients, ginseng (300 mg for 8 weeks) resulted in decreased fasting blood glucose level, IL-6, and highly sensitive C-reactive protein without changing anthropometric parameters, HbA1c, as well as TNF-α when compared to placebo group (Hosseini et al. 2016). Furthermore, in an updated systematic review and meta-analysis, ginseng improved fasting glucose and postprandial insulin levels although it did not change HbA1c, postprandial

glucose, or fasting insulin when compared to the control groups (Gui et al. 2016b). It should be important to emphasize that ginseng was reported to be useless for reducing fasting blood glucose level in the diabetic patients receiving oral glycemic agents or insulin (Gui et al. 2016a; Gui et al. 2016b).

The Cardiovascular Effects of Ginseng

The actions of ginseng and ginsenosides on cardiovascular diseases have been reviewed in detail (Lee and Kim 2014; Sun et al. 2016); however, there are limited studies on the efficiency of ginseng and ginsenosides in diabetic heart. Ginsenoside Rb1 (40 mg/kg 10 min before ischemia) decreased myocardial infarct size, apoptosis, caspase-3 activity, and LDH and creatine kinase-MB (CK-MB) levels in STZ-induced diabetic rats as well as improved hemodynamic parameters such as blood pressure at the end of reperfusion. These protective effects might be mediated via activation of PI3K/Akt pathway in the diabetic hearts (Wu et al. 2011). A comprehensive experimental study also revealed that ginseng might be cardioprotective in the different experiment models of diabetes: type I, STZ-induced C57BL/6 mice, and type II, *Lepr*^{db} mice (Sen et al. 2013). The results of the mentioned study indicated that ginseng (200 mg/kg for 2 or months) enhanced ejection fraction (EF), SV, and CO, and reduced stroke work (SW) in both types. Ginseng also attenuated the expression of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and some vasoactive factors such as VEGF, ET-1, and TGF-β1 in addition to suppression of superoxide anion accumulation and HO-1 in diabetic hearts (Sen et al. 2013). Ginseng (150 mg/kg for 7 days) enhances cardiac performances in the diabetic rats as indicated by increased SBP, DBP, CO, and cardiac contraction via upregulating PPARδ expression and restoring troponin I (TnI) phosphorylation in the diabetic hearts (Tsai et al. 2014). Diabetic angiopathy, a risk factor for ischemic heart disease, is defined as one of blood vessel diseases. A recent study revealed that ginsenoside attenuated VEGF, IL-6, total cholesterol, triglyceride, and lipoprotein, and it was proposed that the mechanism of anti-angiopathy effects might be related to the activation of p38 MAPK, ERK1/2, and JNK signaling pathways (Shi et al. 2016).

The Relationship of Ginseng with MicroRNAs

There are two important reviews on the modulation of miRNAs by ginseng in cancer (Dai et al. 2017; Mohammadi et al. 2017); on the other hand; the impact of ginseng and its active constitutes on diabetes and diabetes-induced cardiovascular dysfunctions via modulating miRNAs remain to be investigated. It was reported that one of the active ingredients of ginseng, ginsenoside Rg1, induced angiogenesis by increasing eNOS via downregulating miR-124 expression (Chan et al. 2009). In

addition, miRNAs play an important role in the cardioprotective effect of ginsenoside Rg1 against hypoxia/ischemia injury in vitro. It was indicated that ginsenoside Rg1 increased miR-1, miR-29a, and miR-208 expression as well as decreased miR-21 and miR-320 expression (Yan et al. 2015). Depending on the knowledge from a previous study showing downregulation of miR-1 and upregulation of miR-21 in the diabetic heart (Yildirim et al. 2013) as well as the mentioned study above, it may be stated that ginsenoside Rg1 would be effective in preventing or decreasing cardiovascular complications such as arrhythmias and cardiomyopathy by improving the expression profile of miRNAs in the diabetic heart. Another potential miRNA may be miR-21 as a target for ginseng in the diabetes and related complications. It is known that miR-21 has a crucial role in cell proliferation and apoptosis, which is generally upregulated in various diseases (Yildirim et al. 2013; Sekar et al. 2016). Based on this information, ginseng would also exert anti-apoptotic actions in the diabetes via downregulating miR-21.

Curcumin

Curcumin is the most active ingredient of turmeric plant (*Curcuma longa*) belonging to the ginger family Zingiberaceae, which is mainly cultivated in South and Southeast Asia. The name of curcumin shows differences in various countries with some different turmeric species. In Turkey, curcumin is commonly known as "Zerdeçal and Safran kökü" (Prasad and Aggarwal 2011). For thousands of years, curcumin has been used in the prevention and treatment of various diseases, with increasing potential (Gupta et al. 2012).

The Antidiabetic Effects of Curcumin

Controversial results from experimental and clinical studies are present about the efficacy of curcumin on the control of hyperglycemia in diabetes. An early study indicated that curcumin (0.5% in diet for 8 weeks) did not change fasting blood glucose level (Suresh Babu and Srinivasan 1995). Another investigation reported that curcumin (200 mg/kg for 24 weeks) had no effect on blood glucose level in STZ-induced diabetic rats due to failing to alter oxidative stress (Majithiya and Balaraman 2005). In addition, although curcumin diet (0.002 and 0.01% for 8 weeks) was indicated to reduce the SOD activity in the pancreas, it did not change the glucose and insulin levels in STZ-induced diabetic rats (Suryanarayana et al. 2007). A recent study also demonstrated that curcumin (100 mg/kg for 12 weeks) did not have influence on the blood glucose level in STZ-induced diabetic rats (Li et al. 2015). On the other hand, there are several studies indicating that curcumin is effective in the management of hyperglycemia. In isolated mouse pancreatic islets, curcumin pretreatment (10 μM for 24 h) was reported to be protective against

STZ-induced cell death and β-cell destruction as well as increased insulin secretion because of its free radical scavenger features (Meghana et al. 2007). Moreover, curcumin (80 mg/kg for 15 days) reduced fasting plasma glucose level and improved insulin resistance in rats receiving HFD due to its anti-inflammatory and anti-lipolytic effects (El-Moselhy et al. 2011). The results of mentioned study also indicated that curcumin was as effective as rosiglitazone (1 mg/kg). Another study showed that the novel water-soluble curcumin derivative (10 mg/kg for 45 days) decreased plasma glucose and increased plasma insulin levels by increasing the expression and the activity of HO-1 in different tissues such as pancreas, liver, and aorta (Abdel Aziz et al. 2012). Moreover, curcumin (60 mg/kg for 14 days) exerted antihyperglycemic effect as evidenced by reducing blood glucose level and increasing insulin level (Xavier et al. 2012). Its antidiabetic mechanisms might be related to improving the functions of residual β-cells or peripheral glucose utilization as proved by reversal of insulin receptor downregulation in skeletal muscle. Curcumin (15 mg/kg for 6 weeks) was also reported to have antihyperglycemic effect via upregulating insulin-like growth factor 1 (IGF1) and antioxidant enzymes as well (El-Bahr 2013). In cell culture, curcumin was shown to increase glucagon-like peptide 1 (GLP1) secretion via Ca^{2+}/CaMKII pathway, which might act as the underlying mechanism for antihyperglycemic effect (Takikawa et al. 2013). Another in vitro study also indicated that a novel curcumin derivative resulted in increased synthesis and secretion of insulin via upregulating HO-1, transcription factor 7-like 2, and GLP as well as the c-Jun N-terminal kinase (JNK) pathway inhibition which improve insulin gene expression (Aziz et al. 2014). A recent study demonstrated that the combination of curcumin (60 mg/kg for 30 days) with insulin significantly increased the CAT activity and decreased aspartate aminotransferase (AST) levels when compared to insulin- and curcumin-treated rats, indicating that the combination treatment might be more effective in the improvement of diabetes-induced oxidative damage (Palma et al. 2014). Recently, it was shown that curcumin (100 mg/kg for 8 weeks) showed antidiabetic effects in STZ-induced diabetic rats. The antidiabetic effects might be associated with its anti-inflammatory, antioxidant, and anti-apoptosis mechanisms without any significant adverse effects in vivo and in vitro (Rashid and Sil 2015). It should be important to emphasize that the healing features of curcumin were observed as effective as glibenclamide (5 mg/kg) in controlling blood glucose level as well as reducing pro-inflammatory cytokines such as TNF-α, IL1-β, and interferon gamma (IFN-γ) in the mentioned study. Within this context, it may be speculated that curcumin may take the role of glibenclamide in the management of diabetes when considering the cardiovascular side effect of glibenclamide.

In addition to experimental studies, clinical data exert contradictory results. The usage of curcumin in prediabetic individuals is demonstrated to decrease the number of individuals who are eventually diagnosed with type II diabetes and improve β-cell function after 9 months (Chuengsamarn et al. 2012). A clinical study suggests that curcumin combined with glyburide, an oral antihyperglycemic agent, might be better in the management of hyperglycemia and hyperlipidemia in type II diabetic

patients as an adjuvant therapy (Neerati et al. 2014). A nano-micelle form of curcumin (80 mg/day for 3 months) was shown to improve fasting blood glucose, HbA1c, and estimated average glucose without any effect on LDL, HDL, total triglyceride, and total cholesterol when compared to placebo (Rahimi et al. 2016). On the other hand, in type II diabetic patients, curcumin (500 mg/day for 15 days) did not alter fasting blood glucose, total cholesterol, total triglyceride, and HDL but decreased LDL (Yang et al. 2015).

The Cardiovascular Effects of Curcumin

Curcumin is known to possess protective effects against myocardial I/R injury in nondiabetic hearts (Ilyas et al. 2016; Xiao et al. 2016; Pang et al. 2015b; Wongcharoen and Phrommintikul 2009). On the other hand, curcumin remains to be elucidated in the diabetic hearts. A recent review has summarized the potential efficiency of curcumin in the diabetic cardiomyopathy (Karuppagounder et al. 2017). However, up to now, little attention has been given on the role of curcumin in decreasing or preventing myocardial I/R injury in the diabetic hearts. There is no direct evidence regarding whether pre- or post-curcumin treatment ameliorates myocardial injury such as infarction and arrhythmias in experimental and clinical studies. Although curcumin is known to possess antioxidant effects, a previous study indicated that curcumin (200 mg/kg for 24 weeks) had no effects on antioxidant enzymes such as SOD, CAT, and glutathione levels in aorta as well as mean blood pressure in STZ-induced diabetic rats (Majithiya and Balaraman 2005). Nevertheless, it was shown that curcumin (100 mg/kg for 8 weeks) reduced cardiomyocyte hypertrophy and cardiac fibrosis as well as improved hemodynamic parameters in STZ-induced diabetic rats (Soetikno et al. 2012). Curcumin (200 mg/kg for 16 weeks) also improved left ventricular dysfunctions and pathophysiological changes in myocardium and inhibited myocardial injury, inflammation, and oxidative stress as well as reduced myocardial apoptosis in STZ/HFD-induced diabetic rats (Yu et al. 2012). The possible mechanism in such effects was reported to participate in PKC-MAPK signaling pathway as evidenced by curcumin-mediated inhibition of PKC-α and β_2-MAPK activities (Soetikno et al. 2012). Its cardioprotective effects might also associate with Akt/GSK-3β signaling pathways (Yu et al. 2012). The other previous study revealed that curcumin (20 mg/kg for 45 days) and novel water-soluble curcumin derivate (20 mg/kg for 45 days) improved left ventricular functions such as increased HR and decreased SBP as well as reduced gene expression of cardiac hypertrophy markers including ANP and myocyte enhancer factor 2A and 2C in STZ-induced diabetic rats (Aziz et al. 2013). These effects of curcumin could also be related to its antioxidant effects, e.g., glutathione, CAT, SOD, and glutathione-S-transferase, as well as anti-inflammatory such as attenuation of IL-6 and TNF-α in the heart of STZ-induced diabetic rat at a dose of 200 mg/kg for 6 weeks (Abo-Salem et al. 2014). Moreover, the restoration of cardiac dysfunction by curcumin in STZ-induced diabetic mRen2.Lewis and ovariectomized rats was

reported to rely on modulation of renin-angiotensin system, resulting in decreasing of plasma angiotensin II levels and expression of angiotensin II type receptor as well (VonCannon et al. 2014). It is well known that high glucose and insulin could induce hypertrophy at cardiomyocytes; however, curcumin was reported to restore ANP mRNA expression, total protein, and cell surface area via PPAR γ/Akt/NO signaling pathway; in contrary, the pathway antagonist or inhibitors abolish the effects of curcumin (Chen et al. 2015). The curcumin has not only protective effect against macrovascular complication such as cardiovascular disease, but also microvascular complications resulting from damaging of small blood vessels. One of the previous studies indicated that curcumin (200 mg/kg for 8 and 12 weeks) improved abnormality of right coronary artery, veins, and cardiac arteries in the diabetic hearts (Anupunpisit et al. 2015). These protective effects might be based on its prevention of ROS production by inhibiting NADPH oxidase and inhibition of apoptosis via enhancing Bcl-2 expression and reducing Bax expression (Yu et al. 2016). In addition, the result suggested that activation of PI3K/Akt/GSK-3β signaling pathway might be involved in the effects of curcumin on high glucose-exposed cardiomyocytes. Another possibility of its protective effect is to prevent atherosclerosis associated with diabetes by using one of the analogs L3 of curcumin via improving several factors such as dyslipidemia, hyperglycemia, endothelial dysfunction, oxidative stress and ox-LDL, and lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) in aortic arch (Zheng et al. 2016).

The Relationship of Curcumin with MicroRNAs

Several studies indicate that curcumin exerts its protective effects through altering miRNA expression in several types of cancers (Momtazi et al. 2016; Sun et al. 2008; Kronski et al. 2014). For example, it was proposed that curcumin might decrease tumorigenesis in human pancreatic cancer cells via downregulating estrogen receptor 1 expression via upregulating miR-22 (Sun et al. 2008). A recent study indicates that curcumin might be effective against oxidative stress by modulating miRNAs (Howell et al. 2013). Curcumin downregulated expression of 17 miRNAs such as miR-15b, miR-17, miR-26b, miR-27b, miR-28–3p, miR-30b, miR-30d, miR-92a, miR-125a-5p, miR-141, miR-196b, miR-195, miR-302a, miR-302c, miR-320a, and miR-9 in hydrogen peroxide-exposed cell culture and alleviated expression of AT1R, NF-κB, and VEGF as well as antioxidant genes. Results of this study revealed that curcumin might modulate the expression of miRNAs that play a role in antioxidant defense and renin-angiotensin systems. Oxidative stress due to hyperglycemia is known to be one of the main causes of diabetes leading to cardiovascular dysfunctions. In this case, it is possible that curcumin would be cardioprotective in the diabetes through altering oxidative stress-induced miRNAs. However, the role of miRNAs in the cardiac action of curcumin remains to be investigated in diabetes.

Ginkgo

Ginkgo biloba L. is a "living fossil" tree species belonging to Ginkgoaceae family and is also known as gingko, maidenhair tree, and kew tree. Gingko is one of the most popular traditional herbal remedies in China over a million years and has been attracting a great interest in Europe and the USA (Jacobs and Browner 2000; Isah 2015). EGb 761 is a well-known standardized extract from the leaves of *Ginkgo biloba L.*, which has been commonly preferred in the scientific researches. EGb 761 includes flavone glycosides, terpene lactones, and ginkgolic acids (Jacobs and Browner 2000). Gingko has antioxidant, anti-stress, neuroprotective, vasoregulatory, anti-inflammatory, anti-atherosclerotic, memory, and sexual function enhancement effects (DeFeudis 2003; Dziwenka and Coppock 2016; Zhang et al. 2008). There is a need to summarize current articles about the actions of gingko on cardiovascular dysfunctions in diabetes.

The Antidiabetic Effects of Gingko

Gingko reveals antidiabetic effects due to antioxidant and anti-apoptotic features. In STZ-induced diabetic rats, EGb761 treatment (300 mg/kg for 30 days) significantly decreased blood glucose level as well as increased antioxidant enzyme activities such as SOD, CAT, and GSH-Px in hepatic and pancreatic tissue (Cheng et al. 2013). It should be important to state that EGb 761 showed a similar beneficial effect as glibenclamide (5 mg/kg) in terms of anti-hyperglycemia, anti-hyperlipidemia, and antioxidant capacity. Another study reported that EGb 761 (3 mg/kg for 20 days) reduced blood glucose level and increased insulin level in STZ-induced diabetic rats (Ren et al. 2013). Another important result of the mentioned study was that the treatment of diabetic rats with EGb 761 before bone marrow mesenchymal stem cell injection, an alternative therapy for diabetes, increased the efficiency of bone marrow mesenchymal stem cells on the control of blood glucose level. This effect might be related with the antioxidant features of EGb 761 as evidenced by decreasing the levels of MDA, IL-6, and TNF-α as well as increasing SOD and GSH-Px, which indicates that EGb protects bone marrow mesenchymal stem cells against apoptosis after transplantation by attenuating oxidative stress. Furthermore, EGb 761 exerts different effects in the control of hyperglycemia depending on the types of diabetes. EGb 761 (50 mg/kg for 20 days) decreased blood glucose level and increased insulin level in STZ-induced diabetic mice although EGb 761 (50 mg/kg for 40 days) did not alter blood glucose and insulin levels in HFD-induced diabetic mice (Rhee et al. 2015). This is the reason why different effects observed in the different models of diabetes have not been clearly explained yet. However, anti-inflammatory actions of EGb 761 as proved by decreasing pro-inflammatory cytokine levels including IL-1β and TNF-α in the pancreas of STZ-induced diabetic mice were involved in its antihyperglycemic

effect. In addition, the leaf extract of gingko (100 mg/kg in diet for 14 weeks) showed antidiabetic and antioxidative effects via modulating the key gene expression such as upregulation of PPAR-α and GLUT-4 expression and downregulation of TNF-α in alloxan/HFD-induced diabetic rats (Naseem et al. 2016). In contrary to antidiabetic effects of gingko, there are studies to show the failure of gingko in the control of blood glucose level in the diabetes as well. For example, EGb 761 (100 and 200 mg/kg for 6 weeks) was reported to have no effects on fasting blood glucose and insulin levels in Otsuka Long-Evans Tokushima Fatty rats (Lim et al. 2011). Similarly, EGb 761 (100 mg/kg for 14 days) did not have a pronounced effect on blood glucose level compared to non-treated diabetic rats despite the antioxidative/nitrosative stress (Taliyan and Sharma 2012). Moreover, EGb 761 (50 mg/kg for 3 weeks) did not affect the glucose levels (Saini et al. 2014). The extract of *Ginkgo biloba* leaves (50, 100, 200 mg/kg for 8 weeks) did not modulate fasting blood glucose level in STZ-induced diabetic rats (Lu et al. 2015). These contradictory results of ginkgo might be associated with some factors, such as variability of the extraction methods, application route and dosage of gingko, types of diabetes models, as well as animal species.

Despite the presence of numerous experimental studies showing antidiabetic effects of ginkgo, there are limited clinical trials on the efficiency of ginkgo in the diabetic patients. In addition, there is still ongoing debate whether gingko is effective in the management of hyperglycemia and diabetes-associated cardiovascular dysfunctions or not. For example, one previous study reported that EGb (120 mg/day for 3 months) decreased HbA1c without changing fasting glucose and insulin levels (Kudolo et al. 2006b; Kudolo et al. 2006a). On the other hand, dry extract of *Ginkgo biloba* (160 and 240 mg/day for 9 and 18 months) did not significantly change HbA1c in type II diabetic patients (Spadiene et al. 2013).

The Cardiovascular Effects of Gingko

Diabetic patients are vulnerable to vascular complications due to hyperglycemia. An in vitro study reported that EGb might have protective endothelial dysfunctions induced by high glucose in human aortic endothelial cells. The endothelial protection of ginkgo was associated with a reduction in endothelial adhesion by increasing HO-1 expression via activating the Akt/eNOS and p38/MAPK pathways (Tsai et al. 2013). Also, one of the recent pilot clinical studies reported that EGb1 761 (240 mg/day for 2 months) improved insulin resistance, inflammatory and oxidative stress, as well as arteriosclerosis in metabolic syndrome patients, suggesting that gingko might be effective in decreasing cardiovascular disease and associated mortality risk (Siegel et al. 2014). The other vascular complication of diabetes is reported to develop hypertension. However, EGb 761 (120 mg/day for 3 months) is indicated to fail to restore SBP and DBP in type II diabetic patients (Kudolo et al. 2006b). In vitro model of I/R injury and pretreatment of diabetic rats with EGb 761 (50 mg/kg for 10 days before I/R protocol) significantly attenuated the incidence of

reperfusion-induced VF and VT and improved aortic flow as well as left ventricular pressure in both non-preconditioned and preconditioned diabetic hearts due to its free radical scavenger (Tosaki et al. 1996). Another experimental study reported that EGb 761 (100 mg/kg for 3 months) increased the resistance of diabetic heart to hypoxia by improving ultrastructural and morphometric parameters, including volume of myofibrils, sarcoplasmic reticulum, t-tubules, vacuoles, and mitochondria (Fitzl et al. 2000). One of the diabetes complications is neuropathy belonging to microvascular complication. So, it was reported that gingko could be protective against autonomic neuropathy in the diabetic myocardium. In spontaneously diabetic BioBreeding/Ottawa Karlsburg rats, EGb 761 (100 mg/kg for 3 months) improved autonomic nerves, Schwann cells in the myocardium, and postsynaptic β1-adrenergic receptor-adenylate cyclase coupling system (β1-AR-AC), demonstrating the protective effect of EGb 761 on the cardiovascular autonomic neuropathy in the diabetic myocardium (Schneider et al. 2010). One of the macrovascular complications of diabetes is also atherosclerosis. So, EGb 761 (100 and 200 mg/kg for 6 weeks) was reported to have protective effect against atherosclerosis in Otsuka Long-Evans Tokushima Fatty rats by inhibiting proliferation and migration of vascular smooth muscle cells (VSMCs) and promoting apoptosis via increasing apoptotic activity of caspase 3 after balloon-injured carotid artery (Lim et al. 2011). A recent experimental study also demonstrated that EGb 761 (50 mg/kg for 3 weeks) ameliorated cardiovascular dysfunctions such as reduced protein content and LV collagen content, and serum LDH levels via stimulating antioxidant activity and inhibiting opening of mitochondrial transitional permeability pore (mPTP) in STZ-induced diabetic rats (Saini et al. 2014).

The Relationship of Ginkgo with MicroRNAs

Up to now, there have not been any investigations focusing on the role of miRNAs in the biological and physiological actions of gingko as a mechanism in the cardiovascular disease in both diabetic and nondiabetic organisms. It should be stated that there are limited articles showing the effect of gingko in cancer via altering miRNAs (Zhi et al. 2016). The results from this study indicate that Ginkgolide B, a constitute of ginkgo leaf, abolishes the invasion of bladder cancer cells by upregulating miR-223-3p. Another study demonstrates that Ginkgolide B exerts protective effect against superoxide generation and mitochondrial apoptosis by suppressing p53-regulated NOX4 and $p66^{shc}$ through upregulating miR214, indicating that gingko might decrease cisplatin-induced cytotoxicity (Ma et al. 2016). Depending on these knowledges, it may be suggested that gingko may exert its protective effect in diabetes and subsequent cardiovascular disorders mentioned before by changing miRNAs. Unfortunately, there is no direct evidence between miRNAs and gingko in diabetes. Further studies are needed to clarify the role of miRNAs in the effect of gingko.

Conclusion

The prevalence of diabetes and mortality rate of diabetes-induced cardiovascular disease continues to be the highest in developed or developing countries. Therefore, there is still a need to develop novel therapies for prevention of diabetes or management of hyperglycemia and treatment of diabetes-related cardiovascular disease. The adverse effects of diabetes on heart remain to be in a critical level even if hyperglycemia is controlled; at this point the importance of medicinal herbs and ingredients having both antidiabetic and cardioprotective effects is increasing in case of the long-term treatment. Not surprisingly, the herbal medicine mentioned here has diverse physiological actions and sophisticated mechanisms. Although contradictory results on the effects of resveratrol, berberine, ginseng, curcumin, and gingko are present, growing evidences reveal their healing actions in the treatment of diabetes and cardiovascular dysfunctions. Of all of the herbal medicine mentioned here, resveratrol and berberine seem to have the most therapeutic potential in the matter of both control of hyperglycemia and improvement of diabetic cardiovascular dysfunctions. Regarding ginseng, curcumin, and ginkgo, more study needs to be done to clarify the protective effects of them on cardiovascular diseases in diabetes as well as possible underlying mechanism(s) of their actions despite identified antidiabetic effects. It should be kept in mind that as more mechanisms involved in actions of herbal medicine have been elucidated in preclinical and clinical studies, the development of new and creative therapeutic approaches is so accelerating. Herein, researches on miRNAs as a target for the herbal medicine would open a new door to advances in the prevention of diabetes and diabetic cardiovascular diseases in future.

References

Abdel Aziz MT, El-Asmar MF, El-Ibrashy IN, Rezq AM, Al-Malki AL, Wassef MA, Fouad HH, Ahmed HH, Taha FM, Hassouna AA, Morsi HM (2012) Effect of novel water soluble curcumin derivative on experimental type-1 diabetes mellitus (short term study). Diabetol Metab Syndr 4:30

Abo-Salem OM, Harisa GI, Ali TM, El-Sayed El SM, Abou-Elnour FM (2014) Curcumin ameliorates streptozotocin-induced heart injury in rats. J Biochem Mol Toxicol 28:263–270

American Diabetes Association (2010) Diagnosis and classification of diabetes mellitus. Diabetes Care 33(Suppl 1):S62–S69

Amin KA, Awad EM, Nagy MA (2011) Effects of Panax quinquefolium on streptozotocin-induced diabetic rats: role of C-peptide, nitric oxide and oxidative stress. Int J Clin Exp Med 4:136–147

Anupunpisit V, Petpiboolthai H, Khimmaktong W (2015) Microvasculature improvement of heart in diabetic rat with curcumin supplementation. J Med Assoc Thail 98(Suppl 10):S74–S83

Ar'rajab A, Ahren B (1993) Long-term diabetogenic effect of streptozotocin in rats. Pancreas 8:50–57

Ates O, Cayli SR, Yucel N, Altinoz E, Kocak A, Durak MA, Turkoz Y, Yologlu S (2007) Central nervous system protection by resveratrol in streptozotocin-induced diabetic rats. J Clin Neurosci 14:256–260

Atkinson MA, Eisenbarth GS, Michels AW (2014) Type 1 diabetes. Lancet 383:69–82
Aziz MT, El Ibrashy IN, Mikhailidis DP, Rezq AM, Wassef MA, Fouad HH, Ahmed HH, Sabry DA, Shawky HM, Hussein RE (2013) Signaling mechanisms of a water soluble curcumin derivative in experimental type 1 diabetes with cardiomyopathy. Diabetol Metab Syndr 5:13
Aziz MT, El-Asmar MF, Rezq AM, Wassef MA, Fouad H, Roshdy NK, Ahmed HH, Rashed LA, Sabry D, Taha FM, Hassouna A (2014) Effects of a novel curcumin derivative on insulin synthesis and secretion in streptozotocin-treated rat pancreatic islets in vitro. Chin Med 9:3
Baeg IH, So SH (2013) The world ginseng market and the ginseng (Korea). J Ginseng Res 37:1–7
Bagul PK, Dinda AK, Banerjee SK (2015) Effect of resveratrol on sirtuins expression and cardiac complications in diabetes. Biochem Biophys Res Commun 468:221–227
Balakumar P, Sharma NK (2012) Healing the diabetic heart: does myocardial preconditioning work? Cell Signal 24:53–59
Balakumar P, Maung UK, Jagadeesh G (2016) Prevalence and prevention of cardiovascular disease and diabetes mellitus. Pharmacol Res 113:600–609
Bhatt LK, Veeranjaneyulu A (2014) Enhancement of matrix metalloproteinase 2 and 9 inhibitory action of minocycline by aspirin: an approach to attenuate outcome of acute myocardial infarction in diabetes. Arch Med Res 45:203–209
Bhatt JK, Thomas S, Nanjan MJ (2012) Resveratrol supplementation improves glycemic control in type 2 diabetes mellitus. Nutr Res 32:537–541
Blade C, Baselga-Escudero L, Arola-Arnal A (2014) microRNAs as new targets of dietary polyphenols. Curr Pharm Biotechnol 15:343–351
Bo S, Ponzo V, Ciccone G, Evangelista A, Saba F, Goitre I, Procopio M, Pagano GF, Cassader M, Gambino R (2016) Six months of resveratrol supplementation has no measurable effect in type 2 diabetic patients. A randomized, double blind, placebo-controlled trial. Pharmacol Res 111:896–905
Bonnefont-Rousselot D (2016) Resveratrol and cardiovascular diseases. Nutrients 8. https://doi.org/10.3390/nu8050250
Brasnyo P, Molnar GA, Mohas M, Marko L, Laczy B, Cseh J, Mikolas E, Szijarto IA, Merei A, Halmai R, Meszaros LG, Sumegi B, Wittmann I (2011) Resveratrol improves insulin sensitivity, reduces oxidative stress and activates the Akt pathway in type 2 diabetic patients. Br J Nutr 106:383–389
Brindisi MC, Bouillet B, Verges B, Halimi S (2010) Cardiovascular complications in type 1 diabetes mellitus. Diabetes Metab 36:341–344
Carolo Dos Santos K, Pereira Braga C, Octavio Barbanera P, Seiva FR, Fernandes Junior A, Fernandes AA (2014) Cardiac energy metabolism and oxidative stress biomarkers in diabetic rat treated with resveratrol. PLoS One 9:e102775
Chan LS, Yue PY, Mak NK, Wong RN (2009) Role of microRNA-214 in ginsenoside-Rg1-induced angiogenesis. Eur J Pharm Sci 38:370–377
Chang W (2017) Non-coding RNAs and berberine: a new mechanism of its anti-diabetic activities. Eur J Pharmacol 795:8–12
Chang W, Zhang M, Meng Z, Yu Y, Yao F, Hatch GM, Chen L (2015) Berberine treatment prevents cardiac dysfunction and remodeling through activation of 5′-adenosine monophosphate-activated protein kinase in type 2 diabetic rats and in palmitate-induced hypertrophic H9c2 cells. Eur J Pharmacol 769:55–63
Chang W, Li K, Guan F, Yao F, Yu Y, Zhang M, Hatch GM, Chen L (2016) Berberine pretreatment confers cardioprotection against ischemia-reperfusion injury in a rat model of type 2 diabetes. J Cardiovasc Pharmacol Ther 21:486–494
Chen ZC, Cheng YZ, Chen LJ, Cheng KC, Li Y, Cheng J (2012) Increase of ATP-sensitive potassium (K(ATP)) channels in the heart of type-1 diabetic rats. Cardiovasc Diabetol 11:8
Chen K, Li G, Geng F, Zhang Z, Li J, Yang M, Dong L, Gao F (2014) Berberine reduces ischemia/reperfusion-induced myocardial apoptosis via activating AMPK and PI3K-Akt signaling in diabetic rats. Apoptosis 19:946–957

Chen R, Peng X, Du W, Wu Y, Huang B, Xue L, Wu Q, Qiu H, Jiang Q (2015) Curcumin attenuates cardiomyocyte hypertrophy induced by high glucose and insulin via the PPAR-gamma/Akt/NO signaling pathway. Diabetes Res Clin Pract 108:235–242

Cheng D, Liang B, Li Y (2013) Antihyperglycemic effect of Ginkgo biloba extract in streptozotocin-induced diabetes in rats. Biomed Res Int 2013:162724

Chi TC, Chen WP, Chi TL, Kuo TF, Lee SS, Cheng JT, Su MJ (2007) Phosphatidylinositol-3-kinase is involved in the antihyperglycemic effect induced by resveratrol in streptozotocin-induced diabetic rats. Life Sci 80:1713–1720

Chueh WH, Lin JY (2011) Berberine, an isoquinoline alkaloid in herbal plants, protects pancreatic islets and serum lipids in nonobese diabetic mice. J Agric Food Chem 59:8021–8027

Chueh WH, Lin JY (2012a) Berberine, an isoquinoline alkaloid, inhibits streptozotocin-induced apoptosis in mouse pancreatic islets through down-regulating Bax/Bcl-2 gene expression ratio. Food Chem 132:252–260

Chueh WH, Lin JY (2012b) Protective effect of berberine on serum glucose levels in non-obese diabetic mice. Int Immunopharmacol 12:534–538

Chuengsamarn S, Rattanamongkolgul S, Luechapudiporn R, Phisalaphong C, Jirawatnotai S (2012) Curcumin extract for prevention of type 2 diabetes. Diabetes Care 35:2121–2127

Costantino S, Paneni F, Luscher TF, Cosentino F (2016) MicroRNA profiling unveils hyperglycaemic memory in the diabetic heart. Eur Heart J 37:572–576

Dai P, Wang J, Lin L, Zhang Y, Wang Z (2015) Renoprotective effects of berberine as adjuvant therapy for hypertensive patients with type 2 diabetes mellitus: evaluation via biochemical markers and color Doppler ultrasonography. Exp Ther Med 10:869–876

Dai D, Zhang CF, Williams S, Yuan CS, Wang CZ (2017) Ginseng on cancer: potential role in modulating inflammation-mediated angiogenesis. Am J Chin Med 45:13–22

Defeudis FV (2003) A brief history of EGb 761 and its therapeutic uses. Pharmacopsychiatry 36(Suppl 1):S2–S7

Dong SF, Hong Y, Liu M, Hao YZ, Yu HS, Liu Y, Sun JN (2011) Berberine attenuates cardiac dysfunction in hyperglycemic and hypercholesterolemic rats. Eur J Pharmacol 660:368–374

Dong H, Wang N, Zhao L, Lu F (2012) Berberine in the treatment of type 2 diabetes mellitus: a systemic review and meta-analysis. Evid Based Complement Alternat Med 2012:591654

Dziwenka M, Coppock RW (2016) Ginkgo biloba. In: Nutraceuticals: efficacy, safety and toxicity. Elsevier, Amsterdam, pp 681–691

El-Bahr SM (2013) Curcumin regulates gene expression of insulin like growth factor, B-cell CLL/lymphoma 2 and antioxidant enzymes in streptozotocin induced diabetic rats. BMC Complement Altern Med 13:368

El-Moselhy MA, Taye A, Sharkawi SS, El-Sisi SF, Ahmed AF (2011) The antihyperglycemic effect of curcumin in high fat diet fed rats. Role of TNF-alpha and free fatty acids. Food Chem Toxicol 49:1129–1140

Fan Y, Liu L, Fang K, Huang T, Wan L, Liu Y, Zhang S, Yan D, Li G, Gao Y, Lv Y, Chen Y, Tu Y (2016) Resveratrol ameliorates cardiac hypertrophy by Down-regulation of miR-155 through activation of breast cancer type 1 susceptibility protein. J Am Heart Assoc 5:e002648

Fancher IS, Dick GM, Hollander JM (2013) Diabetes mellitus reduces the function and expression of ATP-dependent K(+) channels in cardiac mitochondria. Life Sci 92:664–668

Fitzl G, Welt K, Martin R, Dettmer D, Hermsdorf T, Clemens N, Konig S (2000) The influence of hypoxia on the myocardium of experimentally diabetic rats with and without protection by Ginkgo biloba extract I. Ultrastructural and biochemical investigations on cardiomyocytes. Exp Toxicol Pathol 52:419–430

Forbes JM, Cooper ME (2013) Mechanisms of diabetic complications. Physiol Rev 93:137–188

Frendo-Cumbo S, Macpherson RE, Wright DC (2016) Beneficial effects of combined resveratrol and metformin therapy in treating diet-induced insulin resistance. Physiol Rep 4:e12877

Gao Y, Kang L, Li C, Wang X, Sun C, Li Q, Liu R, Wang J (2016) Resveratrol ameliorates diabetes-induced cardiac dysfunction through AT1R-ERK/p38 MAPK signaling pathway. Cardiovasc Toxicol 16:130–137

Gencoglu H, Tuzcu M, Hayirli A, Sahin K (2015) Protective effects of resveratrol against streptozotocin-induced diabetes in rats by modulation of visfatin/sirtuin-1 pathway and glucose transporters. Int J Food Sci Nutr 66:314–320

Gilmartin AB, Ural SH, Repke JT (2008) Gestational diabetes mellitus. Rev Obstet Gynecol 1:129–134

Gu Y, Zhang Y, Shi X, Li X, Hong J, Chen J, Gu W, Lu X, Xu G, Ning G (2010) Effect of traditional Chinese medicine berberine on type 2 diabetes based on comprehensive metabonomics. Talanta 81:766–772

Gui QF, Xu ZR, Xu KY, Yang YM (2016a) The efficacy of ginseng-related therapies in type 2 diabetes mellitus. Medicine (United States) 95:e2584

Gui QF, Xu ZR, Xu KY, Yang YM (2016b) The efficacy of ginseng-related therapies in type 2 diabetes mellitus: an updated systematic review and meta-analysis. Medicine (Baltimore) 95:e2584

Guo S, Yao Q, Ke Z, Chen H, Wu J, Liu C (2015) Resveratrol attenuates high glucose-induced oxidative stress and cardiomyocyte apoptosis through AMPK. Mol Cell Endocrinol 412:85–94

Gupta SC, Patchva S, Koh W, Aggarwal BB (2012) Discovery of curcumin, a component of golden spice, and its miraculous biological activities. Clin Exp Pharmacol Physiol 39:283–299

Hayat SA, Patel B, Khattar RS, Malik RA (2004) Diabetic cardiomyopathy: mechanisms, diagnosis and treatment. Clin Sci (Lond) 107:539–557

Hosseini SA, Alipour M, Ghadiry A, Zakerkish M (2016) The effects of standardized extract of ginseng (G115) on blood sugar control and inflammatory factors in patients with type 2 diabetes: a double-blind clinical trial. Int J Pharm Res Allied Sci 5:55–59

Howell JC, Chun E, Farrell AN, Hur EY, Caroti CM, Iuvone PM, Haque R (2013) Global microRNA expression profiling: curcumin (diferuloylmethane) alters oxidative stress-responsive microRNAs in human ARPE-19 cells. Mol Vis 19:544–560

Huang JP, Huang SS, Deng JY, Chang CC, Day YJ, Hung LM (2010) Insulin and resveratrol act synergistically, preventing cardiac dysfunction in diabetes, but the advantage of resveratrol in diabetics with acute heart attack is antagonized by insulin. Free Radic Biol Med 49:1710–1721

IDF (2016) Diabetes and cardiovascular disease. International Diabetes Federation, Brussels, Belgium

Ilyas EI, Nur BM, Laksono SP, Bahtiar A, Estuningtyas A, Vitasyana C, Kusmana D, Suyatna FD, Tadjudin MK, Freisleben HJ (2016) Effects of curcumin on parameters of myocardial oxidative stress and of mitochondrial glutathione turnover in Reoxygenation after 60 minutes of hypoxia in isolated perfused working Guinea pig hearts. Adv Pharmacol Sci 2016:6173648

Isah T (2015) Rethinking Ginkgo biloba L.: medicinal uses and conservation. Pharmacogn Rev 9:140–148

Jacobs BP, Browner WS (2000) Ginkgo biloba: a living fossil. Am J Med 108:341–342

Jin Y, Khadka DB, Cho WJ (2016) Pharmacological effects of berberine and its derivatives: a patent update. Expert Opin Ther Pat 26:229–243

Jung CH, Seog HM, Choi IW, Choi HD, Cho HY (2005) Effects of wild ginseng (Panax ginseng C.A. Meyer) leaves on lipid peroxidation levels and antioxidant enzyme activities in streptozotocin diabetic rats. J Ethnopharmacol 98:245–250

Karaca T, Yoruk M, Yoruk IH, Uslu S (2010) Effects of extract of green tea and ginseng on pancreatic beta cells and levels of serum glucose, insulin, cholesterol and triglycerides in rats with experimentally streptozotocin-induced diabetes: a histochemical and immunohistochemical study. J Anim Vet Adv 9:102–107

Karuppagounder V, Arumugam S, Giridharan VV, Sreedhar R, Bose RJ, Vanama J, Palaniyandi SS, Konishi T, Watanabe K, Thandavarayan RA (2017) Tiny molecule, big power: multi-target approach for curcumin in diabetic cardiomyopathy. Nutrition 34:47–54

Khamaneh AM, Alipour MR, Sheikhzadeh Hesari F, Ghadiri Soufi F (2015) A signature of microRNA-155 in the pathogenesis of diabetic complications. J Physiol Biochem 71:301–309

Kim HY, Kang KS, Yamabe N, Nagai R, Yokozawa T (2007) Protective effect of heat-processed American ginseng against diabetic renal damage in rats. J Agric Food Chem 55:8491–8497

Kim YJ, Zhang D, Yang DC (2015) Biosynthesis and biotechnological production of ginsenosides. Biotechnol Adv 33:717–735

Kim JH, Pan JH, Cho HT, Kim YJ (2016a) Black ginseng extract counteracts streptozotocin-induced diabetes in mice. PLoS One 11:e0146843

Kim JS, Jang HJ, Kim SS, Oh MY, Kim HJ, Lee SY, Eom DW, Ham JY, Han DJ (2016b) Red ginseng administration before islet isolation attenuates apoptosis and improves islet function and transplant outcome in a syngeneic mouse marginal islet mass model. Transplant Proc 48:1258–1265

King AJ (2012) The use of animal models in diabetes research. Br J Pharmacol 166:877–894

Kong WJ, Zhang H, Song DQ, Xue R, Zhao W, Wei J, Wang YM, Shan N, Zhou ZX, Yang P, You XF, Li ZR, Si SY, Zhao LX, Pan HN, Jiang JD (2009) Berberine reduces insulin resistance through protein kinase C-dependent up-regulation of insulin receptor expression. Metabolism 58:109–119

Kronski E, Fiori ME, Barbieri O, Astigiano S, Mirisola V, Killian PH, Bruno A, Pagani A, Rovera F, Pfeffer U, Sommerhoff CP, Noonan DM, Nerlich AG, Fontana L, Bachmeier BE (2014) MiR181b is induced by the chemopreventive polyphenol curcumin and inhibits breast cancer metastasis via down-regulation of the inflammatory cytokines CXCL1 and -2. Mol Oncol 8:581–595

Ku CR, Lee HJ, Kim SK, Lee EY, Lee MK, Lee EJ (2012) Resveratrol prevents streptozotocin-induced diabetes by inhibiting the apoptosis of pancreatic beta-cell and the cleavage of poly (ADP-ribose) polymerase. Endocr J 59:103–109

Kudolo GB, Wang W, Elrod R, Barrientos J, Haase A, Blodgett J (2006a) Short-term ingestion of Ginkgo biloba extract does not alter whole body insulin sensitivity in non-diabetic, pre-diabetic or type 2 diabetic subjects – a randomized double-blind placebo-controlled crossover study. Clin Nutr 25:123–134

Kudolo GB, Wang W, Javors M, Blodgett J (2006b) The effect of the ingestion of Ginkgo biloba extract (EGb 761) on the pharmacokinetics of metformin in non-diabetic and type 2 diabetic subjects – a double blind placebo-controlled, crossover study. Clin Nutr 25:606–616

Kumar S, Singh R, Vasudeva N, Sharma S (2012) Acute and chronic animal models for the evaluation of anti-diabetic agents. Cardiovasc Diabetol 11:9

Kumar A, Ekavali CK, Mukherjee M, Pottabathini R, Dhull DK (2015) Current knowledge and pharmacological profile of berberine: an update. Eur J Pharmacol 761:288–297

Lan J, Zhao Y, Dong F, Yan Z, Zheng W, Fan J, Sun G (2015) Meta-analysis of the effect and safety of berberine in the treatment of type 2 diabetes mellitus, hyperlipemia and hypertension. J Ethnopharmacol 161:69–81

Lee CH, Kim JH (2014) A review on the medicinal potentials of ginseng and ginsenosides on cardiovascular diseases. J Ginseng Res 38:161–166

Li KK, Gong XJ (2015) A review on the medicinal potential of Panax ginseng saponins in diabetes mellitus. RSC Adv 5:47353–47366

Li J, Wang P, Zhu Y, Chen Z, Shi T, Lei W, Yu S (2015) Curcumin inhibits neuronal loss in the retina and elevates Ca(2)(+)/calmodulin-dependent protein kinase II activity in diabetic rats. J Ocul Pharmacol Ther 31:555–562

Lim S, Yoon JW, Kang SM, Choi SH, Cho BJ, Kim M, Park HS, Cho HJ, Shin H, Kim YB, Kim HS, Jang HC, Park KS (2011) EGb761, a Ginkgo biloba extract, is effective against atherosclerosis in vitro, and in a rat model of type 2 diabetes. PLoS One 6:e20301

Liu Z, Wang LJ, Li X, Hu JN, Chen Y, Ruan CC, Sun GZ (2009) Hypoglycemic effects of malonyl-ginsenosides extracted from roots of Panax ginseng on streptozotocin-induced diabetic mice. Phytother Res 23:1426–1430

Lu Q, Zuo WZ, Ji XJ, Zhou YX, Liu YQ, Yao XQ, Zhou XY, Liu YW, Zhang F, Yin XX (2015) Ethanolic Ginkgo biloba leaf extract prevents renal fibrosis through Akt/mTOR signaling in diabetic nephropathy. Phytomedicine 22:1071–1078

Ma W, Li J, Hu J, Cheng Y, Wang J, Zhang X, Xu M (2016) miR214-regulated p53-NOX4/p66shc pathway plays a crucial role in the protective effect of Ginkgolide B against cisplatin-induced cytotoxicity in HEI-OC1 cells. Chem Biol Interact 245:72–81

Majithiya JB, Balaraman R (2005) Time-dependent changes in antioxidant enzymes and vascular reactivity of aorta in streptozotocin-induced diabetic rats treated with curcumin. J Cardiovasc Pharmacol 46:697–705

Mccowen KC, Smith RJ (2013) Diabetes mellitus: classification and chemical pathology A2 - caballero, Benjamin. Encyclopedia of human nutrition, 3rd edn. Academic Press, Waltham, pp 17–24

Meghana K, Sanjeev G, Ramesh B (2007) Curcumin prevents streptozotocin-induced islet damage by scavenging free radicals: a prophylactic and protective role. Eur J Pharmacol 577:183–191

Mohammadi A, Mansoori B, Baradaran B (2017) Regulation of miRNAs by herbal medicine: an emerging field in cancer therapies. Biomed Pharmacother 86:262–270

Momtazi AA, Shahabipour F, Khatibi S, Johnston TP, Pirro M, Sahebkar A (2016) Curcumin as a MicroRNA regulator in cancer: a review. Rev Physiol Biochem Pharmacol 171:1–38

Monami M, Luzzi C, Lamanna C, Chiasserini V, Addante F, Desideri CM, Masotti G, Marchionni N, Mannucci E (2006) Three-year mortality in diabetic patients treated with different combinations of insulin secretagogues and metformin. Diabetes Metab Res Rev 22:477–482

Monami M, Dicembrini I, Mannucci E (2014) Dipeptidyl peptidase-4 inhibitors and heart failure: a meta-analysis of randomized clinical trials. Nutr Metab Cardiovasc Dis 24:689–697

Moon HK, Kim KS, Chung SK, Kim JK (2015) Effect of wild Korean ginseng (Panax ginseng) extract on blood glucose and serum lipid contents in rats with multiple low-dose streptozotocin-induced diabetes. Food Sci Biotechnol 24:1505–1511

Movahed A, Nabipour I, Lieben Louis X, Thandapilly SJ, Yu L, Kalantarhormozi M, Rekabpour SJ, Netticadan T (2013) Antihyperglycemic effects of short term resveratrol supplementation in type 2 diabetic patients. Evid Based Complement Alternat Med 2013:851267

Mukhopadhyay P, Pacher P, Das DK (2011) MicroRNA signatures of resveratrol in the ischemic heart. Ann N Y Acad Sci 1215:109–116

Nakou ES, Mavrakis H, Vardas PE (2012) Are diabetic patients at increased risk of arrhythmias? Hell J Cardiol 53:335–339

Naseem M, Zaman MQ, Nazih H, Ouguerram K, Rabbani I, Zaneb H, Yaqoob T, Rehman HU, Michel J, Tahir SK, Yousaf MS, Majeed KA, Hussain MS (2016) The effects of Ginkgo Biloba leaf extract on metabolic disturbances associated to alloxan-induced diabetic rats. J Anim Plant Sci 26:627–635

Neerati P, Devde R, Gangi AK (2014) Evaluation of the effect of curcumin capsules on glyburide therapy in patients with type-2 diabetes mellitus. Phytother Res 28:1796–1800

Oh MJ, Kim HJ, Park EY, Ha NH, Song MG, Choi SH, Chun BG, Kim DH (2017) The effect of Korean red ginseng extract on rosiglitazone-induced improvement of glucose regulation in diet-induced obese mice. J Ginseng Res 41:52–59

Palma HE, Wolkmer P, Gallio M, Correa MM, Schmatz R, Thome GR, Pereira LB, Castro VS, Pereira AB, Bueno A, De Oliveira LS, Rosolen D, Mann TR, De Cecco BS, Graca DL, Lopes ST, Mazzanti CM (2014) Oxidative stress parameters in blood, liver, and kidney of diabetic rats treated with curcumin and/or insulin. Mol Cell Biochem 386:199–210

Palsamy P, Subramanian S (2008) Resveratrol, a natural phytoalexin, normalizes hyperglycemia in streptozotocin-nicotinamide induced experimental diabetic rats. Biomed Pharmacother 62:598–605

Pan ZW, Lu YJ, Yang BF (2010) MicroRNAs: a novel class of potential therapeutic targets for cardiovascular diseases. Acta Pharmacol Sin 31:1–9

Pang B, Zhao LH, Zhou Q, Zhao TY, Wang H, Gu CJ, Tong XL (2015a) Application of berberine on treating type 2 diabetes mellitus. Int J Endocrinol 2015:905749

Pang XF, Zhang LH, Bai F, Wang NP, Shah AI, Garner R, Zhao ZQ (2015b) Dual ACE-inhibition and angiotensin II AT(1) receptor antagonism with curcumin attenuate maladaptive cardiac

repair and improve ventricular systolic function after myocardial infarction in rat heart. Eur J Pharmacol 746:22–30
Park HJ, Kim DH, Park SJ, Kim JM, Ryu JH (2012) Ginseng in traditional herbal prescriptions. J Ginseng Res 36:225–241
Prasad S, Aggarwal BB (2011) Turmeric, the golden spice: from traditional medicine to modern medicine. In: IFF B, Wachtel-Galor S (eds) Herbal medicine: biomolecular and clinical aspects, 2nd edn. CRC Press/Taylor & Francis Llc., Boca Raton (FL), pp 263–288
Rahimi HR, Mohammadpour AH, Dastani M, Jaafari MR, Abnous K, Ghayour Mobarhan M, Kazemi Oskuee R (2016) The effect of nano-curcumin on HbA1c, fasting blood glucose, and lipid profile in diabetic subjects: a randomized clinical trial. Avicenna J Phytomed 6:567–577
Rashid K, Sil PC (2015) Curcumin enhances recovery of pancreatic islets from cellular stress induced inflammation and apoptosis in diabetic rats. Toxicol Appl Pharmacol 282:297–310
Rawal S, Manning P, Katare R (2014) Cardiovascular microRNAs: as modulators and diagnostic biomarkers of diabetic heart disease. Cardiovasc Diabetol 13:44
Ren M, Yang S, Li J, Hu Y, Ren Z, Ren S (2013) Ginkgo biloba L. extract enhances the effectiveness of syngeneic bone marrow mesenchymal stem cells in lowering blood glucose levels and reversing oxidative stress. Endocrine 43:360–369
Rhee KJ, Lee CG, Kim SW, Gim DH, Kim HC, Jung BD (2015) Extract of Ginkgo Biloba ameliorates streptozotocin-induced type 1 diabetes mellitus and high-fat diet-induced type 2 diabetes mellitus in mice. Int J Med Sci 12:987–994
Saini AS, Taliyan R, Sharma PL (2014) Protective effect and mechanism of Ginkgo biloba extract-EGb 761 on STZ-induced diabetic cardiomyopathy in rats. Pharmacogn Mag 10:172–178
Schmatz R, Schetinger MR, Spanevello RM, Mazzanti CM, Stefanello N, Maldonado PA, Gutierres J, Correa Mde C, Girotto E, Moretto MB, Morsch VM (2009) Effects of resveratrol on nucleotide degrading enzymes in streptozotocin-induced diabetic rats. Life Sci 84:345–350
Schmatz R, Perreira LB, Stefanello N, Mazzanti C, Spanevello R, Gutierres J, Bagatini M, Martins CC, Abdalla FH, Daci Da Silva Serres J, Zanini D, Vieira JM, Cardoso AM, Schetinger MR, Morsch VM (2012) Effects of resveratrol on biomarkers of oxidative stress and on the activity of delta aminolevulinic acid dehydratase in liver and kidney of streptozotocin-induced diabetic rats. Biochimie 94:374–383
Schneider R, Welt K, Aust W, Kluge R, Loster H, Fitzl G (2010) Cardiovascular autonomic neuropathy in spontaneously diabetic rats with and without application of EGb 761. Histol Histopathol 25:1581–1590
Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, Mcguire DK, Ray KK, Leiter LA, Raz I, SAVOR-TIMI 53 Steering Committee and Investigators (2013) Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 369:1317–1326
Sekar D, Venugopal B, Sekar P, Ramalingam K (2016) Role of microRNA 21 in diabetes and associated/related diseases. Gene 582:14–18
Sen S, Chen S, Wu Y, Feng B, Lui EK, Chakrabarti S (2013) Preventive effects of north American ginseng (Panax quinquefolius) on diabetic retinopathy and cardiomyopathy. Phytother Res 27:290–298
Seo YS, Shon MY, Kong R, Kang OH, Zhou T, Kim DY, Kwon DY (2016) Black ginseng extract exerts anti-hyperglycemic effect via modulation of glucose metabolism in liver and muscle. J Ethnopharmacol 190:231–240
Sethupathy P (2016) The promise and challenge of therapeutic MicroRNA silencing in diabetes and metabolic diseases. Curr Diab Rep 16:52
Shakibaei M, Harikumar KB, Aggarwal BB (2009) Resveratrol addiction: to die or not to die. Mol Nutr Food Res 53:115–128
Shi Y, Wan X, Shao N, Ye R, Zhang N, Zhang Y (2016) Protective and antiangiopathy effects of ginsenoside re against diabetes mellitus via the activation of p38 MAPK, ERK1/2 and JNK signaling. Mol Med Rep 14:4849–4856

Siegel G, Ermilov E, Knes O, Rodriguez M (2014) Combined lowering of low grade systemic inflammation and insulin resistance in metabolic syndrome patients treated with Ginkgo biloba. Atherosclerosis 237:584–588

Soetikno V, Sari FR, Sukumaran V, Lakshmanan AP, Mito S, Harima M, Thandavarayan RA, Suzuki K, Nagata M, Takagi R, Watanabe K (2012) Curcumin prevents diabetic cardiomyopathy in streptozotocin-induced diabetic rats: possible involvement of PKC-MAPK signaling pathway. Eur J Pharm Sci 47:604–614

Soleas GJ, Diamandis EP, Goldberg DM (1997) Resveratrol: a molecule whose time has come? And gone? Clin Biochem 30:91–113

Spadiene A, Savickiene N, Jurgeviciene N, Zalinkevicius R, Norkus A, Ostrauskas R, Skesters A, Silova A, Rodovicius H, Francaite-Daugeliene M (2013) Effect of ginkgo extract on eye microcirculation in patients with diabetes. Cent Eur J Med 8:736–741

Stein SA, Lamos EM, Davis SN (2013) A review of the efficacy and safety of oral antidiabetic drugs. Expert Opin Drug Saf 12:153–175

Sulaiman M, Matta MJ, Sunderesan NR, Gupta MP, Periasamy M, Gupta M (2010) Resveratrol, an activator of SIRT1, upregulates sarcoplasmic calcium ATPase and improves cardiac function in diabetic cardiomyopathy. Am J Physiol Heart Circ Physiol 298:H833–H843

Suman RK, Borde MK, Mohanty IR, Maheshwari U, Deshmukh YA (2016) Myocardial salvaging effects of berberine in experimental diabetes co-existing with myocardial infarction. J Clin Diagn Res 10:FF13–FF18

Sun M, Estrov Z, Ji Y, Coombes KR, Harris DH, Kurzrock R (2008) Curcumin (diferuloylmethane) alters the expression profiles of microRNAs in human pancreatic cancer cells. Mol Cancer Ther 7:464–473

Sun C, Chen Y, Li X, Tai G, Fan Y, Zhou Y (2014) Anti-hyperglycemic and anti-oxidative activities of ginseng polysaccharides in STZ-induced diabetic mice. Food Funct 5:845–848

Sun Y, Liu Y, Chen K (2016) Roles and mechanisms of ginsenoside in cardiovascular diseases: progress and perspectives. Sci China Life Sci 59:292–298

Suresh Babu P, Srinivasan K (1995) Influence of dietary curcumin and cholesterol on the progression of experimentally induced diabetes in albino rat. Mol Cell Biochem 152:13–21

Suryanarayana P, Satyanarayana A, Balakrishna N, Kumar PU, Reddy GB (2007) Effect of turmeric and curcumin on oxidative stress and antioxidant enzymes in streptozotocin-induced diabetic rat. Med Sci Monit 13:BR286–BR292

Szablewski L (2014) Role of immune system in type 1 diabetes mellitus pathogenesis. Int Immunopharmacol 22:182–191

Szkudelski T, Szkudelska K (2015) Resveratrol and diabetes: from animal to human studies. Biochim Biophys Acta 1852:1145–1154

Takeda N (2010) Cardiac disturbances in diabetes mellitus. Pathophysiology 17:83–88

Takikawa M, Kurimoto Y, Tsuda T (2013) Curcumin stimulates glucagon-like peptide-1 secretion in GLUTag cells via Ca2+/calmodulin-dependent kinase II activation. Biochem Biophys Res Commun 435:165–170

Taliyan R, Sharma PL (2012) Protective effect and potential mechanism of Ginkgo biloba extract EGb 761 on STZ-induced neuropathic pain in rats. Phytother Res 26:1823–1829

Tang LQ, Wei W, Chen LM, Liu S (2006) Effects of berberine on diabetes induced by alloxan and a high-fat/high-cholesterol diet in rats. J Ethnopharmacol 108:109–115

Thazhath SS, Wu T, Bound MJ, Checklin HL, Standfield S, Jones KL, Horowitz M, Rayner CK (2016) Administration of resveratrol for 5 wk has no effect on glucagon-like peptide 1 secretion, gastric emptying, or glycemic control in type 2 diabetes: a randomized controlled trial. Am J Clin Nutr 103:66–70

Thirunavukkarasu M, Penumathsa SV, Koneru S, Juhasz B, Zhan L, Otani H, Bagchi D, Das DK, Maulik N (2007) Resveratrol alleviates cardiac dysfunction in streptozotocin-induced diabetes: role of nitric oxide, thioredoxin, and heme oxygenase. Free Radic Biol Med 43:720–729

Timmers S, De Ligt M, Phielix E, Van De Weijer T, Hansen J, Moonen-Kornips E, Schaart G, Kunz I, Hesselink MK, Schrauwen-Hinderling VB, Schrauwen P (2016) Resveratrol as add-on ther-

apy in subjects with well-controlled type 2 diabetes: a randomized controlled trial. Diabetes Care 39:2211–2217

Tome-Carneiro J, Larrosa M, Yanez-Gascon MJ, Davalos A, Gil-Zamorano J, Gonzalvez M, Garcia-Almagro FJ, Ruiz Ros JA, Tomas-Barberan FA, Espin JC, Garcia-Conesa MT (2013) One-year supplementation with a grape extract containing resveratrol modulates inflammatory-related microRNAs and cytokines expression in peripheral blood mononuclear cells of type 2 diabetes and hypertensive patients with coronary artery disease. Pharmacol Res 72:69–82

Tosaki A, Pali T, Droy-Lefaix MT (1996) Effects of Ginkgo biloba extract and preconditioning on the diabetic rat myocardium. Diabetologia 39:1255–1262

Tsai HY, Huang PH, Lin FY, Chen JS, Lin SJ, Chen JW (2013) Ginkgo biloba extract reduces high-glucose-induced endothelial reactive oxygen species generation and cell adhesion molecule expression by enhancing HO-1 expression via Akt/eNOS and p38 MAP kinase pathways. Eur J Pharm Sci 48:803–811

Tsai CC, Chan P, Chen LJ, Chang CK, Liu Z, Lin JW (2014) Merit of ginseng in the treatment of heart failure in type 1-like diabetic rats. Biomed Res Int 2014:484161

Tsukita S, Yamada T, Takahashi K, Munakata Y, Hosaka S, Takahashi H, Gao J, Shirai Y, Kodama S, Asai Y, Sugisawa T, Chiba Y, Kaneko K, Uno K, Sawada S, Imai J, Katagiri H (2017) MicroRNAs 106b and 222 improve hyperglycemia in a mouse model of insulin-deficient diabetes via pancreatic β-cell proliferation. EBioMedicine 15:163–172

Voncannon JL, Jiao Y, Kim-Shapiro D, Varagic J (2014) Curcumin ameliorates cardiac dysfunction in the ovariectomized diabetic mRen2. Lewis rat by inhibiting renin angiotensin system. Hypertension 64:2

Wang LH, Yu CH, Fu Y, Li Q, Sun YQ (2011) Berberine elicits anti-arrhythmic effects via IK1/Kir2.1 in the rat type 2 diabetic myocardial infarction model. Phytother Res 25:33–37

Wang LH, Li XL, Li Q, Fu Y, Yu HJ, Sun YQ, Zhang L, Shan HL (2012) Berberine alleviates ischemic arrhythmias via recovering depressed I(to) and I(Ca) currents in diabetic rats. Phytomedicine 19:206–210

Wang CW, Su SC, Huang SF, Huang YC, Chan FN, Kuo YH, Hung MW, Lin HC, Chang WL, Chang TC (2015) An essential role of cAMP response element binding protein in Ginsenoside Rg1-mediated inhibition of Na+/glucose Cotransporter 1 gene expression. Mol Pharmacol 88:1072–1083

Wang S, Ding L, Ji H, Xu Z, Liu Q, Zheng Y (2016) The role of p38 MAPK in the development of diabetic cardiomyopathy. Int J Mol Sci 17:1037

Wee JJ, Mee Park K, Chung AS (2011) Biological activities of ginseng and its application to human health. In: IFF B, Wachtel-Galor S (eds) Herbal medicine: biomolecular and clinical aspects, 2nd edn. CRC Press/Taylor & Francis Llc., Boca Raton (FL), pp 157–209

Wei S, Li W, Yu Y, Yao F, A L LX, Guan F, Zhang M, Chen L (2015) Ginsenoside compound K suppresses the hepatic gluconeogenesis via activating adenosine-5'monophosphate kinase: a study in vitro and in vivo. Life Sci 139:8–15

Whittington HJ, Babu GG, Mocanu MM, Yellon DM, Hausenloy DJ (2012) The diabetic heart: too sweet for its own good? Cardiol Res Pract 2012:845698

Wongcharoen W, Phrommintikul A (2009) The protective role of curcumin in cardiovascular diseases. Int J Cardiol 133:145–151

Wu Y, Xia ZY, Dou J, Zhang L, Xu JJ, Zhao B, Lei S, Liu HM (2011) Protective effect of ginsenoside Rb1 against myocardial ischemia/reperfusion injury in streptozotocin-induced diabetic rats. Mol Biol Rep 38:4327–4335

Wu YS, Chen YT, Bao YT, Li ZM, Zhou XJ, He JN, Dai SJ, Li CY (2016) Identification and verification of potential therapeutic target genes in berberine-treated Zucker diabetic fatty rats through bioinformatics analysis. PLoS One 11:e0166378

Xavier S, Sadanandan J, George N, Paulose CS (2012) Beta(2)-adrenoceptor and insulin receptor expression in the skeletal muscle of streptozotocin induced diabetic rats: antagonism by vitamin D(3) and curcumin. Eur J Pharmacol 687:14–20

Xia X, Yan J, Shen Y, Tang K, Yin J, Zhang Y, Yang D, Liang H, Ye J, Weng J (2011) Berberine improves glucose metabolism in diabetic rats by inhibition of hepatic gluconeogenesis. PLoS One 6:e16556

Xianghua F, Weili W, Yangmei Y, Xuechao W, Yanbo W, Weize F, Yunfa J, Guozhen H (2010) e0413 the adverse effects of glibenclamide on myocardial perfusion in patients with acute myocardial infarction and type 2 diabetes mellitus. Heart 96:A127–A128

Xiao J, Sheng X, Zhang X, Guo M, Ji X (2016) Curcumin protects against myocardial infarction-induced cardiac fibrosis via SIRT1 activation in vivo and in vitro. Drug Des Devel Ther 10:1267–1277

Yan X, Xue J, Wu H, Wang S, Liu Y, Zheng S, Zhang C, Yang C (2015) Ginsenoside-Rb1 protects hypoxic- and ischemic-damaged cardiomyocytes by regulating expression of miRNAs. Evid Based Complement Alternat Med 2015:171306

Yan R, Shan H, Lin L, Zhang M, Diao JY, Li Q, Liu X, Wei J (2016) Chronic resveratrol treatment improves cardiac function in a rat model of diabetic cardiomyopathy via attenuation of mitochondrial injury and myocardial apoptosis. Int J Clin Exp Med 9:21156–21167

Yang B, Lin H, Xiao J, Lu Y, Luo X, Li B, Zhang Y, Xu C, Bai Y, Wang H, Chen G, Wang Z (2007) The muscle-specific microRNA miR-1 regulates cardiac arrhythmogenic potential by targeting GJA1 and KCNJ2. Nat Med 13:486–491

Yang H, Xu W, Zhou Z, Liu J, Li X, Chen L, Weng J, Yu Z (2015) Curcumin attenuates urinary excretion of albumin in type II diabetic patients with enhancing nuclear factor erythroid-derived 2-like 2 (Nrf2) system and repressing inflammatory signaling efficacies. Exp Clin Endocrinol Diabetes 123:360–367

Yao J, Kong W, Jiang J (2015a) Learning from berberine: treating chronic diseases through multiple targets. Sci China Life Sci 58:854–859

Yao L, Wan J, Li H, Ding J, Wang Y, Wang X, Li M (2015b) Resveratrol relieves gestational diabetes mellitus in mice through activating AMPK. Reprod Biol Endocrinol 13:118

Yazgan UC, Tasdemir E, Bilgin HM, Deniz Obay B, Sermet A, Elbey B (2015) Comparison of the anti-diabetic effects of resveratrol, gliclazide and losartan in streptozotocin-induced experimental diabetes. Arch Physiol Biochem 121:157–161

Yildirim SS, Akman D, Catalucci D, Turan B (2013) Relationship between downregulation of miRNAs and increase of oxidative stress in the development of diabetic cardiac dysfunction: junctin as a target protein of miR-1. Cell Biochem Biophys 67:1397–1408

Yin J, Xing H, Ye J (2008) Efficacy of berberine in patients with type 2 diabetes mellitus. Metabolism 57:712–717

Yonamine CY, Pinheiro-Machado E, Michalani ML, Freitas HS, Okamoto MM, Correa-Giannella ML, Machado UF (2016) Resveratrol improves glycemic control in insulin-treated diabetic rats: participation of the hepatic territory. Nutr Metab (Lond) 13:44

Yu W, Wu J, Cai F, Xiang J, Zha W, Fan D, Guo S, Ming Z, Liu C (2012) Curcumin alleviates diabetic cardiomyopathy in experimental diabetic rats. PLoS One 7:e52013

Yu W, Zha W, Ke Z, Min Q, Li C, Sun H, Liu C (2016) Curcumin protects neonatal rat cardiomyocytes against high glucose-induced apoptosis via PI3K/Akt signalling pathway. J Diabetes Res 2016:4158591

Yuan HD, Chung SH (2010) Protective effects of fermented ginseng on streptozotocin-induced pancreatic beta-cell damage through inhibition of NF-kappa B. Int J Mol Med 25:53–58

Yuan HD, Kim JT, Kim SH, Chung SH (2012) Ginseng and diabetes: the evidences from in vitro, animal and human studies. J Ginseng Res 36:27–39

Zhang XF, Liang B, Liang ZF, Lin J (2008) Effects of Gingko biloba leaf extract on learning, memory, and hippocampal amyloid precursor protein mRNA expressions in diabetic rats. Neural Regen Res 3:29–32

Zhang H, Morgan B, Potter BJ, Ma L, Dellsperger KC, Ungvari Z, Zhang C (2010a) Resveratrol improves left ventricular diastolic relaxation in type 2 diabetes by inhibiting oxidative/nitrative stress: in vivo demonstration with magnetic resonance imaging. Am J Physiol Heart Circ Physiol 299:H985–H994

Zhang H, Wei J, Xue R, Wu JD, Zhao W, Wang ZZ, Wang SK, Zhou ZX, Song DQ, Wang YM, Pan HN, Kong WJ, Jiang JD (2010b) Berberine lowers blood glucose in type 2 diabetes mellitus patients through increasing insulin receptor expression. Metabolism 59:285–292

Zheng B, Yang L, Wen C, Huang X, Xu C, Lee KH, Xu J (2016) Curcumin analog L3 alleviates diabetic atherosclerosis by multiple effects. Eur J Pharmacol 775:22–34

Zhi Y, Pan J, Shen W, He P, Zheng J, Zhou X, Lu G, Chen Z, Zhou Z (2016) Ginkgolide B inhibits human bladder cancer cell migration and invasion through MicroRNA-223-3p. Cell Physiol Biochem 39:1787–1794

Protective Role of Medicinal Herb *Anethum Graveolens* (Dill) Against Various Human Diseases and Metabolic Disorders

Furkhan Ahmed Mohammed, Syed Shoeb Razvi, Waseem Mohammed Abdul, Kaleemuddin Mohammed, Khalid Rehman Hakeem, Babajan Banaganapalli, Noor Ahmad Shaik, and Ayman I. Elkady

Introduction

Nutraceuticals and bioactive foods as phytomedicines or dietary supplements have gained significant attention from both researchers and health professionals due to its effective results in nutritional therapy to treat various diseases (Gupta et al. 2013; Gupta and Prakash 2014; Bagchi 2014; Berger and Shenkin 2006). Natural food supplement plays a vital role in boosting immunity and maintaining the flow of metabolic and enzymatic reactions for proper functioning of different organ systems in the body. During the recent few years, exploring the role of dietary bioactive components (DBCs) in minimizing the risk of chronic diseases and boosting the

Furkhan Ahmed Mohammed, Syed Shoeb Razvi contributed equally to this work.

F. A. Mohammed (✉) · W. M. Abdul · K. R. Hakeem · A. I. Elkady
Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia

S. S. Razvi
Department of Biochemistry, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia

K. Mohammed
Department of Biochemistry, Faculty of Science, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia

Princess Al-Jawhara Albrahim Center of Excellence in Research of Hereditary Disorders (PACER-HD), King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia

B. Banaganapalli · N. A. Shaik
Princess Al-Jawhara Albrahim Center of Excellence in Research of Hereditary Disorders (PACER-HD), King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia

Department of Genetic Medicine, Faculty of Medicine, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia
e-mail: nshaik@kau.edu.sa

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maintenance of health have become an exciting area of research in the field of nutrition. Various health organizations like National Institute of Health (NIH) and National Fruit and Vegetable Alliance (NFVA) have promoted the use of DBCs among the people to meet the demands of the nutritional requirements. Moreover, several health guidelines and policies like Dietary Guidelines for Americans have been carefully chalked out to promote the public consumption of fruits and vegetables (Wallace et al. 2015). However, more than 8000 DBCs have been identified and declared safe till date within the recommendations of food intake of whole grains, fruits, and vegetables (Wallace et al. 2015).

