Chapter 7
Pharmacological Activities and Phytochemical Constituents

_Glycyrrhiza glabra_ is one of the most popular medicinal plants and it has been used in traditional herbal remedy since ancient times (Blumenthal et al. 2000; Parvaiz et al. 2014; Altay et al. 2016). Many experimental, pharmacological and clinical studies show that liquorice has antimicrobial, antibacterial, antiviral, antifungal, antihematotoxic, antioxidant, antiulcer, anti hemorrhoid antihyperglycemic, antidiuretic, antinephritic, anticarcinogenic, antimutagenic, anticytotoxic, anti-inflammatory, and blood stopper activity (Zani et al. 1993; Paolini et al. 1999; Nomura et al. 2002; Fukai et al. 2003; Zamansoltani et al. 2009; Sofia and Walter 2009). The liquorice root extract has been shown to be beneficial for the eye diseases, throat infections, peptic ulcers, arthritic conditions, liver diseases, joint diseases, immunodeficiency (Gupta et al. 2008), cough, cancer, diabetes, tuberculosis, endocrinial diseases, respiratory diseases (Asl and Hosseinzadeh 2008), kidney diseases (Vivekanand 2010), bronchitis, asthma, psoriasis, eczema, hemorrhoids (Sofia and Walter 2009), epilepsy, chronic hepatitis, heart diseases (Chopra et al. 2013), and orodental diseases (Messier et al. 2012). Also, studies have shown that the extract helps to regulate the estrogen–progesterone ratio (Kumagai et al. 1967; Nomura et al. 2002; Simmler et al. 2013) and gastrointestinal system (Asl and Hosseinzadeh 2008).

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

The wide use of *G. glabra* is due to two main constituents, the saponins and flavonoids (Nomura and Fukai 1998). Glycyrrhizin is the most sweet-tasting triterpene saponin in roots and stolons of the liquorice plant. Its sweetness is measured to be nearly 200 times more than that of sucrose (Blumenthal et al. 2000). Production of a high-concentration glycyrrhizin within a very short time period has been clearly demonstrated in controlled environments (Afreen et al. 2005). However, several active substances in these roots are found which include glycyrrhizin, glycyrrhizinic acid (Tang and Eisenbrand 1992), glabridin, glabrene, glabrol, licoflavonol, glycyrol, glycyretol, isoglaborlide, licoricone, formononetin, phaseollinisoflavan, hispaglabridin A and B, 3-hydroxy glabrol, 3-methoxy glabridin (Kinoshita et al. 2005; Fukai et al. 2003; Williamson 2003), glabranin isomer, narigenin, lupiwightenone (Biondi et al. 2005; Sultana et al. 2010). All these have been isolated previously. The yellow color of liquorice is due to the flavonoid content of the plant, which includes liquiritin, isoliquiritin (a chalcone), and other compounds (Yamamura et al. 1992; Sharma and Agrawal 2013).

The secondary metabolites are mainly the biologically active compounds together with their derivatives such as flavonoids (Kar 2007; Varsha et al. 2013), phenolics (Cai et al. 2004), saponins (Sarker and Nahar 2007; Vashist and Sharma 2013), alkaloids (Sarker and Nahar 2007; Varsha et al. 2013), terpenes (Martinez et al. 2008), glycosides (Firm 2010), tannins (Kar 2007; Varsha et al. 2013), anthraquinones (Maurya et al. 2008; Vashist and Sharma 2013), essential oils (Martinez et al. 2008; Vashist and Sharma 2013), and steroids (Madziga et al. 2010; Varsha et al. 2013). The major constituents of this extract are sugars, starch, bitters, resins, essential oils, tannins, inorganic salts, and low levels of nitrogenous constituents such as proteins, individual amino acids, and nucleic acids (Hoffmann 1990; Isbrucker and Burdock 2006). More than 400 compounds have been isolated from *Glycyrrhiza* species and triterpene saponins and flavonoids are the main constitutes with a wide biological activity (Zhang and Ye 2009). Thus far, at least 80 compounds, including triterpenoid saponins, flavonoid glycosides, and free phenolics have been isolated from *Glycyrrhiza inflata* (Yang et al. 2015).

Kajiyama et al. (1992) have reported that 2 new prenylflavones, licoflavones B and C, and one new dibenzoylmethane, glycyrdione C, have been isolated from the root of *G. inflata* together with two known flavones, licoflavone A and 4’,7-dihydroxyflavone. Their structures have been elucidated on spectroscopic evidence as 4’,7-dihydroxy-3’,6-diprenylflavone, 8-prenyl-4’,5,7-trihydroxyflavone, and 1-(2,2-dimethyl-7-hydroxy-2H-1-benzopyran-6-yl)-3-(4-hydroxy-3-prenyl-phenyl)1-, 3-propanedionone (Kajiyama et al. 1992). The chemical composition of liquorice has actually been studied by means of classical targeted analysis, especially in relation to traditional oriental medicine (Wang et al. 2011). Some recent studies have reported more extensive chemical characterizations. However, these sometimes are lacking in method standardization, identification criteria, or biochemical evaluations (Rizzato et al. 2017).
An untargeted metabolomic analysis of 3 liquorice species (G. glabra, G. inflata, and Glycyrrhiza uralensis) has been performed by Rizzato et al. (2017). Their aim has been to identify the differences in the metabolic pattern of these plants. Most of the identified compounds determined belong to the classes of flavonoids and saponins, which are known to have a large range of biological activity, as shown in previous studies. However, their metabolomic analysis has elucidated the most important differences in the composition pattern of metabolites in these 3 species. By means of chemometrics tools (PCA, HCA), they were able to highlight numerous molecular markers, some already known, but others previously unreported (Rizzato et al. 2017).

The main differences in the metabolome composition of these species are reported to be the presence of prenylated chalcones in G. inflata, as well as the presence of numerous compounds in G. glabra normally found in Moraceae family. These compounds have never been isolated previously in G. glabra (Rizzato et al. 2017). The work undertaken by the latter authors appears to be very useful to improve the comprehension of the species-specific chemical characteristics of liquorice. A group of molecules containing sulfate has also been detected. This has been proved to be useful to distinguish the Chinese liquorice from the European species. The work carried out by Rizzato et al. (2017) demonstrates that from the genetical point of view a notable similarity exists between the two Chinese species, in terms of metabolite composition. They have reported that generally for all species, the highlighted differences can be ascribed mainly to the genetic factors. The role of environmental and geographical factors in the variability of Glycyrrhiza metabolome remains unclear. The work published by these authors substantially contributes to the knowledge of liquorice metabolite composition. In spite of this, further studies are needed for a better characterization of the metabolome of these plants, in order to achieve a deeper understanding of their value as food and herbal medicine.

A study published by Dobrea (2016) deals with the determination of flavonoid characteristics in the roots of the two species (Glycyrrhiza echinata and G. glabra) in Romania, using a sensitive analysis method the Liquid Chromatography—Mass Spectrometry (LC/MS). This study has been conducted to see if they have similarity in composition. Their published data shows that liquorice (G. glabra) extracts contain saponins and flavonoids and exhibit numerous pharmacological activities. In order to establish the degree of similarity between G. glabra and G. echinata roots, liquiritin, liquiritigenin, isoliquiritigenin, and glabridin have been quantified by LC/MS in 1% methanolic total extracts (Dobrea 2016). G. glabra contained all the analyzed flavonoids, among these, liquiritin and glabridin are present in higher concentrations. According to their findings, glabridin is absent in G. echinata roots and the liquiritin, liquiritigenin, and isoliquiritigenin content are by far inferior to G. glabra. In view of this, G. echinata roots should not replace the medicinal product liquiritiae radix as they lack glabridin and possess reduced concentrations of other analyzed flavonoids. So, the phytochemistry of G. glabra roots differs from G. echinata roots. The two are not equivalent. The roots of latter lack the specific compounds correlated to the therapeutic activity of licorice (Dobrea 2016).
7.1.1 Flavanoids

More than 300 flavanoids have been isolated from *Glycyrrhiza* species and they are responsible for its yellow color. Especially, *G. glabra* has yellow color due to the flavonoids like liquiritin, isoliquiritin (Yamamura et al. 1992). The flavanones and chalcones are the main types among these (Herz et al. 1998; Li et al. 2000; Zhang and Ye 2009). A number of flavonoids have been identified in these roots such as liquiritin, liquiritigenin, rhamnolliuiritin, liquiritin apioside, gralbranin, glabrol, licoflavanone, isorhizin, isoliquiritigenin, neoisoliquiritin, licurside, licochalcone A and B, licoricidin, 7-methillicoricidin, hispaglabridin A and B, licoflavone A and B, lico-flavanol, glyzaglabrin, licoisoflavanone, glabroisoflavanone, glabrone, licoricone, gancaonin (Lou and Qin 1995; Xing et al. 2003; Williamson 2003; Zhang and Ye 2009). 5,8-Dihydroxyflavone-7-O-β-d-glucuronide, glychionide A, and 5-hydroxy-8-methoxyl-flvone-7-O-β-d-glucuronide, glychionide B have been isolated from the roots of *G. glabra* (Li et al. 2005). The glabridin, galbrene, glabrone, shimpeterocarpin, licoisoflavonoids A and B, formononetin, glyzarin, and kumatakenin isoflavanoid derivatives too are present in liquorice (Williamson 2003). Also, hispaglabridin A and B, 4’O-methylglabridin and 3’-hydroxy-, 4’-O-methylglabridin (De Simone et al. 2001; Haraguchi 2001), and glabroisoflavanone A and B (Kinoshita et al. 2005) have been found in the liquorice roots.

The flavonoid glycosides have been isolated with feruloyl or coumaroyl groups and with indole conjugates (Hatano et al. 1998). Similarly, bioactive flavonoid compounds, liquiritigenin and isoliquiritigenin, have been isolated and identified from the crude extract of *G. uralensis* by Ma et al. (2005). Franceschelli et al. (2011) have identified the licocalchone C, the structural isomer of licocalchone A. Other flavonoids like licoagrodin, licoagrochalcones, glyinflatin B, and glycyrdione A have also been reported (Asl and HosseinZadeh 2008, 2012; Christensen and Kharazmi 2001; Li et al. 2000). The glabridin and hispaglabridin B have been identified by Gupta et al. (2008) from the ethanolic extract of the roots of *G. glabra*. The bioactive compounds glepidotin B and glepidotin A have been isolated and identified from the extract of *Glycyrrhiza lepidota* by Manfredi et al. (2001), whereas isoflavanoid derivatives such as glabridin, galbrene, glabrone, shimpeterocarpin, licoisoflavonoids A and B, formononetin, glyzarin, kumatakenin have been isolated and identified in 2003 by Williamson. In 2001, other researchers De Simone et al. have reported hispaglabridin A, hispaglabridin B, 4’-O-methylglabridin, and 3’-hydroxy-4’-O-methylglabridin from *Glycyrrhiza* species. The licochalcone A has been isolated and identified from the ethyl acetate extract of the roots of *G. uralensis* (Won et al. 2007). Kinoshita et al. (2005) have studied *G. glabra*, and they identified several compounds from its roots such as glabridin, galbrene, glabrone, shimpeterocarpin, licoisoflavonoids A and B, formononetin, glyzarin, kumatakenin, hispaglabridin A, hispaglabridin B, glabroisoflavanone A, and B glabroiso-flavanone B.
7.1.2 Saponins

In the 1990s, Fenwick and his co-workers have described two aglycone forms of glycyrrhizic acid, 18β-glycyrrhetinic acid and 18α-glycyrrhetinic acid. The anti-inflammatory and antiarthritic activity in animal studies too have been followed and attributed to the glycyrrhetic acid (Amirova 1993). A speedy healing of gastric ulcers is attributed to the presence of glycyrrhizin and the aglycone of glycyrrhizin in the liquorice (Amirova 1993; Blumenthal et al. 2000). *Glycyrrhiza* roots are reported to contain triterpenoid saponins (glycyrrhizin, glycyrrhizic acid). These are the major characteristic constituents of liquorice responsible for the sweet taste (Blumenthal et al. 2000). The major triterpenoid saponin in the root of this plant is glycyrrhizic acid. Latter is the main sweetener in this plant, nearly 50 times sweeter than sugar (Nomura et al. 2002). Other triterpenes too have been reported namely liquiritic acid, glycyrrretol, glabrolide, isoglabrolide, and licorice acid (Isbrucker and Burdock 2006). The described several saponins have been reported by Zhang and Ye (2009) from *Glycyrrhiza* species namely, licorice-saponin A3, 22β-actoxyglycyrrhizin, uralsaponin B, apioglycyrrhizin, araboglycyrrhizin, and icorice-saponin E2. In 2013, Vashist and Sharma have published data mentioning about the presence of ammonium glycyrrhizinate (3.4%) and calcium glycyrrhizinate (4%) in the ethanolic extract of *G. glabra*.

