Chapter 8
Economic Importance

8.1 Traditional Uses

The beneficial effects of liquorice in treating chills, colds, and coughs have been fully discussed in Ayurveda, as well as in the texts of ancient Egyptians, Greeks, and Romans. The plant has been prescribed for dropsy during the period of famous Hippocrates. The reason being that it was quite helpful as thirst-quenching drugs (Biondi et al. 2005; Mamedov and Egamberdieva 2017). Although the clinical use of liquorice in modern medicine started around 1930, its effectiveness in the treatment of stomach and intestinal ulcers has been mentioned in the first century AD by Pedanios Dioscorides of Anazarba from Adana in present day Turkey, who is also regarded as the "Father of Pharmacists". In Ayurveda, people in ancient Hindu culture have used it for improving sexual vigor. Chinese have been using it as a tea for strength and endurance (Davis and Morris 1991). The liquorice roots have been used in the traditional medicine 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, and pancreatic disorders, flatulence, sexual debility, skin diseases, leucorrhoea, hoarseness, and certain viral infections (Blumenthal et al. 2000; Anonymous 2005; Armanini et al. 2002; Sharma et al. 2013; Mamedov and Egamberdieva 2017). In Europe, particularly Britain, France, and Germany, present-day pharmacopeias are in general agreement on the medicinal application of this plant. It is used for the treatment of influenza, eye diseases, uterine complaints, biliousness, liver disease, and arthritis as per the reports published on Indian medicine (Saxena 2005; Mamedov and Egamberdieva 2017). The plant is in use in China since very early times and has been applied to treat acne and pimples, nervous disorders such as hysteria, irritability, epilepsy, as well as reduce the toxic or drastic action of other herbs, and to harmonize herbal formulas (Zhu 1998). The studies undertaken by Kong et al. (1984) reveal that liquorice root extract is used to treat diarrhea in mice, whereas Hong et al. (1988) have demonstrated its strong diuretic activity in rats. *G. glabra* extract has also been used to treat emotional irritability in adults and stress (Tsuda et al. 1986; Shirinyan et al. 1988). The extract has also been used to treat allergic dermatitis and eczema (Sokolov and Zamotayev 1985; Sheehan and Atherton 1992). According to Yang et al. (2015), liquorice has been used for the treatment of gastro and respiratory diseases in traditional treatments as well as for the alleviation of toxicity to other

M. Öztürk et al., *Liquorice*, SpringerBriefs in Plant Science,
https://doi.org/10.1007/978-3-319-74240-3_8

drugs. In traditional Chinese medicine, it is also honored as the "excellent coordinator" as it harmonizes the activities of other ingredients by promoting their rapid absorption into the bloodstream, organs, and target cells (Yang et al. 2015).

8.2 Industrial Uses

Liquorice is among the highly significant medicinal plant species in the trade and business circles of many countries, largely through imports to many countries (Ved and Goraya 2007; Altay et al. 2016). It continues to be used as a pharmacological agent as well as an ingredient in tobacco and confectionery throughout the East and West countries. Studies over the past 50 years have yielded information which has prompted new interest in the pharmacological and physiological effects of this plant (Roshan et al. 2012). In 2007, the value of liquorice trade was around 42 million US $, and evaluation of glycyrrhizin as a natural sweetener has added to its use, and this is further extended because of its application as a pharmaceutical agent in view of its anti-inflammatory and hepatoprotective features (Shibata 2000; Parker 2007). Very extensive studied have been carried out on the chemical constituents of this plant with regard to isolation of glycyrrhizin as well as many triterpene saponins and flavonoids (Nomura and Fukai 1998). The cosmetics industry too is using the flavonoids isolated from liquorice on a large scale. Therefore, liquorice has been used as a pharmaceutical agent, in cosmetics, as a sweetener, food additive, flavor additive for tobacco, and in confectionery food (Fig. 8.1).

During 2001–2005, the imports of liquorice roots at the global level have increased by 3% in value on an average basis. The amount has reached a level of 31.7 million dollars in 2005. On the other hand, the imports of its extracts have gone up by 5% on yearly basis during 2000–2004, and the amount reported for 2005 is said to lie around 92.3 million dollars. The global import value of its extracts is three times more than for roots. The reason being former is a processed value-added product (Stanikzai 2007). Italy and Spain are the main competitors of this plant in Europe. The manufacturing of its extract is conducted on a wide scale in Spain, southern France, Sicily, Calabria, Austria, southern Russia, Greece, and Asia. In Asia, Pakistan, India, China, Iran, and Turkmenistan are the main producers of liquorice extracts (Stanikzai 2007). The main producers and exporters of this plant as underground parts are as follows: Iran, Russia, and China, while the major exporters of the extract are as follows: USA, France, Italy, Iran, Iraq, Israel, Japan, and Turkey (Fig. 8.2a–d) as well as China. The main importer of the roots is America, which is also the main exporter of the extract. Japan is the second largest importer with about 10,000 tons of roots and 200–250 tons dry extracts per year. France and Italy are European pioneers in importing liquorice, main sources being China and Russia. It is worth mentioning here that a small part is used in medicine, while the major part is used for flavoring (Batanouny et al. 1999). Turkey also exports liquorice, both as roots and extract. The exported countries are America, Europe, Africa, Middle East, and some Asian countries (Akan and Balos 2008).


1
2
3
4
5
6
7
9
10
Yogi
Egyptian
Licorice Mint
11
12
13
NATURAL VINES
STRAWBERRY LICORICE
14
MARVIS
MARVIS
15
Soul
Licorice
Aromatic Fragrance Oil
16
love
licorice
17
الباشا
18
Lakrids

◂**Fig. 8.1** Some worldwide industrial uses of liquorice (**1** dried root; **2–5** liquorice sherbet; **6–9** liquorice honey; **10, 11** liquorice tea; **12, 13** liquorice candy; **14** Marvis toothpaste; **15, 16** liquorice shampoo; **17, 18** cigarette). *Note* In this figure, Photo **1–5** www.meyankoku.gen.tr; www.dunyabulteni.net; www.tr.zuhoo.net; www.haberciniz.biz; www.urfa.com; www.sifamarketim.com; Photo **6–9** www.sifamarketim.com; Photo **10, 11** www.healthylifestyleshopper.com; Photo **12, 13** www.azimagess.com; Photo **14** www.gottheknack.blogspot.ru; Photo **15, 16** www.lelong.com.my, www.kozmetikas.blogspot.ru; and Photo **17, 18** www.au.northerner.com; www.katsafados.com

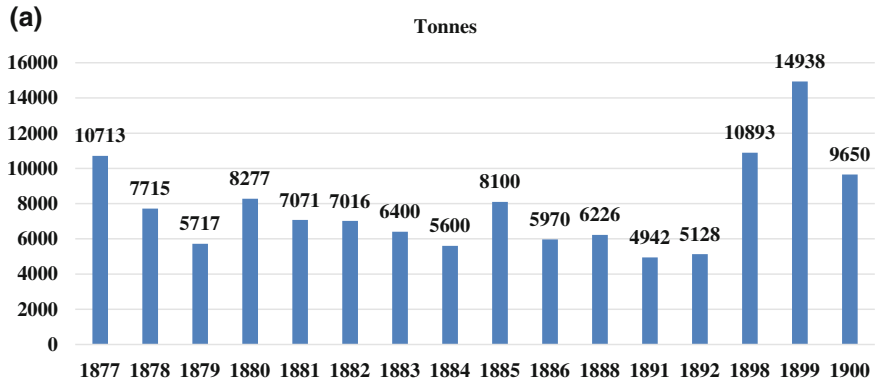

Fig. 8.2 Between 1877 and 2004 years, the amount of liquorice roots exported from Turkey (tons) [İlisulu 1974; İlisulu and Kolsarıcı 1986; Güneş 2004; Akan and Balos 2008; Özgün 2014]. **a** Liquorice production between 1877 and 1900. **b** Liquorice production between 1901 and 1927. **c** Liquorice production between 1963 and 1978. **d** Liquorice production between 1980 and 2004

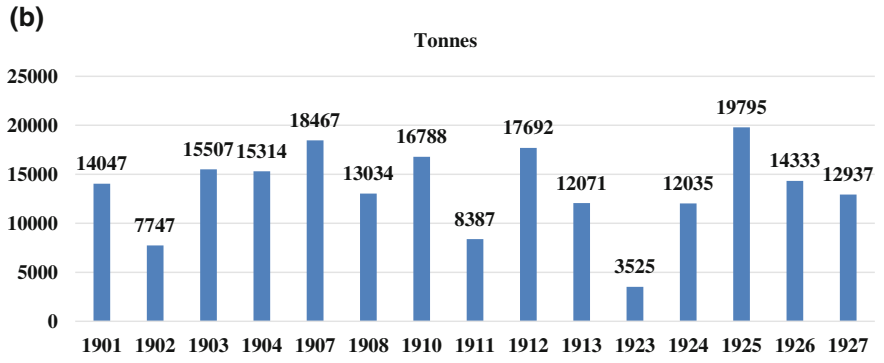

Fig. 8.2 (continued)

This trade has been going on since first days of the establishment of Turkish Republic, and main exporting area has been Izmir. In 2010 alone, the Turkey has exported around 300,000 tons liquorice roots with an export value totalling 525 million dollars (Yoğunlu 2011).

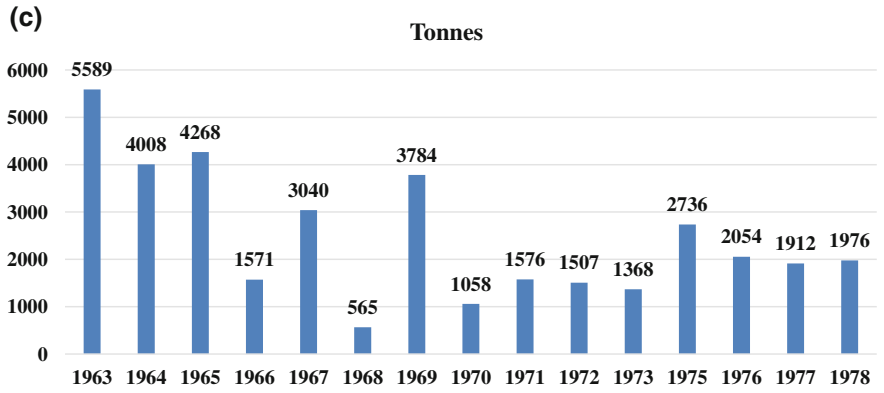

Fig. 8.2 (continued)

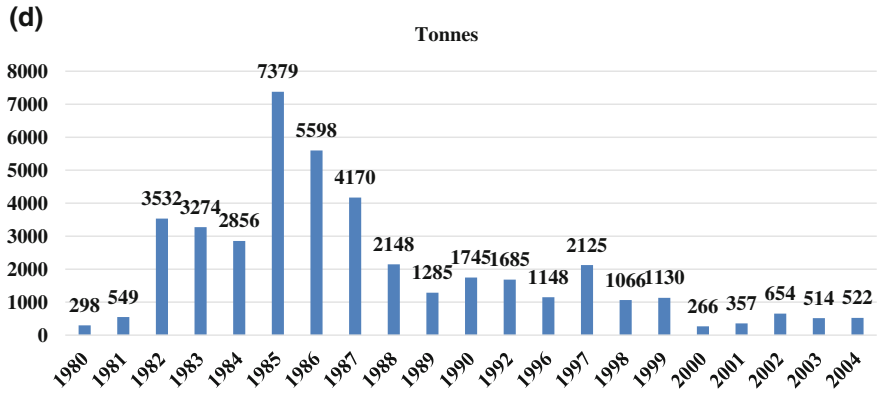

Fig. 8.2 (continued)

The cultivation areas of this plant in nature extend between Turkey and China together with Southern European countries (Rauchensteiner et al. 2005; Khalesi 2015). One of the major producers is Chinese who use it as plant medicine with yearly trading of US 60 billion dollars (Dubey et al. 2008). Although ginseng is the first herbal medicine in China, liquorice distributed mostly in the northwest of country holds the second place. The species evaluated are as follows: *G. uralensis, G. inflata*, and *G. glabra* (Chen et al. 2013). China is expected to become a net importer. Second largest producer on global scale is Iran, where Shiraz, the region located in the southwest of Iran, is the main manufacturer of Iranian liquorice with the variety of *G. violacca* (Ghahraman 1999; Khalesi 2015). Iran has lately faced severe difficulties in the supply of liquorice to the new customers because of the economic sanctions by Europe and America (Khalesi 2015). In Europe, the main producers are listed as follows: the Netherlands, Spain, and Italy, with a total production of about few hundred tons (Khalesi 2015). The manufacturers of

extracts are however, only in China and Iran. The average price for liquorice extract is estimated to lie around 6 Euro per kg, whereas Chinese liquorice is the most expensive due to its high Glycyrrhizic acid content (always above 4.0%) (Cirillo et al. 2011). Main importers of its products on global scale are Japan, Korea, Germany, the Netherlands, and America (Khalesi 2015).

Commercially, liquorice is added to chewing gum, chocolate candy, cigarettes, smoking mixtures, chewing tobacco, and snuff as sweetening agents (Tyler et al. 1988; De Klerk et al. 1997). It gives sparkle and aroma to confectionary products and beer, respectively, and serves as a preservative in food industry. Liquorice is also frequently employed to mask the taste of bitter drugs such as aloe, quinine, and others. The surfactant properties of the saponins facilitate the absorption of poorly absorbed drugs, such as anthraquinone glycosides (Tyler et al. 1988). Some of the products which have glycyrrhizinic acid are presented in Table 8.1 (De Klerk et al. 1997). In addition to industrial uses of glycyrrhizin, it is included as an adhesive agent in insecticides as well wetting agent (surfactant). The liquorice extract residues have been successfully used to extinguish fires in a fire-foam suspension right from 1906 (Houseman 1944). Similarly, it has been used as an emulsifier in UK, to create foam in drinks and alcoholic beverages (Lucas 1976; Houseman 1944). These applications have continued from late 1940s up to 1950s (Roshan et al. 2012). It is also used to insulate fiberboard and serves as a compost for growing mushrooms and as feed for cattle, horses, and chickens (Armanini et al. 2005; Isbrucker and Burdock 2006; Timofeyer 1984; Yumatni et al. 1980).

Liquorice is a common and useful ingredient in cosmetic sector. It is used for depigmentation, as an emollient and soothing agent (Nomura et al. 2002). Modern-day herbalist Jeanne Rose recommends making a steam facial with liquorice, comfrey, together with chamomile or lavender. The topical treatment with a gel containing 2% liquorice extract has successfully lead to significant improvement in erythema, edema, and pruritus in a clinical study (Saeedi et al. 2003). Its extracts are also used as skin depigmenting agents and are effective in the treatment of postinflammatory hyperpigmentation, in particular the one caused by chemical peeling and laser therapy (Callender et al. 2011). It helps to open the pores and allows the other cleansing and healing herbs to penetrate the skin. The use of liquorice root as a shampoo ingredient has been reported to suppress the secretion of scalp sebum for a week after shampooing, thereby postponing the oily sheen (Fig. 8.1). It is also used in mouthwash and toothpastes as a sweetening and flavoring agent, sometimes mixed with anise and used in liqueurs as well as in herbal teas.

Table 8.1 Products containing considerable amounts of glycyrrhizinic acid (De Klerk et al. 1997)

Confectionery	Liquorice sticks, bricks, cakes, toffee, pipes, bars, balls, tubes, Catherine wheels, pastilles and allsorts, Sorbits chewing gum, and Stimorol chewing gum
Health products	Liquorice-flavored diet gum, Throat pearls, Liquorice-flavored cough mixtures, Herbal cough mixtures, and Liquorice tea
All types of liquorice root	Russian, Iranian, Chinese, Turkish, Afghan and unknown origin chewing tobacco, and alcoholic drinks

The liquorice adds flavor, color, and a foamy head when added to the beer and stout preparations. It can at the same time intensify other flavors. The plant has been commercially in use for the preparation of pastries, ice creams, puddings, soy sauce, and soy-based meat substitutes (Rogers 2014). It has been and is used in a number of foods, mainly condiments and confectionery due to its sweet flavor. The soy sauce and sweet chili sauce both contain liquorice powder as a condiment which gives unique sweet flavor, referred to as mellow in English (Kao et al. 2014). In the confectionery products, flavoring with liquorice plant root extract is a common practice; similarly, candies like red vines and London drops are also flavored with it. Tobacco manufacturers use it in considerable amounts in their products. The block, powder, and extract of this plant are used in tobacco for multiple purposes (Kao et al. 2014). According to Carmines et al. (2005), it is added to tobacco to enhance and harmonize the flavor of smoke, reduce mouth and throat dryness, improve the moisture-holding feature of tobacco to increase its stability and shelf life, act as a surface-active agent during the spraying process of the casing ingredients, improve uniformity of the flavor absorption, and minimize the rough smoke character by balancing the overall flavor profile of the tobacco smoke. Although excessive consumption is reported to produce harmful consequences (Rao 1993), it is generally recognized as safe, indicating that it does not represent a hazard to the public when used properly. Liquorice is reported to be the common and useful ingredient in cosmetics (Kao et al. 2014). The extract is also reported to inhibit the rate-limiting first step of the oxidation of tyrosinase (Kim and Uyama 2005). This brings it to the forefront as an effective treatment for melasma (Sheth and Pandya 2011). Moreover, the extract is highly useful in the treatment of aphthous ulcers (Burgess et al. 2008); even its deglycyrrhizinated form (DLG) produces a positive effect (Das et al. 1989).

8.2.1 *Liquorice as an Industrial Resource: A Case Study from Japan*

According to Hayashi and Sudo (2009) for the production of glycyrrhizin, cosmetics, and food additives, very large quantities of liquorice derived from *G. glabra* and *G. inflata* (Xinjiang-Gancao) are imported by Japan as raw materials. Dongbei-Gancao (Tohoku-Kanzo in Japanese) and Xibei-Gancao (Seihoku-Kanzo in Japanese) are also imported from China but are mainly used in the preparation of Japanese Kampo medicines, mainly derived from *G. uralensis*.

The trade statistics related to liquorice import in Japan reveal that since it is not produced locally in Japan, they import it from China, Afghanistan, Turkmenistan, Uzbekistan, and Pakistan (Hayashi and Sudo 2009). The total amount imported has been 10,723,342 kg in 1987, but in 2007, it has decreased to 1,377,213 kg. At present, the major proportion of glycyrrhizin is extracted. Its purification is done in China and few other countries. In view of this, import for glycyrrhizin production has decreased in Japan (Hayashi and Sudo 2009). A part of it imported from China

is the medicinal liquorice, which is more expensive than the one used for glycyrrhizin production as well as few other products. Some are also imported from Australia; 144,710 kg of liquorice has been imported from Australia in 2007, which is quite remarkable. Currently, it is cultivated on a farm owned by a Japanese glycyrrhizin-manufacturing company, namely, Maruzen Pharmaceuticals Co. Ltd., which is used for glycyrrhizin production together with other products (Hayashi and Sudo 2009).

8.2.1.1 Applications of Liquorice and Its Derivatives in Japan (Hayashi and Sudo 2009)

Use in the preparation of Kampo medicines

The indispensable ingredient of the traditional Kampo medicines in Japan is *Glycyrrhiza* radix (root of liquorice). Out of 210 Kampo prescriptions approved by the Ministry of Health, Labour and Welfare of Japan, 71% (150 preparations) contain liquorice. In the Japanese Pharmacopeia, both *G. uralensis* and *G. glabra* are listed, but *G. inflata* is not in the list. *G. uralensis*, imported from China, is the major source of the medicinal liquorice used in Kampo medicines. The standards of the Japanese Pharmacopeia XV clearly make a mention the amount for use in the medicinal application of licorice in Kampo medicines; the minimum glycyrrhizin content in these is mentioned to be only 2.5% (Hayashi and Sudo 2009).

Pharmaceutical preparations

According to Hayashi and Sudo (2009), glycyrrhizin is a prescription drug used in the treatment of liver and allergic diseases in Japan. It is manufactured as an injectable preparation (Stronger Neo-Minophagen® C) and in a tablet form (Glycyron®) by a Japanese company, namely, Minophagen Pharmaceutical Co. Ltd. Stronger Neo-Minophagen® C has been available in the Japanese market for over 60 years. In addition, it is available in China, Korea, Taiwan, Indonesia, India, and Mongolia, where the prevalence of viral hepatitis B and C is relatively high. Glycyrrhizin, glycyrrhetinic acid, and licorice extracts are used in various over-the-counter drugs, including anti-allergic and anti-inflammatory drugs. In addition, in England, the glycyrrhetinic acid derivative glycyrrhetinic acid 3-β-*O*-hemisuccinate (carbenoxolone) is a prescription drug used in the treatment of peptic ulcers (Hayashi and Sudo 2009).