Moreover, significant percentage (34%) of the new medicines are based on the active molecules of the natural products or their derivatives for the preparation of immunosuppressants, statins, and tubulin-binding anticancer drugs (Newman and Cragg 2016). The use of traditional drugs from plant sources has increased in the treatment of a wide range of diseases in both developed and developing countries (Newman and Cragg 2012). As reported by World Health Organization (WHO), nearly 70% of the world population is using medicinal herbs currently as an elementary source of medicine or complementary alternative medicine (CAM) (Fasinu et al. 2012). Herbs contain a wide assortment of antioxidant phytochemicals that neutralize free radicals and check the progress of many more chronic diseases (Xu and Howard 2012). There are many instances in the drug discovery field, wherein the natural products have been used to treat a variety of diseases like Alzheimer's disease (Calcul et al. 2012; Zhu et al. 2013) and diabetic neuropathy (Ji et al. 2013). Therefore, cosmopolitan revival of medicinal herbs or herbal remedies as complementary advanced medicine is rising exponentially.

Recently, many antibiotics have been synthesized to treat infections in humans including tiacumicin-fidaxomicin, lipopeptide-daptomycin, pleuromutilin, and retapamulin derived from the natural products (Harvey et al. 2015). During the past 30 years of natural product research, new class of antifungal drugs—the echinocandins—have been developed (Roemer and Krysan 2014). But it is ironic to state that, with the advances in genomic technologies, there was a rapid shift in the discovery of antibiotics from traditional functional screening to target-based high-throughput screening (HTS) which didn't yield results as anticipated (Chan et al. 2002; Payne et al. 2007). A comprehensive inspection of the reports from antibacterial campaigns of GlaxoSmithKline revealed that no successful candidates were generated for clinical development from 67 HTS campaigns against the targets selected from a panel of 160 genes predicted to be important for cell viability (Payne et al. 2007). Many other major drug companies have gone through similar experiences (Silver 2011); new classes of natural product-based drugs like lomaiviticins, ixabepilone, and patellamide peptides have been developed for treating cancer. However manzamines and Artemisinic acid are used as antimalarial drugs and caspofungin and micafungin as antifungals (Harvey et al. 2015). In a different study, the bioactive components extracted from ginseng (*Panax ginseng*) showed significant antiproliferative effect against breast cancer cells (MCF-7) (Wang et al. 2008).

Many approaches have been developed to compare the properties and bioactivities of the existing standard drugs with those of the herbal medicines.

Given the recent advances in nuclear magnetic resonance (NMR) techniques and technological improvements in combinatorial chemistry and "omics" studies, the understanding of the molecular mechanisms and the targets of bioactive compounds of natural products have become more evidentiary. Advances in the field of bioinformatics accompanied by development of new tools have paved the way for the researchers to study the relationship between the drugs and their protein targets through in silico analysis. In an interesting structure-based drug discovery study, a group of researchers have compiled substantial amount of data on several bioactive components from traditional Chinese medicine (TCM) and protein binding through "reverse docking" (Chen et al. 2006b).

This chapter aims to cover the phytochemicals of *Anethum graveolens* (common name "dill") (family: Apiaceae) with medicinal therapeutic effect, which substantively show anticancer, antihyperlipidemic, antimicrobial, and antidiabetic activities deduced by different in vitro, in vivo, and in silico studies. *A. graveolens* is one of the most popular culinary herbs in the world (Kaur and Arora 2010). *A. graveolens* was found in Southeast Europe or Southwest Asia. It is native towards Central Asia and Mediterranean and southern USSR (Villems et al. 2006). It is cropped for its foliage as a cold weather crop throughout the Malaysian archipelago, Indian subcontinent, and Japan including some other parts of southern Asia (Malhotra and Vashishtha 2007). Usage of *A. graveolens* as a flavoring agent and medicine is chronicled since ancient times in Egypt. It was applied topically in the form of a formulation by Egyptian doctors thousands of years ago (Kaur and Arora 2010; Gugerli et al. 2005).

Botanical/Plant Material

Etymology

The botanical name of genus *Anethum* has been derived from Greek word *aneson* or *aneton*. The species name *graveolens* implies strong odor from *olens* the verb *olere*, and the grave from Latin *gravis*; some globally used synonymous words of *A. graveolens* are *Savaa* in India; in Pakistan it is termed *soya*; Iranians spell it as *Shevid*, but in Arab world it is popular by *Shabat/Shabath*, and in China it is renowned as *Ou Zhou shi luo, Shi luo,* and *Tu hui xiang*. The name of *A. graveolens* in European countries is probably related to Old Norse *dilla* meaning calm/soothe. However, in Indonesia and Malaysia it is more popular by *Adas manis, Adas cina, Adas sowa, Adas pudus,* and *Ender*.

Origin/Distribution

A. graveolens (Fig. 1) grows to a height of up to 90 cm on slender stems and the foliage is eventually separated into three or four pinnate segments, a little wider than the foliage of fennel. During the blooming period, the yellow flowers rise into the umbels. Some seeds lack the actual morphology, which are quite small and are termed as schizocarps (Shekhawat and Jana 2010). *A. graveolens* fruits are flattened oval wide with three longitudinal edges (Shekhawat and Jana 2010). Usual appearance of the fruit is similar to that of "caraway" morphologically. However, the seeds (Fig. 2) are flat, lighter, and smaller than caraway and have a pleasant odor.

The cultivation of *A. graveolens* is favored by iron-rich loose soil. The pH of the soil used for cultivation must range from 5.4 to 7.7. It needs warm sunlight intensity; the yield of the crop will be considerably reduced in incomplete shade (Shekhawat and Jana 2010). The plant bears seed usually in the dry climate and can

Fig. 1 *Anethum graveolens* (dill) plant (adapted fromwww.missouribotanicalgarden.org)

Fig. 2 *Anethum graveolens* seeds (adapted fromwww.missouribotanicalgarden.org)

habitually self-sow wherein the plant is seen rising from an appropriate position. The seeds are feasible for 4–10 years. When the seed is ready to be ripped, it is guided subtly by the flower to bend towards the ground and gives rise to a new plant when it touches it (Shekhawat and Jana 2010).

Economic Importance of *A. Graveolens*

Commonly used treatment strategies towards liver carcinoma remain inadequate owing to the detrimental effects of hepatoprotective medicines in allopathic field of medicine. Woefully, therapies established to put forward the notion or the principle of Western medicine lack proper evidence because of inefficiency to replicate the effects of in vitro studies in the regimens of clinical trials. They carry the risk of countless complexities accompanied by the high pricing in the commercial market of the emerging world (Chaudhary et al. 2010). For instance, the efficiency of treatments which employ corticosteroids and interferons is unpredictable, with high risk of calumnious effects, and they are often out of reach of the common man. In contrast to this, the compounds derived from plants are easily affordable and approachable. There is a never-ending certainty of herb remedies which have garnered fame for its safety and efficacy. Moreover, these natural remedies increase the bioavailability and minimize the losses without any deleterious consequences which are excellent substitutes to synthetic drugs. Various current surveys from the United States and Europe have established a strong increase in the growth and attraction towards the usage of herbal drugs during the recent years. However, nearly 65% of the liver cancer patients have exercised herbally prepared drugs without any documented insidious effects till date. The exploration for natural herbal drugs has gained attention among researchers in the past few decades (Kesarwani and Gupta 2013). This approach employed in Saudi Arabia to exploit the positive results from traditional medicine to protect against various cancers and disorders has become a center of attraction among Arabs (Ahmad et al. 2016; Abu-Elmagd et al. 2015). The use of *A. graveolens* as an aromatic herb and spice dates back to 2000 years. The seeds of this herb had been given a status of household medicine to cure stomach aches and flatulence until the industry found it as an exclusive flavoring agent in the manufacture of many food products (Larijani et al. 2016). *A. graveolens* also helps in stimulating the flow of milk in the breasts of lactating mothers, and is frequently given to cattle to enhance the milk production (Jiljit 2016).

Nutritional Information

Principal constituents of *A. graveolens* comprise mostly essential oil components, viz., fatty oil proteins (15.68%), fiber (14.80%), ash (9.8%), moisture (8.39%), and carbohydrates (36%) and also may include some mineral elements like vitamin A, niacin, magnesium, potassium, sodium, phosphorus, and calcium (Kaur and Arora 2010).

Medicinal Uses of *A. Graveolens*

Traditional Uses

The importance of *A. graveolens*, from the Najd province (tropically recognized as "Karfas") of Saudi Arabia, has attracted attention of researchers recently (Alatar et al. 2012). The seeds *of A. graveolens* have been widely used in conventional medicine designed for the treatment of jaundice, liver, spleen, rheumatism disorders, and other inflammatory gout diseases (Al-Asmari et al. 2014).

A. graveolens is topically applied to prevent colic pain and flatulency in babies (Pulliah 2002). The *A. graveolens* seeds are mildly diuretic, carminative, stimulant, and aromatic (Sharma 2004). The essence oil obtained from the seed of *A. graveolens* palliates griping and intestinal spasms and acts as a relaxant in severe colic pain (Duke 2001). The carminative volatile oil aids in digestion, relieves gas, and increases appetite. Chewing of *A. graveolens* seeds has shown remarkable improvement in the disorders related to unpleasant odor in the breath. In addition, *A. graveolens* is also helpful for the treatment of mental disorders, and can cure piles and urinary ailments (Shekhawat and Jana 2010; Nair and Chanda 2007). Medicinal and pharmaceutical approach towards the traditional medicine in Saudi Arabia has increased due to its efficacy and bioavailability in the treatment of life-threatening diseases, but the exact mechanism of action and the pathways involved still remain a mystery which is an open invitation to the researchers globally (Gurib-Fakim 2006).

Recent Research on A. Graveolens

Antibacterial activity: Ethanolic extract of *A. graveolens* has shown good antibacterial activity against some resistant strains like *Staphylococcus aureus, Alcaligenes faecalis, Bacillus cereus*, and *Proteus mirabilis* (Nair and Chanda 2007).

Antiviral activity: Essential oils of *A. graveolens* have also been effective against most resistant viruses like *herpes simplex* type-1 virus (HSV-1) and parainfluenza virus type-3 (PI-3) (Orhan et al. 2012).

Anticancer activity: Anethofuran, the active compound isolated and characterized from *A. graveolens* seed oil, has shown considerable amount of anticancer activity against different cancers (Ahmad et al. 2016; Zheng et al. 1992).

Antidiabetic activity: The possible mechanisms like binding to bile acids in the intestine, increase in fecal excretion, inhibition of intestinal cholesterol absorption, and increased production of bile acids were reported to confirm the antidiabetic property of *A. graveolens* (Shekhawat and Jana 2010; Goodarzi et al. 2016). However, some researches have showed that some of the constituents of *A. graveolens* such as limonene, ũFC;-phellandrene, and carvone equally take part in the hypolipidemic effects exerted by *A. graveolens*, via 3-hydroxy-3-methylglutaryl-CoA

(HMG-CoA) reductase, reducing acyl CoA carboxylase and hence significantly effecting the cholesterol metabolism and fatty acid absorption (Goodarzi et al. 2016; Hajhashemi and Abbasi 2008).

Highlighting the Action of A. Graveolens Against Various Disorders

The seeds of *A. graveolens* have been reported to be used to cure ulcers, cases of dysentery, abdominal pains, and diseases related to eyes and pain caused by urinary tract infections, while fruits of *A. graveolens* have been in use for regulating the blood pressure and normalizing high blood glucose levels. Disorders of digestion accompanied by flatulence and griping pains due to piles can be effectively relieved by using its fruits (Nair and Chanda 2007; Goodarzi et al. 2016). *A. graveolens* can also increase the flow of the milk in the nursing mothers and hence can be used as a "galactogogue," thereby preventing colic and hiccups in the breast-fed babies (Larijani et al. 2016; Goodarzi et al. 2016). Moreover, it has been reported in the study on ruminants in British Colombia that the seeds of *A. graveolens* are given to the ruminants to enhance the milk production and relieve the symptoms of diarrhea (Lans et al. 2006). The hidden potential of the *A. graveolens* is tapped in the conventional herbal medicine for either the chemoprevention or the cure of the disorders relating to lactation, digestion, and respiration and further for lowering the levels of glucose and cholesterol in blood (Goodarzi et al. 2016).

Further studies have shown that the constituents of *A. graveolens* also modulate lipoprotein homeostasis, fatty acid synthesis, and liver LDL receptors mostly by the enhancement of lipoprotein metabolism in rats (Hajhashemi and Abbasi 2008). Research documented by a recent ethnobotanical evidence of Iran which covers nearly 40 plants also includes *A. graveolens*, wherein it has been indexed that the shoots of *A. graveolens* are used to relieve hypertension (Baharvand-Ahmadi and Asadi-Samani 2017). Currently, many studies have confirmed these properties of *A. graveolens* through in vitro and in vivo studies. It is reported to have shown anti-inflammatory, anticancer, antimicrobial, and antioxidant properties with diverse yet complex mechanisms. Well-documented evidence supports the hypothesis that *A. graveolens* can exhibit hypolipidemic effects (Goodarzi et al. 2016).

What Do Animal Studies on A. Graveolens Have to Say?

Madani and colleagues have demonstrated a significant decrease in the blood glucose, total cholesterol, LDL, VLDL, and TG with an increase in HDL in alloxan-induced diabetic rats after intraperitoneal administration of *A. graveolens* extract with a dose of 300 mg/kg for 48 h (Madani et al. 2005). In another interesting study with hypercholesterolemic rats, it was reported that, with the oral administration of

A. graveolens extract at a dose of 500 mg/day for 30 days, there was a decline in the levels of serum lipids and lipid peroxidation in liver (Bahramikia and Yazdanparast 2007). However, in a different study performed by Hajhashemi and Abbasi, cardioprotective role of *A. graveolens* was demonstrated wherein there was a significant decrease in the lipid levels in the hypercholesterolemic rats after administration of *A. graveolens* powder and its essential oils (Hajhashemi and Abbasi 2008). The crude extract of *A. graveolens* could also help to keep the peptic ulcers at bay and interestingly they also possess potent anti-hypercholesterolemic property which can also act as a natural antioxidant by reduction of lipid peroxidation in hepatic system via modulating the actions of antioxidant enzymes in rats fed on high-fat diet (Bahramika 2008). Recently, an interesting observation was documented by Monsefi and colleagues, wherein the effect of *A. graveolens* extract on oocyte and fertility of adult female rats was observed and it was concluded that *A. graveolens* has a potential contraceptive property (Monsefi et al. 2015).

Randomized Clinical Trials

Sahib et al. conducted a prospective randomized clinical trial to check the antigiardial effects of *A. graveolens* with 28 pediatric patients of both sexes with ages ranging from 3 to 11 months. The patients were segregated into two groups with 14 patients each. For one group, metronidazole (Met) was administered at a dose of 15 mg/kg three times a day for 5 days, while the other group was administered with *A. graveolens* aqueous extract (AGAE) 1 ml three times a day for 5 days. The stool samples of the patients were collected before and after treatment (after 5 days and 14 days). It was demonstrated that with the administration of AGAE, there was a significant decrease in the incidence of *G. lamblia* after 5 days of treatment indicating the efficacy of AGAE in the treatment of giardiasis, a result that is comparable to that of Met (Sahib et al. 2014).

However in another recent study, Eshwar and colleagues conducted a randomized controlled, double-blind parallel-arm study for 90 days on 90 subjects. This study was used to assess the efficacy of commercially available hexodent (0.2% chlorhexidine gluconate) and *A. graveolens* seed oil as mouth rinse. All these subjects were randomly divided into two groups with 45 subjects each and the corresponding baseline data of gingival and plaque index was calculated. It was observed that both hexodent and mouth rinse of *A. graveolens* seed oil possessed similar efficacy (Eshwar et al. 2016). Yet in another study, it was demonstrated that the extract of *A. graveolens* was lowering the triglycerides from baseline in patients with metabolic syndrome (update of adult training panel, ATP III). This was a double-blind, randomized, placebo-controlled trial using a parallel design on 24 patients who were randomly assigned to either *A. graveolens* group ($n = 12$) or a placebo group ($n = 12$) for a duration of 3 months. But however a larger study might be required to prove the safety and efficacy in the long run (Mansouri et al. 2012).

It is a well-known fact that hyperlipidemia is a major factor leading to coronary heart disease. The extract of *A. graveolens* can be a successful candidate in the

development of antihyperlipidemic drug due to its supported evidence in reducing the lipid levels significantly. A double-blind randomized clinical trial was carried out on 65 hyperlipidemic patients and it was concluded that the extract significantly reduced the hovering lipid levels in the patients (Kazemi et al. 2006).

Chemical Constituents and Structure of Active BioMolecules of A. Graveolens

The plant of *A. graveolens* consists of nearly 1–5% of the essential oil containing the key bioactive compounds like carvone (30–60%), α-phellandrene (20%), and limonene (33%), together with other compounds like diterpene, pinene, cineole, isomyristicin, paramyrcene, myrcene, dihydrocarvone, dillapiole, furanocoumarin, myristicin, apiol, myristin, and dillapiol (Kaur and Arora 2010). Additionally, other vital compounds such as oxypeucedanin, falcarindiol 5-(4″-hydroxy-3″ methyl-2″-butenyloxy)-6, 7-furocoumarin, and oxypeucedanin hydrate are also found. The hepatoprotective effect of *A. graveolens* can be ascribed to its antioxidant and anti-inflammatory activities (Kaur and Arora 2010). Its phytochemicals have demonstrated to possess flavonoids, phenolic compounds, tannins, volatile oils, alkaloids, sterols, and triterpenes. Comprehensive chemical studies have also shown the presence of caryophyllene, limonene, ūFC;-selinene, p-dimethyl styrene, N-butyl phthalide, and N-pertyl benzene (Sarfaraj Hussain et al. 2011). Table 1 shows the various reported biological activities of the phytochemicals.

Phytochemicals like limonene, rutin, caffeic aid, kaempferol, isoquercitrin, alpha-tocopherol, hyperoside, and alpha-terpineol have shown a considerable anti-neoplastic effect in numerous studies; ferulic acid and chlorogenic acid have proved to possess protective effect against many hepatic tumors (Sathya and Gopalakrishnan 2012). Two flavonoids have been isolated from the seeds of *A. graveolens*, namely isoharmentin and quercetin known to possess antioxidant activity and free radical scavenging property (Firuzi et al. 2005). Carvone, being the major constituent of the *A. graveolens*, acts as the most active compound against various cancers.

Table 1 Phytochemicals of *Anethum graveolens* and their respective medicinal properties

S. No	Compound	Medicinal property	Reference
1.	α-Phellandrene	Induction of autophagy	Hsieh et al. 2015
2.	Limonene	Antifungal, anticancer, and antioxidant	Fitsiou et al. 2016
3.	Carvone	Hepatoprotective	Thoppil and Bishayee 2011
4.	Pinene	Anticancer	Chen et al. 2015
5.	Cineole	Antimicrobial and cytotoxic	Fitsiou et al. 2016
6.	Caffeic acid	Antidiabetic	Goodarzi et al. 2016
8.	Quercetin	Anticancer	Li et al. 2013
9.	Ferulic acid	Anticancer	Al-Asmari et al. 2014
10.	Kaempferol	Anticancer	Al-Asmari et al. 2014

Recent studies proved that chemically induced carvone prevented lung and stomach carcinomas in mice, and exhibited a significant role in colon cancer treatment (Manesh and Kuttan 2003; Gupta et al. 2011).

Molecular Interaction of Carvone with p53

Apart from the antimicrobial and hepatoprotective role of L-carvone, it is also effective in the prevention of cancer (Hussain et al. 2010). This dietary monoterpene has advantage over the other monoterpenes being a nontoxic dietary antitumorigenic agent (Crowell 1999; Wattenberg et al. 1989). Up till now, the molecular mechanism of carvone in cancer is unclear; recent studies reported that carvone induces apoptosis by activating p53 and caspases in different cancer cell lines (Patel and Thakkar 2014). Table 2 describes the diverse molecular targets of the most active phytochemical carvone. The in silico analysis as depicted in Fig. 3 provides evidence that carvone interacts strongly with p53 at its active site; perhaps this interaction initiates the activation of p53 which plays an important role in suppressing tumors.

Table 2 Protein targets and the associated biological functions of carvone

S. No	Protein target	Biological functions	Reference
1.	TNFα	Anti-inflammatory response	Abe et al. 2003
2.	ERK, P21	Antiproliferative action by cell cycle arrest	Chen et al. 2006a
3.	P53, caspase	Apoptosis and cell cycle arrest in MCF7 cell line	Patel and Thakkar 2014
4.	TRPV1	Increase in cytosolic calcium concentration	Gonçalves et al. 2013
5.	IL-1β	Anti-inflammatory and antinociceptive activity in mice	Marques et al. 2014
6.	PPARγ, MTGPAT	Reduce lipid accumulation in hepatocytes	Wu et al. 2015

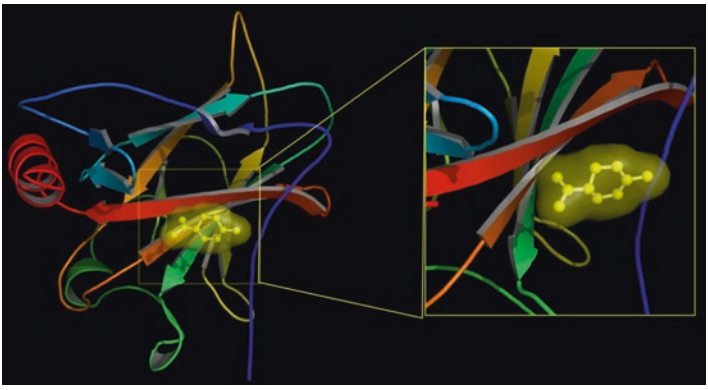

Fig. 3 Molecular interaction of carvone (surface ball and stick) with p53 (cartoon)

Conclusion and Future Perspective

Treatment with medicinal herbs is a trusted practice since ancient times. Herbal medicines particularly *A. graveolens* possess anticancer, antihyperlipidemic, antimicrobial, and antidiabetic properties. Epidemiological experiments stated that *A. graveolens* intake and risk of cardiovascular diseases are conversely related. *A. graveolens* has numerous vital components such as polyphenols, tannins terpenoids, polysaccharides, flavonoids, alkaloids, and saponins that have their individual remedial properties. The in silico molecular docking results corroborate carvone—an active constituent of *A. graveolens*—to be a potential anticancer compound. Nevertheless, the interaction of other drugs with these active compounds must be normalized; the dose and period of consumption must also be standardized by further clinical trials among different populations. The need of additional studies is sensed to identify the key constituents of *A. graveolens* that actively contributes in disease treatment through its valuable properties.

References

Abe S, Maruyama N, Hayama K, Ishibashi H, Inoue S, Oshima H, Yamaguchi H (2003) Suppression of tumor necrosis factor-alpha-induced neutrophil adherence responses by essential oils. Mediat Inflamm 12:323–328

Abu-Elmagd M, Assidi M, Schulten H-J, Dallol A, Natesan PP, Ahmed F, Scherer SW, Al-Qahtani M (2015) Individualized medicine enabled by genomics in Saudi Arabia. BMC Med Genet 8:1755–8794

Ahmad R, Ahmad N, Naqvi AA, Shehzad A, Al-Ghamdi MS (2016) Role of traditional Islamic and Arabic plants in cancer therapy. J Tradit Complement Med 7(2):195–204

Al-Asmari AK, Al-Elaiwi AM, Athar MT, Tariq M, Al Eid A, Al-Asmary SM (2014) A review of hepatoprotective plants used in Saudi traditional medicine. Evid Based Complement Alternat Med 2014:1–22

Alatar A, El-Sheikh MA, Thomas J (2012) Vegetation analysis of Wadi Al-Jufair, a hyper-arid region in Najd, Saudi Arabia. Saudi J Biol Sci 19:357–368

Bagchi D (2014) Nutraceutical and functional food regulations in the United States and around the world, 2nd edn. Elsevier, Amsterdam

Baharvand-Ahmadi B, Asadi-Samani M (2017) A mini-review on the most important effective medicinal plants to treat hypertension in ethnobotanical evidence of Iran. J Nephropharmacol 6:3–8

Bahramika S, Yazdanparast R (2008) Evaluation of the effect of Anethum graveolens L. crude extracts on serum lipids and lipoproteins profiles in hypercholesterolaemic rats. DARU J Pharm Sci 16:88–94

Bahramikia S, Yazdanparast R (2007) Improvement of liver antioxidant status in hypercholesterolemic rats treated with Anethum graveolens extracts. Pharmacology Online 199–132

Berger MM, Shenkin A (2006) Vitamins and trace elements: practical aspects of supplementation. Nutrition 22:952–955

Calcul L, Zhang B, Jinwal UK, Dickey CA, Baker BJ (2012) Natural products as a rich source of tau-targeting drugs for Alzheimer's disease. Future Med Chem 4:1751–1761

Chan PF, Macarron R, Payne DJ, Zalacain M, Holmes DJ (2002) Novel antibacterials: a genomics approach to drug discovery. Curr Drug Targets Infect Disord 2:291–308

Chaudhary GD, Kamboj P, Singh I, Kalia AN (2010) Herbs as liver savers – a review. Indian J Nat Prod Resour 1:397–408

Chen J, Lu M, Jing Y, Dong J (2006a) The synthesis of l-carvone and limonene derivatives with increased antiproliferative effect and activation of ERK pathway in prostate cancer cells. Bioorg Med Chem 14:6539–6547

Chen X, Zhou H, Liu YB, Wang JF, Li H, Ung CY, Han LY, Cao ZW, Chen YZ (2006b) Database of traditional Chinese medicine and its application to studies of mechanism and to prescription validation. Br J Pharmacol 149:1092–1103

Chen W, Liu Y, Li M, Mao J, Zhang L, Huang R, Jin X, Ye L (2015) Anti-tumor effect of a -pinene on human hepatoma cell lines through inducing G2 / M cell cycle arrest. J Pharmacol Sci 127:332–338

Crowell PL (1999) Symposium on phytochemicals: biochemistry and physiology prevention and therapy of cancer by dietary monoterpenes, vol. 1. pp. 775–778

Duke JA (2001) Handbook of medicinal herbs. Herbal reference library: Publisher CRC press. ISBN 0-8493-1284-1

Eshwar S, K R, Jain V, Manvi S, Kohli S, Bhatia S (2016) Comparison of dill seed oil mouth rinse and chlorhexidine mouth rinse on plaque levels and gingivitis – a double blind randomized clinical trial. Open Dent J 10:207–213

Fasinu PS, Bouic PJ, Rosenkranz B (2012) An overview of the evidence and mechanisms of herb – drug interactions. Front Pharmacol 3:1–19

Firuzi O, Lacanna A, Petrucci R, Marrosu G, Saso L (2005) Evaluation of the antioxidant activity of flavonoids by "ferric reducing antioxidant power" assay and cyclic voltammetry. Biochim Biophys Acta 1721:174–184

Fitsiou E, Mitropoulou G, Spyridopoulou K, Tiptiri-Kourpeti A, Vamvakias M, Bardouki H, Panayiotidis MI, Galanis A, Kourkoutas Y, Chlichlia K et al (2016) Phytochemical profile and evaluation of the biological activities of essential oils derived from the Greek aromatic plant species Ocimum basilicum, Mentha spicata, Pimpinella anisum and Fortunella margarita. Molecules 21:1–15

Gonçalves JCR, Silveira AL, de Souza HDN, Nery AA, Prado VF, Prado MAM, Ulrich H, Araújo DAM (2013) The monoterpene (-)-carvone: a novel agonist of TRPV1 channels. Cytometry A 83A:212–219

Goodarzi MT, Khodadadi I, Tavilani H, Abbasi Oshaghi E (2016). The role of *Anethum graveolens* L.(Dill) in the management of diabetes. J Trop Med 1–11. https://doi.org/10.1155/2016/1098916

Gugerli F, Parducci L, Petit RJ (2005) Ancient plant DNA: review and prospects. New Phytol 166:409–418

Gupta C, Prakash D (2014) Phytonutrients as therapeutic agents. J Complement Int Med 11(3):151–169. https://doi.org/10.1515/jcim-2013-0021

Gupta A, Mittal A, Jha PKK, Kumar A (2011) Nature's treasurer: plants acting on colon cancer Nature' s treasurer: plants acting on colon cancer. J Stress Physiol Biochem 7:217–231

Gupta C, Prakash D, Gupta S (2013) Relationships between bioactive food components and their health benefits 2013:66–85

Gurib-Fakim A (2006) Medicinal plants: traditions of yesterday and drugs of tomorrow. Mol Asp Med 27:1–93

Hajhashemi V, Abbasi N (2008) Hypolipidemic activity of Anethum graveolens in rats. Phytother Res 22:372–375

Harvey AL, Edrada-Ebel R, Quinn RJ (2015) The re-emergence of natural products for drug discovery in the genomics era. Nat Rev Drug Discov 14:111–129

Hsieh LC, Hsieh SL, Chen CT, Chung JG, Wang JJ, Wu CC (2015) Induction of α-Phellandrene onAutophagy in Human Liver Tumor Cells. Amer J Chin Med 43(1):121–136

Hussain AI, Anwar F, Nigam PS, Ashraf M, Gilani AH (2010) Seasonal variation in content, chemical composition and antimicrobial and cytotoxic activities of essential oils from four mentha species. J Sci Food Agric 90:1827–1836

Ji HY, Liu KH, Kong TY, Jeong HU, Choi SZ, Son M, Cho YY, Lee HS (2013) Evaluation of DA-9801, a new herbal drug for diabetic neuropathy, on metabolism-mediated interaction. Arch Pharm Res 36:1–5

Jiljit G (2016) Wjpls increase breast milk supply with herbal. World J Pharm Life Sci 2:146–150

Kaur GJ, Arora DS (2010) Bioactive potential of Anethum graveolens, Foeniculum vulgare and Trachyspermum ammi belonging to the family Umbelliferae - current status. J Med Plants Res 4:87–94

Kazemi T, Panahi Shahri H, Hossaini Farash M, Darabi M, Kashanian M, Akbari H (2006) Effect of Dill pearl on serum lipids. Arak Med Univ J 8:35–41

Kesarwani K, Gupta R (2013) Bioavailability enhancers of herbal origin: an overview. Asian Pac J Trop Biomed 3:253–266

Lans C, Turner N, Brauer G, Lourenco G, Georges K (2006) Ethnoveterinary medicines used for horses in Trinidad and in British Columbia. Can J Ethnobiol Ethnomed 2:31

Larijani B, Esfahani MM, Moghimi M, Shams Ardakani MR, Keshavarz M, Kordafshari G, Nazem E, Hasani Ranjbar S, Mohammadi Kenari H, Zargaran A (2016) Prevention and treatment of flatulence from a traditional Persian medicine perspective. Iran Red Crescent Med J 18:e23664

Li T, Zhu J, Guo L, Shi X, Liu Y, Yang X (2013) Differential effects of polyphenols-enriched extracts from hawthorn fruit peels and fleshes on cell cycle and apoptosis in human MCF-7 breast carcinoma cells. Food Chem 141:1008–1018

Madani H, Mahmoodabady NA, Vahdati A (2005) Effects ofhydroalchoholic extract of Anethum graveolens (Dill) on plasma glucose an lipid levels in diabetes induced rats. Iran J Diabet Lipid Dis 5(2):109–116

Malhotra SK, Vashishtha BB (2007) Response of Indian dill (Anethum sowa) and European dill (Anethum graveolens) varieties to different agro-techniques. Indian J Agric Sci 77:519–522

Manesh C, Kuttan G (2003) Effect of naturally occurring allyl and phenyl isothiocyanates in the inhibition of experimental pulmonary metastasis induced by B16F-10 melanoma cells. Fitoterapia 74:355–363

Mansouri M, Nayebi N, keshtkar A, Hasani-Ranjbar S, Taheri E, Larijani B (2012) The effect of 12 weeks Anethum graveolens (dill) on metabolic markers in patients with metabolic syndrome; a randomized double blind controlled trial. Daru 20:47

Marques THC, Marques MLBGCB, Medeiros JVR, Silva RO, Dos Reis Barbosa AL, Lima TC, De Sousa DP, De Freitas RM (2014) Cyane-carvone, a synthetic derivative of carvone, inhibits inflammatory response by reducing cytokine production and oxidative stress and shows antinociceptive effect in mice. Inflammation 37:966–977

Monsefi M, Ghasemi A, Alaee S, Aliabadi E (2015) Effects of Anethum graveolens L. (dill) on Oocyte and Fertility of Adult Female Rats. J Reprod Infertil 16:10–17

Nair R, Chanda SV (2007) Antibacterial activities of some medicinal plants of the western region of India. Turk J Biol 31:231–236

Newman DJ, Cragg GM (2012) Natural products as sources of new drugs over the 30 years from 1981 to 2010. J Nat Prod 75(3):311–335. https://doi.org/10.1021/np200906s

Newman DJ, Cragg GM (2016) Natural products as sources of new drugs from 1981 to 2014. J Nat Prod 79(3):629–661. https://doi.org/10.1021/acs.jnatprod.5b01055

Orhan İE, ÖZÇELİK B, Kartal M, Kan Y (2012). Antimicrobial and antiviral effects of essential oils from selected Umbelliferae and Labiatae plants and individual essential oil components. Turk J Biol 36(3):239–246. https://doi.org/10.3906/biy-0912-30

Patel PB, Thakkar VR (2014) L-Carvone induces p53, Caspase 3 mediated apoptosis and inhibits the migration of breast cancer cell lines. Nutr Cancer 66:453–462

Payne DJ, Gwynn MN, Holmes DJ, Pompliano DL (2007) Drugs for bad bugs: confronting the challenges of antibacterial discovery. Nat Rev Drug Discov 6:29–40

Pulliah T (2002) Medicinal plants in India. Daya Books (Regency Publications): pp580, ISBN 8187498579, 9788187498575

Roemer T, Krysan DJ (2014) Antifungal drug development: challenges, unmet clinical needs, and new approaches. Cold Spring Harb Perspect Med 4. https://doi.org/10.1101/cshperspect.a019703

Sahib AS, Mohammed IH, Sloo SA (2014) Antigiardial effect of Anethum graveolens aqueous extract in children. J Intercult Ethnopharmacol 3:109–112
Sarfaraj Hussain M, Fareed S, Ali M (2011) Preliminary phytochemical and pharmacognostical screening of the ayurvedic drug hygrophila auriculata (K. Schum) heine. Pharm J 3:28–40
Sathya V, Gopalakrishnan VK (2012) Study of drug likeness activity of phytochemicals in medicinal plants. Int Res J Pharm 3:127–128
Sharma R (2004) Agrotechniques of medicinal plants. Daya Publishing House, New Delhi
Shekhawat G, Jana S (2010) Anethum graveolens: an Indian traditional medicinal herb and spice. Pharmacogn Rev 4:179
Silver LL (2011) Challenges of antibacterial discovery. Clin Microbiol Rev 24:71–109
Thoppil RJ, Bishayee A (2011) Terpenoids as potential chemopreventive and therapeutic agents in liver cancer. World J Hepatol 3:228–249
Villems R, Metspalu M, Kivisild T, Bandelt H-J, Richards M (2006) The pioneer settlement of modern humans in Asia. Nucleic Acids Mol Biol 18:181–199
Wallace TC, Blumberg JB, Johnson EJ, Shao A (2015) Dietary bioactives: establishing a scientific framework for recommended intakes. Adv Nutr 6:1–4
Wang Y, Jin Y, Zhou C, Qu H, Cheng Y (2008) Discovering active compounds from mixture of natural products by data mining approach. Med Biol Eng Comput 46:605–611
Wattenberg LW, Sparnins VL, Barany G, Sparnins VL (1989) Inhibition of N -nitrosodiethylamine carcinogenesis in mice by naturally occurring organosulfur compounds and monoterpenes inhibition of Af-Nitrosodiethylamine carcinogenesis in mice by naturally occurring organosulfur compounds and monoterpenes'. pp. 2689–2692.
Wu C, Jia Y, Lee JH, Kim Y, Sekharan S, Batista VS, Lee SJ (2015) Activation of OR1A1 suppresses PPAR-γ expression by inducing HES-1 in cultured hepatocytes. Int J Biochem Cell Biol 64:75–80
Xu Z, Howard LR (2012) Analysis of antioxidant-rich phytochemicals. John Wiley & Sons, ISBN: 978-0-813-82391-1; https://doi.org/10.1002/9781118229378
Zheng GQ, Kenney PM, Lam LK (1992) Anethofuran, carvone, and limonene: potential cancer chemopreventive agents from dill weed oil and caraway oil. Planta Med 58:338–341
Zhu L, Zhong M, Zhao J, Rhee H, Caesar I, Knight EM, Volpicelli-Daley L, Bustos V, Netzer W, Liu L et al (2013) Reduction of synaptojanin 1 accelerates a clearance and attenuates cognitive deterioration in an Alzheimer mouse model. J Biol Chem 288:32050–32063

Fern to Pharma: Potential Neuroameliorative Properties of Pteridophytes

Girish Chandran, S. R. Smitha Grace, and Jyoti Bala Chauhan

Introduction

Neurodegeneration is a concrete term referring to the progressive damage of structure and function of neurons involving a cocktail of cellular pathways (Shukla et al. 2011) leading to a condition termed as neurodegenerative disease (NDD). Various NDDs are classified and each one is characterized by the loss or functional compromise among specific neuronal populations in the central nervous system (CNS) which results in the expression of particular neurobehavioral phenotype (motor activity, mood, and cognition). The subset of CNS regions related to the pathophysiology of major NDD are cerebral cortical (Alzheimer's disease), substantia nigra (Parkinson's disease), motor neurons (amyotrophic lateral sclerosis), and striatal neurons (Huntington's disease) (Ayala et al. 2007). The type of susceptible neuronal populations vary in different NDDs; however the progressive pathways leading to the pathophysiology and hence the neuronal damage involve similar mechanisms. Irrespective of the various pathways and cascades involved in initiation and progression, the general pathophysiology of NDD involves oxidative stress and mitochondrial dysfunction. Unmitigated generation of free radicals and obvious inadequacy in their detoxification in brain cells result in lipid peroxidation, nucleic acid-base oxidation, protein damages, and aggregation gradually culminating in neuronal cell death. In addition, aging is also demonstrated to have significant deleterious effects on brain functions (Seet et al. 2013). Due to neonatal loss of the ability to regenerate among majority of the neuronal tissues and because degeneration is a continuous process, the piled-up effect makes these neurons susceptible to cytotoxicity.

G. Chandran (✉) · S. R. Smitha Grace · J. B. Chauhan
Biochemistry, Department of Lifesciences, Pooja Bhagavat Memorial Mahajana Education Centre, Post Graduate Wing of SBRR Mahajana First Grade College, Metagalli, Mysuru, Karnataka, India

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Oxidative Stress and Neurodegeneration

Oxidative stress is the imbalance between the formation and degradation of reactive oxygen species (ROS) or reactive nitrogen species (RNS) in the cellular environment. Oxygen/nitrogen-related free radicals (superoxide and hydroxyl radicals, hydrogen peroxide, nitric oxide, peroxynitrite, and hypochlorous acid) produced in the body, primarily as a result of aerobic metabolism, are crucial in the normal functioning of numerous cellular signal pathways (Emerit et al. 2004). ROS/RNS participate directly in defense against infection and also are important coordinators of the inflammatory response (Halliwell 2006, 2009). However their accumulation over time initiates degenerative pathways among the neurons and other cells which lead to neurodegeneration (Vaya et al. 2011; Zhao 2009; Shin et al. 2011). Numerous genetic factors also affect the compromised redox status among neurons making them susceptible to incoming physiological stress (Jenner 2003). Besides, the imbalance in the redox homeostasis and mitochondrial dysfunction is also associated with normal aging as well as pathophysiology of numerous diseases/pathological conditions including cancer, cardiovascular diseases (atherosclerosis, hypertension, and ischemia), diabetes, pulmonary diseases, and asthma (Watfa et al. 2011; Birben et al. 2012). Microsomes, peroxisomes, and endoplasmic reticulum are the next major sources of ROS/RNS generation in the cell. During reactions catalyzed by cytochrome P450 and NADPH oxidase enzyme, microsomes produce superoxides and hydrogen peroxides (Letelier et al. 2011). Peroxisomes harbor flavin-containing oxidases and catalase which produce and decompose hydrogen peroxide, respectively (Schrader and Fahimi 2006; Nordgren and Fransen 2014). These reactions participate significantly in the inflammatory pathways and imbalance in these mechanisms among specific neurons would ultimately lead to neurodegeneration.

Plant-Derived Bioactives for Neuroprotective Strategies

Modern neurotherapeutic strategies must involve agents that protect the brain from the deleterious effects of oxygen free radicals and slow down the disease progression. Though genetic causes of major NDD exist, the environmental factors also prevail the development of these diseases (Sanchez-Danes et al. 2012). Accordingly, the therapeutic strategies for neuronal disorders should include both noninvasive (exercise, counseling) and invasive therapies (oral antioxidants, inhibitors of AChE/MAO-B; minor surgeries; deep-brain stimulation; stem cell therapy). Plants make nearly 80% of therapeutic resources globally and have the only part of the traditional medicine. Traditional knowledge about the medicinal plants has been emphasized for the ethnobotanical studies (Albuquerque et al. 2014). Owing to the central role played by oxidative stress in the pathophysiology of NDD, the use of antioxidants as therapeutic agents is valid. The epidemiological data suggest the lower

incidence of neurodegeneration upon dietary intake or supplementary intake of natural antioxidants. Diet is the major source of antioxidants, though medicinal herbs are gaining attention in this regard (Uttara et al. 2009). Several lines of evidence suggest that the ability of polyphenols to attenuate the redox status in vivo can be exploited to achieve neuroprotection (Jimenez-Del-Rio et al. 2010; Dumont and Beal 2011; Zhong and Zhou 2013). However, besides the regular antioxidant capacity, phytophenols, at concentrations much lower than required for the antioxidant activity, are reported to interact with various cellular targets at different levels ranging from receptors on the cell membrane to mitochondrial matrix enzymes (Virgili and Marino 2008; Richard et al. 2011). The current incurable status of major CNS disorders (e.g., AD, PD, and HD) leads to huge socioeconomic impacts. Therefore, there exists a constant need for developing newer and efficient therapeutic approaches, which act on multiple biochemical targets, without detrimental side reactions and least toxicity (Zhao 2009). Hence consistent with this conceptual thinking, various plant products are being explored as therapeutic adjuvants (Denny Joseph and Muralidhara 2013; Khurana and Gajbhiye 2013; Prasad and Muralidhara 2013; Sudati et al. 2013).

Various antioxidant compounds isolated from plant origin, such as quercetin, resveratrol, curcumin, ferulic acid, vitamin C, vitamin E, and coenzyme Q10 and phytoextracts like *Bacopa monnieri*, *Curcuma longa*, *Gymnema sylvestre*, *Centella asiatica*, *Hemidesmus*, and *Ginkgo biloba* have been found to be beneficial in animal and cell models of various NDDs. These compounds are also used for human use for neurobehavioral improvement. In Ayurveda, phytochemicals find a significant therapeutic application for treatment against various severe pathological conditions. Numerous reports show possible interactions of phytochemicals at various molecular levels in major degenerative diseases, employing various study models, viz. cell lines, primary cell culture, Drosophila, rodents, etc. The herbal preparations generally contain a cocktail of phenolics, alkaloids, catechols, flavonoids, lignans, phenolics, stilbenoids, and terpenes which are known to modulate signaling cascades in the pathogenesis of major NDDs apart from their antioxidant properties.

There exist a vast number of unexplored lower plants, which are potential candidates for neurotherapy. Ferns or pteridophytes are a group of plants unexplored for their neurotherapeutic potential despite many references in folk and Ayurvedic medicine (Ma et al. 2010). Pteridophytes/ferns are a group of nonflowering plants with primitive vasculature, and habitat mostly limited to humid/high-altitude regions of the world. Ferns offer a great deal of therapeutic applications in different ailments according to various systems of medicine such as Ayurvedic, Unani, homeopathic, and tribal medicine (Talukdar et al. 2011). It is well established that chemicals extracted from plants are considered for a wide range of therapeutic strategies. However, studies on the pharmacology of plant-derived bioactives have mainly focused on angiosperm sources rather than pteridophytes in general. This may be due to the limited distribution of the habitat and fading conventional undocumented therapeutic knowledge among the local communities. Also because angiosperms exhibit greater biodiversity and more varied adaptations, and are more widely

distributed, making them accessible to a greater number of research groups (Chandran et al. 2015; Chandran and Muralidhara 2016; Maroyi 2016). Although pteridophytes are less widely distributed than angiosperms, they are reportedly used for medicinal purposes in places where they do occur, suggesting that they produce secondary metabolites with specialized ecological functions relating to herbivore defense (Maroyi 2014; Xavier et al. 2014). It appears that ferns and lycophytes are rich sources of compounds with antioxidant and anti-inflammatory activity. Additionally medicinal properties, such as analgesic, antimutagenic, immunomodulatory, and neuromodulatory, have been observed in pharmacological studies of ferns (Chandran and Muralidhara 2014; Cao et al. 2017). Many of these properties result from the biological activity of secondary metabolites present in these plants, e.g., triterpenes, alkaloids, phenols, flavonoids, saponins, and tannins (Dos Santos Jr. et al. 2005). Nonetheless, ferns have not been often indicated as medicinal in most epidemiological surveys. Though limited data are reported about the pharmacological properties of ferns and their phytoextracts there are a few significant leads for the identification of potent neuromodulators. There is an obvious yearly increasing trend in the number and variety of publications that identify never-ending list of bioactives from ferns (Fig. 1).

Approximately 12,000 species of ferns are documented around the world mostly native to tropical and subtropical areas. Nearly 1000 species are found in India in Himalayan range, Western Ghats, and other hilly areas (Chandran and Muralidhara 2014, 2016). Nearly 300 ferns are cited in the traditional/tribal medicine for human and animal ailments. Phytochemical studies on ferns have revealed the presence of alkaloids, flavonoids, polyphenols, terpenoids, and steroids (Xia et al. 2014). The secondary metabolites in ferns differ in their structure and derivatives in comparison

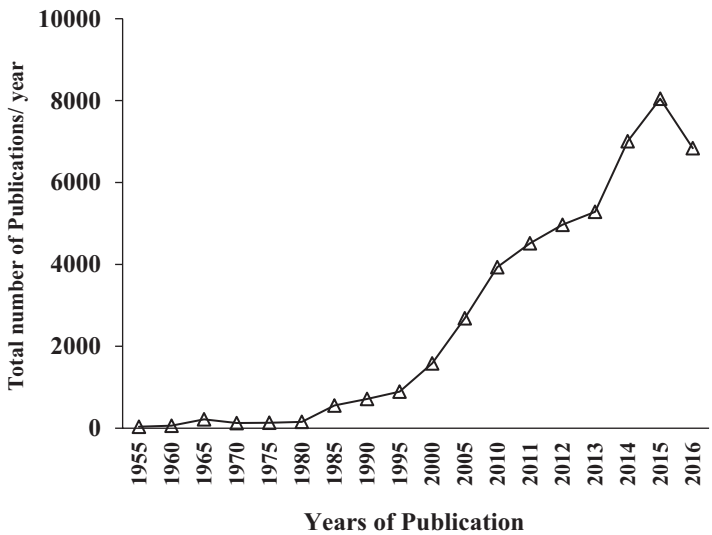

Fig. 1 Schematic representation of yearly increasing publications based on the Pubmed scale

with higher plants. In the recent past there is an increase in the number of scientific reports about the phytoconstituents isolated from ferns as well as their range of potential pharmacological applications.

History of Ferns in General or Therapeutic Applications

Ferns find uses as ornamental plants, in handicrafts, as components of cosmetic formulations and foodstuffs, and as medicine. There is a revived interest on the therapeutic effectiveness, as well as scientific curiosity about ferns as medicines. The constant need for newer drugs owing to their side effects and gradually decreasing efficacy has prompted several groups to conduct pharmacological research on plant-derived preparations, especially ferns. Experimental reports suggest an array of biological properties for the actives isolated from various fern species which include but not limited to cancer cytotoxicity, anti-inflammatory, antioxidant, antihyperglycemic, hepatoprotective, and anti-nociceptive activity (Zheng et al. 2011; Morais-Braga et al. 2012).

General Phytochemistry of Ferns

The phytochemicals identified from most of the fern species belong to flavonoid class. However, many of the plants host dimers or tetramers of these flavonoids making biflavonoids and tetraflavonoids, respectively. Particularly biflavonoids are reported from *Selaginellaceae* members and a few gymnosperms as well (Chandran et al. 2015). Flavonoids have proven to be potent biological modulators in terms of anti-inflammatory, anticancer, and antimicrobial effects. Hence presence of double the flavonoid moieties in one structure would enable these compounds to be more efficient in exerting the biological activities of their monomeric counterparts.

Potential Neuromodulatory Properties of Actives from Ferns

The neuromodulatory potency of a phytochemical is initially evaluated by its antioxidant and anti-inflammatory properties. Hence, we have made efforts here to list such properties of ferns from the recent reports with specific relevance to the possible neuroameliorative interventions. Pteridaceae is one of the largest fern families which finds its habitat distributed from temperate to tropical, planes to hilly peaks, arid to irrigated, and coastal to inlands worldwide. Members of *Pteridaceae* are cited for significant pharmacological applications among the tribal medicine. The bioactives identified from the family *Pteridaceae* belong to an array ranging from alkaloids to flavonoids and their glucoside derivatives like kaurene, kauroic acid,

Table 1 Phytochemical diversity from various ferns

Ferns	Bioactives	References
1. *Pteridaceae*		
Pteris semipinnata, *P. Multifida*, *P. esculentum*, *P. aquilinum*, *P. Semipinnata*, *Pityrogramma calomelanos*, *Pteridium spp.*	Kaurene, kauroic acid, apigenin, caffeic acid, rutin, luteolin, ptaquiloside, pterosine, multifedoside	Bai et al. 2013; Wang et al. 2013; Reinaldo et al. 2015
2. *Huperziaceae*		
Huperzia serrata, *Lycopodium serratum*, *Phlegariurus spp.*	Lycobeline alkaloids, huperzine, serratine, lycopodine, serratine-diols, lycoclavanol	Ma et al. 2007; Jiang et al. 2010; Yang et al. 2010; Ying et al. 2014
3. *Gleicheniaceae*		
Gleichenia quadriparitta, *G. hirta*, *G. blotiana*, *Dicranopteris dichotoma*, *D. prelata*	Ecdysteroids, diterpenes	Cao et al. 2017
4. *Equisetaceae*		
Equisetum arvense	Peteosins, equisetolic acid, kaempferol, quercetin-glucoside	Dos Santos Jr. et al. 2005; Singh et al. 2011
5. *Lygodiaceae*		
Lygodium venustum, *L. japonicum*	Acacetin, rutinoside, phenyl propanoids, glucosides	Morais-Braga et al. 2012; Cao et al. 2017
6. *Helminthostachyaceae*		
Helminthostachys zeylanica	Ugonins, prenylated flavonoids, thermalic acids	Cao et al. 2017 (Review)
7. *Ophioglossaceae*		
Ophioglossum pedunculosum, *O. petiolotum*, *O. thermale*, *Botrychium ternatum*	Quercetin glycosides, ophioglonin, kaempferol glucopyranosides	Cao et al. 2017 (Review)
8. *Selaginellaceae*		
Selaginella amassae, *S. bryopteris*, *S. delicatula*, *S. involvens*, *S longistrobilina*, *S. tamariscina*, *S. wangpeishanii*	Biflavonoids-amentoflavone, hinokiflavone, involvenflavone; terpenoids, selaginellins, phenolics	Lee et al. 2008; Girish and Muralidhara 2012; Ha et al. 2012; Chandran and Muralidhara 2013, 2014; Chandran et al. 2014, 2015
9. *Polypodiaceae*		
Polypodium leucotomos, *P. hastata*, *P. triloba*	Caffeic acid, coumaric acid, gallic acid, glucopyranoside	Cao et al. 2017 (Review)

apigenin, caffeic acid, rutin, luteolin, ptaquiloside, and pterosine (Table 1) (Bai et al. 2013; Wang et al. 2013). The hexane isolates from *Adiantum capillus-veneris* demonstrated anti-inflammatory effects among mice (Ibraheim et al. 2011). Additionally anti-inflammatory effect of ethanol extract from *A. capillus-veneris* via inhibition of the transcription factor (NF-κB) pathway was also documented (Yuan et al. 2013).

Various acetylcholinesterase inhibitors are being employed to alleviate cognitive symptoms of Alzheimer's disease. Traditional medicine suggests the use of *Huperzia* phytoextracts to treat contusions, strain, swelling, and schizophrenia (Jiang et al. 2010). Among the fern bioactives, huperzine A from *Huperzia spp.* is a famous acetylcholinesterase (AChE) inhibitor (AChEI) (Ma et al. 2007). Huperzine A being a significant AChEI has applications in the treatment of mild-to-moderate dementia and was also a part of a clinical trial to evaluate its safety, tolerability, and efficacy (Rafii et al. 2011). This alkaloid improved learning and reduced memory impairment in patients, and has a proven neuroprotective effect in rats as a result of modulating the oxidative stress and amyloid beta-induced apoptosis of rat cortical neurons. These findings have prompted huperzine A as a significant lead for developing a new anti-Alzheimer's drug (Wu et al. 2011; Sun et al. 2013). Huperzine A and its derivatives are already marketed as a potent drug for Alzheimer's disease (AD) and related disorders in China and Europe. Huperzine A is demonstrated to be a potent AChEI with higher oral bioavailability than a few standard AChEI drugs, and has the ability to cross blood–brain barrier along with a longer in vivo half-life. Similar to huperzine, its derivatives like 12-deoxyhuperzine O antagonize the NMDA receptor with an impressive lower IC50 (0.92 μM) (Yang et al. 2010).

The neuroameliorative properties of Huperzia bioactive is not limited to its AChEI activity. Crude alcohol extracts of *H. serrata* containing huperzine A and specific triterpenoids are demonstrated to be potent antiproliferants against human leukemia cells (HL-60) via inducing pro-apoptotic pathways (Ham et al. 2012). Further a novel lycopodium alkaloid was obtained from another species, *H. saururus*; however its AChE inhibitory activity was found to be matching that of huperzine A though significant (Vallejo et al. 2007). In addition, the other lycopodium-type alkaloid from this genus with potent AChE inhibitory activity includes lycotetrastine A and huperserine E from *H. tetrasticha*. An important member of this genus, *H. saururus* (a native Argentine species), is used in ethnomedicine as aphrodisiac and memory improver (Vallejo et al. 2007). The main alkaloid, sauroine, is found to improve memory retention among experimental rats as evidenced by a battery of neurobehavioral tests. Additionally a critical electrophysiological observation revealed improved hippocampal plasticity among sauroine rats. An alkaloid fraction of *H. saururus* strongly inhibited AChE with as low as IC50 = 0.58 μg/mL. Sauroxine, another major alkaloid, also showed significant inhibition of AChE activity (IC50 = 8.9 μg/mL). Further there were few more bioactives identified from the genus like 6-hydroxylycopodine and N-demethyl-sauroxine with AChEI activity at IC50 = 78.1 and 54.5 μg/mL, respectively. However, the crude alkaloid fraction had much higher AChE inhibitory activities than the isolated individual alkaloids which suggests an interesting synergy between these alkaloids (Konrath et al. 2013; Vallejo et al. 2013). Additionally huperzine A also indicated to promote hippocampal neurogenesis and attenuate cognitive deficits in rats exposed to acute hypobaric hypoxia (Ma et al. 2013). Interestingly in a separate study, it is shown to ameliorate chronic pain phenotype among rats in a spinal cord compression injury model (Yu et al. 2013). Further, the triterpenoids from Pteridaceae members showed significant anticancer activity on lymphoblastic leukemia and human hepatoma

cells. Lycoposerramine and lycopodine derivatives were demonstrated to be potent AChEIs and inhibitors of α-glucosidase (Ying et al. 2014). The huperzine A and its derivatives already are marketed for their AChEI activities; however, there needs to be a vigil lookout for such potent bioactives from these fern members.

Middle American indigenous communities have used *Lygodium venustum* as a medicinal plant for its antiseptic, fungicidal activities as a topical medicine as well as to treat gastrointestinal and gyneco-obstetric disorders, and as a postpartum anti-inflammatory agent. *L. venustum* is also used in making a pleasure beverage or intoxicant by a few Amazonian tribes. Interestingly in Brazil it is used to treat nervousness and emotional instability which may be related to its intoxicating property (Cao et al. 2017). These traditional references indicate a potent use for *L. venustum* as an antidepression drug; however it needs to be evaluated on a larger scale to explore its possible differential effects among different human ethnicities.

Members of *Equisetaceae*, particularly equisetum, are found to be potent neuromodulators. The phytoextracts from *E. arvense* and the related species are shown to possess significant antioxidant, anti-inflammatory, analgesic, and antimicrobial properties. Rodent-based investigations revealed that stem extracts of this fern are reported to possess anticonvulsant, sedative, anxiolytic, neuroprotective, as well as antidiabetic activity in streptozotocin model (Singh et al. 2011). In another study, flavonoid-rich extract of *E. arvense* is reported to possess antitumor propensity. Flavonoid preparation from Thelypteridaceae member *Abacopteris penangiana* attenuated the hyperglycemic complications among streptozotocin rats in a high-fat diet. Abacopterin A (a flavonoid) demonstrated hypolipidemic and anti-inflammatory activity against high-fat diet in a mice model. Further investigations revealed that Abacopteris flavonoids possess modulatory properties against diabetes-associated general oxidative stress and inflammatory complications (Lei et al. 2011). Abacopterin has been indicated to be a potent antioxidant against hydrogen peroxide-induced cell death and complications in PC12 cells. Flavonoids from *Abacopteris* are found to be neuroprotective against a galactose-induced age-accelerated model of mice in terms of reversal of neurotoxicity among specific brain regions (Fu et al. 2013).

Selaginellaceae is a major fern family in the tropical and subtropical areas that is strictly limited to high-altitude areas. Selaginellaceae members are mentioned for various ailments among the tribal medicinal practitioners across India and China. Interestingly, *Selaginella bryopteris* is suggested to be the "resurrection" herb mentioned in the Indian myth "Ramayana" wherein it is employed to cure a Kind Lord (Lakshmana) from poisoning and coma. *Selaginella* which is known as "*Kara-jodi-kanda*" and "*Hatthaa jodi*" in Ayurveda is recommended for post-childbirth wounds, skin disease, headache, fever, asthma, pulmonary infection, urinary infection, hepatitis, amenorrhea, bleeding piles, and cancer (Antony and Thomas 2011). The usage of *Selaginella* ranges from short-term external application to oral medication (Sah et al. 2005). In an Indian community, *S. tamariscina* (Assam) is used as an age-sustaining tonic. *Selaginella* is an excellent liver purifier and suggested as a liver tonic, and hence used to cure jaundice (Singh and Upadhyay 2012). Nevertheless, *Selaginella* is not very popular in current Indian medicinal practice, despite its tribal references, which is attributed to the limited awareness and availability. It is sold in

India but as an ornamental plant exploiting its resurrection efficacy as an ornamental illusion though not for medicinal uses. There are no side effects reported for Selaginella phyto-preparations as yet; however it is not recommended for those with cold management problems (Suganya et al. 2011). Most *Selaginella* species have antimicrobial and antifungal properties mainly attributable to the characteristic biflavonoids. Biflavonoids are a group of flavonoid-dimers with biological properties ranging from antimicrobial to anti-tumorigenesis (Chandran et al. 2015).

Recent developments in pharmacological field have revealed the wide spectrum of bioactives from *Selaginellaceae* and their potent biological properties. The newly revealed properties range from antioxidant, anti-inflammatory, antimicrobial, antimetastatic, and anticancer to neuroprotective implications (Yang et al. 2007). *Selaginella doederleinii* extracts are indicated to contain biflavonoids like biapigenin and binaringenin derivatives that have been linked to cytotoxicity towards human cancer cell lines (Woo et al. 2006). Selagin isolated from *S. involvens* proved to be an antifungal agent in a mice model. *Selaginella* biflavonoids are reported to protect PC12 cells against an anoxic shock in vitro and UV-induced oxidative stress in sf9 cells (Sah et al. 2005; Zheng et al. 2011). *Selaginella* biflavonoids inhibit the trans-activations of iNOS and COX-2 genes by blocking NF-kB activation in RAW 264.7 macrophages and CaCO2 cells (Lee et al. 2008; Tan et al. 2009). The immunomodulatory properties of Selaginella were further demonstrated with an aqueous extract of *S. tamariscina* which blocked MAP-kinase and NF-kB activation, leading to the inhibition of expression/transcription of osteoclastic genes RAW264.7 cells. Aqueous preparations of *S. delicatula*, *S. involvens*, and *S. wightii* reduced lipid peroxides and rendered protection against an immunosuppressed mice model (Gayathri et al. 2011). Further an ethanolic preparation inhibited chemically induced systemic anaphylactic shock and reduced histamine release from rat peritoneal mast cells in vitro *and* in vivo (Dai et al. 2005).

A thesis was awarded doctor of philosophy (Ph.D.) by the University of Mysore (2014) for the studies conducted on "*Mechanisms underlying the neuromodulatory properties of Selaginella and its flavonoids in cell and animal models of neurodegeneration*." Flavonoid-rich preparations from *Selaginella delicatula* significantly attenuated the elevated levels of mitochondrial oxidative markers among Drosophila. Selaginella extracts significantly enhanced the average life span of Drosophila and protected against rotenone (a mitochondrial complex I inhibitor and Parkinson's disease inducer)-induced mortality. Rotenone-induced neurotoxic perturbations, viz. dopamine levels and AChE activity, were also normalized among flies maintained on *S. delicatula* extracts. The protective effects were evident in mitochondrial fractions as the extracts alleviated the activity levels of complexes I–III, citrate synthase, and membrane potential (Girish and Muralidhara 2012). In the larvae, a glutathione-depletion model (using buthionine sulfoximine), Selaginella attenuated the oxidative stress (Chandran and Muralidhara 2014). In addition, Selaginella oral supplements were demonstrated to be a potent neurotonic against neurotoxin-based models (rotenone/3-nitropropionic acid) in mice which were observed in terms of neurochemical implications and neurobehavioral changes (Chandran and Muralidhara 2013, 2016). Cumulatively these reports from both in vitro and in vivo models clearly prove *Selaginella* to possess the propensity to modulate experimentally induced oxi-

dative stress and neurotoxicity. Based on these evidences, it is proposed that the extracts of *Selaginella delicatula* may be exploited as therapeutic adjuvants in protecting the CNS against an unmitigated oxidative stress and related major neurodegenerative disorders such as Parkinson's disease. Recent publications have also discussed phosphodiesterase-inhibiting properties of Selaginella preparations, suggesting that they may have applications in the treatment of Parkinson's disease and pulmonary conditions (Chandran and Muralidhara 2014; Chandran et al. 2015).

Conclusion

Based on the recent experimental data and ethnobotanical surveys, ferns prove to be an abundant source of therapeutic phytophenols. However, the gradually disappearing traditional knowledge among the medicinal possibilities for the ferns should be saved by creating a library which shall also be updated by the modern scientific reports (Fig. 2). Despite the potential health benefits exhibited by the various

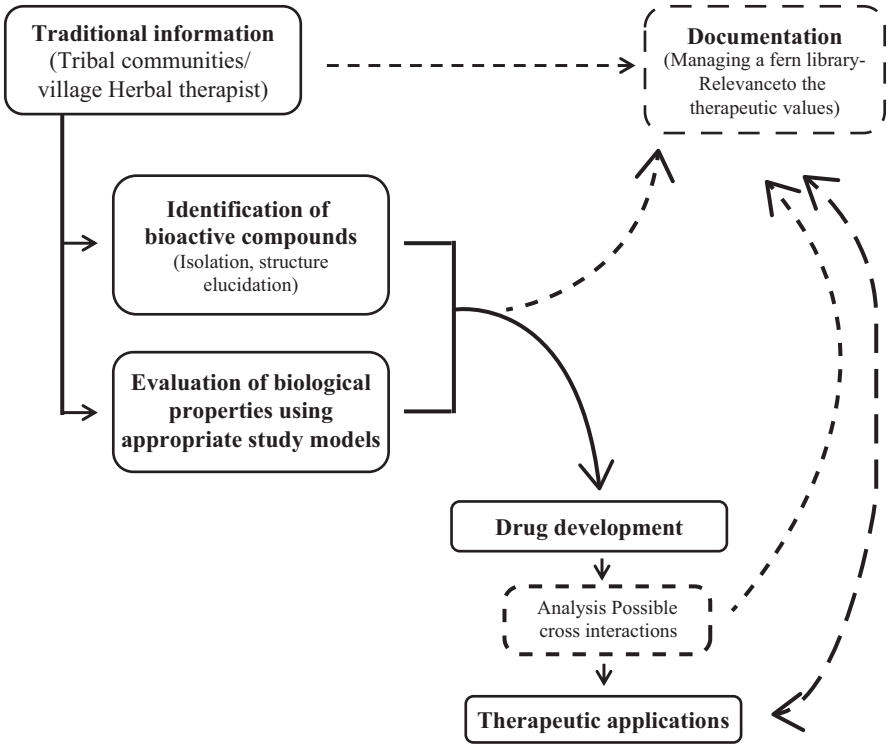

Fig. 2 General major phases involved in the identification of novel drugs from ferns

phytochemicals identified in the ferns, their inclusion in the actual therapy requires elaborate investigations for possible side effects in vivo. Here we have made conscious efforts to present the recent developments in the fern pharmacology.

Conflict of Interest Authors declare that there is no conflict of interest.