7.1.3 Phenolic Compounds

Nomura and Fukai (1998) have published several reports on the phenolic constituents of *Glycyrrhiza* species. The main phenols include liquiritin, isoliquiritin, liquiritin apioside, and isoprenoid-substituted flavonoids, chromenes, coumarins, dihydrosilbenes. For example, isobavachin has been reported from *Glycyrrhiza pallidiflora*, sigmoidin B in *G. uralensis*, liquiritigenin in some *Glycyrrhiza* species by the same workers. Nomura et al. (2002) have investigated several *Glycyrrhiza* species from the point of view of phenolic compounds. They have found isoprenoid-substituted flavonoid (pyranoisoflavan, glabridin) (*G. glabra*), isoflavans (*G. uralensis*), licochalcone A (*G. inflata, Glycyrrhiza eurycaarpa*), licoricidin (6), and licorisoflavan A (*Glycyrrhiza aspera*). Similar observations have been reported in 2003 by Williamson. Latter identified liquiritin, liquiritigenin, rhamnoliquiritin, neoliquiritin, chalcones isoliquiritin, isoliquiritigenin, neoisoliquiritin, licuraside, glabrolide, and licoflavonol. In 2008, Zhu et al. worked on the biologically active compounds of *G. uralensis* collected from Mongolia. They have reported 3 flavanone constituents (liquiritin apioside, liquiritin, and liquiritigenin) and 3 chalcones (isoliquiritin apioside, isoliquiritin, and isoliquiritigenin). In 2009, Zhang and Ye described several phenolic compounds derived from *Glycyrrhiza* species including glycycoumarin, glabrocoumarin, glycyrin, inflacoumarin A, lico.pyranocoumarin, isoglycerol, neoglycerol, licobenzofuran, licocoumarone, glabrocoumarone, gancaonin, and
kanzonol. Isolation and identification of isoliquiritigenin from Chinese liquorice have been carried out by Chin et al. (2007) and liquiritin by Huang et al. (2010).

In a study by Ammar et al. (2012), the researchers have isolated phenolic compounds namely liquiritigenin, liquiritin apioside, neoliquiritin apioside, isoliquiritin, isoliquiritin apioside, licuriside2-(5-P-coumaryl apiosyl), and isoliquiritin from the total polar extract of *G. glabra* utilizing different chromatographic techniques.

In an attempt to discover bioactive agents in *G. glabra*, 11 new phenolic compounds, glycybridins A–K, along with 47 known phenolics have been isolated by Li et al. (2017). They have conducted enzyme or cell-based bioactivity screenings of 1–58 according to the clinical therapeutic effects of liquorice. A number of compounds have been reported to significantly activate Nrf2, inhibit tyrosinase or PTP1B, inhibit lipopolysaccharide-induced NO production and NF-κB transcription, and inhibit the proliferation of human cancer cells (HepG2, SW480, A549, and MCF7). Glycybridin D has shown moderate cytotoxic activities against the four cancer cell lines, with IC50 values ranging from 4.6 to 6.6 µM (Li et al. 2017). Further studies have indicated that Glycybridin D (10 mg/kg) decreases tumor mass by 39.7% on an A549 human lung carcinoma xenograft mice model with little toxicity (Li et al. 2017).

These workers have carried out studies to discover bioactive natural products from one botanical source of *G. inflata*. A total of 67 free phenolics have been isolated to form a compound library. Based on the licorice bioactivity, these compounds have been subjected to screening using cell- or enzyme-based bioassay methods. A total of 11 compounds have exhibited potent cytotoxic activities against 3 human cancer cell lines (HepG2, SW480, and MCF7), but have shown little toxicity on human normal cell lines LO2 and HEK293T. A number of chalcones have been observed to show remarkable anti-inflammatory activities. Out of these, licochalcone B, IC50 8.78 µM, licoagrochalcone C, IC50 9.35 µM, and licochalcone E, IC50 9.09 µM have exhibited the most potent inhibitory activities on lipopolysaccharide-induced NO production, whereas IC50 13.9, 7.27, 2.44, 6.67, and 3.83 µM have shown potent inhibitory activities on NF-KB transcription. Nine prenylated phenolics have been found to be PTP1B inhibitors. Particularly, licoagrochalcone A, kanzonol C, 2’-hydroxyisolupalbigenin, gancaonin Q, glisoflanone, and glabrol with IC50 values of 0.31–0.97 µM. Compounds semilicoisoflavone B, IC50 0.25 µM, allolicoisoflavone B, IC50 0.80 µM, and glabridin, IC50 0.10 µM have shown noticeable tyrosinase inhibitory activities (Lin et al. 2017). Most of the above bioactive compounds have been reported for the first time by these workers.

### 7.1.4 Coumarins

The most important other constituents are coumarins including liqcoumarin, glabrocoumarone A and B, herniarin, umbelliferone, glycyrin, glycocoumarin, licofuranocoumarin, licopyranocoumarin, and glabrocoumarin. All are present in *G. glabra* (De Simone et al. 2001; Haraguchi 2001; Williamson 2003; Kinoshita et al.
Also, four dihydrostilbenes—dihydro-3,5-dihydroxy-4′-acetoxy-5′-isopentenylstilbene, dihydro-3,3′,4′-trihydroxy-5-O-isopentenyl-6-isopentenylstilbene, dihydro-3,5,3′-trihydroxy-4′-thoxystilbene, and dihydro-3,3′-dihydroxy-5β-d-O-glucopyranosylxyloxy-4′-methoxystilbene—have been isolated from the leaves of *G. glabra* grown in Sicily (Biondi et al. 2005).

In 2014 Qiao and co-workers have identified glycerol, glycycoumarin, dehydroglyasperin in the root extract of *G. uralensis*. Two coumarins of *G. glabra*, glycocoumarin and licopyranocoumarin, have also been described by De Simone et al. (2001), these are able to inhibit giant cell formation in HIV-infected cell cultures.

### 7.1.5 Essential Oils and Other Compounds

Nearly 3 decades ago, Frattini et al. (1977) reported 63 compounds never found before in heated liquorice essential oil. They used GLC, GLC-MS coupling, and IR spectrometry. In the same year, Frattini et al. (1977) found many heated liquorice compounds, the furan derivatives. The reason given for this is pyrolysis and condensation reactions which occur during heating, when sugars in liquorice roots are very rich. Acetol, propionic acid, 2-acetylpyrrole, Z-acetylfuran, and furfuryl alcohol are the most abundant components. None of the identified compounds alone are responsible for the flavor in liquorice. On the other hand, total extract shows a typical liquorice aroma, possibly due to an integrated response to the proper mixture of the proper volatiles, rather than to the odor of one or two components (Frattini et al. 1977).

In 2006, Näf and Jaquier have studied the lactonic fraction of a commercial liquorice root extract (*G. glabra*), exhibiting a pleasant sweet, woody, dried fruit-like odor, containing mainly fatty acids (C2–C16) and phenols (phenol, guaiacol), together with common saturated linear γ-lactones (C6–C14) and, in trace amounts, a series of new 4-methyl-γ-lactones and 4-ethyl-γ-lactones. Other compounds such as asparagines, glucose, sucrose, starch, polysaccharides (arabinogalactants), and sterol (β-sitosterol, dihydrostigmasterol) have also been reported (Hayashi et al. 1998; Blumenthal et al. 2000). Other secondary metabolites have also been reported such as fatty acids, phenol, guaiacol, asparagines, glucose, sucrose, starch, polysaccharides, and sterols (β-sitosterol, dihydrostigmasterol) (Näf and Jaquier 2006).

In Turkey, the essential oil from aerial parts and roots of *Glycyrrhiza* taxa has been analyzed by gas chromatography and mass spectroscopy (GC–MS) systems by Çakmak (2011). The major components identified by him are listed as follows: hexanal, β-vi pinene, furan-2-pentyl, benzaldehyde, 4-terpineol, 1-pentylcyclobutene, acetophenone, α-caryophyllen, naphtaleine, 1-phenyl-1H-pyrazol-3-amine, m-cresol, nerolidol, hexahydro farnesyl acetone, E-neryl linalool, 1-tetracosanol, p-hexylacetophenone, phytol, 4-pyridinecarbonitrile, dimethylamine, and n-hexadecanoic acid. Fatty acid profiles of these taxa have also been examined by...
GC-FID and 22 fatty acids are reported, palmitic, linoleic, and linolenic acid being the main components (Çakmak 2011).

Farag and Wessjohann (2012) have undertaken investigations to provide insight into *Glycyrrhiza* species aroma composition and for its use in food and pharmaceutical industry. They profiled volatile constituents from *G. glabra*, *G. inflata*, and *G. echinata* roots using steam distillation and solid-phase microextraction. Two phenols, thymol and carvacrol, have been found exclusively in essential oil and headspace samples of *G. glabra*, and with highest amounts of samples that originated from Egypt. In *G. echinata* oil, (2E, 4E)-decadienal (21%) and β-caryophyllene oxide (24%) have been reported as the main constituents, whereas 1α, 10α-epoxyamorpha-4-ene (13%), and β-dihydroionone (8%) have predominated *G. inflata* (Farag and Wessjohann 2012). Moreover, Farag and Wessjohann (2012) have also reported that principal component and hierarchical cluster analyses have clearly separated *G. echinata* and *G. inflata* from *G. glabra*, with phenolics and aliphatic aldehydes contributing mostly for species segregation.

The essential oil composition of *G. glabra* has been investigated by Ali (2013). He has reported compounds such as α-pinene, β-pinene, octanol, γ-terpinene, estragole, isofenchon, β-caryophyllene, citronellyl acetate, caryophyllene oxide, and geranyl hexanolate. Out of these, geranyl hexanolate represents the higher percentage (34%) whereas β-pinene the lowest (1.7%). The phytoestrogens have been investigated in the roots of *G. glabra* from Syria by Khalaf et al. (2010). They have identified daidzein, daidzin, genistin, ononin, glycine, genistein, and coumestrol, whereas dihydrostilbenes from the root extract of *G. glabra* grown in Sicily has been reported by Sultana et al. (2010).

Wagner et al. (2016) have studied the application of the molecular sensory science concept including aroma extract dilution analysis (AEDA) on the basis of gas chromatography-olfactometry combined with gas chromatography–mass spectrometry. They elucidated the key odorants of raw liquorice (*G. glabra*) and found 50 aroma-active compounds via AEDA; 16 of these have been identified in raw liquorice for the first time. γ-Nonalactone, 4-hydroxy-2,5-dimethylfuran-3(2H)-one, and 4-hydroxy-3-methoxybenzaldehyde have shown the highest flavor dilution (FD) factor of 1024. Nearly, 43 compounds have been quantified using stable isotope dilution analysis (SIDA); 6 more compounds have been quantified using labeled standards and odor activity values (OAVs), which is the ratio of concentration to the respective odor threshold. OAVs have been calculated revealing OAVs ≥ 1 for 39 compounds. The highest OAVs were shown by (E,Z)-2,6-nonadienal, 5-isopropyl-2-methylphenol, hexanal, and linalool (Wagner et al. 2016). On the basis of the data obtained by these workers, an aqueous reconstitution model has been prepared by mixing the 39 odorants in their naturally occurring concentrations. The recombinate has elicited an aroma profile very similar to the profile of raw liquorice, proving that all key aroma compounds have been correctly identified and quantified (Wagner et al. 2016).