Cosmetics

Liquorice extracts and many glycyrrhizin derivatives are widely used in the preparation of cosmetics in Japan. Glycyrrhizin as well as powdered *Glycyrrhiza* roots, *Glycyrrhiza* extracts, glycyrrhetinic acid, stearyl glycyrrhetinate, pyridoxine glycyrrhetinate, and glycyrrhetinic acid 3-β-*O*-hemisuccinate (carbenoxolone) are used in cosmetics for their anti-inflammatory action. Furthermore, glabridin-containing glycyrrhiza flavonoids isolated from *G. glabra* are used in cosmetic preparations owing to their skin

whitening, anti-sensitizing, and anti-inflammatory properties (Yokota et al. 1998; Hayashi and Sudo 2009).

Food additives

Glycyrrhizin imparts a sweet taste to foods; moreover, it has salt-softening and flavor-enhancing properties and is also heat stable (Hayashi and Sudo 2009). Most Japanese people do not like the long-lasting sweet taste of glycyrrhizin; however, a more acceptable sweetness can be created by using a combination of glycyrrhizin and natural sugars or other sweeteners. Therefore, glycyrrhizin and licorice extracts are used as food additives in a variety of foods; such as snacks, instant noodles, and sauces contain licorice extracts. Glycyrrhizin is used in sweet foods such as sweet snacks, ice creams, and sherbets to enhance their sweetness. It is also used to reduce the saltiness of salty foods such as soy sauce, other sauces, savory snacks, *Kamaboko* (boiled fish paste), *Tsukudani* (fish boiled in soy sauce), *tsukemono* (Japanese pickles), and sausages in Japan (Hayashi and Sudo 2009).

In Japan, enzymatically modified licorice extract (α-glycosyl-glycyrrhizin) and enzymatically hydrolyzed licorice extract (glycyrrhetinic acid 3-*O*-glucuronide) are also used as sweeteners (Hayashi and Sudo 2009). The former is produced by treating the extract with cyclodextrin glycosyltransferase, and it is used as a sweetener because of it has higher solubility and better taste than the untreated licorice extract (Liu et al. 2000). The latter is obtained by enzymatic hydrolyzation of the licorice extract. The sweetness of this licorice is attributable to glycyrrhetinic acid 3-*O*-glucuronide (Kuramoto et al. 1994), which imparts a strong sweetness that is approximately 941 times that of sucrose (Mizutani et al. 1994).

Flavor additives for tobacco

Large quantities of licorice extracts are used in the tobacco industry (Hayashi and Sudo 2009). Licorice not only imparts a sweet taste but also an aroma to tobacco, which makes it mild (Nieman 1957). It also prevents the desiccation of tobacco (Hayashi and Sudo 2009). The licorice extracts used in the tobacco industry are supplied by an American company, namely, MAFCO (Hayashi and Sudo 2009). The liquorice used for this purpose in Japan is imported from countries such as China and USA in 1987; USA, Israel, China, and India in 2007 (Hayashi and Sudo 2009). The trade statistics related to licorice extracts in Japan in 1987 and 2007. Japan imported large quantities (848,704 kg in 1987 and 458,179 kg in 2007) of licorice extracts for tobacco production from the USA, and the value for the same in 2007 was more than 500 million Yen (Hayashi and Sudo 2009).

Confectionery

Liquorice extracts were first used for flavoring confectionery products in England during the eighteenth century; it was blended with sugar, flour, and other ingredients to make Pontefract cakes (Nieman 1957). Nowadays, liquorice confectionery is widely available in Western countries, and large quantities of licorice are used in the confectionery industry. However, since the Japanese do not like the long-lasting sweet taste of glycyrrhizin, licorice confectionery is not popular in Japan (Hayashi and Sudo 2009).

8.3 Other Uses

8.3.1 Liquorice Drinks

In Turkey, Southeastern Anatolia, especially in Adana, Hatay, Sanliurfa, Diyarbakir, Batman, Mardin, Adıyaman, Siirt, and Gaziantep, an extract obtained for consuming the liquorice drink is prepared by mixing roots with water. It is used in abundance in these regions. The fresh roots are carefully washed with water to remove any adherents and sun-dried. Dried roots are crushed to get fiber-like product. These fibers are mingled with some carbonate and cinnamon powder added to give good smell. It is placed in a big wooden bowl with a tap at the bottom and water added. Water is withdrawn by tap from the wooden bowl taken and poured again and again over the fiber, till the extract gives desired taste and color. The extract is taken from the tap and sent for sale (Fig. 8.3) (Akan and Balos 2008).

The two general forms of liquorice are offered in the markets, these are either roots or the extract. The long brown roots are usually harvested from the field from 3 to 4 years old plants and sun-dried (Cheel et al. 2013). The residual stems and fibrous roots are separated (Ariño et al. 2007b). The extract is prepared by chopping roots followed by their steam extraction (Ariño et al. 2007a), and liquor is filtered and concentrated. The final product may be a solid block or spray-dried powder (Khalesi 2015).

8.3.2 Meyan Balı (the Succus Liquiritiae)

The sun-dried shrinked liquorice roots are treated with boiling water to get a sweet and delicious dark colored extract, with slightly bitter taste in some cases. This is called “liquorice syrup” or “succus liquiritiae”. If this extract is not consumed in short time, it is degraded and to prevent this from happening the extract is concentrated to get a solidified extract, also named as block extract. In succus liquiritiae, glycyrrhizin content varies between 15 and 25%, and it is sold in the market as 5–10 kg blocks (Baytop 1952; İlisulu 1974).

The fresh liquorice roots brought to the factory for the production of succus liquiritiae contain 20–25% water-soluble substance, but the values go up to 30–40% after drying. The former are sugars, glycyrrhizin, resins (small amount), starch (small amount), colorant (small amount), and a small amount of other chemical substances. The remaining pulp is mainly cellulose (Baytop 1952).

The composition of the succus liquiritiae prepared from liquorice roots in the Aegean region of Turkey is as follows: 14–15.9% water, 5–6.9% ash, 4–6% water insoluble portion, 3.5–5.2% glucose, 5.8–6.2% sucrose, 10.9–33% gum and starch, and 23.2–25.4% glycyrrhizin (Baytop 1952; İlisulu 1974; İlisulu and Kolsarıcı 1986).

Fig. 8.3 Liquorice root and drinks seller

Its preparation passes through the following stages:

- Cleaning and washing of roots.
- Extraction with "reverse current" operation in extraction batteries.
- Brewing and reposing.
- Separation of the sweet drink in three-stage evaporators.
- Repose and filter.
- Cake production in moulds.
- Transportation to the packaging hall.

8.3.3 Use as Animal Feed

Ozhan and Gol (1975) showed that the leaves of *G. glabra* can be used to meet the forage requirements of ruminant animals when quality and quantity of forage is limited. Although *G. glabra* is one of the naturally grown plants used to meet requirements of small ruminants in some semiarid regions of Turkey during the critical periods of the year there are very few studies available to validate the nutritional quality of *G. glabra* leaves (Kamalak 2006).

Kamalak (2006) has studied the nutritive values of *G. glabra* leaves, hand harvested at prebud, mid, and late flower stages from three plots. He has evaluated this in terms of chemical composition, in vitro gas production, and in situ dry matter (DM) and crude protein (CP) degradation. As per his observations, the chemical composition is significantly effected together with gas production, metabolizable energy (ME), DM, and CP degradability of the leaves of *G. glabra* by the maturity stage. Neutral detergent fiber (NDF), acid detergent fiber (ADF), and condensed tannin (CT) contents increase with increase in the maturity stage whereas crude protein decreases. Gas production, DM, CP disappearance, and estimated parameters also decrease with increase in maturity. CP, ADF, and CT contents range between 16.19 and 26.93%, from 20.74 to 29.07% and from 1.57 to 10.83%, respectively (Kamalak 2006). The potential gas production and ME have been recorded to range from 65.34 to 72.12 ml/0.200 g of DM and from 10.14 to 12.12 MJ/kg DM, respectively. The effective DM degradability (EDMD) and effective CP degradability (ECPD) have given the values ranging between 58.70 and 70.59% and from 57.32 to 73.72%. Gas production, DM and CP disappearance, and estimated parameters of *G. glabra* leaves harvested at prebud stage are significantly higher than those harvested at mid and late flower stages. Gas production, DM and CP disappearance, and estimated parameters are negatively correlated with NDF, ADF, and CT, but show a positive correlation with CP. *G. glabra* harvested at the proper stage of maturity offers considerable potential as a high-quality forage for ruminants during critical periods in the semiarid and arid regions (Kamalak 2006).

8.3.4 Use as Dye Plant

Different colors have been obtained from liquorice root without using mordant, with the mordant alone, and with potassium bichromate mordant kept constant and the two mordants mixed. These colors include open straw yellow, open henna green, honey color, milky coffee, chick yellow, green yellow, dirty yellow, dry oak leaf, open dirty yellow, open earth, hay yellow, open quince feather, dark quince feather, open dry oak leaf, and dark dry oak leaf colors. These colors are the most used ones in hand weaved carpets and rugs. These are strongly recommended for use in environmentally friendly herbal dyeing of rugs and carpets (Arlı et al. 2002).

Arlı et al. (2002) have conducted a study on the colors obtained from *G. glabra* root and their fastness values. They recommend that mordants should be used singly; moreover, the colors obtained from the liquorice root in terms of light-fastness are usually medium. For this reason, it is therefore suitable to use these in the dyeing of carpets and rugs (Arlı et al. 2002).

8.3.5 Evaluation of Liquorice Wastes

G. glabra root extracts are commonly used for medicinal purposes as well as a flavoring agent in the food and tobacco industries (Medina et al. 2011). Almost 10,000 tones of liquorice root residues annually accumulate in some countries and must be properly treated, because the untreated residues produce unwanted environmental effects as these are phytotoxic (Medina et al. 2011). Their direct application to the soil is not suitable. No alternative use has been proposed for this waste in recent evaluations. The burning of this waste is strictly forbidden. Landfilling is costly; currently, nearly 40 dollars per ton are required to solve this problem which includes the transportation cost as well. This type of application is regarded as ecologically unfriendly solution, due to extensive production of greenhouse gases, especially methane, under the anaerobic conditions prevailing in landfills (Lou and Nair 2009; Medina et al. 2011).

Medina et al. (2011) have tried to develop a reliable protocol for management of liquorice root wastes and their composting. They suggest that it is possible to use these wastes as a peat substitute in growing media. They have also looked on their suppressiveness against *Fusarium oxysporum* f. sp. *melonis* (FOM)—the causal agent of *Fusarium* wilt of melon. According to Medina et al. (2011), these wastes can be cocomposted. For this purpose, temperature-controlled forced aeration system with the coarse fraction of separated cow manure can be used for an enrichment both its nutrient content as well as microbial population. Thermophilic conditions prevailing in the pile for approximately 3 months allow the compost to get stabilized and reach an ambient temperature 110 days from the beginning. The resulting compost shows physical characteristics which are well comparable to the peat, with a high nutrient content and relatively low salinity, and no phytotoxicity is seen in the extract from compost, according to the cress germination test. They have grown tomato plants as well in compost which have shown enhancement in development when compared to the peat. The number of surviving FOM spores incubated in the compost has declined faster than in peat. *Fusarium* infected melon plants have survived much better if planted in liquorice compost, as compared to peat. It can be said that liquorice compost can serve as a peat substitute with preferable qualities as proposed by Medina et al. (2011). Latter workers have suggested that the waste can be successfully composted during a reasonable time period, provided enough inoculum and sufficient nutrients are supplied, for example, cattle manure. The composting duration of the chosen mix until full compost maturity (110 days) is reported to be much shorter than that of liquorice

waste alone (Hadar and Mandelbaum 1986) and comparable to that of most types of organic matter, in spite of the recalcitrant nature of the waste from these roots (Gagnon et al. 1999; Shi et al. 1999). Medina et al. (2011) have also proposed that resulting compost has adequate chemical and physical characteristics for its use as a component of growth media, and its performance has been clearly demonstrated. The resulted compost has a potential nutritional effect, especially in terms of N and K. The compost negatively affects the survival rate of FOM spores and shows marked suppression against Fusarium wilt of melon. It therefore has a clear potential as an ingredient of growth media (Medina et al. 2011).

8.3.6 Antimicrobial and Antifungal Activity

Lately, several clinical and pharmacological investigations have been undertaken, which demonstrate the antimicrobial activities of liquorice aqueous, ethanol, and supercritical fluid extract (Bodet et al. 2008; Park et al. 2008; Al-Turki et al. 2008; Jain et al. 2013). Such an activity in plant oils and extracts has been recognized since years. It has been indicated that it can be attributed to alkaloids, saponins, flavonoides, tannin, glycosides, and phenols (Shinwari et al. 2009). Antimicrobial activity of ethanolic extract of *G. glabra* has been tested 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 have been reported (Patil et al. 2009). The inhibition by ethanolic extracts of *G. glabra* and their fractions has been shown by Meghashri (2009) as well. However, *G. glabra* methanolic extracts seem to show more fungicidal effect against *Arthrinium sacchari* and *Chaetomium funicola* (Hojo and Sato 2002). Tharkar et al. (2010) too have recorded the antifungal activity of *G. glabra* extracts. Similarly, Gupta et al. (2008) have published data related to the antimicrobial activity of *G. glabra* against *Mycobacterium tuberculosis.* The liquorice extracts with ethanol, chloroform, and acetone show antibacterial activity against *Bacillus subtilis, Stapphylococcus aureus, Escherichia coli,* and *Pseudomonas aeruginosa* (Nitalikar et al. 2010). A high antibacterial activity against *Staphylococcus epidermidis, Staphylococcus aureus,* and *Propionibacterium acnes* has been recorded with *G. glabra* extracts (Nand et al. 2012). The antibacterial effect of *G. glabra* extract against *Pseudomonas aeruginosa*, *Shigella flexneri, Escherichia coli, Staphylococcus epidermidis, S. aureus,* and *Baillus subtilis* has been enlightened by Varsha et al. (2013). According to the results published by Statti et al. (2004), *G. glabra* methanolic extract also shows 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. An antibacterial activity of *G. glabra* extracts against *Pseudomonas aeruginosa* and *B. subtilis* has also been reported (Shinwari et al. 2009). The upper respiratory tract bacteria such as *Streptococcus pyogenes*,

Haemophilus influenza, and *Moraxella catarrhalis* studied by Tanaka et al. (2001) reveal that secondary metabolites obtained from *Glycyrrhiza* species show antibacterial activity against these. Licoricidin and coumarin derivatives like glycyrol, glycyrin, and glycycoumarin too exhibit high activity against all tested microorganisms. Glabridin derived from root of *G. glabra* has been found to be active against both yeast and filamentous fungi (Fatima et al. 2009). It has shown various biological activities like antimicrobial activity against *Helicobacter pylori*, *Staphylococcus aureus*, and inflammation (Hatano et al. 2000; Fukai et al. 2002; Nerya et al. 2003). *G. glabra* essential oils also show an inhibitory effect against *Aspergillus flavus* (Ali 2013).

Two new pterocarpenes—glycyrrhizol A (1) and glycyrrhizol B (2)—with structures elucidated by spectroscopic data interpretation along with four known isoflavonoids—5-*O*-methylglycryol (3), isoglycyrol (4); both identified by comparison of their spectroscopic data with reported values in the literature; 6,8-diisoprenyl-5,7,4′-trihydroxyisoflavone (5), and gancaonin G (6)—have been isolated from the roots of *G. uralensis* using a bioassay-guided fractionation method. Out of these, compounds 1 and 5 have shown potent antibacterial activity against *Streptococcus mutans* with minimum inhibitory concentrations of 1 and 2 μg/mL, respectively, while glycyrrhizol B (2) and gancaonin G (6) have shown more moderate activity (He et al. 2006). In all, 12 phenolic compounds have been isolated from the fractions of a supercritical fluid extract of *G. uralensis* roots (Villinski et al. 2014). Seven of the metabolites from this extract have been reported earlier. Moreover, four known components have been characterized from this material for the first time, namely, 1-methoxyerythrabyssin II (4), 6,8-diprenylgenistein, gancaonin G (5), and isoglycyrol (6), and one new isoflavan, licorisoflavan C (7). When licoricidin (1) was treated by these workers with palladium chloride larger amounts of licorisoflavan C (7) been produced together with two new isoflavans, licorisoflavan D (8); subsequently detected in the liquorice extract; and licorisoflavan E (9). A study on the antibacterial activity of compounds 1–9 against the cariogenic *Streptococcus mutans* and the periodontopathogenic *Porphyromonas gingivalis* has revealed that licoricidin (1), licorisoflavan A (2), and 7–9 show antibacterial activity against *P. gingivalis* (MICs of 1.56–12.5 μg/mL). Most potent activity against *S. mutans* has been recorded with 7 (MIC of 6.25 μg/mL), followed by 1 and 9 (MIC of 12.5 μg/mL). All these findings support the evidence for the therapeutic potential of liquorice extracts for the treatment and prevention of oral infections (Villinski et al. 2014).

The compounds like 18β-glycyrrhetinic acid, liquiritigenin, glabridin, licochalcone A, licochalcone E, licorisoflavan A, licoricidin, and glycyrrhizol A isolated from liquorice possess antimicrobial effects against *S. aureus, C. albicans, Mycobacterium bovis*, yeast, and several cariogenic bacteria like *S. mutans* and *Streptococcus sobrinus* (Long et al. 2013; Fatima et al. 2009; Messier and Greiner 2011; Zhou et al. 2012a, b; Dai et al. 2013; Kim et al. 2013b; Gafner et al. 2011; Hu et al. 2011).

According to Yang et al. (2015) liquorice has great application prospects as an alternative therapy in treating dental caries, periodontal disease, digestive anabrosis, and tuberculosis. It also has a potential alternative to synthetic fungicides, or as a lead compound for new classes of synthetic fungicides (Yang et al. 2015).

A new prenylated isoflavan, iconisoflavan (1), and a new prenylated isoflav-3-ene, iconisoflaven (2) have been isolated from the roots of *G. iconica* together with four known earlier (3S)-licoricidin (3), licorisoflavan A (4), topazolin (5), and glycycoumarin (6) (Kırmızıbekmez et al. 2015). Their structures have been elucidated on the basis of extensive spectroscopic analysis including 1D and 2DNMR as well as HR-MS. Kırmızıbekmez et al. (2015) have also established the configurations of compounds 1, 3, and 4 by electronic circular dichroism (ECD). An in vitro evaluation of all the isolated compounds (1–6) has revealed that they show antimicrobial activities against five pathogenic bacteria and one yeast (*Candida albicans*) using an in vitro microdilution method. Compounds 1 and 3–5 have displayed significant activity against *Salmonella typhimurium* ATCC 13311 with MIC values ranging from 2 to 8 μg/mL. All compounds have been screened for their in vitro free radical scavenging activities using an in vitro microdilution DPPH assay spectrophotometrically. The tested compounds have exhibited IC50 values in the range of 0.18–0.56 mg/mL. This suggests that they show an activity comparable with that of ascorbic acid (IC50: 0.07 mg/mL). The investigations undertaken by Kırmızıbekmez et al. (2015) are the first phytochemical and bioactivity investigation on *G. iconica*.

Very important differences have been reported by Karahan et al. (2016) in the antimicrobial and antioxidant activities of root extracts of *G. glabra* var. *glandulifera* from different habitats in Hatay (Turkey). The extracts with most potent antioxidant characteristics were those from populations originating from the regions with similar climatic features (rainy Mediterranean climate and low-rain Mediterranean climate). On the other hand, the extracts showing strongest antimicrobial effect have come from the specimens originating from habitats under anthropogenic pressure. This implies that the differences in the biological activities can be attributed partly to the influence of environmental factors (Karahan et al. 2016).

An experimental work has been carried out by Gaur et al. (2016) to explore in vitro as well as in vivo combination effects of liquiritigenin and isoliquiritigenin isolated from *G. glabra* with β-lactam antibiotics (penicillin, ampicillin, and oxacillin) against mec A-containing strains of methicillin-resistant *Staphylococcus aureus*. Minimum inhibitory concentration (MIC) of the both components has exhibited significant anti-methicillin-resistant *Staphylococcus aureus* activity (50–100 μg/mL) against clinical isolates of methicillin-resistant *Staphylococcus aureus*. In vitro combination study has shown that isoliquiritigenin significantly reduces MIC of β-lactam antibiotics up to 16-folds, while liquiritigenin reduces up to 8-folds. Time-kill kinetics at graded MIC combinations (isoliquiritigenin/liquiritigenin + β-lactam) have indicated 3.27–9.79-fold and 2.59–3.48-fold reduction in the growth of clinical isolates of *S. aureus,* respectively. In *S. aureus*-infected Swiss albino mice model, the combination of isoliquiritigenin with oxacillin has significantly lowered the systemic microbial burden in blood, liver, kidney, lung, and spleen tissues in comparison with isoliquiritigenin, oxacillin alone as well as untreated control (Gaur et al. 2016). According to Gaur et al. (2016), considering its synergistic antibacterial effect both isoliquiritigenin and

liquiritigenin prove to be the promising compounds for the development of novel antistaphylococcal combinations.