References

Albuquerque UP, Medeiros PM, Ramos MA, Ferreira Junior WS, Nascimento ALB, Avilez WMT, De Melo JG (2014) Are ethnopharmacological surveys useful for the discovery and development of drugs from medicinal plants? Revista Bras De Farmacog, 24:110–115

Antony R, Thomas R (2011) A mini review on medicinal properties of the resurrecting plant Selaginella bryopteris (Sanjeevani). Int J Pharm Life Sci 2:933–939

Ayala A, Venero JL, Cano J, Machado A (2007) Mitochondrial toxins and neurodegenerative diseases. Front Biosci J Virtual Libr 12:986–1007

Bai R, Zhou Y, Deng S, Dong P-P, Zhang B, Huang S, Wang C, Zhang H-L, Zhao Y-Y, Wang L, Ma X (2013) Two new ent-kaurane diterpenoids from Pteris semipinnata. J Asian Nat Prod Res 15:1107–1111

Birben E, Sahiner UM, Sackesen C, Erzurum S, Kalayci O (2012) Oxidative stress and antioxidant defense. World Allergy Organ J 5:9–19

Cao H, Chai T-T, Wang X, Morais-Braga MFB, Yang J-H, Wong F-C, Wang R, Yao H, Cao J, Cornara L, Burlando B, Wang Y, Xiao J, Coutinho HDM. (2017). Phytochemicals from fern species: potential for medicine applications. Phytochem Rev 16:1–62

Chandran G, Muralidhara (2013) Neuroprotective effect of aqueous extract of Selaginella delicatula as evidenced by abrogation of rotenone-induced motor deficits, oxidative dysfunctions, and neurotoxicity in mice. Cell Mol Neurobiol 33:929–942

Chandran G, Muralidhara (2014) Insights on the neuromodulatory propensity of Selaginella (Sanjeevani) and its potential pharmacological applications. CNS Neurol Disord Drug Targets 13:82–95

Chandran G, Muralidhara (2016) Biochemical and behavioral evidences for neuromodulatory properties of Selaginella delicatula against 3-nitropropionic acid model in mice. Int J Neurol Res 2:226–237

Chandran G, Venkareddy L, Muralidhara (2015) Biflavonoids: therapeutic potential of novel flavonoid dimers. In: Govil, J.N. and Pathak, M. eds. Recent progress in medicinal plants Volume 40 - Flavonoids and antioxidants. Studium Press LLC, USA. p. 316–330

Chandran G, Leelabai S, Srinivas Bharath M, Rajini P, Muralidhara M (2014) Understanding the role of neuronal thioredoxin and glutathione systems in motor disorder pathophysiology: relevance to natural product therapy. Mov Disord 29:S307

Dai Y, But PP-H, Chu L-M, Chan Y-P (2005) Inhibitory effects of Selaginella tamariscina on immediate allergic reactions. Am J Chin Med 33:957–966

Denny Joseph KM, Muralidhara (2013) Enhanced neuroprotective effect of fish oil in combination with quercetin against 3-nitropropionic acid induced oxidative stress in rat brain. Prog Neuro-Psychopharmacol Biol Psychiatry 40:83–92

Dos Santos JG Jr, Blanco MM, Do Monte FHM, Russi M, Lanziotti VMNB, Leal LKAM, Cunha GM (2005) Sedative and anticonvulsant effects of hydroalcoholic extract of Equisetum arvense. Fitoterapia 76:508–513

Dumont M, Beal MF (2011) Neuroprotective strategies involving ROS in Alzheimer disease. Free Radic Biol Med 51:1014–1026

Emerit J, Edeas M, Bricaire F (2004) Neurodegenerative diseases and oxidative stress. Biomed Pharmacother Biomédd Pharmacothérapie 58:39–46

Fu D, Du G, Liu D et al (2013) Neuroprotective effect of a Caffeic acid derivative from Abacopteris Penangiana. Pharm Biol 51:376–382
Gayathri V, Asha VV, John JA, Subramoniam A (2011) Protection of immunocompromised mice from fungal infection with a thymus growth-stimulatory component from Selaginella involvens, a fern. Immunopharmacol Immunotoxicol 33:351–359
Girish C, Muralidhara (2012) Propensity of Selaginella delicatula aqueous extract to offset rotenone-induced oxidative dysfunctions and neurotoxicity in Drosophila melanogaster: implications for Parkinson's disease. Neurotoxicology 33:444–456
Ha L, Thao D, Huong H, Minh C, Dat N (2012) Toxicity and anticancer effects of an extract from Selaginella tamariscina on a mice model. Nat Prod Res 26:1130–1134
Halliwell B (2006) Oxidative stress and neurodegeneration: where are we now? J Neurochem 97:1634–1658
Halliwell B (2009) The wanderings of a free radical. Free Radic Biol Med 46:531–542
Ham Y-M, Yoon W-J, Park S-Y, Jung Y-H, Kim D, Jeon Y-J, JP WW a, Kang S-M, Kim K-N (2012) Investigation of the component of Lycopodium serratum extract that inhibits proliferation and mediates apoptosis of human HL-60 leukemia cells. Food Chem Toxicol 50:2629–2634
Ibraheim ZZ, Ahmed AS, Gouda YG (2011) Phytochemical and biological studies of Adiantum capillus-veneris L. Saudi Pharm J 19:65–74
Jenner P (2003) Oxidative stress in Parkinson's disease. Ann Neurol 53 Suppl 3:S26–S36. discussion S36–S38
Jiang J, Liu Y, Min K, Jing B, Wang L, Zhang Y, Chen Y (2010) Two new Lycopodine alkaloids from Huperzia serrata. Helv Chim Acta 93:1187–1191
Jimenez-Del-Rio M, Guzman-Martinez C, Velez-Pardo C (2010) The effects of polyphenols on survival and locomotor activity in Drosophila melanogaster exposed to iron and Paraquat. Neurochem Res 35:227–238
Khurana N, Gajbhiye A (2013) Ameliorative effect of Sida cordifolia in rotenone induced oxidative stress model of Parkinson's disease. Neurotoxicology 39:57–64
Konrath EL, Passos C dos S, Klein LC, Henriques AT (2013) Alkaloids as a source of potential anticholinesterase inhibitors for the treatment of Alzheimer's disease. J Pharm Pharmacol 65:1701–1725
Lee C-W, Choi H-J, Kim H-S, Kim D-H, Chang I-S, Moon HT, Lee S-Y, Oh WK, Woo E-R (2008) Biflavonoids isolated from Selaginella tamariscina regulate the expression of matrix metalloproteinase in human skin fibroblasts. Bioorg Med Chem 16:732–738
Lei Y-F, Chen J-L, Wei H, Xiong C-M, Zhang Y-H, Ruan J-L (2011) Hypolipidemic and anti-inflammatory properties of Abacopterin A from Abacopteris penangiana in high-fat diet-induced hyperlipidemia mice. Food Chem Toxicol 49:3206–3210
Letelier ME, López-Valladares M, Peredo-Silva L, Rojas-Sepúlveda D, Aracena P (2011) Microsomal oxidative damage promoted by acetaminophen metabolism. Toxicol Vitro 25:1310–1313
Ma X, Tan C, Zhu D, Gang DR, Xiao P (2007) Huperzine a from Huperzia species – an ethnopharmacological review. J Ethnopharmacol 113:15–34
Ma X-Y, Xie C-X, Liu C, Song J-Y, Yao H, Luo K, Zhu Y-J, Gao T, Pang X-H, Qian J, Chen S-L (2010) Species identification of medicinal pteridophytes by a DNA barcode marker, the chloroplast psbA-trnH intergenic region. Biol Pharm Bull 33:1919–1924
Ma T, Gong K, Yan Y, Zhang L, Tang P, Zhang X, Gong Y (2013) Huperzine a promotes hippocampal neurogenesis in vitro and in vivo. Brain Res 1506:35–43
Maroyi A (2014) Not just minor wild edible forest products: consumption of pteridophytes in sub-Saharan Africa. J Ethnobiol Ethnomed 10:78
Maroyi A (2016) Ximenia caffra Sond. (Ximeniaceae) in sub-Saharan Africa: a synthesis and review of its medicinal potential. J Ethnopharmacol 184:81–100
Morais-Braga MFB, Souza TM, Santos KKA, Guedes GMM, Andrade JC, Tintino SR, Sobral-Souza CE, Costa JGM, AAF S, HDM C (2012) Phenolic compounds and interaction between aminoglycosides and natural products of Lygodium venustum SW against multiresistant bacteria. Chemotherapy 58:337–340

Nordgren M, Fransen M (2014) Peroxisomal metabolism and oxidative stress. Biochimie 98:56–62
Prasad SN, Muralidhara (2013) Neuroprotective efficacy of eugenol and isoeugenol in acrylamide-induced neuropathy in rats: behavioral and biochemical evidence. Neurochem Res 38:330–345
Rafii MS, Walsh S, Little JT, Behan K, Reynolds B, Ward C, Jin S, Thomas R, Aisen PS, Alzheimer's Disease Cooperative Study (2011) A phase II trial of huperzine a in mild to moderate Alzheimer disease. Neurology 76:1389–1394
Reinaldo RC, Santiago ACP, Medeiros PM, Albuquerque UP (2015) Do ferns and lycophytes function as medicinal plants? A study of their low representation in traditional pharmacopoeias. J Ethnopharmacol 175:39–47
Richard T, Pawlus AD, Iglésias ML, Pedrot E, Waffo-Teguo P, Mérillon JM, Monti JP (2011) Neuroprotective properties of resveratrol and derivatives. Ann N Y Acad Sci 1215:103–108
Sah NK, Singh SN, Sahdev S, Banerji S, Jha V, Khan Z, Hasnain SE (2005) Indian herb 'Sanjeevani'(Selaginella bryopteris) can promote growth and protect against heat shock and apoptotic activities of ultra violet and oxidative stress. J Biosci 30:499–505
Sanchez-Danes A, Richaud-Patin Y, Carballo-Carbajal I, Jiménez-Delgado S, Caig C, Mora S, Di Guglielmo C, Ezquerra M, Patel B, Giralt A, Canals JM, Memo M, Alberch J, López-Barneo J, Vila M, Cuervo AM, Tolosa E, Consiglio A, Raya A (2012) Disease-specific phenotypes in dopamine neurons from human iPS-based models of genetic and sporadic Parkinson's disease. EMBO Mol Med 4:380–395
Schrader M, Fahimi HD (2006) Peroxisomes and oxidative stress. Biochim Biophys Acta 1763:1755–1766
Seet RCS, Quek AML, Lim ECH, Halliwell B (2013) Biomarkers of oxidative damage are elevated among individuals with high cardiovascular risk: refining subject selection strategies for antioxidant trials. Free Radic Res 47:283–290
Shin EJ, Bach JH, Nguyen TT, Nguyen XK, Jung BD, Oh KW, Kim MJ, Ko SK, Jang CG, Ali SF, Kim HC (2011) Gastrodia Elata Bl attenuates methamphetamine-induced dopaminergic toxicity via inhibiting oxidative burdens. Curr Neuropharmacol 9:118
Shukla V, Mishra SK, Pant HC (2011) Oxidative stress in neurodegeneration. Adv Pharmacol Sci 1–13
Singh B, Upadhyay R (2012) Ethno-botanical importance of pteridophytes used by the tribe of Pachmarhi, Central India. J Med Plants Res 6:14–18
Singh N, Kaur S, Bedi PMS, Kaur D (2011) Anxiolytic effects of Equisetum arvense Linn. extracts in mice. Indian J Exp Biol 49:352–356
Sudati JH, Vieira FA, Pavin SS, Dias GRM, Seeger RL, Golombieski R, Athayde ML, Soares FA, Rocha JBT, Barbosa NV (2013) Valeriana officinalis attenuates the rotenone-induced toxicity in Drosophila melanogaster. Neurotoxicology 37:118–126
Suganya S, Irudayaraj V, Jhonson M (2011) Pharmacognostical studies on an endemic spike-Moss Selaginella tenera (Hook. & Grev.) spring from the Western Ghats, South India. J Chem Pharm Res 3:721–731
Sun Z-K, Yang H-Q, Chen S-D (2013) Traditional Chinese medicine: a promising candidate for the treatment of Alzheimer's disease. Transl Neurodegener 2:6
Talukdar AD, Tarafdar R, Choudhury M (2011) A review on Pteridophyte antioxidants and their potential role in discovery of new drugs. Assam Univ J Sci Technol 7:151–155
Tan W-J, Xu J-C, Li L, Chen K-L (2009) Bioactive compounds of inhibiting xanthine oxidase from Selaginella labordei. Nat Prod Res 23:393–398
Uttara B, Singh AV, Zamboni P, Mahajan RT (2009) Oxidative stress and neurodegenerative diseases: a review of upstream and downstream antioxidant therapeutic options. Curr Neuropharmacol 7:65–74
Vallejo MG, Ortega MG, Cabrera JL, Carlini VP, de Barioglio SR, Agnese AM (2007) Huperzia saururus increases memory retention in rats. J Ethnopharmacol 111:685–687
Vallejo MG, Ortega MG, Cabrera JL, Agnese AM (2013) N-demethyl-sauroxine, a novel Lycodine group alkaloid from Huperzia saururus. Tetrahedron Lett 54:5197–5200

Vaya J, Aluf Y, Finberg JPM (2011) Oxidative stress in Parkinson's disease. In: Gadoth N, Göbel HH (eds) Oxidative stress and free radical damage in neurology. Humana Press, New York, pp 191–223

Virgili F, Marino M (2008) Regulation of cellular signals from nutritional molecules: a specific role for phytochemicals, beyond antioxidant activity. Free Radic Biol Med 45:1205–1216

Wang Y-S, Li F-Y, Huang R, Li Y, Feng X-F, Yang J-H (2013) Chemical constituents of Pteris multifida. Chem Nat Compd 49:629–631

Watfa G, Dragonas C, Brosche T, Dittrich R, Sieber CC, Alecu C, Benetos A, Nzietchueng R (2011) Study of telomere length and different markers of oxidative stress in patients with Parkinson's disease. J Nutr Health Aging 15:277–281

Woo E-R, Pokharel YR, Yang JW, Lee SY, Kang KW (2006) Inhibition of nuclear factor-kappaB activation by 2′,8″-biapigenin. Biol Pharm Bull 29:976–980

Wu T-Y, Chen C-P, Chen C-P, Jinn T-R (2011) Traditional Chinese medicines and Alzheimer's disease. Taiwan J Obstet Gynecol 50:131–135

Xavier TF, Kannan M, Lija L, Auxillia A, Rose AKF, kumar SS (2014) Ethnobotanical study of Kani tribes in Thoduhills of Kerala, South India. J Ethnopharmacol 152:78–90

Xia X, Cao J, Zheng Y, Wang Q, Xiao J (2014) Flavonoid concentrations and bioactivity of flavonoid extracts from 19 species of ferns from China. Ind Crop Prod 58:91–98

Yang SF, Chu SC, Liu SJ, Chen YC, Chang YZ, Hsieh YS (2007) Antimetastatic activities of Selaginella tamariscina (Beauv.) on lung cancer cells in vitro and in vivo. J Ethnopharmacol 110:483–489

Yang Y-F, Qu S-J, Xiao K, Jiang S-H, Tan J-J, Tan C-H, Zhu D-Y (2010) Lycopodium alkaloids from Huperzia serrata. J Asian Nat Prod Res 12:1005–1009

Ying Y-M, Liu X-S, Tong C-P, Wang J-W, Zhan Z-J, Shan W-G (2014) Lycopodium Alkaloids from Huperzia serrata. Helv Chim Acta 97:1433–1439

Yu D, Thakor DK, Han I, Ropper AE, Haragopal H, Sidman RL, Zafonte R, Schachter SC, Teng YD (2013) Alleviation of chronic pain following rat spinal cord compression injury with multimodal actions of huperzine A. Proc Natl Acad Sci U S A 110:E746–E755

Yuan Q, Zhang X, Liu Z, Song S, Xue P, Wang J, Ruan J (2013) Ethanol extract of Adiantum capillus-veneris L. suppresses the production of inflammatory mediators by inhibiting NF-κB activation. J Ethnopharmacol 147:603–611

Zhao B (2009) Natural antioxidants protect neurons in Alzheimer's disease and Parkinson's disease. Neurochem Res 34:630–638

Zheng JX, Zheng Y, Zhi H, Dai Y, Wang NL, Fang YX, Du ZY, Zhang K, Li MM, Wu LY, Fan M (2011) New 3′, 8′′-linked Biflavonoids from Selaginella uncinata displaying protective effect against anoxia. Molecules 16:6206–6214

Zhong R, Zhou D (2013) Oxidative stress and role of natural plant derived antioxidants in animal reproduction. J Integr Agric 12:1826–1838

Ajwa Dates: A Highly Nutritive Fruit with the Impending Therapeutic Application

Muqtadir Baig Mirza, Fareeduddin Quadri Syed, Fazal Khan, Ayman I. Elkady, Atef M. Al-Attar, and Khalid Rehman Hakeem

Introduction

Phoenix dactylifera (date palm) that belongs to an Asteraceae family (Table 1) is one of the oldest plants cultivated for its edible sweet fruit in arid and semiarid parts of the world, including Asia, Africa, the Middle East, and Arabian Peninsula. It is a crucial food and plays an important role in day-to-day life of people of these regions (Al-Farsi et al. 2005). Its name dactylifera means "date-bearing" drive from two Greek words dáktulos (Liddell and Scott 1987), which mean date and fero mean bearing. It has been mentioned in Holy Quran and poses great importance from the economic, medicinal, and nutritional points of view. Date fruit is a rich source of minerals and sugars; its various constituents like phytochemicals, carotenoids, steroids, and flavonoids are screened for numerous medicinal activities. Date palm is marketed throughout the world as a high-value fruit crop and low-cost food. Production of dates increased from 4.60 million tons in 1994 to 6.9 million tons in 2004 worldwide (FAO 2007). This flowering plant reaches a height of 21–23 m long and grows singly or with multiple stems from a single root. Date palm leaves are 4–6 cm long with spines on petiole and showing pinnate arrangement with 75 leaflets of 2 cm wide and 30 cm long on either side. Date fruit poses three main parts, outer skin, middle flesh, and inner seed or stone (Shafiei et al. 2010). Because of different varieties and growth, they differ in size and shape. Usually, they are small

M. B. Mirza (✉) · F. Q. Syed · A. I. Elkady · A. M. Al-Attar · K. R. Hakeem
Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia

F. Khan
Department of Genetics and Molecular Medicine, Kamineni Hospital, Hyderabad, India

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Table 1 Taxonomy of date palm

Kingdom	Plantae
Division	Angiosperms
Class	Monocots
Unranked	Commelinids
Order	Arecales
Family	Arecaceae
Genus	Phoenix
Species	*Phoenix dactylifera*

Table 2 Few famous varieties of date palm in different countries

Country	Famous variety	Reference
Pakistan	Aseel, Begum Jangi, Dhakki, Karabalian, Fasli, Muzawati, Halawi	Al-Shahib and Marshall (2002)
Iran	Khenizi, Sayer, Lasht, Kabkab, Shahabi, Majoul, Khazui, Zahedi	Ardekani et al. (2010)
Algeria	Deglet nour (semidry), Degla beida (dry dates)	Mansouri et al. (2005)
Tunisia	Alligh, Goundi, Ikhouat, Lagou, Touzerzaillet, Tranja	Borchani et al. (2010)
Saudi Arabia	Suqaey, Sofry, Ajwa, Safawy	Al-Shahib and Marshall (2002)
Egypt	Lobanah, Masery, Saidi	Al-Shahib and Marshall (2002)
Iraq	Shorcy, Tamriraq	Al-Shahib And Marshall (2002)

oval fruits 3–7 cm long and 2–7 cm in diameter and stone size ranges from 2 to 2.5 cm (Ateeq et al. 2013). Color and softness of date fruit depend on the stage of maturity. Approximately 5000 of cultivars of date palm are recognized worldwide but few of them are evaluated because of their quality. Some of the famous varieties from different nations are listed in Table 2; Fig. 1.

Date Ripening Stages

The ripening of date fruit is a lengthy process and it takes roughly 7 months to reach full ripening stage post-pollination. They pass through five main stages of ripening as per Arabic tradition and internationally accepted terminology, viz. Hababouk, Kimri, Khalal, Rutab, and Tamr (Al-Shahib and Marshall 2003). Color, texture, size, sugar content, moisture content, and sweetness vary from one stage to another (Table 3); apart from that chemical composition also varies.

Fig. 1 Date palm (*Phoenix dactylifera*)

Table 3 Ripening stages of date palm

Stage	Color	Duration	Moisture content	Sugar content (g/100 g)	Image
Hababouk	Green	4–5 weeks	–	–	
Kimri	Green	9–14 weeks	80%	6.2 g	
Khalal	Greenish, yellow, or red	6 weeks	65%	26.6 g	
Rutab	Yellow, brown	2–4 weeks	43%	45.2 g	
Tamr	Brown or black	4 weeks	24%	50.8	
Tamr (dry)	Yellowish brown	–	Hydrated	–	

Fig. 2 Ajwa dates

Proximate Composition of Dates

The moisture content of Ajwa date is 22.8 g/100 g dry weight. On an average moisture content of dates is 28.8 g/100 g of dry weight. The moisture content varies in the maturity stage of dates. The moisture content is relatively low in dried dates due to the drying process. Carbohydrates are the major source of energy in dates; in Ajwa dates carbohydrates constitute 74.3 g/100 g of dry weight and on average dates contain 54.9 g/100 g of dry weight and dried dates contain 80.6 g/100. Protein and fats are present in small amount in dates. Ajwa dates contain fats 0.47 g/100 g, ash 3.43 g/100 g, and protein 2.91 g/100 g of dry weight (Khalid et al. 2016; Fig. 2).

Nutritional Value of Date Palm (Table 4)

Sugars

Dates are found to be a high-energy diet because of excessive sugar constitute. Glucose, fructose, and sucrose are the main sugars detected in dates; the amount of sugar varies with the variety and ripening stage of date, but on an average reducing sugars like fructose and glucose are 19% and 22.8%, respectively, and nonreducing sugars like sucrose are detected in lesser amount, i.e., 4% in fresh dates with exception in few varieties of dates like Deglet Noor where sucrose amount constitutes higher than reducing sugars (Elleuch et al. 2008). Ajwa dates from Madina Al Munawwara contain glucose 54.5%, fructose 52.03%, maltose 22.5%, and galactose 12.2% (Khalid et al. 2016). Sugars are found to be higher in dried dates than in fresh dates, maybe due to the reduction of moisture content and maturity level. Sugar provides a rich source of energy on consumption, total calories/100 g equal to 284 calories, almost all from carbohydrates.

Table 4 Nutritional composition of Ajwa dates in contrast to average composition of dates

Composition	Average composition of dates (Al-Farsi and Lee 2008)	Composition of Ajwa (Khalid et al. 2016)
Moisture (g/100 g)	28.8	22.8
Fat (g/100 g)	0.75	0.47
Ash (g/100 g)	1.45	3.43
Protein (g/100 g)	1.85	2.91
Amino acids (mg/100 g)		
Alanine	81.5	82
Arginine	91	93
Aspartic acid	184	186
Cysteine	40	–
Glutamic acid	241	205
Glycine	155	83
Histidine	28.05	26
Isoleucine	29.5	44
Leucine	141.5	57
Lysine	98	73
Methionine	33	27
Phenylalanine	46	45
Proline	37	86
Serine	78.5	59
Threonine	59	53
Tryptophan	49.5	44
Tyrosine	85.5	–
Valine	–	65
Carbohydrates (g/100 g)		
Fructose	25.2	48.5
Glucose	29.5	51.3
Sucrose	4.3	3.2
Minerals (mg/100 g)		
Magnesium	90.5	1.5
Sodium	131	7.5–8.1
Calcium	105.5	2.0
Phosphorus	54.5	1.9–2.3
Potassium	812	6.45
Manganese	0.205	0.36–0.5
Iron	0.8	0.15–0.5
Zinc	0.31	0.46–0.52
Cobalt	0.405	0.37–0.5
Selenium	0.32	–

Minerals

Nowadays dates can be considered as the important and richest source of dietary minerals among other common fruits consumed by humans. 100 g of dates is enough to provide 15% of daily recommended important minerals like copper, selenium, potassium, magnesium, and a modest amount of iron, manganese, calcium, and

phosphorus, that is, 7% of daily recommended intake. On the average, date fruit contains potassium (7.1 mg/g), magnesium (6.4 mg/g), copper (240 μg/g), and selenium (310 μg/g) (Al-Farsi and Lee 2008). Minerals of Ajwa date flesh constitute manganese (0.36–0.5 mg/100 g), magnesium (1.5 mg/100 g), zinc (0.46–0.52 mg/100 g) (Khalid et al. 2016), sodium (7.5 mg/100 g), potassium (476.3 mg/100 g), phosphorus (27.0 mg/100 g), calcium (187.0 mg/100 g) (Abdul and Assirey 2015), iron (0.15 mg/100 g), cadmium (0.001 mg/100 g), and copper (0.37 mg/100 g) (Saafi et al. 2011; Hamad et al. 2015). Date fruits are considered as potassium-enriched, low-sodium diet that makes the fruit ideal for hypertensive patients. Selenium helps glutathione peroxidase be a coenzyme and plays a key role in modulation, growth, and development, protecting against oxidative stress and infections.

Vitamins

Vitamins are the essential nutrients found in the food and required in little amount for the normal growth and development of organisms. Cell signaling mediator, antioxidant, hormones, antioxidants, and regulators of cell growth and differentiation are some of the functions of vitamins. The dates supply a modest amount of vitamins like B2, B3, B6, and B9, i.e., 9% of the recommended daily amount and relatively low amount of vitamin B1, vitamin C, and vitamin A, which account for 7% of the RDA in 100 g of dry dates (USDA 2007). The complex of vitamin B like riboflavin, thiamine, niacin, folate B9, B6, pantothenic acid, and vitamin K is found in higher amount in dates than other common fruits in the USA. Vitamin C helps the tissue by protecting from oxidative stress and other diseases (Whitney and Rolfes 2002).

Amino Acids

Dates contain very little amount of proteins and it is not considered as an important nutritional source. However amino acids are present and varied through different stages of maturity. Amino acid content reduces as date passes through different stages of maturity which may be because of reduction in moisture content (Ishurd et al. 2004). Essential amino acids that cannot be synthesized by the human body and must be provided by diet are found in dates. Leucine, glycine, aspartic acid, lysine, and glutamic acids are predominant in fresh dates while leucine, proline, glycine, glutamic acid, and aspartic acid are dominant in dried dates. Ajwa dates contain a good amount of essential amino acids (table) as reported by Abdul and Assirey (2015) and Hamad et al. (2015). The predominant essential amino acids in Ajwa dates are glutathione (205 mg/100 g), followed by aspartic acid (186 mg/100 g), proline (86 mg/100 g), glycine (83 mg/100 g), lysine (73 mg/100 g), leucine (57 mg/100 g), and histidine (26 mg/100 g).

Dietary Fiber

Dietary fiber plays a crucial role in human health and low intake of dietary fiber linked to several diseases like diverticular disease and bowel cancer in developed nations. Dates are appreciated as a good source of dietary fiber; it is the lignin and polysaccharide part of the plant that is not digestible in the human intestinal tract. The amount of dietary fiber content ranges from 6.5% to 11.5% depending on the variety and stage of maturity. Dietary fiber increases from fresh dates 7.5 g/100 g to 8 g/100 g in dry dates due to the reduction of moisture content; on an average, 0.87 g of soluble dietary fiber like pectin and 5.75 g of insoluble dietary fiber like cellulose, hemicellulose, and lignin are present in date fruit (Al-Shahib and Marshall 2002). The total dietary fiber in Ajwa date ranges from 6.2% to 8.9%. Date fruit provides over 32% recommended daily allowance (RDA) of dietary fiber which is double the amount of any other common fruit in the USA (Al-Shahib and Marshall 2003).

Phytochemistry of Date Palm (Table 5)

The phytochemistry of date fruit is very rich; it contains different phytochemicals like polyphenols, carotenoids, steroids, and flavonoids like procyanidins and anthocyanins. The concentration and ratio of these phytochemicals depend on

Table 5 Phytochemistry of Ajwa dates

Phytochemistry of Ajwa	Quantity (mg/100 g DW)
Phenolic acid	
Caffeic acid	0.026–0.050
Ferulic acid	2.52–2.20
Protocatechuic acid	1.27–2.20
Catechin	0.50–0.80
Gallic acid	13.90–14.10
p-Coumaric acid	3.08–3.50
Resorcinol	0.03–0.05
Chlorogenic acid	0.18–0.20
Syringic acid	0.82
Total phenolic	22.10–455.80
Flavonoids	
Quercetin	1.21
Luteolin	0.04
Apigenin	0.26
Isoquercitrin	0.41
Rutin	0.86
Total flavonoid	2.78
Organic acid	
Oxalic	1.46
Malic	10.12
Succinic	0.76
Citric	2.01
Isobutyric	3.12
Formic	0.35

the maturation stage of date fruit, a variety of date fruit, and soil condition of cultivation site. These constituents contribute to the organoleptic and nutritional properties of the fruit. The total polyphenol content of date fruit is 3.0 g/100 g as reported by Duke's phytochemical and ethnobotanical database and it is the highest among other dried fruits. Fresh date contains six times more polyphenols than the dried ones.

Phenolic Acids

Phenolic acid is the major class of secondary metabolites in plants that help in defending against pathogens and pests. It contains benzene ring which is hydroxylated either directly or indirectly and attached to one or more carboxyl groups. Date fruit can be considered as the rich source of phenolic acids. Total phenolic content of date fruit is based on variety, maturation, and type. The concentration of the phenolic compound is higher in dried dates than the fresh one. One study reported that the difference in phenolic content in fresh and dried is due to drying process, where maturation of degrading enzymes is followed by degradation of tannins (Al-Farsi et al. 2005). The total content of phenolic acid in Ajwa dates ranges between 245 and 455 mg/100 g based on the extraction method and solvent used. Hydroxybenzoic acid (figure 3), protocatechuic acid (figure 3), gallic acid (figure 3), vanillic acid (figure 3), ferulic acid (figure 3), chlorogenic acid, isovanillic acid, caffeic acid (figure 3), cinnamic acid (figure 3), sinapic acid (figure 3), and isoferulic acid are some of the phenolic acids found by Eid et al. (2013) in Ajwa dates (Fig. 3).

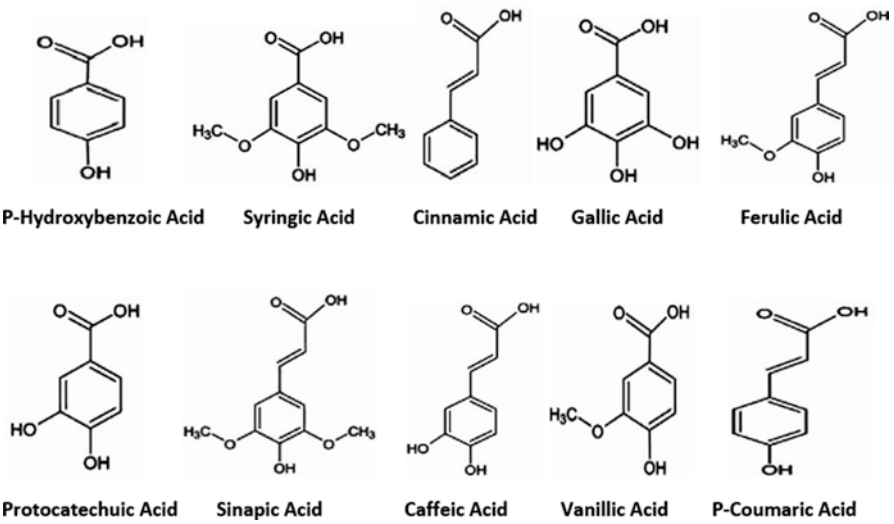

Fig. 3 Phenolic acid of Ajwa dates

Similarly, Hamad et al. (2015) found the derivatives of gallic acid (figure 3), ferulic acid (figure 3), and *p*-coumaric acid (figure 3).

Phytosterols

Phytosterols are the plant's sterols that resemble cholesterol, and it owns numerous health benefits. Fruits and vegetables are the exclusive sources of naturally occurring phytosterols. Date fruit contains several phytosterols, not only in the flesh of dates but also in seed and pollen grains (Duke 2001; Duke and Beckstrom-Sternberg 2007). The concentration of phytosterols varies based on cultivars and ripening stage. Stigmasterol (figure 4), campesterol, isofucosterol, and β-sitosterol (figure 4) are the phytosterols found in date fruit including stigmasta-5, lupenone, lupeol, γ-sitosterol, 24-methylenecy-cloartanol, spinasterone, cholesta-3,5-diene, and 5-diene,cholest-4-en3-one, reported in the recent study. In addition to this brassicasterol, estrogen, ergosterol, and estrone are identified in date pits (Duke 2001; Duke and Beckstrom-Sternberg 2007). β-Sitosterol (figure 4), β-sitosteryl-3-*O*-β-glucoside (figure 4), and β-sitosteryl-3-β-glucopyranoside-6′-*O*-palmitate are the sterols reported in Ajwa dates (Nair 2013) (Fig. 4).

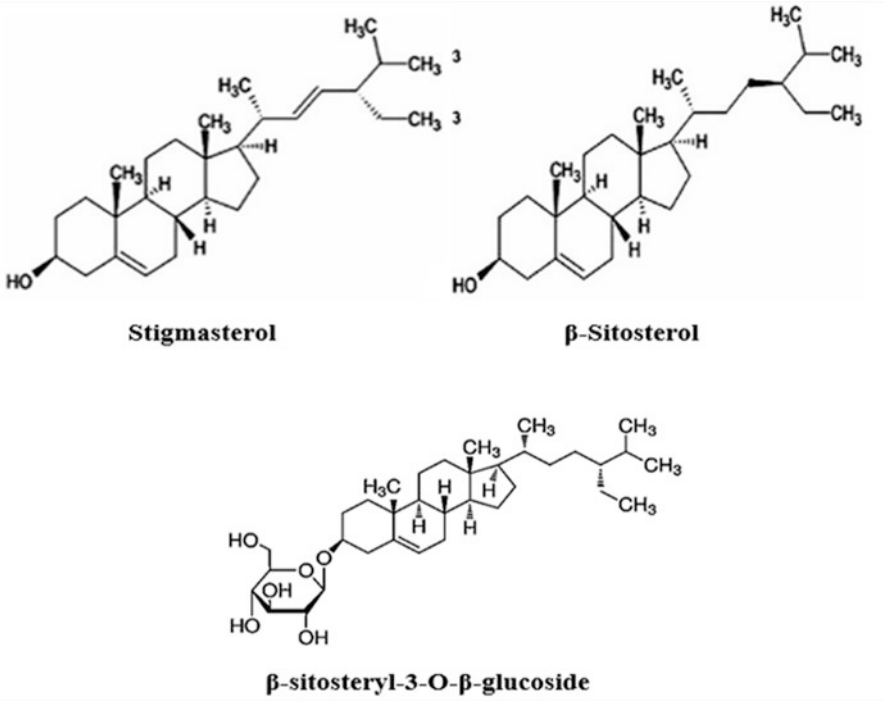

Fig. 4 Sterols of Ajwa dates

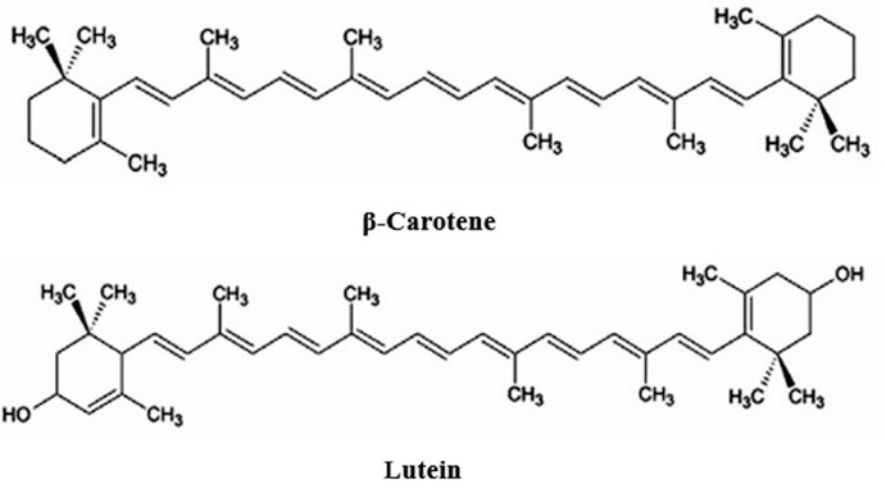

Fig. 5 Carotenoids of Ajwa dates

Carotenoids

Carotenoids are the diverse group of phytochemicals present in plants, bacteria, and fungi. They are fat-soluble pigments and give bright coloration to plants; they reported to have important health benefits and prevention in chronic diseases. Carotenoids are the major part of phytochemicals in the lipid fraction of date fruit (Baliga et al. 2011). The study has revealed that date fruits are a rich source of carotenoids and its concentration decreases as the fruit ripens. Al-Farsi et al. (2005) reported the decreased concentration of carotenoid from 4% to 30%, after sun drying. The total carotenoid concentration varied between 0.22 and 3.0 mg/100 g based on maturity and variety of date fruit. The average source of carotenoid in date fruit is 0.97 mg/100 g and it is a moderate concentration compared to other dried fruits. The main carotenoids of date fruits are β-carotene (figure 5), and lutein (figure 5) (Boudries et al. 2007); lycopene, flavoxanthin, violaxanthin, and leukoxanthin are also reported in Duke's ethnopharmacological database (Fig. 5).

Flavonoids

Flavonoids are extensively spread in plants and involved in an important function like flower coloration, a chemical messenger, and physiological regulators. Flavonoids pose numerous health benefits to humans like radical scavenging, antioxidant activities, anticancer activity, and reduction in chronic and preventing cardiovascular diseases. Dates include procyanidins, anthocyanins, and flavonoid

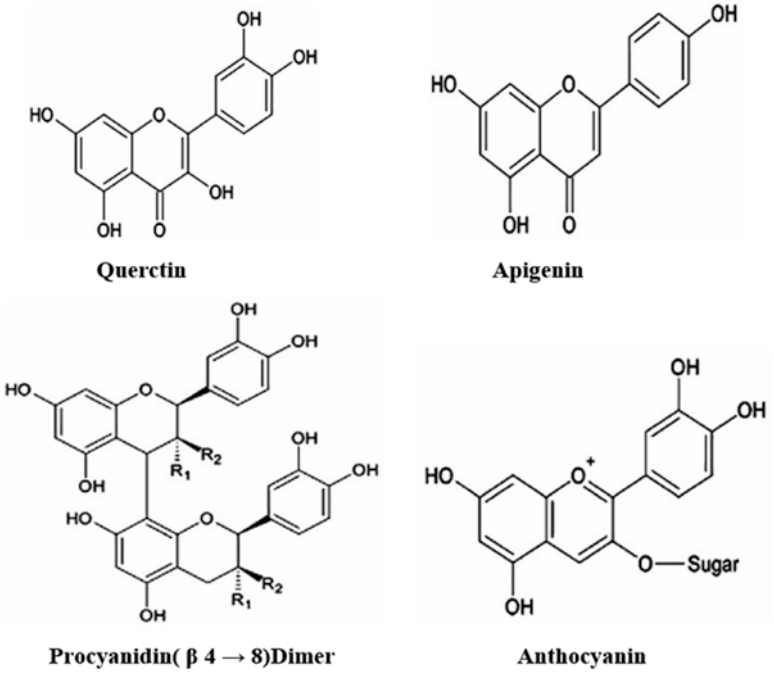

Fig. 6 Flavonoids and anthocyanin of Ajwa dates

glycosides. Apart from that detailed study of Ajwa date revealed that flavonoid glycosides of luteolin, apigenin (figure 6), rutin, quercetin (figure 6), and isoquercetin were identified (Hamad et al. 2015; Ragab et al. 2012). Until now, date fruits are the only food that contains flavonol glycosides in sulfated form and not detected in any other vegetables and fruits (Hong et al. 2006; Chaira et al. 2009) (Fig. 6).

Anthocyanins and Procyanidins

Anthocyanins are another flavonoids that are found in date fruit; they are water-soluble pigments and can be seen in purple, red, and blue colors. They are present in many fruits and vegetables and studied extensively for their potent natural color and antioxidant properties. Anthocyanins (figure 6) are present only in fresh dates and undetectable in dry dates and reported to undergo 100% destruction upon sun drying (Al-Farsi et al. 2005). The concentration of anthocyanin varied based on the variety and stages of date fruit and ranges from 0.24 to 1.52 mg/100 g in fresh dates. Ajwa date contains a significant amount of anthocyanidins at the kimri stage (Eid et al. 2013), while Kasab variety of date contains the highest amount of anthocyanidins. Procyanidins (figure 6) are tannins present in condensed form as the main

precursor of red, blue, and violet pigments in vegetables, fruits, seeds, nuts, barks, and flowers. Date fruit also contains procyanidins; they exist in higher molecular weight and undecamers through heptadecamers (Hong et al. 2006).

Therapeutic Properties of Dates

Anti-inflammatory Activity of Dates

Inflammation is an important process that defends against various factors like burns, infection, allergens, toxic chemicals, and other stimuli. The unbalanced inflammatory process leads to the development of various diseases such as diabetes and arthritis. Transcription factors (TF) play a major role in inflammation and many other diseases; its regulation is a key step in controlling diseases. TF inhibitors are employed to control the action of transcription factors but they are expensive and show adverse side effects. Date fruit contains many phytochemical constituents such as polyphenols, flavonoids, proanthocyanidins, β-carotene, and minerals like selenium that possess anti-inflammatory properties. Anti-inflammatory effect of aqueous, methanolic, and ethyl acetate extract of Ajwa is reported as inhibiting COX-1 and COX-2 in vitro (Zhang et al. 2017) and in vivo using formalin-induced paw edema test in mice (Kehili et al. 2016) and carrageenan-induced acute paw edema in mice (Ali Haimoud et al. 2016).

Antioxidant Activity of Dates, a Protection from Many Diseases

Oxidative stress is caused by the free radicals present in the body and causes damage to cells and tissue. Antioxidants are the chemicals that subside the free radicals and prevent the body from many diseases. Many herbs possess bioactive compounds that possess antioxidant activity and date palm is one of them. Date palm contains many phenolic compounds that play a crucial role in free radical scavenging and strong antioxidant activity. Many studies have been done on the antioxidant effect of date palm. Recently Ajwa date seed extract was reported to balance the oxidative stress condition in diabetic rats (Hasan and Mohieldein 2016). In other studies, Ajwa date fruit extract proved to have antioxidant activity in vitro by lipid peroxidation assay, MTT assay (Nair 2013), and free radical scavenging assay (Saleh et al. 2011). Different varieties of date palm from Egypt (Farouk et al. 2015), Oman (Khan et al. 2016b), Morocco (Bouhlali et al. 2015), and Algeria (Louaileche et al. 2015) are also reported to have antioxidant activity in vitro and in vivo.

Antitumor and Anticancer Activity of Date Palm

Mortality and morbidity from cancer are increasing day by day in the developing and developed nations. Diet, environmental factors, and lifestyle changes are the major factors that play a key role in cancer. Conventional therapies such as radiotherapy, chemotherapy, and surgery are employed for treating cancer. Natural products contain numerous phytochemicals that act as anticancer agents and are good alternative medicines for cancer. Date palm contains such phytochemicals that are the potent anticancer agents through upregulating anti-apoptotic genes or downregulating apoptotic genes. Date palm contains such phytochemicals; in one recent study, methanolic extract of Ajwa dates was reported to inhibit malignant human breast cancer cell line (MCF7) in vitro by upregulating Bax, p53, Fas, and FasL and downregulating Bcl-2 (Khan et al. 2016a). In another study, digested date extract and polyphenol-rich date extract of Ajwa were reported to inhibit human epithelial colorectal adenocarcinoma (caco-2) cell lines in vitro (Eid et al. 2014). Methanolic extract of 29 varieties of Saudi dates showed antitumor activity in prostate (DU-145 and LNCaP), breast (MCF-7), lung (NCI-H460), gastric (AGS), and colon (HCT-116) cancer cell lines in vitro (Zhang et al. 2017).

Antidiabetic Activity of Date Palm

Among various chronic disorders, diabetes mellitus is one of the common metabolic disorders that ailed 2.8% of the world population (Hafez El-Far et al. 2016). The contemporary approach to treating diabetes is diabetes retinopathy grounded on synthetic medicine; it is effective but also shows adverse side effects and alters the metabolic pathways. Natural herbs and their constituents are the good alternatives for diabetes which are less toxic and have lesser side effects. Date fruit also possesses various compounds such as minerals, phenols, flavonoids, saponins, and sterols that play a role as an antidiabetic agent (Ahmed et al. 2016). Minerals like manganese play a vital role in the regulation of insulin action and insulin-mediated glucose uptake, zinc helps in production and release of insulin, and chromium potentiates the insulin. Whereas the high amount of selenium in date fruit regulates glycolysis, pentose phosphate pathway stimulates the glucose uptake. Phenols of date fruit are the potent inhibitors of α-glycosidase and α-amylase (Ranilla et al. 2008).

Ajwa date seed extract is reported to have strong antidiabetic activity in streptozotocin-induced diabetic rats. In another experimental study seed or pits of date palm have shown the antidiabetic activity in vitro (Khan et al. 2016b). Another combined in vitro and in vivo study of date fruit leaf extract reported having an antidiabetic effect (Chakroun et al. 2016). From the above studies, it was concluded that date palm has strong antidiabetic activity.

Date Palm Ameliorates Male Fertility

The demand for herbal medicine for sexual improvement is increasing day by day in developing countries. Date fruit can be a good herbal medicine for male and female reproductive health and many studies have proved in vitro and in vivo. In one experimental study, aqueous extract of date fruit was reported to have anti-infertility activity in amitraz-induced infertility in male rats (Farag El-Kott et al. 2014). In another study, aqueous extract of date seed enhanced the testosterone level in male albino rats and proved to have a potential anti-infertility effect (Orabi and Shawky 2014). Apart from date flesh and seed, date pollens have the best anti-infertility effect. In a recent study, date pollen extract was reported to ameliorate the harmful effect of cadmium, a well-known testicular toxicant in male Wistar rats (El-Neweshy et al. 2013). Comparative study of date pollen extract and *Astragalus ovinus* extract showed that date pollen has increased the fertility levels (sperm count and motility, LH, testosterone, and estradiol levels, and the diameter of seminiferous tubules) whereas *Astragalus ovinus* has a deleterious effect and acts as an anti-fertility agent (Mehraban et al. 2014). In another study, date pollen extract has shown a protective effect against the adverse effect of EMF in NMRI mice exposed to the low-frequency electromagnetic field (50 Hz) (Baharara et al. 2015).

Date Palm, a Remedy for Estrogenic Hormonal Deficiency

Estriol, estrone, and estradiol are the three estrogenic hormones found in women; among the three estradiol is the most potent hormone for reproducing females and estrone is found in non reproductive females or menopausal women. In a phytochemical study of date pollen extract, ethyl acetate and n-hexane fraction of pollen date were examined in which five and ten compounds were detected by HPLC, respectively, including estrone and estradiol (Abbas and Ateya 2011). It can be concluded that date pollen extract can be a potent anti-infertility agent if infertility is due to hormonal deficiency.

The Cardioprotective and Antihyperlipidemic Activity of Date Palm

Cholesterol is carried in the blood by a protein called lipoprotein; there are two forms of lipoprotein, high-density lipoprotein (HDL) and low-density lipoprotein. Atherosclerosis or coronary heart diseases are strongly related to increase in LDL that is also called as bad cholesterol and decrease in HDL that is called as good cholesterol. Plants and its derivatives have many phytochemicals that have shown antihyperlipidemic and cardioprotective activity. Phytochemicals improve the

activity of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase that regulates the serum lipid profile or inhibits lipid production or inhibits lipid accumulation. Date fruit extract has many phytochemicals such as catechin, caffeic acid, quercetin, β-sitosterol, anthocyanins, proanthocyanidin, and selenium, which have shown antihyperlipidemic effect.

Antihyperlipidemic effect of palm date is reported in many recent studies. An experimental study of date palm seeds from Saudi (Ajwa and Sukkary) and Iran reported to have a hypolipidemic effect on streptozotocin-induced diabetic rats (Hasan and Mohieldein 2016) and hypercholesterolemic rat (Takaeidi et al. 2014), respectively. Another experimental study proved that date fruit (Aseel) extract has significantly decreased the cholesterol and triglyceride level in male albino rats (Ahmed 2016). Hence from the above experimental study it has been proved that date palm has the capability of maintaining the cholesterol level and protect the heart.

The Hepatoprotective Activity of Date Palm Against Multiple Chemically Induced Hepatotoxicity

The liver is a vital organ in the humans and other vertebrates that perform many important functions like the production of biochemical required for digestion, detoxification of various metabolites, hormone production, etc. Protection from toxins and other serious acute and chronic liver diseases is a major concern and no proper drugs are available. The hepatoprotective ability of date palm is discussed below. A recent study reported that date palm extracts significantly decrease ALT, γ-GT, and total bilirubin in rats fed a high-fat diet and proved its hepatoprotective activity (Ahmed 2016). Methanolic extract of date fruit (Atta et al. 2015), proanthocyanidin-rich date seed extract (Ahmed et al. 2015), and an aqueous suspension of date seed (Abdelaziz and Ali 2014) proved to have the hepatoprotective activity in carbon tetrachloride (CCL_4)-induced hepatotoxicity in three different studies. Other two similar studies where CCL_4 induced hepatotoxicity in rats (Al-Qarawi et al. 2004) and rabbits (El-Gazzar et al. 2009) were ameliorated by date palm extract. In another study, liver toxicity induced by dichloroacetic acid (DCA) resulted in hepatic oxidative stress by exacerbated lipid peroxidation and modified antioxidant enzyme activity. However, the date fruit extract protects the liver against DCA toxicity by reducing TBARS level, attenuates the activities of antioxidant enzymes, and conserves the normal histoarchitecture of rat's livers (El Arem et al. 2014a). Furthermore, dimethoate-induced liver toxicity was monitored by hepatic marker enzymes (alkaline phosphatase, transaminases, lactate dehydrogenase, and gamma-glutamyl transferase), and treatment with date fruit extract ameliorates the GPx, SOD, and CAT activities and improves the histopathology changes (Saafi et al. 2011). Hence, the hepatoprotective activity of date palm is confirmed by the above studies but further investigation is required for active constituents of the date palm and its mode of action.

Cerebroprotective, Neuroprotective, and Neuropharmacological Effect of Date Palm

Neuroprotection is a protection from brain injuries that involves genetic, nutritional, metabolic, endocrinological, infectious, and toxic mechanisms in ante and postnatal periods. Chemotherapy agents such as cisplatin, paclitaxel, ifosfamide, and cytarabine and environmental toxicants like lead and mercury are associated with central and peripheral neurotoxicity. Neuroprotective effect of Ajwa date palm has been investigated by Sheikh et al. (2016) in mice and it is concluded that it extended the pentobarbitone-induced sleeping time, reduced locomotor activity in open-field test, and reduced exploratory behavior in hole board test. Date palm-rich diet improves the memory and reduces beta-amyloid in transgenic mouse model of Alzheimer's disease (Subash et al. 2015). Aqueous extract of date fruit was found neuroprotective in artesunate-induced cerebellar damage in Wistar rats (Agbon et al. 2014). The seed extract reduces neural damage and oxidative stress in brain and restoration of antioxidant enzyme occurs. In another study date fruit extract induced significant reductions in grooming frequency and sciatic motor nerve conduction velocity in comparison to control, in streptozotocin-induced diabetic rats (Zangiabadi et al. 2011).

Date as a Laxative and Anti-ulcer Agent That Protects Gastrointestinal Tract

Prophet Muhammad (Peace Be upon Him) commands Muslims to consume dates for breaking fast in Ramadan. Prophet said in a hadith "When you break the fast, you should do it with a date-fruit for there is a blessing in it, and if you do not find a date-fruit, break it with water for it is pure." Dates are easy-to-digest food, don't exhaust the empty stomach of fasting person, help in secretion of digestive enzymes, and protect from constipation. In one study, the effect of flesh and seed extract of date palm was measured on gastrointestinal tract (GIT) transit, against yohimbine, a laxative, and clonidine, a drug that decreases the GIT transit. In animals treated with aqueous extract of date flesh and seed, 4–22% saw increase in GIT transit (Al-Qarawi et al. 2003). In another similar study, date pulp extract and date palm sap were reported to increase GIT transit by 18.34% (300 mg/kg) and 8.10% (4 mL/kg), respectively (Souli et al. 2014). Aqueous and ethanolic extracts of date flesh and seed were reported to ameliorate the ethanolic induced gastric ulcer in male Wistar rats (Al-Qarawi et al. 2005). The aqueous spathe extract of date palm was reported to possess anti-diarrheal activity (Abdullah 2008).

Nephroprotective Activity of Date Palm Through Ameliorating Oxidative Stress

Some important functions of the kidneys are to detoxify the body, maintaining the electrolyte fluid balance, etc. At times kidney also needs protection from toxic metabolites produced during metabolism of drugs and ROS that leads to renal injuries. The nephroprotective role of date fruit has been reported in many studies. In a recent study, date palm extract of Berne variety was reported to have strong nephroprotective activity against cisplatin-induced nephrotoxicity in Swiss albino rats through anti-inflammatory and antioxidant properties (Mansour and Ghobara 2015). In another study seed extract of date ameliorates the early diabetic complication of liver and kidney in streptozotocin-induced diabetic rats by the potent antioxidant property (Abdelaziz et al. 2015). In other two separate studies date fruit extract and proanthocyanidin-rich date fruit extract showed strong nephroprotective activity against trichloroacetic acid (El Arem et al. 2014b) and carbon tetrachloride (Ahmed et al. 2015) induced nephrotoxicity by increasing the antioxidant activity of the CAT and GPx enzymes, normalizing the SOD activity and the MDA level. Furthermore, investigation on date palm fruit and seed extract confirms the nephroprotective activity by reducing the plasma creatinine and urea concentrations and ameliorating the proximal tubular damage as gentamycin significantly increased the plasma concentrations of creatinine and urea and induced a marked necrosis of the renal proximal tubules (Al-Qarawi et al. 2008). In all the above studies, the nephroprotective effect can be explained by the potent antioxidant constituent present in date palm. However, further studies are required to confirm the molecular mechanism and the active constituents present in date palm.

Antimicrobial Activity of Date Palm

Deaths due to infectious diseases are increasing day by day in developing countries. Pathogenic microorganism resistant to many standard drugs is significantly increasing worldwide and resistance is a major problem in treatment. Switching to herbal medicine is the best way to avoid resistance and it has been used in traditional medicine for many infectious diseases. Date palm contains numerous antimicrobial phenolic compounds and is reported in several studies. Date palm extract is reported to inhibit gram (−) and gram (+) bacteria and showed strong activity with 25 mm of inhibition zone against *Escherichia coli* (Kchaou et al. 2016). In another study, date palm extract inhibits gram (+) bacteria like *Bacillus subtilis*, *Bacillus cereus,* and *Staphylococcus aureus* and gram (−) bacteria like *Escherichia coli*, *Pseudomonas aeruginosa*, and *Salmonella abony* (Bouhlali et al. 2016). Apart from antibacterial activity date palm is reported to have antifungal activity. The methanolic extract of date fruit and pit inhibits *A. alternata*, *Oxysporum*, *F. solani*, *Fusarium* sp., *A. alternata*, and *Alternaria* sp. (Bokhari and Perveen 2012).

Antiviral Activity of Date Palm

An in vitro study was done to evaluate antiviral activity of acetone date pit extract on pseudomonas phage ATCC 14209-B1 using *Pseudomonas aeruginosa* as a host cell (Jassim and Naji 2010). The date pit extracts strongly inhibit the infectivity of pseudomonas phage at minimum inhibitory concentration MIC <10 μg/mL and completely prevented bacterial lysis. The decimal reduction time, concentration exponent, and phage inactivation kinetics were determined that strongly agree with the antiviral potential of *Phoenix dactylifera*. The ability of date pit extract to inhibit the infectivity of Pseudomonas phage ATCC 14209-B1 without bacterial lysis is an inexpensive way to treat viral infection and provides hope for treatment of HIV and other virus infections to humans.

Clinical Study of Date Palm on Delivery and Labor Relaxation

Many herbs and their active constituents play a key role as a pain reliever and cause relaxation in childbirth including date palm. A prospective study was done on 114 pregnant women divided into two groups. Date palm group comprises 69 women and non-date palm group comprises 45 women. Date palm group consumes six dates per day and another group was nonconsumer of dates. Date palm has shown a significant effect as higher mean cervical dilation, and reduced the induction in labor rise in women. Constituents of date fruit might play a significant role as a pain reliever and also cause relaxation in childbirth (Al-Kuran et al. 2011). This study concluded that date palm group needs less labor induction or augmentation compared to control.

Conclusion

Discussed pharmacological properties of date palm advocate its traditional practice in multiple diseases. The unique nutritional composition of dates can serve as a vital food in the diet of humans and plays a major role in human nutrition and health that provide a part of required daily recommend allowance. Date fruit also possesses numerous bioactive phytochemicals such as phenols, carotenoids, flavonoids, anthocyanin, and dietary fiber that possess multiple curative potentials like antioxidant, anti-inflammatory, anticancer, and antimicrobial properties. This positive effect of date fruit on human health suggested for further research on identification and isolation of bioactive compounds that help in the treatment of various diseases like neuronal, gastric, and cardiac. Thus, an affordable, safe, and effective approach can be reached to control diseases, development, and progression in contrast to synthetic drugs that are expensive, show the adverse effect, and alter the metabolic and genetic pathway.

References

Abbas FA, Ateya A-M (2011) Estradiol, esteriol, estrone and novel flavonoids from date palm pollen. Aust J Basic Appl Sci 5(8):606–614

Abdelaziz DHA, Ali SA (2014) The protective effect of Phoenix dactylifera L. seeds against CCl_4-induced hepatotoxicity in rats. J Ethnopharmacol 155(1):736–743. https://doi.org/10.1016/j.jep.2014.06.026

Abdelaziz DHA, Ali SA, Mostafa MMA (2015) Phoenix dactylifera seeds ameliorate early diabetic complications in streptozotocin-induced diabetic rats. Pharm Biol 53(6):792–799. http://www.ncbi.nlm.nih.gov/pubmed/25612778

Abdul E, Assirey R (2015) Nutritional composition of fruit of 10 date palm (Phoenix dactylifera L.) cultivars grown in Saudi Arabia. Integr Med Res 9(1):75–79. https://doi.org/10.1016/j.jtusci.2014.07.002

Abdullah YA (2008) Possible anti-diarrhoeal effect of the date palm (Phoenix dactylifera L.) spathe aqueous extract in rats. Group 9(1):131–138

Agbon AN, Ingbian SD, Dahiru AU (2014) Preliminary histological and histochemical studies on the neuroprotective effect of aqueous fruit extract of Phoenix dactylifera L. (date palm) on atesunate-induced cerebellar damage in Wistar rats. Sub-Saharan Afr J Med 1(4):204–209

Ahmed AF et al (2015) Proanthocyanidin-rich date seed extract protects against chemically induced hepatorenal toxicity. J Med Food 18(3):280–289. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4350264&tool=pmcentrez&rendertype=abstract

Ahmed S (2016) Anti hyperlipidemic and hepatoprotective effects of native date fruit variety Aseel (Phoenix dactylifera). Pak J Pharm Sci 29:1945–1950

Ahmed A, Bano N, Tayyab M (2016) Phytochemical and therapeutic evaluation of date (Phoenix dactylifera). A review. J Pharm Alternat Med 9 (November 2015), 11–17

Al-Farsi MA, Lee CY (2008) Nutritional and functional properties of dates: a review. Crit Rev Food Sci Nutr 48(10):877–887

Al-Farsi M et al (2005) Compositional and sensory characteristics of three native sun-dried date (Phoenix dactylifera L.) varieties grown in Oman. J Agric Food Chem 53(19):7586–7591

Ali Haimoud S, Allem R, Merouane A (2016) Antioxidant and anti-inflammatory properties of widely consumed date palm (Phoenix dactylifera L.) fruit varieties in Algerian Oases. J Food Biochem 40(4):463–471

Al-Kuran O et al (2011) The effect of late pregnancy consumption of date fruit on labour and delivery. J Obstet Gynaecol 31(1):29–31

Al-Qarawi AA, Ali BH, Al-Mougy SA, Mousa HM (2003) Gastrointestinal transit in mice treated with various extracts of date (Phoenix dactylifera L.). Food Chem Toxicol 41(1):37–39. http://www.sciencedirect.com/science/article/pii/S027869150200203X

Al-Qarawi A et al (2004) Protective effect of extracts from dates (Phoenix dactylifera L.) on carbon tetrachloride-induced hepatotoxicity in rats. Int J Appl Res Vet Med 2(3):176–180. http://jarvm.com/articles/Vol2Iss3/ELMOUGHJARVMVol2No304.pdf

Al-Qarawi AA et al (2005) The ameliorative effect of dates (Phoenix dactylifera L.) on ethanol-induced gastric ulcer in rats. J Ethnopharmacol 98(3):313–317

Al-Qarawi AA et al (2008) Nephroprotective action of Phoenix dactylifera in gentamicin-induced nephrotoxicity. Pharm Biol 46(4):227–230. http://www.scopus.com/inward/record.url?eid=2-s2.0-41349116154&partnerID=tZOtx3y1

Al-Shahib W, Marshall RJ (2002) Dietary fibre content of dates from 13 varieties of date palm Phoenix dactylifera L. Int J Food Sci Technol 37(6):719–721

Al-Shahib W, Marshall RJ (2003) The fruit of the date palm: its possible use as the best food for the future? Int J Food Sci Nutr 54(4):247–259

Ardekani MRS, Khanavi M, Hajimahmoodi M, Jahangiri M, Hadjiakhoondi A (2010) Comparison of antioxidant activity and total phenol contents of some date seed varieties from Iran. Iran J Pharmaceut Res 9(2):141–146

Ateeq A, Dutta Sunil S, Varun SK, Santosh MK (2013) Phoenix dactylifera Linn. (Pind Kharjura): a review. Int J Res Ayurveda Pharm 4(3):447–451

Atta H, Abo-EL-Sooud K, Ahmed SS, Ibrahim S, Zaher S (2015) Synergistic hepatoprotective effect of grape juice with date palm fruit methanolic extracts. Wulfenia J 22(12):282–297

Baharara J et al (2015) Protective effect of date palm pollen (Phoenix dactylifera) on sperm parameters and sexual hormones in male NMRI mice exposed to low frequency electromagnetic field (50 Hz). J Herbmed Pharmacol 4(3):75–80

Baliga MS et al (2011) A review of the chemistry and pharmacology of the date fruits (Phoenix dactylifera L.). Food Res Int 44(7):1812–1822. https://doi.org/10.1016/j.foodres.2010.07.004

Bokhari NA, Perveen K (2012) In vitro inhibition potential of Phoenix dactylifera L. extracts on the growth of pathogenic fungi. J Med Plants Res 6(6):1083–1088. http://www.academicjournals.org/journal/JMPR/article-abstract/8C79E5325796

Borchani C, Besbes S, Blecker C, Masmoudi M, Baati R, Attia H (2010) Chemical properties of 11 date cultivars and their corresponding fiber extracts. Afr J Biotechnol 9(12):4096–4105. http://www.ajol.info/index.php/ajb/article/view/82578

Boudries H, Kefalas P, Hornero-Méndez D (2007) Carotenoid composition of Algerian date varieties (Phoenix dactylifera) at different edible maturation stages. Food Chem 101(4):1372–1377

Bouhlali ET et al (2016) Evaluation of antioxidant, antihemolytic and antibacterial potential of six Moroccan date fruit (Phoenix dactylifera L.) varieties. J King Saud Univ Sci 28(2):136–142. https://doi.org/10.1016/j.jksus.2016.01.002

Bouhlali EDT, Ramchoun M, Alem C, Ghafoor K, Ennassir J, Zegzouti YF (2015) Functional composition and antioxidant activities of eight Moroccan date fruit varieties (Phoenix dactylifera L.). J Saudi Soc Agric Sci (September)

Chaira N et al (2009) Simple phenolic composition, flavonoid contents and antioxidant capacities in water-methanol extracts of Tunisian common date cultivars (Phoenix dactylifera L.). Int J Food Sci Nutr 60(Suppl 7):316–329. http://www.ncbi.nlm.nih.gov/pubmed/19736597

Chakroun M et al (2016) Evaluation of anti-diabetic and anti-tumoral activities of bioactive compounds from Phoenix dactylifera L's leaf: in vitro and in vivo approach. Biomed Pharmacother 84:415–422. https://doi.org/10.1016/j.biopha.2016.09.062

Duke JA (2001) Handbook of phytochemical constituents of GRAS herbs and other economic plants. CRC Press, Boca Raton, FL

Duke JA, Beckstrom-Sternberg S (2007) Dr. Duke's Ethnobotanical databses. http://www.ars-grin.gov/duke/plants.html

Eid NMS et al (2013) Effect of cultivar type and ripening on the polyphenol content of date palm fruit. J Agric Food Chem 61(10):2453–2460

Eid N et al (2014) The impact of date palm fruits and their component polyphenols, on gut microbial ecology, bacterial metabolites and colon cancer cell proliferation. J Nutr Sci 3(22):e46. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4473134&tool=pmcentrez&rendertype=abstract

El Arem A, Ghrairi F et al (2014a) Hepatoprotective activity of date fruit extracts against dichloroacetic acid-induced liver damage in rats. J Funct Foods 9(1):119–130. https://doi.org/10.1016/j.jff.2014.04.018

El Arem A, Zekri M et al (2014b) Oxidative damage and alterations in antioxidant enzyme activities in the kidneys of rat exposed to trichloroacetic acid: protective role of date palm fruit. J Physiol Biochem 70(2):297–309

El-Gazzar UB, El-Far AH, Abdel Maksoud HA (2009) The ameliorative effect of Phoenix dactylifera extract on CCl_4 hepatotoxicity in New Zealand rabbits. J Appl Sci Res 5(9):1082–1087

Elleuch M et al (2008) Date flesh: chemical composition and characteristics of the dietary fibre. Food Chem 111:676–682

El-Neweshy MS, El-Maddawy ZK, El-Sayed YS (2013) Therapeutic effects of date palm (Phoenix dactylifera L.) pollen extract on cadmium-induced testicular toxicity. Andrologia 45(6):369–378

FAO (2007) Statistical databases. http://faostat.fao.org. Accessed 2 June 2007

Farag El-Kott A, Ali Sayed A, El-Sayad SM, Abdoulrahman MH (2014) The pharmaceutical effect of date palm fruit extract (Phoenix dactylifera L.) against Amitraz-induced infertility in male rats. Adv Life Sci Technol 22:14–27

Farouk A, Metwaly A, Mohsen M (2015) Chemical composition and antioxidant activity of date palm pollen grains (Phoenix dactylifera L. Palmae) essential oil for Siwe cultivar cultivated in Egypt. Middle East J Appl Sci 5:945–949

Hafez El-Far A et al (2016) Date palm (Phoenix dactylifera): protection and remedy food. Curr Trends Nutraceuticals 1:2

Hamad I et al (2015) Metabolic analysis of various date palm fruit (Phoenix dactylifera L.) cultivars from Saudi Arabia to assess their nutritional quality. Molecules 20(8):13620–13641

Hasan M, Mohieldein A (2016) In vivo evaluation of anti diabetic, hypolipidemic, antioxidative activities of Saudi date seed extract on streptozotocin induced diabetic rats. J Clin Diagn Res 10(3):6–12

Hong YJ, Tomas-Barberan FA, Kader AA, Mitchell AE (2006) The flavonoid glycosides and procyanidin composition of Deglrt Noor Dates (Pheonix dactylifera). J Agric Food Chem 54:2405–2411

Ishurd O, Zahid M, Xiao P, Pan Y (2004) Protein and amino acids contents of libyan dates at three stages of development. J Sci Food Agric 84(5):481–484

Jassim SAA, Naji MA (2010) In vitro evaluation of the antiviral activity of an extract of date palm (Phoenix dactylifera L.) pits on a Pseudomonas phage. Evid Based Complement Alternat Med 7(1):57–62

Kchaou W et al (2016) Phenolic profile, antibacterial and cytotoxic properties of second grade date extract from Tunisian cultivars (Phoenix dactylifera L.). Food Chem 194:1048–1055. https://doi.org/10.1016/j.foodchem.2015.08.120

Kehili HE, Zerizer S, Beladjila KA, Kabouche Z (2016) Anti-inflammatory effect of Algerian date fruit (*Phoenix dactylifera*). Food Agric Immunol 27(6):820–829. https://www.tandfonline.com/doi/full/10.1080/09540105.2016.1183597

Khalid S et al (2016) Nutritional assessment of Ajwa date flesh and pits in comparison to local varieties. J Anim Plant Sci 26(4):1072–1080

Khan F, Ahmed F, Natesan Pushparaj P, Abuzenadah A (2016a) Ajwa date (Phoenix dactylifera L.) extract inhibits human breast adenocarcinoma (MCF7) cells in vitro by inducing apoptosis and cell cycle arrest. PLoS One 11:1–17

Khan SA et al (2016b) In vitro inhibitory effects on α-glucosidase and α-amylase level and antioxidant potential of seeds of Phoenix dactylifera L. Asian Pac J Trop Biomed 6(4):322–329

δάκτυλος. Liddell, Henry George; Scott, Robert; A Greek–English Lexicon at the Perseus Proj- ect.

Louaileche H, Hammiche D, Hamoudi F (2015) Total phenolic, flavonoid contents and in vitro antioxidant activity of Algerian date palm varieties: a comparative study. Am J Food Sci Health 1(3):63–68

Mansour AM, Ghobara MY (2015) Abrogation of cisplatin-induced nephrotoxicity in rats by Berne date extract through ameliorating oxidative stress, inflammation and apoptosis. Int J Ther Appl 6(9):1226–1233

Mansouri A, Embarek G, Kokkalou E, Kefalas P (2005) Phenolic profile and antioxidant activity of the Algerian ripe date palm fruit (Phoenix dactylifera). Food Chem 89(3):411–420

Mehraban F et al (2014) Effects of date palm pollen (Phoenix dactylifera L.) and Astragalus ovinus on sperm parameters and sex hormones in adult male rats. Iran J Reprod Med 12(10):705–712

Nair MG (2013) Antioxidant and anti-inflammatory assays confirm bioactive compounds in Ajwa date fruit. J Agric Food Chem 61:5834–5840

Orabi SH, Shawky SM (2014) Effect of date palm (Phoenix dactylifera) seeds extracts on hematological, biochemical parameters and some fertility indices in male rats. Int J Sci Basic Appl Res (IJSBAR) 17(1):137–147

Ragab AR, Elkablawy MA, Sheik BY, Baraka HN (2012) Antioxidant and tissue-protective studies on Ajwa extract: dates from Al-Madinah Al-Monwarah, Saudia Arabia. J Environ Anal Toxicol 3(1):1–8

Ranilla LG et al (2008) Antidiabetes and antihypertension potential of commonly consumed carbohydrate sweeteners using in vitro models. J Med Food 11(2):337–348 http://www.ncbi.nlm.nih.gov/pubmed/18598178

Saafi EB et al (2011) Protective effect of date palm fruit extract (Phoenix dactylifera L.) on dimethoate induced-oxidative stress in rat liver. Exp Toxicol Pathol 63(5):433–441 https://doi.org/10.1016/j.etp.2010.03.002

Saleh EA, Tawfik MS, Abu-tarboush HM (2011) Phenolic contents and antioxidant activity of various date palm (Phoenix dactylifera L.) fruits from Saudi Arabia. Food Nutr Sci 2:1134–1141

Shafiei M, Karimi K, Taherzadeh MJ (2010) Palm date fibers: analysis and enzymatic hydrolysis. Int J Mol Sci 11(11):4285–4296

Sheikh BY et al (2016) Comparative study of neuropharmacological, analgesic properties and phenolic profile of Ajwah, Safawy and Sukkari cultivars of date palm (Phoenix dactylifera). Orient Pharm Exp Med 16:175–183. https://doi.org/10.1007/s13596-016-0239-5

Souli A et al (2014) Effects of dates pulp extract and palm sap (Phoenix dactylifera L.) on gastrointestinal transit activity in healthy rats. J Med Food 17(7):782–786 http://www.scopus.com/inward/record.url?eid=2-s2.0-84904326085&partnerID=tZOtx3y1

Subash S et al (2015) Effect of dietary supplementation of dates in Alzheimer's disease APPsw/2576 transgenic mice on oxidative stress and antioxidant status. Nutr Neurosci 18(6):281–288 http://www.ncbi.nlm.nih.gov/pubmed/24954036

Takaeidi MR et al (2014) The effect of date seed (Phoenix dactylifera) extract on paraoxonase and arylesterase activities in hypercholesterolemic rats. Jundishapur J Nat Pharm Prod 9(1):30–34

USDA. National Nutrient Database for Standard Reference, United States Department of Agriculture; www.nal.usda.gov/fnic/foodcomp/search/. Accessed 15 May 2007

Whitney E, Rolfes S (2002) Understanding nutrition. Ninth edition. Wadsworth/Thomson Learning, Belmont, CA

Zangiabadi N et al (2011) Date fruit extract is a neuroprotective agent in diabetic peripheral neuropathy in streptozotocin-induced diabetic rats: a multimodal analysis. Oxid Med Cell Longev 2011:976948

Zhang CR, Aldosari SA, Vidyasagar PSPV, Shukla P, & Nair MG (2017) Health-benefits of date fruits produced in Saudi Arabia based on in vitro antioxidant, anti-inflammatory and human tumor cell proliferation inhibitory assays. J Saudi Soc Agric Sci 16(3):287–293. https://doi.org/10.1016/j.jssas.2015.09.004

An Insight of Multitudinous and Inveterate Pharmacological Applications of *Foeniculum vulgare* (Fennel)

Fareeduddin Quadri Syed, Muqtadir Baig Mirza, Ayman I. Elkady, Khalid Rehman Hakeem, and Saleh Alkarim

Introduction

Foeniculum vulgare commonly known as fennel belongs to the Apiaceae family. It is a very popular traditional medicinal herb used by humans for a long time (He and Huang 2011). Basically, fennel plant has been originated in the southern Mediterranean region but cultivated throughout the world. Since ancient times Egyptians, Indians, Romans and Chinese cultivated and used fennel in many ways.

Various research studies show that fennel is effective to control viral, bacterial, fungal, mycobacterium and protozoal infections (Badgujar et al. 2014). For the relief of spams and colic due to gas accumulation, gastrointestinal motility, menstruation and lactation fennel was used since earlier time. Antitumour, chemopreventive, hepatoprotective, hypoglycaemic and antihirsutic properties of fennel are reported in many studies (Cioanca et al. 2015). More recent studies suggest that fennel essential oil can be used in controlling anxiety, depression and Alzheimer's disease.

Fennel is used as a seasoning herb. In France and Italy, it is the crucial ingredient in modern cuisine. Being aromatic, all parts are used in cooking. It is used to improve the palatability of meat and fish dishes. And it can be used raw in salads and shakes, as a spice, in herbal teas, as a mouth freshener, etc. (Lim 2013) (Figs. 1, 2, and 3).

Taxonomy

Kingdom: Plantae.
Division: Tracheophyta.
Subdivision: Spermatophytina.

F. Q. Syed (✉) · M. B. Mirza · A. I. Elkady · K. R. Hakeem · S. Alkarim
Department of Biological Science, King Abdulaziz University, Jeddah, Saudi Arabia

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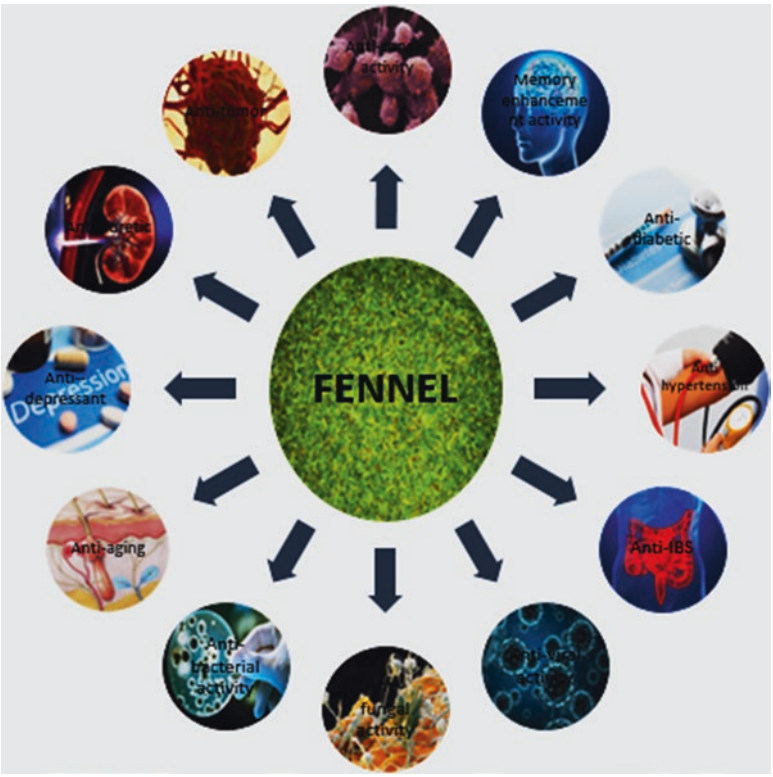

Fig. 1 Multitudinous pharmaceutical applications of fennel

Fig. 2 (**a**) Fennel plant with finely divided foliage. (**b**) Compound umbel with mature flowers. (**c**) Fennel mericarps (seeds)

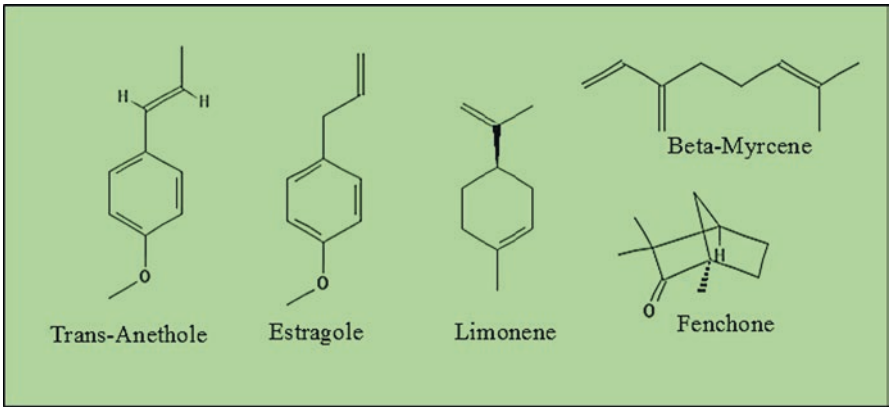

Fig. 3 The molecular structures of the major bioactive essential oil components of fennel

Class: Magnoliopsida.
Subclass: Rosidae.
Order: Apiales.
Family: Apiaceae.
Genus: Foeniculum.
Species: vulgare.