Ata et al. (2017) have studied the ion-pair extraction combined with liquid chromatography–tandem mass spectrometry method. They have proposed the determination of biogenic amines in liquorice samples (*G. glabra*). Their
evaluations have revealed that limit of detection and limit of quantitation for the biogenic amines are 1.4–2.7 and 4.7–9.1 ng mL\(^{-1}\), respectively. Relative standard deviations based on 5 replicate extractions of 100 ng mL\(^{-1}\) of each biogenic amine were <4.7% for intra-day and 7.4% for inter-day precision. The method described by Ata et al. (2017) has been in accordance with the satisfactory accuracy and good reproducibility for the quantitative determination of biogenic amines in liquorice samples. Nine biogenic amines (putrescine, cadaverine, histamine, spermine, spermidine, tyramine, tryptamine, agmatine, and phenylethylamine) have been detected in liquorice samples and total biogenic amine concentrations have been determined at 369 ng mL\(^{-1}\) in fresh and 3532 ng mL\(^{-1}\) in non-fresh samples. Putrescine has been found at the highest concentrations—up to 704 ng mL\(^{-1}\) in all the analyzed samples, followed by tyramine (675 ng mL\(^{-1}\)) and tryptamine (282 ng mL\(^{-1}\)). Putrescine, tyramine, and spermine concentrations have dramatically increased, whereas agmatine concentration has significantly decreased, in non-fresh liquorice samples compared to fresh ones (Ata et al. 2017). Moreover, they have reported that the consumption of freshly prepared liquorice is recommended because of the relatively low concentration of total biogenic amines.

Ye et al. (2017) have examined the bioactive constituents of *G. uralensis* leaves. Seven chemical components have been isolated by repeat column chromatography and using spectroscopic methods. Their structures have been determined to be a novel prenylated dihydrostilbene, \(\alpha,\alpha'-\text{dihydro-3,5,3',4'-tetrahydroxy-2,5'-diprenylstilbene}\), a methylated flavonoid, quercetin-3-Me ether, and 5 prenylated flavonoids: 5'-prenylquercetin, 8-[(E)-3-hydroxymethyl-2-butenyl]eriodictyol, 6-prenyleriodictyol, 5'-prenyleriodictyol, and 6-prenylquercetin-3-Me ether. These compounds show strong radical scavenging activity toward DPPH, and most of them have demonstrated greater inhibitory activity against \(\alpha\)-glucosidase than their unprenylated counterparts (Ye et al. 2017).

7.2 Bioactive Components and Biological Functions

Liquorice is not used only in food, tobacco, and cosmetics, and it has great value in medicine, because this herb is accepted as a herbal remedy for many disorders (Kao et al. 2014). Some of its traditional uses like diabetes, cough, wound treatment, and tuberculosis have been discussed by Asl and Hosseinzadeh (2008). It is also well known as one of the most frequently used herbs in China, as it has been in use in their traditional medicine for centuries. This herb is commonly used in herbal formulas to harmonize other ingredients and applied under 12 regular meridians in Chinese traditional medicine. As per the compendium of Materia Medica (Bencao Gangmu) liquorice acts as an effective antidote, a detoxicant, a beneficial agent in the development of bone and muscle, and a remedy for throat disorders and cough (Li 2003). It is also included in many traditional Chinese medicine formulas for treating liver disease. Similarly, in Japan sho-saiko-to (TJ-9) is used for liver disorders (e.g., chronic active hepatitis), (Hirayama et al. 1989). This formula is said to
have come from Xiao Chai Hu Tang (Minor Bupleurum Formula) in Shang Han Lun of TCM (Chang 1981).

Recent investigations depict that in traditional Chinese medicine uses of licorice vary much (Kao et al. 2014). A mixture of Ephedra, Cassia twig, bitter apricot kernel, and liquorice, known as Ma Huang Tang—a classic Chinese Formula has recently been confirmed to be effective in the treatment of pulmonary disorders like bronchial asthma, acute bronchitis, colds, and influenza. Direct effects of the bitter apricot kernel and liquorice are mentioned to be nonsignificant but, the two drugs have a significant synergetic effect when administered with Ephedra or Cassia twigs (He et al. 2012). This clearly shows that liquorice has ability to harmonize with the other ingredients in the formula. Liquorice gargles are reported to be highly effective in the incidence and severity of postoperative sore throat (Agarwal et al. 2009). This confirms the findings for its use in traditional Chinese medicine. Some liquorice healing effects in the traditional Chinese medicine is fully confirmed by modern medicine. However, we still need to enlighten the fact which compound(s) in this herb mediate these effects (Kao et al. 2014).

7.2.1 Glycyrrhizic Acid and 18β-Glycyrrhetinic Acid

The sweetness of liquorice comes from glycyrrhizic acid or glycyrrhizin, a triterpenoid saponin glycoside; 30–50 times sweeter than sucrose. It induces impulses from sugar receptor-containing cells at a concentration (3.0 mM), much lower than sucrose (Ahamed et al. 2001; Kao et al. 2014). Glycyrrhizin maintains its sweetness after heating as against the sugar substitute aspartame. Although sugar and glycyrrhizic acid taste sweet, but glycyrrhizic acid induces a lower onset sweet flavor than sugar. Its sweetness remains in the mouth for a longer time (Kao et al. 2014). Another triterpenoid in liquorice is glycyrrhetinic acid (18α-glycyrrhetinic acid and 18β-glycyrrhetinic acid) obtained from the hydrolysis of glycyrrhizic acid. Presystemic metabolism by intestinal bacteria performing glycolysis can complete this process (Ploeger et al. 2001). The glycyrrhizic acid is metabolized by human intestinal bacteria through the action of the glucuronidases of Bacteroides J-37 and Eubacterium sp. to yield 18β-glycyrrhetinic acid (18βGA) (Kim et al. 1999). In the Chinese Materia Medica, dry-roasting or honey-roasting are the two processes used to obtain liquorice preparation which accelerates the hydrolysis of the sugar chains in the saponin and glycosidic flavonoid constituents (Sung and Li 2004; Kuwajima et al. 1999). Both raw liquorice as well as liquorice preparata are important agents in traditional Chinese medicine, each having different function. Anti-inflammatory activities and neuroprotective effects of roasted form is said to be more potent than raw one, which goes against the characteristics described by traditional Chinese medicine (Hwang et al. 2006; Kim et al. 2010). As per “Bencao Gangmu” raw form can be used to treat the syndrome known as inflammation in modern medicine (Xie Huo in Chinese), and roasted form for reinforcement (Bu Zhong in Chinese) (Li 2003). The roasted form is used in Buzhong Yiqi Tang instead of raw, suggesting
that glycyrrhizic acid and 18β-glycyrrhetinic acid may have distinct biological characteristics (Kao et al. 2014).

This herb has also been used alone and as a component in many formulas to treat liver diseases. Multiple mechanisms have been proposed for the hepatoprotective effects of glycyrrhizic acid and 18β-glycyrrhetinic acid (Kao et al. 2014). The glycyrrhizic acid and 18β-glycyrrhetinic acid are reported to have an ability to protect hepatocytes from bile acid-induced cytotoxicity (Gumpricht et al. 2005). A beneficial effect of glycyrrhizic acid on hepatitis has been demonstrated recently. The intravenous administration of glycyrrhizic acid is said to decrease serum alanine transaminase (ALT) and necro-inflammation and fibrosis in the liver (Manns et al. 2012). The protective effects of glycyrrhizic acid and 18β-glycyrrhetinic acid are controlled by several mechanisms, which likely are involved in the reduced AST (aspartate transaminase, also called GOT) and ALT (also called GPT) activities. The glycyrrhizic acid can also modulate the pregnane X receptor (PXR), as well as cytochrome P450 family 3 subfamily A (CYP3A), to protect against lithocholic acid-induced injury (Wang et al. 2012). The treatments with glycyrrhizic acid and 18β-glycyrrhetinic acid can inhibit liver fibrosis, which otherwise may lead to cancer (Moro et al. 2008; Kao et al. 2014). Both may be effective in the protection of other organs, as they have positive effects on brain damage induced by ischemia and 6-hydroxydopamine. A recent study has demonstrated that both of these can penetrate the blood–brain barrier (BBB) indicating that they are potent agents for the treatment of neural diseases, ischemic brain diseases, and Parkinson’s disease (Kao et al. 2009, 2014; Tabuchi et al. 2012). Glycyrrhizic acid also exhibits protective effects in the kidney. It has been demonstrated that it protects against cisplatin-induced genotoxicity and nephrotoxicity. The protective effects have also been observed with a renal hypoxia-reoxygenation model, however 18β-glycyrrhetinic acid does not exhibit the same potential (Yokozawa et al. 2000; Arjumand and Sultana 2011). Glycyrrhizic acid seems to be effective against ischemic damage, including damage to the spinal cord, myocardium, liver, and gut (Yokozawa et al. 2000; Di Paola et al. 2009; Haleagrahara et al. 2011; Ogiku et al. 2011).

Glycyrrhizic acid and 18β-glycyrrhetinic acid are considered inhibitors of inflammation induced by both bacterial and viral infection, as inflammation is frequently triggered by bacteria or viral infection, and antibacterial and antiviral activities are possible anti-inflammatory strategies. Former can inhibit the replication of and infection by various viruses (Fiore et al. 2008; Kao et al. 2014), including severe acute respiratory syndrome (SARS)-associated coronavirus (Cinatl et al. 2003), human immunodeficiency virus (HIV) (De Clercq 2000), hepatitis A virus (HAV) (Crance et al. 1990), hepatitis B virus (HBV) (Takahara et al. 1994), hepatitis C virus (HCV) (Orlent et al. 2006), herpesviridae (varicella zoster virus, VZV) (Baba and Shigeta 1987), herpes simplex virus 1 (HSV-1) (Lampi et al. 2001), Epstein–Barr virus (EBV) (Lin 2003), cytomegalovirus (CMV) (Numazaki et al. 1994), and influenza viruses, including H1N1 (Pompei et al. 1979) and H5N1 (Michaelis et al. 2011). The glycyrrhizic acid also inhibits the growth of Helicobacter pylori, and thus can be used in the treatment of gastric ulcers, 18βGA has also been shown to be effective against clarithromycin-resistant
strains of *H. pylori* (Chung 1998; Krausse et al. 2004). Glycyrrhizic acid and 18β-glycyrrhetinic acid are also reported to modulate inflammation-related mechanisms. Traditional Chinese medicine often incorporates this herb to enhance the effect of other formulas that act as anti-inflammatory agents. Anti-inflammatory effect of liquorice extract is enhanced by glycyrrhizic acid without glycyrrhizic acid (Uto et al. 2012). Glycyrrhizic acid is reported to possess an ability to inhibit H5N1-induced proinflammatory gene expression without affecting the cytolytic activity of natural killer cells (Michaelis et al. 2011). These findings depict that glycyrrhizic acid probably modulates inflammation by two regulatory methods namely, inhibition of proinflammatory cytokines and the promotion of immune function. In this regulation PI3K probably plays a role. The inflammation is very effectively modulated by glucocorticoids and the glucocorticoid receptor, latter is extensively used in clinical treatments (e.g., dexamethasone). Several potential mechanisms exist for the involvement of glycyrrhizic acid and 18β-glycyrrhetic acid in the induction of cortisone activity. The two can activate glucocorticoid receptor (GR) signaling by binding to the GR and inhibit the activity of corticosterone 11β-dehydrogenase isozyme 2 (11β-HSD2), which converts active cortisol into inactive cortisone (Whorwood et al. 1993; Kao et al. 2010; Ma et al. 2011). Both may also enhance GR signaling by eliminating intracellular oxidative stress (Kao et al. 2013). No increase in the glucocorticoid-induced side effects is seen, although glycyrrhizic acid enhances glucocorticoid activity. Excessive glucocorticoid levels are reported to exert diverse effects on bone microstructure, integrity, and mineral metabolism (Iba et al. 1995). It has been demonstrated that glycyrrhizic acid has the potential for use as an agent to protect the bones against glucocorticoid-induced osteoporosis (Ramli et al. 2013). A nuclear component (high-mobility group box 1 (HMGB1) that functions extracellularly as a signaling molecule in acute and chronic inflammation has been reported to get inhibited by binding to glycyrrhizic acid (Mollica et al. 2007). According to Kao et al. (2013), glycyrrhizic acid and 18β-glycyrrhetic acid can modulate PI3K signaling to alleviate inflammation. All these results demonstrate that glycyrrhizic acid and 18β-glycyrrhetic acid possess considerable potential for development as novel inflammation-modulating agents (Kao et al. 2014).