Pandian and Chidambaram (2017) have succeeded in synthesizing "silver nanoparticles" from aqueous extract of *G. glabra*. The biological reduction of these particles has been carried out in appropriate condition and characterization of synthesized nanoparticles followed by UV-Vis spectroscopy, FT IR, and SEM. The phytochemicals present in the extract of *G. glabra* have reduced the silver ions into metallic nanoparticles. The synthesized silver nanoparticle has exhibited a strong antibacterial activity against *P. aeruginosa* and *S. aureus*. The synthesized SNPs have exhibited potential anticancer activity and are reported to be nontoxic on mammalian Vero cell line. Hence, the SNPs from plant extracts may be used to develop nanomedicine against pathogens (Pandian and Chidambaram 2017).

Several reports clearly depict that liquorice has potent effects in inhibiting the activities of gram-positive and gram-negative bacteria such as *Staphylococcus aureus* (Long et al. 2013; Snowden et al. 2014; Lau and Plotkin 2013), *Porphyromonas gingivalis* (Wittschier et al. 2009), *Streptococcus mutans* (Ahn et al. 2012; Peters et al. 2010), *Candida albicans* (Irani et al. 2010; Fatima et al. 2009), *Escherichia coli* (Awandkar et al. 2012), *Enterococcus faecalis* (Badr et al. 2011), *Pseudomonas aeruginosa* (Yoshida et al. 2010), *Helicobacter pylori* (Asha et al. 2013), and *Bacillus subtilis* (Irani et al. 2010). It also has effects in inhibiting the activities of pathogenic fungi such as *Alternaria solani*, *Botrytis cinerea*, and *Phytophthora* (Treutwein et al. 2010). The liquorice extracts with 80% methanol (oil-based extract of liquorice) have shown great fungicidal effects against *Arthrinium sacchari* M001 and *Chaetomium funicola* M002 (Hojo and Sato 2002). An inhibitory effect of the *G. glabra* extract on *Candida albicans* and some gram-positive bacteria has also been reported (Irani et al. 2010).

Attempts have been made to evaluate the antifungal activity as well as antitoxin activity of *G. glabra* extract (Mohseni et al. 2014). Strain American Type Culture Collection 15517 of *Aspergillus parasiticus* has been used to perform antifungal susceptibility test. The tests have been followed according to clinical and laboratory standards institute document M27-A3, and the rate of aflatoxin production was determined using high-performance liquid chromatography technique after exposure to different concentrations of liquorice extract. Mohseni et al. (2014) have followed the quantitative changes in the expression of the aflR gene, analyzed by measuring the cognate aflR mRNA level with quantitative real-time reverse transcription polymerase chain reaction assay. Their results demonstrate the inhibitory effect of liquorice extract on *Aspergillus parasiticus* growth at 500 mg/mL. A significant decrease in aflatoxin production has been recorded at the same concentration. The production of aflatoxin B1 has been entirely inhibited in 10 g/mL of the extract. A significant decrease has been observed in the level of aflR gene expression has after exposure of fungal cells to 500 g/mL of extract. The antifungal and antitoxin activities of the extract on *Aspergillus parasiticus* have revealed its antifungal features together with its effective ability to decrease aflatoxin production (Mohseni et al. 2014).

8.3.7 *Antiviral Activity*

Several virus diseases including chronic hepatitis B and C, together with human acquired immunodeficiency syndrome (AIDS), have been treated with licorice and glycyrrhizate compounds obtained from the liquorice extract as a potential therapeutic agent (Wang et al. 2000; Chen et al. 2004; Orlent et al. 2006; Tandon et al. 2002). Many reports have indicated antiviral activity of glycyrrhizin and glycyrrhizic acid with the ability to inhibit 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). The glycyrrhizin and its derivatives from *G. glabra* do reduce the hepatocellular damage in chronic hepatitis B and C, and show antiviral activity against HIV-1, SARS-related coronavirus, respiratory syncytial virus, arboviruses, vaccinia virus, and vesicular stomatitis virus (Fiore et al. 2008). Glycyrrhizin also shows antiviral effect, through an inhibition of viral particle to cell membrane binding, or through cellular signal transduction mechanisms (Crance et al. 2003). 18β-glycyrrhetinic acid is reported as the promising biological alternative for the topical treatment of persistent vulvovaginal candidiasis (Pellatti et al. 2009). In vitro antiviral effects for viruses causing respiratory tract infections like influenza virus and the severe acute respiratory syndrome (SARS) coronavirus, human immunodeficiency virus (HIV) too have been reported (Cinatl et al. 2003)

The potential use *G. uralensis* for treatment of human infection by enterovirus type 71 (EV71) which can cause life-threatening meningoencephalitis has also been investigated (Kuo et al. 2009). The treatment of viral hepatitis since the late 1970s with liquorice preparations is a well-known fact. Recently, many papers published depict that liquorice extract has significant antiviral activity against HIV, severe acute respiratory syndrome-coronavirus (SARS), HSV, influenza virus (H3N2), rotavirus, respiratory syncytial virus, varicella zoster virus, coxsackievirus, and enterovirus (Booth et al. 2003; Wang et al. 2013a; Kwon et al. 2010; Shebl et al. 2012). As against this, as far as a single compound is concerned, many compounds have been isolated from liquorice but only two triterpenoids, glycyrrhizin and 18β-glycyrrhetinic acid, have been reported to possess antiviral activity, with a significant positive impact on HIV, H3N2, HSV, DHV, HCV, PrV, and IAV (Yang et al. 2015). In addition, other virus types have been worked include the following: H5N1, herpes virus, influenza virus, and rotavirus (Wolkerstorfer et al. 2009; Matsumoto et al. 2013; Huang et al. 2012; Soufy et al. 2012; Michaelis et al. 2010; Sasaki et al. 2002; Kang and Lieberman 2011; Smirnov et al. 2012; Moisy et al. 2012; Sui et al. 2010; Hardy et al. 2012a; Baltina et al. 2012; Yang et al. 2015). The in vitro experiments with glycyrrhizin have shown that it inhibits HCV by suppressing the release of infectious particles (Matsumoto et al. 2013), HSV by depressing the cellular adhesion (Huang et al. 2012), influenza virus by reducing HMGB1 binding to DNA and suppressing interactions between viral macromolecules and host proteins (Moisy et al. 2012), HIV by preventing the virus from replication (Sasaki et al. 2002), and H5N1 not by interfering with H5N1 replication,

but by controlling H5N1-induced proinflammatory gene expression (Michaelis et al. 2010). However, does glycyrrhizin inhibit virus replication still needs more research work. It also interacts with the cell membrane and reduces endocytic activity (Wolkerstorfer et al. 2009), and causes deregulation of generating the mature forms of viral mRNA encoding, which is a process important for viral stability (Kang and Lieberman 2011). The glycyrrhetinic acid is reported to show a significant antiviral activity against rotavirus replication by reducing the amounts of viral proteins VP2, VP6, and NSP2 at a step or steps subsequent to virus entry, together with an effective inhibition of HIV-1 by reducing the accumulation of virus antigen p24 and protecting cells from the cytopathogenic action of the virus (Hardy et al. 2012a; Baltina et al. 2012).

In all, 13 new oleanane-type triterpenoid saponins, uralsaponins M-Y (1–13), and 15 known analogues (14–28) have been isolated from the roots of *G. uralensis* (Song et al. 2014). The structures of 1–13 have been identified on the basis of extensive NMR and MS data analysis. The sugar residues have been identified by gas chromatography and ion chromatography coupled with pulsed amperometric detection after hydrolysis. For the first time, saponins containing a galacturonic acid (1–3) or xylose (5) residue have been reported from *Glycyrrhiza* species. Compounds 1, 7, 8, and 24 are reported to exhibit good inhibitory activities against the influenza virus A/WSN/33 (H1N1) in MDCK cells with IC50 values of 48.0, 42.7, 39.6, and 49.1 μM, respectively, versus 45.6 μM of the positive control oseltamivir phosphate. Moreover, compounds 24 and 28 have shown anti-HIV activities with IC50 values of 29.5 and 41.7 μM, respectively (Song et al. 2014). Adianti et al. (2014) have reported that glycycoumarin, glycyrin, glycyrol, and liquiritigenin isolated from *G. uralensis*, as well as isoliquiritigenin, licochalcone A. and glabridin, can be good candidates for seed compounds to develop antivirals against HCV. Glycyrrhizin demonstrates a pronounced lymphocytic proliferation response on white Pekin ducklings and reveals a good immune stimulant and antiviral effect against DHV following in vivo studies (Soufy et al. 2012). A protective effect is exerted by a combination of glutamyl-tryptophan and glycyrrhizin in reducing the death of H3N2 virus-infected mice (Smirnov et al. 2012).

We can conclude that both glycyrrhizin and glycyrrhetinic acid exert antiviral activity mainly by inhibiting the replication and release of the virus. They suppress the interactions between the virus and host cells, activate immune responses in host cells, and attenuate a virus-induced anti-inflammatory response (Yang et al. 2015).

8.3.8 Anti-inflammatory

The report published by Matsui et al. (2004) clearly shows that many allergies and other inflammatory diseases have been treated with liquorice species. The anti-inflammatory effects of glycyrol (benzofuran coumarin) isolated from *G. uralensis* have been investigated at length (Shin et al. 2008). They found that glycerols have potential anti-inflammatory effect. According to Vibha et al. (2009),

the steroid-like anti-inflammatory activity of liquorice root constituents is similar to the action of hydrocortisone. The explanation given by them in connection with this finding is that it occurs due to inhibition of phospholipase A2 activity, an enzyme critical to numerous inflammatory processes. The glycyrrhetinic acid (ED 50, 200 mg kg^{-1}) is reported to show an inhibitory effect on carrageenan-induced rat paw edema and anti-allergic activity (Matsui et al. 2004). *G. glabra* secondary metabolites such as glycyrrhizic acid, glabridin, and licochalcone A also show an anti-inflammatory effect (Furuhashi et al. 2005; Kang et al. 2005).

The liquorice looks like an excellent alternative choice for the treatment of inflammation in the epidemic diseases among populations especially children (Yang et al. 2015). A large number of reports stress the fact that two triterpenoids, glycyrrhizin and 18β-glycyrrhetinic acid, and several flavonoids isolated from liquorice such as glabridin, isoliquiritigenin, licochalcone A, licochalcone B, licochalcone C, licochalcone D, licochalcone E, isoangustone A, dehydroglyasperin C, licoricidin, licorisoflavan A, echinatin, and glyurallin B, possess anti-inflammatory activity (Yang et al. 2015). The effects of these compounds (dehydroglyasperin C, echinatin, glycyrrhizin, 18β-glycyrrhetinic acid, licochalcone A, licochalcone B, licochalcone C, licochalcone D, licochalcone E, licoricidin, licorisoflavan A, isoliquiritigenin, and glabridin) on different inflammatory types have been investigated by different workers (Yang et al. 2015).

The types of inflammations studied are as follows: postischemic brain with middle cerebral artery occlusion (Luo et al. 2013); chronic liver diseases (Imai et al. 2013); mastitis (Fu et al. 2014); acute lung injury (Ni et al. 2011); LPS-induced inflammatory response (Wang et al. 2011; Furusawa et al. 2009); leishmania donovani-infected macrophages (Bhattacharjee et al. 2012); indomethacin-induced small intestinal damage (Ishida et al. 2013); ischemia/reperfusion (Oztanir et al. 2014); LPS-induced J774A.1 murine macrophages (Thiyagarajan et al. 2011); periodontitis (La et al. 2011); lipid peroxidation in rat liver microsomes (Fu et al. 2013); LPS-induced BV-2 microglia (Kim et al. 2013c); glutamate-induced hippocampal HT22 cells (Kim et al. 2012); childhood atopic dermatitis (Wananukul et al. 2013); allergic airway inflammation (Chu et al. 2013); LPS-induced RAW264.7 cell (Fu et al. 2013; Cho et al. 2010); LPS-induced macrophage cells (Fu et al. 2013); in rat liver microsomes (Fu et al. 2013); LPS-induced macrophage cells (Fu et al. 2013); LPS and interferon-gamma-induced inflammatory response (Wang et al. 2013b); allergic inflammation (Tanifuji et al. 2010); and TPA-induced mouse ear edema (Lee et al. 2013a), respectively.

In addition the about studies, Fuhr et al. (2015) have reported that in TNF-α-stimulated colon cells, amorfrutin A (1) (isoprenoid-substituted benzoic acid derivatives, which were found in *G. foetida*) significantly reduces the expression and secretion of several inflammation mediators, in part due to interaction with PPARγ. Fuhr et al.'s (2015) results support the hypothesis that amorfrutins may have the potential to treat inflammation disorders such as chronic inflammatory bowel diseases.

The glycyrrhizin has also been used in leishmania donovani-infected macrophages as per the in vitro studies published (Bhattacharjee et al. 2012). In

lipopolysaccharide-stimulated macrophage models, glycyrrhetinic acid, glabridin, and isoliquiritigenin have been used and in actinobacillus actinomycetemcomitans lipopolysaccharide-treated macrophages, licoricidin and licorisoflavan A have been used (La et al. 2011). Licochalcone A, licochalcone B, and licochalcone E have been used in lipopolysaccharide-induced RAW 264.7 macrophage cells (Fu et al. 2013; Cho et al. 2010), and DGC has been used in lipopolysaccharide-induced BV-2 microglia and mice hippocampal cells (Wang et al. 2011; Thiyagarajan et al. 2011; Kim et al. 2012, 2013c).

Glycyrrhizin has also been used in the postischemic brain with a middle cerebral artery occlusion mouse model both in vivo and clinical studies as well as in a lipopolysaccharide-induced acute lung injury mouse model plus a mastitis mouse model (Ni et al. 2011; Luo et al. 2013; Fu et al. 2014). For the treatment of oxidative and neuronal damage in brain tissue caused by global cerebral ischemia/reperfusion in a C57BL/J6 mouse model also glycyrrhetinic acid has been used (Oztanir et al. 2014). In the childhood atopic dermatitis and in a murine model of asthma licochalcone A has been used, whereas in TPA-induced mice ear edema licochalcone E has been used (Wananukul et al. 2013; Chu et al. 2013; Yang et al. 2013; Lee et al. 2013a). Several studies show that liquorice extracts have benefits in the treatment of acute and chronic inflammatory conditions, indicating that studies on the anti-inflammatory activity of liquorice are very important and meaningful (Nirmala and Selvaraj 2011; Wu et al. 2011; Yang et al. 2015).

8.3.9 Anti-ulcer

The anti-ulcer activity of deglycyrrhizinated liquorice formulations has been demonstrated in Bennett et al. 1980 by Bennett and coworkers. They used a rat model of aspirin-induced gastric mucosal damage. The results have shown that these formulations promote healing by increasing mucous production and blood supply to the damaged stomach mucosa, thus enhancing mucosal healing (Van Marle et al. 1981; Da Nagao et al. 1996). An anti-ulcerogenic effect of carbenoxolone derived from the root of liquorice too has been reported (Masoomeh and Kiarash 2007). This is explained through an inhibition of the secretion of gastrin. The reason is that liquorice compound raises the concentration of prostaglandins in the digestive system and in this way promotes mucus secretion from the stomach. Anti-pepsin effect of liquorice secondary metabolites too has been reported, which prolongs the life span of surface cells in the stomach (Adel et al. 2005).

8.3.10 Anti Tumor

Almost all in vivo and in vitro studies on the liquorice phytochemical constitutes have revealed that it has anticancer effects (Salvi et al. 2003). An inhibition of

tumor formation and growth in breast, liver, and skin cancer has been reported (Liu et al. 1998; Shiota et al. 1999; Tamir et al. 2000). In 1998, Fukai and his coworkers 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 in vivo assay, Sheela et al. (2006) have observed that the extract of *G. glabra* inhibits proliferation of tumor cells and angiogenesis. Antiproliferative effects are displayed by the ethanolic extract and glycyrrhizin against the MCF-7 in dose-dependent manner (Dong et al. 2007). Similar results have been reported by Jo et al. (2005) who used ethanol extract of *G. uralensis* root which induced apoptosis and G1 cell cycle arrest in MCF-7 human breast cancer cells. The licochalcone E from the roots of *G. inflata* also exhibits most potent cytotoxic effect compared with the known antitumor agents, licochalcone A, and isoliquiritigenin (Yoon et al. 2005). Many compounds have been derived from *G. glabra*, namely, glyasperin A, gancaonin P, licochalcone B, topazolin, and gancaonin O by Nomura et al. (2002), which have shown relatively higher cytotoxic activity against human oral squamous cell carcinoma cell line HSC-2. A new retrochalcone derived from the *G. inflata* by Yoon et al. (2005), during their studies on licochalcone E, has exhibited the potent cytotoxic effect. Isoliquiritigenin has also been reported to inhibit the proliferation of the human non-small cell lung cancer A549 cell line, inducing apoptosis and locking cell cycle progression in the G1 phase (Hsu et al. 2004). Kanazawa et al. (2003) too have reported similar findings, where isoliquiritigenin has inhibited the growth of prostate cancer. It has been suggested as a chemopreventive compound for cancer in humans. In short, the biologically active compound from the liquorice root can be very useful as antiproliferative and antitumor agents (Rahman and Rashid 2008; Hossain et al. 2004).

High mortality due to cancer is one of the leading causes of humans deaths; as such, the use of natural compounds without side effects is currently attracting much attention of researchers. Many studies have proven that various natural compounds in liquorice possess effective antitumor activity, including three triterpenoids, glycyrrhizin, glycyrrhetinic acid, and 11-deoxyglycyrrhetinic acid, and six flavonoids, isoangustone A, glabridin isoliquiritigenin, licochalcone A, licochalcone B, and licochalcone E (Kim et al. 2010, 2013d; Hsu et al. 2011; Li et al. 2012; Kwon et al. 2013; Khan et al. 2013; Lin et al. 2014; Yuan et al. 2014; Huang et al. 2014a; Yang et al. 2015; Park et al. 2016).

The effects of these compounds (glycyrrhizin, 18β-glycyrrhetinic acid, 11-deoxyglycyrrhetinic acid, isoangustone A, licochalcone A, licochalcone B, licochalcone E, isoliquiritigenin, and glabridin) on different cancer types such as colon carcinogenesis, leukemia, prostate cancer, gastric cancer, colorectal cancer, human melanoma, liver cancer, bladder cancer, oral cancer, and breast cancer have been investigated by different investigators (Shetty et al. 2011; Hsu et al. 2011; Xiao et al. 2011; Chueh et al. 2012; Khan et al. 2013; Lee et al. 2013b; Song et al. 2013; Kwon et al. 2013; Wang et al. 2013c; Lin et al. 2014; Huang et al. 2014a; Tsai et al. 2014; Choi et al. 2014; Yuan et al. 2014; Jiang et al. 2014; Kim et al. 2014). Several single compounds isolated from liquorice as well as ethanol extracts and hexane/ethanol

extracts of roasted liquorice are reported to show antitumor activity (Seon et al. 2012; Lee et al. 2013c). According to Yang et al. (2015), the liquorice compounds interfere with antitumor activities mainly by attenuating the level of cytokines, blocking cell cycle progression, and inducing cancer cell apoptosis. Isoangustone A has been applied to SW480 human colorectal adenocarcinoma cells during in vitro studies, DU145 to human prostate cancer cells as well as 4T1 murine breast cancer cells; isoliquiritigenin to HeLa human cervical cancer cells and MDA-MB-231 to human breast cancer cells; glycyrrhizin has been applied to WEHI-3 mouse leukemia cells, glycyrrhetinic acid to DU-145 prostate cancer cells, and licochalcone to MKN-28, AGS, MKN-45 gastric cancer cells, HA22T/VGH, SK-Hep-1, HepG2 to human hepatocellular cancer cells, KB human oral cancer cells, and T24 to the bladder cancer cells (Wolkerstorfer et al. 2009; Shetty et al. 2011; Xiao et al. 2011; Chueh et al. 2012; Seon et al. 2012; Wang et al. 2013c; Huang et al. 2014a; Tsai et al. 2014; Jiang et al. 2014; Choi et al. 2014; Kim et al. 2014). Glycyrrhizin has also been applied under in vivo studies and has shown to inhibit 1,2-dimethylhydrazine-induced colon precancerous lesions of Wistar rats (Khan et al. 2013), while glycyrrhetinic acid applied to gastric cancer has inhibited tumor growth in a nude mouse model (Lin et al. 2014). Glabridin has inhibited MDA-MB-231 breast cancer angiogenesis in a nude mouse model; licochalcone B has inhibited MB49 bladder tumor growth in a C57BL/6 mouse model; licochalcone E has suppressed 4T1 mammary tumor growth and lung metastasis in the mammary fat pads in a syngeneic BALB/c mouse model; isoangustone A has significantly suppressed PTEN-deleted human prostate tumor growth and SK-MEL-28 human melanoma tumor growth in xenograft mice models (Hsu et al. 2011; Kwon et al. 2013; Lee et al. 2013b; Song et al. 2013; Yuan et al. 2014). In summary, liquorice embodies interesting and important hits for antitumor drug discovery and development (Yang et al. 2015).