Botanical Description

F. vulgare is a bright green, erect, perennial herb which can grow up to 2 m tall. The foliage is dissected, soft hairy-like dill leaves which cut into fine segments with the length of about 40 cm.

The inflorescence is umbels producing on large branches with thirteen to twenty yellow-colour ray flowers (Barros et al. 2010).

Typically, fennel fruits are greenish yellow, elliptical, elongated shape with vertical ribs over it. The length of the fruit varies from 0.3 cm to 0.5 cm. Fennel can be propagated by root fragments and reproduced by seeds as well.

Nutritional Value of Fennel

Dried *F. vulgare* fruit or seed is the most commonly edible part of the plant. These seeds are commonly referred as fennel. It is sweet and often commercially available in the dried state. According to USDA fennel seeds are rich in sodium, calcium, potassium and phosphorus (Table 1). Besides this, it has abundant fibre and vitamins (USDA 2016).

Table 1 Nutritional value of fennel (USDA 2016)

Nutrient	Per 100 g
Water	8.81 g
Energy	345Kcal
Protein	15.8 g
Total lipid (fat)	14.87 g
Carbohydrate	52.29 g
Fiber, total dietary	39.8 g
Minerals	
Calcium, Ca	1196 mg
Iron, Fe	18.54 mg
Magnesium, Mg	385 mg
Phosphorus, P	487 mg
Potassium, K	1694 mg
Sodium, Na	88 mg
Zinc, Zn	3.7 mg
Vitamins	
Vitamin C, ascorbic acid	21 mg
Thiamin	0.408 mg
Riboflavin	0.353 mg
Niacin	6.05 mg
Vitamin B-6	0.47 mg
Vitamin B-12	0 µg
Vitamin A, RAE	7 µg
Vitamin A, IU	135 IU
Vitamin D (D2 + D3)	0 µg
Vitamin D	0 IU
Lipids	
Fatty acids, total saturated	0.48 g
Fatty acids, total monounsaturated	9.91 g
Fatty acids, total polyunsaturated	1.69 g
Cholesterol	0 mg

Phytochemical Constituents of Fennel

Fennel plant is endorsed by abundant bioactive phytochemicals. Essential oil, flavonoids, phenolic compounds, few secondary metabolites, etc. are accountable for the pharmacological interests.

Essential Oil of Fennel

Essential oils of fennel are the cause of its flavouring properties. Essential oil content varies from geographical variations. Percentage of about 1.1–4.8% essential oil is found in fennel.

Table 2 Fennel essential oil composition (%), obtained by GC–MS (Anwar et al. 2009)

Compound	Composition (%)
Monoterpene hydrocarbons	
Limonene	5.10 ± 0.10
β-Myrcene	0.87 ± 0.10
(z)-β-Ocimene	0.60 ± 0.02
α-Pinene	0.55 ± 0.02
Sabinene	0.19 ± 0.04
α-Phellandrene	0.19 ± 0.02
γ-Terpinene	0.16 ± 0.02
Camphene	0.13 ± 0.03
β-Pinene	0.09 ± 0.02
(z)-β-Ocimene	Trace (<0.05%)
p-Cymene	Trace (<0.05%)
Oxygenated monoterpenes	
Trans-anethole	69.87 ± 0.65
Fenchone	10.23 ± 0.20
Estragole	5.45 ± 0.20
Fenchyl acetate (exo)	0.54 ± 0.10
Fenchyl alcohole	0.40 ± 0.04
Cis-anethole	0.27 ± 0.03
1,8-Cineol	0.23 ± 0.02
p-Anisaldehyde	0.19 ± 0.01
Fenchyl acetate (endo)	0.12 ± 0.03
Sesquiterpene hydrocarbons	
β-Caryophyllene	0.26 ± 0.00
Germacrene D	0.09 ± 0.00

Trans-anethole, methyl chavicol, fenchone and limonene are the prime essential oil components of fennel with the respective percentage of 1.2–88.4%, 0.2–59.1%, 1.1–14.7% and 5.3–15.7% (Bahmani et al. 2016).

Anethole is the most studied compound from fennel. It is an aromatic compound present in the essential oil of fennel. About 70–80% of essential oil of fennel is composed of anethole. It is clear, colourless liquid with very low solubility in water but readily soluble in ethanol. It is 13 times sweeter than sugar having a distinct sweet anise-like flavour (Chen 2014) (Table 2).

Flavonoids and Phenols of Fennel

Apiaceae members are rich in flavonoids and phenols, so as fennel. Farooq Anwar et al. reported that the extract of fennel seeds contains 627.21–967.50 GAE, mg/mL of total phenols, and the total flavonoid content is 374.88–681.96 CE, mg/100 g. Because of their pharmacological importance, various flavonoids and phenols are isolated from fennel (see Table 3).

Table 3 Phenolic compounds in fennel (Parejo et al. 2004)

S. No.	Phenolic compound	S. No.	Phenolic compound
1	p-Hydroxybenzoic acid-O-glucoside	22	3-Caffeoylquinic acid (neochlorogenic acid)
2	5-Caffeoylquinic acid (chlorogenic acid)	23	Esculetin-O-glucoside (esculin)
3	1-Caffeoylquinic acid	24	3-Feruloylquinic acid
4	4-Caffeoylquinic acid (cryptochlorogenic acid)	25	Isorhamnetin-O-dihexoside
5	Isorhamnetin-O-dihexoside	26	6, 8-C-dihexosylapigenin
6	4-Coumaroylquinic acid	27	5-Coumaroylquinic acid
7	5-Feruloylquinic acid	28	Quercetin-O-dihexoside
8	1-Feruloylquinic acid	29	Quercetin-O-dihexoside
9	4-Feruloylquinic acid	30	Quercetin-3-O-rutinoside (rutin)
10	Eriodictyol-7-O-rutinoside (eriocitrin)	31	Luteolin-7-O-rutinoside
11	Quercetin-3-O-galactoside (hyperoside)	32	Naringerin-7-O-rutinoside (narirutin)
12	Quercetin-3-O-glucoside (isoquercitrin)	33	Kaempferol-3-O-rutinoside
13	Kaempferol-3-O-glucoside	34	Isorhamnetin-3-O-rutinoside
14	Quercetin-3-O-glucuronide (miquelianin)	35	Luteolin-7-O-glucuronide
15	Isorhamnetin-3-O-galactoside	36	Isorhamnetin-3-O-glucoside
16	1,3-Dicaffeoylquinic acid	37	Dicaffeoylquinic acid
17	1,5-Dicaffeoylquinic acid	38	Kaempferol-3-O-glucuronide
18	Isorhamnetin-3-O-glucuronide	39	Rosmarinic acid
19	Apigenin-7-O-glucuronide	40	Acacetin-7-O-rutinoside
20	Acacetin	41	Kaempferol
21	Naringenin	42	Isorhamnetin

Pharmacological Importance of Fennel

Foeniculum vulgare has been used since a long time as a remedial herb for many diseases. Many traditional herbal formulations contain fennel as a constituent. Even today fennel is one among the extensively studied plant for its pharmacological importance. Here we compile some of the uses of fennel in various disease, disorders and human well-being (Table 4).

Antibacterial Activity of Fennel

Ample number of studies were carried out for provident evidence for the antibacterial property of fennel and its components. Methanolic extract of fennel seeds and leaf extract from different countries was tested for the antibacterial activity. *Escherichia coli, Staphylococcus aureus, Salmonella typhimurium and Bacillus subtilis* were used in this study to examine the effect of the extract. MICs ranging from 62.5

Table 4 Anti-proliferative and apoptotic activity of fennel on various cancer cell lines

Cell lines	IC50	Fennel extract	References
MCF-7	24.5 ± 0.08 µg/mL	Methanolic extract of fennel seeds	Zaahkouk et al. (2016)
HEPG-2	28.7 ± 0.04 µg/mL		
HCT 116	59.8 ± 0.09 µg/mL		
Hela	129.7 ± 2.05 µg/mL	Acetone extract of aerial parts of fennel	Berrington and Lall (2012)
Vero	85.37 ± 5.26 µ/mL		
MCF-7	5.78 ± 0.59 g/mL	Methanolic extract of fennel seed	Mohamad et al. (2011)
HEPG-2	27.96 ± 0.54 g/mL		
HT-29	41.87 ± 2.72 g/mL		
H460	50.22 ± 3.03 g/mL		
Hela	79.33 ± 3.37 g/mL		
U251	85 ± 2.54 g/mL		
Eol	50 µg/mL	80 % Ethanolic fennel seed extract	Bogucka-Kocka et al. (2008)
C8166	122 µg/mL		
J45	150 µg/mL		
WICL	155 µg/mL		
ML1	300 µg/mL		
H9	300 µg/mL		
1301	300 µg/mL		
HL60	300 µg/mL		
U266	300 µg/mL		
MCF-7	›100	Ethanol extract of fennel	Lall et al. (2015)
HeLa	19.97 ± 0.048		
SNO	›100		
DU145	56.41 ± 0.28		
Vero	›100		
V79	448.00 ± 19.52	Essential oils extracted from leaves of fennel	de Oliveira et al. (2015)
B16F10	112.78 ± 13.74		
MO59J	406.00 ± 1.57		
Normal human dermal fibroblasts (UV irradiation)	Non-efficient (but decrease in the ROS and LDH level)	50 % Ethanolic extract of fennel seeds	Sun et al. (2016)
4 T1	50 µg/mL	80 % Methanolic extract of fennel seeds	Mansourabadi et al. (2015)
MCF-7	69.41 mg/mL	96% of ethanolic extract of fennel fruit	Agustini et al. (2015)
HT29–19(A) HT29-(MS)	~77 µL/mL ~80 µL/mL	Essential oil (commercially available)	Al-Tamimi et al. (2016)
THP-1	No significant effect	Essential oil (commercially available)	Aazzaa et al. (2014)
AGS	25µg/mL	Essential oil	Ghasemi (2015)
L929aA	700 ± 28 µg/mL	100% Methanolic extract of aerial plant parts	Kaileh et al. (2007)
MDA-MB231	500 ± 17 µg/mL		
MCF7	No effect		

to125 μg/mL were observed with the methanolic extract of fennel from various countries (Salami et al. 2016). In another similar study the antimicrobial activity of methanolic extract showed maximum activity of 20 mm inhibition zone against *Staphylococcus aureus,* also showing activity against *Escherichia coli, Bacillus pumilus, Listeria monocytogenes and Enteropathogenic E. coli (EPEC)* (Kumar et al. 2014). Production of cholera toxin (CT) by a various strain of *Vibrio cholerae* was examined under the stress of methanolic extract of fennel seeds. There was a significant inhibitory effect on the production of CT regardless of the strains. The similar inhibitory effect was demonstrated with trans-anethole and 4-allylanisole, essential oil of fennel seeds (Chatterjee et al. 2016). *Helicobacter pylori* are responsible for many gastric problems, peptic ulcers and gastroduodenal cancers. The methanol extract of fennel showed 50 μg/mL MIC to *Helicobacter pylori* (Abdallah 2016). Essential oil of fennel exhibited the antibacterial activity against *Staphylococcus albus, Bacillus subtilis, Salmonella typhimurium, Shigella dysenteriae* and *Escherichia coli*. With the MIC and MBC of 0.125 and 0.25 mg/mL, respectively, *S. dysenteriae* was the most subtle to fennel's essential oil (Diao et al. 2014). Peptides isolated from the fennel seed showed good inhibition in many bacterial strains with the zone of inhibition ranging from 11 to 12.5 mm. When compared with the standard antibiotic chloramphenicol (25 μg), fennel seed peptides have the better activity to most of the strains (Al Akeel et al. 2014). With the MICs ranging from 64 to 256 μg/mL, the fennel oil was found to be active against *Staphylococcus aureus*. With the sublethal concentration, the expression of endotoxins of *S. aureus* was decreased (Qiu et al. 2012). Except for *Klebsiella pneumoniae* and one strain of *Pseudomonas aeruginosa,* both hot water and organic fraction extracts showed substantial antibacterial activity against *Enterococcus faecalis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* 1, *Salmonella typhi*, *Salmonella typhimurium* 1, *S. typhimurium* 2 and *Shigella flexneri.* Ranging from 20 to 80 mg/mL and 5 to 15 mg/mL were the MICs for aqueous and acetone seed extracts, respectively (Kaur and Arora 2009). Essential oils of fennel, anethole and n-hexane extract were tested for the efficacy against the various foodborne bacteria. All these fractions of fennel seeds were found to possess antimicrobial activity (Cetin et al. 2010). Different strains of *Mycobacterium tuberculosis* were used for the testing of anti-mycobacterial activity of twenty compounds isolated from the active fractions of fennel. Among these compounds, 2,4-undecadienal was the most effective with MIC 25–50 μg/mL. Other compounds from fennel with anti-mycobacterial activity are linoleic acid (MIC 100 μg/mL), oleic acid (MIC 100 μg/mL), 1,3-benzenediol (MIC 100–200 μg/mL) and undecanal (MIC 50–200 μg/mL) (Esquivel-Ferriño et al. 2012).

Antiviral Activity of Fennel

Quercetin and isoquercetin are the two flavonoids showing a virostatic effect against *Bluetongue virus* (BTV) in an *in vitro* study. These two compounds were effective on viral growth retardation in BHK cells at a concentration of 0.75 ± 0.11 μM and

1.07 ± 0.17 μM, respectively (Tharanath et al. 2013). Essential oil of fennel exhibited toxicity to *herpes simplex* type-1 (*HSV-1*) and parainfluenza type-3 (PI-3), expressing the cytotoxicity by the cytopathogenic effect. The antiviral activity ranges from 0.8 to 0.025 μg/mL and 1.6 to 0.2 μg/mL, respectively (Erdoğan Orhan et al. 2012). Syncytia formation inhibition assay showed 26.2 ± 11.3% inhibition of HIV-1 fusion by methanol extract of *Foeniculum vulgare* fruit at a concentration of 100 μg/mL (Chang and Woo 2003). Volatile oils of fennel and acetone extract of fennel seeds were effective against papaya ring spot virus with 25–100% of inhibition at various concentrations (Maurya et al. 2005).

Antifungal Activity of Fennel

In a study essential oil of fennel seeds was investigated for antifungal activity against *Trichophyton rubrum, T. tonsurans, T. mentagrophytes* and *Microsporum gypseum*. It was found that the antifungal effect of fennel seeds essential oil was more prominent than the commonly used antifungal fluconazole and amphotericin B (Zeng et al. 2015). A study to evaluate the anti-mycotic effect of essential oil obtained from the seeds and leaves of fennel demonstrates the complete inhibition of mycelial growth of *Alternaria sp., Fusarium oxysporum f. sp. albedinis, Aspergillus brasiliensis* and *Rhizopus stoloniferawas* with the MIC 0.25 μL/mL (Khalid et al. 2015).

Anti-inflammation Effect of Fennel

Scopoletin, 8-methoxypsoralen, bergapten and imperatorin are the four compounds which are isolated from the methylene chloride fraction of fennel fruit that were assessed for the anti-inflammatory and antioxidant effect in macrophages and in mice stimulated by 12-O-tetradecanoylphorbol-13-acetate. All four compounds were found to be effective anti-inflammatory and antioxidant agents. Most effective was imperatorin in both in vivo and in vitro model (Yang et al. 2015). Lipopolysaccharide (LPS)-induced acute lung injury mice model was used in the demonstration of fennel as an anti-inflammatory agent. Fennel reduced the production of inflammatory cytokines interleukin 6 and tumour necrosis factor-alpha. It also reduced pro-inflammatory mediator matrix metalloproteinase 9 and nitric oxide blocking inflammation process effectively (Lee et al. 2015). Methanolic extract of fennel fruit exerts an inhibitory effect on inflammatory diseases and IV allergic reactions in mice (Choi and Hwang 2004). Another study on rodents established that essential oils of fennel have an anti-inflammatory effect comparable to etodolac at 0.05–0.20 mL/kg (Özbek 2005).

Antioxidant Activity of Fennel

Using DPPH method for determination of anti-oxidation capacity G. Angelov and S. Boyadzhieva concluded that extraction of fennel using water as a solvent has high anti-oxidation potential (Angelov 2016). Another study proved that fennel beverage prepared in in-house conditions is an effective antioxidant, measuring >80% anti-oxidation rate by DPPH assay. The anti-oxidation capacity of fennel was comparable to NDGA and Trolox, standard antioxidant compounds (Kontogiorgis et al. 2016). Paraoxonase 1 (PON1), a hydrolase enzyme, was suggested to have a role in the regulation of oxidative stress, fibrosis and hepatic cell apoptosis in chronic liver disease. It has been concluded that fennel seed extract increases the activity of PON1 and mitigates the oxidative stress caused by tienilic acid in mice liver (Abdel-Wahhab et al. 2016). The damage induced by Fenton reaction to the calf thymus DNA was alleviated by fennel seed extract proving fennel as a good source of anti-oxidants in biological systems as well (Goswami and Chatterjee 2014). Antioxidant potential of different parts of fennel plant was used to study the antioxidant potential of each part of the plant. The highest radical scavenging activity and lipid peroxidation inhibition capacity were recorded with the shoots (Barros et al. 2009).

Anti-proliferative and Apoptotic Effect (In Vitro) of Fennel

Samir A.M. Zaahkouk1 et al. reported that methanolic extract of fennel seeds have anti-proliferative effect on MCF-7, HEPG-2 and HCT 116 cells with the IC50 24.5 ± 0.08, 28.7 ± 0.04 and 59.8 ± 0.09 μg/mL (Zaahkouk 2016). Acetone extract of aerial parts of fennel plant shows the growth inhibition of HeLa cells with the IC50 of 129.7 ± 2.05 and to the Vero cells, the IC50 is 85.37 ± 5.26 μg/mL (Berrington and Lall 2012). Methanolic extract of fennel seed shows cytotoxicity to MCF-7, HEPG-2, HT-29, H460, HeLa and U251 with the IC50 (1 g/mL) 15.78 ± 0.59, 27.96 ± 0.54, 41.87 ± 2.72, 50.22 ± 3.03, 79.33 ± 3.37 and 85 ± 2.54, respectively (Mohamad et al. 2011). 80% Ethanolic fennel seed extract shows cytotoxicity to nine human leukaemia cell lines. IC50 (μg/mL) of different cell lines is as follows: Eol 50 μg/mL, C8166 122 μg/mL, J45 150 μg/mL, WICL 155 μg/mL, ML1 300 μg/mL, H9 300 μg/mL, 1301 300 μg/mL, HL60 300 μg/mL and U266 300 μg/mL (Bogucka-Kocka et al. 2008). Effects of ethanol extract of fennel on various cell lines like MCF-7, HeLa, SNO, DU145 and monkey Vero cells were studied and their IC50 was ˃100, 19.97 ± 0.048, ˃100, 56.41 ± 0.28 and ˃100, respectively (Lall et al. 2015). Essential oils extracted from leaves of fennel show the cytotoxicity to V79 (IC50 448.00 ± 19.52), B16F10 (IC50 112.78 ± 13.74) and MO59J (IC50 406.00 ± 1.57) cell lines. In the same study, it was shown that the essential oil of fennel was not effective to HT29, MCF-7, HeLa, HepG2, U343 and U251 cell lines (de Oliveira et al. 2015). 50% Ethanolic extract of fennel seeds was effective against the skin cancer. It decreased the production of ROS and LDH, and enhanced the production

of Nrf and GSH in UV irradiation normal human dermal fibroblasts (Sun et al. 2016). 50 μg/mL of 80% methanolic extract of fennel seeds has shown the best inhibitory effect on mouse breast cancer 4 T1 cell line (Mansourabadi et al. 2015). 96% of ethanolic extract of fennel fruit showed toxicity to MCF-7 cells with the 69.41 mg/mL IC50 (Agustini et al. 2015). Commercially available essential oil of fennel (from city Tulkarm, Palestine) showed apoptotic activity on HT29–19(A) non-muco-secreting and HT29-muco-secreting (MS) cell lines with the IC50 of ~77 μL/mL and ~80 μL/mL, respectively (Al-Tamimi et al. 2016). In a study conducted by Smail Aazza et al. on the anti-proliferative activity of different Moroccan commercial essential oils, THP-1 cells show insignificant effect with fennel essential oils (Aazzaa et al. 2014). The proliferation of AGS cell line of stomach cancer was inhibited by commercially available essential oil of fennel in Iran. The concentration of inhibition of growth of 50% is 25 μg/mL (Ghasemi 2015). With the IC50 values of 700 ± 28 μg/mL and 500 ± 17 μg/mL, the 100% methanolic extract of aerial part of fennel plant showed the anti-proliferative activity on L929aA and MCF-7, respectively. The same extract doesn't show cytotoxicity to MDA-MB231 cell line (Kaileh et al. 2007). Anethole induced apoptosis in MCF-7 and MDA-MB-231 cell lines in ER-independent manner. The study demonstrated the activation of caspase 9 and PARP1/2 cleavage with the increased expression of c-FLIP(s) and p53. There was a suppression in NF-κB in both the cell lines treated with anethole (Chen and DeGraffenried 2012).

Antitumour Activity (In Vivo) of Fennel

UV ray is one of the causes of the skin cancer and hence a study conducted by Zhengwang Sun et al. showed the UV protective effect of fennel on hairless mice. Production of matrix metalloproteinases induced by UV irradiation was inhibited by fennel by inhibiting MAPK signalling pathway and activation of Nrf2 pathway (Sun et al. 2016). Methanolic extract of fennel seed exhibited an antitumour effect in a mouse model of Ehrlich ascites carcinoma tempering lipid peroxidation and enhancing the antioxidants. Fennel extract was cytoprotective by regulating the MDA levels, GSH and catalase activity, against gamma irradiation (Mohamad et al. 2011). B. Singh and R.K. Kale observed the chemopreventive effect of fennel seed for DMBA-induced skin cancer and B(a)P-induced forestomach papilloma genesis in Swiss albino mice. There was a considerable increase in the level of glutathione, glyoxalase I and antioxidant enzyme activity. The peroxidative damage level and lactate dehydrogenase activity were reduced in the treated mice (Singh and Kale 2008).

In one of the studies, a Thai herbal formulation by name Pra-Sa Prao-Yhai with fennel seed as one of a constituent was reported with anticancer activities against cholangiocarcinoma nude mouse xenograft model (Plengsuriyakarn et al. 2012). A study on rats projecting fennel as a chemoprotective against a carcinogen trichloroacetic acid (TCA) concluded that fennel prevented oxidative stress, hence providing evidence of fennel as a chemopreventive and chemoprotective agent (Celik and Isik 2008).

In murine sarcoma-180 transplantable tumour model, combination therapy of cyclophosphamide-anethole was exhibited antitumour activity more than that of anethole alone. But, pretreatment of anethole showed a protective effect on the liver, bone marrow and other organs from the toxicity of cyclophosphamide (Jana et al. 2015).

Antimetastatic Activity

The antimetastatic activity of anethole was elucidated in DU145 cell line. The study suggests that the antimetastatic activity was via regulation of crosstalk between epithelial to mesenchymal transition molecules and matrix metallopeptidases-9 (Ha et al. 2014).

Clinical Trials of Irritable Bowel Syndrome (IBS) and Fennel

Among gastrointestinal disorders, IBS is a frequently diagnosed, one of the most common problems of many throughout the world. Fennel is used for this disorder since a long time. Recent clinical studies show the marvellous effect of fennel for IBS. In a study of 121 patients suffering from IBS, curcumin and fennel essential oil (CU-FEO) capsules were given for 30 days. Symptoms of IBS were prominently reduced with CU-FEO (Portincasa et al. 2016). In another randomised controlled trial, 20 patients with chronic constipation receiving the fennel tea along with other plant products concluded that this tea has laxative efficacy without any adverse effect (Picon et al. 2010).

Anti-diabetes Effect of Fennel

In alloxan-induced diabetic rats, *Foeniculum vulgare* showed a decrease in fasting blood glucose, superoxide dismutase (SOD) and malondialdehyde (MDA) level. A significant increase in the levels of insulin, glutathione-S-transferase (GST), hepatic reduced glutathione (GSH) and catalase is observed (Zaahkouk et al. 2016).

In glucose-loaded mice model methanolic extract of fennel significantly reduced the blood glucose level (Monalisa and Rahmatullah 2015). In vitro evaluation of fennel's phenolic compound was done for the study of antidiabetic effect. It was concluded that the phenolic component from methanolic extract was very effective for diabetes as it inhibited α-amylase and α-glucosidase (Abu-zaiton et al. 2015). In streptozotocin-induced diabetic rats, administration of essential oils at a concentration of 30 mg/kg body weight corrected the hyperglycaemic condition and the activity of serum glutathione peroxidase was also improved. Essential oil of fennel showed positive effects on kidney and pancreas in the pathological studies (El-Soud et al. 2011). In a similar study with the aqueous extract of fennel seeds, comparable

results showed the reduction of hyperglycemic effect in rats (Anitha et al. 2014). Methanolic extract of the whole plant of fennel was also anti-hyperglycemic to diabetic rats. Elevated levels of various enzymes associated with the diabetic were decreased with the administration of the fennel plant extract (Mhaidat et al. 2014).

Hypotensive Effect of Fennel

The water extract of fennel plant was hypotensive when investigated in hypertensive rats. It decreased the systolic blood pressure in hypertensive rats by increasing the excretion of water, sodium and potassium (El Bardai et al. 2001).

Eye Diseases and Fennel

An extensive study conducted on the various plants bearing ophthalmic benefits in Navarra (Spain) has identified fennel as potential phyto-remedy for ophthalmological problems (Calvo and Cavero 2016). Trans-anethole active component of essential of fennel was shown to have an anti-cataract effect. In an in vitro study of cataract, the chicken eye lens was treated with 55 mM glucose to induce cataract. Trans-anethole was effective in reducing cataract by increasing the solubilising lens protein. Besides this, there was a reduced glutathione, SOD and catalase activity. There was also reduction of aldose reductase in the lens treated with anethole. Thus, anethole can be a protective agent of cataract (Dongare et al. 2012).

Water-loaded and steroid-induced glaucoma rabbit model was used to evaluate the oculo-hypotensive activity of fennel. Aqueous extract of fennel showed significant oculo-hypotensive effect (Agarwal et al. 2008).

Osteoporosis Prevention by Fennel

The new bone tissue is produced by osteoblast and the old bone tissue's resorption is done by osteoclasts. The cause of the most adult skeletal disease including osteoporosis is the imbalance in the bone remodelling by osteoblast and osteoclasts. One of the therapeutic approaches to osteoporosis is to inhibit the differentiation of osteoclasts and prevention of bone resorption.

In a study on cultured bone marrow, the aqueous extract of fennel inhibited the osteoclast differentiation and bone resorption. Furthermore, oral administration of fennel to ovariectomy-induced bone loss patients for six weeks has a preventive effect on femoral bone mineral density, bone mineral contact and decreased bone turnover markers. Overall, fennel has a preventive role in postmenopausal osteoporosis (Kim et al. 2012).

Anti-obesity Effect of Fennel

In Korea, a placebo-controlled, single-blinded, randomised study was conducted on overweight women to examine the effect of fennel tea on subjective appetite. Consumption of fennel tea increased the feeling of fullness, decreased hunger and lessened prospective food consumption. Fennel tea might help in appetite control and could reduce the further food consumption in overweight women (Bae et al. 2015)

Hypolipidaemic and Anti-atherogenic Effect of Fennel

Administration of methanolic extract to C57B1/6 mice substantially decreased the plasma lipid levels along with the decrease in the levels of total cholesterol, triglycerides, LDL cholesterol and apolipoproteins. Levels of HDL cholesterol and apolipoprotein were elevated. Histopathology suggested the decrease in the deposition of fat in the liver. The flow of blood in the coronary arteries was facilitated by fennel extract, as it prevented the deposition of lipids (Oulmouden et al. 2014).

The Vasorelaxant Activity of Fennel

Isolated rat aortic ring was used to demonstrate the vasorelaxant effect of fennel. Methylene chloride fraction of the crude methanolic extract holds endothelium-dependent vasorelaxant effect which occurs through the nitric oxide (NO)-3′,5′-cyclic monophosphate pathway (Tettey et al. 2015).

Anxiolytic Activity of Fennel

Adult Swiss albino male mice receiving a various concentration of fennel's essential oil showed decent anxiolytic activity. The activity of fennel's essential oil was comparable to the anxiolytic drug diazepam (Mesfin et al. 2014).

The Anti-depression Activity of Fennel

Methanolic extract of fennel holds noteworthy anti-depression activity. In haloperidol-induced catalepsy mice, the reduction in the duration of catalepsy was observed in the group treated with fennel. Methanolic extract of fennel (500 mg/kg) was more effective than imipramine (30 mg/kg) (Singh et al. 2013).

Fennel and Alzheimer's Disease

In an in vitro study, essential oils and aqueous extracts of aerial parts of fennel plant were reported to have an inhibitory activity of acetylcholinesterase and butyrylcholinesterase. The results were much better than a cholinergic agent, rivastigmine. Fennel could be a potent therapeutic agent in the treatment of Alzheimer's disease (Arantes et al. 2017).

Memory-Enhancing Activity of Fennel

A study on amnesic rats showed the reversing effect of memory loss by fennel. Extract of fennel seeds diminishes scopolamine-induced memory deficit of above 95% over a period of above 12 days (Koppula and Kumar 2013). Another study using a methanolic extract of fennel plant was carried out in amnesic mice model. There was a paradigm shift in learning and remembering ability of scopolamine-induced memory-impaired mice when treated with fennel extract. There was a prominent upsurge in step-down latency and acetylcholinesterase inhibition (Joshi and Parle 2006). Abana, clinically proven cardioprotective herbal formulation containing fennel seed as one of its components, showed the anti-amnesic effect on mice (Parle and Vasudevan 2007).

Cosmetics and Fennel

4% Ethanolic extract of fennel seeds loaded in the emulsion showed a significant effect on skin moisture and transepidermal water loss (TEWL). This study proves fennel as an antiaging agent (Rasul et al. 2012a). Rasul et al. used the same cream for topical application by male volunteers for 3 months. A cream containing fennel extract decreased the skin melanin and sebum content. And also this formulation of fennel possesses anti-erythemic effects. In conclusion, we can say that it is a safe formulation for the treatment of acne and a skin-whitening agent (Rasul et al. 2012b).

Anti-hirsutism Effect of Fennel

A clinical trial carried out in Iran during 2009–2011 on forty-four women with idiopathic hirsutism showed the reduction of the thickness of facial hair by using 3% fennel gel for 6 months (Akha et al. 2014).

The Diuretic Action of Fennel

In a rodent study, hydroalcoholic extract of fennel's dried roots indicates the diuretic effect. The extract administrated to rat showed the increase in urine flow and sodium excretion (Beaux et al. 1997).

The Antithrombotic Activity of Fennel

The potential of anethole as an antithrombotic agent was tested in the guinea pig. Anethole inhibits arachidonic acid, collagens, and ADP- and U46619-induced aggregation. Anethole possesses antiplatelet, clot-destabilising and vasorelaxant activity (Tognolini et al. 2007).

The Bronchodilatory Activity of Fennel

Methacholine-induced contraction of tracheal chains in guinea pig was evidently relieved by essential oil and ethanolic extract of fennel. Bronchodilatory effect of the ethanolic extract was greater than that of diltiazem (Boskabady and Khatami 2003).

Premenstrual Syndrome and Fennel

As it occurs cyclically with various physical and psychological symptoms, the premenstrual syndrome can be clearly identified. In a randomised clinical trial consisting of 48 females of age 16–18, the PMS was reduced significantly in fennel-receiving group for eight weeks (Pazoki et al. 2016).

Dysmenorrhoea and Fennel

Among the gynaecological problems, primary dysmenorrhoea is the most prevalent with the rate of 90% among menstruating women. In a trial of 80 female students given soft capsules of fennel, the intensity of nausea and weakness decreased along with the reduction in the duration of the menstrual period. These findings support the use of fennel as herbal medicine to relieve dysmenorrhea and menstrual duration (Ghodsi and Asltoghiri 2014). A placebo-controlled trial conducted on sixty virgin girls with the complaint of dysmenorrhoea reveals that the fennel is an effective herb to control menstrual pain (Omidvar et al. 2012).

Vaginal Atrophy and Fennel

Among postmenopausal women, vaginal atrophy is one of the major distresses. A double-blind randomised controlled trial conducted on sixty postmenopausal women in Iran concluded that 5% fennel vaginal cream could manage the symptoms of vaginal atrophy effectively in postmenopausal women without any side effects (Yaralizadeh et al. 2016).

Galactagogic Effect of Fennel

Female albino mice were administrated with 100 mg/kg and 200 mg/kg of an ethanolic extract of fennel. The treated group were recorded with the increase in the levels of serum oestrogen, progesterone and prolactin. Prolactin promotes the production of milk (Sadeghpour et al. 2015).

Infantile Colic and Fennel

Administration of fennel extract to infants could treat infantile colic. Fennel extract is beneficial to colic infants. The effect is comparable to the gripe water (Ghazanfarpour et al. 2014).

Anti-ulcer Activity of Fennel

Aqueous extract of fennel has a protective effect against ethanol-induced gastric mucosal lesions in rats. Treatment with fennel extract significantly increased GSH, nitrite, nitrate, ascorbic acid, retinol and β-carotene levels and reduced lipid peroxidation (Birdane et al. 2007).

Hepato-renal Protective Effect of Fennel

Sodium-valproic (SVP) has the toxic effect to liver and kidney. A study on albino rats using sodium-valproic proved the hepato- and renal protective effect of fennel oil. The results show a positive effect of fennel in histopathological examination of liver and kidney besides the encouraging results of biochemical parameters (Al-Amoudi 2017).

Anthelmintic Effect of Fennel

In vitro schistosomicidal activity of essential oil of fennel is moderate against *S. mansoni* worms but has an incredible inhibitory effect on development of eggs (Wakabayashi et al. 2015).

Toxic Effect of Fennel on Pest

Fumigation of essential oil of fennel was toxic to the pest *Tetranychus turkestani* of Iran. It was also toxic to the predator of the pest *O. albidipennis* but to a less extent (Faraji et al. 2016).

Mosquito Larvicidal Effect of Fennel

Essential oil of fennel is a potential remedy to control the vector of dengue, the *Aedes aegypti*. Fennel essential oil displayed prominent larvicidal effect against *Aedes aegypti* (Rocha et al. 2015).

Interaction of Fennel with Drug

Fennel extract was potentially adequate to inhibit all main metabolic pathways regulating the oxidation of acetaminophen (paracetamol) and formation of the hepatotoxic metabolite, NAPQI (N-acetyl-p-benzoquinone imine). The enzyme CYP2E1 is inhibited by fennel with the IC50 value of 23 ± 4 (Langhammer and Nilsen 2014). 5-Methoxypsoralen, a compound isolated from fennel, inhibits CYP3A4 (human liver microsomal cytochrome) by mechanism-based inactivation. The inhibition is time dependent, requiring that NADPH and CYP3A4 activity is recovered by the competitive inhibition (Subehan et al. 2007).

Toxicity

A study on rat embryo limb bud mesenchymal cells suggests that essential oil of fennel reduced the number of stained differentiated foci because of the cell loss. Essential oil of fennel may have a toxic effect on foetal cells without the indication of teratogenicity (Ostad et al. 2004).

Conclusion

Foeniculum vulgare is one of the most commonly used and extensively studied medicinal herbs throughout the world. Multitudinous health benefits are reported by many researchers. Fennel exhibits ethnomedical treatments of chronic health problems like cancer, diabetes, irritable bowl syndrome, dysmenorrhoea and insomnia.

Due to its bioactive constituent fennel shows a diverse range of pharmacological actions which include anti-oxidation, anti-inflammation, anti-pyretic, anti-allergic, antibacterial, antifungal, antiviral, anti-colitic, anti-hirsutism, antistress, anxiolytic, diuretic, etc.

Fennel has chemopreventive, hepatoprotective, anti-ulcer, hypoglycemic, laxative, oestrogenic, hypolipidaemic, memory-enhancing and oculohypotensive properties.

The pharmacological benefits of fennel can be attributed to the phytochemical composition consisting of volatile compounds, flavonoids, phenolic compounds, etc. Minerals and vitamins present in fennel play their own role in making it a multifaceted beneficial herb.

Fennel is extensively studied but mostly in its crude form because of which it is difficult to trace the bioactive compound responsible for attributing particular properties and making the commercial pharmacological application limited. Specific compound-based studies and understanding the mechanism of action could help in bringing the product from lab bench to clinical use.

References

Aazzaa S, Lyoussi B, Megías C, Cortés-Giraldo I, Vioquec J, Figueiredod AC, Miguel MG (2014) Proliferative activities of moroccan commercial essential oils. Nat Prod Commun 9(4):587–594

Abdallah EM (2016) Medicinal plants with antibacterial properties against Helicobacter Pylori: a brief review. iMedPub J 1:13

Abdel-Wahhab KG, Fawzi H, Mannaa FA (2016) Paraoxonase-1 (PON1) inhibition by tienilic acid produces hepatic injury: antioxidant protection by fennel extract and whey protein concentrate. Pathophysiology 23(1):19–25. https://doi.org/10.1016/j.pathophys.2015.10.002

Abu-zaiton A, Alu M, Ali WM (2015) Evaluating the effect of *Foeniculum vulgare* extract on enzymes related with blood pressure and diabetes (in vitro study). Int J Chem Engg Biol Sci 2(2):77–80

Agarwal R et al (2008) Oculohypotensive effects of *Foeniculum vulgare* in experimental models of glaucoma. Indian J Physiol Pharmacol 52(1):77–83

Agustini K et al (2015) Cytotoxic and apoptotic activity on Mcf7 Cell from ethanolic extract of Trigonella Foenum-Graecum L. Aglaia. Indonesian Journal of Cancer Chemoprevention 6(3):78–83

Akha O et al (2014) The effect of fennel (*Foeniculum vulgare*) gel 3% in decreasing hair thickness in idiopathic mild to moderate hirsutism, a randomized placebo controlled clinical trial. Caspian J Intern Med 5(1):26–29

Al Akeel R et al (2014) Evaluation of antibacterial activity of crude protein extracts from seeds of six different medical plants against standard bacterial strains. Saudi J Biol Sci 21(2):147–151. https://doi.org/10.1016/j.sjbs.2013.09.003

Al-Amoudi WM (2017) Protective effects of fennel oil extract against sodium valproate-induced hepatorenal damage in albino rats. Saudi J Biol Sci 24(4):915–924

Al-Tamimi A, Mohammad BR, Abu-Reidah IM (2016) Chemical composition, cytotoxic, apoptotic and antioxidant activities of main commercial essential oils in palestine: a comparative study. Medicines 3(4):27 http://www.mdpi.com/2305-6320/3/4/27

Angelov G (2016) Extraction of fennel (*Foeniculum vulgare*) seeds: process optimization and antioxidant capacity of the extracts. Chem Biochem Eng Q 30(2):245–253 http://silverstripe.fkit.hr/cabeq/assets/Uploads/10-2-16.pdf

Anitha T et al (2014) Antidiabetic activity of the aqueous extracts of *Foeniculum vulgare* on streptozotocin-induced diabetic rats. Int J Adv Pharm Biol Chem 3(2):487–494

Arantes S et al (2017) Antioxidant activity and cholinesterase inhibition studies of four flavouring herbs from alentejo. Nat Prod Res 6419(January):1–5. https://doi.org/10.1080/14786419.2017.1278598

Badgujar SB, Patel VV, Bandivdekar AH (2014) *Foeniculum vulgare* mill: a review of its botany, phytochemistry, pharmacology, contemporary application, and toxicology. Biomed Res Int 2014:32

Bae JY, Kim JE, Choue R, Lim H (2015) Fennel (*Foeniculum vulgare*) and Fenugreek (Trigonella Foenum-Graecum) tea drinking suppresses subjective short-term appetite in overweight women. Clin Nutr Res 4(3):168–174 http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4525133&tool=pmcentrez&rendertype=abstract

Bahmani K, Izadi Darbandi A, Faleh Alfekaiki D, Sticklen M (2016) Phytochemical diversity of fennel landraces from various growth types and origins. Agron Res 14(5):1530–1547

Barros L, Heleno SA, Carvalho AM, Ferreira ICFR (2009) Systematic evaluation of the antioxidant potential of different parts of *Foeniculum vulgare* mill from Portugal. Food Chem Toxicol 47(10):2458–2464. https://doi.org/10.1016/j.fct.2009.07.003

Barros L, Carvalho AM, Ferreira ICFR (2010) The nutritional composition of fennel (*Foeniculum vulgare*): shoots, leaves, stems and inflorescences. LWT—Food Sci Technol 43(5):814–818. https://doi.org/10.1016/j.lwt.2010.01.010

Beaux D, Fleurentin J, Mortier F (1997) Diuretic action of hydroalcohol extracts of *Foeniculum vulgare* Var Dulce (D.C.) roots in rats. Phytother Res 11(4):320–322

Berrington D, Lall N (2012) Anticancer activity of certain herbs and spices on the cervical epithelial carcinoma (HeLa) cell line. Evid Based Complement Alternat Med 2012:11

Birdane FM et al (2007) Beneficial effects of *Foeniculum vulgare* on ethanol-induced acute gastric mucosal injury in rats. World J Gastroenterol 13(4):607–611 http://www.wjgnet.com/1007-9327/mcsy.asp

Bogucka-Kocka A, Smolarz HD, Kocki J (2008) Apoptotic activities of ethanol extracts from some Apiaceae on human Leukaemia cell lines. Fitoterapia 79(7–8):487–497 https://doi.org/10.1016/j.fitote.2008.07.002

Boskabady MH, Khatami A (2003) Relaxant effect of *Foeniculum vulgare* on isolated guinea pig tracheal chains. Pharm Biol 41(3):211–215

Calvo MI, Cavero RY (2016) Medicinal plants used for ophthalmological problems in Navarra (Spain). J Ethnopharmacol 190:212–218. https://doi.org/10.1016/j.jep.2016.06.002

Celik I, Isik I (2008) Determination of chemopreventive role of *Foeniculum vulgare* and Salvia Officinalis infusion on Trichloroacetic acid-induced increased serum marker enzymes lipid peroxidation and antioxidative defense systems in rats. Nat Prod Res 22(1):66–75 http://www.ncbi.nlm.nih.gov/pubmed/17999340

Cetin B et al (2010) Antimicrobial activities of essential oil and hexane extract of florence fennel [*Foeniculum vulgare* Var. Azoricum (Mill.) Thell.] against foodborne microorganisms. J Med Food 13(1):196–204 http://www.ncbi.nlm.nih.gov/pubmed/20136455

Chang YS, Woo ER (2003) Korean medicinal plants inhibiting to human immunodeficiency virus type 1 (HIV-1) Fusion. Phytother Res 17:426–429

Chatterjee S et al (2016) In vitro inhibition of cholera toxin production in vibrio cholerae by methanol extract of sweet fennel seeds and its components. Jpn J Infect Dis 69(5):384–389 https://www.jstage.jst.go.jp/article/yoken/69/5/69_JJID.2015.421/_article

Chen C-y (2014) Review on the pharmacological activities of anethole. 5(4):289–292
Chen CH, DeGraffenried LA (2012) Anethole suppressed cell survival and induced apoptosis in human breast cancer cells independent of estrogen receptor status. Phytomedicine 19(8–9):763–767 https://doi.org/10.1016/j.phymed.2012.02.017
Choi EM, Hwang JK (2004) Anti-inflammatory, analgesic and antioxidant activities of the fruit of *Foeniculum vulgare*. Fitoterapia 75(6):557–565
Cioanca O et al (2015) Essential oils from Apiaceae as valuable resources in neurological disorders: Foeniculi vulgare aetheroleum. Ind Crop Prod 88:51–57. https://doi.org/10.1016/j.indcrop.2016.02.064
Diao W-R, Hu Q-P, Zhang H, Jian-Guo X (2014) Chemical composition, antibacterial activity and mechanism of action of essential oil from seeds of fennel (*Foeniculum vulgare* mill.). Food Control 35(1):109–116 http://www.sciencedirect.com/science/article/pii/S0956713513003393
Dongare V, Kulkarni C, Kondawar M, Magdum C (2012) Inhibition of aldose reductase and anticataract action of trans-anethole isolated from *Foeniculum vulgare* mill. fruits. Food Chem 132(1):385–390. https://doi.org/10.1016/j.foodchem.2011.11.005
El Bardai S et al (2001) Pharmacological evidence of hypotensive activity of Marrubium vulgare and *Foeniculum vulgare* in spontaneously hypertensive rat. Clin Exp Hypertens 23(4):329–343
El-Soud NA et al (2011) Antidiabetic activities of *Foeniculum vulgare* mill. essential oil in streptozotocin-induced diabetic rats. Maced J Med Sci 4(2):139–146
Esquivel-Ferriño PC et al (2012) Antimycobacterial activity of constituents from *Foeniculum vulgare* Var. Dulce Grown in Mexico. Molecules 17(7):8471–8482
Faraji N, Seraj AA, Yarahmadi F, Rajabpour A (2016) Contact and fumigant toxicity of *Foeniculum vulgare* and citrus limon essential oils against Tetranychus Turkestani and its predator Orius Albidipennis. J Crop Prot 5(2):283–292
Ghasemi M (2015) Investigation of compositions and effect of herbal essential oils local Silybum Marianum, *Foeniculum vulgare* and Glycyrrhiza Glabra on cell line of stomach cancer by MTT assays in Ardabil, Iran. J Minim Invasive Gynecol 22(6): S166.
Ghazanfarpour M et al (2014) Most common herbal medicines in the treatment of Iranian children: a systematic review most common herbal medicines in the treatment of Iranian children: a systematic review. Int J Pediatr 2:421–425
Ghodsi Z, Asltoghiri M (2014) The effect of fennel on pain quality, symptoms, and menstrual duration in primary dysmenorrhea. J Pediatr Adolesc Gynecol 27(5):283–286. https://doi.org/10.1016/j.jpag.2013.12.003
Goswami N, Chatterjee S (2014) Assessment of free radical scavenging potential and oxidative DNA damage preventive activity of Trachyspermum Ammi L. (Carom) and *Foeniculum vulgare* mill. (Fennel) seed extracts. Biomed Res Int 2014:8
Ha B et al (2014) Regulation of crosstalk between epithelial to mesenchymal transition molecules and MMP-9 mediates the antimetastatic activity of Anethole in DU145 prostate cancer cells. J Nat Prod 77(1):63–69
He W, Huang B (2011) A review of chemistry and bioactivities of a medicinal spice: *Foeniculum vulgare*. J Med Plant Res 5(16):3595–3600
Jana S, Patra K, Mukherjee G (2015) RSC advances antitumor potential of anethole singly and in combination with cyclophosphamide in murine sarcoma-180 transplantable tumor model. RSC Adv 5:56549–56559. https://doi.org/10.1039/C5RA07230A
Joshi H, Parle M (2006) Short communication cholinergic basis of memory-strengthening effect of group. Indian J Pharm Sci 9(3):413–417
Kaileh M et al (2007) Screening of indigenous palestinian medicinal plants for potential anti-inflammatory and cytotoxic activity. J Ethnopharmacol 113(3):510–516
Kaur GJ, Arora DS (2009) Antibacterial and phytochemical screening of Anethum Graveolens Linn., *Foeniculum vulgare* mill. and Trachyspermum Ammi Linn. Indian J Nat Prod Resour 8(6):611
Khalid S et al (2015) Antifungal potential of the seed and leaf *Foeniculum vulgare* mill essential oil in liquid and vapor phase against phytopathogenic fungi. J Appl Pharm Sci 5(11):50–54

Kim TH, Kim HJ, Lee SH, Kim SY (2012) Potent Inhibitory effect of *Foeniculum vulgare* miller extract on osteoclast differentiation and ovariectomy-induced bone loss. Int J Mol Med 29(6):1053–1059

Kontogiorgis C et al (2016) Antioxidant protection: the contribution of proper preparation of Fennel (*Foeniculum vulgare* mill.) beverage. Ind Crop Prod 79:57–62

Koppula S, Kumar H (2013) *Foeniculum vulgare* mill (Umbelliferae) Attenuates stress and improves memory in wister rats. Trop J Pharm Res 12(4):553–558

Kumar MD et al (2014) Phytochemical Investigation and evaluation of antimicrobial and antitubercular activity of Kunstleria Keralensis. World J Pharm Pharm Sc 4(2):465–479

Lall N et al (2015) Natural product research: formerly natural product letters cytotoxicity of syringin and 4- methoxycinnamyl alcohol isolated from *Foeniculum vulgare* on selected human cell lines. Nat Prod Res 29:37–41

Langhammer AJ, Nilsen OG (2014) Fennel and raspberry leaf as possible inhibitors of acetaminophen oxidation. Phytother Res 28(10):1573–1576

Lee HS, Kang P, Kim KY, Seol GH (2015) *Foeniculum vulgare* mill. protects against lipopolysaccharide-induced acute lung injury in mice through ERK-dependent NF-κB activation. Korean J Physiol Pharmacol 19(2):183–189 http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4342739&tool=pmcentrez&rendertype=abstract

Lim, T. K. 2013. Edible medicinal and non-medicinal plants. 5: 36–59. http://link.springer.com/10.1007/978-94-007-5628-1

Mansourabadi AH et al (2015) Effects of fennel, asafetida and ginseng ethanolic extracts on growth and proliferation of mouse breast cancer 4T1 cell lines. Adv Herbal Med 1(2):34–39

Maurya S et al (2005) Antiviral activity of essential oils and acetone extracts of medicinal plants against papaya ring spot virus. J Essent Oil Bear Plants 8(3):233–238 http://www.tandfonline.com/doi/abs/10.1080/0972060X.2005.10643452

Mesfin M, Asres K, Shibeshi W (2014) Evaluation of anxiolytic activity of the essential oil of the aerial part of *Foeniculum vulgare* miller in mice. BMC Complement Altern Med 14:310 http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4156641&tool=pmcentrez&rendertype=abstract

Mhaidat NM et al (2014) Anti-hyperglycemic properties of *Foeniculum vulgare* in streptozotocin induced diabetes in rats. Int J Pharmacol 11(1):72–75

Mohamad RH et al (2011) Antioxidant and anticarcinogenic effects of methanolic extract and volatile oil of fennel seeds (*Foeniculum vulgare*). J Med Food 14(9):986–1001 http://www.liebertonline.com/doi/abs/10.1089/jmf.2008.0255

Monalisa MN, Rahmatullah M (2015) Antihyperglycemic, analgesic activity, and acute toxicity studies with methanol extract of *Foeniculum vulgare* seeds. World J Pharm Pharm Sci 4(9):198–206

de Oliveira PF et al (2015) Cytotoxicity screening of essential oils in cancer cell lines. Braz J Pharmacogn 25(2):183–188. https://doi.org/10.1016/j.bjp.2015.02.009

Omidvar S, Esmailzadeh S, Baradaran M, Basirat Z (2012) 11-effect of fennel on pain intensity in dysmenorrhoea: a placebo-controlled trial. Ayu 33(2):311–313 http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3611645&tool=pmcentrez&rendertype=abstract

Orhan E, Ilkay BÖ, Kartal M, Kan Y (2012) Antimicrobial and antiviral effects of essential oils from selected Umbelliferae and Labiatae plants and individual essential oil components. Turk J Biol 36(3):239–246

Ostad SN, Khakinegad B, Sabzevari O (2004) Evaluation of the teratogenicity of fennel essential oil (FEO) on the rat embryo limb buds culture. Toxicol In Vitro 18(5):623–627

Oulmouden F et al (2014) Hypolipidemic and anti-atherogenic effect of methanol extract of Fennel (*Foeniculum vulgare*) in hypercholesterolemic mice. Int J Sci Knowledge 3(1):42–52

Özbek H (2005) The anti-inflammatory activity of the *Foeniculum vulgare* L. essential oil and investigation of its median lethal dose in rats and mice. IJP—Int J Pharmacol 1(4):329–331 http://ansijournals.com/3/detail.php?id=1&jid=ijp&theme=3&issueno=159&articleno=55029

Parle M, Vasudevan M (2007) Memory enhancing activity of Abana®: an Indian ayurvedic poly-herbal formulation. J Health Sci 53(1):43–52 http://joi.jlc.jst.go.jp/JST.JSTAGE/jhs/53.43?from=CrossRef

Pazoki H, Bolouri G, Farokhi F, Azerbayjani MA (2016) Comparing the effects of aerobic exercise and *Foeniculum vulgare* on pre-menstrual syndrome. Middle East Fertil Soc J 21(1):61–64. https://doi.org/10.1016/j.mefs.2015.08.002

Picon PD et al (2010) Randomized clinical trial of a phytotherapic compound containing Pimpinella Anisum, *Foeniculum vulgare*, Sambucus nigra, and Cassia augustifolia for chronic constipation. BMC Complement Altern Med 10:17 http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2874511&tool=pmcentrez&rendertype=abstract

Plengsuriyakarn T et al (2012) Anticancer activities against Cholangiocarcinoma, toxicity and pharmacological activities of Thai medicinal plants in animal models. BMC Complement Altern Med 12(1):23 http://www.scopus.com/inward/record.url?eid=2-s2.0-84858844417&partnerID=tZOtx3y1

Portincasa P et al (2016) Curcumin and fennel essential oil improve symptoms and quality of life in patients with irritable bowel syndrome. JGLD 25(2):151–157 http://www.ncbi.nlm.nih.gov/pubmed/27308645

Qiu J et al (2012) Chemical composition of fennel essential oil and its impact on Staphylococcus aureus exotoxin production. World J Microbiol Biotechnol 28(4):1399–1405

Rasul A et al (2012a) Formulation development of a cream containing fennel extract: in vivo evaluation for anti-aging effects. Pharmazie 67(1):54–58

Rasul A et al (2012b) Sebumetric and mexametric evaluation of a fennel based cream. Sci Asia 38(3):262–267

Rocha, Diara Kady et al (2015) Larvicidal activity against Aedes Aegypti of *Foeniculum vulgare* essential oils from Portugal and Cape Verde. Nat Prod Commun 10(4): 677–682.

Sadeghpour N et al (2015) Study of *Foeniculum vulgare* (fennel) seed extract effects on serum level of estrogen, progesterone and prolactin in mouse. Crescent J Med Biol Sci 2(1):23–27

Salami M, Rahimmalek M, Ehtemam MH (2016) Inhibitory effect of different fennel (*Foeniculum vulgare*) samples and their phenolic compounds on formation of advanced glycation products and comparison of antimicrobial and antioxidant activities. Food Chem 213:196–205. https://doi.org/10.1016/j.foodchem.2016.06.070

Singh B, Kale RK (2008) Chemomodulatory action of *Foeniculum vulgare* (fennel) on skin and forestomach papillomagenesis, enzymes associated with xenobiotic metabolism and antioxidant status in murine model system. Food Chem Toxicol 46(12):3842–3850. https://doi.org/10.1016/j.fct.2008.10.008

Singh JN, Sunil K, Rana AC (2013) Antidepressant activity of methanolic extract of *Foeniculum vulgare* (Fennel) fruits in experimental animal models. J Appl Pharm Sci 3(9):65–70

Subehan, Zaidi SF, Kadota S, Tezuka Y (2007) Inhibition on human liver cytochrome P450 3A4 by constituents of fennel (*Foeniculum vulgare*): identification and characterization of a mechanism-based inactivator. J Agric Food Chem 55(25):10162–10167

Sun Z et al (2016) Dietary *Foeniculum vulgare* mill extract attenuated UVB irradiation-induced skin photoaging by activating of Nrf2 and inhibiting MAPK pathways. Phytomedicine 23(12):1273–1284. https://doi.org/10.1016/j.phymed.2016.06.008

Tettey CO, Yang I, Ocloo A, Shin HM (2015) Vasorelaxant and anti-inflammatory activities of the methylene chloride fraction of *Foeniculum vulgare* fruit extract. J Food Biochem 39:1–9

Tharanath V, Peddanna K, Kotaiah Y, Venkataramana D (2013) Flavonoids isolated from *Foeniculum vulgare* (Fennel) have virostatic efficiency against bluetongue virus. Int J Pharm Sci Rev Res 23(1):237–242

Tognolini M et al (2007) Protective effect of *Foeniculum vulgare* essential oil and anethole in an experimental model of thrombosis. Pharmacol Res 56:254–260

USDA. 2016. National nutrient database for standard reference release 28 Slightly Revised May, 2016 Full Report: 1–5

Wakabayashi KAL et al (2015) Anthelmintic effects of the essential oil of fennel (*Foeniculum vulgare* mill., Apiaceae) against Schistosoma Mansoni. Chem Biodivers 12(7):1105–1114

Yang IJ, Lee DU, Shin HM (2015) Anti-inflammatory and antioxidant effects of coumarins isolated from *Foeniculum vulgare* in lipopolysaccharide-stimulated macrophages and 12-O-tetradecanoylphorbol-13-acetate-stimulated mice. Immunopharmacol Immunotoxicol 37(3):308–317 http://www.ncbi.nlm.nih.gov/pubmed/25990850

Yaralizadeh M et al (2016) Effect of *Foeniculum vulgare* (Fennel) vaginal cream on vaginal atrophy in postmenopausal women: a double-blind randomized placebo-controlled trial. Maturitas 84:75–80

Zaahkouk SAM (2016) Anti carcinogenic activity of methanolic extract of fennel seeds (*Foeniculum vulgare*) against breast, colon, and liver cancer cells. Int J Adv Res 3:1525–1537

Zaahkouk SAM, Ibrahim DF, Elarabi BE (2016) Antioxidants and hypoglycemic studies on Egyptian propolis and *Foeniculum vulgare* on alloxan induced diabetic rats. Int J Animal Biol 2(1):1–10

Zeng H, Chen X, Liang J (2015) In vitro antifungal activity and mechanism of essential oil from fennel (*Foeniculum vulgare* L.) on dermatophyte species. J Med Microbiol 64(1):93–103

Anti-sickling Herbs

Shweta Jain, Ankur Vaidya, Kamal Shah, Durgesh Nandini Chauhan, and Nagendra Singh Chauhan

Introduction

Millions of people worldwide suffer from sickle cell disease. About 100,000 people in the United States and several million in Africa are suffering from sickle cell disease (SCD). Many of them die before they reach adulthood. SCD is a genetic blood disorder due to the presence of an abnormal form of haemoglobin, called haemoglobin S or sickle haemoglobin. Usually β-globin gene is mutated which causes the sixth amino acid to be changed from glutamic acid to valine. These haemoglobin molecules tend to aggregate after unloading oxygen forming long, rodlike structures that force the red cells to assume a sickle shape, as in sickle cell anaemia. The sickle cells block small blood vessels and thus the organs are deprived of blood and oxygen, which leads to periodic episodes of pain and damages to the vital organs. The gene for sickle cell disorder must be inherited from both parents for the illness to occur in children. A child with only one copy of the gene may have sickle cell traits, but no symptoms of illness (Booth et al. 2010).

Instead of 120 days, the average lifespan of a red blood cell, sickle red cells have lifespan of only about 10–20 days and thus the blood is chronically short of red cells

S. Jain
Pharmacy College, Sir Madanlal Group of Institute, Etawah, Uttar Pradesh, India

A. Vaidya
Pharmacy College, Uttar Pradesh University of Medical Sciences, Saifai, Etawah, Uttar Pradesh, India

K. Shah
Institute of Pharmaceutical Research, GLA University, Mathura, Uttar Pradesh, India

D. N. Chauhan
Columbia Institute of Pharmacy, Raipur, Chhattisgarh, India

N. S. Chauhan (✉)
Drugs Testing Laboratory Avam Anusandhan Kendra, Raipur, Chhattisgarh, India

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and thus it causes anaemia. Sickle cell disorders mainly include sickle cell anaemia (SCA) (12–15%), sickle cell trait (SCT) (80–85%), sickle B thalassemia (2–3%) and sickle C, sickle D and sickle E diseases (Roseff 2009).

Pathophysiology

The first pathophysiological scheme of sickle cell disease (SCD) based on molecular mechanism was introduced in the 1960s–1970s. According to this mechanism the sickle haemoglobin (HbS) in its deoxy form polymerises and forms long fibres within the red blood cell that deform it and make it fragile. This mechanism explains the mechanistic aspects of the vaso-occlusive crises (VOCs) and also gives details of the haemolytic anaemia but it does not explain the processes that actually trigger VOCs. More recently a precise pathophysiology of sickle cell disease was introduced under the following heads:

1. Haemoglobin S polymerisation and red blood cell alterations.
2. Increased adhesion of sickle red blood cells to the endothelium.
3. All the cells in the blood vessel are implicated.
4. Sickle red blood cells are activable and activated.
5. Haemolysis alters nitric oxide metabolism and vessel biology.

Sickle haemoglobin was discovered by Linus Pauling and colleagues in 1949; the result of this mutation has the singular property of polymerising when deoxygenated. Exactly how normal tissue perfusion is interrupted by abnormal sickle cells is complex and poorly understood. Despite the genetic identity at the site of the sickle haemoglobin mutation, all patients with sickle cell anaemia are not affected equally by this disease. Secondary genetic determinants and acquired erythrocyte and vascular damage are likely to be central components of the pathophysiology of sickle cell anaemia (Panigrahi et al. 1997; Parise and Berliner 2016) (Fig. 1).

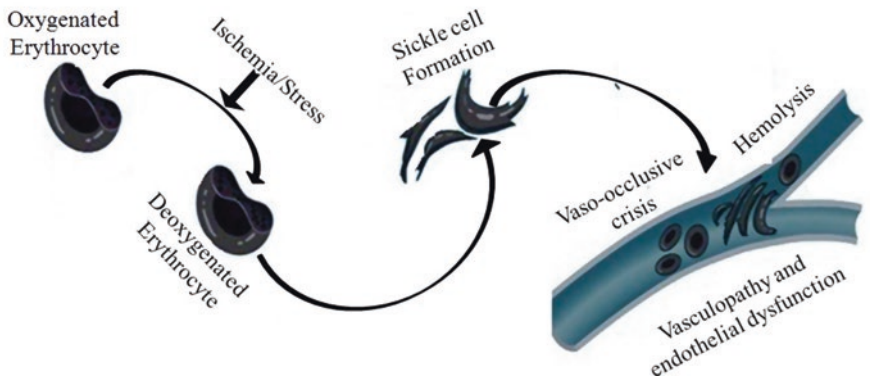


Fig. 1 Pathophysiology of sickle cell disease

Treatment

Proper execution of SCD begins with finding the correct diagnosis early in life, ideally during the newborn period. Nowadays allopathy, homeopathy and Ayurveda claim for the treatment of sickle cell disorders. All of these treatments have their traits and shortcomings. The complete cure of sickle cell anaemia is not available in modern medical science (allopathic medicine system) but it can be managed through some medications and blood transfusion at regular/irregular intervals and sometimes needs bone marrow transplantation (Sahu et al. 2012). The prime aim of the physician is to prescribe those medicines that can control the bone marrow function to restrict abnormal haemoglobin. Ayurveda is the oldest system of medicine, originated and used in Indian since. Ayurvedic treatment for sickle cell anaemia is focused on treating the main cause of the disease and trying to prevent serious complications (Dash et al. 2013). In Ayurveda too, sickle cell disease can only be managed and the causes of the crisis can be reduced. Some of the most effective Ayurvedic medicines used for treating sickle cell anaemia include drumstick (*Moringa oleifera*), tiger nut (*Cyperaceae esculentus*), guduchi (*Tinospora cordifolia*), garlic (*Allium sativum*) and green tea (*Camellia sinensis*). To manage pains and swelling in sickle cell anaemia, pigeon pea (*Cajanus cajan*), sweet orange (*Citrus sinensis*), grains of selim (*Xylopia aethiopica*) and rapeko (*Zanthoxylum macrophylla*) are used. The other herbals that are used include African white wood, bitter leaf, guinea hen weed, myrobalan, wild leadwort and Congo goober. Both natural sources and/or synthetic molecules have been reported for potential anti-sickling activity. These molecules are helpful for reducing the clinical morbidity of the patients. A number of plant extracts/isolates have been reported by various researchers possessing anti-sickling activity (Table 1). The majority of studies are based on *in vitro* red cell sickling activities and few *in vivo* studies pertaining to transgenic sickle animal model have also been reported. There is a scarcity of data on the human studies and mode of action of anti-sickling agent has not been properly understood (Ameh et al. 2012). Here we discuss the various plants used in the management of sickle cell disease.

Acacia catechu

Acacia catechu (family: Leguminosae) is also known as cutch tree, terra japonica as well as black catechu. In Hindi it is called khair and khadira in Sanskrit. This tree is indigenous in India, China, Japan, Europe, Persia and Arabia. The tree is heighted up to 9–12 m, with bipinnate leaves and flattened and glabrous fruit. The bark of the tree is greyish brown with yellow flowers. Alkaloids, phenols, flavonoids, terpens and tannins are the chief chemical components of *A. catechu*. *A. catechu* plants have numerous medicinal activities including astringent, bactericide, refrigerant, stimulant, masticator and expectorant (Sulaiman and Gopalakrishnan 2013). Li et al. (2010)

Table 1 Medicinal plants used in the management of SCD

S. No.	Medicinal plant	Phytoconstituents	Biological action other than anti-sickling activity	Part used for anti-sickling activity	Mechanism of anti-sickling activity	References
1	*Acacia catechu* (Leguminosae)	Alkaloids, phenols, flavonoids, terpenes and tannins	Astringent, bactericide, refrigerant, stimulant, masticator and expectorant	Leaf	Anti-platelet aggregatory, antioxidant and free radical scavenging	Li et al. (2010)
2	*Adansonia digitata* (Malvaceae)	Flavonoids, phytosterols, amino acids, fatty acids, vitamins and minerals	Antimicrobial, antimalarial, anti-inflammatory, asthma, antiviral and antioxidant	Bark	Boosting red blood cells and white blood cell count	Adesanya et al. (1988)
3	*Aframomum alboviolaceum* (Zingiberaceae)	Alkaloids, flavonoids, tannins, saponin, steroids, cardiac glycosides and terpenes	Antimicrobial	Rhizomes and leaves	–	Abreu and Noronha (1997)
4	*Alchornea cordifolia* (Euphorbiaceae)	Terpenoids, steroid, glycosides, flavonoids, tannins, saponins, carbohydrates and several guanidine alkaloids	Anti-inflammatory, abortifacient, amoebicide and anthelmintic	Leaf	Normalised sickle cell erythrocytes	Mpiana et al. (2007)
5	*Allium sativum* (Alliaceae)	Diallyl disulfide, flavonoids and carotenoids	Anthelmintic, antiasthmatic, anticholesterolaemic, antiseptic, antispasmodic, anticancer, diuretic, expectorant, cholagogue, diaphoretic, hypoglycaemic, stimulant, stomachic and vasodilator	Rhizome	Improves erythrocyte deformability through stabilisation of erythrocyte membranes in non-sickle RBC	Takasu et al. (2002)
6	*Aloe barbadensis* (Liliaceae)	Alkaloids, flavonoids, saponins, tannins, vitamins and nutrients	Anti-burn, psoriasis, skin infections, eczema, arthritis and antiulcer	Leaf	Inhibition of sickle cell polymerisation and the improvement of the Fe^{2+}/Fe^{3+} ratio of HbSS	Nwaoguikpe et al. (2010)

7	*Annona senegalensis* (Annonaceae)	Essential oils, flavonoid, saponins, alkaloids, glycoside steroids and volatile oils	Yellow fever, tuberculosis, small pox, snakebite, hernia, gastritis, male sexual impotence and erectile dysfunction	Leaf, stem bark and root	Reverses the shape of the erythrocytes and makes normal	Mpiana et al. (2012)
8	*Bridelia ferruginea* Benth (Euphorbiaceae)	Polyphenols, steroids, saponins, tannins, terpenoids and alkaloids	Antimalarial, antimicrobial, analgesic, anti-inflammation, antispasmodic and antidiabetic	Leaf	Prolongs red cell life and produces anti-sickling activity	Folashade and Omoregie (2013)
9	*Cajanus cajan* (Fabaceae)	Proteins and amino acids like methionine, lysine and tryptophan, phenylalanine tannins, globulins and saponins	Antidiabetic, sores, skin irritations, hepatitis, measles, jaundice, dysentery	Seeds	Reversal of presickled erythrocyte (HbSS) cells	Ogoda et al. (2002)
10	*Camellia sinensis* (Theaceae)	Caffeine, epicatechin, epicatechin-3-gallate, epigallocatechin, epigallocatechin-3-gallate	Antioxidant, anti-inflammatory, anticarcinogenic, thermogenic, probiotic and antimicrobial	Leaf	Inhibits the formation of dense cells	Ohnishi et al. (2000)
11	*Carica papaya* or papaya (Caricaceae)	Glycine, phenylalanine and tryptophan	Jaundice and management of sickle cell anaemia	Fruit pulp	Prevents dense cell formation and prolongs red cell life	Mojisola et al. (2008)
12	*Chenopodium ambrosioides* (Amaranthaceae)	α-Terpinene, *p*-cymene, ascaridole and *p*-mentha-1,8-diene, saponins, tannins and alkaloids	Analgesic, antiasthmatic, antifungal, carminative, stomachic and vermifuge sickle cell disease	Leaf	Lysis of sickled cell erythrocytes	Adejumo et al. (2011a, b)
13	*Cissus populnea* (Ampelidaceae)	Alkaloids, carbohydrate, flavonoids, saponins, tannins, anthraquinone derivatives (physcion and chrysophanol), steroidal glycosides and cardiac glycosides	Sore breast, indigestion, venereal diseases, intestinal parasites, oedema, eye problems, cathartic, aphrodisiac and antidote to arrow wounds	Root	Restabilise sickled HbSS red blood cells	Moody et al. (2003)

(continued)

Table 1 (continued)

S. No.	Medicinal plant	Phytoconstituents	Biological action other than anti-sickling activity	Part used for anti-sickling activity	Mechanism of anti-sickling activity	References
14	*Citrus sinensis* or *Citrus aurantium* (Rutaceae)	Vitamin C, carotenoid, acids and volatile oils	Appetizer, blood purifier, carminative and tonic	Juice, fruit	Reduces the painful crises associated with sickle cell disease. Sustained reduction in the number of sickle cells	Iweala et al. (2010)
15	*Cyperaceae esculentus* (Cyperaceae)	Amino acids, proteins, saponins, tannins, alkaloids, sterols, lipids, carbohydrates, resins, cyanogenic glycosides	Flatulence, indigestion, colic, diarrhoea, dysentery, debility and excessive thirst	Seed	Inhibition of haemoglobin-S (HbS) gelation	Monago and Uwakwe (2008)
16	*Enantia chlorantha* (Annonaceae)	Alkaloids, flavonoids, glycosides, phenols, saponins, steroid/ triterpenes and tannins	Antimicrobial, antiviral, antimalarial and antipyretic	Leaf	Reverting already sickled erythrocytes to their normal morphology	Ejele et al. (2012)
17	*Entandrophragma utile (Meliaceae)*	Lactone entandrophragmin, tetranortriterpenoid called utilins, heptanortriterpenoid called entilins, methyl angolensate and an ergosterol derivative	Antimalarial, antiulcer, anti-inflammatory and analgesic	Bark	*Lysis of* sickled cell erythrocytes	Adejumo et al. (2011a, b)
18	*Garcinia kola* (Guttiferae)	Alkaloids, tannins, terpenoids, saponins, steroids and flavonoids	Coughs, throat infections, bronchitis, hepatitis, liver disorders, anti-inflammatory, antiparasitic, antimicrobial, antiviral, antioxidant, bronchodilator and purgative	Leaf, seed	Produces membrane stabilisation effect	Egunyomi et al. (2009)
19	*Hymenocardia acida (Euphorbiaceae)*	Carbohydrates, tannins, flavonoids, saponins, alkaloids, cardiac glycosides and terpene	Antimicrobial, sickle cell infection	Leaf	Reverses sickled human red blood cells (RBC)	Ibrahim et al. (2007)

20	*Ipomoea involucrata* (Convolvulaceae)	Alkaloids, phenols, terpenes and lignans	Antimicrobial, analgesic, spasmolytic, spasmogenic, hypotensive, psychotomimetic and anticancer activities	Leaf	Inhibits sickle cell polymerisation and also reduces lactate dehydrogenase activity in both HbSSM- and HbSSF-treated blood	Afolabi et al. (2012)
21	*Justicia secunda* (Acanthaceae)	Alkaloids, flavonoids, tannins, leucoanthocyanins, quinones and anthocyanins	Anaemia, cough, cold, fever, malaria, measles and whooping cough	Leaf	Both direct binding of the extract with deoxy-HbS molecules and stabilisation of the SS RBC membrane	Mpiana et al. (2010)
22	*Khaya senegalensis* (Meliaceae)	2,6-Dihydroxyfissinolide, a limonoid	Vermifuge, taenicide, depurative syphilis, jaundice, dermatoses, scorpion bite, allergies, infection of the gums, hookworm, bleeding wounds (disinfectant), laxative	Stem bark and leaf	–	Fall et al. (1999)
23	*Moringa oleifera* (Moringaceae)	Alkaloids, saponins, free anthraquinones	Antibacterial, antifungal, antioxidant, anti-inflammatory, antiulcer, antispasmodic, diuretic, anticarcinogenic and antinociceptive	Leaf, seed and flower	Reversal of sickled erythrocytes	Cáceres et al. (1992); Sulaiman et al. (2008)
24	*Parquetina nigrescens* (Asclepiadaceae)	Cardenolides, glycosides, alkaloids flavonoids, glycosides, cardiac glycosides, tannins, saponins, anthraquinones and macronutrients	Antioxidant, antianaemic	Leaf and stem	Erythrocyte membrane-stabilising effects, by the reduction in haemolysis of the HbSS cells	Imaga et al. (2010)
25	*Persea americana* (Lauraceae)	Phenols, saponins, flavonoids, alkaloid and sterols	Analgesic, anti-inflammatory, hypoglycaemic, anticonvulsant, antidiabetic and vasorelaxant	Fruit juice	Sustained reduction in the number of sickle cells in both HbAS and HbSS blood samples	Iweala et al. (2010)

(continued)

Table 1 (continued)

S. No.	Medicinal plant	Phytoconstituents	Biological action other than anti-sickling activity	Part used for anti-sickling activity	Mechanism of anti-sickling activity	References
26	*Petiveria alliacea* (Phytolaccaceae)	Benzaldehyde, benzoic acid, coumarin, isoarborinol, cinnamate, isothiocyanates, polyphenols, senfol, tannins and trithiolaniacine, cysteine sulphoxide derivatives	Antioxidant and antimicrobial, arthritis, antiallergies, analgesic and antimalarial	Root	*Lysis of* sickled cell erythrocytes	Adejumo et al. (2011a, b)
27	*Plumbago zeylanica* (Plumbaginaceae)	Anthraquinones, flavonoids, saponins, tannins	Skin diseases, infections and intestinal worms, viz. leprosy, scabies, ringworm, hookworm, dermatitis, acne, sores and ulcers	Root	–	Adejumo et al. (2011a, b)
28	*Solenostemon monostachyus* (Lamiaceae)	Flavonoids, coumarin, polyphenols and essential oil	Analgesic, antipyretic, sedative, stomachic, hypotensive and antioxidant	Leaf	Increases sickle cell polymerisation and inhibits or reduces lactate dehydrogenase activity in both HbSSM- and HbSSF-treated blood	Afolabi et al. (2012)
29	*Terminalia catappa* (Combretaceae)	Phenol, flavonoid and carotenoid	Antimicrobial, anti-inflammatory, antidiabetic, antioxidant, hepatoprotective and anticancer	Leaf	Reverses the sickling of human 'SS' erythrocytes, prolongs the clotting time of uncoagulated blood and thus is utilised in sickle cell disease	Mgbemene and Ohiri (1999)

30	*Tinospora cordifolia* (Menispermaceae)	Alkaloids, glycosides, steroids, diterpenoid, lactones, sesquiterpenoid, phenolics, aliphatic compounds and polysaccharides	Anticancer, antidiabetic, anti-periodic, antispasmodic, anti-inflammatory, anti-allergic, anti-arthritis, antiulcer and also boosts the immune system	Whole plant	–	US 20100189814 A1
31	*Uvaria chamae* (Annonaceae)	Alkaloids, cardiac glycosides, tannins and oleo-resin	Anti-inflammatory, astringent, febrifuge, galactagogue and styptic	Root	Inhibits osmotically induced haemolysis of human erythrocytes	Adejumo et al. (2010)
32	Vernonia amygdalina (Asteraceae)	Alkaloids, saponins, terpenes, steroids, coumarins, flavonoids, phenolic acids, lignans, xanthones and anthraquinone	Amoebic dysentery, gastrointestinal disorders, antimicrobial, antiparasitic and cytotoxic effects	Leaf	Decreases the number of sickle cell RBCs	Afolabi et al. (2012)
33	*Vigna subterranea* (Fabaceae)	Protein, carbohydrate, glycosides, alkaloids, saponins, reducing sugar, fats and oil and steroids	Antimicrobial and antioxidant	Seed	Increases delayed time before polymerisation of HbSS erythrocyte and reverts sickling effect	Simeone et al. (2012)
34	*Vigna unguiculata* (*Leguminosae*)	Protein, flavonoids, saponins, carbohydrates, fats and oil, resins, terpenoids, steroids, glycosides and alkaloids	Antimicrobial, antioxidant and anti-sickling	Seed	Sickling reversal effect and also increases delayed time before polymerisation of HbSS erythrocyte	Simeone et al. (2012)
35	*Xylopia aethiopica* (Annonaceae)	Amino acids such as Arg. Tyr and Asp	Cough, stomach ache, dizziness, amenorrhoea, bronchitis (when smoked and inhaled), dysentery, enema, lumbago and neuralgia, calmative, purgative, repulsive to pain, skin eruptions		Inhibits HbSS polymerisation	Uwakwe and Nwaoguikpe (2008)
36	*Zanthoxylum macrophylla* (Zanthoxylum)	Essential oil, alkaloids and saponins	Lowers blood pressure, combats cancer growths, relieves pain and combats infections and parasites, analgesic, aphrodisiac and vermifuge	Root	Stabilises the erythrocyte membranes by decreasing viscosity of the HbSS blood	Elekwa et al. (2005)

isolated twelve compounds, viz. catechin, epicatechin, quercetin, kaempferol, afzelechin, mesquitol, epiafzelechin, 4-hydroxybenzoic acid, 3,4′,7-trihydroxyl-3′,5-dimethoxyflavone, aromadendrin, ophioglonin and phenol, from *A. catechu*. 4-Hydroxybenzoic acid, kaempferol and quercetin were found to possess anti-sickling activity of *A. catechu*. The aqueous leaf extract of three *Acacia* species shows remarkable anti-sickling activity by antioxidant, anti-platelet aggregatory and free radical scavenging mechanism.