They can also affect the biological mechanism of cancer formation. Glycyrrhizic acid may inhibit angiogenesis by targeting ERK signaling, and can be protective against UV-B-induced carcinogenesis in the epidermis of SKH-1 hairless mice (Cherng et al. 2011; Kim et al. 2013). GA also prevents hepatocarcinogenesis associated with hepatitis because it is effective against HCV-induced liver disorders (Ikeda et al. 2006; Ikeda 2007). AS compared to GA glycyrrhetinic acid has a more potent anticarcinogenesis effect. According to Lee et al. (2008), 18β-glycyrrhetinic acid not only induces apoptotic cell death but also exhibits a synergistic toxic effect with antibiotics and anticancer drugs like camptothecin, mitomycin c, and doxorubicin. The report published by Farina et al. (1998) reports that glycyrrhetinic acid, oleanolic acid, and ursolic acid have similar chemical structures and potent antiulcer activities. A satisfactory anticarcinogenesis outcome is found in the compounds whose chemical structures are similar to that of glycyrrhetinic acid.
(Csuk et al. 2011). The glycyrrhetinic acid and its derivatives are highly effective in the treatment of many cancer cells as they are sensitive to treatment, including human epithelial ovarian carcinoma cell lines OVCAR-3 and SK-OV-3 (Lee et al. 2010a; Yang et al. 2012), the human prostate cancer cell lines DU145 (Shetty et al. 2011; Szpak et al. 2011) and PC3, the human breast cancer cell line MCF7 (Sharma et al. 2012; Zhao et al. 2012), the human bladder cancer cell line NTUB1 (Lin et al. 2011), the human leukemia cell line HL60 (Gao et al. 2010), the human erythromyeloblastoid leukemia cell line K562 (Song et al. 2010), the human colon cancer cell lines RKO and SW480 (Chintharlapalli et al. 2009), the pancreatic cancer cell lines Panc1 and Panc28 (Jutooru et al. 2009), and many other cell lines. 18β-glycyrrhetinic acid is more toxic than glycyrrhizic acid, glycyrrhizic acid displays no obvious cell toxicity, even at 200 μM (Kao et al. 2009, 2010, 2013).

DNA and RNA binding has been observed in both GA as well as glycyrrhetinic acid (Naﬁsi et al. 2012a, b), which implies that both may directly interfere with the pattern of transcription factors, the targeting of gene expression, and the interactions of DNA and RNA. This is a promising research topic for understanding the biological functions of these two. Glycyrrhizic acid and 18β-glycyrrhetinic acid have distinct biological functions, which may be due to the differences in their chemical structures (Kao et al. 2014).

7.2.2 Liquiritin, Isoliquiritin, Liquiritigenin, and Isoliquiritigenin

The first two are the chalconoids of liquorice, whereas other two are the glycone forms of the former respectively (Kao et al. 2014). Studies on their antioxidant abilities are limited. These compounds are reported to be the potent protective agents against cancer and all four compounds may have a potent antispasmodic effect (Lee et al. 2013). These four compounds are said to play an important role in healing effects, their chemical structures are similar, a simultaneous study on these compounds may facilitate the elucidation of the relationship between their biological effects and structure (Kamei et al. 2005; Kao et al. 2014).

The biological functions of liquiritin are similar to those of glycyrrhizic acid. Liquiritin promotes neurite outgrowth in PC12 cells with nerve growth factor treatment (Chen et al. 2009), suggesting its potential as a remedy for neurodegenerative diseases such as Alzheimer’s disease or Parkinson’s disease. Furthermore, liquiritin may exhibit an antidepressant-like effect in chronic variable stress-induced depression model rats by modulating oxidative stress (Zhao et al. 2008). It proves beneficial in patients with diabetes mellitus because it attenuates the induction of the RAGE/NFκB pathway in human umbilical vein endothelial cells (HUVECs) by advanced glycation end products (AGE), (Zhang et al. 2013). According to Cheel et al. (2010), liquiritin and glycyrrhizic acid can stimulate immune responses, enhance antioxidant enzymes like superoxide dismutases (SOD), catalase, and glutathione peroxidase in mice focal cerebrum (Sun et al.
2010). These may act as protective agents against epithelial injury in chronic obstructive pulmonary disease (COPD) (Guan et al. 2012). Liquiritin may bind to DNA like glycyrrhizic acid (Gao et al. 2009) and may directly affect gene expression or other DNA-related mechanisms. Both are glycones or glycosides, the functional groups important for DNA binding, but this characterization is yet to be confirmed (Kao et al. 2014).

Not much work is done on isoliquiritin listed in the PubMed database, because of its lack of commercial availability, most of the data published deals with its isolation and identification (Kao et al. 2014). It is thought to prevent angiogenesis and tube formation in granulomas and may also have a potent antitussive effect (Kobayashi et al. 1995; Kamei et al. 2003). Its other possible application is skin depigmentation due to tyrosinase inhibition (Fu et al. 2005).

Liquiritigenin is a well-known selective estrogen receptor β agonist implicated in the weight-reducing effects of liquorice oil (Mersereau et al. 2008; Jungbauer and Medjakovic 2014). It facilitates the recovery of learning and memory deficits induced by amyloid beta Aβ(25-35) and also helps to enhance osteoblast function (Liu et al. 2010; Choi 2012). Liquiritigenin as well as isoliquiritigenin are able to inhibit xanthine oxidase, a promoting factor in many disorders (Kong et al. 2000). The IC50 values of these compounds are 49.3 and 55.8 μM for liquiritigenin and isoliquiritigenin respectively. Both are effective anti-inflammatory agents displaying potential PPARγ activating activity, suggesting their potential for use in recovery from metabolic syndrome (Zhou et al. 2009). Latter is also an inhibitor of aldose reductase, suggesting it might be effective in treating diabetic complications (Aida et al. 1990). Liquiritigenin inhibits iNOS and proinflammatory cytokines by blocking NFκB (Kim et al. 2008), while isoliquiritigenin is involved in the intercellular adhesion molecule-1 (ICAM-1) and the vascular cell adhesion molecule-1 (VCAM-1) to modulate inflammation (Tanaka et al. 2001). Liquiritigenin has a protective role against a number of injuries in many cells and organs, including acetaminophen-induced rat liver damage, cadmium-induced rat hepatoma Reuber H35 cell (H4IIE) damage, D-galactosamine/ lipopolysaccharide- or CCl4-mediated rat hepatitis, Aβ(25-35)-induced injury of rat hippocampal neurons, and infection by Candida albicans (Kim et al. 2004, 2006; Lee et al. 2009; Liu et al. 2009; Kang et al. 2010a). On the other hand isoliquiritigenin also protects cells and organs by inhibiting cisplatin-induced rat anorexia, the diabetes-induced hyperaggregability of platelets, the accumulation of cyclic AMP in rat ventricular heart muscle, and by potently promoting neuronal health by inhibiting monoamine oxidase A and B among other mechanisms (Tawata et al. 1992; Wegener and Nawrath 1997; Pan et al. 2000; Takeda et al. 2008). Liquiritigenin can enhance bile secretion in the liver through choleretic effect and can enhance the activity of transporters and phase II enzymes in the liver, which is thought to be related to the antidote ability of liquorice (Kim et al. 2009). In addition to an increase in the bile secretion, it might increase the rate of hepatic blood flow, and may exhibit chemopreventive activity in liver and lung cancers (Zhang et al. 2009; Jayaprakasam et al. 2009; Kang et al. 2010b; Zhou et al. 2010). The mechanisms by which it modulates chemoprevention may involve apoptotic molecular targets, like cytochrome c, caspases, matrix metalloproteinases...
(MMPs), PI3K, Akt, and vascularization (Liu et al. 2011, 2012; Xie et al. 2012). C8-prenylation of a flavonoid such as liquiritigenin may enhance the induction of H4IIE and C6 glioma cell apoptosis without affecting its antioxidative properties (Watjen et al. 2007). This compound has been reported to inhibit lipoxygenase and prostaglandin E2 (PEG2), induce cell cycle arrest in the human prostate cancer cell lines DU145 and LNCaP cells, induce cell death in the human breast cancer cell line MCF7 at high concentration, suppress pulmonary metastasis of mouse renal cell carcinoma, inhibit human lung cancer cell growth, inhibit colon cancer in ddY mice, induce apoptosis in human MGC803 gastric cancer cells, and activate the apoptosis in hepatoma cells among other effects in cancer cell, and therefore liquiritigenin is a potent protectant in cells and organs, whereas isoliquiritigenin exhibits greater potential in cancer chemoprevention (Yamamoto et al. 1991; Ma et al. 2001; Baba et al. 2002; Maggiolini et al. 2002; Yamazaki et al. 2002; Kanazawa et al. 2003; Takahashi et al. 2004; Li et al. 2004; Hsu et al. 2005a, b; Kao et al. 2014).

Both these compounds have also been applied in the treatment of cocaine addiction, but the results are preliminary. Liquiritigenin improves the selective molecular and behavioral disorders associated with cocaine use and isoliquiritigenin inhibits the dopamine release induced by cocaine (Jang et al. 2008, 2011). This research has high practical value and is worth further study (Kao et al. 2014).

7.2.3 Dehydroglyasperin C and D

Dehydroglyasperin is an isoﬂavonoid isolated from licorice that has two isoforms, dehydroglyasperin C (DGC) and dehydroglyasperin D (DGD). These two are classified as phenylisoﬂavonoids and are strong antioxidants, although the potency of DGC is greater. The isoangustone A, another phenylisoﬂavonoid has also been identiﬁed, with lower antioxidant activity than that of DGD (Lee et al. 2010b, c; Kim et al. 2012a). Both DGC as well as DGD are potent ligands of peroxisome proliferator-activated receptor γ (PPARγ), which is thought to play a role in metabolic syndrome. The liquorice ethanolic extract containing DGC and DGD when used for the treatment in KK-Ay and obese C57BL mice has been observed to prevent and ameliorate metabolic syndrome in diabetic forms (Mae et al. 2003). According to Seo et al. (2010), DGC is not only a ligand of PPARγ but also an activating factor of Nrf2 and detoxifying enzymes. It also modulates PI3K/Akt and Nrf2-Keap1 to protect against glutamate-induced neuronal cell damage (Kim et al. 2012b). Both DGC and DGD are relatively newly isolated compounds from liquorice and exhibit various potent activities, but further study of their biology and toxicity is needed (Kao et al. 2014).

7.2.4 Glabridin

Another isoﬂavonoid reported from liquorice is glabridin with a structure similar to estradiol-17β, and showing antimicrobial and antioxidant features (Mitscher et al. 2003).
It is frequently used in oxidative stress studies, including LDL oxidation due to its well-described antioxidant capabilities (Belinky et al. 1998). Glabridin might modulate bone disorders in postmenopausal women and increase osteoblastic cell function (Somjen et al. 2004; Choi 2005). Although a potent antioxidant, its brain penetration through the BBB is altered by p-glycoprotein, which might limit its application in central nervous system (CNS) diseases (Yu et al. 2007). The main application of glabridin seems to be in cosmetics. The antioxidant ability can help to modulate anti-inflammatory mechanisms in skin tissue (Kao et al. 2014). The clinical studies are lacking however, some commercial formulations with liquorice extract claim that glabridin is useful for skin depigmentation (Leyden et al. 2011). According to Jirawattanapong et al. (2009), glabridin and its derivatives inhibit tyrosinase. There are reports of a reduction in UV-B-induced pigmentation and erythema in brownish guinea pigs after glabridin administration for 3 weeks following UV-B irradiation (Yokota et al. 1998). In addition to this potent anti-inflammatory activity, it has been reported to inhibit inducible nitric oxide synthase (iNOS) expression and upregulate manganese SOD, catalase, and paraoxonase 2 expression (Kang et al. 2005; Yehuda et al. 2011).