8.3.11 Antioxidant

The data published by Siracusa et al. in 2011 clearly depicts the fact that extract of *G. glabra* leaves shows antioxidant, anti-genotoxic, and anti-inflammatory activities. Many phytochemical constitutes have been found in the roots of *Glycyrrhiza*. These are considered as a potential source of antioxidants (Singh 2010; Lateef et al. 2012). According to Vaya et al. (1997), isoflavones glabridin and hispaglabridins A and B show significant antioxidant activity. The luteolin, rutin, and apigenin flavonoids found in the *G. glabra* roots show significant antioxidant characteristics (Hesham and Shgeru 2002). The main compound linked to antioxidant activity is mentioned as phenolic compounds (Škrovánková et al. 2012). The ethanol extract of *G. glabra* has been reported to possess a cerebroprotective effect in hypoxic rats, which may be mediated by its antioxidant effects (Muralidharan et al. 2009). *G. glabra* essential oil also exhibits DPPH radical scavenging activity (85.2%) at dose 400 µg/ml (Ali 2013), whereas methanolic extract shows 91.3% scavenging activity at dose of 62.5 µg (Lateef et al. 2012). Licochalcone C is reported to possess antioxidant because it reduces the production of superoxide radicals and

consequently reduces the activity of inducible nitric oxide synthase (iNOS) (Franceschelli et al. 2011).

8.3.12 Hepatoprotective Activity

G. glabra is used in the traditional medicine to treat various liver diseases as well (Subramoniam and Pushpangadan 1999). Secondary metabolites derived from liquorice have been observed to lower serum liver enzyme levels and improve tissue pathology in hepatitis patients (Van Rossum et al. 2001).

Isoflavan derivatives, glabridin, hispaglabridin A, hispaglabridin B, 4′-*O*-methylglabridin, and 3′-hydroxy-4′-*O*-methylglabridin, isolated from *G. glabra* have been investigated by Haraguchi et al. (2000) for their ability to protect liver mitochondria against oxidative stresses. These workers have reported that mitochondrial lipid peroxidation linked to respiratory electron transport is induced nonenzymatically and an inhibition of these isoflavans takes place. Hispaglabridin A strongly inhibits both peroxidations and 3′-hydroxy-4′-*O*-methylglabridin, the most effective at preventing NADH-dependent peroxidation. 3′-Hydroxy-4′-*O*-methylglabridin protects the mitochondrial respiratory enzyme activity against NADPH-dependent peroxidation injury (Haraguchi et al. 2000). Moreover, dihydroxyfumarate—induced mitochondrial peroxidation is also prevented by this isoflavan. *G. glabra* isoflavans are highly effective in protecting mitochondrial function against oxidative stresses (Haraguchi et al. 2000). *G. glabra* root extract also shows radioprotective effect via lipid peroxidation in rat liver microsomes and plasmid pBR322 (Shetty et al. 2002). The extract protects microsomal membranes, which is evident from the reduction in lipid peroxidation, and could also protect plasmid DNA from radiation-induced strand breaks (Shetty et al. 2002).

A significant reduction in serum aminotransferases is induced by glycyrrhizic acid which then improves the liver histology (Curreli et al. 2007). Al-Razzuqi et al. (2012) have demonstrated that *G. glabra* aqueous extract shows a significant effect in ameliorating liver functions in acute liver diseases if given in a single dose per day of 2 mg/kg body weight. The protective effects of glycyrrhetinic acid against the carbon tetrachloride-induced hepatotoxicity and retrorsine-induced liver damage has also been published by Jeong et al. (2002).

Only three compounds, glycyrrhetinic acid, glycyrrhizin, and dehydroglyasperin C, have been reported until now to possess hepatoprotective activity, especially glycyrrhizin, which according to Yang et al. (2015) is effective in almost the whole process of liver diseases. During the clinical treatment of liver disease, glycyrrhizin preparation has been widely used. After this date, it has been used on a large scale in the treatment of a variety of liver diseases, such as hepatitis B, hepatitis C, liver fibrosis, and cirrhosis of the liver (Yang et al. 2015). Glycyrrhizin has an obvious protective effect in liver injury induced by CCl4 as revealed by different in vivo animal models (Huo et al. 2011; Yin et al. 2011), together with hepatotoxicity induced by xanthium, α-naphthyl isothiocyanates, and liver fibrosis (Zhai et al. 2007; Abe et al. 2008; Sharifzadeh et al. 2008). Moreover, glycyrrhizin,

glycyrrhetinic acid, and dehydroglyasperin C have also shown hepatoprotective activity (Abe et al. 2008; Wang et al. 2012; Rasool et al. 2014; Tripathi et al. 2009; Guo et al. 2013; Fujisawa et al. 2000; Chen et al. 2014b; Wu et al. 2008; Hasan et al. 2014; Seo et al. 2014).

Some of the mechanisms that can lead to liver dysfunction are oxidative stress, lipid peroxidation, and transaminase reactions. The downregulation of these factors found recently enlightens the hepatoprotective effect of liquorice. It also exerts its hepatoprotective effect by regulating the expression of CYP enzymes, attenuating oxidative stress, improving the stability of the cell structure as well as biological membrane systems, and inhibiting the cytolytic activity of the complement and apoptosis systems (Yang et al. 2015). Latter also mentions that this extract significantly inhibits the aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase activities, and decreases total protein, albumin, and globulin levels. The liver superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and glutathione S-transferase activities are also enhanced by this extract together with glutathione level (Huo et al. 2011; Yin et al. 2011; Rasool et al. 2014; Al-Razzuqi et al. 2012). Liquorice therefore appears to be a highly potent therapeutic agent for the treatment of liver diseases (Yang et al. 2015). The findings of Park et al. (2016) are considered as scientific evidence that isoLQ in liquorice has the function of being a hepatic protectant against oxidative damages through ERK-mediated Nrf2 activation.

8.3.13 Dermatological Effect

As early as 1997 Lee and coworkers have observed many activities like skin whitening, depigmenting, antiaging, anti-acne, and anti-erythemic affiliated to the use of *Glycyrrhiza* root originating bioactive compounds. Recently, a significant decrease in skin melanin by formulation of *G. glabra* extracts has been reported by Akhtar et al. (2011). According to Lee et al. (2005), glycyrrhizin derived from the root of *G. glabra* induces melanin formation; this is probably mediated through an activation of a tyrosinase gene expression.

8.3.14 Antidepressant and Memory-Enhancing Activity

According to Dhingra and Sharma (2005, 2006), the mouse immobility tests have clearly demonstrated that liquorice is highly effective as an antidepressant as well as in the memory-enhancing activity. The studies undertaken by Zhao et al. (2006) have revealed that liquiritin and many other secondary metabolites from *G. uralensis* show an antidepressant effect on chronic stress following the experiments carried out on the depressed rats. Wang et al. (2008) too have published data related to the antidepressant-like activity of liquiritin and isoliquiritin in the forced

swimming test (FST) as well as tail suspension test (TST) in mice. Latter have depicted that an increase in the 5-Hydroxytryptamine and norepinephrine in the mouse hippocampus, hypothalamus, and cortex could be the mechanism of action of these compounds. The sedative and muscle relaxant activities in mice due to another compound in liquorice the carbenoxolone in genetically epilepsy-prone rats (GEPRs) have also been reported by Gareri et al. (2004). The studies on the root extract of *G. glabra* on learning and memory in another experiment has revealed that 150 and 225 mg/kg doses show an effective enhancement in learning and memory as compared to the control. The reason may be antioxidant and anti-inflammatory action of plant extract. Under these circumstances, the susceptible brain cells get exposed to less oxidative stress resulting in reduced brain damage and improved neuronal function (Chakravarthi et al. 2012).

A large number of workers have investigated the effects of liquorice aqueous extract on learning and memory. One of these is Chakravarthi and Avadhani (2014), who investigated the function of such extract in the dendritic morphology of hippocampal cornu ammonis area three (CA3) neurons. According to these workers, 150 and 225 mg/kg doses show obvious enhancement of dendritic arborization and dendritic intersections in hippocampal pyramidal neurons. This has demonstrated its neuronal dendritic growth stimulating features. These researchers have also found that all doses of such an extract significantly enhances the memory. An application of 150 and 225 mg/kg doses significantly enhance learning as well as memory (Chakravarthi and Avadhani 2013). The nootropic and antiamnestic effects of these extracts are mediated through augmenting monoaminergic transmission in the cortex, hippocampus, and striatum (Michel et al. 2013).

Out of a large number of compounds isolated from liquorice glabridin and 2,2,4-trihydroxychalcone is reported to improve learning and memory. These are commonly used in the treatment of cardiovascular and central nervous system diseases (Yang et al. 2015). The higher doses of former compound effectively antagonize amnesia induced by scopolamine (Cui et al. 2008). According to Hasanein (2011), this compound also prevents the deleterious effects of diabetes on memory and learning as per the experiments carried out on rats. Inhibition of beta-site amyloid precursor protein cleaving enzyme 1 is regarded as an effective strategy for anti-Alzheimer's disease drug discovery. As a new beta-site amyloid precursor protein 2,2,4-trihydroxychalcone cleaving enzyme 1 inhibitor has been tested to ameliorate impairment in mice (Zhu et al. 2010). All these findings enlighten the fact that liquorice seems to be a promising drug for improving memory, impaired learning, Alzheimer's disease, dementia, and other neurodegenerative disorders (Yu et al. 2007; Cui et al. 2008; Yang et al. 2015).

8.3.15 Immunoregulatory Activity

Most of the research work undertaken during the last decade reveals an immunoregulatory activity of liquorice. Out of the liquorice compounds,

glycyrrhiza polysaccharides are believed to play an important role in stimulating the body's immune ability, by affecting the body's nonspecific and specific immune functions and through activating immune cells (Hong et al. 2009; Li et al. 2012). In addition, glycyrrhizin, 18β-glycyrrhetinic acid, licochalcone A, liquiritigenin, glycyrol, and glycyrrhiza polysaccharides also showed immunoregulatory activity (Abe et al. 2003; Lee et al. 2009; Li et al. 2010a, 2012; Hendricks et al. 2012; Soufy et al. 2012; Kim et al. 2013a; Ma et al. 2013; Fontes et al. 2014). The compounds isolated from liquorice exert immunoregulatory activity by regulating the production of cytokines and interleukin together with the expression of cell surface molecules and immune responses (Yang et al. 2015). Many in vivo and clinical studies have proved that these compounds produce a protective effect against disseminated candidiasis (Lee et al. 2009). It reduces the severity of experimental autoimmune encephalomyelitis as well (Fontes et al. 2014). It also increases the end point serum antibody titers (Hendricks et al. 2012). The production of IL-10 also increases with Con A-induced hepatitis (Abe et al. 2003). It acts as an immune stimulant against DHV (Soufy et al. 2012). All these reports affirm the immunoregulatory activity of liquorice and indicate that it can be developed as a novel immunomodulatory drug (Yang et al. 2015).

8.3.16 Inhibitory Effect on Diabetes

Liquorice inhibits series of pathological and physiological changes induced by D-galactose, such as insulin resistance and oxidative stress/free radical damage, so as to delay the development of diabetes (Yang et al. 2015). Several compounds isolated from licorice, such as glycyrrhizin, glycyrrhetinic acid, liquiritigenin, isoliquiritigenin, glabridin, licochalcone A, licochalcone E, and some other flavonoids, have been reported to possess an inhibitory effect in diabetes (Choi et al. 2010; Lee et al. 2010; Sen et al. 2011; Yehuda et al. 2011; Park et al. 2012; Alqahtani et al. 2013; Feng et al. 2013; Li et al. 2013; Wu et al. 2013; Gaur et al. 2014; Yao et al. 2014). The liquorice extract can be a highly potent therapeutic agent for the prevention and treatment of diabetes nephropathy led by mesangial fibrosis and glomerulosclerosis through blocking Akt activation and transforming growth factor-β signaling (Li et al. 2010b). It alleviates blood glucose levels, restores renal function, attenuates body weight loss, and modulates the adverse effect of diabetes on renal glutathione and malondialdehyde as well as the activity of catalase and superoxide dismutase. It also restores the total antioxidant capacity of diabetic kidneys, and at the same time has a potential therapeutic effect in diabetes due to its antioxidant and antihyperglycemic features (Kataya et al. 2011; Saleem et al. 2011). All these reports indicate that liquorice is a highly potent therapeutic agent for diabetes treatment (Yang et al. 2015).

The data published by Zhang et al. (2016) indicates that liquiritin has a protective effect against high fructose-induced myocardial fibrosis via suppression of NF-kB and MAPKs signaling pathways. It may be a promising candidate for

diabetes-related myocardial fibrosis treatment. Moreover, Xie's (2017) results indicate that liquiritigenin has a protective role in high fructose feeding-triggered cardiac injury through fibrosis and inflammation response suppression by inactivating NF-kB signaling pathway. Thus, liquiritigenin may be a potential candidate for diabetes-associated cardiac injury (Xie 2017).

8.3.17 Adrenal Cortical Hormone-like Function

Some reports demonstrate that liquorice extracts and compounds show adrenal cortical hormone-like function, increased adrenocorticotropic hormone formation, and stimulated steroidogenesis in adrenal glands. It will also stimulate the secretion of glucocorticoids, mineralocorticoids, and anterior pituitary corticotroph-releasing hormone and vasopressin from the adrenal cortex (Lee et al. 2007; Kratschmar et al. 2011). Out of the compounds isolated from liquorice, 18β-glycyrrhetinic acid, glycyrrhizin, and isoliquiritigenin produce an adrenal cortical hormone-like function (Yang et al. 2015). Isoliquiritigenin has significant estrogenic activities due to its estrogen responsive β selectivity, partial estrogen agonist activity, and the nonenzymatic transformation between isoliquiritigenin and liquiritigenin (Hajirahimkhan et al. 2013). 18β-glycyrrhetinic acid and glycyrrhizin play a very important role in the treatment of glucocorticoid-dependent diseases as a well-known inhibitor of 11β-hydroxysteroid dehydrogenases (Kratschmar et al. 2011; Raikkonen et al. 2010; Sasaki et al. 2010). Glycyrrhetinic acid shows its mineralocorticoid actions by inhibiting the conjugation of deoxycorticosterone and dehydroepiandrosterone at a source within the adrenal cortex (Al-Dujaili et al. 2011). All the abovementioned findings lend support to the reasonable use of liquorice as a promising strategy for the treatment of hormone-dependent diseases (Yang et al. 2015).

8.3.18 Other Effects

A vast number of reports have been published on the pharmacological activities of liquorice extracts and biologically active compounds. The secondary metabolites liquiritigenin and isoliquiritigenin derived from the root of *G. glabra* have shown dose-related anti-allergic activities (Kakegawa et al. 1992). Moreover, glabridin and glabrene have an estrogen-like effect stimulating the synthesis of epithelial cell DNA. It prevents postmenopausal women from vascular injury and atherosclerosis (Kwon et al. 2008). According to Akasaka et al. (2011), glycyrrhetinic acid is effective in suppressing pain-related behaviors caused by sciatic nerve injury. Isoliquiritigenin has a spasmolytic effect on uterine contraction, an effective function in reducing pain, and an antiangiogenic property (Jhanji et al. 2011; Shi et al. 2012). The traditional compound prescription "gancao wheat jujube soup" has

demonstrated a potential antidepressant-like effect by liquiritin treatment in chronic, variable, stress-induced depression; this can be related to the defense of liquiritin against oxidative stress (Zhao et al. 2008). Liquorice is also used to relieve menopausal symptoms in postmenopausal women (Menati et al. 2014; Hajirahimkhan et al. 2015). Nagai et al. (2007) have indicated that licochalcone A may be responsible for the relaxant activity of *G. inflata* root, which acts through the inhibition of cAMP PDE.

Chen et al.'s (2009) results indicate that isoliquiritigenin plays a dual role in regulating gastrointestinal motility, both spasmogenic and spasmolytic. The spasmogenic effect may involve the activating of muscarinic receptors, while the spasmolytic effect is predominantly due to blockade of the calcium channels. According to Mishra et al. (2011), anti-arthritic activity of *G. glabra* is due to its significant reduction of paw edema volume and its ability to stabilize lysosomal enzyme activity such as ACP. The results justify the benefit of *G. glabra* in the treatment of inflammation associated diseases like arthritis. The investigations carried out by Asgary et al. (2007) have revealed that *G. glabra* extract has an effect of on the blood lipids and atherosclerosis. These workers have found that *G. glabra* extract significantly decreases total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) levels and increases high-density lipoprotein cholesterol (HDL-C) and lessens atherosclerotic lesion in aorta. Won et al. (2007) have reported the use of liquorice as a food ingredient for obesity, because licochalcone A derived from *G. uralensis* reduces the lipase activity as a new inhibitor of pancreatic lipase.

8.3.18.1 Clinical Therapeutics

Many reports about the clinical applications of liquorice ingredients and preparations have been published as the modern pharmacology developed (Yang et al. 2015). The development of glycyrrhizin preparations, mostly used to treat liver diseases, has a long history in Asia among all active compounds isolated from this plant (Li et al. 2014). This preparation has developed four generations so far, from glycyrrhizin tablets to ammonium glycyrrhizinate, diammonium glycyrrhizinate, and magnesium isoglycyrrhizinate. A comparison with its first three preparations, magnesium isoglycyrrhizinate has a better lipotropy, higher targeting, and fewer adverse reactions, because of its use in protecting hepatic L02 cells from ischemia/reperfusion-induced injury (Huang et al. 2014b). It has been successfully used to slow down the process of pulmonary fibrosis (Xiao et al. 2014), inhibiting ethanol-induced testicular injury (He et al. 2010), and restoring hepatic impairments caused by paclitaxel in other cancer treatments (Chen et al. 2014a).

The addition of liquorice and its active compounds to the oral cortisone acetate increases the amount of cortisol available to tissues in Addison's disease (Methlie et al. 2011). A double-blind clinical trial study conducted on patients with allergic rhinitis has shown that the rate of its symptoms including severe rhinorrhea, sneeze, pruritus, and congestion are lowered significantly after using glycyrrhizin nasal

drops (Akhavan et al. 2012). According to Agarwal et al. (2009), the liquorice gargle is effective in attenuating the incidence and severity of postoperative sore throat. Jain et al. (2013) have reported that both aqueous and ethanolic extracts of this plant exert cariostatic activities through a clinical trial carried out among 60 pediatric patients aged 7–14. With the discovery of more and more pharmacology activities, liquorice has shown a great potential for acting as a novel drug or complement agent to treat different diseases (Yang et al. 2015).

8.3.19 Side Effects and Toxicity

The toxic effects of liquorice are well documented, but potentially toxic compounds in it have not been confirmed fully. According to Asl and Hosseinzadeh (2008), although deglycyrrhizinated liquorice (DGL) is reported to be free of adverse effects, the large amounts of this plant may result in severe hypertension, hypokalemia, and other signs of mineralocorticoid excess. The doses exceeding 10 times the standard dose when consumed over a long period can lead to a number of dangerous conditions (McGuffin et al. 1997). The use of this plant is contradicted in persons with high blood pressure due to hypertension caused by its overuse, which may be due to its effect on the aldosterone system; however, a treatment with its extract results in dose-dependent increase in plasma renin and sodium with concomitant decrease in plasma cortisol, adrenocorticotropic hormone (ACTH), aldosterone, and potassium levels (Olukoga and Donaldson 2000; Al Qarawi et al. 2002; Sharma and Agrawal 2013). Its prolonged use leads to hypertension, hypokalemia, and edema, since insulin-dependent diabetics appear to be predisposed to hypokalemia and sodium retention, and use of this plant is contradicted by diabetes (McGuffin et al. 1997; De Smet et al. 1997; Asl and Hosseinzadeh 2008; Isbrucker and Burdock, 2006). This plant should not be used with stimulant laxatives or hypotensive diuretics (such as thiazides) because of the potassium loss associated with the laxatives and diuretics (De Smet et al. 1997; Asl and Hosseinzadeh 2008). Glycyrrhizin has been shown to interfere with 5β-reductase breakdown of corticosteroids, thus prolonging the biological half-life of these steroids. The glycyrrhizin or the aglycone, or glycyrrhetinic acid are reported to increase the effect of corticoid treatment (Brinker 1997).