Adansonia digitata

Adansonia digitata (family: Malvaceae) is also called baobab tree. The baobab tree is the most widespread, long-lived tree which is native to the African continent. The baobab tree is a multipurpose, long-lived tree which is heighted up to 28 m. The bark is greyish brown enriched with hand-sized leaves. Phytochemical investigation reveals the presence of phytosterols, flavonoids, fatty acids, amino acids, vitamins and minerals. This plant is also rich in vitamin C and vitamin E. *A. digitata* has numerous pharmacological actions, including antimicrobial, antimalarial, antioxidant, anti-inflammatory and antiviral activities (Kaboré et al. 2011). The aqueous and methanolic bark extract of *A. digitata* shows anti-sickling activity by boosting both red and white blood cell counts (Adesanya et al. 1988).

Aframomum alboviolaceum

Aframomum alboviolaceum (family: Zingiberaceae) is also known as *amomum bitacoum*, *cardamomum latifolium* and *ceratanthera beaumetzii*. *A. alboviolaceum* is a herbaceous perennial plant which is rich in alkaloids, flavonoids, tannins, saponin, steroids, cardiac glycosides and terpenes. The active phytochemicals present in *A. alboviolaceum* are methyl (E)-14,15-epoxylabd-8(17),12-dien-16-oate, (E)-β-17-epoxy-labd-12-ene-15,16-dial and (E)-labda-8(17),12-diene-15,16-dial (Marlier et al. 1993). *A. alboviolaceum* shows antimicrobial activity. Rhizomes and leaf extract of *A. alboviolaceum* possess anti-sickling activity (Abreu and Noronha 1997).

Alchornea cordifolia

Alchornea cordifolia (family: Euphorbiaceae) is also known as Christmas bush which is widely distributed throughout tropical Africa. The plant is a widely used and important traditional medicine in Africa. It is a shrub or small tree which grows

up to 8 m height. The leaves, roots and stem bark of *A. cordifolia* contain terpenoids, steroid, glycosides, flavonoids, tannins, saponins, carbohydrates and several guanidine alkaloids (Okwu and Ukanwa 2010). Medicinally *A. cordifolia* is used as antibacterial, anti-inflammatory, abortifacient, amebicide and anthelmintic. The aqueous and ethanolic leaf extract of *A. cordifolia* shows anti-sickling activity. Aqueous extract shows higher anti-sickling activity in comparison to ethanolic one. The anti-sickling activity of *A. cordifolia* is due to presence of anthocyanidin flavonoid which normalizes sickle cell erythrocytes (normalize SS blood erythrocytes) (Mpiana et al. 2007).

Allium sativum

Allium sativum (family: Alliaceae) is a strongly aromatic bulb crop commonly known as garlic. *A. sativum* is a species in the onion genus *Allium*, which has been cultivated for thousands of years. *A. sativum* was domesticated long ago and is mentioned in ancient Greek, Indian, Egyptian and Chinese writings. It is a bulbous herb (rounded bulb composed of 15 smaller bulblets known as cloves) growing to about 60 cm tall. Usually four to twelve sword-shaped leaves are attached to an underground stem. Fresh or crushed *A. sativum* contains sulphur-containing compounds like alliin, ajoene, diallyl polysulphides, vinyldithiins, *S*-allylcysteine and enzymes, saponins and flavonoids. Garlic has been used for numerous medicinal purposes, i.e., anthelmintic, antiasthmatic, anticholesterolemic, antiseptic, antispasmodic, anticancer, diuretic, expectorant, cholagogue, diaphoretic, hypoglycaemic, stimulant, stomachic and vasodilator (Otunola et al. 2010). Aged garlic extract (AGE) possesses antioxidant activities. Based on these antioxidant activities of aged garlic extract (AGE), Takasu et al. (2002) examined the potential role of AGE in sickle cell disease. Results showed that Heinz bodies were decreased over the 4-week period in RBC. AGE also improves erythrocyte deformability via stabilization of erythrocyte membranes in non-sickle RBC. The anti-sickling activity of *A. sativum* is due to the presence of diallyl disulphide, flavonoids and carotenoids.

Aloe barbadensis

Aloe vera or *Aloe barbadensis* or secret plant originated from ancient Egypt belongs to the family Liliaceae. *A. vera* is cultivated for agricultural and medical uses across the world and is growing wild in tropical climates. *Aloe vera* contains alkaloids, flavonoids, saponins and tannins. Other compounds like vitamins and nutrients are also present. These diverse phytoconstituents exhibit remarkable medicinal properties. *A. vera* is used in the treatment of psoriasis, skin infections, eczema, severe burn, arthritis and ulcer (Zhang and Tizard 1996). *A. vera* is also reported to possess

anti-sickling activity. *A. vera* plant extracts with the preponderance of phytochemicals, amino acids, nutrients and other compounds can be very beneficial in the management of sickle cell disease. The anti-sickling effects of gel and leaf extracts of *A. vera* were directed towards the inhibition of sickle cell polymerisation and the improvement of the Fe^{2+}/Fe^{3+} ratio of sickle cell anaemia in the homozygous state (HbSS). Numerous amino acids (i.e., arginine, phenylalanine, aspartic acid, tyrosine, histidine) and others (including *m*-coumaric acid, emodin, aloin, etc.) of *A. vera* was identified to show anti-sickling activity (Nwaoguikpe et al. 2010).

Annona senegalensis

Annona senegalensis (family: Annonaceae) is also known as African custard apple, wild soursop and wild custard apple. The plant is grown in western tropical Africa from Senegal to Kenya and from South Africa to Zimbabwe. *A. senegalensis* is a multipurpose shrub which grows 2–6 m tall. All parts of the plant contain varying amounts of essential oils, flavonoid, saponins, alkaloids, glycoside steroids and volatile oils. It also contains numerous minerals such as Ca, Mg, K, Zn, Fe, Cu and Mn. Different parts of plant are used for different purposes; for example, leaves have been used in treating yellow fever, tuberculosis and small pox; stem bark has been used in snakebite and hernia treatment and root is used in conditions such as difficulty in swallowing, gastritis, snakebites, male sexual impotence and erectile dysfunction (Yisa et al. 2010). The aqueous and ethanolic leaf extract of *A. senegalensis* contains anthocyanin possessing anti-sickling activity. The anthocyanin crude extracts of *A. senegalensis* reverse the shape of the erythrocytes and become normal, indicating the anti-sickling properties of anthocyanin extracts (Mpiana et al. 2012).

Bridelia ferruginea

Bridelia ferruginea (family: Euphorbiaceae) is a gnarled shrub that is widely distributed in Africa, Australia, southern Asia and various islands of the Indian and Pacific Oceans. *B. ferruginea* is chiefly used in African folkloric medicine. The presence of phytochemicals such as polyphenols, steroids, saponins, tannins, terpenoids and alkaloids makes this plant an important herb. It is used for its antimalarial, antimicrobial, analgesic, anti-inflammatory, antispasmodic and antidiabetic activities (Fabiyi et al. 2012). The β-amyrin fraction of *B. ferruginea* leaves possesses antioxidant activity. This antioxidant activity of *B. ferruginea* prolongs red cell life and produces anti-sickling activity (Folashade and Omoregie 2013).

Cajanus cajan

The *Cajanus cajan* (family: Fabaceae) is a perennial legume more commonly known as pigeon pea. Its seeds have become a common food grain in Africa, Asia and Latin America and domestication in India since last 3500 years. *C. cajan* is rich in proteins and amino acids (i.e., lysine, methionine and tryptophan) and possesses remarkable medicinal applications. *C. cajan* is reported as analgesic in traditional Chinese medicine and explored for the treatment of diabetes, skin irritations, sores, hepatitis, measles, dysentery, jaundice and many other illnesses. *C. cajan* contains free amino acids, globulins, tannins, phenolic compounds and saponins (Akinsulie et al. 2005). Presence of free amino acids, especially phenylalanine, is responsible for anti-sickling activity of *C. cajan.* The 70% anti-sickling potency of *C. cajan* was found due to the presence of free phenylalanine in the methanol (water-soluble) extract. Results also showed that the extract has potential use in the management of painful episodes experienced by sickle cell patients. *In vitro* activity showed reversal of presickle erythrocyte (HbSS) cells using the *C. cajan* extract with an average half-life of 115.6 min (Ogoda et al. 2002).

Camellia sinensis

Camellia sinensis (family: Theaceae) is commonly known as green tea. *C. sinensis* is cultivated across the world in tropical and subtropical regions, but most commonly grown in East Asia, the Indian Subcontinent and Southeast Asia. It is a shrub or tree that can grow to a height of 30 ft. In cultivation the plant is usually clipped to a height of 2–5 ft. The shrub or tree is heavily branched with hairy, dark-green, oblong-ovate leaves cultivated and preferentially picked as young shoots. *C. sinensis* contains caffeine, epicatechin, epicatechin-3-gallate, epigallocatechin and epigallocatechin-3-gallate and demonstrates significant antimicrobial, antioxidant, anti-inflammatory, anticarcinogenic, thermogenic and probiotic properties. Sickle cells have an elevated density and possess an abnormal membrane. These “dense cells” have a tendency to adhere to platelets, neutrophils and vascular endothelial cells, and thus they could trigger vaso-occlusion and the subsequent painful crisis from which these patients suffer. Nutritional antioxidant supplements could inhibit the formation of dense cells *in vitro* (Mbata et al. 2008). Since *C. sinensis* is a rich source of nutrition supplement it is utilized in the treatment of sickle cell disease. A study showed that 0.13 mg/mL green tea extract inhibits dense cell formation by 50% patients and is thus effective in the treatment of sickle cell disease (Ohnishi et al. 2000).

Carica papaya

Carica papaya (family: Caricaceae) is a giant herbaceous plant known as papaya. It resembles a tree, but not woody. *Carica papaya* is originated in tropical areas worldwide for its large, sweet, melon-like fruits and chiefly in southern Mexico and Central America. The unripe fruit of *C. papaya* contains glycine, phenylalanine and tryptophan and it is used traditionally among the Yoruba tribe of Nigeria for treating jaundice and sickle cell anaemia (Maisarah et al. 2013). Mojisola et al. (2008) proposed anti-sickling properties of *C. papaya* fruit pulp. The anti-sickling activity of aqueous, methanolic and chloroform extract of *C. papaya* was performed using sodium metabisulphite sickled red blood cells. Results showed 55% reversal and 64% inhibitory anti-sickling activities with methanolic extract while the chloroform extract was found to be inactive. The 5-day fermentation products of *C. papaya* showed highest anti-sickling potencies of 74% reversal and 87% inhibitory activities at the optimum concentration of 2.5 mg/mL. The presence of phenylalanine, tyrosine and glycine was found to be responsible for anti-sickling activity. The presence of nutrition and antioxidant in *C. papaya* fruit pulp prevents dense cell formation and free radical-mediated oxidative cell injury and thus prolongs red cell life.

Chenopodium ambrosioides

Chenopodium ambrosioides (family: Amaranthaceae) formerly known as Mexican tea is an annual or short-lived perennial herb native to South America, Central America and southern Mexico. It grows to 1–2 m tall, and is irregularly branched, with oblong-lanceolate leaves up to 12 cm long. *C. ambrosioides* contains essential oil chiefly monoterpenes. The chemical composition of essential oil includes ascaridole, α-terpinene, *p*-cymene and *p*-mentha-1,8-diene. The plant also contains saponins, tannins and alkaloids. *C. ambrosioides* is used as an analgesic, antiasthmatic, antifungal, carminative, stomachic and vermifuge (Monzote et al. 2011). Traditionally the plant is also used in the treatment of sickle cell disease. The methanolic extracts/fractions of leaf of *C. ambrosioides* were observed to exhibit significant anti-sickling activity with lysis of sickled cell erythrocytes (Adejumo et al. 2011a, b).

Cissus populnea

Cissus populnea (family: Ampelidaceae) has been described by Burkill in the year 2000. *C. populnea* is a strong woody liane, 8–10-meter-long, 7.5-cm-in-diameter tree and distributed generally across west tropical Africa, from the coast to the Sudanian and Sahelian woodland. The stem bark has been reported to contain

alkaloids, carbohydrate, flavonoids, steroidal glycosides, cardiac glycosides, saponins, tannins and anthraquinone derivatives (physcion and chrysophanol). Ethno-medicinal uses of *C. populnea* include treatment of indigestion, sore breast, oedema, eye problems, intestinal parasites and venereal diseases. The plant is also used as aphrodisiac, cathartic and antidote to arrow wounds (Ibrahim et al. 2011). The root aqueous/methanol extract of *C. populnea* contains steroidal glycosides, anthraquinone derivatives and cardiac glycoside that shows anti-sickling activity by restabilising the sickled HbSS red blood cells. The aqueous extract possesses higher anti-sickling activity over ethanol extract (Moody et al. 2003).

Citrus sinensis

Citrus sinensis or *Citrus aurantium* (family: Rutaceae) is commonly known as the sweet orange. *C. sinensis* has been cultivated for thousands of years, and is grown in southern and East Asia. It is an evergreen tree which grows to 9 m, but occasionally reaching heights up to 15 m. Leaves are leathery and evergreen with 6.5–15 cm length and 2.5–9.5 cm width, and range from elliptical to oblong to oval. The fruits are globose to oval (6.5–9.5 cm wide) and ripen to orange or yellow. *C. sinensis* contains a wide range of active ingredients. The plant is enriching in vitamin C, carotenoid, acids and volatile oils (Hernández et al. 2016). *C. sinensis* is used as appetizer, blood purifier, carminative and tonic. Crude juice extracts of *C. sinensis* have been shown to reverse sickling disease and clinically reduce the painful crises associated with sickle cell disease. Crude juice extract of *C. sinensis* fruit, including aqueous, alcoholic, acidic and alkaline extracts, produces a sustained reduction in the number of sickle cells in both haemoglobin S carriers (HbAS) and sickle cell anaemia in the homozygous state (HbSS) blood samples (Iweala et al. 2010).

Cyperus esculentus

Cyperaceae esculentus (family: Cyperaceae) is a monocotyledonous plant, commonly known as tiger nut sedge, having 90–4000 species worldwide. It is also known as nut grass, yellow nut sedge, tiger nut sedge, chufa sedge, or earth almond. *C. esculentus* is found worldwide in warm and temperate zones, occurring in southern Europe to Ukraine, Africa, China, Hawaii, Indochina, Java, New Guinea and New South Wale. *C. esculentus* is an annual or perennial plant. It grows to 90 cm (3.0 ft) height, with solitary stems growing from a tuber. The stems are triangular in section and bear slender leaves 3–10 mm (1/8–1/2 in.) wide. The tubers are 0.3–1.9 cm (1/8–3/4 in.) in diameter with yellow, brown and black colours. In Ayurvedic medicine, *C. esculentus* is used for the treatment of flatulence, indigestion, colic, diarrhoea, debility, dysentery and excessive thirst (Nwaoguikpe 2010). *C. esculentus*

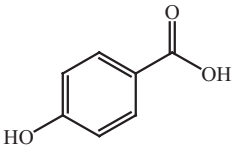
is widely consumed in southern Nigeria by healthy persons and SCD patients alike, and there are undocumented and unverified claims of health improvements in SCD persons who consumed these seeds regularly. Both methanolic and aqueous seed extracts were reported to possess anti-sickling activity. The proposed anti-sickling mechanism of *C. esculentus* was inhibition of haemoglobin-S (HbS) gelation. The methanolic extract was found to be reported as a more pronounced inhibitor of HbS over aqueous extracts. The methanolic extract reduced up to 48.21% HbS gelation compared to 82.14% of aqueous extract from 100% (Monago and Uwakwe 2008) (Fig. 2).

Enantia chlorantha

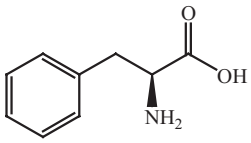
Enantia chlorantha (family: Annonaceae) is also known as African white wood. *E. chlorantha* is widely distributed along the coasts of West and Democratic Republic of Congo. This plant is also very common in the forest regions of Nigeria. It is an ornamental tree of up to 30 m high, with fluted stem and leaf displaying prominent lateral veins (up to 20 pairs) and parallel secondary nerves. The plant contains numerous phytochemicals like alkaloids, flavonoids, glycosides, phenols, saponins, steroid/triterpenes and tannins. These phytochemicals of *E. chlorantha* are responsible for numerous pharmacological actions, including antimicrobial, antiviral, antimalarial and antipyretic (Dawodu et al. 2014). The ethanolic leaf extract of *E. chlorantha* shows anti-sickling activity. The coenzyme Q10 is responsible for the anti-sickling activity of *E. chlorantha* by reverting already sickled erythrocytes to their normal morphology (Ejele et al. 2012).

Entandrophragma utile

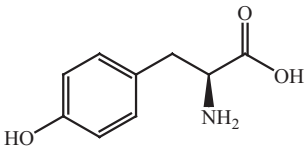
Entandrophragma utile (family: Meliaceae*), known as* sipo mahogany, *is a* deciduous tree with a regular crown comprised of a few massive branches. The plant can grow up to 55 m tall, with occasional specimens reaching 65 m and indigenous to Tropical Africa from Sierra Leone to Uganda and from south to Angola. Research reported a wide range of medically active substances in *E. utile. These* include the lactone entandrophragmin, tetranortriterpenoid called utilins, heptanortriterpenoid called entilins, methyl angolensate and an ergosterol derivative. This plant possesses numerous pharmacological activities including antimalarial, antiulcer, anti-inflammatory and analgesic (John and Onabanjo 2010). The extracts/fractions of bark of *E. utile show anti-sickling activity. The mechanism involved in anti-sickling activity is the lysis of* sickled cell erythrocytes (Adejumo et al. 2011a, b).



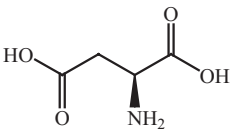
4-hydroxybenzoic acid



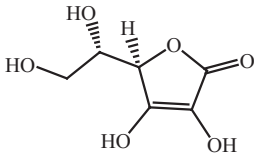
Phenylalanine



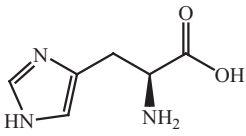
Tyrosine



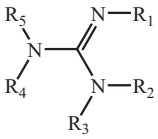
Aspartic acid



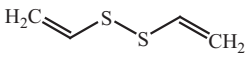
Ascorbic acid or Vitamin C



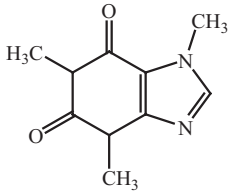
Histidine



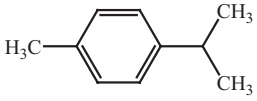
Guanidine alkaloid



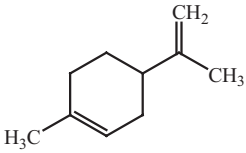
Diallyl disulfide



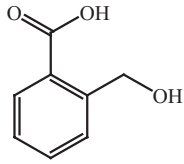
Caffeine



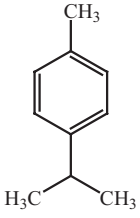
Terpinene



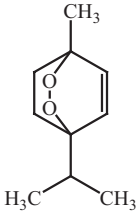
p-mentha-1,8-diene



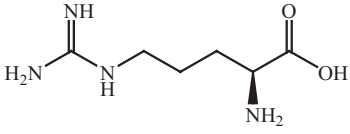
2-hydroxymethylbenzoic acid



p-cymene

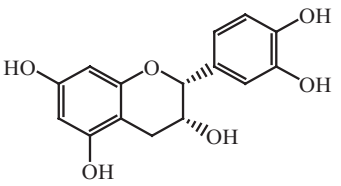


Ascaridole

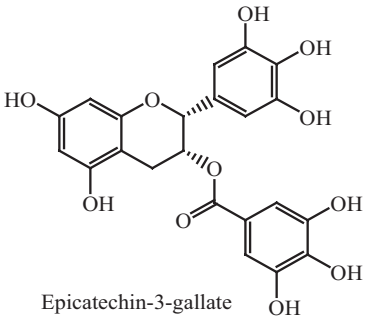


Arginine

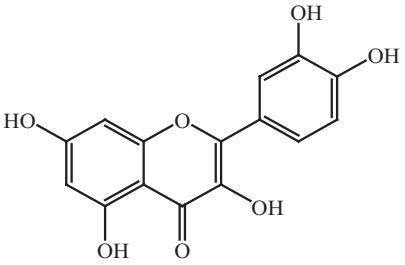
Fig. 2 Structures of active phytoconstituents of medicinal plants used in SCD



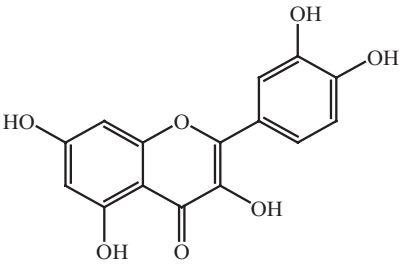
Epicatechin



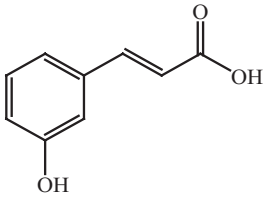
Epicatechin-3-gallate



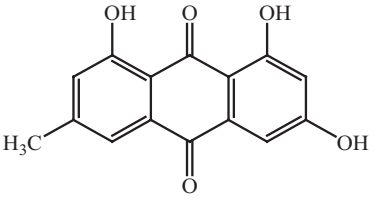
Quercetin



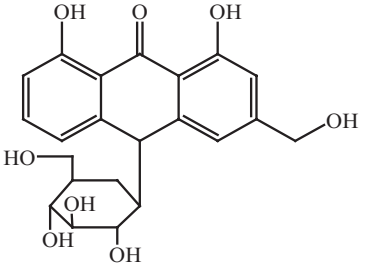
Kaemferol



m-coumaric acid



Emodin



Aloin A

Fig. 2 (continued)

Garcinia kola

Garcinia kola (family: Guttiferae), also called bitter kola, is an indigenous medicinal tree. It is a well-branched, evergreen, medium-size tree, reaching 12 m high in 12 years, and found in Cameroon, Liberia, Nigeria, Gabon, Ghana, Senegal and Sierra Leone. *G. kola* contains alkaloids, tannins, terpenoids, saponins, steroids and flavonoids and is reported for pharmacological uses in treating throat infections, coughs, bronchitis, hepatitis and liver disorders. This plant has also been used as anti-inflammatory, antiparasitic, antimicrobial, antiviral, antioxidant, bronchodilator and purgative (Adejumo et al. 2011a, b). The use of *G. kola* in the treatment of SCD in South West Nigeria has been documented by Egunyomi et al. (2009). Both leaf and seed methanol extracts and the aqueous fractions of *G. kola* possess anti-sickling activity. However, leaf extracts exhibited greater anti-sickling activity compared to seed extract due to a higher membrane stabilisation effect of leaf extract over seed extract.

Hymenocardia acida

Hymenocardia acida (family: Euphorbiaceae) is a shrub also known as jan yaro, ikalaga, yawa satoje and orupa. It belongs to H. acida widely distributed from South Africa to Sudan and is native to Central African Republic, Congo, Kenya, Lesotho, Namibia, Sierra Leone, South Africa, Sudan, Tanzania and Uganda. *H. acida is rich in carbohydrates, tannins, flavonoids, saponins, alkaloids, cardiac glycosides and terpene, which makes it valuable for medicinal purpose. It is used as an antimicrobial and reported in the treatment of sickle cell infection (*Abu and Uchendu 2011). *This plant is most commonly used for sickle cell management in northern Nigeria. The leaf extract (ethanolic extract) contains flavonoids, saponins and carboxylic acids and shows anti-sickling activity by reverse sickled human red blood cells (RBC) (Ibrahim et al.* 2007*).*

Ipomoea involucrata

Ipomoea involucrata (family: Convolvulaceae) is a herb that grows up to 4 m with vigorous twiner, sometimes covering surrounding vegetation. The leaves of this herb are broadly heart shaped with a deeply cordate base, up to 13 cm long, hairy on both surfaces, often more densely so below. Flowers are funnel shaped, whitish to pink, often darker in the throat. *I. involucrate* is native to Angola, Gambia, Mascarene Islands and South Africa. The herb is rich in alkaloids, phenols, terpenes and lignans and shows analgesic, antimicrobial, spasmogenic, spasmolytic, hypotensive, psychotomimetic and anticancer activities (Meira et al. 2012). The methanolic

whole-plant extract of *I. involucrate* shows positive action against sickle cell disease. Normal RBCs were significantly higher in sickle cell blood after treatment with *I. involucrate* plant ethanol extract. The plant extract inhibits significantly sickle cell polymerisation and also reduces lactate dehydrogenase activity in both HbSSM- and HbSSF-treated blood (Afolabi et al. 2012).

Justicia secunda

Justicia secunda (family: Acanthaceae) is an evergreen, perennial plant that can grow from 90 to 200 cm tall. The plant is harvested in South America including Ecuador, Colombia and the Guyanas and in Central America like Panama. The phytochemical screening of the plant reveals the presence of alkaloids, flavonoids, tannins, leucoanthocyanins, quinones and anthocyanins. *J. secunda* is used in the treatment of anaemia, cough, cold, fever, malaria, measles and whooping cough (Corrêa and Alcântara 2012). This plant is also used in Congo by Jehovah's Witnesses for their refusal of blood transfusions against anaemia. Anthocyanin from *J. secunda* shows anti-sickling activity. The aqueous/ethanolic anthocyanin extracts of leaves of *J. secunda* normalise sickled erythrocytes. The mechanism involves both direct binding of the extract with deoxy-HbS molecules and stabilisation of the SS RBC membrane. Indeed, the anthocyanin extract decreased intracellular haemoglobin concentration by inhibiting cell dehydration (Mpiana et al. 2010).

Khaya senegalensis

Khaya senegalensis (family: Meliaceae) is also known as African mahogany, Benin mahogany, dry zone mahogany and Senegal mahogany that is native to Africa. It is an evergreen tree with a widely spreading, rounded crown that can grow 15–30 m tall. It has a bole that is up to 1 m in diameter, unbranched for 8–16 m; the buttresses are neither prominent nor absent. *K. senegalensis's* bark is used as a depurative, taenicide and vermifuge and for treating syphilis. Bark extract is used for treating allergies, bleeding wounds (disinfectant), dermatoses, hookworm, infection of the gums, jaundice and scorpion bite and as a laxative. Seeds and leaves are used for treating headache and fever; roots are used for the treatment of mental illness, against syphilis, sterility and leprosy, and as an aphrodisiac (Fastre et al. 1999). The *K. senegalensis* aqueous extracts of stem bark and leaves possess anti-sickling activity. 2,6-Dihydroxyfissinolide, a limonoid, which is present in the bark of *K. senegalensis* is responsible for its anti-sickling activity. The anti-sickling activity of this limonoid was found to be higher compared to pentoxifylline. In addition, this limonoid did not alter significantly the corpuscular indices (Fall et al. 1999).

Moringa oleifera

Moringa oleifera (family: Moringaceae) (MO) is commonly known as drumstick or horseradish and is one of the most traditional medicines for the treatment and management of various ailments, including the sickle cell disease (SCD). It is native to the Sub-Himalaya tracts of India, Bangladesh, Pakistan, Afghanistan, Central America and Africa. *M. oleifera* has been reported for its diverse use including antibacterial, antifungal, antioxidant, anti-inflammatory, antiulcer, antispasmodic, diuretic, anticarcinogenic and antinociceptive properties (Bharali et al. 2003; Caceres et al. 1991). It is widely consumed in southern Nigeria for a variety of uses. Extracts (both aqueous and methanolic) of the seed and flower of *M. oleifera* demonstrated a higher anti-sickling activity in comparison to the leaf extract. The leaf, seed and flower extracts demonstrate a reversal of sickled erythrocytes (Cáceres et al. 1992; Sulaiman et al. 2008).

Parquetina nigrescens

Parquetina nigrescens (family: Asclepiadaceae) is also known as *Periploca nigrescens. P. nigrescens* is woody at the base, up to 8 m long, glabrous, latex copious with leaves opposite, simple and entire. This plant occurs in large parts of Africa, from Senegal to Nigeria and over to Congo basin down to south tropical Africa. The plant contains alkaloids, glycosides and cardenolides. *P. nigrescens* has shown haematopoietic activities with increasing erythrocyte indices in anaemic rats on a dose basis. Plant also stimulates increased uterine contraction as a result of the mobilisation of extracellular calcium in a manner that is similar to the effects of oxytocin. The aqueous methanolic extract contains flavonoids, glycosides, cardiac glycosides, tannins, saponins, anthraquinones and macronutrients (Ayoola et al. 2011). This aqueous methanolic extract of the *P. nigrescens* plant was found to have an appreciable anti-sickling activity. The leaves and stem aqueous methanolic extract of *P. nigrescens* produces erythrocyte membrane-stabilising effects for anti-sickling activity. *P. nigrescens* possesses appreciable anti-sickling activity, with no toxic effect when administered at low concentrations, and protects the integrity of the erythrocyte membrane as evidenced in the fragiliogram by the reduction in haemolysis of the HbSS cells (Imaga et al. 2010).

Persea americana

Persea americana (family: Lauraceae) or avocado is a large, spreading, evergreen tree which grows up to 8–10 m. The leaves are alternate, dark green, glossy on the upper surface and oval to obovate. The tree is extensively cultivated in south central

Mexico and contains phenols, saponins, flavonoids, alkaloid and sterols. *P. americana* has been greatly appreciated in recent times for its many medicinal applications. The extract of various parts of *P. americana* has been used as analgesic, anti-inflammatory, hypoglycaemic, anticonvulsant, antidiabetic and vasorelaxant (Owolabi et al. 2010). The crude fruit juice extract (including aqueous, acidic, alkaline and alcoholic extracts) of *P. americana* shows anti-sickling effect. All four extracts show sustained reduction in the number of sickle cells in both HbAS and HbSS blood samples. Also the alkaline and alcoholic extracts produce significant reduction in the number of sickle cells (Iweala et al. 2010).

Petiveria alliacea

Petiveria alliacea (family: Phytolaccaceae) is commonly known as guinea hen weed. It is sub-shrub with a deep, thick taproot and tough stems growing 60–150 cm tall. Leaves are alternate, simple and entire, blade elliptic to oblong or obovate. Flowers are bisexual and zygomorphic and fruits are narrowly oblong achenes subtended by persistent bracts and perianth (Kubec and Musah 2001). The plant is native to America, Mexico and West Indies. It has been introduced in India and tropical Africa and is grown as a medicinal herb. The plant contains numerous active phytoconstituents including benzaldehyde, benzoic acid, coumarin, isoarborinol and its acetate and cinnamate, isothiocyanates, polyphenols, senfol, tannins and trithiolaniacine (Kubec et al. 2002). It also contains cysteine sulphoxide derivatives. *P. alliacea* possesses antioxidant and antimicrobial properties and is also used for arthritis and allergies, and as therapy for fever and malaria. The root extract/fraction of *P. alliacea* possesses anti-sickling activity by *lysis of* sickled cell erythrocytes (Adejumo et al. 2011a, b).

Plumbago zeylanica

Plumbago zeylanica (family: Plumbaginaceae) is commonly known as Ceylon leadwort, doctorbush or wild leadwort. *P. zeylanica* is distributed throughout most of the tropics and subtropics, growing in deciduous woodland, savannas and scrublands from sea level up to 2000 m altitude. It is a shrub that grows up to 2.5 m long. The leaves are ovate with short lobes at their base and can grow up to 12.5 cm long and 5 cm wide. *P. zeylanica* is used as a remedy for infections, skin diseases and intestinal worms, viz. hookworm, ringworm, leprosy, scabies, dermatitis, acne, sores and ulcers, since time immemorial (Arunachalam 2010). The roots of *P. zeylanica* have been used in folklore medicine in the management of sickle cell disease (SCD) in southwest Nigeria. Methanolic extract and aqueous fraction of *P. zeylanica* possess *in vitro* anti-sickling activities. *P. zeylanica* extracts/fractions had a significantly higher anti-sickling activity at the tested concentrations of 10.0, 1.0 and 0.1 mg/mL

by inhibition of sickling (anti-sickling) and reversal of sickled erythrocytes (Adejumo et al. 2010).

Solenostemon monostachyus

Solenostemon monostachyus (family: Lamiaceae) is an erect, branched annual herb. It grows in Senegal to Chad, Central African Republic, DR Congo and Angola. *S. monostachyus* grows up to 100 cm with erect or decumbent stem. Leaves are simple, opposite, with 1.5–4 cm long petiole. *S. monostachyus* contains flavonoids, coumarin, polyphenols and essential oil and possesses numerous pharmacological activities including analgesic, antipyretic, sedative, stomachic, hypotensive and antioxidant. Methanolic leaf extract of *S. monostachyus* exhibits particular anti-sickling properties coupled with the potential to reduce stress in sickle cell patients. With the treatment of *S. monostachyus* leaf ethanolic extract haemoglobin concentration increases while inhibiting sickle cell polymerisation. Simultaneously plant extracts also reduce lactate dehydrogenase activity in both HbSSM (male)- and HbSSF (female)-treated blood (Afolabi et al. 2012).

Terminalia catappa

Terminalia catappa (family: Combretaceae) is also known as myrobalan, Indian almond, false kamani, Malay almond, tavola nut, country almond, tropical almond and Fijian almond. *T. catappa* is a large tropical tree in the lead wood tree that grows mainly in the tropical regions of Africa, Asia and Australia. It has been well recognized in Ayurveda for its medicinally essential phytoconstituents including phenol, flavonoid and carotenoid. Numerous pharmacological investigations have confirmed that *T. catappa* exhibits antimicrobial, anti-inflammatory, antidiabetic, antioxidant, hepatoprotective and anticancer activities (Anand 2015). *T. catappa* leaf extracts have potential in the management of sickle cell disorders. The ethanolic extract of *T. catappa* was effective in preventing and reversing the sickling of human ‘SS’ erythrocytes induced by 2% sodium metabisulphite solution by inhibiting osmotically induced haemolysis of human erythrocytes in a dose-dependent manner. It also prolongs the clotting time of uncoagulated blood and is thus utilised in sickle cell disease (Mgbemene and Ohiri 1999).

Tinosporia cordifolia

Tinospora cordifolia (family Menispermaceae) is also known as heart-leaved moonseed, guduchi or amrita. *T. cordifolia* is a herbaceous vine that is indigenous to the tropical areas of Myanmar, India and Sri Lanka. It is a large, deciduous extensively

spreading climbing shrub with several elongated twining branches. Its leaves are simple, alternate, exstipulate, long petioles up to 15 cm long. Flowers are greenish yellow, small and unisexual and appear when the plant is leafless. Male flowers are clustered, and female usually solitary. It is a promising anticancer herb and also possesses antidiabetic, anti-periodic, antispasmodic, anti-inflammatory, anti-allergic, anti-arthritis and antiulcer activities and also boosts the immune system (Salkar et al. 2014). A US patent Desai (n.d.) (US 20100189814 A1) has been obtained for herbomineral formulation having Sunthi (*Zingiber officinale Roscoe,* 25 mg), Jivanti Ghana (*Leptadenia reticulata,* 37.5 mg), Haritaki Ghana (*Terminalia chebula*, 25 mg), Guduchi Ghana (*Tinospora cordifolia,* 37.5 mg), Shatavari Ghana (*Asparagus racemosus*, 25 mg), Dadima (*Punica granatum Linn.*, 12.5 mg), Pippali (*Piper longum Linn.*, 37.5 mg) and Lohabhasma calyx of iron (Krantloha-Fe_3O_4, 12.5 mg) for treating sickle cell disease.

Uvaria chamae

Uvaria chamae (family: Annonaceae) is also called finger root or bush banana. It is a shrub or small tree growing up to 4 m tall. The tree is used locally, being harvested from the wild for its edible fruit, and medicinal and other uses. The tree is native to tropical Central and West Africa, where it grows in wet and dry forests and coastal scrublands. The fruit grows in small bunches and is edible and widely eaten. The plant has been shown to contain several medically active compounds, including alkaloids, cardiac glycosides, tannins and oleo-resin (Okwu and Iroabuchi 2009). The root bark is sometimes sold in local markets, mainly for medicinal use including anti-inflammatory, astringent, febrifuge, galactagogue and styptic. The roots of *U. chamae* have been used in traditional medicine in the management of sickle cell disease (SCD). The methanol extract of roots and its aqueous fraction shows *in vitro* anti-sickling activities by inhibiting osmotically induced haemolysis of human erythrocytes (Adejumo et al. 2010).

Vernonia amygdalina

Vernonia amygdalina (family: Asteraceae) is also called bitter leaf. It is a shrub that grows up to 3 m high. The bark is rough and leaves are elliptical up to 20 cm (7.9 in.) long. The shrub is grown in the African tropics and other parts of Africa, particularly in Nigeria, Cameroon and Zimbabwe. *V. amygdalina* contains alkaloids, anthraquinone, coumarins, flavonoids, lignans, phenolic acids, saponins, steroids, terpenes and xanthones (Farombi and Owoeye 2011). The plant extract is effective against gastrointestinal disorders and amoebic dysentery and has antimicrobial, antiparasitic and cytotoxic effects towards human carcinoma cells of the nasopharynx

activities. The leaf of *V. amygdalina* possesses potent antioxidant activity and also shows anti-sickling activity. The methanolic extract of *V. amygdalina* decreases the number of sickle cell RBCs (Afolabi et al. 2012).

Vigna subterranea

Vigna subterranea (family: Fabaceae) is commonly known as Congo goober, earth pea or ground bean. *The plant is* leafy, annual, creeping legume with glabrous (hairless) leaves usually up to 11 cm. Plant flowers are clustered 1–3 on an unbranched axis, known as a raceme. Congo goober most likely originated in Asia, Australia, West Africa, Nigeria and Cameroon. *V. subterranea* (particularly seed) contains protein, carbohydrate, alkaloids, glycosides, saponins, fats and oil and steroids. Similar to *V. unguiculata*, *Vigna subterranea* also shows antimicrobial and antioxidant properties. Ethanolic seed extract of *V. unguiculata* also shows anti-sickling activity. Ethanolic seed extract increases delayed time before polymerisation of HbSS erythrocyte and reverts sickling effect (Simeone et al. 2012).

Vigna unguiculata

Vigna unguiculata (family: *Leguminosae*) or cowpea is a shrub that grows 15–80 cm high. Leaves are alternate and trifoliolate while the flowers are white, cream, yellow, mauve or purple. Seeds of *V. unguiculata* are square to oblong variable in size and shape with different colours, including white, brown, maroon, cream and green. This plant is native to West Africa, but nowadays cowpea is cultivated across Asia and Oceania, the Middle East, southern Europe and Central and South America (Haq et al. 2013). The plant is a rich source of protein, carbohydrates, fats and oil, flavonoids, saponins, resins, steroids, terpenoids, glycosides and alkaloids. *V. unguiculata* possesses antimicrobial properties and also shows antioxidant and anti-sickling activities. Ethanol seed extract of *V. unguiculata* has sickling reversal effect and also increases delayed time before polymerisation of HbSS erythrocyte which is a major event in the pathophysiology of sickle cell disease (Simeone et al. 2012).

Xylopia aethiopic

Xylopia aethiopica (family: Annonaceae) is also known as grains of selim, African grains of selim, moor pepper, kani pepper and Senegal pepper. It is an aromatic evergreen tree that grows up to 20 m high and native to the moist fringe forests and lowland rainforest in the savanna zones of Africa. The fruits of *X. aethiopica* are

used against amenorrhoea, bronchitis (when smoked and inhaled), cough, dizziness, dysentery, enema, lumbago, stomach ache and neuralgia. *X. aethiopica* is also used as calmative, purgative and repulsive to pain and in the treatment of boils and skin eruptions. The extracts of *X. aethiopica* could be used as a target in the prevention of SCD crisis in infants. Uwakwe and Nwaoguikpe (2008) reported that the fat-soluble (FAS), butanol-soluble (BUS) and water-soluble extracts (WAS) of *X. aethiopica* exhibit profound anti-sickling effectiveness by inhibiting HbSS polymerisation. These FAS, BUS and WAS fractions also reverse already sickled erythrocytes. WAS fractions showed less time for reversal than the CAE fractions. The presence of amino acids such as arginine, tyrosine and aspartic acid is also responsible for anti-sickling activity.

Zanthoxylum macrophylla

Zanthoxylum macrophylla (family: Rutaceae) is an African strain wood also known as rapeko or barkeley. It is a tree grown up to 10–30 m. The fruits are used to produce the spice uzazi. The plant is an important component of traditional medicine. The plant consists of important medically active compounds, including an essential oil, alkaloids and saponins. Various alkaloids have shown important pharmacological actions, including lowering blood pressure, combating cancer growths, relieving pain and combating infections and parasites. The plant is also used as an analgesic, aphrodisiac and vermifuge. The anti-sickling activity of aqueous extracts of *Z. macrophylla* roots was first reported by Soforowa in 1975. 2-Hydroxymethylbenzoic acid was found responsible for the anti-sickling activity which was present in the root of this plant. The anti-sickling activity of *Z. macrophylla* was further supported by Elekwa et al. (2005). The aqueous extracts of *Z. macrophylla* roots stabilise the erythrocyte membranes by decreasing viscosity of the HbSS blood and this reduction was significantly different ($p < 0.05$) from that for HbAA and HbAS.

References

Abreu PM, Noronha RG (1997) Volatile constituents of the rhizomes of *Aframomum alboviolaceum* (Ridley) K. Schum. from Guinea-Bissau. Flav Frag J 12:79–83

Abu AH, Uchendu CN (2011) Effect of aqueous ethanolic extract of *Hymenocardia acida* stem bark on oestrous cycle of albino rats. J Med Plants Res 5(8):1280–1283

Adejumo E, Adelodun LK, Oladimeji PR, Lateef SK (2010) *In vitro* anti-sickling activities and phytochemical evaluation of *Plumbago zeylanica* and *Uvaria chamae Olufunmilayo*. Afr J Biotechnol 9(53):9032–9036

Adejumo OE, Agbanah OIS, Kolapo AL, Ayoola MD (2011a) Phytochemical and anti-sickling activities of *Entandrophragma utile*, *Chenopodium ambrosioides* and *Petiveria alliacea*. J Med Plants Res. 5(9):1531–1535

Adejumo OE, Ayoola MD, Kolapo AL, Orimoyegun VO, Olatunji PO (2011b) Anti-sickling activities of extracts of leaf, seed and seed pod of *Garcinia kola* Heckel. Afr J Pharm Pharmacol 5(1):48–52

Adesanya SA, Idowu TB, Elujoba AA (1988) Anti-sickling activity of *Adansonia digitata*. Planta Med 54(4):374

Afolabi IS, Osikoya IO, Fajimi OD, Usoroh PI, Ogunleye DO, Bisi-Adeniyi T, Adeyemi AO, Adekeye BT (2012) *Solenostemon monostachyus*, *Ipomoea involucrate* and *Carica papaya* (seed oil) versus Glutathione, or *Vernonia amygdalina*: methanolic extract of novel plants for the management of sickle cell anemia disease. BMC Complement Altern Med 12:262–271

Akinsulie AO, Temiye EO, Akanmu AS, Lesi FE, Whyte CO (2005) Clinical evaluation of extract of *Cajanus cajan* (Ciklavit) in sickle cell anaemia. J Trop Pediatr 51(4):200–205

Ameh SJ, Tarfa FD, Ebeshi BU (2012) Traditional herbal management of sickle cell anemia: lessons from Nigeria. Anemia 2012:1–9

Anand V (2015) An updated review of *Terminalia catappa*. Pharmacol Rev 9(18):93–98

Arunachalam KD (2010) Anti-inflammatory and cytotoxic effects of extract from *Plumbago zeylanica*. Afr J Microbiol Res 4(12):1239–1245

Ayoola AO, Akinloye O, Oguntibeju OO, Oke JM, Odetola AA (2011) Antioxidant activities of *Parquetina nigrescens*. Afr J Biotechnol 10(24):4920–4925

Bharali R, Tabassum J, Azad MR (2003) Chemomodulatory effect of *Moringa oleifera*, Lam on hepatic carcinogen metabolizing enzymes, antioxidant parameters and skin papillomagenesis in mice. Asian Pac J Cancer Prev 4:131–139

Booth C, Inusa B, Obaro SK (2010) Infection in sickle cell disease: a review. Int J Infect Dis 14(1):e2–e12

Caceres A, Cabrere O, Morales O, Mollinedo P, Mendia P (1991) Pharmacological properties of *Moringa oleifera*. 1: preliminary screening for antimicrobial activity. J Ethnopharmacol 33:213–216

Cáceres A, Saravia A, Rizzo S, Zabala L, De Leon E, Nave F (1992) Pharmacologic properties of *Moringa oleifera*. 2: Screening for antispasmodic, anti-inflammatory and diuretic activity. J Ethnopharmacol 36:233–237

Corrêa GM, Alcântara AFDC (2012) Chemical constituents and biological activities of species of Justicia—a review. Braz J Pharmacogn 22(1):220–238

Dash BP, Archana Y, Satapathy N, Naik SK (2013) Search for antisickling agents from plants. Pharmacogn Rev 7(13):53–60

Dawodu AO, Moses UD, Apena A, Adetoro A, Dairo JO (2014) The proximate evaluation and phytochemistry of *Enantia chlorantha* stem bark in aqueous and ethanolic extract. Middle-East J Sci Res 21(11):2145–2148

Desai AM. Herbomineral formulation for treating sickle cell disease. US20100189814. A1

Egunyomi A, Moody JO, Eletu OM (2009) Anti-sickling activities of two ethnomedicinal plant recipes used for the management of sickle cell anaemia in Ibadan Nigeria. Afr J Biotechnol 8:20–25

Ejele AE, Akpan IO, Ogukwe CE, Onyeocha VO, Ukiwe LN (2012) Bioassay-guided isolation and partial characterization of an anti-sickling compound from *Enantia chlorantha*. Int Res J Biochem Bioinforma 2(7):149–154

Elekwa I, Monanu MO, Anosike EO (2005) Effects of aqueous extracts of *Zanthoxylum macrophylla* roots on membrane stability of human erythrocytes of different genotypes. Biokemistri 17(1):7–12

Fabiyi OA, Atolani O, Adeyemi OS, Olatunji GA (2012) Antioxidant and cytotoxicity of β-amyrin acetate fraction from *Bridelia ferruginea* Leaves. Asian Pac J Trop Biomed 2(2):S981–S984

Fall AB, Fastré RV, Vanhaelen M, Lo I, Toppet M, Ferster A, Fondu P (1999) *In vitro* anti-sickling activity of a rearranged limonoid isolated from *Khaya senegalensis*. Planta Med 65(3):209–212

Farombi EO, Owoeye O (2011) Antioxidative and chemopreventive properties of *Vernonia amygdalina* and *Garcinia biflavonoid*. Int J Environ Res Public Health 8:2533–2555

Fastre VR, Vahaelen M, Lo I, Toppet M, Ferster A, Fondu P (1999) *In vitro* antisickling activity of a rearranged limonoid isolated from *Khaya senegalensis*. Planta Med 65(3):209–212

Folashade KO, Omoregie EH (2013) Chemical constituents and biological activity of medicinal plants used for the management of sickle cell disease-A review. J Med Plants Res 7(48):3452–3476

Haq MZU, Ahmad S, Amarowicz R, Feo VD (2013) Antioxidant activity of the extracts of some cowpea (*Vigna unguiculata* (L) Walp.) cultivars commonly consumed in Pakistan. Mole 18:2005–2017

Hernández JMJF, Santiago OG, Cabrera MAR, Ferriño PCE, Corona MDRC (2016) Chemistry and pharmacology of citrus sinensis. Molecules 21(247):1–24

Ibrahim H, Sani FS, Danladi BH, Ahmadu AA (2007) Phytochemical and anti-sickling studies of leaves of Hymenocardia acida. Pakistan J Biol Sci 10(5):788–791

Ibrahim H, Mdau BB, Ahmed A, Ilyas M (2011) Anthraquinones of *Cissus populnea Guill* & *Perr* (Amplidaceae). Afr J Tradit Complement Altern Med 8(2):140–143

Imaga NOA, Gbenle GO, Okochi VI, Adenekan SO, Edeoghon SO, Kehinde MO, Bamiro SB, Ajiboye A, Obinna A (2010) Anti-sickling and toxicological profiles of leaf and stem of *Parquetina nigrescens* L. J Med Plants Res 4(8):639–643

Iweala EEJ, Uhegbu FO, Ogu GN (2010) Preliminary *in vitro* antisickling properties of crude juice extracts of *Persia americana*, *Citrus sinensis*, *Carica papaya* and *Ciklavit*. Afr J Tradit Complement Altern Med 7(2):113–117

John TA, Onabanjo AO (2010) Effect of an aqueous extract of *Entandrophragma utile* bark on gastric acid secretion in rat and isolated ileum contractility in guinea pig. Afr J Biomed Res 13:197–206

Kaboré D, Lingani HS, Diawara B, Compaoré CS, Dicko MH, Jakobsen M (2011) A review of baobab (*Adansonia digitata*) products: effect of processing techniques, medicinal properties and uses. Afr J Food Sci 5(16):833–844

Kubec R, Musah RA (2001) Cysteine sulfoxide derivatives in *Petiveria alliacea*. Phytochemistry 58:981–985

Kubec R, Kim S, Musah RA (2002) S-Substituted cysteine derivatives and thiosulfinate formation in *Petiveria alliacea*-Part II. Phytochemistry 61:675–680

Li X, Wang H, Liu C, Chen R (2010) Chemical constituents of Acacia catechu. Zhongguo Zhong Yao Za Zhi 35(11):1425–1427

Maisarah AM, Amira NB, Asmah R, Fauziah O (2013) Antioxidant analysis of different parts of *Carica papaya*. Int Food Res J 20(3):1043–1048

Marlier M, Guellec GL, Lognay G, Wathelet JP, Severin M (1993) Characterization of three labdane diterpenes from *Aframomum alboviolaceum*. Planta Med 59(5):455–457

Mbata TI, Debiao LU, Saikia A (2008) Antibacterial activity of the crude extract of Chinese green tea (*Camelia sinensis*) on listeria monocytogenes. Afr J Biotechnol 7(10):1571–1573

Meira M, Silva EPD, David JM, David JP (2012) Review of the genus Ipomoea: traditional uses, chemistry and biological activities. Braz J Pharmacogn 22(3):682–713

Mgbemene CN, Ohiri FC (1999) Anti-sickling potential of *Terminalia catappa* leaf extract. J Pharma Biol 37(2):152–154

Mojisola OC, Adebolu EA, Alani DM (2008) Anti-sickling properties of *Carica papaya* Linn. J Nat Prod 1:56–66

Monago CC, Uwakwe AA (2008) Proximate composition and *in-vitro* anti sickling property of *Nigerian Cyperus esculentus* (tiger nut sedge). Trees Life J 4(2):1–6

Monzote L, Nance MR, García M, Scull R, Setzer WN (2011) Comparative chemical, cytotoxicity and antileishmanial properties of essential oils from *Chenopodium ambrosioides*. Nat Prod Commun 6(2):281–286

Moody JO, Ojo O, Omotade OO, Adeyemo AA, Olusese PE, Ogundipe A (2003) Anti-sickling potential of a Nigerian herbal formular and the major plant component (*Cissus populnea* L. CPK). Phytother Res 10:1137–1176

Mpiana PT, Mudogo V, Tshibangu DST, Ngbolua KN, Shetonde OM, Mangwala KP, Mavakala BK (2007) *In vitro* anti-sickling activity of anthocyanins extract of a Congolese plant: *Alchornea cordifolia* M. Arg. J Med Sci 7(7):1182–1186

Mpiana PT, Ngbolua KTNN, Bokota MT, Kasonga TK, Atibu EK, Tshibangu DST, Mudogo V (2010) *In vitro* effects of anthocyanin extracts from *Justicia secunda* Vahl on the solubility of Haemoglobin S and membrane stability of sickle erythrocytes. Blood Transfus 8(4):248–254

Mpiana PT, Dianzenza EN, Ngbolua KN, Tshibangu DST, Mbala BM, Mhigo SO, Atibu EK, Kakule MK, Bokota MT (2012) Antisickling properties, thermal and photochemical degradations of anthocyanin extracts from *Annona senegalensis* (Annonaceae). Int J Biol Chem Sci 6(5):2241–2251

Nwaoguikpe RN (2010) The phytochemical, proximate and amino acid compositions of the extracts of two varieties of tiger nut (*Cyperus esculentus*) and their effects on sickle cell hemoglobin polymerization. J Med Med Sci 1(11):543–549

Nwaoguikpe RN, Braide W, Ezejiofor TIN (2010) The effect of *Aloe vera* plant (*Aloe barbadensis*) extracts on sickle cell blood (HbSS). Afr J Food Sci Technol 1(3):58–63

Ogoda OJ, Akubue PI, Okide GB (2002) The kinetics of reversal of pre-sickled erythrocytes by the aqueous extract of *Cajanus cajan* seeds. Phytother Res 16(8):748–750

Ohnishi ST, Ohnishi T, Ogunmola GB (2000) Sickle cell anemia: a potential nutritional approach for a molecular disease. Nutrition 16(5):330–338

Okwu DE, Iroabuchi F (2009) Phytochemical composition and biological activities of *Uvaria chamae* and *Clerodendron splendens*. E J Chem 6(2):553–560

Okwu DE, Ukanwa N (2010) Isolation, characterization and antibacterial activity screening of anthocyanidin glycosides from *Alchornea cordifolia* (Schumach. and Thonn.) Mull. Arg. leaves. E J Chem 7(1):41–48

Otunola GO, Oloyede OB, Oladiji AT, Afolayan AJ (2010) Comparative analysis of the chemical composition of three spices–*Allium sativum* L., *Zingiber officinale* Rosc. and *Capsicum frutescens* L. commonly consumed in Nigeria. Afr J Biotechnol 9(41):6927–6931

Owolabi MA, Coker HAB, Jaja SI (2010) Bioactivity of the phytoconstituents of the leaves of Persea Americana. J Med Plants Res. 4(12):1130–1135

Panigrahi HK, Kushawa H, Sharma SS (1997) Treatment of sickle cell disorders by ayurvedic medicine. Anc Sci Life 17(1):15–22

Parise LV, Berliner N (2016) Sickle cell disease: challenges and progress. Blood J 127(7):789

Roseff SD (2009) Sickle cell disease: a review. Immunohematology 25(2):67–74

Sahu M, Singh V, Yadav S, Harris KK (2012) Plant extracts with antisickling propensities: a feasible succour towards sickle cell disease management- a mini review. J Phytology 4(3):24–29

Salkar K, Suthar A, Chotalia C (2014) Study of immunomodulatory activity of *Tinospora cordifolia* extract. Int J Adv Pharma Biol Chem 3(4):880–883

Simeone EI, Tufon EN, Victor ON, Noel NN (2012) Anti-sickling potential of the ethanol seed extracts *of Vigna unguiculata* and *Vigna subterranean*. Int J Biochem Biotechnol 1(9):226–229

Soforowa EA (1975) Isolation and characterization of an anti-sickling agent from *Fagara zanthoxyloides*. Lloydia 38:169–171

Sulaiman CT, Gopalakrishnan VK (2013) Radical scavenging and *in vitro* hemolytic activity of aqueous extracts of selected acacia species. J Appl Pharma Sci 3(3):109–111

Sulaiman MR, Zakaria ZA, Bujarimin AS, Somcent MN, Israf DA, Moin S (2008) Evaluation of *Moringa oleifera* aqueous extract for antinociceptive and anti-inflammatory activities in animal models. Pharm Biol 46:838–845

Takasu J, Uykimpang R, Sunga M, Amagase H, Niihara Y (2002) Aged garlic extract therapy for sickle cell anemia patients. BMC Blood Disord 2(1):1–3

Uwakwe AA, Nwaoguikpe RN (2008) *In vitro* anti-sickling effects of *Xylopia aethiopica* and *Monodora myristica*. J Med Plants Res. 2(6):119–124

Yisa J, Egila JN, Darlinton AO (2010) Chemical composition of *Annona senegalensis* from Nupe land, Nigeria. Afr J Biotechnol 9(26):4106–4109

Zhang L, Tizard IR (1996) Activation of a mouse macrophage cell line by acemannan: The major carbohydrate fraction from *Aloe vera* gel. Immunopharmacology 35(2):119–128

Pharmacology and Toxicology of *Nepeta cataria* (Catmint) Species of Genus *Nepeta*: A Review

Ajay Sharma, G. A. Nayik, and Damanjit Singh Cannoo

Introduction

Peoples from ancient time use secondary metabolites (SMs) of plant origin in their everyday life for the treatment of many diseases, to keep away and eradicate insects, as food preservatives and flavoring agent, etc. World Health Organization in its survey estimated that 80% of the world's population largely depends on conventional drugs obtained from SMs for their health care (Gopal et al. 2014). Peoples in countries like India, China, and Egypt used SMs of plant origin as medicine, which forms the basis of the conventional medical system (Ravishankar and Shukla 2007). Nowadays, in different countries 119 chemicals isolated from 90 plant species are used as significant drugs (Siddiqui et al. 2014). With the course of time, synthetic chemicals have replaced SMs of plant origin as the former have more precise action and provide early results. However, these synthetic chemicals have many side effects and cause many serious problems, viz. human health issues, gene mutation, resistance developed by insects and pests, biodiversity reduction of agroecosystems, and environmental pollution. Due to these reasons in the present scenario, strategies have been made to replace synthetic chemicals with SMs of plant origin because these are ecofriendly, biodegradable, less toxic, and cost effective in nature. The SMs of plant origin belong to different classes of natural products, viz. alkaloids, carotenoids, flavonoids, phenolics, tannins, terpenoids, etc., and have been well known for their biological potential. The biological potential of secondary metabolites depends on their nature and composition (Celis et al. 2008). The plant families such as Apiaceae, Asteraceae, Cupressaceae, Lauraceae, Myrtacea, Piperaceae,

A. Sharma · D. S. Cannoo (✉)
Department of Chemistry, Sant Longowal Institute of Engineering and Technology, Sangrur, Punjab, India

G. A. Nayik
Department of Food Engineering & Technology, Sant Longowal Institute of Engineering and Technology, Sangrur, Punjab, India

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Poceace, Rutaceae, and Zingiberaceae have been known for their valuable and useful bioactive SMs and Lamiaceae is one of them.

Nepeta has been a multiregional genus of the Lamiaceae (labiatae or mint) family and have a rich source of bioactive SMs. The essential oils and various extracts isolated from different species of this genus have been a wealthy source of special class of terpenoids known as iridoids along with other classes of SMs. These SMs showed a wide range of biological activities and have been used since prehistoric times in various traditional medicines. These have been used as diuretic, expectorant, antispasmodic (Rapisarda et al. 2001; Dabiri and Sefidkon 2003; Formisano et al. 2011), anti-inflammatory, antitussive, antiasthmatic, antiseptic (Aggarwal et al. 2007; Sharma and Cannoo 2013), sedative, diaphoretic, febrifuge, antioxidant (Tepe et al. 2007), insecticidal, antimicrobial (Edewor and Usman 2011), antiviral, and fungicidal (Sharma and Cannoo 2016a). Further, these have also been used against scorpion and snakebites (Rapisarda et al. 2001; Formisano et al. 2011), stomach diseases (Sharma and Cannoo 2013), kidney and teeth troubles, liver diseases (Baser et al. 2000), and many problems of heart such as tachycardia, angina pectoris, cardiac thrombosis, and heart weakness and have showed numerous biological activities, viz. analgesic, antiasthmatic, anticancer, anti-inflammatory, antimicrobial, antioxidant, antipyretic, antiseptic, antispasmodic, diaphoretic, diuretic, fungicidal, herbicidal, insecticidal, sedative, and insect repellent.

Nepeta cataria (catnip or catmint), an aromatic perennial herb, belongs to genus *Nepeta* of Lamiaceae family and has been well known for its medicinal and therapeutic values. It has acted as the representative plant of this genus because it has been the most studied species of this genus. The name *Cataria* has been originated from "Cathus," an old Latin word, which mean "of cats." Like other aromatic plants which have showed flavoring and medicinal properties (Tapsell et al. 2006; Aggarwal et al. 2007) and act as renewable source for the same (Sherman and Hash 2001), *N. cataria* has also been known for its essential oil and secondary metabolites, which showed tremendous applications in pharmaceutical, agrochemical, and food industries. It was shown by the different research groups that the essential oil and different extracts isolated from *N. cataria* have been a rich source of nepetalactones and related compounds (iridoids), which have been mainly responsible for different biological activities of the plant, viz. cat attractant, insect pheromone, insecticidal and insect repellent, etc. (Peterson and Coats 2001; Peterson et al. 2002; Baranauskiene et al. 2003; Herron 2003; Peterson and Ems-Wilson 2003; Chauhan et al. 2005; Amer and Mehlhorn 2006; Formisano et al. 2011). It has been reported that the biological activity of nepetalactone mainly depends upon the configuration at C-7 (Zimmermann et al. 2012). Nepetalactone has also been found to be the major component in the defensive secretions of lubber grasshopper and the coconut stick insect (Peterson and Coats 2001). Besides these compounds the plant also contains other compounds related to different classes of natural products like flavonoids (luteolin 7-O-glucuronide, 7-O-glucurono-glucoside, apigenin 7-O-glucuronide, etc.); phenolic acid (caffeic, rosmarinic acids, gallic acid, etc.) (Modnicki et al. 2007); steroids (ursolic acid, oleanolic acid, β-sitosterol, stigmasterol, β-amyrin, etc.) (Jamila et al. 2011); and terpenoids (1,8-cineole, α-bisbolene, α-citral, β-caryophyllene,

β-farnesene, geraniol, α-humulene, α-terpineol, etc.) (Sajjadi 2005; Rather et al. 2012; Sharma and Cannoo 2013).

The presence of medicinally active phytoconstituents in *N. cataria* and tremendous potential of these compounds in agrochemicals, food, cosmetics, and pharmaceutical industries allow us to write this review in order to provide valuable information regarding this plant to scientific communities.

Traditional Uses

The knowledge of traditional usage of any plant has been very important in order to attract different research groups belonging to different fields of science with an aim to get more and more and to explore extensive application of research plant in human well-being. *N. cataria* has a long history of association with the traditional medicine practices of the peoples of different tribes and countries (Kafaru 1994; Sharma and Cannoo 2013). The French peoples used young leaves and shoots of *N. cataria* for seasoning. England's public hangmen chewed this plant while performing their duties due to its hallucinogenic properties. The tea prepared from its leaves traditionally has been used as soporific and sedative and against gastrointestinal and respiratory diseases, viz. diarrhea, asthma, cough, bronchitis, etc. (Baser et al. 2000; Shafaghat and Oji 2010; Formisano et al. 2011). Many Indian tribes from North America and Chippewa used leaves of this plant to prepare herbal tea. Iroquois, Cherokee, and Okanagan-Colville Indian tribes used this plant as a remedy to cure colds, coughs, and stomach upsets. On the other hand, Iroquois Indian tribes took this plant for the treatment of diarrhea, vomiting, sore throats, and headaches. Menominee peoples used this plant to induce sweating and for the cure of pneumonia, Rappahannock for pain relief, and Cherokee for ease of fever and blood and female disorders. Further Cherokee Indians took this plant for the treatment of convulsions, boils, and worms and Shinnecock used dried leaves for smoking to cure rheumatism (Sue Eland 2008). Furthermore, flowering tops and dried leaves have been aromatic in nature and therapeutically used as diaphoretic, carminative, tonic, antiseptic, emmenagogue, refrigerant, soporific, and stimulant and against tooth ache in traditional medicine system.

Other biological and medicinal properties of *N. cataria* are the following:

- The extract isolated from *N. cataria* showed inhibitory activity on growth, production, and adhesion of enzyme and some bacteria (Nostro et al. 2001; Adiguzel et al. 2009). Juvenile hormone activity has also been reported from catnip plant extract (Louey et al. 2001).
- *N. cataria* has been employed traditionally for the cure of painful swellings in English folk medicine (Turner 1995).
- Fresh or dried scented flowering tops and leaves have been used in soups and cheese and as flavoring agents particularly for cooked foods and sauces and in medicine (Leung and Foster 1996).

- It has been used in the production of insect pheromones and a part of strategies for insect pest management (Birkett and Pickett 2003).
- It has been used in popular medicine, dyes, and teas in North America (Ricci et al. 2010).
- This plant has promoted sweating and has also been useful against insomnia, colds, flu, and fevers when taken as hot infusion. Further, it has been supposed to be helpful in allaying morning sickness and preventing miscarriage and premature birth.

Apart from these *N. cataria* showed many biological activities, viz. anti-inflammatory and anti-nociceptive activity (Ricci et al. 2010), antimicrobial and antifungal activity (Nostro et al. 2001; Suschke et al. 2007; Bisht et al. 2010), anti-oxidant activity (Adiguzel et al. 2009; Lee et al. 2010; Kraujalis et al. 2011), anthelmintic activity (Bandh et al. 2011), cytotoxic activity (Suschke et al. 2007), feline attractant activity (Formisano et al. 2011; Sharma and Cannoo 2016b), insect repellent and insecticidal activity (Peterson, 2001; Schultz et al. 2004; Bernier et al. 2005; Trongtokit et al. 2005; Zhu et al. 2006; Birkett et al. 2011), nematicidal activity (Pavaraj et al. 2012), spasmolytic and bronchodilatory activities (Gilani et al. 2009), and trypanocidal activity (Saeidnia et al. 2008).

Phytochemistry

The composition, quality, and quantity of secondary metabolites obtained from different extracts and essential oils of different plants depend upon the age and growth stage of plant, plant organ, time of collection of plant part, climate, and soil composition (Angioni et al. 2006). So, for the extraction of essential oils and extracts of identical composition again and again these have to be extracted from the same plant organ collected at the same time, age, and growth stage of plant under same climate conditions.