Many evidence indicate that this compound may be beneficial in the treatment of diabetes mellitus and related diseases. Glabridin is found in the liquorice flavonoid oil (LFO, also called Kaneka glavonoid-rich oil) as a bioactive flavonoid. It is reported to suppress abdominal fat accumulation and blood glucose levels in KK-Ay mice (Nakagawa et al. 2004). Licorice flavonoid oil (LFO) can activate AMP-activated protein kinase (AMPK) and ameliorate the increases in fatty liver and in the triglyceride and cholesterol plasma levels induced by obesity (Lee et al. 2012). If administered daily up to 1200 mg/day it is accepted as safe in humans (Aoki et al. 2007). LFO seems to be as safe as a functional food. Glabridin also is involved in the cancer prevention, because it blocks FAK/Rho signaling in human nonsmall cell lung cancer A549 cells and inhibits the migration, invasion, and angiogenesis of A549 cells (Tsai et al. 2011). In view of this, uses of glabridin beyond cosmetics need to be explored (Kao et al. 2014).

### Carbenoxolone

Carbenoxolone or CBX known as sodium carbenoxolone is the 3-hemisuccinate of glycyrrhetinic acid, with a chemical structure similar to that of glucocorticoids. It may be the best-known derivative of glycyrrhetinic acid, because the disodium salt of the 3-o-hydrogen succinate, carbenoxolone is freely soluble in water (Lennon and Lennard 1964). According to the report published by Connors in 2012, CBX can be used as an anti-inflammatory agent and an inhibitor of 11β-hydroxysteroid dehydrogenase type 1. Its most important characteristic is sterol regulation, which is involved in its effectiveness in the prevention of fatty liver (Rhee et al. 2012). This compound might have a nootropic effect due to the regulatory ability of glucocorticoids, thus improving verbal fluency and verbal memory in humans (Sandeep et al.
The quotes from traditional Chinese medicine “Bencao Gangmu” state that liquorice consumption may enhance memory. Its best-known modern application is for the treatment for gastric ulcer, which is based on the spironolactone, and has a good outcome in aphthous ulcers (Doll et al. 1968; Porter and Scully Cbe 2007).

It is also a well-known gap junction inhibitor, widely used in neuroscience research (Davidson et al. 1986). Gap junctions are also important in glutamate-induced neurotoxicity, and carbenoxolone can decrease the toxic effects of glutamate (Ozog et al. 2002). This compound is said to show a protective role against ischemic injury in skeletal muscle and the hippocampus resulting from gap junction inhibition (Hosseinzadeh et al. 2005). The gap junctions are also related to pain control. The reason being the spinal cord glia exhibits extensive gap junctional connectivity, which is involved in the contralateral spread of excitation resulting in mirror image pain (Spataro et al. 2004). Carbenoxolone is also an inhibitor of gap junctions, its application in pain relief seems reasonable. Connexin gap junction proteins (Cx43 and Cx26) initiate brain metastatic lesion formation in association with the vasculature. It can prevent tumor cell extravasation and blood vessel involvement (Stoletov et al. 2013) and is frequently used in cancer research to probe the relationship between gap junctions and cancer formation. A typical study is the relationship between gap function and breast cancer metastasis or melanoma brain colonization (Stoletov et al. 2013). This compound looks like a useful agent for many research fields and is widely applied in clinical treatments (Kao et al. 2014).

References

Afreen F, Zobayed SMA, Kozai T (2005) Spectral quality and UV-B stress stimulate glycyrrhizin concentration of Glycyrrhiza uralensis in hydroponic and pot system. Plant Physiol Biochem 43:1074–1081

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

Ahamed A, Tsurumi S, Ozaki M, Amakawa T (2001) An artificial sweetener stimulates the sweet taste in insect: dual effects of glycyrrhizin in Phormia regina. Chem Senses 26:507–515

Aida K, Tawata M, Shindo H, Onaya T, Sasaki H, Yamaguchi T, Chin M, Mitsuhashi H (1990) Isoliquiritigenin: a new aldose reductase inhibitor from glycyrrhizae radix. Planta Med 56:254–258

Akhtar N, Khan MS, Iqbal A, Khan BA, Bashir S (2011) Glycyrrhiza glabra extract cream: effect on skin pigment melanin. In: Proceeding book of International Conference on Bioscience, Biochemistry and Bioinformatics, IPCBEE, IACSIT Press, Singapore

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

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

Ambawade S, Kasture VS, Kasturi SB (2001) Anxiolytic activity of Glycyrrhiza glabra Linn. J. Nat. Remedies 2:130–134
Amirova GS (1993) Licorice in Azerbaijan (in Russian). Elm, Baku, 104 pp
Ammar NM, El-Hawary SSED, El-Anssary AA, Othman N, Galal M, El-Desoky AH (2012) Phytochemical and clinical studies of the bioactive extract of Glycyrrhiza glabra L. Family Leguminosae. Int J Phytomed 4(3):429
Aoki F, Nakagawa K, Kitano M, Ikematsu H, Nakamura K, Yokota S, Tominaga Y, Arai N, Mae T (2007) Clinical safety of licorice flavonoid oil (LFO) and pharmacokinetics of glabridin in healthy humans. J Am Coll Nutr 26:209–218
Arjumand W, Sultana S (2011) Glycyrrhizic acid: a phytochemical with a protective role against cisplatin-induced genotoxicity and nephrotoxicity. Life Sci 89:422–429
Asl NM, Hosseinzadeh H (2008) Review of pharmacological effects of Glycyrrhiza sp. and its bioactive compounds. Phytother Res 22(6):709–724
Asl MN, Hosseinzadeh H (2012) Licorice (Glycyrrhiza species). In: Singh R (ed) Genetic resources, chromosome engineering and crop improvement: medicinal plants, vol 6. CRC Press, LLC, Taylor & Francis, USA, pp 935–958
Ata Ş, Akyüz M, Çabuk H (2017) Determination of biogenic amines in licorice (Glycyrrhiza glabra) by ion-pair extraction and liquid chromatography-tandem mass spectrometry. J Sci Food Agric 97:1427–1432
Baba M, Shigeta S (1987) Antiviral activity of glycyrrhizin against varicella-zoster virus in vitro. Antiviral Res 7:99–107
Baba M, Asano R, Takigami I, Takahashi T, Ohmura M, Okada Y, Sugimoto H, Arika T, Nishino H, Okuyama T (2002) Studies on cancer chemoprevention by traditional folk medicines XXV. Inhibitory effect of isoliquiritigenin on aoxymethane-induced murine colon aberrant crypt focus formation and carcinogenesis. Biol Pharm Bull 25:247–250
Belinky PA, Aviram M, Mahmood S, Vaya J (1998) Structural aspects of the inhibitory effect of glabridin on LDL oxidation. Free Radic Biol Med 24:1419–1429
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
Cai Y, Luo Q, Sun M, Corke HA (2004) Antioxidant activity and phenolic compounds of 112 traditional Chinese medicinal plants associated with anticancer. Life Sci 74:2157–2184
Çakmak YS (2011) Determination of chemical composition by using chromatographic techniques and antioxidant capacities of Glycyrrhiza L. species in Turkey. Ph.D. Thesis, The Graduate School of Natural and Applied Science of Selçuk University, Konya-Turkey
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
Chang C (1981) c.f. Shang Han Lun. Oriental Healing Arts Institute, Los Angeles
Chintharlapalli S, Papineni S, Abdelrahim M, Abudayyeh A, Jutooru I, Chadalapaka G, Wu F, Mertens-Talcott S, Vanderlaag K, Cho SD, Smith R III, Safe S (2009) Oncogenic microRNA-27a is a target for anticancer agent methyl 2-cyano-3,11-dioxo-18beta-olean-1,12-dien-30-oate in colon cancer cells. Int J Cancer 125:1965–1974
Choi EM (2005) The licorice root derived isoflavan glabridin increases the function of osteoblastic MC3T3-E1 cells. Biochem Pharmacol 70:363–368
Choi EM (2012) Liquiritigenin isolated from *Glycyrrhiza uralensis* stimulates osteoblast function in osteoblastic MC3T3-E1 cells. Int Immunopharmacol 12:139–143
Chopra PKPG, Saraf BD, Inam F et al (2013) Antimicrobial and antioxidant activities of methanol extract roots of *Glycyrrhiza glabra* and HPLC analysis. Int J Pharm Pharmacol Sci 5(2): 157–160
Christensen SB, Kharazmi A (2001) Antimalarial natural products. In: Tringali C (ed) Bioactive compounds from natural sources: isolation, characterization and biological properties. Taylor and Francis, New York, pp 379–432
Chung JG (1998) Inhibitory actions of glycyrrhizic acid on arylamine N-acetyltransferase activity in strains of *Helicobacter pylori* from peptic ulcer patients. Drug Chem Toxicol 21:355–370
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
Connors BW (2012) Tales of a dirty drug: carbenoxolone, gap junctions, and seizures. Epilepsy Curr 12:66–68
Crance JM, Biziagos E, Passagot J, van Cuyck-Gandre H, Deloine R (1990) Inhibition of hepatitis A virus replication in vitro by antiviral compounds. J Med Virol 31:155–160
Csuk R, Schwarz S, Siewert B, Kluge R, Strohl D (2011) Synthesis and antitumor activity of ring A modified glycyrrhetinic acid derivatives. Eur J Med Chem 46:5356–5369
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
Davidson JS, Baumgarten IM, Harley EH (1986) Reversible inhibition of intercellular junctional communication by glycyrrhetinic acid. Biochem Biophys Res Commun 134:29–36
De Clercq E (2000) Current lead natural products for the chemotherapy of human immunodeficiency virus (HIV) infection. Med Res Rev 20:323–349
De Simone F, Aquino R, De Tommasi N, Mahmood N, Piacente S, Piza C (2001) Anti-HHV aromatic compounds from higher plants. In: Tringali C (ed) Bioactive compounds from natural sources: isolation, characterization and biological properties. Taylor & Francis Inc., New York, p 325
Di Paola R, Menegazzi M, Mazzon E, Genovese T, Crisafulli C, Dal Bosco M, Zou Z, Suzuki H, Cuzzocrea S (2009) Protective effects of glycyrrhizin in a gut hypoxia (ischemia)-reoxygenation (reperfusion) model. Intensive Care Med 35:687–697
Dobrea C (2016) Liquiritiae radix and possible substituents—comparative LC/MS analysis of specific flavonoids. AMT 21(4):111–113
Doll R, Langman MJ, Shawdon HH (1968) Treatment of gastric ulcer with carbenoxolone: antagonistic effect of spiranolactone. Gut 9:42–45
Farag MA, Wessjohann LA (2012) Volatiles profiling in medicinal licorice roots using steam distillation and solid-phase microextraction (SPME) coupled to chemometrics. J Food Sci 77(11):179–184
Farina C, Pinza M, Pifferi G (1998) Synthesis and anti-ulcer activity of new derivatives of glycyrrhetic, oleandric and ursolic acids. Farmaco 53:22–32
Fenwick GR, Lutomski J, Nieman C (1990) Liquorice, *Glycyrrhiza glabra* L.—composition, uses and analysis. Food Chem 38:119–143
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
Firm R (2010) Nature’s chemicals: the natural products that shaped our world. Oxford University Press, Oxford, pp 74–75
Franceschelli S, Pesce M, Vinciguerra I, Ferrone A, Riccioni G, 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
Frattini C, Bicchi C, Baretetti C, Nano GM (1977) Volatile flavor components of licorice. J Agric Food Chem 25(6):1238–1241
Fu B, Li H, Wang X, Lee FS, Cui S (2005) Isolation and identification of flavonoids in licorice and a study of their inhibitory effects on tyrosinase. J Agric Food Chem 53:7408–7414

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, Satoh K, Nomura T, Sakagami H (2003) Preliminary evaluation of antinephritis and radical scavenging activities of glabridin from Glycyrrhiza glabra. Fitoterapia 74(7):624–629

Gao W, Li K, Yan S, Gao X, Hu L (2009) Effects of space flight on DNA mutation and secondary metabolites of licorice (Glycyrrhiza uralensis Fisch.). Sci China, Ser C Life Sci 52:977–981

Gao Y, Guo X, Li X, Liu D, Song D, Xu Y, Sun M, Jing Y, Zhao L (2010) The synthesis of glycyrrhetinic acid derivatives containing a nitrogen heterocycle and their antiproliferative effects in human leukemia cells. Molecules 15:4439–4449

