

Munir Ozturk · Khalid Rehman Hakeem
Editors

Plant and Human Health, Volume 3

Pharmacology and Therapeutic Uses

 Springer

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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.

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Preface

The major diseases of the twenty-first century in the developed countries are reported as age-related and viral diseases, cardiovascular failures, and psychiatric 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 led 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.

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Jeddah, Saudi Arabia

Munir Ozturk
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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

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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). Licorice has several names such as sweetwood, licorice, liquorice radix, réglisse (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 from 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).

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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 *Arthrimum 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
<i>G. glabra</i> <i>G. uralensis</i>	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)
<i>G. glabra</i> <i>G. uralensis</i>	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), Masoomah and Kiarash (2007), Adel et al. (2005)
<i>G. inflata</i> <i>G. glabra</i> <i>G. uralensis</i>	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 influenzae*, and *Moraxella catarrhalis* was studied by Tanaka et al. (2001). The authors observed that licoricidin and coumarin derivatives such as glycyrol, glycyrin, and glycy coumarin 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. 18 β -Glycyrrhetic 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 glycyrrhetic 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. inflata* 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-Razuqi 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 glycyrrhethinic 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-arthritis 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; Isbruckner 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, isoflavones, 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, rhamnoliquiritin, liquiritin apioside, galbranonin, galbrol, licoflavanone, isoliquiritigenin, neoisoliquiritin, licuraside, licochalcone A and B, licoricidin, 7-methyllicoricidin, hispaglabridin A and B, licoflavone A and B, licoflavanol, glyzylglabrin, licoisoflavanone, galbroisoflavanone, 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 licoagro-din, licoagro-chalcones, 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, galbroisoflavanone A and B, and galbroisoflavanone 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, glycyrrhetol, glabrolide, isoglabrolide, and licorice acid.

Fenwick et al. (1990) described two aglycone forms of glycyrrhizic acid 18 β -glycyrrhetic acid and 18 α -glycyrrhetic 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, 22 β -acetoxyglycyrrhizin, 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. inflata*, *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 glycycomarin, glabrocoumarin, glycyrin, inflacoumarin A, licopyranocoumarin, isoglycerol, neoglycerol, licobenzofuran, licocoumarone, glabrocoumarone, gancaonin, and kanzonol. In another study Ammar et al. (2012) isolated phenolic compounds, namely liquiritigenin, liquiritin apioside, neoliquiritin apioside, isoliquiritin, isoliquiritin 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, glycyocoumarin, 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, dihydrostigmatsterol) 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 deglycyrrhized 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