The genus *Nepeta* and the species *N. cataria* have been known for their special class of terpenoids known as iridoids, viz. nepetalactone, dihydronepetalactone, 5,9-dehydronepetalactone, iridomyrmecin, and neptelic acid. These compounds are present in higher concentration in essential oils isolated from different species of this genus and have been responsible for their biological activities.

Biological Activity (Pharmacology)

Anti-inflammatory, Anti-nociceptive and Cytotoxic Activity

Ricci et al. (2010) noted anti-nociceptive and anti-inflammatory action of the essential oil extracted from the leaves of *N. cataria*. Essential oil of *N. cataria* (EONC) at dosages of 0.0005 and 0.001 mL/kg has resulted in increased general activity of

female mice but a dose of 0.0005 mL/kg reduced the immobility of test organism. Suschke et al. (2007) reported cytotoxicity of essential oils isolated from *N. cataria* and *N. cataria* var. *citriodora* against bronchial epithelial cell lines and human keratinocyte by microculture tetrazolium (MTT) essay. The essential oils have shown cytotoxic activity against both bronchial epithelial cells and keratinocytes at CC_{50} (cytostatic concentration) values 0.0012–0.015% (v/v). Further, it has been reported that the different extracts of *N. cataria* and *Teucrium chamaedrys* have acted as retardant for calcineurin (inflammation mediated through T cell). The bioactive fractions have been isolated with the help of HPLC and showed the presence of lamiuside A (teupolioside), verbascoside, and caffeoyl phenylethanoid glycoside teucrioside. These compounds have played an important role in calcineurin inhibition (both in the absence and presence of calmodulin).

Antimicrobial and Antifungal Activity

The essential oil isolated from *N. cataria* rich in β-caryophyllene, 4aα, 7α, 7aα-nepetalactone, and 4aα, 7α, and 7aβ-nepetalactone showed antimicrobial activity against seven fungi and five bacteria (Sharma and Cannoo 2013 and references therein). Further, Nostro et al. (2001) evaluated the diethyl ether extract isolated from same plant against 44 *Staphylococcus aureus* strains (some resistant to methicillin) and *S. aureus* 6538P (American Type Culture Collection) for their antibacterial activity by noting the effect of subminimum inhibitory concentrations on in vitro adherence, DNase, coagulase, thermonuclease, and lipase production. Thermonuclease, DNase, and lipase have been retarded at concentrations equal to 1/2 and 1/4 MIC (minimum inhibitory concentration). Suschke et al. (2006) tested the essential oil of *Melissa officinalis* (lemon balm), *N. cataria* var. *citriodora* (lemon catnip), and *N. cataria* (catnip) against clinical isolates of respiratory tract bacteria. The antibacterial activity has been tested in vitro with modified broth microdilution method. These results have indicated the occurrence of cross resistance towards standard antibiotics and natural resistance towards tested essential oils in these bacteria.

The essential oils obtained from *N. cataria*, *N. atlantica*, and *N. tuberosa* have been tested for their antimicrobial (against *Escherichia coli*, *Staphylococcus aureus*, *Salmonella enteritidis*) potential by Zenasni et al. (2008). The results have shown that the biological potential of genus *Nepeta* alters according to the chemical composition and concentration of nepetalactone plays an important role in case of antibacterial potential against tested bacteria. The tested essential oils have showed comparable antibacterial potential. Adiguzel et al. (2009) reported the biological potential of *N. cataria* essential oil and methanol extracts individually against 1 yeast, 24 bacteria, and 15 fungal stains. Only 5 bacterial and 7 fungal stains have shown sensitivity towards methanol extracts whereas essential oil has shown activity against 1 yeast, 11 bacteria, and 12 fungi. Maximal inhibition zones and MIC values in case of oil-sensitive bacterial stains range from 10–32 mm to 15.62–250 μL/mL,

whereas in case of yeast and fungal stains it ranges from 10–39 mm to 15.62–125 μL/mL, respectively.

The presence of glycosides, coumarins, and flavonoids in *N. cataria* leaf extracts (dichloromethane and methanol) was reported by Edewor and Usman (2011). The extracts showed outstanding antibacterial activity against gram-positive bacteria compared to gram-negative. This biological potential of the different extracts of *N. cataria* against tested microorganisms has been attributed to the presence of different flavonoids in these extracts (Bisht et al. 2010; Sharma and Cannoo 2016a).

Bandh et al. (2011) analyzed antibacterial and antifungal potential of *N. cataria* methanolic extracts against animal pathogenic bacterial and fungal strains (viz. *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus*, *Pasteurella multocida*, *Klebsiella pneumonia, Aspergillus flavus*, and *Candida albicans*). The extracts have possessed more antibacterial activity in comparison to its antifungal activity. Further, in the same year Bandh et al. (2011) evaluated the antimicrobial activity of aqueous extracts obtained from leaves of *N. cataria* at different concentrations against two fungal (*Candida albicans* and *Aspergillus flavus*) and five bacterial stains (*Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus*, *Bacillus subtilis*, *Klebsiella pneumoniae*).

Antioxidant Activities

Lee et al. (2010) reported that rosmarinic acid has been one of the major antioxidants present in different extracts of *N. cataria.* Kraujalis et al. (2011) tested methanol extracts of *N. cataria* var. c*itriodora*, *N. transcaucasica, N. cataria*, and *N. bulgaricum* for their antioxidant potential and established that methanol extracts of *N. cataria*, *N. transcaucasica*, and *N. bulgaricum* retarded approximately 80% of DPPH (2,2-diphenyl-1-picrylhydrazyl) radicals present in the reaction, while *N. cataria* var. *citriodora* retarded DPPH radicals present in the reaction only up to 44%. The strong antioxidant rosmarinic acid has been the chief component present in all extracts, while luteolin and caffeic acid have been present in lower amounts. Mihaylova et al. (2013) studied the antioxidant potential of three extracts obtained from *N. cataria*, viz. 70% ethanol extract obtained by heat reflux method and water and 70% ethanol extract obtained by ultrasonication-assisted method (UAE with water and UAE with 70% ethanol) with ferric-reducing antioxidant power (FRAP), 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging, and 2,2′-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS) radical decolorization assay. The results indicated that the extract obtained from conventional heat reflux method showed highest antioxidant potential in comparison to UAE extracts, which have been further supported by the high-concentration polyphenol and flavonoid compounds in 70% ethanol extract obtained by heat reflux as compared to UAE extracts.

Anthelmintic, Nematicidal, and Trypanocidal Activity

Bandh et al. (2011) studied the anthelmintic activity of methanol extract obtained from *N. cataria* both in vitro and in vivo. Anthelmintic effects ($p > 0.05$) of methanolic extract on live *Haemonchus contortus* worms have been revealed from their death and/or paralysis after 8-h exposure by an in vitro study. On the other hand, in vivo study of extract in sheep (infected naturally with mixed species of gastrointestinal nematodes) has demonstrated a maximum (73.69%) egg count reduction on day 15 after treatment in treated sheep at a dose of 2 g/kg body weight. Pavaraj et al. (2012) evaluated the nematicidal activity of methanol extracts isolated from ten plants against second-stage juveniles and egg hatchability of *Meloidogyne incognita.* The nematode juveniles and eggs have been exposed to different concentrations of plant extract ranging from 10 ppm (*parts per million)* to 100 ppm for 24, 48, and 72 h. *N. cataria* and *Couroupita guianensis* extracts have shown mortality of 73–86% after exposure of 72 h. The egg-hatching capacity has been declined with increase in concentration of plant extracts. The extracts obtained from *N. cataria, Pentanema indicum*, and *Couroupita guianensis* have shown more reduction in egg hatching in comparison to extracts obtained from other tested plants. Nematode mortality and larval hatching have been affected strongly by selected plant species, concentration of extracts, and exposure duration of nematode and larvae. These activities of different plant extracts have been attributed to the presence of different oxygenated compounds and their derivatives, which interact with biomembrane and cytoplasm of the nematode. Saeidnia et al. (2008) evaluated diethyl ether extract of *N. cataria* isolated from young leaves for its trypanocidal activity against epimastigotes of *Trypanosoma cruzi*. The diethyl ether extract revealed strong trypanocidal activity with minimum lethal concentration of 6.2 μM.

Effects on Central Nervous System

Nepetalactone, nepetalic acid, and commercial sample of *N. cataria* oil have been screened for their behavioral and toxicological effects in rats and mice (Ali et al. 2012). Biphasic effect of alcoholic extract of *N. cataria* has been reported on the behavior of chicks by Fareed et al. (2013). High dose greater than 2 g/kg has induced sleep in a less number of chicks, whereas low and moderate dose greater than 25–1800 mg/kg has induced sleep in a large number of chicks. This agent has been very effective in promoting sleep, calming nervous system, and relieving pressure.

The antidepressant effect of 10% enriched chow with *N. cataria* leaves and apolar extracts has been evaluated in male mice by Bernardi et al. (2010) with the help of behavioral despair test (BDT), elevated plus maze (EPM), and open-field test (OF). The BDT essay revealed the reduction of immobility time in mice upon repeated feeding with chow-enriched leaves ($p < 0.0007$), whereas no differences have been observed with EPM or OF test in case of repeated feeding groups with

chow-enriched leaves. Further, OF test in mice (treated acutely) with apolar extract of *N. cataria* leaves has shown reduction in rearing frequency ($p < 0.0042$) and locomotory activity ($p < 0.0001$) in comparison to control group. The time of immobility has been decreased in BDT, when mice have been treated with apolar extract repeatedly ($p < 0.001$) and acutely ($p < 0.0001$). Furthermore, when apolar extract has been administrated repeatedly it decreased the latency for the first immobility ($p < 0.0001$). The data revealed that apolar extract of *N. cataria* has antidepressant activity. Apart from this there have been many other reports attributed to anxiolytic and antidepressant properties of *N. cataria* plant (Bhat and Moskoviz 2009).

Feline Attractant

Different *Nepeta* species have been known for their feline attractant properties for a long time. These properties of different *Nepeta* species have been due to the presence of nepetalactone and its isomers in different extracts of aforementioned species. The unique behavior pattern has been observed in most of the species of Felidae family towards compounds obtained from *N. cataria*. These compounds have showed pseudo-narcotic effects and might either act as hallucinogens or cross-react with social odors of natural origin. Birkett et al. (2011) synthesized the unnatural (4aR,7R,7aS)-nepetalactone and enantiomer of (4aS,7S,7aR)-nepetalactone. These two molecules have been bioassayed against two American short-hair, three Abyssinian, and four Japanese cats. Almost all cats reacted strongly especially the female ones towards both the enantiomers. Female cats have been found to be extremely attractive even at the dose of 0.01 mg.

Insect Repellent, Attractant, and Insecticidal Activity

The essential oil isolated from different parts of *N. cataria* has been reported to protect well from several insect pests, cockroaches, and many mosquito species, which transmit several diseases (Peterson 2001; Schultz et al. 2004; Bernier et al. 2005; Trongtokit et al. 2005; Zhu et al. 2006). Further, essential oil obtained from catmint plant repels about 13 families of insects (Maia and Moore 2011). Peterson and Coats (2001) reported that the *E,Z*-isomer of nepetalactone obtained from catnip oil has been more active in comparison to *Z,E*-isomer and DEET (N,N-diethyl-3-methylbenzamide) as insect repellent. Schultz et al. (2004) evaluated catnip essential oil for its repellence activity against houseflies (*Musca domestica*) and American cockroaches (*Periplaneta americana*) and found that catnip essential oil has been good and in some cases better repellent as compared to citronellal or DEET. Catnip essential oil has shown more repellent activity than citronellal and DEET in the short-term bioassay. Further, Chauhan et al. (2005) observed that compounds isolated from catnip oil have showed greater bite deterrence effect as compared to ethanol control against yellow fever mosquito (*Aedes aegypti)*, whereas

racemic nepetalactone and their individual isomers have showed less effective deterrence effect as compared to DEET or (1*S*,2'*S*)-2-methylpiperidinyl-3-cyclohexene-1-carboxamide (SS220) against biting of *A. aegypti*. Amer and Mehlhorn (2006) tested the essential oil of catnip for its repellent activity and protection potential using the skin of human volunteers against yellow fever mosquito. The oil has shown protection time of 8 h with 100% repellent potential against all three tested species. Gonzalez and Hallahan (2007) observed that dihydronepetalactone minor component of catnip essential oil has been more stable and has pleasant fragrance as compared to nepetalactone. Further, it has shown insect repellent activity with improved properties as compared to nepetalactone and in some cases this activity exceeded than synthetic compound DEET.

Spasmolytic and Bronchodilatory Activities

Gilani et al. (2009) evaluated essential oil of *N. cataria* for their spasmolytic and bronchodilatory activities on gastrointestinal and respiratory disorders. The essential oil, verapamil, and papaverine have suppressed spontaneous and high pre-contractions of K^+ (80 mM) in isolated rabbit jejunum and also shifted concentration–response curves of Ca^{2+} to right, indicating the blocking activity in calcium channel. Further, this essential oil and papaverine suppressed the K^+ and carbachol (1 μm) pre-contractions in isolated trachea of guinea pig. The oil has shown PDE (phosphodiesterase) inhibitor activity like papaverine. Furthermore, the oil at 25–80 times higher concentrations caused cardiodepression similar to papaverine in isolated atria of guinea pig. The above study indicated that *N. cataria* possesses myorelaxant and spasmolytic activities regulated through dual inhibition of PDE and calcium channels. This study has explained the traditional use of essential oil of *N. cataria* in cough, diarrhea, and asthma.

Safety and Toxicity

Zhu et al. (2009) evaluated catnip (*N. cataria*) essential oil for its dermal, acute oral, primary dermal, eye irritation, and inhalation toxicity.

Acute Oral Toxicity

Catnip oil has not caused any mortality and also not even induced any toxicity in treated male and female mice when exposed to a dose of 1000–2150 mg/kg BW (body weight) with exception of death of one male mouse. The study revealed that the catnip oil has showed medium lethal dose (LD_{50}) at 2710 mg/kg BW in case of male and 3160 mg/kg BW in case of female mice.

Acute Dermal Toxicity

The test for acute dermal toxicity using single dose of catnip oil (5000 mg/kg BW) on Wistar rats showed that all rats have survived and remained active after the testing. It revealed that the catnip oil has not shown any acute dermal toxicity and no major abnormalities have been observed in any of the tested animals. The catnip oil has showed acute dermal $LD_{50} > 5000$ mg/kg BW.

Acute Inhalation Toxicity

The catnip oil when applied at a concentration of 10 g/m^3 to a group of mice has showed no toxicity effect and abnormalities in treated animals after two weeks. For acute inhalation $LC_{50} > 10$ g/m^3 has been observed in case of both sexes of mice.

Primary Skin Irritation

No signs of erythema or edema have been observed in four New Zealand white rabbits during first two days of the application at a dose of 0.5 g of catnip oil. On the third day of application minor erythema has been reported in one animal on the treated area, but in case of other animals it has been observed on fourth day. However no edema and skin irritation have been observed in case of any tested animals during the whole testing period.

Primary Eye Irritation

The catnip oil has not been exhibiting any signs of corneal opacity and iritis on three tested rabbits. During the first hour of test, conjunctival irritation has been observed, but it has not persisted for twenty four hours. During the testing period no gross toxicity signs have been observed in tested animals.

Toxicology Study of Refined Oil of **N. cataria** *(Biochemical Pesticide)*

US Environmental Protection Agency has categorized the refined oil of *N. cataria* (hydrogenated catmint oil) into different toxicological category I, II, III, and IV depending upon the hazards recognized from the study of information given to the agency. Category IV indicates lowest whereas category I indicates highest toxicity.

The agency has categorized the technical grade refined oil into category III for primary eye irritation and acute oral toxicity and into category IV for acute dermal, skin, and acute inhalation irritation.

Future Prospective

Ethnopharmacological Prospective

It has been reported by different research groups that the different extracts obtained from *N. cataria* have showed prominent anti-inflammatory, anti-nociceptive, cytotoxic, anthelmintic, nematicidal, trypanocidal, spasmolytic, and bronchodilatory activity, but only a few papers have been published on these topics (Suschke et al. 2007; Saeidnia et al. 2008; Ricci et al. 2010; Bandh et al. 2011; Pavaraj et al. 2012). Apart from these many species of genus *Nepeta*, viz. *N. juncea*, *N. hindostana*, *N. pannonica*, *N. nuda ssp. albiflora*, etc., have been known to show prominent vasorelaxant, platelet aggregation, anti-atherosclerotic, and phytotoxic activity (Ashraf et al. 1999; Hussain et al. 2009; Mancini et al. 2009). These species have comparable chemical composition to *N. cataria*. So, there has been remarkable scope for exploring ethnopharmacology of *N. cataria.*

Integrated Pest Management (Sex Pheromone Defensive Secretions)

Nepetalactone and related iridoid compounds having 1-R configuration have acted as sex pheromones in many species of aphids, viz. *Megoura viciae*, greenbug (*Schizaphis graminum*), pea aphid (*Acyrthosiphon pisum*), black bean aphid (*Aphis fabae*), bird-cherry aphid (*Rhopalosiphum pad*), peach-potato aphid (*Myzus persicae*), potato aphid (*Macrosiphum euphorbiae*), and hop aphid (*Phorodon humuli*) (Goldansaz et al. 2004). Due to these aforementioned properties of nepetalactone and related compounds, there have been a great opportunity to use these compounds in integrated pest management strategies for the control of different harmful insect pest species, as this is the need of present world to explore the new compounds for this purpose due to the resistance developed by the insect pests against different chemicals used in present time. Further nepetalactone and its derivatives have been well known for their insect repellent properties.

Biosynthesis of Alkaloids

Iridoid compounds have acted as a key intermediate for the synthesis of different kinds of alkaloids, i.e., secologanin monoterpene glycoside has been the chief compound in the alkaloid biosynthesis. Iridoid loganin has acted as the biosynthetic

precursor for the synthesis of secologanin. Nepetalactone and its isomers can act as the precursors for the synthesis of loganin and hence for the synthesis of different kinds of alkaloids. This opens the new field for the synthetic chemists for the synthesis of useful alkaloids from the precursor which have not been of amino acid origin. Apart from these essential oils and different extracts obtained from *N. cataria* may find many applications in cosmetic, pharmaceutical, and agrochemical industries.

Conclusion

Although many pharmacologically active secondary metabolites have been discovered so for, yet the nature must have many more in her basket. So, a detailed and systematic study is required in order to identify and document the plants, which have been pharmacologically important and provided a variety of secondary metabolites of biological importance. *N. cataria* has been a representative species of genus *Nepeta*, which belongs to family Lamiaceae. The plant has been known for its wide range of traditional usages and used to relieve pain, and for the cure of different gastrointestinal and respiratory ailments, female disorders, pneumonia, rheumatism, etc. The chemical diversity of *N. cataria* has mainly been represented by terpenoids, flavonoids, polyphenols, and steroids; out of these iridoid compounds (unique class of terpenoids) such as nepetalactone and its derivatives have been the representative chemical constituents of this plant and genus *Nepeta*. These chemical constituents have been chiefly responsible for the numerous biological activities shown by the plant, out of which their anti-inflammatory, antidiabetics, antioxidant, and insecticidal have been the most outstanding. Further, the toxicological studies of this plant have revealed that the essential oils and different extracts obtained from the plant have mostly been nontoxic in nature. In spite of this, there have been numerous areas of its usage in traditional medicine system that still need pharmacological justification. This review would be supportive in the enhancement of today's research in the development of new biologically potent compounds derived from plants (of genus *Nepeta*) and which would find many applications in the well-being of mankind.

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References

Adiguzel A, Ozer H, Sokmen M, Gulluce M, Sokmen A, Kilic H, Sahin F, Baris O (2009) Antimicrobial and antioxidant activity of the essential oil and methanol extract of *Nepeta cataria*. Pol J Microbiol 58:69–76

Aggarwal BB, Sundaram C, Malani N, Ichikawa H (2007) Curcumin: the Indian solid gold. Adv Exp Med Biol 595:71–75

Amer A, Mehlhorn H (2006) Persistency of larvicidal effects of plant oils under different storage conditions. Parasitol Res 99:478–490

Angioni A, Barra A, Coroneo V, Dessi S, Cabras P (2006) Chemical composition, seasonal variability, and antifungal activity of *Lavandula stoechas* L. ssp. stoechas essential oils from stem/leaves and flowers. J Agric Food Chem 54:4364–4370

Ashraf MZ, Khan MSY, Hameed HA, Hussain ME, Fahim M (1999) J Ethnopharmacol 66:97–102

Ali T, Javan M, Sonboli A, Semnanian S (2012) Evaluation of the antinociceptive and anti-inflammatory effects of essential oil of *Nepeta pogonosperma* Jamzad et Assadi in rats. Daru J Pharm Sci 20:48. https://doi.org/10.1186/2008-2231-20-48

Bandh SA, Kamili AN, Ganai BA, Lone BA, Saleem S (2011) Evaluation of antimicrobial activity of aqueous extracts of *Nepeta cataria*. J Pharm Res 4:3141–3142

Baranauskiene R, Venskutonis RP, Demyttenaere JCR (2003) Sensory and instrumental evaluation of catnip (*Nepeta cataria* L.) aroma. J Agric Food Chem 51:3840–3848

Baser KHC, Kirimer N, Kurkcuoglu M, Demirci B (2000) Essential oils of *Nepeta* species growing in Turkey. Chem Nat Compd 36:356–359

Bernardi MM, Kirsten TB, Salzgeber SA, Ricci EL, Romoff P, Lago JHG, Lourenco LM (2010) Antidepressant-like effects of an apolar extract and chow enriched with *Nepeta cataria* (catnip) in mice. Psychol Neurosci 3:251–258

Bernier UR, Furman KD, Kline DL, Allan SA, Barnard DR (2005) Comparison of contact and spatial repellency of catnip oil (*Nepetea*) and *N,N*-diethyl-3- methylbenzamide (deet) against mosquitoes. J Med Entomol 42:306–311

Bhat RD, Moskoviz G (2009) Herbal medicinal test from South Africa. Int J Exp Bot 78:67–73

Bisht DS, Lal P, Mathela CS, Padalia RC, Singh L, Pande V, Lal P, Mathela CS (2010) Constituents and antimicrobial activity of the essential oils of six Himalayan Nepeta species. J Serb Chem Soc 75:739–747

Birkett MA, Hassanali A, Hoglund S, Pettersson J, Pickett JA (2011) Repellent activity of catmint, *Nepeta cataria*, and iridoid nepetalactone isomers against Afro-tropical mosquitoes, ixodid ticks and red poultry mites. Phytochemistry 72:109–114

Birkett MA, Pickett JA (2003) Aphid sex pheromones: from discovery to commercial production. Phytochemistry 62:651–656

Celis A, Mendoza C, Pachon M, Cardona J, Delgado W, Cuca L (2008) Plant extracts used as biocontrol with emphasis on Piperaceae family. A review. Agron Colomb 26:97–106

Chauhan KR, Klun JA, Debboun M, Kramer M (2005) Feeding deterrent effects of catnip oil components compared with two synthetic amides against *Aedes aegypti*. J Med Entomol 42:643–646

Dabiri M, Sefidkon F (2003) Composition of essential oil of *Nepeta crassifolia* Boiss Buhse. Flav Fragr J 18:157–158

Edewor TI, Usman LA (2011) Phytochemical and antibacterial activities of leaf extracts of *Nepeta cataria*. Afr J Pure Appl Chem 5:503–506

Fareed G, Afza N, Mali A, Fareed N, Lateef M, Iqbal L, Mughal UR (2013) Phytochemical screening, total phenolic contents and biological evaluation of aerial parts of *Nepeta praetervisa*. J Chem Soc Pak 35(5):1366–1370

Formisano C, Rigano D, Senatore F (2011) Chemical constituents and biological activities of Nepeta species. Chem Biodivers 8:1783–1818

Gilani AH, Shah AJ, Zubair A, Khalid S, Kiani J, Ahmed A, Rasheed M, Ahmad VU (2009) Chemical composition and mechanisms underlying the spasmolytic and bronchodilatory properties of the essential oil of *Nepeta cataria* L. J Ethnopharmacol 121:405–411

Goldansaz SH, Dewhirst S, Birkett MA, Hooper AM, Smiley DWM, Pickett JA, Wadhams LJ, McNeil J (2004) Identification of two sex pheromone components of the potato aphid, *Macrosiphum euphorbiae* (Thomas). J Chem Ecol 30:819–834

Gonzalez YI, Hallahan DL (2007) Abstracts of papers, 233rd. ACS National Meeting, AGRO-068, Chicago, IL, United States, 25–29 March 2007

Gopal N, Tejaswini J, Mantry S, Kumar SA (2014) International standards of medicinal plants. Int J Innov Pharm Sci Res 2:2498–2532

Hussain J, Jamila N, Gilani SA, Abbas G, Ahmed S (2009) Platelet aggregation, antiglycation, cytotoxic, phytotoxic and antimicrobial activities of extracts of Nepeta juncea. Afr J Biotechnol 8:935–940

Herron S (2003) Catnip, Nepeta cataria, a morphological comparison of mutant and wild type specimens to gain an ethnobotanical perspective. Econ Bot 57:135–142
Jamila N, Ullah R, Alwahsh MAA, Haider S, Wong KC, Ullah Z (2011) Secondary metabolites from *Nepeta juncea*. Afr J Biotechnol 10:17884–17886
Kraujalis P, Venskutonis PR, Ragazinskiene O (2011) Antioxidant activity and phenolic composition of extracts from *Nepeta* plant species. Foodbalt 79–83
Kafaru EO (1994) Simple ways of staying healthy. Elikaf Health Services Ltd, pp 32–33
Lee SY, Lee CY, Eom SH, Kim YK, Park NI, Park SU (2010) Rosmarinic acid production from transformed root cultures of Nepeta Cataria L. Sci Res Essays 5:1122–1126
Leung AY, Foster S (1996) In encyclopedia of common natural ingredients used in foods, drugs, and cosmetics. Wiley, New York, pp 137–138
Louey J, Petersen N, Salotti D, Shaeffer H, James KD (2001) Oil of catnip by supercritical fluid extraction. http://www.oceantech.co.in/pdf/TN-19%20-%20Oil%20of%20Catnip%20by%20SFE.pdf. Accessed 25 Dec 2015
Maia MF, Moore SJ (2011) Plant-based insect repellents: a review of their efficacy, development and testing. Malar J 10(Suppl 1):S11
Mancini E, Arnold NA, Feo VD, Formisano C, Rigano D, Piozzi F, Senatore F (2009) Phytotoxic effects of essential oils nepeta curviflora boiss, and nepeta nuda. L. subsp. albiflora growing wild in Libnan. J Plant Interact 4:253–259
Mihaylova D, Georgieva L, Pavlov A (2013) In vitro antioxidant activity and phenolic composition of *Nepeta Cataria* L. extracts. Int J Agric Sci Technol 1:74–79
Modnicki D, Tokar M, Klimek B (2007) Flavonoids and phenolic acids of Nepeta cataria var. citriodora (Becker) balb. (*Lamiaceae*). Acta Pol Pharm. 64:247–252.
Nostro A, Cannatelli MA, Crisafi G, Alonzo V (2001) The effect of *Nepeta cataria* extract on adherence and enzyme production of *Staphylococcus aureus*. Int J Antimicrob Agents 18:583–585
Pavaraj M, Bakavathiappan G, Baskaran S (2012) Evaluation of some plant extracts for their nematicidal properties against root-knot nematode, *Meloidogyne incognita*. J Biopest 5:106–110
Peterson C, Coats J (2001) Insect repellents. Past, present and future. Pestic Outlook 12:154–158
Peterson CJ, Ems-Wilson J (2003) Catnip essential oil as a barrier to subterranean termites (*Isoptera: Rhinotermitidae*) in the laboratory. J Econ Entomol 96:1275–1282
Peterson CJ (2001) Insect repellent of natural origin: catnip and osage orange. Ph. D. dissertation. Iowa State University, Ames
Peterson CJ, Nemetz LT, Jones LM, Coat JR (2002) Behavioral activity of catnip (Lamiaceae) essential oil components to the German cockroach (Blattodea: Blattellidae). J Econ Entomol 95:377–380
Rapisarda A, Galati EM, Tzakou O, Flores M, Miceli N (2001) *Nepeta sibthorpii* Bentham (Lamiaceae): micromorphological analysis of leaves and flowers. Farmaco 56:413–415
Rather MA, Hassan T, Dar BA, Shawl AS, Qurishi MA, Ganai BA (2012) Essential oil composition of *Nepeta raphanorhiza* Benth growing in Kashmir valley. Rec Nat Prod 6:67–70
Ravishankar B, Shukla VJ (2007) Indian systems of medicine: a brief profile. Afr J Tradit Complement Altern Med 4(3):319–337
Ricci EL, Toyama DO, Lago JHG, Romoff P, Kirsten TB, Reis-Silva TM, Bernardi MM (2010) Anti-nociceptive and anti-inflammatory actions of *Nepeta cataria* L. var. citriodora (Becker) Balb. essential oil in mice. J Health Sci Inst 28:289–293
Saeidnia S, Gohari AR, Hadjiakhoondi A (2008) Trypanocidal activity of oil of the young leaves of *N. cataria* L. obtained by solvent extraction. J Med Plants 7:54–57
Sajjadi SE (2005) Analysis of the essential oil of *Nepeta sintenisii* Bornm. from Iran. Daru 13:61–64
Schultz G, Simbro E, Belden J, Zhu J, Coats J (2004) Catnip, Nepeta cataria (Lamiales: Lamiaceae)—A closer look: Seasonal occurrence of nepetalactone isomers and comparative repellency of three terpenoids to insects. Environ Entomol 33:1562–1569

Shafaghat A, Oji K (2010) Nepetalactone content and antibacterial activity of the essential oils from different parts of *Nepeta persica*. Nat Prod Commun 5:625–628

Sharma A, Cannoo DS (2013) Phytochemical composition of essential oils isolated from different species of genus Nepeta of Labiatae family: A review. Pharmacophore 4:181–201

Sharma A, Cannoo DS (2016a) Comparative evaluation of extraction solvents/techniques for antioxidant potential and phytochemical composition from roots of Nepeta leucophylla and quantification of polyphenolic constituents by RP-HPLC-DAD. Food Measure 10(3):658–669

Sharma A, Cannoo DS (2016b) Effect of extraction solvents/techniques on polyphenolic contents and antioxidant potential of the aerial parts of Nepeta leucophylla and the analysis of their phytoconstituents using RP-HPLC-DAD and GC-MS. RSC Adv 6:78151–78160. https://doi.org/10.1039/C6RA12038E

Sherman PW, Hash GA (2001) Why vegetable recipes are not very spicy. Evol Hum Behav 22:147–163

Siddiqui AA, Iram F, Siddiqui S, Sahu K (2014) Role of Natural Products in Drug Discovery Process. Int J Drug Dev Res 6(2):172–204

Sue Eland (2008) Catmint. http://www.plantlives.com/docs/N/Nepeta_cataria.pdf

Suschke U, Sporer F, Schneele J, Geiss HK, Reichling J (2007) Antibacterial and cytotoxic activity of *Nepeta cataria* L., *N. cataria* var. *citriodora* (Beck.) Balb and *Melissa officinalis* L. essential oils. Nat Prod Commun 2:1277–`1286

Suschke U, Geiss HK, Reichling J (2006) Antibacterial activity of essential oils of catnip (N. cataria) and lemon balm (Melissa officinalis) against clinical isolate from respiratory track. Planta Med 72:027

Tepe B, Daferera D, Tepe AS, Polissiou M, Sokmen A (2007) Antioxidant activity of the essential oil and various extracts of *Nepeta flavida* Hub. Mor from Turkey. Food Chem 103:1358–1364

Trongtokit Y, Rongsriyam Y, Komalamisra N, Apiwathnsorn C (2005) Comparative repellency of 38 essential oils against mosquito bites. Phytother Res 19:303–309

Tapsell LC, Hemphill I, Cobiac L, Sullivan DR, Fenech M, Patch CS, Roodenrys S, Keogh JB, Clifton PM, Williams PG, VA F, Inge KE (2006) Health benefits of herbs and spices: the past, the present, the future. Med J Aust 185:S4–S24

Turner W (1995) A new herball. Cambridge university press, Cambridge

Zenasni L, Bouidida H, Hancali A, Boudhane A, Amzal H, Idrissi AI, Aouad RE, Bakri Y, Benjouad A (2008) The essentials oils and antimicrobial activity of four *Nepeta species from Morocco*. J Med Plants Res 2:111–114

Zimmermann N, Hilgraf R, Lehmann L, Ibarra D, Francke W (2012) Stereoselective synthesis of trans-fused iridoid lactones and their identification in the parasitoid wasp Alloxysta victrix, Part I: Dihydronepetalactones. Beilstein J Org Chem 8:1246–1255

Zhu JJ, Zeng XP, Berkebile D, Du HJ, Tong Y, Qian K (2009) Efficacy and safety of catnip (Nepeta cataria) as a novel filth fly repellent. Med Vet Entomol 23:209–216

Zhu J, Zeng X, Ma Y (2006) Comparisons of adult repellency and larvicidal activity of plant essential oils against mosquitoes. J Am Mosq Control Assoc 22:515–522

Chemistry and Pharmacology of Guggulsterone: An Active Principle of Guggul Plant

Musadiq Hussain Bhat, Mufida Fayaz, Amit Kumar, and Ashok Kumar Jain

Abbreviations

BCL-2	B-cell lymphoma 2
COX-2	Cyclooxygenase-2
DMSO	Dimethyl sulfoxide
DSS	Dextran sulfate sodium
FXR	Farnesoid X receptor
GS	Guggulsterone
HNSC	Head and neck squamous carcinoma
IAP	Inhibitor of apoptosis proteins
IFN	Interferon
IL	Interleukin
iNOS	Inducible nitric oxide synthase
JNK	c-Jun NH(2)-terminal kinase
LPS	Lipopolysaccharide
MAPKAP1	Mitogen-activated protein kinase associated protein 1
MCL-1	Myeloid cell leukemia 1
mTOR	Mammalian target of rapamycin
NF-kB	Nuclear factor-kB
THF	Tetrahydrofuran
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
XIAP	X-linked inhibitor of apoptosis protein

M. H. Bhat (✉) · M. Fayaz
School of Studies in Botany, Jiwaji University, Gwalior, MP, India

A. Kumar · A. K. Jain
Institute of Ethnobiology, Jiwaji University, Gwalior, MP, India

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Introduction

Steroids form a group of structurally related compounds widely distributed in animals and plants. Steroids have the fundamental structure of four carbon rings called the steroid nucleus. The addition of different chemical groups at different positions forms a large number of different types of steroidal compounds (Yokota 1997; Benveniste 1986). The steroids that are obtained from plant sources are known as phytosterols.

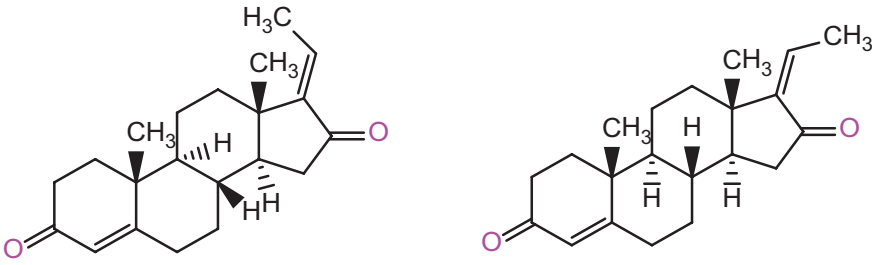
Plant steroids are further metabolised owing to the enzymatic conversion to produce biologically active steroids (Hubert 2003). Plant steroids have been classified into different classes based on their chemical structure, pharmacological activities and source from which they have been isolated. These include brassinosteroids, bufadienolides, cardenolides, cucurbitacins, ecdysteroids, steroid saponins, steroidal alkaloids and withasteroids (Patel and Savjani 2015). Plant steroids possess many interesting medicinal and pharmaceutical activities like antitumour, immunosuppressive, hepatoprotective, antibacterial, antihelminthic, cytotoxic and cardioprotective activities.

Guggulsterone is a natural alkaloid steroid derived from the resin of the traditional medicinal plant "guggul." It exists in two stereoisomers, i.e. *E*-guggulsterone and *Z*-guggulsterone. In order to get further insights into the pharmacological profile of this secondary metabolite, valuable synthetic mechanisms were developed to synthesise guggulsterone in sufficient quantities to put in evidence of interesting biological properties of this compound. The gum resin from guggul plants has been used for 1000 years in Ayurveda to treat various disorders, including internal tumours, cancer, obesity, intestinal worms, liver disorders, leucoderma, ulcers, urinary complications, sinuses and oedema. Guggulsterone has been identified as a bioactive component of this gum resin. The aim of this review is to examine in detail the properties of the compound so far reported in the literature from a chemical, phytochemical and pharmacological points of view.

Chemistry

Guggulsterone (GS) [4,17(20)-pregnadiene-3,16-dione] is a plant polyphenol extracted from the gum resin of the *Commiphora mukul* tree. It is an analogue of progesterone and exists in two forms, viz. *E*-isomer and *Z*-isomer (Fig. 1). The occurrence of guggulsterones in nature was first reported by Patil et al. (1972) by isolating *E*- and *Z*-guggulsterone in addition to a number of other important bioactive compounds from the gum resin of *Commiphora mukul*, commonly used for the treatment of rheumatoid arthritis and related problems.

The synthesis and stereochemistry of these compounds were reported long before their isolation by Benn and Dodson (1964). The compounds isolated were found identical to the synthesised compounds in all aspects. Due to its low yield



***cis*-guggulsterone**
pregna-4,17-diene-3,16-dione,
(17E)-isomer

***trans*-guggulsterone**
pregna-4,17-diene-3,16-dione,
(17Z)-isomer

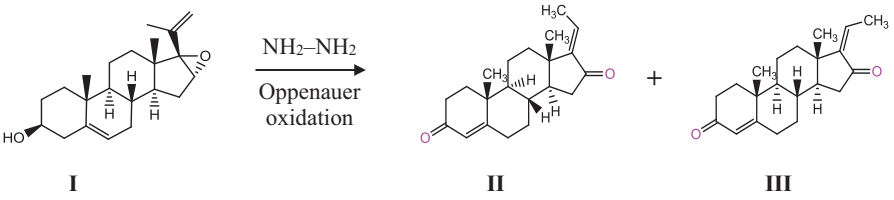
Fig. 1 Structures of *E*- and *Z*-isomers of guggulsterone

from natural sources and rising demand, synthetic mechanisms were recently developed for synthesis of this important sterol to make it available in sufficient quantities. Gupta et al. (2006) synthesised these compounds by following Benn and Dodson method in which 16,17-epoxypregnenolone (**I**) was refluxed with hydrazine hydrate to obtain a mixture of the isomeric diols 5,17(20)-*cis*-pregnadiene-3β,16α-diol and 5,17(20)-*trans*-pregnadiene-3β,16α-diol. This diol mixture when subjected to Oppenauer oxidation using toluene, cyclohexanone and aluminium isopropoxide yields a mixture of dienones. Chromatographical studies showed that elution with hexane and ethyl acetate (9:1) gave the *trans*-isomer (**II**), 4,17(20)-*trans*-pregnadiene-3,16-dione (*Z*-form), followed by the *cis*-isomer (**III**), 4,17(20)-*cis*-pregnadiene-3,16-dione (*E*-form) (Scheme 1).

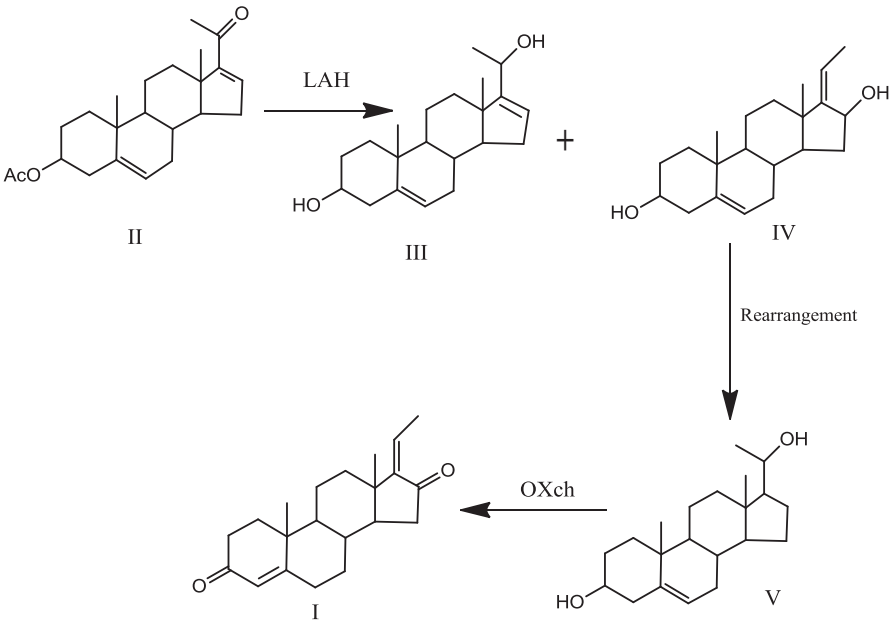
In 2004, Pratap and co-workers developed an improved mechanism for the preparation of guggulsterones which comprises epoxidation of 16-dihydropegnenolone acetate (16 DPA) by reacting it with hydrogen peroxide reagent in presence of a co-base in a polar solvent to obtain 3-β-hydroxy-16-α and 17-oxido-5 pregnen-20-one, converting these in reaction with hydrazine in the presence of a strong base at refluxing temperature followed by oxidation to obtain desired guggulsterones (Scheme 2).

Due to many drawbacks in the above process they developed another alternative mechanism in which the unsaturated carbonyl function of 16-DPA is converted to 16,17-epozy carbonyl followed by Kishner reduction-elimination under Huang-Minlon condition (Scheme 3) to produce the key intermediate (Pratap et al. 2008).

Due to simultaneous formation of pyrazone in high yields, this mechanism was also found unsuitable for large-scale preparation. Ham et al. (2011) successfully prepared *E*-guggulsterone (84% yield) by regioselective method, a two-step process from 16,17-epoxy-pregnenolone via hydrazine reduction and Oppenauer oxidation. Additionally, isomerisation was induced by heat, light ($h\nu$) and acid catalysis to convert *E*-guggulsterone into the corresponding *Z*-isomer. In the first step, *cis*-diol



Scheme 1 Synthesis of stereoisomers of guggulsterone from 16,17-epoxypregnenolone (**I**) refluxed with hydrazine hydrate

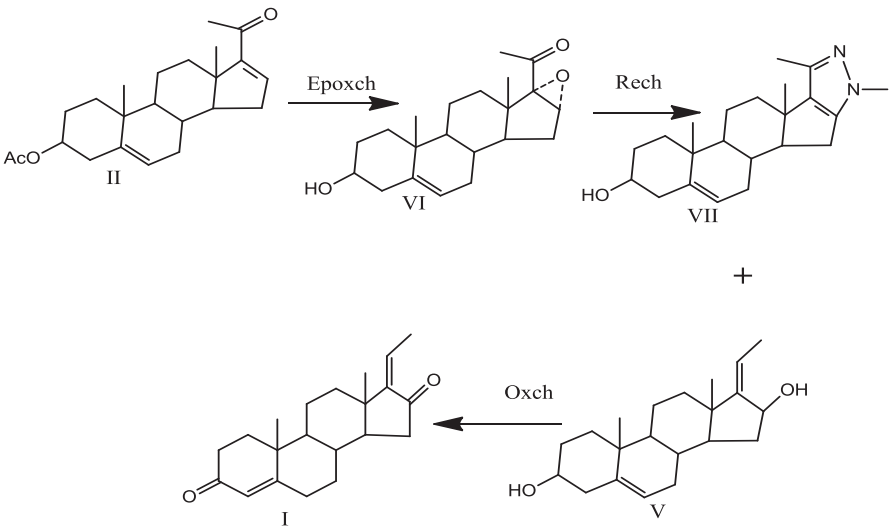


Scheme 2 Synthesis of guggulsterone through epoxidation of 16-dihydropegnenolone acetate (16 DPA) in reaction with hydrogen peroxide reagent in a polar solvent

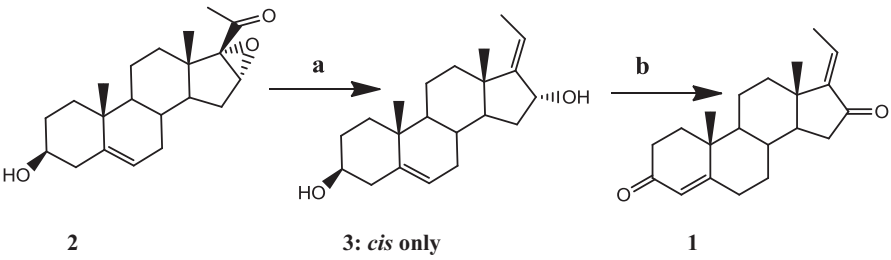
(**3**) was prepared from steroid (**2**) using hydrazine monohydrate (98% pure) and 9.0 equiv. of KOH at 160 °C for 2 h (91% yield). The stereoselectivity and yield were quite different from earlier reports for the same reaction. Two important factors that were identified to affect the regioselectivity and yield of *cis*-**3** were the purity of hydrazine monohydrate and the reaction time (Scheme 4). In the second and final step, *E*-guggulsterone was prepared through an Oppenauer oxidation.

Different solvents were also tested to prove the important role of using different solvents in the regioselectivity of the reaction and it was found that when benzene and 0.5 equiv. of Al(O-*i*-propyl)$_3$ were used, pure *E*-guggulsterone in 92% yield was obtained (Fig. 2).

Gioiello et al. (2012) reported a new, efficient and gram-scale regioselective synthesis of *E*-guggulsterone and described the valuable HPLC protocol for the



Scheme 3 Unsaturated carbonyl function of 16-DPA converted to 16,17-epozy carbonyl followed by Kishner reduction-elimination under Huang-Minlon condition



Scheme 4 Regioselective synthesis of *E*-guggulsterone from 16,17-epoxypregnenolone (**2**) and conversion of *E*-guggulsterone into the corresponding *Z*-isomer. (**a**) KOH, NH_2NH_2 monohydrate, di(ethylene glycol), 160 °C for 2 h (91% yield); (**b**) Al(O-*i*-propyl)$_3$, cyclohexanone, benzene, 80 °C for 2 h (92% yield)

chromatographic evaluation of both isomers and attempts made to obtain the *Z*-isomer 2 from 1 (Scheme 5).

For synthesis of *E*-guggulsterone, androsten-3,17-dione (**II**) was used as the starting material. Thus, in order to prevent side reactions on the enone system at ring A, androsten-3,17-dione was initially treated with triethyl orthoformate in the presence of catalytic amounts of *p*-toluene sulphonic acid (*p*-TSA) in a mixture of THF/EtOH (30:1 v/v) to provide the corresponding enol ether (**III**) in nearly quantitative yield. Through Wittig reaction, C-17 side chain was generated by using phosphorus ethyl triphenyl bromide and potassium *t*-butoxide (*t*-BuOK) as a base in THF. The reaction was conducted at reflux for 18 h. The next step in this reaction is acidic hydrolysis to give *Z*-4,17(20)-pregnadiene-3-one (**V**) as a single isomer. The selec-

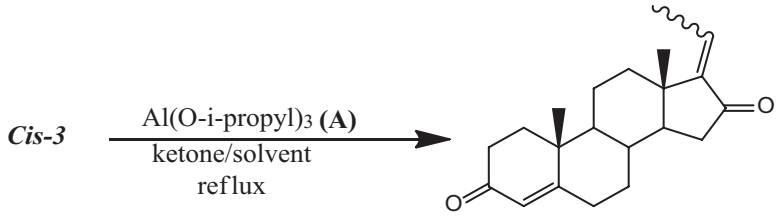
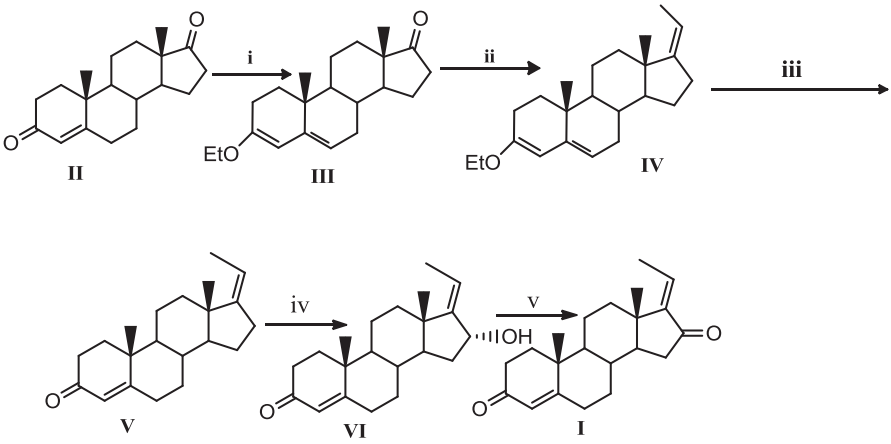


Fig. 2 Optimisation of Oppenauer oxidation conditions for *E*-guggulsterone synthesis



Scheme 5 Stereoselective synthesis of *E*-guggulsterone (**I**) from 4-androsten-3,17-dione (**II**). (i) $CH(OEt)_3$, *p*-TSA, THF/EtOH, quantitative; (ii) EtPPh3Br, *t*-BuOK, THF, reflux; (iii) HCl, THF, 95% from **III**; (iv) SeO_2, *t*-BuO_2H, 90%; (v) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 85%

tive allylic oxidation at C-16 was carried out using selenium dioxide (SeO_2) and *t*-BuO_2H in CH_2Cl_2 at 0 °C. Stereochemistry was assigned by using NMR COSY and NOE analysis. Finally, 4,17(20)-*cis*-pregnadiene-3,16-dione (**I**) (*E*-guggulsterone) was synthesised by using Swern oxidation and silica gel purification in an appreciable yield (73%).

Pharmacology

Hypolipidaemic

The hypolipidaemic effects of guggulsterone have been well established through clinical trials. Several studies on animal models revealed that guggulsterone reduces hyperlipidaemia in the animals fed with high-fat diet. Guggulsterone treatment decreased liver cholesterol in mice fed with cholesterol diet but was found to be

ineffective in FXR null mice. The basis for the cholesterol-lowering activity of guggulsterone is the inhibition of FXR activation (Urizar et al. 2002). Treatment with guggulsterone inhibited the brain dopamine β-hydroxylase activity with marked stimulation in heart. Similar effects were shown by catecholamines. Serotonin and histamine content decreased in heart but conversely increased in brain. Alteration in these amines and dopamine β-hydroxylase activity is considered as one of the possible mechanisms for the antilipidaemic action of guggulsterone (Srivastava and Kapoor 1986). This compound enhanced the activity of agonists of BSEP expression as guggulipid treatment lowered serum triglyceride and raised the levels of high-density lipoprotein (HDL) in rats (Cui et al. 2003). For comparison high-fat-fed diabetes-induced rats resembling H-type diabetic condition in humans were used to assess the hypolipidaemic and antidiabetic activity of this compound. Guggulsterone showed varying effects with improved PPAR gamma expression in in vitro and in vivo conditions (Sharma et al. 2009). Guggulsterone induced caspase-dependent apoptosis. It reduced lipid content in adipocytes and also downregulated transcription factors like PPARγ2, C/EBPα and C/EBPβ (Pal et al. 2013; Yang et al. 2008). Guggulsterone inhibited the chenodeoxycholic acid activated nuclear farnesoid X receptor cholesterol metabolic activity in the liver. The cambrenoids lowered the cholate-activated rate of human pancreatic IB phospholipase A2 which regulates absorption of cholesterol and fat in gastrointestinal system, but did not show any clear effect on farnesoid X factor FXR (Yu et al. 2009). It reversed CAAT/enhancer-binding protein, adipogenesis-related gene, peroxisome proliferator-activated receptor (PPAR)γ, sterol regulatory element-binding protein-1c, fatty acid-binding protein, adipoQ and mRNA expression carried out by a FXR ligand in preadipocytes (Rizzo et al. 2006). Hypercholesterolaemia-induced male Albino rabbits administered with guggul diet (2 g/kg of body weight) exhibited significantly lower serum and liver cholesterol levels (Satyavati et al. 1969). In high-fat-fed mice, guggulsterone treatment enhanced glucose tolerance, plasma insulin level, low-density proteins (LDL), fasting blood glucose, very-low-density lipoproteins (VLDL), cholesterol, triglycerides and expression of various genes involved in lipid metabolism (Sharma et al. 2009). Sexual clinical trials have also been conducted to evaluate the hypolipidaemic effect of guggul and most of the studies have shown that it lowers serum cholesterol and triglycerides. A clinical trial reported in 1970 demonstrates that when the extract of guggul (0.5 g daily) was given to patients with high lipid levels for 12 weeks, serum cholesterol, phospholipid levels and triglycerides were lowered by 27%, 18% and 29%, respectively (Malhotra and Ahuja 1971). Treatment with gum guggul (3 g thrice a day) and ether extract of guggul (0.5 g daily) for 3 weeks decreased serum lipid levels in hypercholesteraemic and hypolipidaemic patients but not in hyperlipidaemic patients (Ulbricht et al. 2005). In a double-randomized controlled study on obese patients, when guggul extract was given in a dosage of 1 g daily for 3 weeks, reduction in serum lipid levels in the hyperlipidaemic patients was observed (Kuppurajan et al. 1973).

Thyroid-Stimulating Action

Z-form of guggulsterone showed a strong thyroid-stimulatory action when administered to Albino rats (1 mg/100 g body weight). This increased the iodine uptake by the thyroid and enhanced activities by thyroid peroxidise and protease. It also increased the oxygen consumption by isolated slices of liver and muscle biceps (Tripathi et al. 1984). Rats pretreated with carbimazole (10 mg/kg body weight) showed no thyroid stimulation by guggulsterone through pituitary activation (Tripathi et al. 1988).

Cardioprotective Activity

Several studies have reported the cardioprotective activity of guggulsterone. The cardioprotective effects of guggulsterone (both forms) were compared with those of gemfibrozil at the same doses. Guggulsterones and both the isomers at different concentrations (5–20 mM) inhibited the oxidative degradation of lipids in human low-density lipoprotein (LDL) and rat liver microsomes induced by metal ions (Chander et al. 2003). A marked activity was shown by guggulsterone on cardiac enzymes and P450 system against myocardial necrosis induced by isoproterenol in rats (Kaul and Kapoor 1989). Guggulsterone decreased DOX-induced apoptosis in cardiomyocyte H9C2 (Wang et al. 2012). siRNA-mediated silencing of endogenous FXR or post-ischaemic myocardial apoptosis showed reduction by guggulsterone in murine myocardial ischaemia. The functional receptor in cardiac tissue being FXR regulated apoptosis in cardiomyocytes and contributed to myocardial ischaemia (Pu et al. 2013). Guggulsterone showed marked reversal of metabolic change in heart with increased levels of phospholipase and cytosolic lipid peroxide, and reduction of cardiac glycogen, related to ischaemia of heart in rats (Chander et al. 2003). Guggulsterone enhanced endothelial tissue factor pathway inhibitor and impaired plasminogen activator inhibitor-I and vascular cell adhesion molecule-I protein. It also showed marked effect in inflammatory disease associated with increased rate of thrombosis (Gebhard et al. 2009).

Antidiabetic

Several studies revealed the antidiabetic potential of guggulsterone. Guggulsterone prevented IL-1β- and iFN-γ-induced β-cell damage. Besides this, it also reduced iNOS and PGE2 production. These effects reduced the levels of iNOS and COX-2 expression. It also prevented Janus kinase/STAT activation, downregulated suppressor of cytokine signalling-3 and impaired glucose-stimulated secretion of insulin (Lv et al. 2008). Guggulsterone also attenuated the reduction in pancreatic β-cell

size, increase in adipocytes and steatosis of the liver in high-fat-diet-fed rats. It also inhibited 3T3-L1 preadipocyte differentiation and had both hypoglycaemic and hypolipidaemic effects that can help to cure type 2 diabetes (Sharma et al. 2009). Guggulsterone suppressed the insulin secretion by mouse β-cells via FXR activation and KATP channel inhibition stimulated by bile acids (Dufer et al. 2012).

Anti-inflammatory

Guggulsterone inhibited LPS-induced upregulation of tumour necrosis factor-alpha and cyclooxygenase-2. Guggulsterone pretreatment suppressed cyclooxygenase-2 protein production (Song et al. 2010). Guggulsterone abolished the increases of NI-Kappa B binding activity of nuclear P50 and P65 levels along with I Kappa B alpha depletion in cells stimulated with IL-1β (Lee et al. 2008). Several studies implicated this compound as the best option in the treatment of inflammatory bowel disease. It strongly inhibited LPS- or IL-1β-induced intracellular adhesion molecule 1 gene expression, NF-κB DNA binding activity, NF-κB transcriptional activity and IκB-phosphorylation in colon cancer cells or rat epithelial cells. It also blocked IKK activity (Cheon et al. 2006) and reduced the generation of IL-2, IL-4 and IFN-γ and T-cell proliferation (Li et al. 2009). Guggul decreased the joint swelling in rabbit induced with arthritis resembling rheumatoid arthritis in humans (Sharma and Sharma 1977). Endotoxin-induced uveitis induced by lipopolysaccharide (150 μg) into Lewis rats treated with guggulsterone (30 mg/kg body weight) prevented endotoxin-induced uveitis, and reduced the number of inflating cells, total protein and inflammatory markers. It also prevented the expression of MMP-2, COX-2 proteins, iNOS, IκB and NF-κB in eye tissues of rats. It inhibited LPS-induced expression of inflammatory proteins in non-pigment ciliary epithelial cells in humans (Kalariya et al. 2010). Guggulsterone significantly reduced the DSS-induced murine colitis. It also attenuated tissue upregulation of IκB and IKK phosphorylation induced by dextran sulphate sodium in mice (Cheon et al. 2006).

Pancreatitis

Guggulsterone attenuated histological damage, decreased serum lipase levels and lessened pancreas weight/body weight ratio. It also inhibited infiltration of macrophages and neutrophils and also suppressed cytokine production in murine-induced pancreatitis (Kim et al. 2015a).

Anticancer

Natural compounds have always been of considerable interest as potential anticancer agents. Guggulsterone has been reported to possess anticancer potential well established by in vitro and in vivo studies.

Pancreatic Cancer

Guggulsterone reduced the motility and suppressed the invasion in pancreatic cells which leads to the inhibition of FAK, disruption of cytoskeletal organisation and Src kinase signalling (Macha et al. 2013). Significant reduction in cell migration and invasion has been reported in pancreatic cancer cells by guggulsterone-mediated FXR inhibition (Lee et al. 2011). In vitro, combined treatment of guggulsterone with gemcitabine resulted in more inhibition in growth and apoptosis by downregulating the NFκ-B activity with AKT and Bcl-2 and through JNK and Bax activation in pancreatic cancer cells. In vivo, the combination altered tumour growth inhibition through the same mechanism as in tumour tissue (Ahn et al. 2012).

Head and Neck Cancer

A number of studies provide the evidence that guggulsterone induced apoptotic cell death of head and neck squamous cell carcinoma (Grandis et al. 1998, 2000a, b). Guggulsterone induced apoptosis and cell cycle arrest; enhanced the efficacy of erlotinib, cetuximab and cisplatin; and inhibited the invasion in head and neck squamous cell carcinoma cell lines (Leeman-Neill et al. 2009). Besides inhibited proliferation, guggulsterone treatment also induced apoptosis by abrogating the effects of smokeless tobacco/nicotine on PBk AKT pathway in head and neck cancer cells (Macha et al. 2011a). Guggulsterone decreased the level of ST and nicotine-induced secreted interlukin-6 in culture media of head and neck carcinoma cancer cells (Macha et al. 2011b). Guggulsterone treatment reduced the expression of anti-apoptotic proteins, Bcl-2, Mcl1, survivin, xIAP, c-Myc and cyclin D1 leading to apoptosis followed by activation of caspase-9, caspase-8 and caspase-3 (Macha et al. 2010).

Breast Cancer

Breast cancer is the most common and most challenging cancer in women worldwide and second most common cancer overall. Various mechanisms are believed to be responsible for the initiation and development of breast cancer. In breast cancer NF-κB pathway is highly activated (Gilmore 1997; Rayet and Gelinas 1999) which is an important molecule regulating the expression of many apoptotic genes that

cause tumours (Shishodia and Aggarwal 2004; Singh et al. 2005a). It has been reported that stereoisomers of guggulsterone (*E* form and *Z* form) prevented MMP-9 expression and MAPK/AP-1 signal pathway in MCF7 breast cancer lines, respectively. These isomers in combination provide an additive effect in cell invasion inhibition (Mencarelli et al. 2009). Combined treatment of guggulsterone and bexarotene reduced cellular levels of BCRP to 20% by inducing its association and secretion with exosomes. Exogenous C6 ceramide also induced secretion of breast cancer resistance protein-associated exosomes, while as siRNA-mediated knockdown or GW4869-mediated inhibition of neutral sphingomyelinase, an enzyme generating ceramide, restored cellular breast cancer-sensitive protein (Kong et al. 2015). Heme oxygenase-1 expression is induced by *E*-guggulsterone through inhibition of AKT phosphorylation and NF-E2-related factor 2 human mammary cells (Almazari et al. 2012). Guggulsterone inhibited NF-κB activation along with dephosphorylation and degradation of IκBα. It also interferes with nuclear translocation of P65- and NF-κB-mediated reporter gene activity (Shishodia and Aggarwal 2004). *Z*-guggulsterone reduced b-catechin/TCF-4 complex and Wnt/b-catenin targeting genes like cyclin D1, TCF-4 and c-Myc in breast cancer cells, indicating that b-catenin signalling pathway is the target for guggulipid-induced apoptosis and growth inhibition in human breast cancer (Jiang et al. 2013). Guggulsterone reduced VEGFR2 expression and angiogenesis in endothelial cell culture, and hence promoted ceramide-mediated apoptosis of breast cancer cells (Krishnamurthy et al. 2008). Guggulsterone treatment inhibited the expression of DNA (cytosome 5) methyltransferase 1 (DNMT 1) and HDAC1 (Mirza et al. 2013).

Prostate Cancer

A number of studies showed the anticancer activity of guggulsterone in prostate cancers. Guggulsterone treatment of human prostate cancer cells (PC3) resulted in efficient cytotoxic effects without affecting normal prostate epithelial cells (Dufer et al. 2012). The study made by Gao et al. (2015) revealed the normal mechanism of guggulsterone anticancer activity. As per this study, ATP lyase-regulated AKT inactivation is involved in guggulsterone-mediated prostate cancer growth inhibition. Guggulsterone retarded prostate cancer growth via inactivation of AKT regulation by ATP citrate lyase signalling in human prostate cancer cells (PC-3 and LNCaP). Guggulsterone induced caspase-dependent apoptosis mediated by Bax and Bak in prostate cancer cells (Singh et al. 2005b). Cell death induced by guggulsterone in human prostate cancer cells was regulated by ROI-dependent activation of JNK but not in normal prostate cancer cells (PrEC) (Singh et al. 2007).

Lung Cancer

Guggulsterone has also been reported to suppress NF-κB activation induced by tumour necrosis factor, okadaic acid, cigarette smoke condensate, phorbol ester and hydrogen peroxide. It occurs through inhibition of IκB degradation in lung cancer cells. It also suppressed COX-2, VEGF, MMP-9 and cyclin D1 expression along with proliferation and apoptosis inhibition (Shishodia et al. 2007).

Leukaemia

The first study to show the antileukaemic effects of guggulsterones was carried out by Samidio and his co-workers. This study demonstrates that *cis*-guggulsterone and *trans*-guggulsterone and 16-dehydroprogestrone inhibited the proliferation of HL60 and U937 cells. These effects were through induction of apoptosis and proliferation (Samudio et al. 2005). Guggulsterone inhibited the proliferation of human leukaemia cells. It induced S-phase arrest in the cell cycle, with decrease in cyclin D1 and cdc2. It also induced caspase-dependent apoptosis through JNK activation and AKT suppression in leukaemia cells (Shishodia and Aggarwal 2004).

Melanoma

Guggulsterone inhibited isobutyl methyl xanthine-induced melanogenesis and cellular tyrosine activity with no cytotoxic effects in melanoma cells. It also inhibited α-melanocyte hormone, suggesting an action on the cAMP-dependent melanogenic pathway (Koo et al. 2012).

Gallbladder Cancer

Combination of guggulsterone and gemcitabine inhibited cell proliferation and invasion in gallbladder cancer cells more significantly as compared to treatment with gemcitabine alone. The combination also decreased NF-κB P65 activation when compared to gemcitabine treatment alone (Yang et al. 2012).

Oesophageal Cancer

Guggulsterone in combination with amiloride showed additive effects in suppressing oesophageal cancer cell growth in vitro and in nude mouse xenografts. This study suggested that inhibition of gastric acid-inducing gene Na^+H^+ exchanger-1 expression or combination of amiloride and guggulsterone could be beneficial to control oesophageal adenocarcinoma (Guan et al. 2014). Guggulsterone induced apoptosis and caspase 3 activity in Barrett's oesophagus-derived cells in which FXR

was significantly overexpressed (De Gottardi et al. 2006). FXR, macrophage inflammatory protein 3α, IL-8 mRNA and IBABP expression has been found to be induced by DCA. The expression of FXR, IBABP, SHP and chemokines IL-8 and macrophage protein 3α was found to be higher in Barrett's epithelium. Guggulsterone terminated DCA-induced mRNA expression (Capello et al. 2008). Guggulsterone blocked DNA-induced and NF-κB-dependent activation of Cdx2 and COX-2 expression. It also reduced the viability of oesophageal adenocarcinoma cells (Yamada et al. 2014).

Colon Cancer

Guggulsterone markedly increased apoptosis in HT-29 cells by the activation of caspase-3 and caspase-8. Guggulsterone also decreased Bcl-2, cIAP-1 and cIAP-2 levels and raised the levels of Fas, p-JNK, truncated Bid and p-c-Jun. Guggulsterone-treated mice showed significantly smaller size of HT-29 xenograft tumours than the size of tumours in control mice (An et al. 2009). Guggulsterone inhibited angiogenesis by blocking STAT 3 and VEGF expression and reduction of MMP-2 and MMP-9 enzyme activity in HT-29 cells (Kim et al. 2008).

Brain Tumours

Although sonic hedgehog pathway effector Gli 1 showed overexpression in gliomas, SANT-1 (a sonic hedgehog inhibitor) failed to induce apoptosis in glioblastoma cells. Guggulsterone inhibited Ras and NF-κB activity and sensitised glioblastoma cells to SANT-1-induced apoptosis (Dixit et al. 2013).

Hepatoprotective Effect

Guggulsterone inhibited intracellular adhesion molecule-I expression by GW4064 in human hepatocytes (Qin et al. 2005). It reduced HIF-1a expression in hypoxic condition in hepatocytes (Moon et al. 2015). Guggulsterone by inhibiting NF-κB activation and inducing apoptosis attenuated activation of hepatic stellate cells. High doses decreased the extent of collagen deposition and the percentage of activated hepatic stellate cells undergoing apoptosis in mice (Kim et al. 2013). It reduced the bile acid-mediated increase in HCV RNA in hepatocytes (Chang and George 2007). It also blocked upregulation by bile acids and hepatic C virus replication levels in Hull cells of HCV replication model (Scholtes et al. 2008).

Kidney Protection Effects

Guggulsterone treatment inhibited the production of proinflammatory molecules like COX-2, IL-6, iNOS and TNF-α, produced by LPS-treated inner medullary collecting cells of mice. It inhibited the degradation of Iκ-Bα and translocation of NF-κB. Guggulsterone also shows inhibition of inflammatory responses in collecting duct cells which may lead to kidney injuries due to infection (Kim et al. 2015b).

Gastroprotective

Pretreatment with a novel derivative of guggulsterone (GG-52) suppressed TNF-α-induced activation of IκB kinase and NF-κB signalling in MkN-45 cells. In a model of ethanol-induced murine gastritis, GG-52 significantly reduced the gastritis as assessed by macroscopic and histological evaluation of gastric mucosal damage (Kim et al. 2015a).

Neuroprotective Activity

Guggulipid showed protective effects in a streptozotocin-induced memory deficit model of dementia that can be attributed to its antioxidant and anti-acetylcholinesterase activities. This study demonstrated that guggulipid has significant effect against streptozotocin-induced memory deficit (Saxena et al. 2007).

Conclusions and Future Perspectives

This review suggests that guggulsterone is a good pharmacological drug with potential anticancer, anti-inflammatory, hypolipidaemic, antitumour, antidiabetic, hepatoprotective, gastroprotective and neuroprotective properties. Numerous research results demonstrated the potential applications of guggulsterone both in vitro and in vivo. Guggulsterone is a natural product with a low molecular weight and is a biologically active component of traditional medicinal plant ‘guggul’ which has been used for 1000 years in Ayurveda to treat various disorders, including cancer, obesity, tumours, liver disorders, urinary complications, intestinal worms, leucoderma and inflammation, making it an ideal therapeutic agent. Guggulsterone analogues with improved pharmacodynamics may also promote more advances. Many extensive studies have shown that guggulsterone induces apoptosis of many types of cancer cells, but mechanisms of actions have not been fully explained. This plant steroid has been reported to work as an antagonist of certain nuclear receptors,

especially farnesoid X receptor, which regulates bile acids and cholesterol metabolism. This review suggests that guggulsterone may set up direct medicinal application as a pharmaceutical agent or may serve as chemical template for the design and synthesis of new substances for the treatment of human diseases. Further studies and clinical trials are required to find out its specific intracellular sites of action and targets to fully know the mechanism of its anti-inflammatory, anticancer, hipolipidaemic and other activities to further validate its potential role as a therapeutic agent in the prevention and cure of various diseases.