Guan Y, Li FF, Hong L, Yan XF, Tan GL, He JS, Dong XW, Bao MJ, Xie QM (2012) Protective effects of liquiritin apioside on cigarette smoke-induced lung epithelial cell injury. Fundam Clin Pharmacol 26:473–483

Gumpricht E, Dahl R, Devereaux MW, Sokol RJ (2005) Licorice compounds glycyrrhizin and 18 beta-glycyrrhetinic acid are potent modulators of bile acid-induced cytotoxicity in rat hepatocytes. J Biol Chem 280:10556–10563

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

Haleagrahara N, Varkkey J, Chakravarthi S (2011) Cardioprotective effects of glycyrrhizic acid against isoproterenol-induced myocardial ischemia in rats. Int J Mol Sci 12:7100–7113

Haraguchi H (2001) Antioxidative plant constituents. In: Tringali C (ed) Bioactive compounds from natural sources: isolation, characterization and biological properties. Taylor & Francis Inc., New York, pp 348–352

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

Hayashi H, Hiroaka N, Ikeshiro Y, Yamamoto H, Yoshikawa T (1998) Seasonal variation of glycyrrhizin and isoliquiritigenin glycosides in the root of Glycyrrhiza glabra L. Biol Pharm Bull 21(9):987–989

He Y, Gai Y, Wu X, Wan H (2012) Quantitatively analyze composition principle of Ma Huang Tang by structural equation modeling. J Ethnopharmacol 143:851–858

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

Hirayama C, Okumura M, Tanikawa K, Yano M, Mizuta M, Ogawa N (1989) A multicenter randomized controlled clinical trial of Shosaiko-to in chronic active hepatitis. Gastroenterol Jpn 24:715–719

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

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

Hosseinzadeh H, Nassiri Asl M, Parvardeh S (2005) The effects of carbonoxolone, a semisynthetic derivative of glycyrrhizic acid, on peripheral and central ischemia-reperfusion injuries in the skeletal muscle and hippocampus of rats. Phytomedicine 12:632–637

Hsu YL, Kuo PL, Lin LT, Lin CC (2005a) Isoliquiritigenin inhibits cell proliferation and induces apoptosis in human hepatoma cells. Planta Med 71:130–134

Hsu YL, Kuo PL, Lin CC (2005b) Isoliquiritigenin induces apoptosis and cell cycle arrest through p53-dependent pathway in Hep G2 cells. Life Sci 77:279–292

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

Hwang IK, Lim SS, Choi KH, Yoo KY, Shin HK, Kim EJ, Yoon-Park JH, Kang TC, Kim YS, Kwon DY, Kim DW, Moon WK, Won MH (2006) Neuroprotective effects of roasted licorice, not raw form, on neuronal injury in gerbil hippocampus after transient forebrain ischemia. Acta Pharmacol Sin 27:959–965
Iba K, Chiba H, Sawada N, Hirota S, Ishii S, Mori M (1995) Glucocorticoids induce mineralization coupled with bone protein expression without influence on growth of a human osteoblastic cell line. Cell Struct Funct 20:319–330

Li T, Satomi Y, Katoh D, Shimada J, Baba M, Okuyama T, Nishino H, Kitamura N (2004) Induction of cell cycle arrest and p21(CIP1/WAF1) expression in human lung cancer cells by isoliquiritigenin. Cancer Lett 207:27–35

Ikeda K (2007) Glycyrrhizin injection therapy prevents hepatocellular carcinogenesis in patients with interferon-resistant active chronic hepatitis C. Hepatol Res: Official J Jpn Soc Hepatol 37 (Suppl 2):S287–S293

Ikeda K, Arase Y, Kobayashi M, Saitoh S, Someya T, Hosaka T, Sazaki H, Akuta N, Suzuki Y, Suzuki F, Kumada H (2006) A long-term glycyrrhizin injection therapy reduces hepatocellular carcinogenesis rate in patients with interferon-resistant active chronic hepatitis C: a cohort study of 1249 patients. Dig Dis Sci 51:603–609

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

Jang EY, Choe ES, Hwang M, Kim SC, Lee JR, Kim SG, Jeon JP, Buono RJ, Yang CH (2008) Isoliquiritigenin suppresses cocaine-induced extracellular dopamine release in rat brain through GABA(B) receptor. Eur J Pharmacol 587:124–128

Jang EY, Hwang M, Yoon SS, Lee JR, Kim KJ, Kim HC, Yang CH (2011) Liquiritigenin decreases selective molecular and behavioral effects of cocaine in rodents. Curr Neuropharmacol 9:30–34

Jayaprakasam B, Doddaga S, Wang R, Holmes D, Goldfarb J, Li XM (2009) Licorice flavonoids inhibit eotaxin-1 secretion by human fetal lung fibroblasts in vitro. J Agric Food Chem 57:820–825

Jirawattanapong W, Saifah E, Patarapanich C (2009) Synthesis of glabridin derivatives as tyrosinase inhibitors. Arch Pharm Res 32:647–654

Junghauer A, Medjakovic S (2014) Phytoestrogens and the metabolic syndrome. J Steroid Biochem Mol Biol 139:277–289

Jutooru I, Chadalapaka G, Chintharlapalli S, Papineni S, Safe S (2009) Induction of apoptosis and nonsteroidal anti-inflammatory drug-activated gene 1 in pancreatic cancer cells by a glycyrrhetinic acid derivative. Mol Carcinog 48:692–702

Kajiyama K, Demizu S, Hiraga Y, Kinoshita K, Koyama K, Takahashi K, Tamura Y, Okada K, Kinoshita T (1992) New prenylflavones and dibenzoylmethane from Glycyrrhiza inflata. J Nat Prod 55(9):1197–1203

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

Kamei J, Nakamura R, Ichiki H, Kubo M (2003) Antitussive principles of Glycyrrhizae radix, a main component of the Kampo preparations Bakumondo-to (Mai-men-dong-tang). Eur J Pharmacol 469:159–163

Kamei J, Saitoh A, Asano T, Nakamura R, Ichiki H, Iiduka A, Kubo M (2005) Pharmacokinetic and pharmacodynamic profiles of the antitussive principles of Glycyrrhizae radix (licorice), a main component of the Kampo preparation Bakumondo-to (Mai-men-dong-tang). Eur J Pharmacol 507:163–168

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 JS, Yoon YD, Cho IJ, Han MH, Lee CW, Park SK, Kim HM (2005) Glabridin, an isoflavon 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

Kang HE, Kim YW, Sohn SI, Baek SR, Lee JW, Kim SG, Lee I, Lee MG (2010a) Pharmacokinetics of liquiritigenin and its two glucuronides, M1 and M2, in rats with acute hepatitis induced by dgalactosamine/lipopolysaccharide or CCl(4). Xenobiotica 40:424–436

Kang HE, Chung HJ, Kim HS, Lee JW, Lee MG (2010b) Pharmacokinetic interaction between liquiritigenin (LQ) and DDB: increased glucuronidation of LQ in the liver possibly due to increased hepatic blood flow rate by DDB. Eur J Pharm Sci 39:181–189
Kao TC, Shyu MH, Yen GC (2009) Neuroprotective effects of glycyrrhizic acid and 18beta-glycyrrhetic acid in PC12 cells via modulation of the PI3K/Akt pathway. J Agric Food Chem 57:754–761
Kao TC, Shyu MH, Yen GC (2010) Glycyrrhizic acid and 18beta-glycyrrhetic acid inhibit inflammation via PI3K/Akt/GSK3beta signaling and glucocorticoid receptor activation. J Agric Food Chem 58:8623–8629
Kao TC, Wu CH, Yen GC (2013) Glycyrrhizic acid and 18beta-glycyrrhetic acid recover glucocorticoid resistance via PI3K-induced AP1, CRE and NFAT activation. Phytomedicine 20:295–302
Kao T-C, Wu C-H, Yen G-C (2014) Bioactivity and potential health benefits of licorice. J Agric Food Chem 62:542–553
Kar A (2007) Pharmacognosy and pharmacobiotechnology. New Age International Ltd. Publishers, New Delhi, pp 332–600
Khalaf I, Vlase L, Lazăr D, Corciova A, Ivănescu B, Lazăr MI (2010) Hplc-Ms study of phytoestrogens from Glycyrrhiza glabra. Farmacia 58(1):89–94
Kim DH, Lee SW, Han MJ (1999) Biotransformation of glycyrrhizin to 18beta-glycyrrhetic acid-3-O-beta-D-glucuronide by Streptococcus LJ-22, a human intestinal bacterium. Biol Pharm Bull 22:320–322
Kim SC, Byun SH, Yang CH, Kim CY, Kim JW, Kim SG (2004) Cytoprotective effects of Glycyrrhiza radix extract and its active component liquiritigenin against cadmium-induced toxicity (effects on bad translocation and cytochrome c-mediated PARP cleavage). Toxicology 197:239–251
Kim YW, Ki SH, Lee JR, Lee SJ, Kim CW, Kim SC, Kim SG (2006) Liquiritigenin, an aglycone of liquiritin in Glycyrrhiza radix, prevents acute liver injuries in rats induced by acetaminophen with or without buthionine sulfoximine. Chem Biol Interact 161:125–138
Kim YW, Zhao RJ, Park SJ, Lee JR, Cho JJ, Yang CH, Kim SG, Kim SC (2008) Anti-inflammatory effects of liquiritigenin as a consequence of the inhibition of NF-kappaB-dependent iNOS and proinflammatory cytokines production. Br J Pharmacol 154:165–173
Kim YW, Kang HE, Lee MG, Hwang SJ, Kim SC, Lee CH, Kim SG (2009) Liquiritigenin, a flavonoid aglycone from licorice, has a choleric effect and the ability to induce hepatic transporters and phase-II enzymes. Am J Physiol Gastrointest Liver Physiol 296:G372–G381
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 collageninduced arthritis in mice. J Biomed Biotechnol 709378
Kim HJ, Seo JY, Suh HJ, Lim SS, Kim JS (2012a) Antioxidant activities of licorice-derived prenylflavonoids. Nutr Res Pract 6:491–498
Kim HJ, Lim SS, Park IS, Lim JS, Seo JY, Kim JS (2012b) Neuroprotective effects of dehydroglyasperin C through activation of heme oxygenase-1 in mouse hippocampal cells. J Agric Food Chem 60:5583–5589
Kim ME, Kim HK, Kim DH, Yoon JH, Lee JS (2013) 18beta-Glycyrrhetic acid from licorice root impairs dendritic cells maturation and Th1 immune responses. Immunopharmacol Immunotoxicol 35:293–309
Kinoshiba T, Tamura Y, Mizutani K (2005) The isolation and structure elucidation of minor isoflavonoids from licorice of Glycyrrhiza glabra origin. Chem Pharm Bull 53:847–849
Kobayashi S, Miyamoto T, Kimura I, Kimura M (1995) Inhibitory effect of isoliquiritin, a compound in licorice root, on angiogenesis in vivo and tube formation in vitro. Biol Pharm Bull 18:1382–1386
Kong LD, Zhang Y, Pan X, Tan RX, Cheng CH (2000) Inhibition of xanthine oxidase by liquiritigenin and isoliquiritigenin isolated from Sinofranchetia chinensis. Cell Mol Life Sci 57:500–505
Krausse R, Bielenberg J, Blaschek W, Ullmann U (2004) In vitro anti-Helicobacter pylori activity of extractum liquiritiae, glycyrrhizin and its metabolites. J Antimicrob Chemother 54:243–246
Kroes BH, Beukelman CJ, van den Berg AJ, Wolbink GJ, van Dijk H, Labadie RP (1997) Inhibition of human complement by beta-glycyrrhetic acid. Immunology 90(1):115–120
Kumagai A, Nishino K, Shimomura A, Kin T, Yamamura Y (1967) Effect of glycyrrhizin on estrogen action. Endocrinol Japon 14:34–38
References

Kuwajima H, Taneda Y, Chen WZ, Kawanishi T, Hori K, Taniyama T, Kobayashi M, Ren J, Kitagawa I (1999) Variation of chemical constituents in processed licorice roots: quantitative determination of saponin and flavonoid constituents in bark removed and roasted licorice roots. Yakugaku Zasshi 119:945–955