Some studies on liquorice report (ethanol extracts of *G. glabra*), containing glycyrrhizin and glycyrrhetic acid, negative results in the TA98 and TA100 strains (Mitscher et al. 1986; Zani et al. 1993). Genotoxic potential of *G. glabra* has been investigated using the Ames IITM, chromosomal aberration, and micronucleus test systems. The results indicate that this plant possesses no mutagenic activities, either with or without metabolic activation (Nakagawa et al. 2008; Chandrasekaran et al. 2011). TA98 has been reported to be more sensitive to the mutagens present in the liquorice water extract (Martinez et al. 1999). The cytotoxic activity of liquorice extract is 63% at 0.24 mg/mL, with greater percentages apparent as its concentrations increase up to 4.8 mg/mL. IC50 values of chloroform, methanol, and water

extracts of *G. glabra* in the breast MCF7 cell line have been reported as 0.45, 0.99, and 1.29 μM, respectively (Rathi et al. 2009). Abudayyak et al. (2015) have reported that *G. glabra* water extract displays mutagenic activity against the TA100 strain in the presence of metabolic activation, but only at the highest extract concentration. It has been reported that large doses or long-term injections of this plant extract sometimes produce an acquired form of apparent mineralocorticoid excess syndrome, expressed as sodium retention, hypokalemia, and high blood pressure (Wang and Nixon 2001; Shen et al. 2007).

The medical records of patients treated with liquorice herbal complexes from January 1 to December 31, 2010 have revealed changes in the levels of creatinine, potassium, and blood urea nitrogen before and after herbal complex intake and the prevalence of hypokalemia among these patients. A total of 360 patients have not shown significant changes in the levels of potassium and creatinine ($p = 0.815$ and 0.289, respectively). Hypokalemia has been observed in six patients; however, in five patients, the hypokalemia did not appear to be related to liquorice. The results show that herbal complexes containing liquorice have not significantly influenced the potassium levels in routine clinical herbal therapies (Jung et al. 2014). 4T1 mammary carcinoma cells injected into the mammary fat pads of syngeneic BALB/c mice have revealed that 7 days after the injection, the mice received licochalcone E (7 or 14 mg/kg body weight/day) via oral gavage for 25 days. Licochalcone E suppresses solid tumor growth and lung metastasis, without exhibiting kidney or liver toxicity (Kwon et al. 2013). Russo et al. (2000) have proposed that some people could be susceptible to low doses of glycyrrhizin because of a 11β-hydroxysteroid dehydrogenase deficiency. Harahap et al. (2011) believe that liquorice ingestion and mutations in the HSD11B2 gene, inhibit 11β-hydroxysteroid dehydrogenase type 2 enzyme activity and cause the syndrome of apparent mineral corticoid excess. This supposed that liquorice ingestion is an environmental risk factor for hypertension or an apparent mineral corticoid excess state in patients with a mutation in HSD11B2.

The liquorice is generally recorded as a nontoxic herb in TCM but some health concerns have been reported with its use (Kao et al. 2014). It causes edema and apparent mineralocorticoid excess syndrome as per the clinical studies, because glycyrrhizic acid and glycyrrhetinic acid inhibit the activity of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) which converts biologically active cortisol into the inactive compound cortisone, thereby preventing the overstimulation of the mineralocorticoid receptor by cortisol (Whorwood et al. 1993; Ma et al. 2011; Hardy et al. 2012b). An overdose of the latter can lead to excessive sodium ion levels and the excretion of potassium ions, which end up with water retention and lead to hypertension. Its excessive daily supplementation may cause low potassium levels due to liquorice-induced hyperaldosteronism and finally hypertension and heart disease. The hypertension induced by its use can be reversed by stopping its intake as well as intake of its products (Ruiz-Granados et al. 2012). 11β-Hydroxysteroid dehydrogenase type 2 is inhibited by liquorice and its constituents; this causes hypertonia and hypokalemia because of the associated change in blood potassium levels. Similar concerns are associated with the intake of carbenoxolone because it is a more potent inhibitor of 11βHSD2 (IC50: 20–50 nM) than 11βHSD1 (IC50: 1.8 μM) (Ma et al. 2011).

Potassium levels are also affected by digoxin (Bielecka-Dabrowa et al. 2012), which might act synergically with liquorice herbal intake. Some products use deglycyrrhizinated liquorice (DGL) instead of raw extract; this reduces glycyrrhizic acid and glycyrrhetinic acid-induced side effects (Kao et al. 2014).

An overuse of liquorice also influences the effects of other medicines. Glabridin may inhibit human cytochrome P450 (Kent et al. 2002) which metabolizes warfarin (coumadin), an anticoagulant agent, into its inactive form (Cavallari and Limdi 2009), and is an important enzyme in drug metabolism and bioactivation (Guengerich 2008). The liquorice increases warfarin clearance and in case treatment with warfarin is required, consulting a physician is strongly advised before consuming foods containing liquorice (Mu et al. 2006; Kao et al. 2014).

Pregnant females should limit intake of extract from this plant (Kao et al. 2014). Very few investigations have been conducted on the teratogenicity of its extract, but a single study has indicated that it may aggravate cyclophosphamide-induced body weight loss and malformations of fetuses by upregulating cytochrome P450 type 2B (Park et al. 2011). However, Korean researchers have reported that women taking liquorice for the treatment of cough and cold did not have an increased risk of stillbirths (Choi et al. 2013). Its extract also increases estrogen levels in humans (Armanini et al. 2002) and may increase the risk of estrogen-mediated cancer (Boucher et al. 2012). The extract of this herb can potentially cause an antiandrogenic effect, which may lead to erectile dysfunction, therefore to avoid such side effects, careful intake of this herb-related food is highly advised (Armanini et al. 2003; Zamansoltani et al. 2009; Kao et al. 2014).

8.3.19.1 Mycotoxin Contamination in Liquorice Products

The microbial growth on liquorice roots is highly expected because of the effects of the environmental conditions (Khalesi et al. 2013). An exposure to the fungal contamination is seen due to old-style harvesting, processing, and storage conditions. Such a contamination has three main effects: deterioration of the chemical composition, reduction of the medicinal effectiveness, and the risk of mycotoxin production (Khalesi 2015). The presence of aflatoxin B1 (AFB1) has been reported to be much lesser extent than ochratoxin A (OTA) on its roots but the reasons are unknown (Pietri et al. 2010; Wang et al. 2013d). According to a recent report published by Pietri et al. (2010), only 16% of the products from this herb contained AFB1, but majority contained OTA, sometimes up to 990.1 ng/g. In view of this, a large number of papers have been published mainly on the OTA contamination of its products (Khalesi 2015).

The presence of OTA in this herb preparation has been reported for the first time by Bresch et al. (2000) and Majerus et al. (2000). They have reported a high percentage of contaminated samples. The report from the former authors mentions that nearly 50% of the liquorice roots showed OTA contamination in the concentration range of 0.3–216.0 ng/g. The homogeneous brownish samples have been reported to contain higher amounts of OTA than bright yellow ones, which is quite

interesting. In another study Majerus et al. (2000) have analyzed 83 liquorice products, as foodstuff or supplements of medicine, all these have indicated low levels of OTA in children's tea (130–440 ng/g), but quite high levels in supplements (300–64300 ng/g). More than 90% of liquorice tablets have been reported to contain OTA in the range of 700–2600 ng/g. Many more studies have confirmed high amounts of OTA in liquorice products, sometimes with values above 200 ng/g (Kabelitz and Sievers 2004).

The Italian liquorice products too have been reported to contain OTA, while its confectionery contained 0.96 ng OTA/g, dried extracts had 89.6 ng OTA/g with the maximum value of 990.1 ng/g, which represents an extremely high level of contamination. In the light of these reports, OTA intake from dried liquorice extract seems to expose a risk for consumers, especially high consumers, patients, and infants (Pietri et al. 2010; Khalesi 2015).

Ariño et al. (2007a) have also reported high levels of OTA in 30 liquorice products from Spain, including food as well as medicine-based samples. They have reported OTA concentrations up to 252.8 ng/g. Dry liquorice roots contained the highest levels with the mean value of 63.6 ng/g and sweets contained the lowest level with the average value of 3.8 ng/g. The extract of the herb contained 16.0 ng OTA/g and its solid blocks had 39.5 ng OTA/g. These workers have also notified that OTA in dry roots may be shifted to corresponding tea from 1% for infusion tea and up to 5% in the case of decoction tea. Nearly 75% of the liquorice hard candies purchased from public markets in Spain are reported to show OTA contamination, with a mean value of 2.96 ng/g, while for the soft candies, contamination is only 39%, with a mean value of 0.34 ng OTA/g sample (Herrera et al. 2009).

In China OTA levels in its roots have revealed that the highest level of contamination occurred in the samples from Jiangxi (84.4 ng/g) and the lowest from Beijing (1.4 ng/g) (Yang et al. 2010). The ecophysiological and storage conditions may be responsible for the differences together with the variety of the roots. This enlightens the findings that the region of collection plays a significant role for OTA amount. The sustainability of the roots against contamination may be different from one place to another (Khalesi and Khatib 2011; Khalesi 2015).

The risk of fungal contamination of its roots increases in warm humid areas (Khalesi et al. 2013; Khalesi 2015). Large quantities of the roots are typically stocked for a long period before processing or transportation. A successful approach to avoid contamination is managing the storage conditions (Kapetanakou et al. 2009; Cairns-Fuller et al. 2005). Khalesi and Khatib (2011) and Khalesi (2015) have studied the relation between OTA biosynthesis and ecophysiological factors including temperature, water activity (aw), and type of mycobiota in the region at length. Recent reports demonstrate that temperature of 22 °C is the critical point to control the formation of OTA in these roots; below this temperature, the amount of OTA is much lower than the temperatures mentioned. The covering of bulk of the roots during the storage needs to be avoided, as it may increase the inlet temperature and, consequently, the risk of fungal growth as well as OTA biosynthesis (Khalesi et al. 2013; Khalesi 2015).

The major parameter influencing OTA formation is the mycobiota in a region of liquorice root, which should be particularly considered. The distributional map of the fungi in liquorice production regions is still missing (Khalesi 2015). In all, 16 fungal species have been isolated from the root samples collected from four different locations in China, major ones being *Penicillium, Aspergillus*, and *Eurotium* (Chen et al. 2011). *P. polonicum* is the main species in Jiangxi province (with highest levels of OTA), whereas in other regions, *Aspergillus* spp. such as *A. parasiticus, A. flavus, A. versicolor*, and *A. sydowii* and *Eurotium* spp. such as *E. chevalieri, E. repens*, and *E. amstelodami* are dominant. Similar investigations were undertaken by Chen et al. (2013). They reported that *Penicillium* is the major fungus on liquorice in different regions in China with potential of OTA production. They also isolated two new *Penicillium* species, i.e., *P. glycyrrhizacola* sp. nov. and *P. xingjiangense* sp. nov. in the roots of this herb for the first time. *P. chrysogenum* was also reported as one of the main OTA producers on roots in China. Chen et al. (2013) have reported that *P. chrysogenum, P. glycyrrhizacola, P. polonicum*, and *A. westerdijkiae* are main contaminants in dry liquorice with values lying around 39.03 ng/g. However, the data for fresh and dry specimens on mycobiota differs much (Khalesi 2015).

No public reports are available from Iran concerning the mycobiota in the regions where this herb flourishes (Khalesi 2015). However, after observation of OTA, biodegradation on its roots from the natural contamination by *A. fumigatus, A. japonicus*, and *A. niger* is possible. Khalesi et al. (2011) have hypothesized that there may be predominant in OTA producers in Iran.

In case fungal contaminated liquorice is consumed for a long time, this may cause health hazards such as, chronic hypokalemic nephropathy secondary which needs immediate attention (Vivekanand 2010; Khalesi 2015). However, the fundamental mechanism of OTA toxicity has not been fully enlightened (Khalesi 2015). But some investigations have been done to decrease the risk by possible intake of OTA contaminated herbal product. Some research has been conducted on different food-based liquorice products as a normal dietary use to complete the current consumption databases of European Food Safety Authority (EFSA) concerning OTA in liquorice products (Commission Regulation (EU) No. 105/2010). According to Pietri et al. (2010), assuming a total mean value of 1.53 ng OTA/g in sweets corresponding to consumption about 1.4 g liquorice sweets per day means a weekly intake of 12 ng OTA. For an infant with 30 kg weight, a weekly uptake of 0.4 ng/kg body weight has been reported which is extremely high. In another study, it has been shown that children may consume up to 8.94% tolerable weekly intake (TWI) of liquorice confectionary (Herrera et al. 2009). Although liquorice and its derivatives are not the dominant products in dietary intake, for high consumers of this herb, especially children, yet the current amount of OTA in its products is not safe (Khalesi 2015).

At present, the main issue for trading the liquorice products, especially those coming from Asia, is keeping the products safe concerning OTA (Khalesi 2015). To fulfill this criterion, efforts have been made to regulate OTA levels in this herb (Commission Regulation (EU) No. 105/2010). For this purpose, first, the data of

OTA concentration in a variety of its products obtained from public markets has been collected. Commission Regulation (EU) No. 105/2010 amending regulation (EC) No. 1881/2006 sets the regular maximum levels of 20 ng/g for its root and 80 ng/g for the extract. The reason for the difference between the maximum acceptable amount of OTA between root and extract is that from each 3 to 4 kg liquorice roots, around 1 kg of extract is obtained. These rules and calculations are valid for average consumers. Of course for the high consumers, patients, and infants, these amounts need to be reviewed (Khalesi 2015).

The liquorice (*Glycyrrhiza* taxa) plants have a large number of applications in food and pharmaceutical industry. If these are contaminated by fungal OTA, the possibility for a carcinogenic mycotoxin production during growth and storing period can be expected (Khalesi 2015). In EU, the maximum amount of OTA in its roots and extract has been authorized at 20 and 80 ng/g, respectively. Nevertheless, a valid method to quantify this toxin is still lacking. Use of IAC and SPE clean-up methods followed by liquid chromatography has been proposed for determination of OTA in the products of this herb. However, those methods are time-consuming, laborious, costly, and restricted to only a few laboratories, mostly located in Europe. The decontamination of OTA in this herb is also a very challenging topic. Peeling, extraction, and dehydration have been reported to reduce the amount of OTA. Although thermal stability of OTA is an obstacle for heat deterioration of this mycotoxin in the roots of this herb and derived products, it seems that much more studies on determination and decontamination of OTA are needed to overcome the OTA concern in liquorice marketing (Khalesi 2015).

8.3.20 Other Alternative Uses

Abdel-Latif et al. (2015) have studied three natural dyes extracted from *Biota orientalis*, *Piper nigrum*, and *Glycyrrhiza glabra*. They have used these as photosensitizers for dye-sensitized solar cells (DSSCs). The dyes have been tested as sensitizers before and after grinding the materials. Titanium dioxide (TiO_2) nanopowder has been used as a semiconducting material. The best photovoltaic performance has been recorded from the DSSC sensitized with *G. glabra* after grinding the material. They suggest that this performance is significantly improved by acid treatment of the TiO_2 photoelectrode. Electrochemical impedance spectroscopy of the fabricated DSSCs has been carried out and charge recombination resistance, double layer capacitance, effective lifetime of electrons, charge transfer resistance, and constant phase element exponential coefficient determined (Abdel-Latif et al. 2015).

The studies carried out by Ovez et al. (2006) deal with one natural organic substance liquorice (*G. glabra*) for its use as a carbon source in the biological denitrification of drinking water. This material acts as a solid substrate and biofilm carrier. Their experiments have been carried out in batch, semi-batch, and continuous processes. Complete denitrification has been achieved with *G. glabra*. They

found that nitrate removal rate of *G. glabra* is 6.96 mg/L/day NNO_3. The results of Ovez et al. (2006) have clearly revealed that this organic substrate could be used as an alternative carbon source for denitrification with complex process control and continuous monitoring, but this carbon source should be changed periodically for the continuation of the process.

References

Abdel-Latif MS, El-Agez TM, Taya SA, Ghamri HS, Batniji AY (2015) Dyes extracted from *Biota orientalis, Piper nigrum*, and *Glycyrrhiza glabra* as photosensitizers for dye-sensitized solar cells. Int J Renew Energy Res 5(4):1034–1040

Abe M, Akbar F, Hasebe A, Horiike N, Onji M (2003) Glycyrrhizin enhances interleukin-10 production by liver dendritic cells in mice with hepatitis. J Gastroenterol 38:962–967

Abe K, Ikeda T, Wake K, Sato T, Sato T, Inoue H (2008) Glycyrrhizin prevents of lipopolysaccharide/D-galactosamine-induced liver injury through down-regulation of matrix metalloproteinase-9 in mice. J Pharm Pharmacol 60:91–97

Abudayyak M, Nath EO, Ozhan G (2015) Toxic potentials of ten herbs commonly used for aphrodisiac effect in Turkey. Turk J Med Sci 45:496–506

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

Adianti M, Aoki C, Komoto M, Deng L, Shoji I, Wahyuni TS, Lusida MI, Soetjipto, Fuchino H, Kawahara N, Hotta H (2014) Anti-hepatitis C virus compounds obtained from *Glycyrrhiza uralensis* and other *Glycyrrhiza* species. Microbiol Immunol 58(3):180–187

Agarwal A, Gupta D, Yadav G, Goyal P, Singh PK, Singh U (2009) An evaluation of the efficacy of licorice gargle for attenuating postoperative söre throat: a prospective, randomized, single-blind study. Anesth Analg 109:77–81

Ahn SJ, Cho EJ, Kim HJ, Park SN, Lim YK, Kook JK (2012) The antimicrobial effects of deglycyrrhizinated Licorice root extract on *Streptococcus mutans* UA159 in both planktonic and biofilm cultures. Anaerobe 18:590–596

Akan H, Balos M (2008) GAP Bölgesi'nden toplanan meyan kökü (*Glycrrhiza glabra* L.) taksonunun ihracat durumu, etnobotanik özellikleri ve tıbbi önemi. Fırat Üniversitesi Fen ve Mühendislik Bilimleri Dergisi 20(2):233–241 (In Turkish)

Akasaka Y, Sakai A, Takasu K, Tsukahara M, Hatta A, Suzuki H, Inoue H (2011) Suppressive effects of glycyrrhetinic acid derivatives on tachykinin receptor activation and hyperalgesia. J Pharmacol Sci 117:180–188

Akhavan A, Saberi M, Saberi F (2012) Topical effects of Glycirrhizic acid on allergic rhinitis in comparison to the beclomethazone treatment. J Med Plants 11:120–129

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

Al-Dujaili EA, Kenyon CJ, Nicol MR, Mason JI (2011) Liquorice and glycyrrhetinic acid increase DHEA and deoxycorticosterone levels in vivo and in vitro by inhibiting adrenal SULT2A1 activity. Mol Cell Endocrinol 336:102–109

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

Alqahtani A, Hamid K, Kam A, Wong KH, Abdelhak Z, Razmovski-Naumovski V, Chan K, Li KM, Groundwater PW, Li GQ (2013) The pentacyclic triterpenoids in herbal medicines and their pharmacological activities in diabetes and diabetic complications. Curr Med Chem 20:908–931

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

Altay V, Karahan F, Öztürk 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

Al-Turki AI, El-Ziney MG, Abdel-Salam AM (2008) Chemical and anti-bacterial characterization of aqueous extracts of oregano, marjoram, sage and licorice and their application in milk and labneh. JFAE 6:39

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

Ariño A, Herrera M, Langa E, Raso J, Herrera A (2007a) Ochratoxin A in liquorice as affected by processing methods. Food Addit Contam 24(9):987–992

Ariño A, Herrera M, Estopañan G, Juan T (2007b) High levels of ochratoxin A in licorice and derived products. Int J Food Microbiol 114:366–369

Arlı M, Kayabaşı N, Kızıl S (2002) A research on the colours obtained from licorice (*Glycyrrhiza glabra* L.) plant in natural dyeing and their some fastnesses. Tarım Bilimleri Dergisi 8(3):227–231

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

Armanini D, Bonanni G, Mattarello MJ, Fiore C, Sartorato P, Palermo M (2003) Licorice consumption and serum testosterone in healthy man. Exp Clin Endocrinol Diabetes 111:341–343

Armanini D, Fiore C, Bielenberg J, Ragazzi E (2005) Licorice (*Glycyrrhiza glabra*). In: Coates P (ed) Encyclopedia of dietary supplements. Marcel Dekker Inc., New York, pp 391–399

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

Asha MK, Debraj D, Prashanth D, Edwin JR, Srikanth HS, Muruganantham N, Dethe SM, Anirban B, Jaya B, Deepak M, Agarwal A (2013) In vitro anti-*Helicobacter pylori* activity of a flavonoid rich extract of *Glycyrrhiza glabra* and its probable mechanisms of action. J Ethnopharmacol 145:581–586

Asl NM, Hosseinzadeh H (2008) Review of pharmacological effects of *Glycyrrhiza* sp, and its bioactive compounds. Phytother Res 22(6):709–724

Awandkar SP, Mendhe MS, Badukale DM, Kulkarni MB (2012) Antimicrobial action of cold aqueous and cold ethanolic root extracts of *Glycyrrhiza glabra* against bovine mammary pathogens. Anim Sci Rep 6:88–91

Badr AE, Omar N, Badria FA (2011) A laboratory evaluation of the antibacterial and cytotoxic effect of Liquorice when used as root canal medicament. Int Endod J 44:51–58