References

Ahn DW, Seo JK, Lee SH, Hwang JH, Lee JK, Ryu JK, Kim YT, Yoon YB (2012) Enhanced antitumor effect of combination therapy with gemcitabine and guggulsterone in pancreatic cancer. Pancreas 41(7):1048–1057

Almazari I, Park JM, Park SA, Suh JY, Na HK, Cha YN, Surh YJ (2012) Guggulsterone induces heme oxygenase-1 expression through activation of Nrf2 in human mammary epithelial cells: PTEN as a putative target. Carcinogenesis 33(2):368–376

An MJ, Cheon JH, Kim SW, Kim ES, Kim TI, Kim WH (2009) Guggulsterone induces apoptosis in colon cancer cells and inhibits tumor growth in murine colorectal cancer xenografts. Cancer Lett 279:93–100

Benn WR, Dodson RM (1964) The synthesis and stereochemistry of isomeric 16-hydroxy-17 (20)-pregnenes. J Org Chem 29(5):1142–1148

Benveniste P (1986) Sterol biosynthesis. Ann Rev Plant Physiol 37:275–308

Capello A, Moons LM, Van De Winkel A, Siersema PD, Van Dekken H, Kuipers EJ, Kusters JG (2008) Bile acid-stimulated expression of the farnesoid X receptor enhances the immune response in Barrett esophagus. Am J Gastroenterol 103(6):1510–1516

Chander R, Rizvi F, Khanna AK, Pratap R (2003) Cardioprotective activity of synthetic guggulsterone (E and Z-isomers) in isoproterenol induced myocardial ischemia in rats: a comparative study. Indian J Clin Biochem 18(2):71–79

Chang KO, George DW (2007) Bile acids promote the expression of hepatitis C virus in replicon-harboring cells. J Virol 81(18):9633–9640

Cheon JH, Kim JS, Kim JM, Kim N, Jung HC, Song IS (2006) Plant sterol guggulsterone inhibits nuclear factor-kappaB signaling in intestinal epithelial cells by blocking IkappaB kinase and ameliorates acute murine colitis. Inflamm Bowel Dis 12(12):1152–1161

Cui J, Huang L, Zhao A, Lew JL, Yu J, Sahoo S, Meinke PT, Royo I, Pelaez F, Wright SD (2003) Guggulsterone is a farnesoid X receptor antagonist in coactivator association assays but acts to enhance transcription of bile salt export pump. J Biol Chem 278(12):10214–10220

De Gottardi A, Dumonceau JM, Bruttin F, Vonlaufen A, Morard I, Spahr L, Rubbia-Brandt L, Frossard JL, Dinjens WN, Rabinovitch PS, Hadengue A (2006) Expression of the bile acid receptor FXR in Barrett's esophagus and enhancement of apoptosis by guggulsterone in vitro. Mol Cancer 5:48

Dixit D, Ghildiyal R, Anto NP, Ghosh S, Sharma V, Sen E (2013) Guggulsterone sensitizes glioblastoma cells to Sonic hedgehog inhibitor SANT-1 induced apoptosis in a Ras/NFkappaB dependent manner. Cancer Lett 336(2):347–358

Dufer M, Horth K, Wagner R, Schittenhelm B, Prowald S, Wagner TF, Oberwinkler J, Lukowski R, Gonzalez FJ, Krippeit-Drews P, Drews G (2012) Bile acids acutely stimulate insulin secretion of mouse beta-cells via farnesoid X receptor activation and K(ATP) channel inhibition. Diabetes 61(6):1479–1489

Gao Y, Zeng Y, Tian J, Islam MS, Jiang G, Xiao D (2015) Guggulsterone inhibits prostate cancer growth via inactivation of Akt regulated by ATP citrate lyase signaling. Oncotarget 6(30):30420

Gebhard C, Stampfli SF, Gebhard CE, Akhmedov A, Breitenstein A, Camici GG, Holy EW, Luscher TF, Tanner FC (2009) Guggulsterone, an anti-inflammatory phytosterol, inhibits tissue factor and arterial thrombosis. Basic Res Cardiol 104(3):285–294

Gilmore TD (1997) Introduction: the Rel/NF-kappaB signal transduction pathway. Semin Cancer Biol 8:61–62

Gioiello A, Sardella R, Rosatelli E, Sadeghpour BM, Natalini B, Pellicciari R (2012) Novel stereoselective synthesis and chromatographic evaluation of E-guggulsterone. Steroids 77(3):250–254

Grandis JR, Drenning SD, Chakraborty A, Zhou MY, Zeng Q, Pitt AS, Tweardy DJ (1998) Requirement of Stat3 but not Stat1 activation for epidermal growth factor receptor-mediated cell growth in vitro. J Clin Invest 102:1385–1392

Grandis JR, Drenning SD, Zeng Q, Watkins SC, Melhem MF, Endo S, Johnson DE, Huang L, He Y, Kim JD (2000a) Constitutive activation of Stat3 signaling abrogates apoptosis in squamous cell carcinogenesis in vivo. Proc Natl Acad Sci U S A 97:4227–4232

Grandis JR, Zeng Q, Drenning SD (2000b) Epidermal growth factor receptor-mediated stat3 signaling blocks apoptosis in head and neck cancer. Laryngoscope 110:868–874

Guan B, Hoque A, Xu X (2014) Amiloride and guggulsterone suppression of esophageal cancer cell growth in vitro and in nude mouse xenografts. Front Biol (Beijing) 9:75–81

Gupta VK, Bandhoria P, Gupta BD, Gupta KK (2006) Crystal structure of guggulsterone Z. Crystallogr Rep 51(2):265–270

Ham J, Chin J, Kang H (2011) A regioselective synthesis of E-guggulsterone. Molecules 16(5):4165–4171

Hubert S (2003) The role of sterols in plant growth and development. Prog Lipid Res 42:163–175

Jiang G, Xiao X, Zeng Y, Nagabhushanam K, Majeed M, Xiao D (2013) Targeting beta-catenin signaling to induce apoptosis in human breast cancer cells by z-guggulsterone and Gugulipid extract of Ayurvedic medicine plant Commiphora mukul. BMC Complement Altern Med 13:203

Kalariya NM, Shoeb M, Reddy AB, Zhang M, van Kuijk FJ, Ramana KV (2010) Prevention of endotoxin induced uveitis in rats by plant sterol guggulsterone. Invest Ophthalmol Vis Sci 51:5105–5113

Kaul S, Kapoor NK (1989) Cardiac sarcolemma enzymes and liver microsomal cytochrome P450 in isoproterenol treated rats. Indian J Med Res 90:62–68

Kim ES, Hong SY, Lee HK, Kim SW, An MJ, Kim TI, Lee KR, Kim WH, Cheon JH (2008) Guggulsterone inhibits angiogenesis by blocking STAT3 and VEGF expression in colon cancer cells. Oncol Rep 20(6):1321–1327

Kim BH, Yoon JH, Yang JI, Myung SJ, Lee JH, Jung EU, Yu SJ, Kim YJ, Lee HS, Kim CY (2013) Guggulsterone attenuates activation and survival of hepatic stellate cell by inhibiting nuclear factor kappa B activation and inducing apoptosis. J Gastroenterol Hepatol 28(12):1859–1868

Kim DG, Bae GS, Choi SB, Jo IJ, Shin JY, Lee SK, Kim MJ, Kim MJ, Jeong HW, Choi CM, Seo SH, Choo GC, Seo SW, Song HJ, Park SJ (2015a) Guggulsterone attenuates cerulein-induced acute pancreatitis via inhibition of ERK and JNK activation. Int Immunopharmacol 26(1):194–202

Kim DG, Bae GS, Jo IJ, Choi SB, Kim MJ, Jeong JH, Kang DG, Lee HS, Song HJ, Park SJ (2015b) Guggulsterone attenuated lipopolysaccharide-induced inflammatory responses in mouse inner medullary collecting duct-3 cells. Inflammation 39:87–95

Kong JN, He Q, Wang G, Dasgupta S, Dinkins MB, Zhu G, Kim A, Spassieva S, Bieberich E (2015) Guggulsterone and bexarotene induce secretion of exosome-associated breast cancer resistance protein and reduce doxorubicin resistance in MDA-MB-231 cells. Int J Cancer 137(7):1610–1620

Koo JH, Rhee KS, Koh HW, Jang HY, Park BH, Park JW (2012) Guggulsterone inhibits melanogenesis in B16 murine melanoma cells by down regulating tyrosinase expression. Int J Mol Med 30:974–978

Krishnamurthy K, Wang G, Rokhfeld D, Bieberich E (2008) Deoxycholate promotes survival of breast cancer cells by reducing the level of pro-apoptotic ceramide. Breast Cancer Res 10:R106

Kuppurajan K, Rajagopalan SS, Rao TK, Vijayalakshmi AN, Dwarakanath C (1973) Effect of guggulu (Commiphora mukul Engl.) on serum lipids in obese subjects. J Res Ind Med 8:1–8

Lee YR, Lee JH, Noh EM, Kim EK, Song MY, Jung WS, Park SJ, Kim JS, Park JW, Kwon KB et al (2008) Guggulsterone blocks IL-1beta-mediated inflammatory responses by suppressing NF-kappaB activation in fibroblast-like synoviocytes. Life Sci 82:1203–1209

Lee JY, Lee KT, Lee JK, Lee KH, Jang KT, Heo JS, Choi SH, Kim Y, Rhee JC (2011) Farnesoid X receptor, overexpressed in pancreatic cancer with lymph node metastasis promotes cell migration and invasion. Br J Cancer 104:1027–1037

Leeman-Neill RJ, Wheeler SE, Singh SV, Thomas SM, Seethala RR, Neill DB, Panahandeh MC, Hahm ER, Joyce SC, Sen M et al (2009) Guggulsterone enhances head and neck cancer therapies via inhibition of signal transducer and activator of transcription-3. Carcinogenesis 30:1848–1856

Li C, Zang Y, Sen M, Leeman-Neill RJ, Man DS, Grandis JR, Johnson DE (2009) Bortezomib up-regulates activated signal transducer and activator of transcription-3 and synergizes with inhibitors of signal transducer and activator of transcription-3 to promote head and neck squamous cell carcinoma cell death. Mol Cancer Ther 8(8):2211–2220

Lv N, Song MY, Kim EK, Park JW, Kwon KB, Park BH (2008) Guggulsterone, a plant sterol, inhibits NF-kappaB activation and protects pancreatic beta cells from cytokine toxicity. Mol Cell Endocrinol 289:49–59

Macha MA, Matta A, Chauhan S, Siu KM, Ralhan R (2010) 14-3-3 Zeta is a molecular target in guggulsterone induced apoptosis in head and neck cancer cells. BMC Cancer 10:655

Macha MA, Matta A, Chauhan SS, Siu KW, Ralhan R (2011a) Guggulsterone (GS) inhibits smokeless tobacco and nicotine-induced NF-kappaB and STAT3 pathways in head and neck cancer cells. Carcinogenesis 32:368–380

Macha MA, Matta A, Chauhan SS, Siu KW, Ralhan R (2011b) Guggulsterone targets smokeless tobacco induced PI3K/Akt pathway in head and neck cancer cells. PLoS One 6:e14728

Macha MA, Rachagani S, Gupta S, Pai P, Ponnusamy MP, Batra SK, Jain M (2013) Guggulsterone decreases proliferation and metastatic behavior of pancreatic cancer cells by modulating JAK/STAT and Src/FAK signaling. Cancer Lett 341:166–177

Malhotra SC, Ahuja MM (1971) Comparative hypolipidaemic effectiveness of gum guggulu (Commiphora mukul) fraction 'A', ethyl-P-chlorophenoxyisobutyrate and Ciba-13437-Su. Indian J Med Res 59(10):1621–1632

Mencarelli A, Renga B, Palladino G, Distrutti E, Fiorucci S (2009) The plant sterol guggulsterone attenuates inflammation and immune dysfunction in murine models of inflammatory bowel disease. Biochem Pharmacol 78:1214–1223

Mirza S, Sharma G, Parshad R, Gupta SD, Pandya P, Ralhan R (2013) Expression of DNA methyl transferases in breast cancer patients and to analyze the effect of natural compounds on DNA methyltransferases and associated proteins. J Breast Cancer 16:23–31

Moon Y, Choi SM, Chang S, Park B, Lee S, Lee MO, Choi HS, Park H (2015) Chenodeoxycholic acid reduces hypoxia inducible factor-1α protein and its target genes. PLoS One 10(6):e0130911

Pal P, Kanaujiya JK, Lochab S, Tripathi SB, Sanyal S, Behre G, Trivedi AK (2013) Proteomic analysis of rosiglitazone and guggulsterone treated 3T3-L1 preadipocytes. Mol Cell Biochem 376(1–2):81–93

Patel SS, Savjani JK (2015) Systematic review of plant steroids as potential anti-inflammatory agents: current status and future perspectives. J Phytopharmacol 4(2):121–125

Patil VD, Nayak UR, Dev S (1972) Chemistry of ayurvedic crude drugs—I: Guggulu (resin from Commiphora mukul)—1: steroidal constituents. Tetrahedron 28(8):2341–2352

Pratap R, Singh DP, Pal R, Singh S (2008) Council of Scientific and Industrial Research. Process for preparing guggulsterones. US Patent 7,365,218

Pu J, Yuan A, Shan P, Gao E, Wang X, Wang Y, Lau WB, Koch W, Ma XL, He B (2013) Cardiomyocyte-expressed farnesoid-X-receptor is a novel apoptosis mediator and contributes to myocardial ischaemia/reperfusion injury. Eur Heart J 34(24):1834–1845

Qin P, Borges-Marcucci LA, Evans MJ, Harnish DC (2005) Bile acid signaling through FXR induces intracellular adhesion molecule-1 expression in mouse liver and human hepatocytes. Am J Physiol Gastrointest Liver Physiol 289(2):G267–G273

Rayet B, Gelinas C (1999) Aberrant rel/nfkb genes and activity in human cancer. Oncogene 18:6938–6947

Rizzo G, Disante M, Mencarelli A, Renga B, Gioiello A, Pellicciari R, Fiorucci S (2006) The farnesoid X receptor promotes adipocyte differentiation and regulates adipose cell function in vivo. Mol Pharmacol 70(4):1164–1173

Samudio I, Konopleva M, Safe S, McQueen T, Andreeff M (2005) Guggulsterones induce apoptosis and differentiation in acute myeloid leukemia: identification of isomer-specific antileukemic activities of the pregnadienedione structure. Mol Cancer Ther 4:1982–1992

Satyavati GV, Dwarakanath C, Tripathi SN (1969) Experimental studies on the hypocholesterolemic effect of *Commiphora mukul* Engl. (Guggul). Indian J Med Res 57(10):1950–1962

Saxena G, Singh SP, Pal R, Singh S, Pratap R, Nath C (2007) Gugulipid, an extract of *Commiphora whightii* with lipid-lowering properties, has protective effects against streptozotocin-induced memory deficits in mice. Pharmacol Biochem Behav 86:797–805

Scholtes C, Diaz O, Icard V, Kaul A, Bartenschlager R, Lotteau V, Andre P (2008) Enhancement of genotype 1 hepatitis C virus replication by bile acids through FXR. J Hepatol 48(2):192–199

Sharma JN, Sharma JN (1977) Comparison of the anti-inflammatory activity of Commiphora mukul (an indigenous drug) with those of phenylbutazone and ibuprofen in experimental arthritis induced by mycobacterial adjuvant. Arzneimittelforschung 27(7):1455–1457

Sharma B, Salunke R, Srivastava S, Majumder C, Roy P (2009) Effects of guggulsterone isolated from Commiphora mukul in high fat diet induced diabetic rats. Food Chem Toxicol 47:2631–2639

Shishodia S, Aggarwal BB (2004) Guggulsterone inhibits NF-kappaB and IkappaBalpha kinase activation, suppresses expression of anti-apoptotic gene products, and enhances apoptosis. J Biol Chem 279:47148–47158

Shishodia S, Sethi G, Ahn KS, Aggarwal BB (2007) Guggulsterone inhibits tumor cell proliferation, induces S-phase arrest, and promotes apoptosis through activation of c-Jun N-terminal kinase, suppression of Akt pathway, and downregulation of antiapoptotic gene products. Biochem Pharmacol 74(1):118–130

Singh RP, Dhanalakshmi S, Agarwal C, Agarwal R (2005a) Silibinin strongly inhibits growth and survival of human endothelial cells via cell cycle arrest and down regulation of survivin, Akt and NF-kappaB: implications for angioprevention and antiangiogenic therapy. Oncogene 24:1188–1202

Singh SV, Zeng Y, Xiao D, Vogel VG, Nelson JB, Dhir R, Tripathi YB (2005b) Caspase dependent apoptosis induction by guggulsterone, a constituent of ayurvedic medicinal plant Commiphora mukul, in PC-3 human prostate cancer cells is mediated by Bax and Bak. Mol Cancer Ther 4:1747–1754

Singh SV, Choi S, Zeng Y, Hahm ER, Xiao D (2007) Guggulsterone-induced apoptosis in human prostate cancer cells is caused by reactive oxygen intermediate dependent activation of c-Jun NH2-terminal kinase. Cancer Res 67:7439–7449

Song JJ, Kwon SK, Cho CG, Park SW, Chae SW (2010) Guggulsterone suppresses LPS induced inflammation of human middle ear epithelial cells (HMEEC). Int J Pediatr Otorhinolaryngol 74:1384–1387

Srivastava M, Kapoor NK (1986) Guggulsterone induced changes in the levels of biogenic monoamines and dopamine ß-hydroxylase activity of rat tissues. J Biosci 10:15–19

Tripathi YB, Malhotra OP, Tripathi SN (1984) Thyroid stimulating action of Z-guggulsterone obtained from Commiphora mukul. Planta Med 50(1):78–80

Tripathi YB, Tripathi P, Malhotra OP, Tripathi SN (1988) Thyroid stimulatory action of (Z)-guggulsterone: mechanism of action. Planta Med 54(4):271–277

Ulbricht C, Basch E, Szapary P, Hammerness P, Axentsev S, Boon H, Kroll D, Garraway L, Vora M, Woods J (2005) Guggul for hyperlipidemia: a review by the Natural Standard Research Collaboration. Complement Ther Med 13(4):279–290

Urizar NL, Liverman AB, Dodds DT, Silva FV, Ordentlich P, Yan Y, Gonzalez FJ, Heyman RA, Mangelsdorf DJ, Moore DD (2002) A natural product that lowers cholesterol as an antagonist ligand for FXR. Science 296(5573):1703–1706

Wang WC, Uen YH, Chang ML, Cheah KP, Li JS, Yu WY, Lee KC, Choy CS, Hu CM (2012) Protective effect of guggulsterone against cardiomyocyte injury induced by doxorubicin in vitro. BMC Complement Altern Med 12:138

Yamada T, Osawa S, Ikuma M Kajimura M, Sugimoto M, Furuta T, Iwaizumi M, Sugimoto K (2014) Guggulsterone, a plant-derived inhibitor of NF-TB, suppresses CDX2 and COX-2 expression and reduces the viability of esophageal adenocarcinoma cells. Digestion 90(3):208–217

Yang JY, Della-Fera MA, Baile CA (2008) Guggulsterone inhibits adipocyte differentiation and induces apoptosis in 3T3-L1 cells. Obesity (Silver Spring) 16:16–22

Yang MH, Lee KT, Yang S, Lee JK, Lee KH, Moon IH, Rhee JC (2012) Guggulsterone enhances antitumor activity of gemcitabine in gallbladder cancer cells through suppression of NF-κB. J Cancer Res Clin Oncol 138:1743–1751

Yokota T (1997) The structure, biosynthesis and functions of brassinosteroids. Trends Plant Sci 2:137–143

Yu BZ, Kaimal R, Bai S, El Sayed KA, Tatulian SA, Apitz RJ, Jain MK, Deng R, Berg OG (2009) Effect of guggulsterone and cembranoids of Commiphora mukul on pancreatic phospholipase A (2): role in hypocholesterolemia. J Nat Prod 72:24–28

Phytochemical and Pharmacological Approaches of Traditional Alternate *Cassia occidentalis* L.

M. Ali, S. H. Ansari, Sayeed Ahmad, Syeda Sanobar, Arshad Hussain, Shah Alam Khan, Md Sarfaraz Alam, Md Sajid Ali, Md Faruque Ahmad, and Khalid Rehman Hakeem

Introduction (Vernacular Names and Profile)

Vernacular Names

Australia: Ant bush; *Brazil*: Fedegoso, Matapatinho, Paramarioba; *Chinese*: Wang Jiang Nam, Wang Jiang Nam Ming, Jue Ming Zi; *Cambodia*: Phank got; *Cuba*: Sen, Yerbahedionda; *East Africa*: Manuka uvundo, Mwingazini; *English*: ant bush, coffee senna, Negro coffee, rubbish cassia, styptic weed, stinking weed; *French*: Bentama, Bonne casse, Poispuant; *German*: Stink-Kassie, Kaffee-kassie; *Hausa*: Raidor; *India*: Assamese, Bengali—Kalkashunda, Gujarati—Kasodri and Kasundari, Hindi—Badi Kasondi, Chakunda, and Kasonda, Kannada—Anecogate, Malayalam—Natramtakara, Marathi—Kasoda, Ponnaviram, and Doddatagase,

M. Ali (✉) · S. Sanobar
Department of Pharmacognosy, College of Pharmacy, Jazan University, Jizan, Saudi Arabia

S. H. Ansari · S. Ahmad
Department of Pharmacognosy and Phytochemistry, Jamia Hamdard, New Delhi, India

A. Hussain
Department of Pharmacognosy, King Khalid University, Abha, Saudi Arabia

S. A. Khan
Department of Pharmacy, Oman Medical College, Muscat, Sultanate of Oman

M. S. Alam · Md S. Ali
Department of Pharmaceutics, College of Pharmacy, Jazan University, Jizan, Saudi Arabia

Md F. Ahmad
Department of Clinic Nutrition, College of Applied Medical Sciences, Jazan University, Jizan, Saudi Arabia

K. R. Hakeem
Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia

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Oriya—Kasundri and Ponthagarai, Sanskrit—Kasmarda and Rankasvinda, Telugu—Kasinda and Peddakasinda, Tamil—Ponnavarai, Urdu—Kasonji; *Indonesia*: Menting (Java), Kopi andelan (Sumatra); *Japanese*: Habu-Cha; *Kenya*: Inglatiang; *Korea*: Soggjolmjong; *Laos*: Phet; *Malaysia*: Kacang kota, Ketepeng Hutan; *Mauritius*: Casse Puante; *Nepalese*: Kasaindi, Panvar; the *Philippines*: Andadasi, Balatongaso, Duda, Kabal-Kabalan, Katangan-aso, Tambalisa; *Porto Rico*: Cana fista, Vainillo; *Rwanda*: Umuyoka, Kisogera; *South Africa*: Isinyembane, Umnwande-nyoka; *Spanish*: Bicho, Brusca, Frijolillo, Guania; *Swahili*: Mwengajini (Kenya), Mwengia (Congo); *Trinidad and Tobago*: Wild coffee; *Thai*: Chumhet tet, Khet, Lang Khet; *Vietnam*: Moung Hoe; *West Indies*: Pois Puat.

Plant Profile

Cassia occidentalis L., an Ayurvedic plant with great bioactive potential, is an erect reddish purple stem with short height (1.5 m) and semiwoody annual weed which gets converted to woody (depending on physical and geographical conditions) from rectangle to round shapes. Leaves are sessile, alternate, and pinnately compound with 4–6 cm long opposite leaflets with 1.5–2.5 cm wide measurements. The growing plant image was obtained from Northern region of India, given in Fig. 1. Shape of the leaves varies from oval and oblong to lanceolate with white hairs on margin. A colorful gland is attached to rachis in the compound leaf. Arrangements of the flower are axillary with terminal racemes. The plant posseses small and complete flower with five sepals and petals. Fruits are of dry and dehiscent class which are curved and bear 7–12 cm long pod with 50 seeds approximately. Seeds (8–10 mm wide, oval and flattened) are dark brown and shiny with sharp tip at the surface (Yadav et al. 2010). *Cassia occidentalis* L. is a common herbaceous annual weed, indigenous to Brazil (Chukwujekwu et al. 2006) popularly known as Fedegoso or Manjerioba (Aragão et al. 2009), used for various ailments and general weakness (Coimbra 1994) but naturalized it is consumed worldwide by the human beings and animals despite the toxic effects (O'Hara et al. 1969; Martin et al. 1981; Simpson et al. 1971; Graziano et al. 1983; Colvin et al. 1986; Barbosa-Ferreira et al. 2005; Tasaka et al. 2000; Rao et al. 2004; Vashishtha et al. 2007a). According to "The Wealth of India" compilations 1992 edition, Indian Ayurvedic system of medicine practices its medicinal importance to be used as a whole plant. The beneficial outcomes are quite appreciable to meet the requirements of therapeutic challenges. In "Wealth of India" the purgative action is mentioned (Warrier and Nambiar 1994). Traditionally it is more important worldwide (Gupta 1979; Dennis 1988; Dupriez and de Leener 1987; Nagaruja 1990) for antiplasmodial (Tona et al. 2004), laxative, febrifuge, and analgesic avtivities; it is used for anemia, flu, hepatoprotection, tuberculosis, gonorrhea, dysmenorrhea, and urinary tract disorders (Aragão et al. 2009; Coimbra 1994; Di Stasi and Hiruma-Lima 2002; Bardhan et al. 1985); it also possesses anti-inflammatory (Kuo et al. 1996), antibacterial (Samy and Ignacimuthu 2000), antimalarial (Brandão et al. 1992; Tona et al. 2004), eczema, and antifungal

Fig. 1 *Cassia occidentalis* L., plant growing in Northern India

activities (Corrêa 1926; Ogunkunle and Ladejobi 2006; Fenner et al. 2006), and is used for gastritis and throat inflammation (Almeida et al. 2006). The water infusion of the roots of this edible weed (Humphry et al. 1993) along with the roots of *Azadirachta indica* A. Juss. and *Caesalpinia sepiaria* Roxb is employed to treat the

white discharge in ladies (Yadav et al. 2010); seed decoction is used as a potent abortifacient (Rodrigues 2007) and as an antidote (Corrêa 1984). Traditional concepts assisted a lot to explore the scientific studies in the support of the pharmacological potentials of the *C. occidentalis* as antibacterial (Ali et al. 1999), antifungal (Caceres et al. 1993), antitumor, and hepatoprotective (Abongwa et al. 2011). In some African countries the antimalarial formulations consist of this weed as an important ingredient along with the leaves of *Lippia chevalieri* and the flowering tops of *Spilanthes oleracea* (Bodeker and Burford 2007); in Peru the root decoction is used for fever and diuretics (Soukup 1970). Root decoction is used with black pepper for filarial problems (Kumar and Nehar 2007). Leaf decoction is used to develop the immunity to fight against skin diseases among the infants in Orissa state in India (Dhiman 2006) and in Nigeria for fever (Chukwujekwu et al. 2005). Roasted seeds are prepared as coffee beverage but decrease the level of proteins, carbohydrates, and phenolic contents very significantly and this degradation drew attention by following the first-order kinetics (Medoua and Mbofung 2007) though the seeds without roasting are toxic and responsible for muscle degeneration syndrome (Calore et al. 1998; Cavaliere et al. 1997). In 2003 Medoua and Mbofung expressed their concern to show that the roasting procedure helps to remove the toxic components from the seeds and water infusion does not contain the toxins in the beverage (Medoua and Mbofung 2003). However toxicological components of the *C. occidentalis* are believed to develop the formulations to fight against tumor and bacterial infections (Lombardo 2014).

Cassia occidentalis is a widespread weed (Higgins et al. 1985) with special medicinal importance (Pandey 1975); it also carries the history to preserve the cowpea stocks. The therapeutic potential is the attribute of the bioactive compounds which are present in the different parts of *C. occidentalis* which include fatty oils and flavonoid glycosides (Purwar et al. 2003), anthraquinone glycosides (Lal and Gupta 1974), polysaccharides and tannins, etc. These might be affected in the weed by the environmental pollutants, i.e., lead and various external factors by altering the normal plant physiology (Krishanayya and Bedi 1986).

Phytochemical Extraction Protocols for Analysis and Bioactivities

Secondary metabolites and their explorations are quite interesting tasks to deal with phytochemistry which affects not only the plant's biological functions (by affecting electron transport chain) but the consumer and research scholars as well. These metabolites typically mediate the communication between plant and its surroundings where defense and signaling perceptions are main among the several other mechanisms (Wolfender et al. 2015). *Cassia occidentalis* is known to possess a variety of the different phytochemicals where anthraquinones exhibit a major occurrence in different parts of it along with other components. Whole plant is useful to

be used as a drug and food supplement; the mentioned property is the attribute of the presence of various phytoconstituents in all parts of it. The important phytoconstituents have been illustrated in Fig. 2. Naturally found anthraquinones have wide applications to be used as a bioactive remedy for various ailments. The phytochemical screening gives us an idea about the range of phytochemicals in the plants and

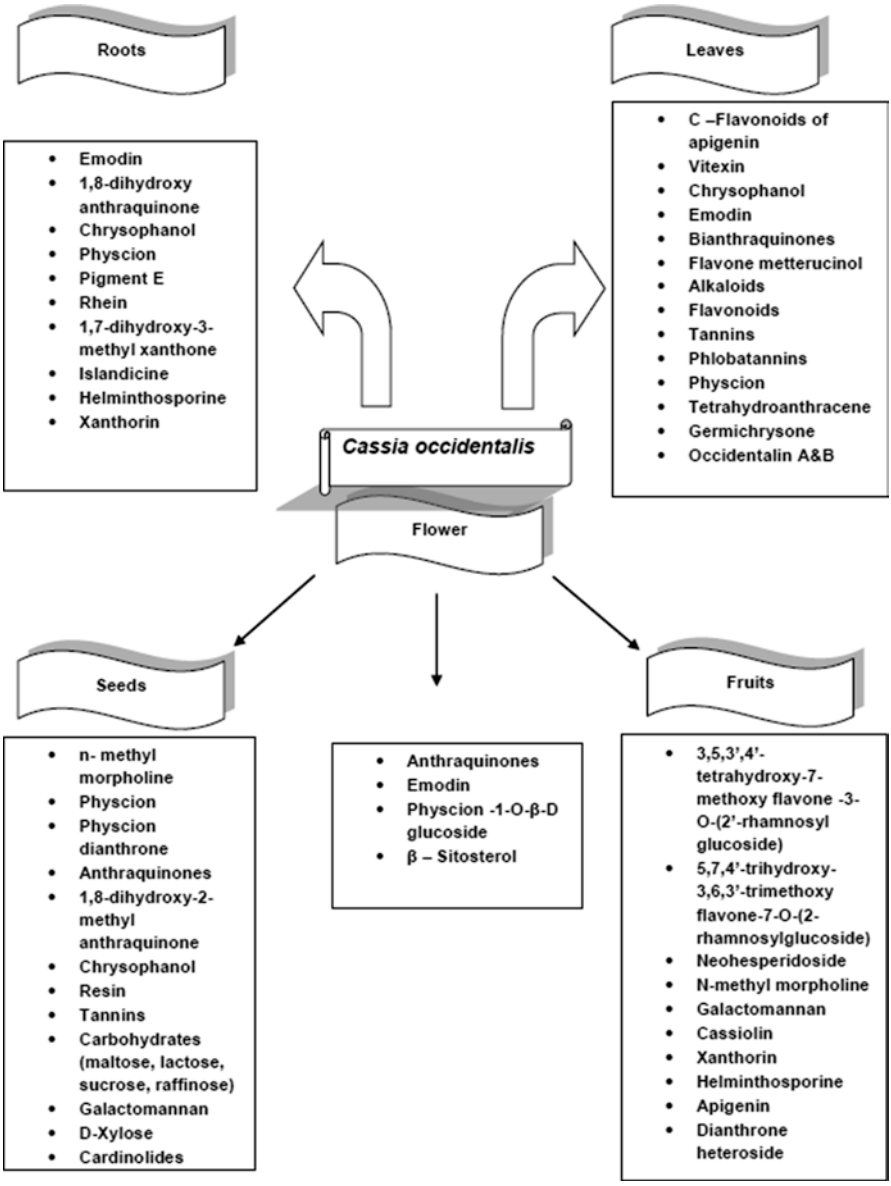

Fig. 2 Phytochemical constituents from different parts of *Cassia occidentalis* L

on the other hand their collective presence in the crude extract is the base to evaluate the bioactive potential of it.

The extraction protocols which are being discussed are the updated approaches for crude form of extract in various organic solvents. Traditional and modern techniques were involved for cold maceration and successive extractions through Soxhlet apparatus. The approaches were oriented upon the extraction of anthraquinones through modern techniques. With the slight differences of extraction protocols the methods are being summarized as follows.

Maceration of air-dried aerial parts of *Cassia occidentalis* was considered to give satisfactory extractive yield by maintaining the normal conditions at room temperature for 7 days by occasional shaking. Ethanol (70%) being polar is preferred to extract the components which were kept at 4 °C to be used orally for experimental studies (Aragão et al. 2009).

Washed and cleaned root pieces of *Cassia occidentalis* were suggested for shade drying and passed through mesh to have the coarse powdered form which is used for Soxhlet extraction by using 70% alcohol as solvent. Distillation was carried out and finally the traces of solvents were removed by using rotary evaporator by maintaining the reduced pressure. Root extract yield 10.2% was obtained to be preserved at 4–8 °C to be used for further studies (Sharma et al. 2014).

Air-dried roots of *Cassia occidentalis* were subjected to extract in 80% hydro-alcoholic solvent with sonication for the duration of 1 h by keeping it on magnetic stirrer overnight. The Buchner funnel was employed using Whatman filter paper (No. 1) to filter out the extract. The protocol was to repeat three times with the same composition of solvents and finally the solvent was to evaporate through reduced pressure in rotary evaporator. Through the vacuum liquid chromatographic (VLC) techniques the various fractions were obtained by altering the compositions of mobile phase (dichloromethane:methanol). A wide range of fractional extract of the roots by VLC was believed to have very promising concentrations of phytoconstituents to possess antimicrobial and antibacterial potentials. Preparative TLC was employed for the purity assurance (Chukwujekwu et al. 2006).

The *Cassia occidentalis* aqueous extract from the company in semisolid form was found to have an interesting chromatogram as fingerprint through thin-layer chromatography (TLC). Firstly the total extract was suspended in different solvents, viz., petroleum ether, ethanol (90%), and chloroform separately and then further extraction was carried out by constant orbital shaking overnight followed by the filtration through Whatman (No. 1) filter paper. TLC was carried out separately for every extract by using different mobile phases, viz., toluene:formic acid (95:5) for petroleum ether extract and toluene:ethyl format:formic acid (5:4:1) for ethanol and chloroform extracts. The fingerprint was observed under low and high wavelengths and showed a variety of constituents (Bin-Hafeez et al. 2001).

Hydro-alcoholic extract of *Cassia occidentalis* stem and leaves is among the choices of extracts for phytochemical analysis and bioactive studies. Cold maceration in 70% hydro-alcoholic composition for 1 week provides the essential components comprising the yield of 17% approximately after the rotary dryer under reduced pressure. Storage at 4 °C avoids the time consumption for repetitive

procedures. Suspension in the distilled water helps to screen the varieties of secondary plant metabolites which are responsible for the bioactive aspects of the plant materials (Silva et al. 2011).

The phytochemical extraction was carried out with a variable composition of hydro-alcoholic solvents. 50% v/v was employed for a cold maceration process to avoid any distortion of thermolabile constituent. Finally the solvent was evaporated under reduced pressure by using rotary evaporator. The yield was comparatively enhanced with the unknown mechanism (Jafri et al. 1999).

Coarsely powdered shade-dried material was subjected to the extraction protocols by using Soxhlet with different solvents of increasing polarity. Finally the extract needs to be concentrated by evaporating the solvents completely under the reduced pressure. Phytochemical and qualitative screening of the phytoconstituents (alkaloids, glycosides, flavonoids, total phenols, tannins, and lignin) was performed through standard references in aqueous extract of *Cassia occidentalis* (Sambasivam et al. 2016).

Aqueous extraction of the fresh leaves of *Cassia occidentalis* was made through cold maceration by keeping it overnight which was followed by filtration through Whatman filter paper (No. 3). The concentrated form for the activity and analysis was achieved through rotary evaporator at 40 °C. The extract was kept at −20 °C for further use (Ntchapda et al. 2015).

Washing of the fresh leaves of *Cassia occidentalis* with deionized water was followed by oven drying at 50 °C prior to the Soxhlet extraction to have the ethanolic crude extract. Sample preparation was completed at the recovery through rotary evaporator. Storing at 4 °C was preferred for bioanalytical purpose (Kundu et al. 2014).

The coarse powdered form of leaves of *Cassia occidentalis* was subjected to the maceration in varying degrees of polarities of the organic solvents. Maceration was preferred to keep the sample for 72 h dipped in hexane, ethyl acetate, and methanol which was followed by the rotary evaporator to concentrate the crude extract (Venkatesan et al. 2014).

Order of sequential polarities was developed from petroleum ether to methanol to have the crude extract at room temperature for 72 h. The extract was filtered and concentrated through rotary evaporator and subsequently was defatted to suit the bioactive purpose by dissolving in normal saline with 0.1% Tween-80. In another method, mortar and pestle were used to grind the fresh leaves of *Cassia occidentalis* in 5% ethanol. Muslin cloth was used to filter the extract. The extract was again dissolved in ethanol and kept on shaker for 2 h. Finally it was filtered with muslin cloth to use for the bioactivity.

One more study says that deionized water was used to wash the leaves of *Cassia occidentalis* and then they were dried in oven for 48 h. Soxhlet extraction was carried out for 24 h in different solvents of increasing polarity from petroleum ether and benzene to methanol and water in order to maintain the reference boiling points. Finally the crude extract was filtered through Whatman filter paper (No. 1) and concentrated in vacuum dryer and at last was lyophilized and kept for further use for bioactive purpose. Most of the studies show that the preliminary screening was done

on the methanolic extract of pulverized leaves of *Cassia occidentalis*. The extract was made by soaking the leaves in 80% of methanol for 2 days. Filtration through Whatman filter paper and drying through rotary evaporator was done to execute the various studies.

The screening of pure isolates was done through ethanol, methanol, and water extracts of leaves of *Cassia occidentalis*. First extract yield in terms of percentage was calculated after the continuous percolation process for 48 h. The leaves were employed to isolate the pure components in all the different and successive extracts of percolation. The column chromatographic conditions were maintained and mobile phase was developed as ethanol and methanol in the ratio of 1:1 (v/v).

Soxhlet apparatus dates back to 1879 as the year of its design. Despite the official establishments through the papers as AOAC, US EPA, and British standards, it has some reluctant mode for thermosensitive compounds (Genovese et al. 2010; Rostagno and Prado 2013). To combat the problematic issues we have cold maceration/percolation protocols as an alternate approach to protect the thermolabile substances. The modern techniques bear a satisfactory precision and better yield by protecting the sensitive components. The approaches are as follows:

- Pressurized liquid extraction
- Ultrasound-assisted extraction
- Microwave-assisted extraction
- Super/subcritical fluid extraction (Duval et al. 2016)

Plant seeds were subjected to shade drying and then coarse powder was made in the Soxhlet apparatus to defat it and then to have methanolic extract to perform antipyretic and antioxidant activity. The defatting was done by petroleum ether which was carried till the complete disappearance of dark yellow color. Then repacking of dried coarse defatted powder was subjected to the methanolic extraction. Finally the extract was filtered and concentrated by vacuum distillation. Good and effective percentage yield of methanolic extract (13.8%) was obtained by the process (Singh et al. 2017).

Phytochemical Screening

Phytochemical screening of the plant extract (*C. occidentalis*) was carried out earlier to be aware of the bioactive potential of secondary plant metabolites which are responsible for bioactivity and defense mechanisms. The isolated phytoconstituents as major anthraquinones have been summarized with their structures in Fig. 3 while the minor but specific components are illustrated in Fig. 4.

Different methods were followed to prepare the crude extracts in order of varying polarity orders. The choice of different solvents for crude extracts was made to fulfill the concept of affinity of a particular constituent towards the particular solvent. Aqueous extract was among the hexane, chloroform, ethyl acetate, and ethanol. The leaf extract was prepared by drying and milling the leaf material and

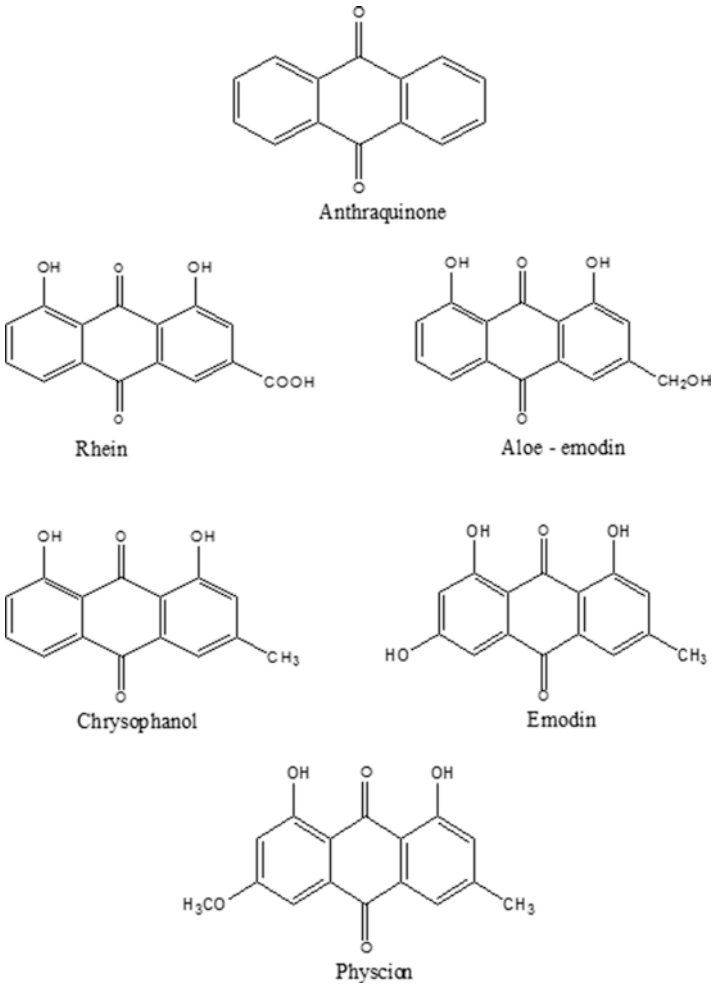

Fig. 3 Major anthraquinones from the different parts of *Cassia occidentalis* L

the extraction was carried out by Soxhlet apparatus at 80 °C. The standard protocol for the detection of major phytoconstituents was followed for alkaloids, glycosides, tannins, saponins, flavonoids, resins, cardiac glycosides, steroids, phlobatannins, and reducing sugars (Herborne 1973). The screening exhibited the presence of alkaloids in aqueous extract; reducing sugars in ethanol extract; carbohydrates in ethanol and aqueous extracts; steroids in hexane, chloroform, ethyl acetate, and ethanol extracts but absent in aqueous extract; flavonoids in ethanol and aqueous extracts; phenolic compounds in hexane, chloroform, and aqueous extracts; tannins in chloroform, ethyl acetate, and aqueous extracts; anthraquinones in chloroform extract; lignin in chloroform, ethyl acetate, ethanol, and aqueous extracts but absent in hexane extract; and proteins and amino acids in ethanol extract. Quantitative estimations

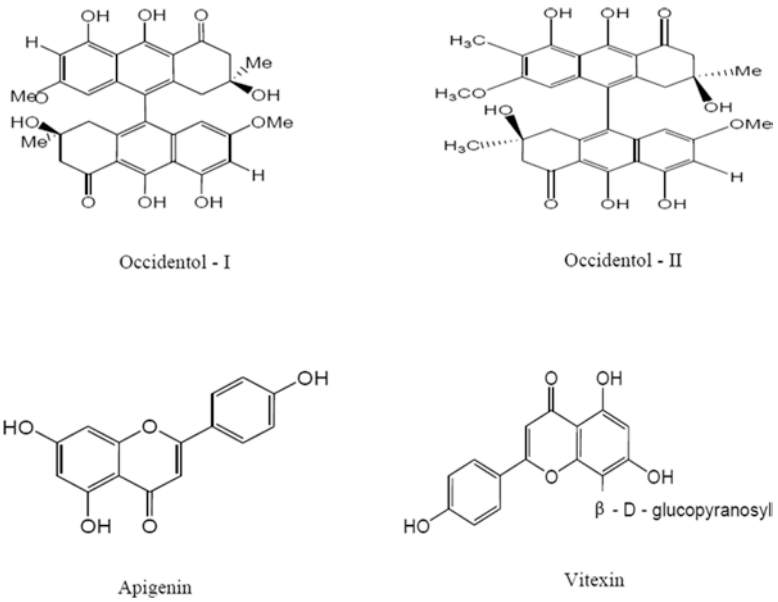

Fig. 4 Minor components from the different parts of *Cassia occidentalis* L

of major components were analyzed and found to be as the decreasing sequence of flavonoids (2.45 mg/g sample) > alkaloids (1.56 mg/g sample) > lignin (0.34 mg/g sample) > tannins (0.21 mg/g sample) > phenol (0.16 mg/g sample) (Sambasivam et al. 2016).

Nutritive Values Through the Phytochemical Measures

Nutritional values of the plant *C. occidentalis* were estimated through the various analytical techniques and summarized as 34.44 kcal energy value along with the crude fiber content as 5.69 mg/g. Intake of dietary fibers helps to lower the serum cholesterol level, risk of cardiac problems, high blood pressure, constipation, hyperglycemia, and colon and breast cancer (Ishida et al. 2000). That's why the mentioned plant can act as a valuable source of energy and dietary fibers for human beings. Other nutritional components are free amino acids and carbohydrates. The plant also possesses the considerable amount of vitamins such as thiamine, niacin, and riboflavin and the enzymes as amylase, catalase, lipase, alkaline phosphatase, and acid phosphatase.

X-ray fluorescence spectrophotometry technique revealed the presence of minerals as iron, manganese, magnesium, calcium, potassium, zinc, sodium, phosphorous, copper, and sulfur. A high content of iron was found in plant; that's why it is useful for the treatment of anemia. Somehow the plant might be used as the source

of deficient minerals to recover from the associated disorders in particular. Zinc deficiency bears a significant alarming note on worldwide perceptions for public health especially in developing countries; hence the plant is beneficial (Osendarp et al. 2003; Hussain et al. 2009). As per the findings of Food and Agricultural Organization's (FAO) food balance data, it is reported that about 20% of the world's population might be at a risk of zinc deficiency because of the less zinc intake approximately <70 mg/day (Holt and Brown 2004). The nutritional potential of *Cassia occidentalis* was found so significant, and hence it can be used as a herbal supplement for the betterment of ongoing treatment for various disorders. The plant holds a better and secured nutritious capacity to work as a medicinally active edible supplement (Sambasivam et al. 2016).

Biological and Toxicological Studies of *Cassia occidentalis*

The crude form of the extract comprises the mixture of several phytoconstituents which exhibit the activity to bring the physiological change in the biological system. The main constituents in major amounts are anthraquinones which carry always the credit of bearing innumerable pharmacological actions, which are illustrated in Fig. 5. The other activities which are being claimed over here are the collective results of a whole crude extract where anthraquinones are present along with the other components. The activities are as follows.

Hepatoprotective Activity

C. occidentalis seed components play an important role to regulate many transcripts which are concerned with many metabolic pathways including xenobiotic metabolism, oxidative stress, carbohydrate metabolism, apoptosis, etc. The seed component exposure was found to decrease the level of Phase 1 and Phase 2 hepatic enzymes which indicates the impairment of related metabolism and detoxification capacities of hepatocytes (Panigrahi et al. 2014). The concept and regulations might be useful to formulate the strategies for therapeutic developments. On the other hand the plant is considered as an important ingredient of several polyherbal preparations marketed for liver diseases. The hepatoprotective role of hydro-alcoholic extract of leaves of *C. occidentalis* was studied on rat liver. The liver injury was induced by paracetamol and ethanol by monitoring the various enzymatic parameters as alkaline phosphatase, serum transaminase, serum cholesterol, total lipids, and variable histopathological findings. The conclusive remark was in the favor of significant hepatoprotection (Jafri et al. 1999). The reduced DNA damage is the attribute of chelating property of the seed extract when the degradation was caused by iron (ii)-driven Fenton reaction. Induced toxicities are also observed to be overcome by the plant formulations where antioxidant potential is the key factor to

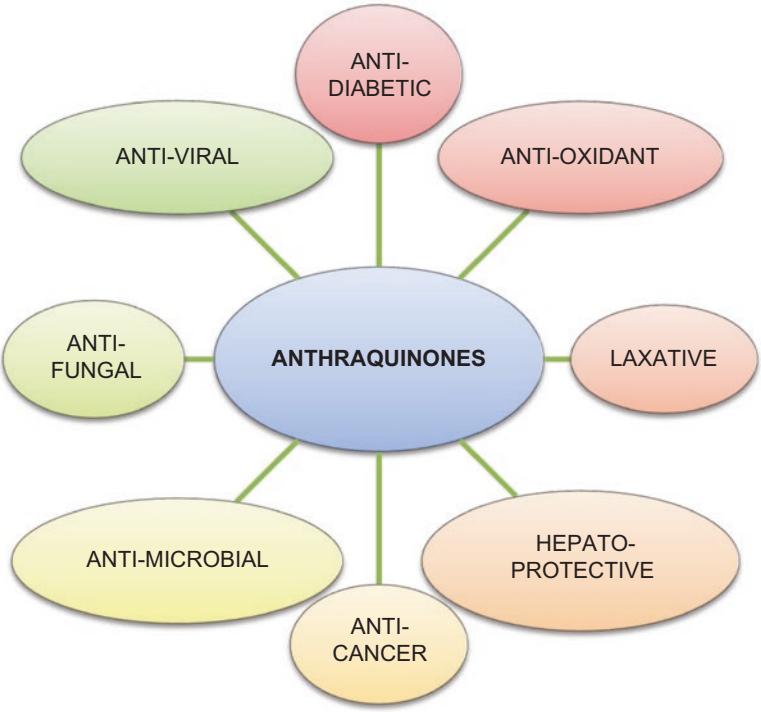

Fig. 5 Activities attributed to the anthraquinone moiety

protect the liver cells (Bhattacharyya et al. 2003). Another side of the protective effects of the plant extracts can also never be ruled out. The previous findings to exhibit hypoproteinemic effects along with the elevated levels of alkaline phosphatase (ALP), alanine amino transferase (ALT), and aspartate amino transferase (AST) are the serious attention-withdrawing facts towards the toxicity measures (Nuhu and Aliyu 2008).

Hypoglycemic Activity

Hypoglycemic activity was carried out by preparing the alcoholic root extract of *Cassia occidentalis* and the dose was adjusted to 250 and 500 mg/kg body weight. The activity was evaluated by making one of the groups as streptozotocin (STZ)-induced noninsulin-dependent diabetes mellitus (NIDDM) mice models. Biochemical parameters, i.e., blood glucose, urea, protein, serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), creatinine, serum cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG), and various physical parameters like change in food intake, body weight, water intake, and pathological changes in liver were performed

for the precise estimation of hypoglycemic effects. Both the doses of alcoholic root extract (250 and 500 mg/kg of body weight) caused a significant lowering of fasting blood glucose (FBG) levels in STZ-induced NIDDM mice models. The findings support the traditional practice of the roots of *C. occidentalis* by revealing the factual reports concerning NIDDM for the current studies where regeneration of β-cells was a significant aspect of the study (Sharma et al. 2014).

Alloxan-induced diabetes is linked with the destruction of β-cells of islets of Langerhans of pancreas which results in the reduced secretion of endogenous insulin, hence the utilization of glucose by the cells. This induced diabetes was shown to be controlled by the methanolic extract of leaves of *C. occidentalis* orally administered with the adjusted dose of 300 mg/kg body weight. A significant reduction of fasting blood glucose level in 6–12 h supports its traditional use for antidiabetic purpose. More hypoglycemic results were corresponding to the dose adjustment up to 450 mg/kg body weight. In one more study it was also revealed that the aqueous extract of *C. occidentalis* shows a significant lowering in fasting blood glucose levels in normal group and alloxan-induced diabetic rat group. Histopathological studies for the alloxan-induced diabetes group showed proper regeneration of β-cells of pancreas (Verma et al. 2011).

Antimalarial Activity

Ethanol and chloroform extract of leaves of *C. occidentalis* shows the significant antimalarial activity. The lyophilized aqueous extract was found less active than corresponding ethanolic extract. The activity was carried out in vivo, against *Plasmodium berghei* ANKA in mice (Tona et al. 2004).

Anti-inflammatory Activity

Significant anti-inflammatory activity was assayed and observed in carrageenan-induced paw edema model. It was found to a considerable extent at the dose of 2000 mg/kg of leaf extract. The reduced level of lipid peroxide content, phospholipase A2, and gamma-glutamyl trans-peptidase was the significant finding (Sadique et al. 1987).

Immunosuppressant Activity

Immunosuppressant activity was determined by administering cyclophosphamide (CP) as the standard drug in a single dose of 50 mg/kg b.w. intraperitoneally to one of the groups. Plant extracts show suppressive effects on the parameters of

humoral immunity along with lymphoid organ weight and cellular effects. Quantitative hemolysis of sheep red blood cells (SRBC) was also analyzed. The CP-exposed animal group was administered with plant extract and showed significant humoral responses. *C. occidentalis* extract revealed the protection in CP-treated animals. The bone marrow cell counts were found much higher in extract-treated groups comparative to the CP-treated animals. The modulation of hepatic drug-metabolizing enzymes might be the probable mechanism for CP-induced suppression (Bin-Hafeez et al. 2001).

Hypolipidemic/Anti-atherosclerogenic

Aqueous extracts of *C occidentalis* were studied for hypolipidemic and anti-atherosclerogenic activities in rat models through the high-fat-diet-induced (enriched cholesterol) hypercholesterolemia. The results supported well to reduce the bad cholesterols, i.e., low-density lipoprotein (LDL), and triglycerides (TG) corresponding to increasing good cholesterols, i.e., high-density lipoprotein (HDL), in animal models. The results also supported the traditional use of the drug extract of this plant to control the raised blood pressure and raised glucose level. The diuretic activity of this extract is a valid correlation with the controlled blood pressure (Ntchapda et al. 2017).

Antipyretic Activity

Antipyretic activity of methanolic extracts of *C. occidentalis* was evaluated by inducing pyrexia on mice models by injecting 15% aqueous solution of Brewer's yeast. Four groups of mice were made and each group was having six animals. The extract doses of 250 and 500 mg/kg body weights were given and the standard drug paracetamol with the dose of 20 mg/kg body weight was used to compare the bioactive potentials of the extracts. Finally the extracts showed a better hypothermal activity against the yeast-induced hyperthermia (Singh et al. 2017).

Toxicities Associated with the Plant

Toxicities were observed mainly on liver, kidney, and skeletal and cardiac muscles. Toxic dose of *C. occidentalis* beans varies from 0.05% to 0.5% of body weight. Different animals show the different symptoms of intoxication which include muscle degenerations, liver congestion (Bruere 1943), and weakness; the following models show the toxic effects as follows.

Chicken: weight loss, diarrhea, weakness, hypothermia, ataxia, and death. Other studies exhibit focal swelling, necrosis of myofibers, and fragmentation (Simpson et al. 1971). On liver mitochondria lower phosphorylation ratio was reported (Graziano et al. 1983).

Pigs: Ataxia and neuromuscular dysfunction.

Rats: Lethargy, recumbence, weakness, depression, and emaciation (Colvin et al. 1986; Barbosa-Ferreira et al. 2005). Toxicity was observed at the dose of 12.5 g/kg body weight (Nwude and Ibrahim 1980). One of the investigations was also carried out to find out the effects of oral subacute administration of *C. occidentalis* in female Wistar rats during pregnancy and was suggested that it is not recommended during pregnancy (Aragão et al. 2009). The effect of seeds on the transcriptional expression was also investigated with patterns of mRNAs in rat liver and the significant outcomes were obtained by the exposure of seeds in diet to rats. The results were in concern with the 60 transcripts belonging to various metabolic pathways. The involvement of oxidative stress was observed along with the significant reduction in the levels of Phase 1 and Phase 2 enzymes. Finally hepatotoxicity was revealed (Panigrahi et al. 2014).

Rabbits: Centrolobular degeneration, myocardial necrosis, muscular atrophy, and declined cytochrome oxidase activity (Tasaka et al. 2000).

Human beings: The tissue-related pathological and clinical impacts of *C. occidentalis* poisoning in children affect mainly skeletal muscles, hepatic, and brain. It shows some resemblance to the animal toxicity where it affects adversely the same. Pod consumption by children has resulted in fatal coma in western UP state in India. Though it is dose dependent and proven that 2–3 beans have no impact if it exceeds then it leads to serious diseases, coma, and death. The death rate in children in acute and severe poisoning has been documented to be 75–80% (Vashishtha et al. 2007b).

Herbal Formulation

C. occidentalis is used as a single component and in combination as an ingredient of polyherbal formulations. Very-well-known product Liv.52 is available as tablet and syrup which is widely used in the management of liver diseases, i.e., hepatitis A (HA). The mentioned formulation is the result of thorough clinical studies and analysis for a long span of time around 30 years where several thousands of patients were examined for the statistical conclusions and safety parameters along with efficacy. Finally it was concluded as the safe and effective product for the best management of hepatitis A (HA). The major products belong to Indian companies where one tincture product is from the USA. The products are listed in Table 1 with their appropriate uses. Gericare is the tablet formulation available since a very long time to rejuvenate body and mind. Geriforte is considered to be the important drug for postmenopausal depression. No significant adverse effects were reported in this

Table 1 Herbal formulations containing *Cassia occidentalis* as the important ingredient

S. no.	Product (brand name)	Company	Uses	Web links
1.	BONNISAN	The Himalaya Drug Company, India	Keeps baby healthy	http://www.himalayawellness.com/herbfinder/cassa-occidentalis.htm http://www.tropilab.com/yorkapesi.html http://www.itmonline.org/arts/unani.htm
2.	GERIFORTE	The Himalaya Drug Company, India	Rejuvenates body and mind	
3.	HERBOLAX	The Himalaya Drug Company, India	Bowel regulator	
4.	LIV 52	The Himalaya Drug Company, India	Hepatoprotective	
5.	LIV 52 DROPS	The Himalaya Drug Company, India	Hepatoprotective	
6.	LIV 52 VET	The Himalaya Drug Company, India	Hepatoprotective	
7.	LIV 52 VET DS	The Himalaya Drug Company, India	Hepatoprotective	
8.	DIGYTON	The Himalaya Drug Company, India	Digestive stimulant	
9.	GERIFORTE AQUA	The Himalaya Drug Company, India	Immune booster	
10.	GERIFORTE VET	The Himalaya Drug Company, India	Immune booster	
11.	FEDEGOSO-TINCTURE	Tropi Lab INC, USA	Dietary supplement	
12.	SAFI	Hamdard laboratory, India	Blood purifier	
13.	Bonny-care	Tibb, South Africa	Health supplement	

Table 2 Patents on *Cassia occidentalis* as an important ingredient of polyherbal formulations

S. no.	Patent title	Patent numbers	Published date
1.	Herbal formulation for the treatment of piles	WO 2006070386 A1 (https://patents.google.com/patent/WO2006070386A1/en)	6 July 2006
		US 20070172529 A1 (https://patents.google.com/patent/US20070172529A1/en?oq=US+20070172529+A1)	26 July 2007
2.	Development of herbal nutritious chocolate and its processing Herbal nutritious chocolate formulation and process for preparation thereof	248,784US20060141066 (https://patents.google.com/patent/US20060141066A1/en)	26 August 2011 29 June 2006
3.	*Cassia occidentalis*—honey beverage for treating irritable bowel syndrome	CN 105434492 A (https://patents.google.com/patent/CN105434492A/en#legalEvents)	30 May 2016

concern and the overall drug formulation acceptability is excellent (Kolhapure and Mitra 2004). Some selective patents have been listed in Table 2, with their brief details mentioning about the importance in polyherbal formulations. The web links are as follows: https://www.google.com/patents/WO2006070386A1?cl=en.

Conclusion

Since *Cassia occidentalis* has remained in traditional practice for a long time it opened the ways to explore its hidden bioactive potential. As the phytochemical-based potential supports a plant to be laxative it indicates the presence of various anthraquinones, which was confirmed by the chromatographic analyses. A long range of phytoconstituents are responsible for bioactivities, either to treat the diseases or to induce toxicities. The toxic potential of the plant supports the extracts to be effective against microorganisms and various tumor cells. However the plant is safe and effective which has been assured and validated by various reliable standardization protocols. Further work is the need of the hour for the sake of pure isolations of the compounds which might be helpful for various diseases. The advanced techniques for the isolation must be adopted for the recent developments to explore the wide concepts of its utility. The existing polyherbal formulations might be used as an innovative approach to develop various other dosage forms. The chapter covers the updated information to move for the next step pertaining to the phytochemical and pharmacological aspects.

References

Abongwa M, Ahmed GR, Oluwadamilola A (2011) Protective effect of *Senna occidentalis* on tetracycline-induced hepatotoxicity and nephrotoxicity in rabbits. Toxicol Lett 205:S270

Ali MS, Azhar I, Amtul Z, Ahmad VU, Usmanghani K (1999) Antimicrobial screening of some Caesalpiniaceae. Fitoterapia 70:299–304

Almeida CF, Amorim EL, Albuquerque UP, Maia MBS (2006) Medicinal plants popularly used in the Xingó region—a semi-arid location in Northeastern Brazil. J Ethnobiol Ethnomed 2:15–21

Aragão TP, Lyra MMA, Silva MG, Andrade BA, Ferreira PA, Ortega LF et al (2009) Toxicological reproductive study of *Cassia occidentalis* L. in female Wistar rats. J Ethnopharmacol 123:163–166

Barbosa-Ferreira M, Dagli ML, Maiorka PC, Gorniak SL (2005) Sub-acute intoxification by *Senna occidentalis* seeds in rats. Food Chem Toxicol 43:497–503

Bardhan P, Sharma SK, Garg NK (1985) *In vitro* effect of an Ayurvedic liver remedy on hepatic enzymes in carbon tetrachloride treated rats. Indian J Med Res 82:359–364

Bhattacharyya D, Mukherjee R, Pandit S, Das N, Sur TK (2003) Prevention of carbon tetrachloride induced hepatotoxicity in rats by Himoliv. A polyherbal formulation. Indian J Pharmacol 35:183–185

Bin-Hafeez B, Ahmad I, Haque R, Raisuddin S (2001) Protective effect of *Cassia occidentalis* L. on cyclophosphamide-induced suppression of humoral immunity in mice. J Ethnopharmacol 75(1):13–18

Bodeker G, Burford G (2007) Traditional, complementary and alternative medicine: policy & public health perspectives. Imperial College Press, London, pp 1–247

Brandão MG, Grandi TS, Rocha EM, Sawyer DR, Krettli AU (1992) Survey of medicinal plants used as antimalarial in the Amazon. J Ethnopharmacol 36:175–182

Bruere P (1943) Bemerkungen uber ein in ungebranntem Zustand giftiges kaffessurrogat *Cassia occidentalis*. Chem Zentralblatt I:1728

Caceres A, Lopez B, Juarez X, Del Aguila J, Garcia S (1993) Plants used in Guatemala for the treatment of dermatophytic infections. 2. Evaluation of antifungal activity of seven American plants. J Ethnopharmacol 40:207–213

Calore EE, Cavalier MJ, Haraguchi M, Gorniak SL, Dagli ML, Raspantini PC (1998) Toxic peripheral neuropathy of chicks fed *Senna occidentalis* seeds. Ecotoxicol Environ Saf 39(1):27–30

Cavaliere MJ, Calore EE, Haraguchi M, Gorniak SL, Dagli ML, Raspantini PC (1997) Mitochondrial myopathy in *Senna occidentalis* seeds fed chicken. Ecotoxicol Environ Saf 37(2):181–185

Chukwujekwu JC, Van Staden J, Smith P (2005) Antibacterial, anti-inflammatory and antimalarial activities of some Nigerian medicinal plants. S Afr J Bot 71:316–325

Chukwujekwu JC, Coombes PH, Mulholland DA, Staden JV (2006) Emodin, an antibacterial anthraquinone from the roots of *Cassia occidentalis*. S Afr J Bot 72:295–297

Coimbra R (1994) Manual de Fitoterapia. Editora CEJUP, Belém, p 26

Colvin BM, Harrison LR, Sangaster LT, Gosser HS (1986) *Cassia occidentalis* toxicosis in growing pigs. J Am Vet Med Assoc 189:423–426

Corrêa MP (1926) Dicionário das plantasúteis do Brasil e das exóticascultivadas. Imprensa Nacional, Rio de Janeiro

Corrêa MP (1984) Dicionário de PlantasÚteis do Brasil e das Exóticas Cultivadas. Ministério da Agricultura, Rio de Janeiro, pp 55–57

Dennis PA (1988) Herbal medicine among Miskito of Eastern Nicaragua. Econ Bot 42(1):16–28

Dhiman AK (2006) Ayurvedic drug plants. Daya Books, New Delhi, p 277

Di Stasi LC, Hiruma-Lima CA (2002) Plantas medicin aisna Amazônia e na Mata Atlântica. Editora UNESP, São Paulo, p 604

Dupriez H, de Leener P (1987) Jardinset vergers d'Afrique. Terre et vie, Ed. L'Harmattan, Paris, p 354

Duval J, Virginie P, Marion P, Leselliera E (2016) Research advances for the extraction, analysis and uses of anthraquinones: a review. Ind Crop Prod 94:812–833

Fenner R, Betti AH, Mentz LA, Rates SMK (2006) Planta sutilizadasna medicina popular brasileira com potencial atividа de antifúngica. Braz J Pharm Sci 42:369–394

Genovese S, Tammaro F, Menghini L, Carlucci G, Epifano F, Locatelli M (2010) Comparison of three different extraction methods and HPLC determination of the anthraquinones aloe-emodine, emodine, rheine, chrysophanol and physcione in the bark of *Rhamnus alpinus* L. (Rhamnaceae). Phytochem Anal 21:261–267

Graziano MT, Flory W, Seger CL, Hebcrt CD (1983) Effects of *Cassia occidentalis* extract in the domestic chicken. Am J Vet Res 44:1238–1244

Gupta MP (1979) Ethnopharmacognostics observations on Panamanian medicinal plants. Part I. Q J Crude Drug Res 17(3/4):115–130

Herborne JB (1973) Phytochemical methods, 1st edn. Chapman & Hall, London, pp 49–188

Higgins JM, Walker RH, Whitwell T (1985) Coffee senna (*Cassia occidentalis*) competition with cotton (*Gossypium hirsutum*). Weed Sci 34:52–56

Holt C, Brown KH (2004) International Zinc Nutrition Consultative Group (IZINCG) assessment of the risk of zinc deficiency in populations and options for its control. Food Nutr Bull 25:94–103

Humphry CM, Clegg MS, Keen CL, Grivetti LE (1993) Food diversity and drought survival. The Hausa example. Int J Food Sci Nutr 44:1–16

Hussain J, Khan AL, Rehman N, Hamayun M, Shah T, Nisar M, Bano T, Shinwari ZK, Lee IJ (2009) Proximate and nutrient analysis of selected vegetable species: a case study of Karak region of Pakistan. Afr J Biotechnol 8:2725–2729

Ishida H, Suzuno H, Sugiyama N, Innami S, Todokoro T, Maekawa A (2000) Nutritional evaluation of chemical component of leaves, stalks and stems of sweet potatoes (Ipomoea batatas Poir.). Food Chem 68:359–367

Jafri MA, Subhani MJ, Javed K, Singh S (1999) Hepatoprotective activity of leaves of *Cassia occidentalis* against paracetamol and ethyl alcohol intoxification in rats. J Ethnopharmacol 66:355–361

Kolhapure SA, Mitra WS (2004) Meta-analysis of 50 phase III clinical trials in evaluation of efficacy and safety of Liv. 52 in infective hepatitis. Med Update 12:51–61

Krishanayya NS, Bedi SJ (1986) Effect of automobile lead pollution on *Cassia tora* L. and *Cassia occidentalis* L. Environ Pollut (Ser A) 40:221–226

Kumar A, Nehar S (2007) Environmental protection, Daya Books, New Delhi, p 157

Kundu S, Roy S, Lyndem LM (2014) Broad spectrum anthelmintic potential of Cassia plants. Asian Pac J Trop Biomed 4(Suppl 1):S436–S441

Kuo SC, Chen SC, La CF, Teng CM, Wang JP (1996) Studies on the anti-inflammatory and antiplatelet activities of constituents isolated from the roots and stem of *Cassia occidentalis* L. Chin Pharm J 48:291–302

Lal J, Gupta PC (1974) Two new anthraquinones from the seeds of Cassia occidentalis. Exp Dermatol 30:850–851

Lombardo M (2014) Coffee senna: an important species for different ethnic groups. Commun Plant Sci 4(3–4):43–47

Martin BW, Terry MK, Bridges CH, Bailey CM (1981) Toxicity of *Cassia occidentalis* in the horse. Vet Hum Toxicol 23:416–417

Medoua GN, Mbofung CM (2003) Evaluation du potential toxicologique de la boissonpre'pare'e a' partir des graines de *Cassia occidentalis*. In: Food-Africa international working meeting on improving food systems in sub-Saharan Africa, Yaounde, Cameroon, 5–9 May

Medoua GN, Mbofung CM (2007) Kinetics studies of some physico-chemical substances during roasting and preparation of beverage made by *Cassia occidentalis* seeds. LWT—Food Sci Technol 40:730–736

Nagaruja N (1990) A survey of plant crude drugs of Rayalaseema, Andhra Pradesh, India. J Ethnopharmacol 29(2):137–158

Ntchapda F, Joseph B, David R, Kemeta A, Paul F, Seke E, Théophile D (2015) Diuretic and antioxidant activities of the aqueous extract of leaves of Cassia occidentalis (Linn.) in rats. Asian Pac J Trop Med 8(9):685–693

Ntchapda F, Barama J, Talla E, Dimo T (2017) Hypolipidemic, antioxidant and antiatherosclerogenic effect of aqueous extract leaves of *Cassia occidentalis* Linn (Caesalpiniaceae) in diet-induced hypercholesterolemic rats. BMC Complement Altern Med 17:76

Nuhu AA, Aliyu R (2008) Effects of *Cassia occidentalis* aqueous leaf extract on biochemical markers of tissue damage in rats. Trop J Pharm Res 7(4):1137–1142

Nwude N, Ibrahim MA (1980) Plants used in traditional veterinary medical practice in Nigeria. J Vet Pharmacol Ther 3:261–273

O'Hara PJ, Pierce KR, Reid WK (1969) Degenerative myopathy associated with ingestion of *Cassia occidentalis*: clinical and pathologic features of the experimentally induced disease. Am J Vet Res 30:2173–2180

Ogunkunle AT, Ladejobi TA (2006) Ethnobotanical and phytochemical studies on some species of Senna in Nigeria. Afr J Biotechnol 5:2020–2023

Osendarp SJ, West CE, Black RE (2003) The need for maternal zinc supplementation in developing countries: an unresolved issue. J Nutr 133:817–827

Pandey YN (1975) Cassia seeds used as drug in the indigenous medical systems of India. Q J Crude Res 13:61–64

Panigrahi GK, Yadav A, Yadav A, Ansari KM, Chaturvedi RK, Vashistha VM, Raisuddin S, Das M (2014) Hepatic transcriptional analysis in rats treated with *Cassia occidentalis* seed: involvement of oxidative stress and impairment in xenobiotic metabolism as a putative mechanism of toxicity. Toxicol Lett 229(1):273–283

Purwar C, Rai R, Srivastava N, Singh J (2003) New flavonoid glycosides from *Cassia occidentalis*. Ind J Chem 42B:434–436

Rao PN, Kumar PA, Rao TA, Prasad YA, Rao CJ, Rajyam PL (2004) Role of Chandipura virus in an "epidemic brain attack" in Andhra Pradesh, India. J Pediatr Neurol 2:131–143

Rodrigues E (2007) Plants of restricted use indicated by three cultures in Brazil (Caboclo-river dweller, Indian and Quilombola). J Ethnopharmacol 111:295–302

Rostagno MA, Prado JM (2013) Natural product extraction: principles and applications, RSC green chemistry series. Royal Society of Chemistry, Cambridge

Sadique J, Chandra T, Thenmozhi V, Elango V (1987) Biochemical modes of action of *Cassia occidentalis* and *Cardiospermum halicacabum* in inflammation. J Ethnopharmacol 19:201–212

Sambasivam M, Vellingiri V, Pemaiah B (2016) Studies on physicochemical and nutritional properties of aerial parts of *Cassia occidentalis* L. J Food Drug Anal 24:508–515

Samy RP, Ignacimuthu S (2000) Antibacterial activity of some folklore medicinal plants used by tribals in Western Ghats of India. J Ethnopharmacol 69:63–71

Sharma S, Choudhary M, Bhardwaj S, Choudhary N, Rana AC (2014) Hypoglycemic potential of alcoholic root extract of *Cassia occidentalis* Linn. in streptozotocin induced diabetes in albino mice. B-FOPCU 52:211–217

Silva MG, Aragão TP, Vasconcelos CF, Ferreira PA, Andrade BA, Costa IM, Costa-Silva JH, Wanderley AG, Lafayette SS (2011) Acute and subacute toxicity of Cassia occidentalis L. stem and leaf in Wistar rats. J Ethnopharmacol 136:341–346

Simpson CF, Damrona BL, Hahrms RH (1971) Toxic myopathy of chicks fed *Cassia occidentalis* seeds. Avian Dis 15:284–290

Singh VV, Jain J, Mishra AK (2017) Determination of antipyretic and antioxidant activity of Cassia occidentalis Linn methanolic seed extract. Pharm J 9(6):913–916

Soukup J (1970) Vocabulary of the common names of the Peruvian Flora and catalog of the genera. Editorial Salesiano, Lima, p 436

Tasaka AC, Weg R, Calore EE, Sinhorini IL, Dagli MLZ, Haraguchi M (2000) Toxicity testing of *Senna occidentalis* seed in rabbits. Vet Res Commun 24:573–582

Tona L, Cimanga RK, Mesia K, Musuamba CT, De B, Apers S, Hernans N, Van Miert S, Pieters L, Totte J, Vlientinck AJ (2004) *In vitro* antiplasmodial activity of extracts and fractions from seven medicinal plants used in the Democratic Republic of Congo. J Ethnopharmacol 93:27–32

Vashishtha VM, Nayak NC, John TJ, Kumar A (2007a) Recurrent annual outbreaks of a hepatomyo-encephalopathy syndrome in children in Western Uttar Pradesh India. Indian J Med Res 125:523–533

Vashishtha VM, Kumar A, John TJ, Nayak NC (2007b) *Cassia occidentalis* poisoning causes fatal coma in children in Western Uttar Pradesh. Indian Pediatr 44:522–524

Venkatesan R, Ravindran J, Alex Eapen A, John William J (2014) Insecticidal and growth regulating activity of crude leaf extracts of Cassia occidentalis L. (Caesalpiniaceae) against the urban malaria vector Anopheles stephensi Liston (Diptera: Culicidae). Asian Pac J Trop Dis 4(Suppl 2):S578–S582

Verma L, Khatri A, Kaushik B, Patil UK, Pawar R (2011) Antidiabetic activity of *Cassia occidentalis* (Linn) in normal and alloxan-induced diabetic rats. Indian J Pharmacol 42(4):224–228

Warrier PK, Nambiar VP (1994) Indian medicinal plants: a compendium of 500 species. Orient Blackswan 2:21

Wolfender JL, Marti G, Thomas A, Bertrand S (2015) Current approaches and challenges for the metabolite profiling of complex natural extracts. Ed Choice IX 1382:136–164 https://doi.org/10.1016/j.chroma.2014.10.091

Yadav JP, Arya V, Yadav S, Panghal M, Kumar S, Dhankhar S (2010) *Cassia occidentalis* L—a review on its ethnobotany, phytochemical and pharmacological profile. Fitoterapia 81:223–230

Tamarix aphylla (L.) Karst. Phytochemical and Bioactive Profile Compilations of Less Discussed but Effective Naturally Growing Saudi Plant

M. Ali, Hassan Ahmad Alhazmi, S. H. Ansari, Arshad Hussain, Sarfaraz Ahmad, Md Sarfaraz Alam, Md Sajid Ali, Karam A. El-Sharkawy, and Khalid Rehman Hakeem

Introduction

Plants are known to provide a wide range of benefits which include medicinal and economical aspects. The literature claims that approximately 80% of the world population is directly or indirectly the user of traditional drugs in developing countries. It is worthy to go through the World Health Organization (WHO) report which claims more than 150 plants to show more frequent antidiabetic potentials where *Tamarix aphylla* holds an excellent position in this report (Hebi and Eddouks 2017). The traditional medicines carry the history of thousands of years which not only covers its importance in health care but the cultural and spiritual beliefs as well. The advantage of low incidence of adverse reactions always promotes the

M. Ali (✉)
Department of Pharmacognosy, College of Pharmacy, Jazan University, Jazan, Saudi Arabia

H. A. Alhazmi · K. A. El-Sharkawy
Department of Pharmaceutical Chemistry, College of Pharmacy, Jazan University, Jazan, Saudi Arabia

S. H. Ansari
Department of Pharmacognosy, Faculty of Pharmacy, Jamia Hamdard, New Delhi, India

A. Hussain
Department of Pharmacognosy, King Khalid University, Abha, Saudi Arabia

S. Ahmad
Department of Clinical Pharmacy, College of Pharmacy, Jazan University, Jazan, Saudi Arabia

Md S. Alam · Md S. Ali
Department of Pharmaceutics, College of Pharmacy, Jazan University, Jazan, Saudi Arabia

K. R. Hakeem
Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia

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compliances by the majority of the countries. Despite the low incidence of side effects the drug interaction possibilities can never be ruled out. The cost-effectiveness is also an attractive aspect for the acceptability to a wide range. Traditional practice of natural products is ancient but complementary medicines or alternative medicine has the incorporations of new technologies which was a lacuna in ancient traditional practices. In Saudi Arabia the enormous range of flora exists because of a wide range of climatic conditions. This flora needs to be evaluated on the basis of the traditional herbalist and practitioners. Innumerable Wadis and old villages in the Kingdom still rely on to the use of this natural flora. Unfortunately the plant *Tamarix aphylla* L. has not drawn the deserving attention for its phytochemical and bioactive explorations, but the available data and publications expressed that the plant needs to be attended attentively for its hidden potentials. The updated compilations, neither a chapter nor a review article in this concern, have been found during the literature survey. This effort is an attempt to collect the authentic information which would be beneficial for the common man and the research scholars for the interest in particular. The compilation of the work is inspired by the traditional values of the plant in the kingdom and the recent bioactive explorations in Moroccan university.