Lampi G, Deidda D, Pinza M, Pompei R (2001) Enhancement of anti-herpetic activity of glycyrrhizic acid by physiological proteins. Antiviral Chem Chemother 12:125–131

Lee CS, Kim YJ, Lee MS, Han ES, Lee SJ (2008) 8beta-Glycyrrhetinic acid induces apoptotic cell death in SiHa cells and exhibits a synergistic effect against antibiotic anti-cancer drug toxicity. Life Sci 83:481–489

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, helps mice resist disseminated candidiasis due to Candida albicans by Th1 immune response, whereas liquiritin, its glycoside form, does not. Int Immunopharmacol 9:632–638

Lee CS, Yang JC, Kim YJ, Jang ER, Kim W, Myung SC (2010a) 18beta-Glycyrrhetinic acid potentiates apoptotic effect of trichostatin A on human epithelial ovarian carcinoma cell lines. Eur J Pharmacol 649:354–361

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

Lee YS, Kim SH, Jung SH, Kim JK, Pan CH, Lim SS (2010c) Aldose reductase inhibitory compounds from Glycyrrhiza uralensis. Biol Pharm Bull 33:917–921

Lee JW, Choe SS, Jang H, Kim J, Jeong HW, Jo H, Jeong KH, Tadí S, Park MG, Kwak TH, Man Kim J, Hyun DH, Kim JB (2012) AMPK activation with glabridin ameliorates adiposity and lipid dysregulation in obesity. J Lipid Res 53:1277–1286

Lee KK, Omiya Y, Yuzurihara M, Kase Y, Kobayashi H (2013) Antispasmodic effect of shakuyakukanzoto extract on experimental muscle cramps in vivo: role of the active constituents of Glycyrrhizae radix. J Ethnopharmacol 145:286–293

Lennon GG, Lennard M (1964) Today’s drugs. Carbenoxolone sodium. Br Med J 1:1690–1691

Leyden JJ, Shergil B, Micali G, Downie J, Wallo W (2011) Natural options for the management of hyperpigmentation. J Eur Acad Dermatol Venereol 25:1140–1145

Li S (2003) Compendium of materia medica. Foreign Languages Press, Beijing

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

Li JR, Wang YQ, Deng ZZ (2005) Two new compounds from Glycyrrhiza glabra. J Asian Nat Prod Res 7:677–680

Li K, Ji S, Song W, Kuang Y, Lin Y, Tang S, Cui Z, Qiao X, Yu S, Ye M (2017) Glycybrids A–K, bioactive phenolic compounds from Glycyrrhiza glabra. J Nat Prod 80(2):334–346

Lin JC (2003) Mechanism of action of glycyrrhizic acid in inhibition of Epstein-Barr virus replication in vitro. Antiviral Res 59:41–47

Lin KW, Huang AM, Hour TC, Yang SC, Pu YS, Lin CN (2011) 18beta-Glycyrrhetinic acid derivatives induced mitochondrialmediated apoptosis through reactive oxygen species-mediated p53 activation in NTUB1 cells. Bioorg Med Chem 19:4274–4285

Lin Y, Kuang Y, Li K, Wang S, Song W, Qiao X, Sabir G, Ye M (2017) Screening for bioactive natural products from a 67-compound library of Glycyrrhiza inflata. Bioorg Med Chem 25(14):3706–3713

Liu RT, Zou LB, Lu QJ (2009) Liquiritigenin inhibits Abeta(25–35)-induced neurotoxicity and secretion of Abeta(1–40) in rat hippocampal neurons. Acta Pharmacol Sin 30:899–906

Liu RT, Zou LB, Fu JY, Lu QJ (2010) Effects of liquiritigenin treatment on the learning and memory deficits induced by amyloid betapetide (25–35) in rats. Behav Brain Res 210:24–31

Liu C, Wang Y, Xie S, Zhou Y, Ren X, Li X, Cai Y (2011) Liquiritigenin induces mitochondria-mediated apoptosis via cytochrome c release and caspases activation in HeLa cells. Phytother Res 25:277–283

Liu Y, Xie S, Wang Y, Luo K, Wang Y, Cai Y (2012) Liquiritigenin inhibits tumor growth and vascularization in a Mouse model of HeLa cells. Molecules 17:7206–7216

Lou ZC, Qin B (1995) Species systematization and quality evaluation of commonly used Chinese traditional drugs, North-Edition vol 1–3. Beijing Medical University Press and Peking Union Medical College Press, Beijing. p 19
Ma J, Fu NY, Pang DB, Wu WY, Xu AL (2001) Apoptosis induced by isoliquiritigenin in human gastric cancer MGC-803 cells. Planta Med 67:754–757

Ma CJ, Li GS, Zhang DL, Liu K, Fan X (2005) One step isolation and purification of liquorifoline and isoliquiritigenin from Glycyrrhiza uralensis. J Chromatogr 1078:188–192

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

Madjiga HA, Sanni S, Sandabe UK (2010) Phytochemical and elemental analysis of Acalypha wilkesiana leaf. J Am Sci 6(11):510–514

Maë T, Kishida H, Nishiyama T, Takahashi K, Kawada T, Nakagawa K, Kitahara M (2003) A licorice ethanolic extract with peroxisome proliferator-activated receptor-gamma ligand-binding activity affects diabetes in KK-Ay mice, abdominal obesity in diet-induced obese C57BL mice and hypertension in spontaneously hypertensive rats. J Nutr 133:3369–3377

Maggiolini M, Statti G, Vivaquca A, Gabriele S, Menichini F, Amdo S (2002) Estrogenic and antiproliferative activities of isoliquiritigenin in MCF7 breast cancer cells. J Steroid Biochem Mol Biol 82:315–322

Mantfredi KP, Vallurupalli V, Demidova M, Kindscher K, Pannell LK (2001) Isolation of an anti-HIV diprenylated bibenzyl from Glycyrrhiza lepidota. Phytochemistry 58:153–157

Manns MP, Wedemeyer H, Singer A, Khomutjanskaja N, Dienes HP, Roskams T, Goldin R, Hennke U, Inoue H, European SSG (2012) Glycyrrhizin in patients who failed previous interferon alpha-based therapies: biochemical and histological effects after 52 weeks. J Viral Hepatitis 19:537–546

Martinez MJA, Lazaro RM, del Olmo LMB, Benito PB (2008) Anti-infectious activity in the Anthemideae tribe. Stud Nat Prod Chem 35:445–516

Maurya R, Singh G, Yadav PP (2008) Antiosteoporotic agents from natural sources. Stud Nat Prod Chem 35:517–545

Mersereau JE, Levy N, Staub RE, Baggett S, Zogovic T, Chow S, Ricke WA, Tagliaferri M, Cohen I, Bjeldanes LF, Leitman DC (2008) Liquiritigenin is a plant-derived highly selective estrogen receptor beta agonist. Mol Cell Endocrinol 283:49–57

Messier C, Epifano F, Genovesi S, Grenier D (2012) Licorice and its potential beneficial effects in common oro-dental diseases. Oral Dis 18:32–39

Michaelis M, Geiler J, Naczk P, Sithisarn P, Leutz A, Doerr HW, Cinatl J Jr (2011) Glycyrrhizin exerts antioxidative effects in H5N1 influenza A virus-infected cells and inhibits virus replication and proinflammatory gene expression. PLoS ONE 6:e19705

Mitscher LA, Park YH, Clark D, Beal JL (1980) Antimicrobial agents from higher plants. Antimicrobial isoavonoids and related substances from Glycyrrhiza glabra L. var. typica. J Nat Prod 43:259–269

Mollica L, De Marchis F, Spitaleri A, Dallacosta C, Pennacchini D, Zamai M, Agresti A, Trisciuoglio L, Musco G, Bianchi ME (2007) Glycyrrhizin binds to high-mobility group box 1 protein and inhibits its cytokine activities. Chem Biol 14:431–441

Moro T, Shimoyama Y, Kushida M, Hong YY, Nakao S, Higashiyama R, Sugioaka Y, Inoue H, Okazaki I, Imagaki Y (2008) Glycyrrhizin and its metabolite inhibit Smad3-mediated type I collagen gene transcription and suppress experimental murine liver fibrosis. Life Sci 83:531–539

Naïr R, Jaquier A (2006) New lactones in licorice (Glycyrrhiza glabra L.). Flavor Fragrance J 21:193–197

Nafisi S, Bonsaii M, Manouchehi F, Abdi K (2012a) Interaction of glycyrrhizin and glycyrhrhetic acid with DNA. DNA Cell Biol 31:114–121

Nafisi S, Manouchehi F, Bonsaii M (2012b) Study on the interaction of glycyrrhizin and glycyrhrhetic acid with RNA. J Photochem Photobiol, B 111:27–34

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, vol 73. Springer Wien-New York, pp 1–140
References

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

Numazaki K, Nagata N, Sato T, Chiba S (1994) Effect of glycyrrhizin, cyclosporin A, and tumor necrosis factor alpha on infection of U-937 and MRC-5 cells by human cytomegalovirus. J Leukoc Biol 55:24–28

Ogiku M, Kono H, Harah M, Tsuchiya M, Fuji H (2011) Glycyrrhizin prevents liver injury by inhibition of high-mobility group box 1 production by Kupffer cells after ischemia-reperfusion in rats. J Pharmaco Exp Ther 339:93–98

Okada K, Tamura Y, Yamamoto M, Inoue Y, Takagaki R, Takahashi K, Demizu S, Kajiyama K, Hiraga Y, Kinoshita T (1989) Identification of antimicrobial and antioxidant constituents from licorice of Russian and Xinjiang origin. Chem Pharm Bull (Tokyo) 37:2528–2530

Orient 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

Ozog MA, Siushansian R, Naus CC (2002) Blocked gap junctional coupling increases glutamate-induced neurotoxicity in neuron-astrocyte co-cultures. J Neuropathol Exp Neuroul 61:132–141

Pan X, Kong LD, Zhang Y, Cheng CH, Tan RX (2000) In vitro inhibition of rat monoamine oxidase by liquiritigenin and isoliquiritigenin isolated from Sinofranchetia chinensis. Acta Pharmacol Sin 21:949–953

Paolini M, Barillari J et al (1999) Effect of liquorice and glycyrrhizin on rat liver carcinogen metabolizing enzymes. Cancer Lett 145:35–42

Parvaz M, Hussain K, Khalid S, Hussnain N, Iram N, Hussain Z, Ali MA (2014) A review: medicinal importance of Glycyrrhiza glabra L. (Fabaceae Family). Global J Pharmaco 8(1):8–13

Patil SM, Patil MB, Sankale GN (2009) Antimicrobial activity of Glycyrrhiza glabra Linn. roots. Int J Chem Sci 7(1):585–591

Ploeger B, Mensinga T, Sips A, Seinen W, Meulenberg J, De Jongh J (2001) The pharmacokinetics of glycyrrhizic acid evaluated by physiologically based pharmacokinetic modeling. Drug Metab Rev 33:125–147

Pompei R, Flore O, Marccialis MA, Pani A, Loddo B (1979) Glycyrrhizic acid inhibits virus growth and inactivates virus particles. Nature 281:689–690

Porter SR, Scully Cbe C (2007) Aphthous ulcers (recurrent). Clin Evid (Online) 1303

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

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

Raml ES, Suhaimi F, Asri SF, Ahmad F, Soelaiman IN (2013) Glycyrrhizic acid (GCA) as 11beta-hydroxysteroid dehydrogenase inhibitor exerts protective effect against glucocorticoid-induced osteoporosis. J Bone Miner Metab 31:262–273

Rhee SD, Kim CH, Park JS, Jung WH, Park SB, Kim HY, Bae GH, Kim TJ, Kim KY (2012) Carbenoxolone prevents the development of fatty liver in C57BL/6-Lep ob/ob mice via the inhibition of sterol regulatory element binding protein-1c activity and apoptosis. Eur J Pharmaco 691:9–18

Rizzato G, Scalabrini E, Radaelli M, Capodaglio G, Piccolo O (2017) A new exploration of licorice metabolome. Food Chem 221:959–968

Sandeep TC, Yau JL, MacLullich AM, Noble J, Deary IJ, Walker BR, Seckl JR (2004) 11Beta-hydroxysteroid dehydrogenase inhibition improves cognitive function in healthy elderly men and type 2 diabetics. Proc Natl Acad Sci USA 101:6734–6739