Baltina LA Jr, Chistoedova ES, Baltina LA, Kondratenko RM, Plyasunova OA (2012) Synthesis and anti-HIV-1 activity of new conjugates of 18β-and 18α-glycyrrhizic acids with aspartic acid esters. Chem Nat Compd 48:262–266

Batanouny KH, Aboutabl E, Shabana M, Soliman F (1999) Wild medicinal plants in Egypt (with contribution of: Aboutabl E, Shabana M, Soliman F). Chapter Two—"Pharmacopoeial Wild Medicinal Plants in Egypt" With support of the Swiss Development Co-operation (SDC). Academy of Scientific Research and Technology, Egypt. The World Conservation Union (IUCN), Switzerland, pp 60–64

Baytop T (1952) Anadolu meyankökü ve meyanbalı üzerinde farmakognostik araştırmalar. Doçentlik Tezi Ist Univ Ecz Fak, Istanbul-Turkiye

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 Pharmacy Pharmacol 32:151

Bhattacharjee S, Bhattacharjee A, Majumder S, Majumdar SB, Majumdar S (2012) Glycyrrhizic acid suppresses Cox-2-mediated anti-inflammatory responses during *Leishmania donovani* infection. J Antimicrob Chemother 67:1905–1914

Bielecka-Dabrowa A, Mikhailidis DP, Jones L, Rysz J, Aronow WS, Banach M (2012) The meaning of hypokalemia in heart failure. Int J Cardiol 158:12–17

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

Bodet C, La VD, Gafner S, Bergeron C, Grenier D (2008) A licorice extract reduces lipopolysaccharide-induced proinflammatory cytokine secretion by macrophages and whole blood. J Periodontol 79:1752–1761

Booth CM, Matukas LM, Tomlinson GA, Rachlis AR, Rose DB, Dwosh HA, Walmsley SL, Mazzulli T, Avendano M, Derkach P et al (2003) Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. JAMA 289:2801–2809

Boucher BA, Cotterchio M, Curca IA, Kreiger N, Harris SA, Kirsh VA, Goodwin PJ (2012) Intake of phytoestrogen foods and supplements among women recently diagnosed with breast cancer in Ontario. Canada Nutr Cancer 64:695–703

Bresch H, Urbanek M, Nusser M (2000) Ochratoxin A in food containing liquorice. Nahrung 44:276–278

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

Burgess JA, van der Ven PF, Martin M, Sherman J, Haley J (2008) Review of over-the-counter treatments for aphthous ulceration and results from use of a dissolving oral patch containing glycyrrhiza complex herbal extract. J Contemp Dent Pract 9:88–98

Cairns-Fuller V, Aldred D, Magan N (2005) Water, temperature and gas composition interactions affect growth and ochratoxin A production by isolates of *Penicillium verrucosum* on wheat grain. J Appl Microbiol 99:1215–1221

Callender VD, St. Surin-Lord S, Davis EC, Maclin M (2011) Postinflammatory hyperpigmentation: etiologic and therapeutic considerations. Am J Clin Dermatol 12:87–99

Carmines EL, Lemus R, Gaworski CL (2005) Toxicologic evaluation of licorice extract as a cigarette ingredient. Food Chem Toxicol 43:1303–1322

Cavallari LH, Limdi NA (2009) Warfarin pharmacogenomics. Curr Opin Mol Ther 11:243–251

Chakravarthi KK, Avadhani R (2013) Beneficial effect of aqueous root extract of *Glycyrrhiza glabra* on learning and memory using different behavioral models: an experimental study. J Nat Sci Biol Med 4:420–425

Chakravarthi KK, Avadhani R (2014) Enhancement of hippocampal CA3 neuronal dendritic arborization by *Glycyrrhiza glabra* root extract treatment in Wistar albino rats. J Nat Sci Biol Med 5:25–29

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

Chandrasekaran CV, Sundarajan K, Gupta A, Srikanth HS, Edwin J, Agarwal A (2011) Evaluation of the genotoxic potential of standardized extract of *Glycyrrhiza glabra* (GutGard). Regul Toxicol Pharmacol 61:373–380

Cheel J, Tůmová L, Areche C, Van Antwerpen P, Nève J, Zouaoui-Boudjeltia K, San Martin A, Vokřál I, Wsól V, Neugebauerová J (2013) Variations in the chemical profile and biological activities of licorice (*Glycyrrhiza glabra* L.), as influenced by harvest times. Acta Physiol Plant 35:1337–1349

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

Chen G, Zhu L, Liu Y, Zhou Q, Chen H, Yang J (2009) Isoliquiritigenin, a flavonoid from licorice, plays a dual role in regulating gastrointestinal motility in vitro and in vivo. Phytotherapy Research 23(4):498–506

Chen AJ, Huang LF, Wang LZ, Tang D, Cai Fb, Gao WW (2011) Occurrence of toxigenic fungi in ochratoxin A contaminated liquorice root. Food Addit Contam A 28(8):1091–1097

Chen AJ, Tang D, Zhou YQ, Sun BD, Li XJ, Wang LZ, Gao WW (2013) Identification of ochratoxin A producing fungi associated with fresh and dry liquorice. PLoS ONE 8:1–13

Chen HJ, Kang SP, Lee IJ, Lin YL (2014a) Glycyrrhetinic acid suppressed NF-kappa B activation in TNF-alpha-induced hepatocytes. J Agric Food Chem 62:618–625

Chen KJ, Chen WY, Chen X, Jia YM, Peng GQ, Chen L (2014b) Increased elimination of paclitaxel by magnesium isoglycyrrhizinate in epithelial ovarian cancer patients treated with paclitaxel plus cisplatin: a pilot clinical study. Eur J Drug Metab Pharmacokinet 39:25–31

Cho YC, Lee SH, Yoon G, Kim HS, Na JY, Choi HJ, Cho CW, Cheon SH, Kang BY (2010) Licochalcone E reduces chronic allergic contact dermatitis and inhibits IL-12p40 production through down-regulation of NF-kappa B. Int Immunopharmacol 10:1119–1126

Choi JH, Choi JN, Lee SY, Lee SJ, Kim K, Kim YK (2010) Inhibitory activity of diacylglycerol acyltransferase by glabrol isolated from the roots of licorice. Arch Pharm Res 33:237–242

Choi JS, Han JY, Ahn HK, Ryu HM, Kim MY, Chung JH, Nava-Ocampo AA, Koren G (2013) Fetal and neonatal outcomes in women reporting ingestion of licorice (*Glycyrrhiza uralensis*) during pregnancy. Planta Med 79:97–101

Choi AY, Choi JH, Hwang KY, Jeong YJ, Choe W, Yoon KS, Ha J, Kim SS, Youn JH, Yeo EJ, Kang I (2014) Licochalcone A induces apoptosis through endoplasmic reticulum stress via a phospholipase C gamma1-, Ca(2+)-, and reactive oxygen species-dependent pathway in HepG2 human hepatocellular carcinoma cells. Apoptosis 19:682–697

Chu X, Jiang L, Wei M, Yang X, Guan M, Xie X, Wei J, Liu D, Wang D (2013) Attenuation of allergic airway inflammation in a murine model of asthma by Licochalcone A. Immunopharmacol Immunotoxicol 35:653–661

Chueh FS, Hsiao YT, Chang SJ, Wu PP, Yang JS, Lin JJ, Chung JG, Lai TY (2012) Glycyrrhizic acid induces apoptosis in WEHI-3 mouse leukemia cells through the caspase- and mitochondria-dependent pathways. Oncol Rep 28:2069–2076

Cinatl 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

Cirillo G, Curcio M, Parisi OI, Puoci F, Iemma F, Spizzirri UG, Restuccia D, Picci N (2011) Molecularly imprinted polymers for the selective extraction of glycyrrhizic acid from liquorice roots. Food Chem 125:1058–1063

Commission Regulation (EU). No. 105/2010 of 5 February 2010 amending Regulation (EC) No. 1881/2006 setting maximum levels for certain contaminants in foodstuffs as regards ochratoxin A. Off J Eur Union 6 February 2010

Crance JM, Biziagos E, Passagot J, van Cuyck-Gandre H, Deloince R (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 flavi viruses. Antiviral Res 58:73–79

Cui YM, Ao MZ, Li W, Yu LJ (2008) Effect of glabridin from *Glycyrrhiza glabra* on learning and memory in mice. Planta Med 74:377–380

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

Dai XH, Li HE, Lu CJ, Wang JF, Dong J, Wei JY, Zhang Y, Wang X, Tan W, Deng XM, Zhao SH, Zhang MJ (2013) Liquiritigenin prevents *Staphylococcus aureus*-mediated lung cell injury via inhibiting the production of alpha-hemolysin. J Asian Nat Prod Res 15:390–399

Das SK, Das V, Gulati AK, Singh VP (1989) Deglycyrrhizinated liquorice in aphthous ulcers. J Assoc Phys India 37:647

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

De Klerk GJ, Nieuwenhuis MG, Beutle JJ (1997) Hypokalaemia and hypertension associated with use of liquorice flavoured chewing gum. Br Med J 314:731–732

De Smet PAGM, Keller K, Hansel R, Chandler RF (1997) Adverse effects of herbal drugs, vol 2–3. Springer-Verlag, 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 Neuro-Psychopharmacol 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

Dubey NK, Kumar A, Singh P, Shukla R (2008) Microbial contamination of raw materials: a major reason for the decline of India's share in the global herbal market. Curr Sci 95:717–718

Fatima A, Gupta VK, Luqman S, Negi AS, Kumar JK, Shanker K, Saikia D, Srivastava S, Darokar MP, Khanuja SP (2009) Antifungal activity of *Glycyrrhiza glabra* extracts and its active constituent glabridin. Phytother Res 23:1190–1193

Feng L, Zhu MM, Zhang MH, Wang RS, Tan XB, Song J, Ding SM, Jia XB, Hu SY (2013) Protection of glycyrrhizic acid against AGEs-induced endothelial dysfunction through inhibiting RAGE/NF-kappaB pathway activation in human umbilical vein endothelial cells. J Ethnopharmacol 148:27–36

Fiore C, Eisenhut M, Krausse R, Ragazzi E, Pellati D, Armanini D, Bielenberg J (2008) Antiviral effects of *Glycyrrhiza* species. Phytother Res 22:141–148

Fontes LB, Dos Santos Dias D, de Carvalho LS, Mesquita HL, da Silva Reis L, Dias AT, Da Silva Filho A, do Amaral Correa J (2014) Immunomodulatory effects of licochalcone A on experimental autoimmune encephalomyelitis. J Pharm Pharmacol 66:886–894

Franceschelli S, Pesce M, Vinciguerra I, Ferrone A, Riccioni G, Antonia P et al (2011) Licocalchone-C extracted from *Glycyrrhiza glabra* inhibits lipopolysaccharide-interferon-γ inflammation by improving antioxidant conditions and regulating inducible nitric oxide synthase expression. Molecules 16(7):5720–5734

Fu Y, Chen J, Li YJ, Zheng YF, Li P (2013) Antioxidant and anti-inflammatory activities of six flavonoids separated from licorice. Food Chem 141:1063–1071

Fu Y, Zhou E, Wei Z, Liang D, Wang W, Wang T, Guo M, Zhang N, Yang Z (2014) Glycyrrhizin inhibits the inflammatory response in mouse mammary epithelial cells and a mouse mastitis model. FEBS J 281:2543–2557

Fuhr L, Rousseau M, Plauth A, Schroeder FC, Sauer S (2015) Amorfrutins are natural PPARγ agonists with potent antiinflammatory properties. J Nat Prod 78:1160–1164

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 44:799–804

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

Furusawa J, Funakoshi-Tago M, Mashino T, Tago K, Inoue H, Sonoda Y, Kasahara T (2009) *Glycyrrhiza inflata*-derived chalcones, Licochalcone A, Licochalcone B and Licochalcone D, inhibit phosphorylation of NF-kappaB p65 in LPS signaling pathway. Int Immunopharmacol 9:499–507

Gafner S, Bergeron C, Villinski JR, Godejohann M, Kessler P, Cardellina JH, Ferreira D, Feghali K, Grenier D (2011) Isoflavonoids and coumarins from *Glycyrrhiza uralensis*: antibacterial activity against oral pathogens and conversion of isoflavans into isoflavan-quinones during purification. J Nat Prod 74:2514–2519

Gagnon B, Robitaille R, Simard RR (1999) Characterization of several on-farm and industrial composted materials. Can J Soil Sci 79(1):201–210

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

Gaur R, Yadav KS, Verma RK, Yadav NP, Bhakuni RS (2014) In vivo anti-diabetic activity of derivatives of isoliquiritigenin and liquiritigenin. Phytomedicine 21:415–422

Gaur R, Gupta VK, Singh P, Pal A, Darokar MP, Bhakuni RS (2016) Drug resistance reversal potential of isoliquiritigenin and liquiritigenin isolated from *Glycyrrhiza glabra* against methicillin-resistant *Staphylococcus aureus* (MRSA). Phytother Res 30:1708–1715

Ghahraman A (1999) Basic botany: anatomy and morphology, vol 1. University of Tehran Press, pp 539

Guengerich FP (2008) Cytochrome p450 and chemical toxicology. Chem Res Toxicol 21:70–83

Güneş G (2004) Osmanlı Devleti'nde meyan kökü tarımı ve ticareti (1840–1922). Kebikeç 18:343–361

Guo XL, Liang B, Wang XW, Fan FG, Jin J, Lan R, Yang JH, Wang XC, Jin L, Cao Q (2013) Glycyrrhizic acid attenuates CCl(4)-induced hepatocyte apoptosis in rats via a p53-mediated pathway. World J Gastroenterol 19:3781–3791

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 Ethnopharm 116:377–380

Hadar Y, Mandelbaum R (1986) Suppression of *Pythium aphanidermatum* damping off in container media containing composted liquorice roots. Crop Protection 5:88–92

Hajirahimkhan A, Simmler C, Yuan Y, Anderson JR, Chen SN, Nikolic D, Dietz BM, Pauli GF, van Breemen RB, Bolton JL (2013) Evaluation of estrogenic activity of licorice species in comparison with hops used in botanicals for menopausal symptoms. PLoS ONE 8:e67947

Hajirahimkhan A, Simmler C, Dong H, Lantvit DD, Li G, Chen SN, Nikolic D, Pauli GF, van Bremen RB, Dietz BM, Bolton JL (2015) Induction of NAD(P)H: quinone oxidoreductase 1 (NQO1) by *Glycyrrhiza* species used for women's health: differential effects of the Michael acceptors isoliquiritigenin and licochalcone A. Chem Res Toxicol 28(11):2130–2141

Haraguchi H, Yoshida N, Ishikawa H, Tamura Y, Mizutani K, Kinoshita T (2000) Protection of mitochondrial functions against oxidative stresses by isoflavans from *Glycyrrhiza glabra*. J Pharm Pharmacol 52:219–223

Harahap IS, Sasaki N, Gunadi Yusoff S, Lee MJ, Morikawa S, Nishimura N, Sasaki T, Usuki S, Hirai M, Ohta M, Takaoka Y, Nishimoto T, Nishio H (2011) Herbal medicine containing licorice may be contraindicated for a patient with an HSD11B2 mutation. Evid Based Complement Altern Med 2011:646540

Hardy ME, Hendricks JM, Paulson JM, Faunce NR (2012a) 18 beta-glycyrrhetinic acid inhibits rotavirus replication in culture. Virol J 9:96

Hardy RS, Raza K, Cooper MS (2012b) Endogenous glucocorticoids in inflammation: contributions of systemic and local responses. Swiss Med Wkly 142:w13650

Hasan S, Khan R, Ali N, Khan A, Rehman M, Tahir M, Lateef A, Nafees S, Mehdi S, Rashid S, Shahid A, Sultana S (2014) 18-beta Glycyrrhetinic acid alleviates 2-acetylaminofluorene-induced hepatotoxicity in Wistar rats: role in hyperproliferation, inflammation and oxidative stress. Hum Exp Toxicol. https://doi.org/10.1177/0960327114554045

Hasanein P (2011) Glabridin as a major active isoflavan from *Glycyrrhiza glabra* (licorice) reverses learning and memory deficits in diabetic rats. Acta Physiol Hung 98:221–230

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

Hayashi H, Sudo H (2009) Economic importance of licorice. Plant Biotechnol 26:101–104

He J, Chen L, Heber D, Shi W, Lu Q-Y (2006) Antibacterial compounds from *Glycyrrhiza uralensis*. J Nat Prod 69:121–124

He Y, Zeng F, Liu Q, Ju W, Fu H, Hao H, Li L, Xie Y (2010) Protective effect of magnesium isoglycyrrhizinate on ethanol-induced testicular injuries in mice. J Biomed Res 24:153–160

Hendricks JM, Hoffman C, Pascual DW, Hardy ME (2012) 18 beta-glycyrrhetinic acid delivered orally induces isolated lymphoid follicle maturation at the intestinal mucosa and attenuates rotavirus shedding. PLoS ONE 7:e49491

Herrera M, Herrera A, Ariño A (2009) Estimation of dietary intake of ochratoxin A from liquorice confectionery. Food Chem Toxicol 47:2002–2006

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

Hojo H, Sato J (2002) Antifungal activity of licorice (*Glycyrrhiza glabra*) and potential applications in beverage. Foods Food Ingredients J Jpn 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

Hong YK, Wu HT, Ma T, Liu WJ, He XJ (2009) Effects of *Glycyrrhiza glabra* polysaccharides on immune and antioxidant activities in high-fat mice. Int J Biol Macromol 45:61–64

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

Houseman PA (1944) In licorice-putting a weed to work, pp 3. 10–15, The Royal Institute of Chemistry of Great Britain and Ireland, London

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

Hsu YL, Wu LY, Hou MF, Tsai EM, Lee JN, Liang HL, Jong YJ, Hung CH, Kuo PL (2011) Glabridin, an isoflavan from licorice root, inhibits migration, invasion and angiogenesis of MDA-MB-231 human breast adenocarcinoma cells by inhibiting focal adhesion kinase/Rho signaling pathway. Mol Nutr Food Res 55:318–327

Hu CH, He J, Eckert R, Wu XY, Li LN, Tian Y, Lux R, Shuffer JA, Gelman F, Mentes J, Spackman S, Bauer J, Anderson MH, Shi WY (2011) Development and evaluation of a safe and effective sugar-free herbal lollipop that kills cavity-causing bacteria. Int J Oral Sci 3:13–20

Huang W, Chen X, Li Q, Li P, Zhao G, Xu M, Xie P (2012) Inhibition of intercellular adhesion in herpex simplex virus infection by glycyrrhizin. Cell Biochem Biophys 62:137–140

Huang W, Tang S, Qiao X, Ma W, Ji S, Wang K, Ye M, Yu S (2014a) Isoangustone A induces apoptosis in SW480 human colorectal adenocarcinoma cells by disrupting mitochondrial functions. Fitoterapia 94:36–47

Huang X, Qin J, Lu S (2014b) Magnesium isoglycyrrhizinate protects hepatic L02 cells from ischemia/reperfusion induced injury. Int J Clin Exp Pathol 7:4755–4764

Huo HZ, Wang B, Liang YK, Bao YY, Gu Y (2011) Hepatoprotective and antioxidant effects of licorice extract against CCl(4)-induced oxidative damage in rats. Int J Mol Sci 12:6529–6543

İlisulu K (1974) Meyankökü çeşitleri, özellikleri, adaptasyonu ve ziraatte faydalabilme olanakları hakkında araştırmalar. AU Zir. Fak. Yıllığı, 96

İlisulu K, Kolsarıcı O (1986) Natural growing areas of the liquorice (*Glycyrrhiza glabra* L.) and the possibilities its cultivation. İlaç Hammaddeleri Toplantısı (16–18 Mayıs 1986). Gazi Üniversitesi Yayınları No: 113, pp 171–182

Imai K, Takagi Y, Iwazaki A, Nakanishi K (2013) Radical scavenging ability of glycyrrhizin. Free Radic Antioxid 3:40–42

Irani M, Sarmadi M, Bernard F, Ebrahim GH, Bazarnov HS (2010) Leaves antimicrobial activity of *Glycyrrhiza glabra* L. Iran J Pharm Res 9(4):425–428

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(3):167–192

Ishida T, Miki I, Tanahashi T, Yagi S, Kondo Y, Inoue J, Kawauchi S, Nishiumi S, Yoshida M, Maeda H, Tode C, Takeuchi A, Nakayama H, Azuma T, Mizuno S (2013) Effect of 18beta-glycyrrhetinic acid and hydroxypropyl gammacyclodextrin complex on indomethacin-induced small intestinal injury in mice. Eur J Pharmacol 714:125–131

Jain E, Pandey RK, Khanna R (2013) Liquorice root extracts as potent cariostatic agents in pediatric practice. J Indian Soc Pedod Prev Dent 31:146–152