Plant Profile and Availability

Tamarix aphylla L. (family Tamaricaceae) is also known as *Thuja aphylla* L., *T. articulate* Vahl., and *T. orientalis* Forsk. In English it is commonly known as Athel tamarisk. In Arabic as Abal, Tarfaa, Ghaz, and Athel. The plant prefers alluvial and saline soil to grow naturally. It is found mainly as tall shrubs or trees up to 12 m, entirely glabrous with reddish brown to grey color bark. Leaves are abruptly mucronate, approx 3 mm long, and inflorescence is raceme (aestival), broad, and spirally curved. Flowers are pinkish, white with pedicle, and bisexual. Sepals are free, broadly ovate to elliptic, and obtuse. Petals are also free. Capsule is trigonous (Marwat et al. 2008). Most of the plants from this family grow well in temperate and subtropical regions where Tamarix is the genera with 55 species that are real native to Mongolia, India, China, the Middle East, Europe, and North Africa with saline soils (Heywood et al. 2007; Baum 1978; DeLoach et al. 2003). The plant is reported to have a natural vegetation property in Abha and Al-Baha regions of Saudi Arabia (Alrumman 2016).

The plant is natural and well grown in Asir province and Al-Baha regions of Saudi Arabia. Though the distribution is not restricted to the selective regions the salty soils with low-temperature-range climate are suitable for its growth. The natural vegetation of the plant is also reported from Jizan province. The original image of the plant has been shown in Fig. 1 which was taken from Hayyal mataar area of Jizan city. Generally the plants from this genera are halophytes which can easily tolerate a wide range of abiotic stresses as temperature, draught, and saline impacts (Saïdana et al. 2008). Though the industrial pollutants are not reported to be of

Fig. 1 *Tamarix aphylla* L. growing in Jizan province, Saudi Arabia

considerable amount in Saudi Arabia the genera Tamarix is believed to possess a significant role for phytoremediation in other continents as well (Marlin et al. 2017).

Traditional Values

Traditionally the plant has been used in various other systems and known as "Mayyin Khurd" in Unani, Macheeka in "Ayurveda," and Sivappattushavukku in "Siddha." The history of folk medicinal uses claims that the plant has remained traditionally so beneficial for antirheumatic, analgesic, and antipyretic activities and gall extract for throat infection and to tighten the vaginal mucous membrane temporarily just prior to sex (Akhlaq and Ali 2011; Ahmad et al. 2009; Qadir et al. 2014;

Laaroussi 2013). The traditional values include antioxidant, antimicrobial, diuretic, anthelmintic, antihemorrhoid, antidiarrheal, gingivitis, carminative, aphrodisiac, eczema and other skin diseases. Other reports include internal tumors, inflammations and joint pains (Ahmad et al. 2009; Shafi et al. 2014). Attention withdrawing potentials also included tuberculosis, smallpox, leprosy, contagious diseases, eye inflammation and fever (Azaizeh et al. 2006). Plant as a folk remedy was used as medicament and tonic (Sharma and Parmar 1998) and foliage decoction for fever (Said et al. 2002; Alzweiri et al. 2011); it has also been reported to be effective for fighting lung and esophageal cancer (Sharma and Tyagi 1996; London et al. 2000). Wound healing and anti-inflammatory role of the *Tamarix aphylla* is also mentioned in Islamic literature and some other sources from the remote areas in Saudi Arabia. In Al-Qassim area of Saudi Arabia the powder of all parts of the plant was in use to treat camel skin diseases (mycotic or allergic dermatitis) by applying it on skin at least for 1 week (Abbas et al. 2002). Powdered leaves of the plant have the history to be used as dental analgesic and for wound healing by passing the burnt smoke over the exposed injury (Kamal et al. 2009). Leaf ashes need to be boiled with water. Its residue is traditionally effective for jaundice when consumed with a Unani medicine 'Sharbat-e-Bazoori'. The wood ash of *Tamarix aphylla* is a spiritual healer when inhaled as smoke with burning "Harmal" seeds. Boiled leaves when tied immediately on the affected skin work effectively for wound healing, abscesses, and rheumatism (Marwat et al. 2011). Root decoction has the traditional history for tuberculosis, smallpox, leprosy, and contagious ailments. Leaf and young branch decoction is used for spleen swelling, tetanus, and gynecological problems (Benhouhou 2005). Tafilalet semiarid region in Morocco has reported the traditional utility for hypertension and cardiovascular diseases (Eddouks et al. 2002). Curative for ulcer, GIT disorders, and epilepsy, it is also beneficial for hair loss and other dermatological problems (Eddouks et al. 2017; Mohsin et al. 2000; Merzouki et al. 2000).

Phytochemical Screenings and Chemistry

The recent studies have showed that the phytochemical screening of *Tamarix aphylla* confirms the presence of some selective secondary metabolites. The aqueous and hydro-alcoholic extracts of different parts of the plant showed the presence of flavonoid glycosides, carboxylic acid steroids, cardiac glycosides, and terpenoids (Ullah et al. 2017). Alkaloids, saponins, and anthraquinones were absent in all the extracts (Mohammedi and Atik 2011). Though alkaloid presence was reported back in 2002 by Abbas et al. in a recent study the presence of alkaloids and saponins was also reported (Hebi and Eddouks 2017). Galls are there which are astringent in action due to tannins. Galls contain hydrolyzable tannins in major proportions, also used as aphrodisiac (Ishak et al. 1972a, b; Panhwar and Abro 2007)). In different parts of the plant including "bark" the phytochemicals are present mainly as polyphenolic compounds. Galls contain polyphenols as gallic acid, ellagic acid,

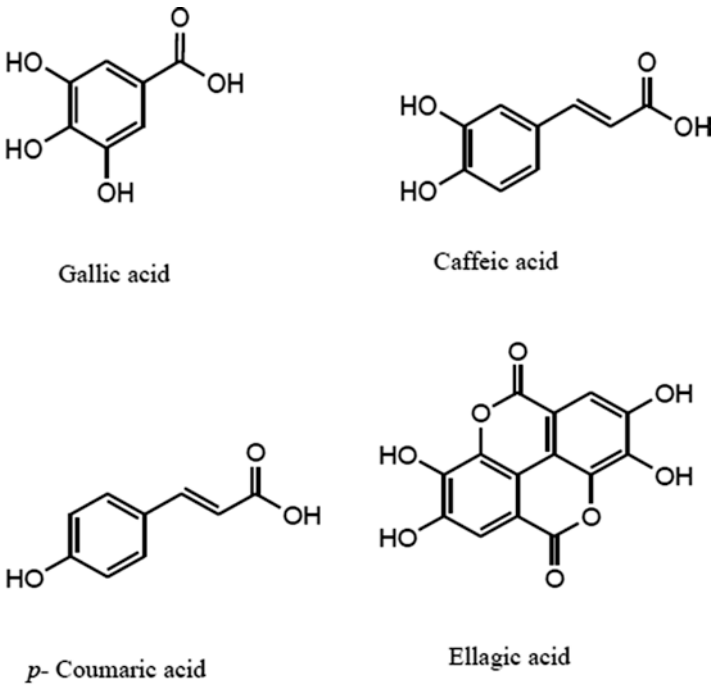

Fig. 2 Chemical structures of phenolic acids from aerial parts of the plant

isoferulic acid, dehydrodigallic acid, and juglanin, and flavonoids including quercetin, its glucoside, isoquercitrin, and its methyl derivatives tamarixin and tamarixetin. Chemical structures of the phenolic acids (Fig. 2) and flavonoids (Fig. 3) are mentioned. The first glycosylated isoferulic acid and tamarixetin 3,3′-disodium sulfate were isolated from flower extract (Nawwar et al. 2009).

Various triterpenoids were isolated from genus Tamarix (Umbetova et al. 2006) and earlier from aphylla species 28-hydroxy-D-fridoolean-14-en-3-b-hydroxy was isolated and confirmed. Colorant dye was extracted through "response surface methodology" (RSM) (Mahfoudhi et al. 2015). The GC-MS analysis revealed the leaf extract to possess various chemical compounds where propenoic acid and β-D-mannofuranose were in significant amount (Alrumman 2016). Solvents from non-polar to polar range were capable to extract the phytoconstituents from leaves. The quantitative analysis reported the higher amount of maximum possible polyphenols as flavonoids and tannins (Shafaghat 2010) in leaves rather than stem (Mahfoudhi et al. 2014). Some previous studies were focused on galls, bark, and floral parts for the detection of flavonoids, ellagic acid, gallic acid, and ellagitannins (Bolous 1999). The abiotic stresses and the time of collection of the plant material are the facts to consider in the context of variable concentrations of secondary metabolites. According to Mahfoudhi et al. (2014) it was the first ever metabolite profiling through HPLC with UV/DAD and ESI-MS^n. Finally the method was optimized and

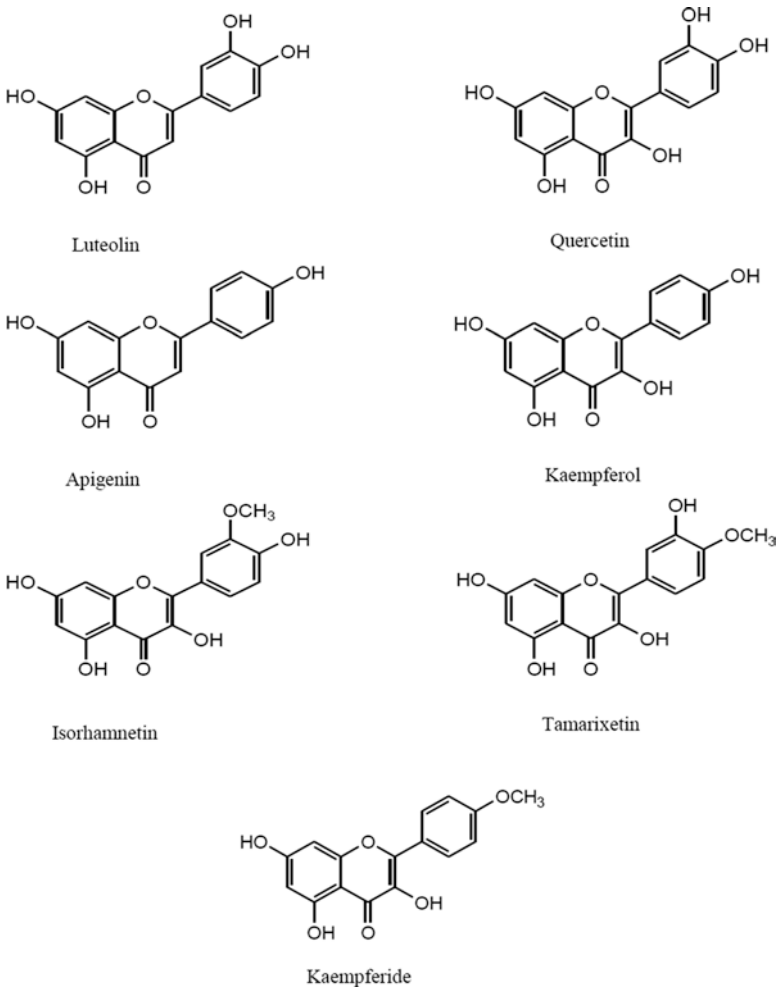

Fig. 3 Chemical structures of flavonoids from aerial parts of the plant

validated for the detection. Chromatographic analysis of aqueous-acetone extract of galls resulted in the isolation of novel compounds as phyllagallin M1, phyllagallin M2, and phyllagallin D1–D4 (Orabi et al. 2015).

Bioactive Potential

Antidiabetic

The doses of methanolic extract of leaves were administered intraperitoneally to evaluate the antidiabetic potential of *Tamarix aphylla*. Hyperglycemic state was induced by streptozotocin (STZ) administration in one of the groups of rat models later on to

compare with the normal control. The antihyperglycemic effect of the extract was probably due to the presence of tannins, flavonoids, and phenolic components in the leaves of *T. aphylla*. In diabetic condition a significant lowering of the glucose level supports the use of plant as remedy. Though the mechanism was not revealed it pointed towards a scientific validation after the traditional claims (Ullah et al. 2017). The presence of coumarins, flavonoids, and terpenoids along with other metabolites is known to be probable causes of a plant to be an antidiabetic (Daisy et al. 2009). One more study was also conducted to evaluate the plant for antihyperglycemic effects along with the antioxidant potential and it was found so significant by comparing with the standard antidiabetic drug glibenclamide (Hebi and Eddouks 2017).

Hypolipidemic

The study showed the significant results of oral administration of aqueous extract of aerial parts of *Tamarix aphylla*. Male Wistar rats were administered orally the extract dose as per (5 mg/kg) body weight. The results were found to indicate the lowering of serum total cholesterol (TC) and triglycerides (TG). The level of high-density lipoprotein cholesterol (HDL-c) was raised. These results were obtained from normal and STZ-induced diabetic rat groups (Hebi and Eddouks 2017).

Antifungal

Crude alcoholic extracts at various concentrations were tested against many pathogenic fungi, i.e., *Aspergillus flavus*, *Saccharomyces cerevisiae*, *A. fumigatus*, *A. niger*, *Penicillium notatum*, and *Fusarium oxysporum*. A significant inhibition of fungal growth was observed when the results were compared to "Terbinafine," the standard antifungal synthetic drug. Crude extracts were also prepared in different organic solvents to observe the effects through polarity order constituent affinities. The stem bark of *T. aphylla* showed the maximum percent inhibition when it was extracted with chloroform and later on followed by ethanol, acetone, methanol, and distilled water (Bibi et al. 2015). In a similar study the methanolic extract of the bark was also evaluated against the fungal strains *Candida albicans* and *Aspergillus flavus* (Iqbal et al. 2015).

Antibacterial

Methanolic extract of *Tamarix aphylla* bark was tested against bacterial strains, i.e., *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus*, and *Salmonella typhi*. The higher concentrations of the extract exhibited the significant zone of inhibition (Iqbal et al. 2015).

Anti-inflammatory and Wound Healing

The ethanolic extract of *Tamarix aphylla* was evaluated for antioxidant, anti-inflammatory, and wound healing properties. Antioxidant property was measured by DPPH (1,1-diphenyl-2-picryl hydrazyl) method and herbal gel of the leaves was formulated to evaluate the anti-inflammatory action by carrageenan-induced paw edema method. The wound healing efficiency of the plant was also checked by tissue excision method on Wistar rat models. The study was succeeded to prove the plant extracts and its gel formulations as having antioxidant, anti-inflammatory, and wound healing properties (Yusufoglu and Alqasoumi 2011).

Conclusion

The effort was made to compile the updated info on recent advancements of *Tamarix aphylla* (Athel in Arabic) which possesses an adorable history to be used as a traditional alternate for various ailments. It was very unfortunate to be acquainted with the fact that it is very less discussed plant despite its proof of having a huge range of active constituents in galls and the aerial parts. The plant is also mentioned in Holy Quran (as Tarfaa, Athel), an Islamic religious scripture, as a curative agent. Different parts of the plant have promising phytoconstituents which are responsible for the prophylactic cure and treatment of diseases. These are the secondary metabolites where polyphenolic compounds comprise a major proportion among all the constituents. Different classes of tannins, flavonoid glycosides, and steroidal compounds are believed to cover many diseases. During the literature survey of the plant, some ambiguous features were also traced regarding the presence or absence of alkaloids. Some authors reported the absence of alkaloid in this halophytic plant while some others confirmed the presence of alkaloid and saponins through the preliminary phytochemical screenings. The significance and role of these compounds have already been discussed separately in many publications. The mechanism of the action of the constituents from *Tamarix aphylla* has not been traced properly at molecular level. Apart from the traditional uses, the plant has a great potential to work as an antidiabetic, hypolipidemic, antifungal, antibacterial, and antioxidant as well. Summarizing the conclusive remark it would be more beneficial for the future research to reinvestigate the phytochemical screenings to confirm the various phytoconstituents through the advanced and modern phytochemical analytical techniques to isolate and characterize the novel compounds. The status of the alkaloids must be checked out by using the modern techniques to isolate and characterize the pure compounds. The mechanism of actions needs to be validated at the molecular level by which the plant could be an important ingredient of polyherbal formulations with a considerable safety index and a source of new molecular development.

References

Abbas B, Al-Qarawi AA, Al-Hawas A (2002) The ethnoveterinary knowledge and practice of traditional healers in Qassim Region, Saudi Arabia. J Arid Environ 50:367–379

Ahmad M, Zafar M, Sultana S (2009) Salvadora persica, Tamarix aphylla and Zizyphus mauritiana—three woody plant species mentioned in Holy Quran and Ahadith and their ethnobotanical uses in North Western Part (DI Khan) of Pakistan. Pak J Nutr 8:542–547

Akhlaq M, Ali M (2011) New phenolic acids from the galls of Tamarix aphylla (L.) Karst. Int Res J Pharm 4:222–225

Alrumman SA (2016) Phytochemical and antimicrobial properties of Tamarix aphylla L. leaves growing naturally in the Abha Region, Saudi Arabia. Arab J Sci Eng 41:2123–2129

Alzweiri M, Al-Sarhan A, Mansi K, Hudaib M, Aburjai T (2011) Ethnopharmacological survey of medicinal herbs in Jordan, the Northern Badia region. J Ethnopharmacol 137:27–35

Azaizeh H, Saad B, Khalil K, Saad O (2006) The state of the art of traditional Arab herbal medicine in the eastern region of the Mediterranean. A review. Evid Based Complement Alternat Med 3:229–235

Baum BR (1978) The genus Tamarix. Israel Academy of Sciences and Humanities, Jerusalem

Benhouhou SA (2005) *Tamarix aphylla* (L.) Karst. In: Guide to medicinal plants in North Africa. IUCN Centre of Mediterranean Cooperation, Malaga, pp 229–230

Bibi S, Afzal M, Aziz N, Din BU, Khan MY, Khan A, Komal H (2015) Antifungal activity of *Tamarix aphylla* (L.) Karst. stem-bark extract against some pathogenic fungi. Am Euras J Agric Environ Sci 15(4):541–545

Bolous L (1999) Flora of Egypt, vol 2. Al Hadara Publishing, Cairo, p 124

Daisy P, Eliza J, Farook KA (2009) A novel dihydroxy gymnemic triacetate isolated from Gymnema sylvestre possessing normoglycemic and hypolipidemic activity on STZ-induced diabetic rats. J Ethnopharmacol 126(2):339–344

DeLoach CJ, Lewis PA, Herr JC, Carruthers RI, Tracy JL, Johnson J (2003) Host specificity of the leaf beetle, Diorhabda elongata deserticola (Coleoptera: Chrysomelidae) from Asia, a biological control agent for saltcedars (Tamarix: Tamaricaceae) in the Western United States. Biol Control 27:117–147

Eddouks M, Maghrani M, Lemhadri A, Ouahidi ML, Jouad H (2002) Ethnopharmacological survey of medicinal plants used for the treatment of diabetes mellitus, hypertension and cardiac diseases in the south-east region of Morocco (Tafilalet). J Ethnopharmacol 82(2–3):97–103

Eddouks M, Ajebli M, Hebi M (2017) Ethnopharmacological survey of medicinal plants used in Draa-Tafilalet region (province of Errachidia), Morocco. J Ethnopharmacol 198:516–530

Hebi M, Eddouks M (2017) Hypolipidemic activity of Tamarix articulate Vahl. in diabetic rats. J Int Med 15(6):476–482

Heywood VH, Brummitt RK, Culham A, Seberg O (2007) Flowering plant families of the world. Royal Botanic Gardens, Kew

Iqbal H, Ishfaq M, Abbas MN, Ahmad I, Rehman A, Amin SB, Shagufta BI, Ullah M (2015) *In vitro* antimicrobial study of *Tamarix aphylla* in view of phytochemical constituents. Pharmacologia 6(8):333–336

Ishak M, El-Sissi H, Nawwar M, El-Sherbieny A (1972a) Tannins and polyphenolics of the galls of Tamarix aphylla. Planta Med 21:246–253

Ishak MS, El-Sissi HI, El-Sherbieny A, Nawwar MA (1972b) Tannins and polyphenolics of the galls of Tamarix aphylla. II. Planta Med 21:374–381

Kamal M, Wazir SM, Hassan M, Subhan M, Khan SU, Muhammad M, Taj S (2009) Ethnobotanically important plants of District Bannu, Pakistan. Pak J Plant Sci 15:87–93

Laaroussi I (2013) Natural product temporarily tightening the mucous membranes of the vagina. European patent; EP 2629751 A1

London SJ, Yuan JM, Chung FL, Gao YT, Coetzee GA, Ross RK, Mimi CY (2000) Isothiocyanates, glutathione S-transferase M1 and T1 polymorphisms and lung-cancer risk: a prospective study of men in Shanghai, China. Lancet 356:724–729

Mahfoudhi A, Prencipe FP, Mighri Z, Pellati F (2014) Metabolite profiling of polyphenols in the Tunisian plant Tamarix aphylla (L.) Karst. J Pharm Biomed Anal 99:97–105

Mahfoudhi A, Baaka N, Haddar W, Mhenni MF, Mighri Z (2015) Development and optimization of the extraction process of natural dye from Tamarix aphylla (L.) Karst. leaves using response surface methodology (RSM). Fibers Polym 16(7):1487–1496

Marlin D, Newete SW, Mayonde SG, Smit ER, Byrne MJ (2017) Invasive Tamarix (Tamaricaceae) in South Africa: current research and the potential for biological control. Biol Invasions 19:2971–2992

Marwat SK, Khan MA, Rehman FU, Ahmad M, Zafar M (2008) *Salvadora Persica*, *Tamarix aphylla* and *Zizyphus mauritiana*: Three woody plant species mentioned in Holy Quran and Ahadith and their ethnobotanical uses in north western part (D.I. Khan) of Pakistan. Ethanobot Leaf 12:1013–1021

Marwat SK, Rehman FU, Khan MA, Ahmad MAQ, Zafar M, Ghulam S (2011) Medicinal folk recipes used as traditional phytotherapies in district Dera Ismail Khan, KPK, Pakistan. Pak J Bot 43(3):1453–1462

Merzouki A, Ed-Derfoufi F, Mesa JM (2000) Contribution to the knowledge of Rifian traditional medicine. II: folk medicine in Ksar Lakbir district (NW Morocco). Fitoterapia 71(3):278–307

Mohammedi Z, Atik F (2011) Impact of solvent extraction type on total polyphenols content and biological activity from Tamarix aphylla (L.) Karst. Int J Pharm Bio Sci 2(1):609–615

Mohsin RM, Choudhary MI, Atta-Ur-Rahman (2000) Medicinal plants with anticonvulsant activities. Stud Nat Prod Chem 22:507–553

Nawwar MA, Hussein SA, Ayoub NA, Hofmann K, Linscheid M (2009) Aphyllin, the first isoferulic acid glycoside and other phenolics from *Tamarix aphylla* flowers. Pharmazie 64:342–347

Orabi MA, Yoshimura M, Amakura Y, Hatano T (2015) Ellagitannins, gallotannins, and gallo-ellagitannins from the galls of Tamarix aphylla. Fitoterapia 104:55–63

Panhwar AQ, Abro H (2007) Ethnobotanical studies of Mahal Kohistan (Khirtar National Park). Pak J Bot 39:2301–2315

Qadir MI, Abbas K, Hamayun R, Ali M (2014) Analgesic, anti-inflammatory and antipyretic activities of aqueous ethanolic extract of Tamarix aphylla L. (Saltcedar) in mice. Pak J Pharm Sci 27:1985–1988

Said O, Khalil K, Fulder S, Azaizeh H (2002) Ethnopharmacological survey of medicinal herbs in Israel, the Golan Heights and the West Bank region. J Ethnopharmacol 83:251–265

Saïdana D, Mahjoub MA, Boussaada O, Chriaa J, Chéraif I, Daami M, Mighri Z, Helal AN (2008) Chemical composition and antimicrobial activity of volatile compounds of Tamarix boveana (Tamaricaceae). Microbiol Res 163:445–455

Shafaghat A (2010) Phytochemical investigation of Quranic fruits and plants. J Med Plants 9:61–66

Shafi U, Khan MR, Shah NA, Shah SA, Majid M, Farooq MA (2014) Ethnomedicinal plant use value in the Lakki Marwat District of Pakistan. J Ethnopharmacol 158:412–422

Sharma SK, Parmar VS (1998) Novel constituents of Tamarix species. J Sci Ind Res 57:873–890

Sharma NK, Tyagi OD (1996) Phytochemical investigation of *Tamarix troupe*. Fitoterapia 67:286–289

Ullah R, Tariq SA, Khan N, Sharif N, Din ZU, Mansoor K (2017) Antihyperglycemic effect of methanol extract of Tamarix aphylla L. Karst (Saltcedar) in streptozotocin–nicotinamide induced diabetic rats. Asian Pac J Trop Biomed 7(7):619–623

Umbetova AK, Choudhary MI, Sultanova NA, Burasheva G, Abilov Z (2006) Triterpenoids from plants of the genus Tamarix. Chem Nat Comp 42(3):332–335

Yusufoglu HS, Alqasoumi SI (2011) Anti-inflammatory and wound healing activities of herbal gel containing an antioxidant Tamarix aphylla leaf extract. Int J Pharmacol 7(8):829–835

Salvadora persica L.: A Medicinal Plant with Multifaceted Role in Maintaining Oral Hygiene

Waseem Mohammed Abdul, Kaleemuddin Mohammed, Furkhan Ahmed Mohammed, Syed Shoeb Razvi, Babajan Banaganapalli, Noor Ahmad Shaik, and Khalid Rehman Hakeem

Introduction

Oral health is a major concern of general well-being, which is integrated with quality of life extending beyond the craniofacial complex functions (Palombo 2011). According to WHO, worldwide, 60–90% of school children and nearly 100% of adults have dental cavities, often leading to pain and discomfort. Oral cavity is home to numerous pathogenic microorganisms, some of which are responsible for progression and development of various systemic diseases such as cancer, diabetes, and myocardial infarctions (Patil et al. 2017). These systematic diseases are associated with oral pathogenesis by three mechanisms: the hematogenous dissemination of pathogenic oral biofilm, the spread of infection to adjacent tissues and spaces, and/or inflammatory mechanisms (Kriebel et al. 2018). There is a strong connection

W. M. Abdul (✉) · F. A. Mohammed · K. R. Hakeem
Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia

K. Mohammed
Department of Biochemistry, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia

Princess Al-Jawhara Albrahim Center of Excellence in Research of Hereditary Disorders (PACER-HD), King Abdulaziz University, Jeddah, Saudi Arabia

S. S. Razvi
Department of Biochemistry, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia

B. Banaganapalli · N. A. Shaik
Princess Al-Jawhara Albrahim Center of Excellence in Research of Hereditary Disorders (PACER-HD), King Abdulaziz University, Jeddah, Saudi Arabia

Department of Genetic Medicine, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
e-mail: babajan@kau.edu.sa; nshaik@kau.edu.sa

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between activity of oral microbiota and diverse oral diseases. About 750 species of bacteria inhabit the oral cavity forming oral biofilms (Palombo 2011). Current trend in dental microbiological research is the discovery of new techniques and methods to combat and eradicate biofilms and dental plaques (Karygianni et al. 2016). Due to persistence of biofilms against various treatment measures, inhibiting bacterial growth is a challenging task. This tendency appertains towards different cell signaling pathways such as horizontal gene transfer, intra-biofilm metabolic transaction, and quorum sensing (Kolenbrander et al. 2010). Biofilm microbes are more persistent and can be up to 1000 times more resistant than planktonic bacteria towards antimicrobial therapies (Karygianni et al. 2014). Hence, there arises an urgent requirement to overcome this resistance by finding alternative strategies.

In the recent few years, natural products have become the backbone of traditional medicine; the use of natural sources for complementary medicine is common in the present world due to its minimal side effects and no denigrative properties, following the treatment of various diseases (Habtemariam 2017). Plants have been the largest source of natural medicines which have a great diversity worldwide and have been reported to have various medicinal properties (Atanasov et al. 2015). Use of natural phytomedicine in dentistry is in practice since ancient times as herbal preparations with medicinal properties have found to be effective against various diseases. Despite reduction in bacterial growth by chemo-mechanical preparation of root canal, there still remains a requisite to enhance disinfection of root canal system by intracanal management (Sinha and Sinha 2014). Herbal preparations are best substitutes of conventional dental therapy and thus can be a replacement for effective control of biofilms and various dental diseases as such. There are a large number of plant species used against oral biofilms, dental caries, and other dental diseases. Some of the herbal plants that are already in use include *Azadirachta indica, Camellia sinensis, Punica granatum, Myristica fragrans*, *and Salvadora persica* (Karygianni et al. 2016). Different plants with their biological activity against oral pathogenic microorganisms are listed in Table 1.

Saudi Arabia is a diverse nation with a large number of medicinal plants. Numerous studies have been carried out on the flora of Saudi Arabia and there are varied medicinal applications of these plants due to the presence of potent bioactive phytochemicals in these plants. Most common plants found in Saudi Arabia include *Nigella sativa, Phoenix dactylophora*, *Anethum graveolens*, and *Salvadora persica. S. persica* is one of the most commonly used plants for cleansing of teeth and oral cavity in the form of slender toothbrushes (Abdul et al. 2015). The plant and its tooth stick made from roots of *S. persica* are shown in Fig. 1. Though the use of *S. persica* was a pre-Islamic custom, it was more commonly practiced by Arabs for cleansing of teeth and in the process giving them a glossy appearance. The major applications of *S. persica* are due to its beneficial effects in maintaining oral hygiene and overall oral wellness which constitutes a major role in boosting the self-confidence and morale of an individual. The pharmacological and therapeutic potential of *S. persica* has been reported in many studies; panoptic medicinal applications have been ascribed to the presence of numerous phytochemicals in this plant. Various biological activities of *S. persica* include antimicrobial, anticancer,

Table 1 List of medicinal plants and their activity against oral pathogens (Karygianni et al. 2016)

Name of the plant extract	Part used	Tested microorganisms
Salvadora persica	Root	*Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Haemophilus influenzae*
Azadirachta indica	Neem bark sticks	*Streptococcus* spp.
Camellia sinesis	Leaves	*Streptococcus mutans, Streptococcus sobrinus*
Coffee arabica	Seeds	*Streptococcus* spp.
Vaccinium macrocarpon	Fruits	*Streptococcus* spp., *Porphyromonas gingivalis*
Mikania laevigata	Aerial parts	*Streptococcus* spp.
Arctium lappa	Peels of fruits	*Enterococcus faecalis, Candida albicans*
Curcuma xanthorrhiza	Fruit	*Streptococcus* spp.
Eucalyptus globulus	Leaves	*Porphyromonas gingivalis*
Morus alba	Leaves	*Streptococcus mutans*
Myristica fragrans	Fruits	*Streptococcus* spp., *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis*
Punica granatum	Fruits	*Prevotella intermedia, Candida albicans, Streptococcus* spp.

Fig. 1 (**a**) Foliage of *Salvadora persica* L. (J.M. Garg 2009). (**b**) Miswak or siwak cleansing stick

antidiabetic, antiplaque formation, anti-inflammatory, analgesic, antioxidant, and anticarcinogenic properties (Siddeeqh et al. 2016; Al-Ayed et al. 2016; Khalessi et al. 2004). Clinical studies have proven that the use of tooth sticks from *S. persica* was effective against various carcinogenic and periodontopathic oral pathogens. Current trends of identifying molecular targets through active phytochemical

docking can be a cost-effective and time-saving approach to study the mechanism of action of different phytochemicals. This chapter summarizes the use of *S. persica* as one of the potential herbal medicines in maintaining oral hygiene as evidenced by in vitro, in vivo, and in silico approaches carried out for the past few years.

Etymology

The term "salvadora" was coined in the year 1749, in the honor of apothecary of Barcelona, Juan Salvadory Bosca by Dr. Laurent Garchin, who was not only a botanist but also a traveler and a plant collector and the species "persica" is derived from the name Persia. The common name of *Salvadora persica* is "Miswak tree," due to the use of roots and twigs for cleansing of teeth since Babylonians (as early as 3500 BC) which is documented in Greek and Roman literature (Halawany 2012). "Miswak" or Arak (synonyms in different Arabic dialects and some countries include "miswak," "miswaki," "meswak," "meswki," "sewak," "siwak," and "siwaki") is an Arabic word meaning tooth-cleaning stick (Ahmad and Rajagopal 2014). These chewing sticks are known by different names in different cultures: "Koyoji" in Japanese, "Qesam" in Hebrew, "Qisa" in Aramaic, "Peelu" in Hindi, and "Mastic" in Latin (Bos 1993).

Classification

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Subclass: Dilleniidae
Order: Capparales
Family: Salvadoraceae
Genus: *Salvadora*
Species: *Persica*

Origin/Distribution

S. persica is a branched shrub which grows to a height of 6 m and has a short trunk with white bark and smooth green leaves with a life span of 25 years. The leaves are oval, small, succulent, and thick with a strong odor of cress or mustard. *S. persica* has a wide geographical distribution throughout the world in many countries like Saudi Arabia, Iran, Iraq, Egypt, India, Pakistan, Malaysia, Sudan, Ethiopia, Central Africa, Southwestern Africa, Mauritania, and South America (Arroyo et al. 2015).

Figure 2 depicts the geographical distribution of *S. persica.* Among the 182 species of plants recognized so far suitable for preparing tooth brushing sticks, roots and twigs of *S. persica* are most commonly used (El-Desoukey 2015).

S. persica grows in dry and desert areas preferably with black and loamy soils and can form up to 10% of the local vegetation in some natural habitats. In desert areas, a high proportion of root to shoot perennials is seen. Under field conditions, the soil salinity is maximum during dry period and greatly reduced during monsoons. *Salvadora* is found both as deep-rooted mesomorphic xerophytes and as facultative halophytes which are highly salt tolerant. Extremely high salt concentrations can reduce the growth of shoot and leaf growth (Orwa et al. 2009).

Chemical and Phytochemical Constituents

Chemical analysis of *S. persica* has demonstrated the presence of various components such as silica, sodium bicarbonate, trimethylamine, chlorides, fluorides, sulfur, tannins, saponins, flavonoids, sterol, salvadoraside, salvadourea, gypsum, pyrrole, piperidine, beta-pinene, 1,8-cineole, sesquiterpene, isoterpinolene, eugenol, beta-caryophyllene, isotymol, and thymol (Ahmad and Rajagopal 2014). Various phytochemicals of *S. persica* along with their structure are mentioned in Table 2.

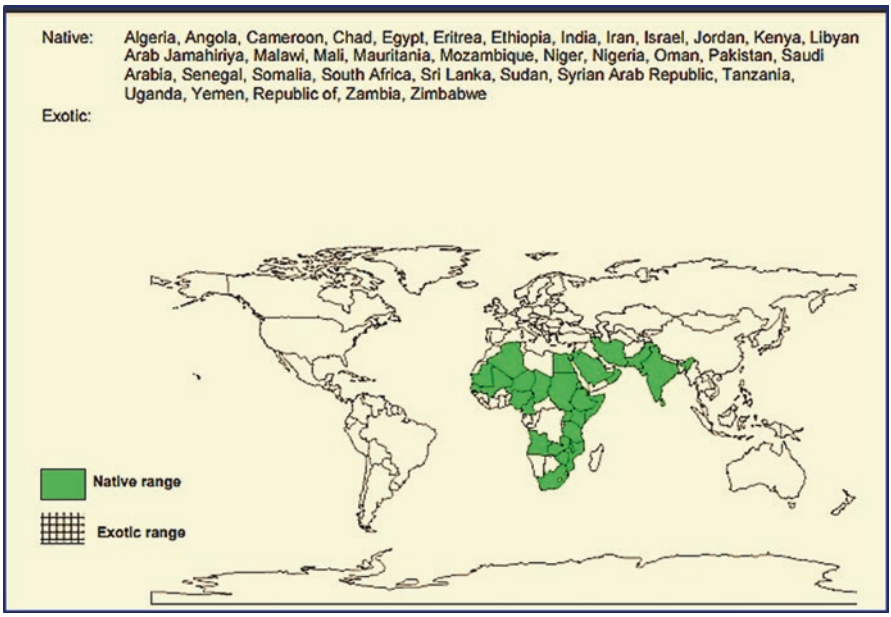
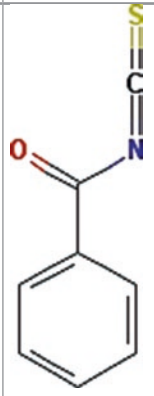
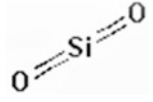
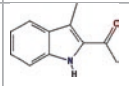
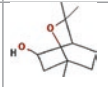
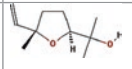
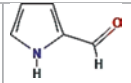
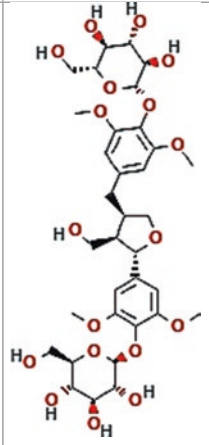
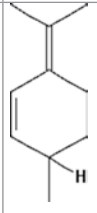


Fig. 2 Geographical distribution of *Salvadora persica* L. (Orwa et al. 2009)

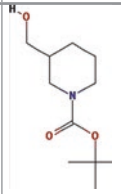
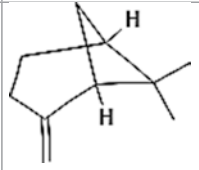
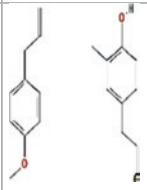
Table 2 Phytochemicals of *Salvadora persica* and their medicinal use

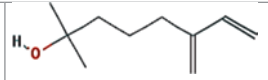
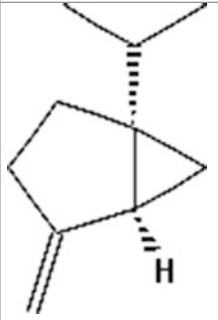
Compound	Structure	Medicinal use	Reference
Benzyl isothiocyanate		Anticancer	Xie et al. (2017)
Silica		As an abrasive for cleaning teeth	Patel et al. (2012)
Salvadorine		Anticarcinogenic and antiplaque	Dabholkar et al. (2016)
1,8-Cineole		Antimicrobial and cytotoxic	Dabholkar et al. (2016)
Linalool		Anticancer	Xu et al. (2013)

Pyrrole		Antitumor	Spanò et al. (2016)
Salvadoraside		Anti-inflammatory	Lee et al. (2016)
Isoterpinolene		Antioxidant	Wencheng Hou

(continued)

Table 2 (continued)

Compound	Structure	Medicinal use	Reference
Piperidine		Anticancer	Coopman et al. (2009)
Beta-pinene		Antimicrobial	Silva et al. (2012)
Methyl chavicol		Antioxidant	Sheweita et al. (2016)

Myrcenol		Antibacterial	Miyamoto et al. (2014)
Sabiene		Antimicrobial	Matasyoh et al. (2008)

Economic and Health Impact of Oral Diseases

Oral hygiene is compromised by various pathogens dwelling in the oral cavity due to chronic infections; the most commonly found oral maladies include dental cavities, periodontal (gum) disease, oral cancer, trauma from injuries, hereditary lesions, and oral infectious diseases to name a few (Fig. 3).

Mouth is considered as a mirror of the body, often reflecting symptoms of systemic diseases. There is a strong relation between general and oral health. A majority of oral diseases share common risk factors with non-communicable diseases (NCDs) such as cardiovascular diseases, diabetes, cancers, and respiratory infections. According to WHO, the primary causes like tobacco consumption, unhealthy diet high in added sugar, and alcohol usage contribute to the development of tooth deformities. Oral diseases are one of the major concerns among millions of individuals worldwide and nearly 291 different pathological conditions have been studied globally (Jin et al. 2016). Oral deformities have affected about 3.9 billion people worldwide in 2010, the most predominant being the tooth decay and severe periodontitis being the sixth most among them (Richards 2013). Globally, oral conditions were responsible for 15 million disability-adjusted years in 2010 (average health loss of 22% years per 100,000 people). Tooth decay constitutes a major global public health challenge and is the most widespread chronic disease worldwide.

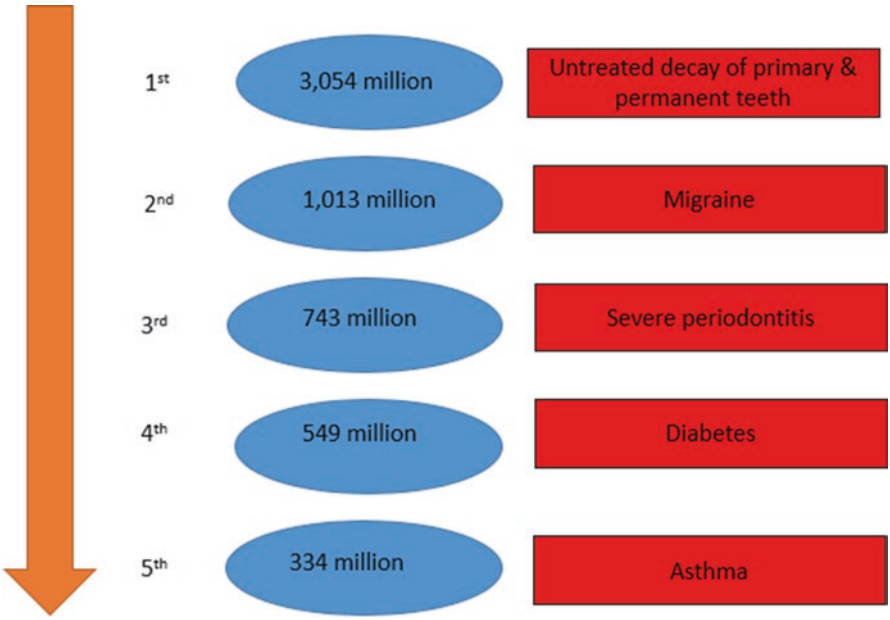


Fig. 3 Data showing the spread of chronic diseases worldwide in decreasing order

Oral cancer is among the topmost common cancers with high mortality rates worldwide. It is estimated that about 300,000–700,000 new cases are reported every year (Coelho 2012). Numerous oral cancers are preceded by the onset of precancerous oral lesions such as persistent white or red patches in the mouth (Yardimci et al. 2014).

Economic impact of oral diseases is on the rise and is considered as the fourth most expensive disease to treat. The annual average spending on oral healthcare for European Union member states was estimated to be 79 billion Euros during 2008–2011 (Damaskinos et al. 2016). To sum up, current data on oral diseases clearly demonstrates that the untreated decay of permanent teeth was 40% for all ages combined and is the most prevalent condition among 291 diseases included in the global burden of disease study.

Multifaceted Role of *S. persica* in Combating Oral Pathogens

Potential of S. persica *in Restricting the Growth of Bacteria*

Maintenance of oral hygiene is a major concern all over the world and bacterial pathogens are a prominent cause in compromising the oral hygiene. Prevention and control of pathogenic bacterial growth in oral cavity are crucial for maintaining good oral hygiene. There are various methods of preventing the growth of bacteria in the oral cavity. However, once the accumulation of bacterial pathogens is initiated, it may lead to various complications resulting in loss of oral hygiene. Moreover, *S. persica* has shown significant antibacterial activity against a number of aerobic and anaerobic microbes, in both in vitro and in vivo studies (Khalessi et al. 2004). The antimicrobial activity of *S. persica* was evaluated by many researchers which have been documented in literature. Aqueous, ethanolic, and methanolic extracts of *S. persica* were tested for evaluation of antibacterial activity; numerous bacteria from oral cavity have been found to be inhibited by *S. persica*, exerting a bacteriostatic effect. Oral pathogens inhibited by *S. persica* include *Staphylococcus aureus, Streptococcus pyogenes, Enterococcus faecalis, Lactobacillus acidophilus, Pseudomonas aeruginosa*, and *Streptococcus mutans* (Abdul et al. 2015).

Methanolic extract was found to be effective in case of *Lactobacillus acidophilus* and *S. mutans* with a zone of inhibition of 21.8 ± 0.76 mm and 20.26 ± 0.76 mm, respectively, whereas *S. aureus* was less susceptible to *S. persica* in petroleum ether extracts. Both ethanolic and methanolic extracts have shown good activity against *S. aureus, Enterococcus faecalis*, *and Klebsiella pneumoniae* (Kumar et al. 2016).

There are a number of intrinsic and extrinsic parameters which influence the formation of zone of inhibition. Presence of various bioactive components and their molecular weights play an important role in the diffusion of extract in agar. Thus, agar assay for antibacterial property is not the only factor which can be relied upon in the assessment of efficiency of the extract based on zone of inhibition. It is the

minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) value that will clearly suggest that the plant extracts have the ability to treat various ailments effectively that originated from bacterial pathogens (Siddeeqh et al. 2016). The MIC values vary based on the type of extraction; *S. aureus* shows MIC at 50 ± 4.2 μg, *S. mutans* at 75 ± 3.2 μg, *Streptococcus salivarius* at 75 ± 2.3 μg, *Lactobacillus casei* at 50 ± 6.2 μg, and *Staphylococcus epidermidis* at 50 ± 5.0 μg (Al-Sieni 2014).

Antimycotic Activity of S. persica

S. persica has shown significant antifungal activity against a number of fungal species. Various solvent fractions of *S. persica* extract such as acetone, ethanol, and aqueous extracts have been tested for possessing antimycotic activity. Among these, acetone has shown the highest antifungal activity. Some of the fungal species inhibited by acetone extract include *Candida albicans, C. glabrate, C. parapsilosis, C. kefyr, C. sake, C. atlantica, C. holmii, C. krusei, C. maritima, Pichia guilliermondii,* and *P. jardinii.* The highest activity was observed against *Candida holmii* and lowest was against *Candida krusei*, with a zone of inhibition of 11.33 ± 0.57 mm and 6 ± 0 mm, respectively (Noumi et al. 2011). Another study by Al Bagich and Almas has proved the inhibition of *Candida albicans* by aqueous extract of *S. persica* (Almas and Al-Bagieh 1999). Akhtar and colleagues have shown the inhibitory activity of aqueous and methanolic extract against *Candida albicans* (Akhtar et al. 2011).

Ability of S. persica *in Diminishing Plaque*

S. persica was found to be effective in controlling formation of plaque by various microbes. Plaque formed by accumulation of large number of pathogens on enamel is responsible for dental caries which later leads to many periodontal diseases. Antiplaque effect of *S. persica* against oral microbes is attributed to the presence of tannins (Ahmad and Rajagopal 2014). Ezoddini-Ardakani and colleagues have reported the activity of *S. persica* against dental caries, gingivitis, and plaque (Ezoddini-Ardakani 2010). However, in a separate study, Rasoli and colleagues have studied the decrease in incidences of periodontal diseases in children using *S. persica* tooth stick (Ghahroudi et al. 2014). Clinical trial studies on Ethiopian school children were performed and a comparison was made between conventional toothbrush and Miswak (from *S. persica*). Hence, by the abovementioned evidences, it can be resolved that the use of *S. persica* is a successful alternative approach in maintaining good oral health, thus keeping a check on the growth of bacteria and fungi which can indirectly control the formation of plaque and dental caries and simultaneously preventing the development of periodontal diseases.

Clinical Trial Studies on *S. persica*

Various studies have been carried out to examine the biological activities of *S. persica* in clinical trials. In an interesting study carried out among the school students in the city of Iran, 380 students were selected for assessing the antimicrobial activity of *S. persica*. This study was carried out for a period of 1 year with two different groups of students: one group was marked as control which did not use toothbrush and another was case study group, supplied with a toothbrush of *S. persica*. It was ascertained from the data collected that there was a rise of 55% in the dental carries among the control students when compared to that of case study group. This might be ascribed to the antimicrobial and antiplaque formation effects of *S. persica* (Ezoddini-Ardakani 2010).

In an another study, which was conducted to detect the changes in the plaque accumulation a combination of green tea and *S. persica* was used to assess their synergistic effect. This study demonstrated that the oral rinsing with green tea and *S. persica* aqueous extracts twice daily can significantly reduce plaque accumulation after 24h regrowth. Khalessi and colleagues have performed a study on a mouthwash containing *S. persica* and observed that it improved gingival health and decreased the number of carcinogenic bacteria in comparison with pretreatment values (Khalessi et al. 2004).

S. persica is an economic and easily available toothbrush, which has captivated the interest of masses in promoting oral health and protecting dental caries.

Mechanistic Details of *S. persica* in Maintaining Oral Hygiene

The mechanistic cleaning action of *S. persica* is the major factor which has earned accolades in maintaining oral health (Sardari et al. 2015). *S. persica* is generally used for a longer duration than a toothbrush and the buccal surfaces of the teeth can be reached easily when compared to the lingual and proximal surfaces (Abdulbaqi et al. 2016).

The following mechanistic factors have been identified for maintaining oral hygiene by *S. persica*:

- The release of diverse bioactive chemicals from the chewing stick
- The soft and flexible property of the fibers contributing to the enhanced mechanical effects (Ahmad and Rajagopal 2014)

S. persica is considered to be an easily available and low-priced must-have oral hygiene tool that can be used by even a commoner. *S. persica* upregulates the production of calcium (22-fold) and chloride (6-fold) and on the other hand represses the levels of phosphate resulting in a decrease in P^H (Khatak et al. 2010).

Diverse Effects of *S. persica* Apart from Oral Hygiene

Antioxidant Activity

The task of preventing an individual from the damage caused by free radical-induced oxidative stress is rendered upon the antioxidants (Halliwell 1994). Several types of antioxidants which are exogenous and endogenous, both natural and synthetic, are effective in the protection against the formation of free radicals. Various studies have been carried out to evaluate the antioxidant potential of *S. persica* employing the bark, seed, and stem of the plant. In a distinguished study, phenolic extracts of *S. persica* were subjected to "β-carotene-linoleic acid assay" to investigate its antioxidant effect (Taha et al. 2010).

Specific techniques like peroxidase and catalase assays were used for determination of antioxidant property of *S. persica* (Ibrahim et al. 2015). The crude methanolic extract of *S. persica* has shown concentration-dependent antioxidant activity with IC_{50} value of 4.8 μg. The total antioxidant activity was based on the reduction of molybdenum (+VI) to molybdenum (+V), which was directly proportional to the increase in the concentration of *S. persica* extract. It has been observed that the furan derivatives are more effectively involved in the antioxidant activity of *S. persica* (Mohamed and Khan 2013). In another study, the "thiobarbituric acid reactive species" (TBRS) method was employed for measuring the total antioxidant activity of *S. persica* extract. The phenolic constituents of the plant, especially D-catechin and flavonoids, most actively participate in the antioxidant activity (Ibrahim et al. 2015).

Antidiabetic Activity

Aqueous extract of *S. persica* has shown significant antidiabetic effect in streptozotocin (STZ)-induced male Albino Wistar diabetic rats. This study was conducted with both positive and negative diabetic controls, wherein at a dose of 500 mg/kg, prominent decrease in blood glucose levels was observed from 387.50 ± 19.76 to 85.25 ± 13.20 mg/dL at the end of 28th day of treatment. On the other hand, accelerated regeneration of pancreatic β-cells was observed in the treatment group when compared to the diabetic control. The values of experimental animal samples were found to be higher (32.6 ± 2.4 mg/dL) compared to those of diabetic control samples (8.1 ± 0.5 mg/dL) at the end of 28th day of treatment (Khan et al. 2014).

Anticancer Activity

The antitumor effects of *S. persica* were observed on human breast carcinoma—MCF7 (IC_{50} = 44.3 μg/mL), human hepatocellular carcinoma—HEPG2 (IC_{50} = 44.3 μg/mL), human colon carcinoma—HCT116 (IC_{50} = 10.2 μg/mL), and

Table 3 Molecular targets of benzyl isothiocyanate and its functional role

Molecular target	Functional role	Reference
P53	Inactivation of GSKβ in oral cancer prevention	Antony et al. (2012)
Nfkb	Downregulation of Nfkb resulting in oral cancer inhibition	Srivastava and Singh (2004)
Notch 2	Inhibition of breast cancer by Notch activation	Antony et al. (2012)
HNSCC	Inhibition of metastasis and assist in chemotherapy	Wolf and Claudio (2014)
AKT	Inhibition of pancreatic cancer	Lai et al. (2010)
STAT3	Inhibition of pancreatic cancer by inhibition of angiogenesis	Boreddy et al. (2011)

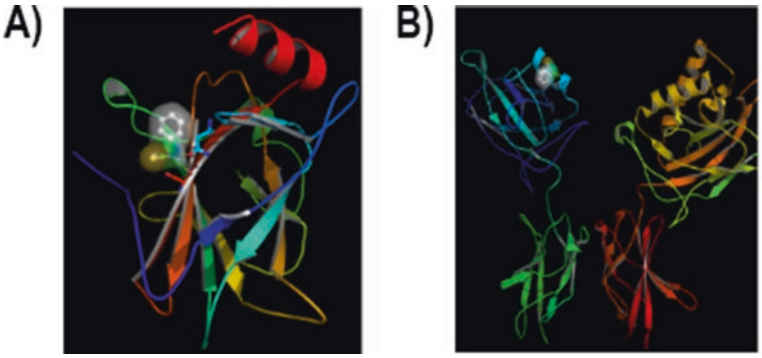


Fig. 4 (**A**) The P53 (cartoon) protein interaction with benzyl isothiocyanate (Surface ball and sticks). (**B**) The NFKB protein interaction with drug benzyl isothiocyanate (unpublished data)

human lung carcinoma—A549 (19.87 μg/mL). Ursolic acid was found to be more effective than oleanolic acid against HepG2, MCF7, and HCT116 (IC_{50} = 26.32, 18.73, and 0.4 μg/mL, respectively) while oleanolic acid was more potent against A549 (IC_{50} = 19.5 μg/mL) (Jaikumar and Jasmine 2016).

In another study, the aqueous extract of *S. persica* was tested against oral squamous cell carcinoma (PE/CA-PJ15) and was found to be effective (Hammad et al. 2014).

Benzyl Isothiocyanate and Cancer Protein Targets

Benzyl isothiocyanate is a dietary bioactive phytochemical found in *S. persica* and has shown potent anticancer properties as described in Table 3. Benzyl isothiocyanate has been reported for its activity against oral cancer. The protein targets P53 and NFkb have been identified to demonstrate the molecular targets and ligands as depicted in Fig. 4 (Xie et al. 2017; Wu et al. 2011; Srivastava and Singh 2004).

Conclusion and Future Perspectives

Routine use of *S. persica* is regarded as one of the effective methods in prevention and containment of dental diseases due to its inexpensive, prophylactic, lucrative properties in the long run. The use of *S. persica* is observed in the Middle East and Far East countries like India and Pakistan. To sum up, we pronounce that the use of *S. persica* as a traditional medicinal plant is reported as long as 3000 years ago. In the present era, many medical practitioners have started the use of *S. persica* in maintaining oral hygiene. Besides oral hygiene, further validation by clinical trials on neurodegenerative diseases and autoimmune diseases may yield promising results. However, the precise mechanisms and the mode of action at the molecular and gene level still remain to be explored which is an intriguing area of research worldwide.

References

Abdul H, Balto G, Halawany HS, Biju N, Jacob V (2015) The efficacy of Salvadora persica extracts in preserving the viability of human foreskin fibroblasts. Saudi Dent J 27:137–140

Abdulbaqi HR, Himratul-aznita WH, Baharuddin NA (2016) Evaluation of Salvadora persica L. and green tea anti-plaque effect: a randomized controlled crossover clinical trial. BMC Complement Altern Med 16:1–7

Ahmad H, Rajagopal K (2014) Salvadora persica L. (Meswak) in dental hygiene. Saudi J Dent Res 5:130–134

Akhtar J, Siddique KM, Bi S, Mujeeb M (2011) A review on phytochemical and pharmacological investigations of miswak (Salvadora persica Linn). J Pharm Bioallied Sci 3:113–117

Al-Ayed MSZ, Asaad AM, Qureshi MA, Attia HG, AlMarrani AH (2016) Antibacterial activity of Salvadora persica L. (Miswak) extracts against multidrug resistant bacterial clinical isolates. Evid Based Complement Alternat Med 2016:7083964

Al-Sieni AII (2014) The antibacterial activity of traditionally used Salvadora persica L. (Miswak) and Commiphora gileadensis (Palsam) in Saudi Arabia. Afr J Tradit Complement Altern Med 11:23–27

Antony ML, Kim S, Singh SV (2012) Critical role of p53 upregulated modulator of apoptosis in benzyl isothiocyanate-induced apoptotic cell death. PLoS One 7:e32267

Arroyo R, Suñé G, Zanzoni A, Duran-Frigola M, Alcalde V, Stracker TH, Soler-López M, Aloy P (2015) Systematic identification of molecular links between core and candidate genes in breast cancer. J Mol Biol 427:1436–1450

Atanasov AG, Waltenberger B, Pferschy-Wenzig EM, et al. (2015) Discovery and resupply of pharmacologically active plant-derived natural products: A review. Biotechnol Adv 33(8):1582–1614

Almas K, Al-Bagieh NH (1999) The antimicrobial effects of bark and pulp extracts of Miswak, Salvadora persica. Biomed Lett 60:71–75

Boreddy SR, Sahu RP, Srivastava SK (2011) Benzyl isothiocyanate suppresses pancreatic tumor angiogenesis and invasion by inhibiting HIF-α/VEGF/Rho-GTPases: pivotal role of STAT-3. PLoS One 6:e25799

Bos G (1993) The miswāk, an aspect of dental care in Islam. Med Hist 37:68–79

Coopman V, De Leeuw M, Cordonnier J, Jacobs W (2009) Suicidal death after injection of a castor bean extract (Ricinus communis L.). Forensic Sci Int 189:e13–e20

Coelho KR (2012) Challenges of the oral cancer burden in India. J Cancer Epidemiol 2012:1–17
Dabholkar CS, Shah M, Kathariya R, Bajaj M, Doshi Y (2016) Comparative evaluation of antimicrobial activity of pomegranate-containing mouthwash against oral-biofilm forming organisms: an invitro microbial study. J Clin Diagn Res 10:ZC65–ZC69
Damaskinos P, Koletsi-Kounari H, Economou C, Eaton KA, Widström E (2016) The healthcare system and provision of oral healthcare in European Union member states. Part 4: Greece. Br Dent J 220(5):253–260
El-Desoukey RMA (2015) Comparative microbiological study between the Miswak (Salvadora persica) and the toothpaste. Int J Microbiol Res 6:47–53
Ezoddini-Ardakani F (2010) Efficacy of Miswak (Salvadora persica) in preventing dental caries. Health 2:499–503
Ghahroudi R, Alireza A, Afsaneh R, Salehifard M, Hosein S, Siamak Y, Afshin K, Zeinab K, Mahvash MJ (2014) Inhibitory activity of Salvadora persica extracts against oral bacterial strains associated with periodontitis: an in-vitro study. J Oral Biol Craniofacial Res 4:19–23
Garg JM (2009) https://www.feedipedia.org/content/saltbush-salvadora-persica-leaves-and-flowers
Halawany HS (2012) A review on miswak (Salvadora persica) and its effect on various aspects of oral health. Saudi Dent J 24:63–69
Halliwell B (1994) Free radicals, antioxidants, and human disease: curiosity, cause, or consequence? Lancet 344:721–724
Hammad H, Al-Qaoud K, Hammad M, Mansi M (2014) Effects of salvadora persica extract on DOK oral epithelial dysplasia and PE/CA-PJ15 oral cancer cell lines. Oral Surg Oral Med Oral Pathol Oral Radiol 118(6):e195–e196
Habtemariam S (2017) Going Back to the Good Old Days: The Merit of Crude Plant Drug Mixtures in the 21st Century. Int J Complement Altern Med 6(2):00182
Ibrahim MM, Al Sahli AA, Alaraidh IA, Al-Homaidan AA, Mostafa EM, El-Gaaly GA (2015) Assessment of antioxidant activities in roots of miswak (Salvadora persica) plants grown at two different locations in Saudi Arabia. Saudi J Biol Sci 22:168–175
Jaikumar B, Jasmine R (2016) A review on a few medicinal plants possessing anticancer activity against human breast cancer. Int J PharmTech Res 9:333–365
Jin L, Lamster I, Greenspan J, Pitts N, Scully C, Warnakulasuriya S (2016) Global burden of oral diseases: emerging concepts, management and interplay with systemic health. Oral Dis 22(7):609–619
Khalessi AM, Pack ARC, Thomson WM, Tompkins GR (2004) An in vivo study of the plaque control efficacy of Persica™: a commercially available herbal mouthwash containing extracts of Salvadora persica. Int Dent J 54:279–283
Khan M, Ali M, Ali A, Mir SR (2014) Hypoglycemic and hypolipidemic activities of Arabic and Indian origin Salvadora persica root extract on diabetic rats with histopathology of their pancreas. Int J Health Sci (Qassim) 8:45–56
Kumar S, Navneet, Gautam SS, Kumar V (2016) Preliminary phytochemical screening and antimicrobial activity of Salvadora persica Linn extracts against oral pathogens. Fung Genomics Biol 6:1–4
Kriebel K, Hieke C, Müller-Hilke B, Nakata M, Kreikemeyer B (2018) Oral biofilms from symbiotic to pathogenic interactions and associated disease -connection of periodontitis and Rheumatic Arthritis by Peptidylarginine Deiminase. Front Microbiol 9(53):1–14
Karygianni L, Al-Ahmad A, Argyropoulou A, Hellwig E, Anderson AC, Skaltsounis AL (2016) Natural Antimicrobials and Oral Microorganisms: A Systematic Review on Herbal Interventions for the Eradication of Multispecies Oral Biofilms. Front Microbiol 6:1529
Kolenbrander PE, Palmer RJ, Periasamy S, Jakubovics NS (2010) Oral multispecies biofilm development and the key role of cell–cell distance. Nat Rev Microbiol 8:471–480
Karygianni L, Ruf S, Follo M, Hellwig E, Bucher M, Anderson AC, Vach K, Al-Ahmad A (2014) Novel Broad-Spectrum Antimicrobial Photoinactivation of In Situ Oral Biofilms by Visible Light plus Water-Filtered Infrared A. Appl Environ Microbiol 80(23):7324–7336

Khatak M, Khatak S, Siddqui AA, Vasudeva N, Aggarwal A, Aggarwal P (2010) *Salvadora persica*. Pharmacogn Rev 4:209–214

Lai K-C, Huang A-C, Hsu S-C, Kuo C-L, Yang J-S, Wu S-H, Chung J-G (2010) Benzyl isothiocyanate (BITC) inhibits migration and invasion of human colon cancer HT29 cells by inhibiting matrix metalloproteinase-2/-9 and urokinase plasminogen (uPA) through PKC and MAPK signaling pathway. J Agric Food Chem 58:2935–2942

Lee JH, Sun YN, Kim YH, Lee SK, Kim HP (2016) Inhibition of lung inflammation by Acanthopanax divaricatus var. Albeofructus and its constituents. Biomol Ther (Seoul) 24:67–74

Matasyoh LG, Matasyoh JC, Wachira FN, Kinyua MG, Thairu Muigai AW, Mukiama TK (2008) Antimicrobial activity of essential oils of Ocimum gratissimum L. from different populations of Kenya. Afr J Tradit Complement Altern Med 5:187–193

Miyamoto T, Okimoto T, Kuwano M (2014) Chemical composition of the essential oil of mastic gum and their antibacterial activity against drug-resistant Helicobacter pylori. Nat Prod Bioprospect 4:227–231

Mohamed SA, Khan JA (2013) Antioxidant capacity of chewing stick miswak Salvadora persica. BMC Complement Altern Med 13:1

Noumi E, Snoussi M, Trabelsi N, Hajlaoui H, Ksouri R (2011) Antibacterial, anticandidal and antioxidant activities of Salvadora persica and Juglans regia L. extracts. J Med Plant Res 5:4138–4146

Orwa C, Mutua A, Kindt R, Jamnadass R, Anthony S (2009) Agroforestree database: a tree reference and selection guide version 4.0. http://www.worldagroforestry.org/sites/treedbs/treedatabases.asp

Patel PV, Shruthi S, Kumar S (2012) Clinical effect of miswak as an adjunct to tooth brushing on gingivitis. J Indian Soc Periodontol 16:84–88

Palombo EA (2011) Traditional medicinal plant extracts and natural products with activity against oral bacteria: potential application in the prevention and treatment of oral diseases. J Evid Based Complement Altern Med 2011:1–15

Patil R, Shailesh M. Gondivkar, Amol R. Gadbail, Monal Yuwanati, Mugdha Mankar (Gadbail), Manoj Likhitkar, Sachin Sarode, Gargi Sarode, Shankargouda Patil (2017) "Role of oral foci in systemic diseases: An update," Int J Contemp Dent Med Rev 2017:1-8

Richards D (2013) Oral diseases affect some 3.9 billion people. Evid Based Dent 14:35

Sardari F, Kazemi Arababadi M, Heiranizade M, Mosadeghi M (2015) Anti-inflammatory and cytotoxicity effects of Salvadora persica (meswak) extracts on Jurkat t-cells. J Microbiol Biotechnol Food Sci 4:379–382

Sheweita SA, El-Hosseiny LS, Nashashibi MA (2016) Protective effects of essential oils as natural antioxidants against hepatotoxicity induced by cyclophosphamide in mice. PLoS One 11:e0165667

Siddeeqh S, Parida A, Jose M, Pai V (2016) Estimation of antimicrobial properties of aqueous and alcoholic extracts of Salvadora persica (Miswak) on oral microbial pathogens—an in vitro study. J Clin Diagn Res 10:13–16

Silva AC, Lopes PM, Azevedo MM, Costa DC, Alviano CS, Alviano DS (2012) Biological activities of a-pinene and β-pinene enantiomers. Molecules 17(12):6305–6316

Sinha D, Sinha A (2014) Natural medicaments in dentistry. AYU (Int Q J Res Ayurveda) 35:113

Spanò V, Attanzio A, Cascioferro S, Carbone A, Montalbano A, Barraja P, Tesoriere L, Cirrincione G, Diana P, Parrino B (2016) Synthesis and antitumor activity of new thiazole nortopsentin analogs. Mar Drugs 14:226

Srivastava SK, Singh SV (2004) Cell cycle arrest, apoptosis induction and inhibition of nuclear factor kappa B activation in anti-proliferative activity of benzyl isothiocyanate against human pancreatic cancer cells. Carcinogenesis 25:1701–1709

Taha E, Mariod A, Abouelhawa S, El-Geddawy M, Sorour M, Matthäus B (2010) Antioxidant activity of extracts from six different Sudanese plant materials. Eur J Lipid Sci Technol 112:1263–1269

Wolf MA, Claudio PP (2014) Benzyl isothiocyanate inhibits HNSCC cell migration and invasion, and sensitizes HNSCC cells to cisplatin. Nutr Cancer 66:285–294

Wu C, Huang A, Yang J, Liao C, Lu H, Chou S, Ma C (2011) Benzyl isothiocyanate (BITC) and phenethyl isothiocyanate (PEITC)-mediated generation of reactive oxygen species causes cell cycle arrest and induces apoptosis via activation of caspase-3, mitochondria dysfunction and nitric oxide (NO) in human OS. J Orthop Res 29:1199–1209

Xie B, Nagalingam A, Kuppusamy P, Munira N (2017) Benzyl isothiocyanate potentiates p53 signaling and antitumor effects against breast cancer through activation of p53-LKB1 and p73-LKB1 axes. Sci Rep 7:1–14

Xu J, Zhou X, Wang J, Li Z, Kong X, Qian J, Hu Y, Fang J-Y, Aramayo R, Sherman MB et al (2013) RhoGAPs attenuate cell proliferation by direct interaction with p53 tetramerization domain. Cell Rep 3:1526–1538

Yardimci G, Kutlubay Z, Engin B, Tuzun Y (2014) Precancerous lesions of oral mucosa. World J Clin Cases 2(12):866–872

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