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, antihepatotoxic, 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, endocrinal 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 hyporcholesterolemic and hypoglycemic activities (Sitohy et al. 1991), anxiolytic activity (Ambawade et al. 2001), antimicrobial (Patil et al. 2009), antiviral (Cinatl 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).

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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 liqourice 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, glycyrretol, 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 flavanoids (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 (Firn 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 dibenzoylmathane, 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-2*H*-l-benzopyran-6-yl)-3-(4-hydroxy-3-prenyl-phenyl)1-, 3-propane dione (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 liquroice 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 exibit 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, isoliquiritigenin, neoisoliquiritin, licuraside, licochalcone A and B, licoricidin, 7-methillicoricidin, hispaglabridin A and B, liocflavone A and B, liocflavanol, 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, shinpterocarpin, licoisoflavones A and B, formononetin, glyzarin, and kumatakenin isoflavonoid 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, glyinflanin 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 isoflavonoid derivatives such as glabridin, galbrene, glabrone, shinpterocarpin, licoisoflavones 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, shinpterocarpin, licoisoflavones 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, glycyrretol, glabrolide, isoglaborlide, 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-actoxylglycyrhhizin, 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, dihydrostilbenes. 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 eurycarpa*), 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, licopyranocoumarin, 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 liquiriteginin, liquiritin apioside, neoliquiritin apioside, isoliquiritin, isoliquritin apioside, licuraside2-(5-P-coumaryl apiosyl), and isoliquiritin from the total polar extract of *G. glabra* utilizing different chromatographic techniques.

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, glisoflavanone, 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.

2005). 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*-glucopyranosyloxy-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-vii pinene, furan-2-pentyl, benzaldehyde, 4-terpineol, 1-pentylcyclobutene, acetophenone, α-caryophyllen, naphtalene, 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, stragole, 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, glycitein, 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(2*H*)-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, α,α′-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 α-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-glycyrrhetinic 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 corticosteroid 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-glycyrrhetinic acid can modulate PI3K signaling to alleviate inflammation. All these results demostrate that glycyrrhizic acid and 18β-glycyrrhetinic 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; Ii 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 phenylflavonoids and are strong antioxidants, although the potency of DGC is greater. The isoangustone A, another phenylflavonoid 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.

1980; Okada et al. 1989). 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).

7.2.5 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.

2004). 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).

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