Sarker SD, Nahur L (2007) Chemistry for pharmacy students: general, organic and natural product chemistry. Wiley, London
Satomi Y, Nishino H, Shibata S (2005) Glycyrrhetinic acid and related compounds induce G1 arrest and apoptosis in human hepatocellular carcinoma HepG2. Anticancer Res 25(6):4043–4047
Seo JY, Lee YS, Kim HJ, Lim SS, Lim JS, Lee IA, Lee CH, Yoon Park JH, Kim JS (2010) Dehydroglauasarpen C isolated from licorice caused Nrf2-mediated induction of detoxifying enzymes. J Agric Food Chem 58:1603–1608
Sharma V, Agrawal RC (2013) Glycyrrhiza glabra—a plant for the future. Mintage J Pharm Med Sci 2(3):15–20
Sharma G, Kar S, Palit S, Das PK (2012) 18beta-glycyrrhetinic acid induces apoptosis through modulation of Akt/FOXO3a/Bim pathway in human breast cancer MCF-7 cells. J Cell Physiol 227:1923–1931
Shetty AV, Thirugnanam S, Dakshinamoorthy G, Samykutty A, Zheng G, Chen A, Bosland MC, Kajdacy-Balla A, Gnanasekar M (2011) 18alpha-glycyrrhetinic acid targets prostate cancer cells by down-regulating inflammation-related genes. Int J Oncol 39:635–640
Simmler C, Pauli GF, Chen SN (2013) Phytochemistry and biological properties of glabridin. Fitoterapia 90:160–184
Sitohy MZ, El-Massry RA, El-Saadany SS, Labib SM (1991) Metabolic effect of licorice roots (Glycyrrhiza glabra) on lipid distribution pattern, liver and renal functions of albino rats. Nahrung 35:799–806
Soﬁa H, Walter TM (2009) Review of Glycyrrhiza glabra Linn. Siddha Pap, Med J 2(1):1–7
Somjen D, Katzburg S, Vaya J, Kaye AM, Hendel D, Posner GH, Tamir S (2004) Estrogenic activity of glabridin and glabrene from licorice roots on human osteoelastic and prepubertal rat skeletal tissues. J Steroid Biochem Mol Biol 91:241–246
Song D, Gao Y, Wang R, Liu D, Zhao L, Jing Y (2010) Downregulation of c-FLIP, XIAP and Mcl-1 protein as well as depletion of reduced glutathione contribute to the apoptosis induction of glycyrrhetinic acid derivatives in leukemia cells. Cancer Biol Ther 9:96–108
Spataro LE, Sloane EM, Milligan ED, Wieseler-Frank J, Schoeniger D, Jekich BM, Barrientos RM, Maier SF, Watkins LR (2004) Spinal gap junctions: potential involvement in pain facilitation. J Pain 5:392–405
Stoletov K, Strnad J, Zardouzian E, Momiyama M, Park FD, Kelber JA, Pizzo DP, Hoffman R, VandenBerg SR, Klemke RL (2013) Role of connexins in metastatic breast cancer and melanoma brain colonization. J Cell Sci 126:904–913
Sultana S, Haque A, Hamid K et al (2010) Antimicrobial, cytotoxic and antioxidant activity of methanolic extract of Glycyrrhiza glabra. Agr Bio J N Am 1(5):957–960
Sun YX, Tang Y, Wu AL, Liu T, Dai XL, Zheng QS, Wang ZB (2010) Neuroprotective effect of liquiritin against focal cerebral ischemia/reperfusion in mice via its antioxidant and antiapoptosis properties. J Asian Nat Prod Res 12:1051–1060
Sung MW, Li PC (2004) Chemical analysis of raw, dry-roasted, and honey-roasted licorice by capillary electrophoresis. Electrophoresis 25:3434–3440
Szpak K, Wybieralska E, Niedzialkowska E, Rak M, Bechye I, Michalik M, Madeja Z, Czyz J (2011) DU-145 prostate carcinoma cells that selectively transmigrate narrow obstacles express elevated levels of Cx43. Cell Mol Biol Lett 16:625–637
Tabuchi M, Imamura S, Kawakami Z, Ikarashi Y, Kase Y (2012) The blood-brain barrier permeability of 18beta-glycyrrhetinic acid, a major metabolite of glycyrrhizin in Glycyrrhiza root, a constituent of the traditional Japanese medicine yokukansan. Cell Mol Neurobiol 32:1139–1146
Takahara T, Watanabe A, Shiraki K (1994) Effects of glycyrrhizin on hepatitis B surface antigen: a biochemical and morphological study. J Hepatol 21:601–609
Takahashi T, Takasuka N, Iigo M, Baba M, Nishino H, Tsuda H, Okuyama T (2004) Isoliquiritigenin, a flavonoid from licorice, reduces prostaglandin E2 and nitric oxide, causes apoptosis, and suppresses aberrant crypt foci development. Cancer Sci 95:448–453
Takeda H, Sadakane C, Hattori T, Katsurada T, Ohkawara T, Nagai K, Asaka M (2008) Rikkunshito, an herbal medicine, suppresses cisplatin-induced anorexia in rats via 5-HT2 receptor antagonism. Gastroenterology 134:2004–2013
Tanaka S, Sakata Y, Morimoto K, Tambe Y, Watanabe Y, Honda G, Tabata M, Oshima T, Masuda T, Umezawa T, Shimada M, Nagakura N, Kamisako W, Kashiwada Y, Ikeshiro Y (2001) Influence of natural and synthetic compounds on cell surface expression of cell adhesion molecules, ICAM-1 and VCAM-1. Planta Med 67:108–113
Tang W, Eisenbrand G (1992) Chinese drugs of plant origin. Springer, Berlin, pp 567–588
Tawata M, Aida K, Noguchi T, Ozaki Y, Kume S, Sasaki H, Chin M, Onaya T (1992) Anti-platelet action of isoliquiritigenin, an aldose reductase inhibitor in licorice. Eur J Pharmacol 212:87–92
Toshibo F, Kazue S, Taro N (2003) Preliminary evaluation of anti nephritis and radical scavenging activities of glabridin from Glycyrrhiza glabra Linn. Fitotherapia 74:624–629
Tsai YM, Yang CJ, Hsu YL, Wu LY, Tsai YC, Hung JY, Lien CT, Huang MS, Kuo PL (2011) Glabridin inhibits migration, invasion, and angiogenesis of human non-small cell lung cancer A549 cells by inhibiting the FAK/rho signaling pathway. Integr Cancer Ther 10:341–349
Uto T, Morinaga O, Tanaka H, Shoyama Y (2012) Analysis of the synergistic effect of glycyrrhizin and other constituents in licorice extract on lipopolysaccharide-induced nitric oxide production using knock-out extract. Biochem Biophys Res Commun 417:473–478
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
Vashist H, Sharma D (2013) Pharmacognostical aspects of Glycyrrhiza glabra. Asian J Pharm Clin Res 6(4):55–59
Vaya J, Belinky PA, Aviram M (1998) Structural aspects of the inhibitory effect of glabridin on LDL oxidation. Free Rad Biol Med 24:1419–1429
Vivekanand JHA (2010) Herbal medicines and chronic kidney disease. Nephro 15(2):10–17
Wagner J, Granvogl M, Schieberle P (2016) Characterization of the key aroma compounds in raw licorice (Glycyrrhiza glabra L.) by means of molecular sensory science. J Agric Food Chem 64:8388–8396
Wang X, Sun H, Zhang A, Sun W, Wang P, Wang Z (2011) Potential role of metabolomics approaches in the area of traditional Chinese medicine: as pillars of the bridge between Chinese and Western medicine. J Pharm Biomed Anal 55(5):859–868
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
Watjen W, Weber N, Lou YJ, Wang ZQ, Chovelou Y, Kampkotter A, Kahl R, Proksch P (2007) Prenylation enhances cytotoxicity of apigenin and liquiritigenin in rat H4IIE hepatoma and C6 glioma cells. Food Chem Toxicol 45:119–124
Wegener JW, Nawrath H (1997) Cardiac effects of isoliquiritigenin. Eur J Pharmacol 326:37–44
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
Williamson EM (2003) Licorice. In: Potter’s cyclopedia of herbal medicines. C.W. Daniels, Saffron Walden, pp 269–271
Won SR, Kim SK, Kim YM, Lee PH, Ryu JH, Kim JW, Rhee HI (2007) Licochalcone A: a lipase inhibitor from the roots of Glycyrrhiza uralensis. Food Res Int 40:1046–1050
Wu YT, Shen C, Yin J, Yu JP, Meng Q (2006) Azathioprine hepatotoxicity and the protective effect of liquorice and glycyrrhizic acid. Phytother Res 20(8):640–645
Xie SR, Wang Y, Liu CW, Luo K, Cai YQ (2012) Liquiritigenin inhibits serum-induced HIF-1alpha and VEGF expression via the AKT/mTOR-p70S6K signalling pathway in HeLa cells. Phytother Res 26:1133–1141
Xing GX, Li N, Wang T, Yang MY (2003) Advances in studies on flavonoids of licorice. China J Chin Mater Med 28(7):593–597
Yamamoto S, Aizu E, Jiang H, Nakadate T, Kiyoto I, Wang JC, Kato R (1991) The potent anti-tumor-promoting agent isoliquiritigenin. Carcinogenesis 12:317–323
Yamamura Y, Kawakami J, Santa T et al (1992) Pharmacokinetic profile of glycerrhizin in healthy volunteers by a new high-performance liquid chromatographic method. J Pharm Sci 81: 1042–1046

Yamazaki S, Morita T, Endo H, Hamamoto T, Baba M, Joichi Y, Kaneko S, Okada Y, Okuyama T, Nishino H, Tokue A (2002) Isoliquiritigenin suppresses pulmonary metastasis of mouse renal cell carcinoma. Cancer Lett 183:23–30

Yang JC, Myung SC, Kim W, Lee CS (2012) 18betaglycyrrhetinic acid potentiates Hsp90 inhibition-induced apoptosis in human epithelial ovarian carcinoma cells via activation of death receptor and mitochondrial pathway. Mol Cell Biochem 370:209–219

Yang R, Wang LQ, Yuan BC, Liu Y (2015) The pharmacological activities of licorice. Planta Med 81(18):1654–1669

Ye R, Fan Y-H, Ma C-M (2017) Identification and enrichment of α-glucosidase-inhibiting dihydrostilbene and flavonoids from Glycyrrhiza uralensis leaves. J Agric Food Chem 65: 510–515

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

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

Yokozawa T, Liu ZW, Chen CP (2000) Protective effects of Glycyrrhizae radix extract and its compounds in a renal hypoxia (ischemia)-reoxygenation (reperfusion) model. Phytotherapy Research 14:439–445

Yu XY, Lin SG, Zhou ZW, Chen X, Liang J, Yu XQ, Chowbay B, Ben 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

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, 18α- and 18β-glycyrrhetinic acids. Planta Med 59:502–507

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

Zhang SP, Zhou YJ, Liu Y, Cai YQ (2009) Effect of liquiritigenin, a flavanone existed from Radix glycyrrhizae on pro-apoptotic in SMMC-7721 cells. Food Chem Toxicol 47:693–701

Zhang X, Song Y, Han X, Feng L, Wang R, Zhang M, Zhu M, Jia X, Hu S (2013) Liquiritin attenuates advanced glycation end products-induced endothelial dysfunction via RAGE/NF-kappaB pathway in human umbilical vein endothelial cells. Mol Cell Biochem 374: 191–201

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

Zhao K, Wang W, Guan C, Cai J, Wang P (2012) Inhibition of gap junction channel attenuates the migration of breast cancer cells. Mol Biol Rep 39:2607–2613

Zhou L, Tang YP, Gao L, Fan XS, Liu CM, Wu DK (2009) Separation, characterization and dose-effect relationship of the PPARγ-activating bio-active constituents in the Chinese herb formulation ‘San-Ao decoction’. Molecules 14:3942–3951

Zhou M, Higo H, Cai Y (2010) Inhibition of hepatoma 22 tumor by liquiritigenin. Phytother Res 24:827–833

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