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

Jhanji V, Liu H, Law K, Lee VY, Huang SF, Pang CP, Yam GH (2011) Isoliquiritigenin from licorice root suppressed neovascularisation in experimental ocular angiogenesis models. Br J Ophthalmol 95:1309–1315

Jiang J, Yuan X, Zhao H, Yan X, Sun X, Zheng Q (2014) Licochalcone A inhibiting proliferation of bladder cancer T24 cells by inducing reactive oxygen species production. Biomed Mater Eng 24:1019–1025

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

Jung W, Kwon S, Im J, Park S, Moon S, Park J, Ko C, Cho K (2014) Influence of herbal complexes containing licorice on potassium levels: a retrospective study. Evid Based Complement Altern Med 2014:970385

Kabelitz L, Sievers H (2004) Contaminants of medicinal and food herbs with a view to EU regulations. Innov Food Technol 2004:25–27

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

Kamalak A (2006) Determination of nutritive value of leaves of a native grown shrub, *Glycyrrhiza glabra* L. using in vitro and in situ measurements. Small Ruminant Res 64:268–278

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 43:580–586

Kang H, Lieberman PM (2011) Mechanism of glycyrrhizic acid inhibition of Kaposi's sarcoma-associated herpesvirus: disruption of CTCF-cohesin mediated RNA polymerase II pausing and sister chromatid cohesion. J Virol 85:11159–11169

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 312:1187–1194

Kao T-C, Wu C-H, Yen G-C (2014) Bioactivity and potential health benefits of licorice. J Agric Food Chem 62:542–553

Kapetanakou AE, Panagou EZ, Gialitaki M, Drosinos EH, Skandamis PN (2009) Evaluating the combined effect of water activity, pH and temperature on ochratoxin A production by *Aspergillus ochraceus* and *Aspergillus carbonarius* on culture medium and Corinth raisins. Food Control 20:725–732

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. https://doi.org/10.1080/13102818.2016.1179590

Kataya HH, Hamza AA, Ramadan GA, Khasawneh MA (2011) Effect of licorice extract on the complications of diabetes nephropathy in rats. Drug Chem Toxicol 34:101–108

Kent UM, Aviram M, Rosenblat M, Hollenberg PF (2002) The licorice root derived isoflavan glabridin inhibits the activities of human cytochrome P450S 3A4, 2B6, and 2C9. Drug Metab Dispos 30:709–715

Khalesi M (2015) Ochratoxin A in liquorice products—a review. Food Additives & Contaminants: Part A. https://doi.org/10.1080/19440049.2015.1094708

Khalesi M, Khatib N (2011) The effects of different ecophysiological factors on ochratoxin A production. Environ Toxicol Phar 32:113–121

Khalesi M, Sheikh-Zeinoddin M, Tabrizchi M (2011) Determination of ochratoxin A in licorice root using inverse ion mobility spectrometry. Talanta 83:988–993

Khalesi M, Tabrizchi M, Sheikh-Zeinoddin M (2013) The effects of temperature and relative humidity on ochratoxin A formation in fresh liquorice root. Food Addit Contam A 30:339–344

Khan R, Khan AQ, Lateef A, Rehman MU, Tahir M, Ali F, Hamiza OO, Sultana S (2013) Glycyrrhizic acid suppresses the development of precancerous lesions via regulating the hyperproliferation, inflammation, angiogenesis and apoptosis in the colon of Wistar rats. PLoS ONE 8:e56020

Kim YJ, Uyama H (2005) Tyrosinase inhibitors from natural and synthetic sources: structure, inhibition mechanism and perspective for the future. Cell Mol Life Sci 62:1707–1723

Kim KR, Jeong CK, Park KK, Choi JH, Park JH, Lim SS, Chung WY (2010) Anti-inflammatory effects of licorice and roasted licorice extracts on TPA-induced acute inflammation and collagen induced arthritis in mice. J Biomed Biotechnol (709378)

Kim HJ, Lim SS, Park IS, Lim JS, Seo JY, Kim JS (2012) Neuroprotective effects of dehydroglyasperin C through activation of heme oxygenase-1 in mouse hippocampal cells. J Agric Food Chem 60:5583–5589

Kim J, Joo I, Kim H, Han Y (2013a) 18beta-glycyrrhetinic acid induces immunological adjuvant activity of Th1 against *Candida albicans* surface mannan extract. Phytomedicine 20:951–955

Kim J, Kim J, Shim J, Lee S, Kim J, Lim SS, Lee KW, Lee HJ (2013b) Licorice-derived dehydroglyasperin C increases MKP-1 expression and suppresses inflammation-mediated neurodegeneration. Neurochem Int 63:732–740

Kim ME, Kim HK, Kim DH, Yoon JH, Lee JS (2013c) 18beta-Glycyrrhetinic acid from licorice root impairs dendritic cells maturation and Th1 immune responses. Immunopharmacol Immunotoxicol 35:329–335

Kim KJ, Choi JS, Kim KW, Jeong JW (2013d) The anti-angiogenic activities of glycyrrhizic acid in tumor progression. Phytother Res 27:841–846

Kim JS, Park MR, Lee SY, Kim DK, Moon SM, Kim CS, Cho SS, Yoon G, Im HJ, You JS, Oh JS, Kim SG (2014) Licochalcone A induces apoptosis in KB human oral cancer cells via a caspase-dependent FasL signaling pathway. Oncol Rep 31:755–762

Kırmızıbekmez H, Uysal GB, Masullo M, Demirci F, Bağcı Y, Kan Y, Piacente S (2015) Prenylated polyphenolic compounds from *Glycyrrhiza iconica* and their antimicrobial and antioxidant activities. Fitoterapia 103:289–293

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

Kratschmar DV, Vuorinen A, Da Cunha T, Wolber G, Classen-Houben D, Doblhoff O, Schuster D, Odermatt A (2011) Characterization of activity and binding mode of glycyrrhetinic acid derivatives inhibiting 11beta-hydroxysteroid dehydrogenase type 2. J Steroid Biochem Mol Biol 125:129–142

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

Kuramoto T, Ito Y, Oda M, Tamura Y, Kitahara S (1994) Microbial production of glycyrrhetic acid 3-*O*-mono-β-D-glucuronide from glycyrrhizin by *Cryptococcus magnus* MG-27. Biosci Biotechnol Biochem 58:455–458

Kwon HS, Oh SM, Kim JK (2008) Glabridin, a functional compound of liquorice, attenuates colonic inflammation in mice with dextran sulphate sodium-induced colitis. Clin Exp Immunol 151:165–173

Kwon HJ, Kim HH, Ryu YB, Kim JH, Jeong HJ, Lee SW, Chang JS, Cho KO, Rho MC, Park SJ, Lee WS (2010) In vitro anti-rotavirus activity of polyphenol compounds isolated from the roots of *Glycyrrhiza uralensis*. Bioorg Med Chem 18:7668–7674

Kwon SJ, Park SY, Kwon GT, Lee KW, Kang YH, Choi MS, Yun JW, Jeon JH, Jun JG, Park JH (2013) Licochalcone E present in licorice suppresses lung metastasis in the 4T1 mammary orthotopic cancermodel. Cancer Prev. Res. (Phila) 6:603–613

La VD, Tanabe S, Bergeron C, Gafner S, Grenier D (2011) Modulation of matrix metalloproteinase and cytokine production by licorice isolates licoricidin and licorisoflavan A: potential therapeutic approach for periodontitis. J Periodontol 82:122–128

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

Lau D, Plotkin BJ (2013) Antimicrobial and biofilm effects of herbs used in traditional Chinese medicine. Nat Prod Commun 8:1617–1620

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

Lee HY, Jung DY, Ha H, Kang SS, Kim JS, Kim C (2007) Induction of growth hormone release by Glycyrrhizae Radix on rat. J Biochem Mol Biol 40:979–985

Lee JY, Lee JH, Park JH, Kim SY, Choi JY, Lee SH, Kim YS, Kang SS, Jang EC, Han Y (2009) Liquiritigenin, a licorice flavonoid, helpsmice resist disseminated candidiasis due to *Candida albicans* by Th1 immune response, whereas liquiritin, its glycoside form, does not. Int Immunopharmacol 9:632–638

Lee YS, Kim SH, Kim JK, Shin HK, Kang YH, Park JH, Lim SS (2010) Rapid identification and preparative isolation of antioxidant components in licorice. J Sep Sci 33:664–671

Lee HN, Cho HJ, Lim DY, Kang YH, Lee KW, Park JH (2013a) Mechanisms by which licochalcone e exhibits potent anti-inflammatory properties: studies with phorbol ester-treated mouse skin and lipopolysaccharide- stimulated murine macrophages. Int J Mol Sci 14:10926–10943

Lee E, Son JE, Byun S, Lee SJ, Kim YA, Liu K, Kim J, Lim SS, Park JH, Dong Z, Lee KW, Lee HJ (2013b) CDK2 and mTOR are direct molecular targets of isoangustone A in the suppression of human prostate cancer cell growth. Toxicol Appl Pharmacol 272:12–20

Lee SK, Park KK, Park JH, Lim SS, Chung WY (2013c) The inhibitory effect of roasted licorice extract on human metastatic breast cancer cell-induced bone destruction. Phytother. Res. 27:1776–1783

Li J, Tu Y, Tong L, Zhang W, Zheng J, Wei Q (2010a) Immunosuppressive activity on the murine immune responses of glycyrol from *Glycyrrhiza uralensis* via inhibition of calcineurin activity. Pharm Biol 48:1177–1184

Li J, Lee YS, Choi JS, Sung HY, Kim JK, Lim SS, Kang YH (2010b) Roasted licorice extracts dampen high glucose-induced mesangial hyperplasia and matrix deposition through blocking Akt activation and TGF-beta signaling. Phytomedicine 17:800–810

Li X, He X, Liu B, Xu L, Lu C, Zhao H, Niu X, Chen S, Lu A (2012) Maturation of murine bone marrow-derived dendritic cells induced by Radix Glycyrrhizae polysaccharide. Molecules 17:6557–6568

Li W, Li S, Higai K, Sasaki T, Asada Y, Ohshima S, Koike K (2013) Evaluation of licorice flavonoids as protein tyrosine phosphatase 1B inhibitors. Bioorg Med Chem Lett 23:5836–5839

Li JY, Cao HY, Liu P, Cheng GH, Sun MY (2014) Glycyrrhizic acid in the treatment of liver diseases: literature review. Biomed Res Int 2014:872139

Lin D, Zhong W, Li J, Zhang B, Song G, Hu T (2014) Involvement of BID translocation in glycyrrhetinic acid and 11-deoxy glycyrrhetinic acid-induced attenuation of gastric cancer growth. Nutr Cancer 66:463–473

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

Liu HM, Sugimoto N, Akiyama T, Maitani T (2000) Constituents and their sweetness of food additive enzymatically modified licorice extract. J Agric Food Chem 48:6044–6047

Long DR, Mead J, Hendricks JM, Hardy ME, Voyich JM (2013) 18beta-Glycyrrhetinic acid inhibits methicillin-resistant *Staphylococcus aureus* survival and attenuates virulence gene expression. Antimicrob Agents Chemother 57:241–247

Lou XF, Nair J (2009) The impact of landfilling and composting on greenhouse gas emissions—A review. Bioresource Technol. 100:3792–3798

Lucas (1976) Nature's medicines. Melvin Powers/Wilshire Book Company, North Hollywood, CA, pp 89–94

Luo L, Jin Y, Kim ID, Lee JK (2013) Glycyrrhizin attenuates kainic Acid-induced neuronal cell death in the mouse hippocampus. Exp. Neurobiol. 22:107–115

Ma X, Lian QQ, Dong Q, Ge RS (2011) Environmental inhibitors of 11beta-hydroxysteroid dehydrogenase type 2. Toxicology 285:83–89

Ma C, Ma Z, Liao XL, Liu J, Fu Q, Ma S (2013) Immunoregulatory effects of glycyrrhizic acid exerts anti-asthmatic effects via modulation of Th1/Th2 cytokines and enhancement of CD4(+)CD25(+) Foxp3+ regulatory T cells in ovalbumin-sensitized mice. J Ethnopharmacol 148:755–762

Majerus P, Max M, Klaffke H, Palavinskas R (2000) Ochratoxin A in Sübholz, Lakritze und daraus hergestellten Erzeugnissen. Deustche Lebensmittel-Rundschau. 96:451–454

Mamedov NA, Egamberdieva D (2017) Phytochemical constituents and pharmacological effects of liquorice: a review. In: Oztürk et al (eds) Herbals and human health-phytochemistry. Springer Nature Publishers, 41 pp

Martinez A, Ikken Y, Cambero MI, Marin ML, Haza AI, Casas C, Morales P (1999) Mutagenicity and cytotoxicity of fruits and vegetables evaluated by the Ames test and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Food Sci Technol Int 5:431–437

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 OT, 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

Matsumoto Y, Matsuura T, Aoyagi H, Matsuda M, Hmwe SS, Date T, Watanabe N, Watashi K, Suzuki R, Ichinose S, Wake K, Suzuki T, Miyamura T, Wakita T, Aizaki H (2013) Antiviral activity of glycyrrhizin against hepatitis C virus in vitro. PLoS ONE 8:e68992

McGuffin M, Hobbs C, Upton R, Goldberg A (1997) Botanical Safety Handbook. CRC Press, Boca Raton, FL

Medina S, Krassnovsky A, Yogev A, Raviv M (2011) Horticultural characteristics of licorice waste compost. Compost Science & Utilization 19(3):163–169

Meghashri SG (2009) In vitro antifungal and antibacterial activities of root extract of *Glycyrrhiza glabra*. J. Appl. Sci. Res. 5:1436–1439

Menati L, Khaleghinezhad K, Tadayon M, Siahpoosh A (2014) Evaluation of contextual and demographic factors on licorice effects on reducing hot flashes in postmenopause women. Health Care Women Int 35:87–99

Messier C, Grenier D (2011) Effect of licorice compounds licochalcone A, glabridin and glycyrrhizic acid on growth and virulence properties of *Candida albicans*. Mycoses 54:e801–e806

Methlie P, Husebye EE, Hustad S, Lien EA, Lovas K (2011) Grapefruit juice and licorice increase cortisol availability in patients with Addison's disease. Eur J Endocrinol 165:761–769

Michaelis M, Geiler J, Naczk P, Sithisarn P, Ogbomo H, Altenbrandt B, Leutz A, Doerr HW, Cinatl J Jr (2010) Glycyrrhizin inhibits highly pathogenic H5N1 influenza A virus-induced pro-inflammatory cytokine and chemokine expression in human macrophages. Med Microbiol Immunol 199:291–297

Michel HE, Tadros MG, Abdel-Naim AB, Khalifa AE (2013) Prepulse inhibition (PPI) disrupting effects of *Glycyrrhiza glabra* extract in mice: a possible role of monoamines. Neurosci Lett 544:110–114

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

Mitscher LA, Drake S, Gollapudi SR, Harris JA, Shankel DM (1986) Isolation and identification of higher plant agents active in antimutagenic assay systems: *Glycyrrhiza glabra*. Basic Life Sci 39:153–165

Mizutani K, Kuramoto T, Tamura Y, Ohtake N, Doi S, Nakaura M, Tanaka O (1994) Sweetness of glycyrrhetinic acid 3-*O*-mono-β-D-glucuronide and related glycosides. Biosci Biotechnol Biochem 58:554–555

Mohseni R, Noorbakhsh F, Moazeni M, Nasrollahi Omran A, Rezaie S (2014) Antitoxin characteristic of licorice extract: the ınhibitory effect on aflatoxin production in *Aspergillus parasiticus*. J Food Saf 34(2):119–125

Moisy D, Avilov SV, Jacob Y, Laoide BM, Ge X, Baudin F, Naffakh N, Jestin JL (2012) HMGB1 protein binds to influenza virus nucleoprotein and promotes viral replication. J Virol 86:9122–9133

Mu Y, Zhang J, Zhang S, Zhou HH, Toma D, Ren S, Huang L, Yaramus M, Baum A, Venkataramanan R, Xie W (2006) Traditional Chinese medicines Wu Wei Zi (*Schisandra chinensis* Baill) and Gan Cao (*Glycyrrhiza uralensis* Fisch) activate pregnane X receptor and increase warfarin clearance in rats. J Pharmacol Exp Ther 316:1369–1377

Muralidharan P, Balamurugan G, Babu V (2009) Cerebroprotective effect of *Glycyrrhiza glabra* Linn. root extract on hypoxic rats. Bangladesh J. Pharmacol. 4:60–64

Nagai H, He JX, Tani T, Akao T (2007) Antispasmodic activity of licochalcone A, a species-specific ingredient of Glycyrrhiza inflata roots. J Pharm Pharmacol 59(10):1421–1426

Nakagawa K, Hidaka T, Kitano M, Asakura M, Kamigaito T, Noguchi T, Hosoe K (2008) Genotoxicity studies on licorice flavonoid oil (LFO). Food Chem Toxicol 46:2525–2532

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

Ni YF, Kuai JK, Lu ZF, Yang GD, Fu HY, Wang J, Tian F, Yan XL, Zhao YC, Wang YJ, Jiang T (2011) Glycyrrhizin treatment is associated with attenuation of lipopolysaccharide-induced acute lung injury by inhibiting cyclooxygenase-2 and inducible nitric oxide synthase expression. J Surg Res 165:e29–e35

Nieman C (1957) Licorice. Advances in Food Research 7:339–381

Nirmala P, Selvaraj T (2011) Anti-inflammatory and anti-bacterial activities of *Glycyrrhiza glabra* L. Int. J. Agric. Technol. 7:815–823

Nitalikar MM, Munde KC, Dhore BV, Shikalgar SN (2010) Studies of antibacterial activities of *Glycyrrhiza glabra* root extract. International J. PharmTech Research 2(1):899–901

Nomura T, Fukai T (1998) Phenolic constituents of licorice (*Glycyrrhiza* species). In: Herz W et al. (eds) Progress in the chemistry of organic natural products 73, Springer Wien-New York, 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 74:1199–1206

Olukoga A, Donaldson D (2000) Liquorice and its health implications. J. Roy. 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 WC, Zondervan PE, Lagging M, Westin J, Schalm SW (2006) Biochemical and histological effects of 26 weeks of glycyrrhizin treatment in chronic hepatitis C: a randomized phase II trial. J Hepatol 45:539–546

Ovez B, Ozgen S, Yuksel M (2006) Biological denitrification in drinking water using *Glycyrrhiza glabra* and *Arunda donax* as the carbon source. Process Biochem 41:1539–1544

Özgün C (2014) Bereketli topraklarda üretmek ve paylaşmak - "İzmir ve çevresinde ticari tarım (1844–1914). İzmir Büyükşehir Belediyesi Kent Kitaplığı, İzmir-Türkiye

Ozhan M, Gol K (1975) Meyan otunun (*Glycyrrhiza* sp.) kabayem olarak kullanılma olanakları. Ataturk Universitesi Ziraat Fakultesi Ziraat Dergisi 1:1–12

Oztanir MN, Ciftci O, Cetin A, Durak MA, Basak N, Akyuva Y (2014) The beneficial effects of 18beta-glycyrrhetinic acid following oxidative and neuronal damage in brain tissue caused by global cerebral ischemia/reperfusion in a C57BL/J6 mouse model. Neurol Sci 35:1221–1228

Pandian N, Chidambaram S (2017) Antimicrobial, cytotoxicty and anti cancer activity of silver nanoparticles from *Glycyrrhiza glabra*. Int J Pharm Sci Res 8(4):1633–1641

Park I, Kim J, Lee Y, Shin S (2008) In vivo fungicidal activity of medicinal plant extracts against six phytopathogenic fungi. Int J Pest Manage 54:63–68

Park D, Yang YH, Choi EK, Yang G, Bae DK, Lee SH, Kim TK, Kyung J, Kim D, Choi KC, Kim YB (2011) Licorice extract increases cyclophosphamide teratogenicity by upregulating the expression of cytochrome P-450 2B mRNA. Birth Defects Res B Dev Reprod Toxicol 92:553–559

Park HG, Bak EJ, Woo GH, Kim JM, Quan Z, Kim JM, Yoon HK, Cheon SH, Yoon G, Yoo YJ, Na Y, Cha JH (2012) Licochalcone E has an antidiabetic effect. J Nutr Biochem 23:759–767

Park SM, Lee JR, Ku SK, Cho IJ, Byun SH, Kim SC, Park SJ, Kim YW (2016) Isoliquiritigenin in licorice functions as a hepatic protectant by induction of antioxidant genes through extracellular signal-regulated kinase-mediated NF-E2-related factor-2 signaling pathway. Eur J Nutr 55(8):2431–2444

Parker PM (2007) The World market for licorice roots. ICON Group Ltd., USA

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

Peters MC, Tallman JA, Braun TM, Jacobson JJ (2010) Clinical reduction of *S. mutans* in pre-school children using a novel liquorice root extract lollipop: a pilot study. Eur Arch Paediatr Dent 11:274–278

Pietri A, Rastelli S, Bertuzzi T (2010) Ochratoxin A and aflatoxins in liquorice products. Toxins 2:758–770

Plyasunova OA, Egoricheva IN, Fedyuk NV, Pokrovsky AG, Baltina LA, Murinov YI, Tolstikov GA (1992) Vopr Virusol 37:235–238

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

Raikkonen K, Seckl JR, Heinonen K, Pyhala R, Feldt K, Jones A, Pesonen AK, Phillips DI, Lahti J, Jarvenpaa AL, Eriksson JG, Matthews KA, Strandberg TE, Kajantie E (2010) Maternal prenatal licorice consumption alters hypothalamic-pituitary-adrenocortical axis function in children. Psychoneuroendocrinology 35:1587–1593

Rao KVS (1993) A review on licorice. Anc Sci Life XIII(1–2):57–88

Rasool M, Iqbal J, Malik A, Ramzan HS, Qureshi MS, Asif M, Qazi MH, Kamal MA, Chaudhary AG, Al-Qahtani MH, Gan SH, Karim S (2014) Hepatoprotective effects of *Silybum marianum* (Silymarin) and *Glycyrrhiza glabra* (Glycyrrhizin) in combination: a possible synergy. Evid Based Complement Altern Med 2014:641597

Rathi SG, Suthar M, Patel P, Bhaskar VH, Rajgor NB (2009) In-vitro cytotoxic screening of *Glycyrrhiza glabra* L. (Fabaceae): a natural anticancer drug. J Young Pharm 1:239–243

Rauchensteiner F, Matsumura Y, Yamamoto Y, Yamaji S, Tani T (2005) Analysis and comparison of Radix Glycyrrhizae (licorice) from Europe and China by capillary-zone electrophoresis (CZE). J Pharmaceut Biomed 38:594–600

Rogers M (ed) (2014) Licorice. In: Herbalpedia. http://www.herbalpedia.com

Roshan A, Verma NK, Kumar CS, Chandra V, Singh DP, Panday MK (2012) Phytochemical constituent, pharmacological activities and medicinal uses through the millenia of *Glycyrrhiza glabra* Linn: a review. Int Res J Pharm 3(8):45–55

Ruiz-Granados ES, Shouls G, Sainsbury C, Antonios T (2012) A salty cause of severe hypertension. BMJ Case Rep 2012

Russo S, Mastropasqua M, Mosetti MA, Persegani C, Paggi A (2000) Low doses of liquorice can induce hypertension encephalopathy. Am J Nephrol 20:145–148

Saeedi M, Morteza-Semnani K, Ghoreishi MR (2003) The treatment of atopic dermatitis with licorice gel. J Dermatol Treat 14:153–157

Saleem MMNM, Mohammad AAW, Al-Tameemi JA, Sulaiman GM (2011) Biological study of the effect of licorice roots extract on serum lipid profile, liver enzymes and kidney function tests in albino mice. Afr J Biotechnol 10:12702–12706

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

Sasaki H, Takei M, Kobayashi M, Pollard RB, Suzuki F (2002) Effect of glycyrrhizin, an active component of licorice roots, on HIV replication in cultures of peripheral blood mononuclear cells from HIV-seropositive patients. Pathobiology 70:229–236

Sasaki H, Suzuki N, Alshwaimi E, Xu Y, Battaglino R, Morse L, Stashenko P (2010) 18beta-glycyrrhetinic acid inhibits periodontitis via glucocorticoidin dependent nuclear factor-kappaB inactivation in interleukin-10-deficient mice. J Periodontal Res 45:757–763

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

Sen S, Roy M, Chakraborti AS (2011) Ameliorative effects of glycyrrhizin on streptozotocin-induced diabetes in rats. J Pharm Pharmacol 63:287–296

Seo JY, Han JH, Kim YJ, Lim SS, Kim J (2014) Protective effects of dehydroglyasperin c against carbon tetrachloride-induced liver damage in mice. Food Sci Biotechnol 23:547–553

Seon MR, Park SY, Kwon SJ, Lim SS, Choi HJ, Park H, Lim DY, Kim JS, Lee CH, Kim J, Park JH (2012) Hexane/ethanol extract of *Glycyrrhiza uralensis* and its active compound isoangustone A induce G1 cycle arrest in DU145 human prostate and 4T1 murine mammary cancer cells. J Nutr Biochem 23:85–92

Sharifzadeh M, Shamsa F, Shiran S, Karimfar MH, Miri AH, Jalalizadeh H, Gholizadeh S, Salar F, Tabrizian K (2008) A time course analysis of systemic administration of aqueous licorice extract on spatial memory retention in rats. Planta Med 74:485–490

Sharma V, Agrawal RC (2013) *Glycyrrhiza glabra*—A plant for the future. Mintage J Pharm Med Sci 2(3):15–20

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

Shebl RI, Amin MA, Emad-Eldin A, Bin DS, Mostafa AS, Ibrahim EH, Mohamed AF (2012) Antiviral activity of liquorice powder extract against varicella zoster virus isolated from Egyptian patients. Chang Gung Med J 35:231–239

Sheehan MP, Atherton DJ (1992) A controlled trial of traditional Chinese medicinal plants in widespread non-exudative atopic eczema. Brit 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

Shen X, Xiao P, Liu C (2007) Research and application of Radix Glycyrrhizae. Asian J Pharmacodyn Pharmacokinet 7:181–200

Sheth VM, Pandya AG (2011) Melasma: a comprehensive update: part II. J Am Acad Dermatol 65:699–714

Shetty TK, Satav JG, Nair CKK (2002) Protection of DNA and microsomal membranes in vitro by *Glycyrrhiza glabra* L. against gamma irradiation. Phytother Res 16:576–578

Shetty AV, Thirugnanam S, Dakshinamoorthy G, Samykutty A, Zheng G, Chen A, Bosland MC, Kajdacsy-Balla A, Gnanasekar M (2011) 18alpha-glycyrrhetinic acid targets prostate cancer cells by down-regulating inflammation-related genes. Int J Oncol 39:635–640

Shi W, Norton JM, Miller BE, Pace MG (1999) Effects of aeration and moisture during windrow composting on the nitrogen fertilizer values of dairy waste composts. Appl Soil Ecol 11(1):17–28

Shi Y, Wu D, Sun Z, Yang J, Chai H, Tang L, Guo Y (2012) Analgesic and uterine relaxant effects of isoliquiritigenin, a flavone from *Glycyrrhiza glabra*. Phytother Res 26:1410–1417

Shibata S (2000) A drug over the millennia: pharmacognosy, chemistry, and pharmacology of licorice. Yakugaku Zasshi 120:849–862 (in Japanese)

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 Biotechn 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 antistress or 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 Tech 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

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

Smirnov VS, Zarubaev VV, Anfimov PM, Shtro AA (2012) Effect of a combination of glutamyl-tryptophan and glycyrrhizic acid on the course of acute infection caused by influenza (H3H2) virus inmice. Vopr Virusol 57:23–27

Snowden R, Harrington H, Morrill K, Jeane L, Garrity J, Orian M, Lopez E, Rezaie S, Hassberger K et al (2014) A comparison of the anti-*Staphylococcus aureus* activity of extracts from commonly used medicinal plants. J Altern Complement Med 20:375–382

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

Song NR, Lee E, Byun S, Kim JE, Mottamal M, Park JH, Lim SS, Bode AM, Lee HJ, Lee KW, Dong Z (2013) Isoangustone A, a novel licorice compound, inhibits cell proliferation by targeting PI3K, MKK4, and MKK7 in human melanoma. Cancer Prev Res (Phila) 6:1293–1303

Song W, Si L, Ji S, Wang H, Fang X-M, Yu L-Y, Li R-Y, Liang L-N, Zhou D, Ye M (2014) Uralsaponins M-Y, antiviral triterpenoid saponins from the roots of *Glycyrrhiza uralensis*. J Nat Prod 77:1632–1643

Soufy H, Yassein S, Ahmed AR, Khodier MH, Kutkat MA, Nasr SM, Okda FA (2012) Antiviral and immune stimulant activities of glycyrrhizin against duck hepatitis virus. Afr J Tradit Complement Altern Med 9(3):389–395

Stanikzai MT (2007) Market report liquorice. Multistakeholder programme natural ingredients Afghanistan. www.tloafghanistan.org/Liquorice%20Market%20Report.pdf

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

Sui X, Yin J, Ren X (2010) Antiviral effect of diammonium glycyrrhizinate and lithium chloride on cell infection by pseudorabies herpesvirus. Antiviral Res 85:346–353

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

Tanifuji S, Aizu-Yokota E, Funakoshi-Tago M, Sonoda Y, Inoue H, Kasahara T (2010) Licochalcones suppress degranulation by decreasing the intracellular Ca^{2+} level and tyrosine phosphorylation of ERK in RBL-2H3 cells. Int Immunopharmacol 10:769–776

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

Thiyagarajan P, Chandrasekaran CV, Deepak HB, Agarwal A (2011) Modulation of lipopolysaccharide-induced pro-inflammatory mediators by an extract of *Glycyrrhiza glabra* and its phytoconstituents. Inflammopharmacology 19:235–241

Timofeyer V (1984) Farm Zh (Kiev) 5:57–60

Treutwein J, Cergel S, Runte J, Nowak A, Konstantinidou-Doltsinis S, Kleeberg H, Schmitt A (2010) Efficacy of *Glycyrrhiza glabra* extract fractions against phytopathogenic fungi. Julius-Kühn-Archiv 428:82

Tripathi M, Singh BK, Kakkar P (2009) Glycyrrhizic acid modulates t-BHP induced apoptosis in primary rat hepatocytes. Food Chem Toxicol 47:339–347

Tsai JP, Hsiao PC, Yang SF, Hsieh SC, Bau DT, Ling CL, Pai CL, Hsieh YH (2014) Licochalcone A suppresses migration and invasion of human hepatocellular carcinoma cells through downregulation of MKK4/JNK via NFkappaB mediated urokinase plasminogen activator expression. PLoS ONE 9:e86537

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

Tyler VE, Bradly LR, Robbers JE (1988) Pharmacognosy, 9th edn. Lea and Febiger, Philadelphia, PA, pp 68–69

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 anti-bacterial and anti-oxidant potential of *Glycyrrhiza glabra* root extracts. J Environ Res Dev 7(4):1552–1558

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

Ved DK, Goraya GS (2007) Demand and supply of medicinal plants in India. National Medicinal Plants Board, New Delhi. Foundation for revitalization of local health traditions, Bangalore; XV

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. Botany Res Int 2(3):157–163

Villinski JR, Bergeron C, Cannistra JC, Gloer JB, Coleman CM, Ferreira D, Azelmat J, Grenier D, Gafner S (2014) Pyrano-isoflavans from *Glycyrrhiza uralensis* with antibacterial activity against *Streptococcus mutans* and *Porphyromonas gingivalis*. J Nat Prod 77:521–526

Vivekanand JHA (2010) Herbal medicines and chronic kidney disease. Nephrology 15(2):10–17

Wananukul S, Chatproedprai S, Chunharas A, Limpongsanuruk W, Singalavanija S, Nitiyarom R, Wisuthsarewong W (2013) Randomized, double-blind, split-side, comparison study of moisturizer containing licochalcone A and 1% hydrocortisone in the treatment of childhood atopic dermatitis. J Med Assoc Thai 96:1135–1142

Wang ZY, Nixon DW (2001) Licorice and cancer. Nutr Cancer 39:1–11

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. Progress in Neuro-Psychopharm Biol Psych 32:1179–1184

Wang CY, Kao TC, Lo WH, Yen GC (2011) Glycyrrhizic acid and 18beta-glycyrrhetinic acid modulate lipopolysaccharide-induced inflammatory response by suppression of NF-kappaB through PI3K p110 delta and p110 gamma inhibitions. J Agric Food Chem 59:7726–7733

Wang YG, Zhou JM, Ma ZC, Li H, Liang QD, Tan HL, Xiao CR, Zhang BL, Gao Y (2012) Pregnane X receptor mediated-transcription regulation of CYP3A by glycyrrhizin: a possible mechanism for its hepatoprotective property against lithocholic acid-induced injury. Chem Biol Interact 200:11–20

Wang J, Chen X, Wang W, Zhang Y, Yang Z, Jin Y, Ge HM, Li E, Yang G (2013a) Glycyrrhizic acid as the antiviral component of *Glycyrrhiza uralensis* Fisch. against coxsackievirus A16 and enterovirus 71 of hand foot and mouth disease. J Ethnopharmacol 147:114–121

Wang Z, Cao Y, Paudel S, Yoon G, Cheon SH (2013b) Concise synthesis of licochalcone C and its regioisomer, licochalcone H. Arch Pharm Res 36:1432–1436

Wang KL, Hsia SM, Chan CJ, Chang FY, Huang CY, Bau DT, Wang PS (2013c) Inhibitory effects of isoliquiritigenin on the migration and invasion of human breast cancer cells. Expert Opin Ther Targets 17:337–349

Wang L, Wang Z, Gao W, Chen J, Yang M, Kuang Y, Huang L, Chen S (2013d) Simultaneous determination of aflatoxin B1 and ochratoxin A in licorice roots and fritillary bulbs by solidphase extraction coupled with high-performance liquid chromatography-tandem mass spectrometry. Food Chem 138:1048–1054

Whorwood CB, Sheppard MC, Stewart PM (1993) Licorice inhibits 11 beta-hydroxysteroid dehydrogenase messenger ribonucleic acid levels and potentiates glucocorticoid hormone action. Endocrinology 132:2287–2292

Wittschier N, Faller G, Hensel A (2009) Aqueous extracts and polysaccharides from liquorice roots (*Glycyrrhiza glabra* L.) inhibit adhesion of *Helicobacter pylori* to human gastric mucosa. J Ethnopharmacol 125:218–223

Wolkerstorfer A, Kurz H, Bachhofner N, Szolar OH (2009) Glycyrrhizin inhibits influenza A virus uptake into the cell. Antiviral Res 83:171–178

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 X, Zhang L, Gurley E, Studer E, Shang J, Wang T, Wang C, Yan M, Jiang Z, Hylemon PB, Sanyal AJ, Pandak WM Jr, Zhou H (2008) Prevention of free fatty acid-induced hepatic lipotoxicity by 18beta-glycyrrhetinic acid through lysosomal and mitochondrial pathways. Hepatology 47:1905–1915

Wu TY, Khor TO, Saw CL, Loh SC, Chen AI, Lim SS, Park JH, Cai L, Kong AN (2011) Anti-inflammatory/Anti-oxidative stress activities and differential regulation of Nrf2-mediated genes by non-polar fractions of tea *Chrysanthemum zawadskii* and licorice *Glycyrrhiza uralensis*. AAPS J 13:1–13

Wu F, Jin Z, Jin J (2013) Hypoglycemic effects of glabridin, a polyphenolic flavonoid from licorice, in an animal model of diabetes mellitus. Mol Med Rep 7:1278–1282

Xiao XY, Hao M, Yang XY, Ba Q, Li M, Ni SJ, Wang LS, Du X (2011) Licochalcone A inhibits growth of gastric cancer cells by arresting cell cycle progression and inducing apoptosis. Cancer Lett 302:69–75

Xiao ZW, Zhang W, Ma L, Qiu ZW (2014) Therapeutic effect of magnesium isoglycyrrhizinate in rats on lung injury induced by paraquat poisoning. Eur Rev Med Pharmacol Sci 18:311–320

Xie XW (2017) Liquiritigenin attenuates cardiac injury induced by high fructose-feeding through fibrosis and inflammation suppression. Biomed Pharmacother 86:694–704

Yang L, Wang L, Pan J, Xiang L, Yang M, Logrieco AF (2010) Determination of ochratoxin A in traditional Chinese medicinal plants by HPLC-FLD. Food Addit Contam A 27:989–997
Yang N, Patil S, Zhuge J, Wen MC, Bolleddula J, Doddaga S, Goldfarb J, Sampson HA, Li XM (2013) Glycyrrhiza uralensis flavonoids present in anti-asthma formula, ASHMITM, inhibit memory Th2 responses in vitro and in vivo. Phytother Res 27(9):1381–1391
Yang R, Wang LQ, Yuan BC, Liu Y (2015) The pharmacological activities of licorice. Planta Med 81(18):1654–1669
Yao K, Chen H, Lee MH, Li H, Ma W, Peng C, Song NR, Lee KW, Bode AM, Dong Z, Dong Z (2014) Licochalcone A, a natural inhibitor of c-Jun N-terminal kinase 1. Cancer Prev Res (Phila) 7:139–149
Yehuda I, Madar Z, Szuchman-Sapir A, Tamir S (2011) Glabridin, a phytoestrogen from licorice root, up-regulates manganese superoxide dismutase, catalase and paraoxonase 2 under glucose stress. Phytother Res 25:659–667
Yin G, Cao L, Xu P, Jeney G, Nakao M, Lu C (2011) Hepatoprotective and antioxidant effects of *Glycyrrhiza glabra* extract against carbon tetrachloride (CCl(4))-induced hepatocyte damage in common carp (*Cyprinus carpio*). Fish Physiol Biochem 37:209–216
Yoğunlu A (2011) Tunceli ekonomik değeri olan bitkiler raporu-"Sektörel araştırmalar serisi-5". Fırat Development Agency. www.fka.org.tr
Yokota T, Nishio H, Kubota Y, Mizoguchi M (1998) The inhibitory effect of glabridin from licorice extracts on melanogenesis and inflammation. Pigment Cell Res 11:355–361
Yoon G, Jung YD, Cheon SH (2005) Cytotoxic allylretrochalcone from the roots of *Glycyrrhiza inflata*. Chem Pharm Bull 53:694–695
Yoshida T, Yoshida S, Kobayashi M, Herndon DN, Suzuki F (2010) Pivotal advance: glycyrrhizin restores the impaired production of β-defensins in tissues surrounding the burn area and improves the resistance of burn mice to *Pseudomonas aeruginosa* wound infection. J Leukoc Biol 87:35–41
Yu XY, Lin SG, Zhou ZW, Chen X, Liang J, Yu XQ, Chowbay B, Wen JY, Duan W, Chan E, Li XT, Cao J, Li CG, Xue CC, Zhou SF (2007) Role of P-glycoprotein in limiting the brain penetration of glabridin, an active isoflavan from the root of *Glycyrrhiza glabra*. Pharm Res 24:1668–1690
Yuan X, Li T, Xiao E, Zhao H, Li Y, Fu S, Gan L, Wang Z, Zheng Q, Wang Z (2014) Licochalcone B inhibits growth of bladder cancer cells by arresting cell cycle progression and inducing apoptosis. Food Chem Toxicol 65:242–251
Yumatni Y, Shigeree T, Kazo T, Isav O, Trukasa T (1980) J Fac Appl Biol Sci Hiroshima Univ 19 (1):113–120
Zamansoltani F, Nassiri-Asl M, Sarookhani MR, Jahani-Hashemi H, Zangivand AA (2009) Antiandrogenic activities of *Glycyrrhiza glabra* in male rats. Int J Androl 32:417–422
Zani F, Cuzzoni MT, Daglia M, Benvenuti S, Vampa G, Mazza P (1993) Inhibition of mutagenicity in *Salmonella typhimurium* by *Glycyrrhiza glabra* extract, glycyrrhizinic acid, 18alpha- and 18beta-glycyrrhetinic acids. Planta Med 59:502–507
Zhai D, Zhao Y, Chen X, Guo J, He H, Yu Q, Yang J, Davey AK, Wang J (2007) Protective effect of glycyrrhizin, glycyrrhetic acid and matrine on acute cholestasis induced by alpha-naphthyl isothiocyanate in rats. Planta Med 73:128–133
Zhang Y, Zhang L, Zhang Y, Xu JJ, Sun LL, Li SZ (2016) The protective role of liquiritin in high fructose-induced myocardial fibrosis via inhibiting NF-κB and MAPK signaling pathway. Biomed Pharmacother 84:1337–1349
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
Zhao Z, Wang W, Guo H, Zhou D (2008) Antidepressant-like effect of liquiritin from *Glycyrrhiza uralensis* in chronic variable stress induced depression model rats. Behav Brain Res 194:108–113
Zhou X, Zhao L, Liu X, Li X, Jia F, Zhang Y, Wang Y (2012a) Antimycobacterial and synergistic effects of 18beta-glycyrrhetinic acid or glycyrrhetinic acid-30-piperazine in combination with isoniazid, rifampicin or streptomycin against *Mycobacterium bovis*. Phytother Res 26:253–258

Zhou T, Deng X, Qiu J (2012b) Antimicrobial activity of licochalcone E against *Staphylococcus aureus* and its impact on the production of staphylococcalalpha-toxin. J Microbiol Biotechnol 22:800–805

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

Zhu Z, Li C, Wang X, Yang Z, Chen J, Hu L, Jiang H, Shen X (2010) 2,2,4-trihydroxychalcone from *Glycyrrhiza glabra* as a new specific BACE1 inhibitor efficiently ameliorates memory impairment inmice. J Neurochem 114:374–385