



Review Article

Licorice a Supernatural Herb for Healthy Life: Bioactive Phytochemicals and Biological activities – A Review

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ABSTRACT

Licorice, a medicinal herb, has been found to contain various phytochemicals including flavonoids, phenolic compounds, saponins, sapogenins, pterocarpenes, coumestan derivatives, 2-arylobenzofuran derivatives, chemopreventive agents, acidic constituents and glycyrrhizin having different biological activities. Licorice is used in medical for treatment of various diseases like atherosclerosis, osteoporosis and Alzheimer's disease. It is used as anti-inflammation, anti-ulcer, anti-cancer, anti-virus and in many other problems. It is also used as additive for flavoring candies, chewing gum and toothpaste. The roots of this plant are majorly used for extracting different phytochemicals. Various licorice species: *Glycyrrhiza glabra*, *G. uralensis*, *G. inflata*, *G. lepidota*, and *G. pallidiflora* contain various phytochemicals with different type of biological activities. This paper provides a brief of the bioactive constituents and biological functions of different licorice species in details.

Keywords: Antioxidants, flavonoids, gan cao, *Glycyrrhiza* species, medicinal plant, saponin.

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INTRODUCTION

Licorice is an herb from *Glycyrrhiza* genus of Leguminosae family. The word *Glycyrrhiza* has been derived from Greek word, glykos rhiza meaning 'sweet root'. Chinese called the licorice as 'gan cao' which means sweet grass (Wang et al., 2015). The genus *Glycyrrhiza* consists of about 30 species. Roots and stolons of some *Glycyrrhiza* species (*G. glabra*, *G. uralensis*, *G. inflata*, *G. eurycarpa*, *G. aspera*, and *G. korshinskyi*) are the economic parts because of sweet taste, which have been used for medicinal purpose for at least 4000 years. In pharmacy, term *Succus liquiritiae* is used for licorice extract (Fenwick et al., 1990). Many isoprenoids substituted flavonoids are extracted from these plants. Kampo which is traditional Japanese medicine also contain licorice (Hayashi and Sudo, 2009). In Chinese pharmacopoeia, three species of *Glycyrrhiza* (*G. uralensis*, *G. glabra*, *G. inflata*) are most commonly used in medicinal prescriptions. In different provinces of China i.e. Inner Mongolia, Gansu, Heilongjiang, Ningxia and Qinghai, it is used as a medicinal plant (Yan et al., 2002). Licorice extract can be modified enzymatically in order to improve its sweetness by addition of cyclodextrin glucanotransferase. Several constituents isolated from this enzymatically modified licorice extract (EMLE) were glycyrrhizin, 3-O-[α -D-glucuronopyranosyl-(1 \rightarrow 2)- α -D-glucuronopyranosyl]-liquiritic acid (2), and their derivatives glucosylated at the C-4 position of the terminal glucuronopyranose with additional one (3 and 4,

respectively) and two (5 and 6, respectively) glucose moieties (Hong et al., 2000). Chinese Herbal Constituents Database (CHCD) and Bioactive Plant Compound Database (BPCD) contain information about classification of phytochemicals and chemical constituents isolated from various herbs and their different uses (Ehrman et al., 2007). Flavonoids/phenolics extracted from different herbs including licorice are found to be associated with antioxidant activity and used as remedy in cardiovascular diseases (Liao et al., 2008). The biologically important compounds found in licorice are triterpenoid saponins, flavonoids, polyamines and polysaccharides. These compounds are biologically active in different species of *Glycyrrhiza*.

ORIGIN AND MORPHOLOGY

Licorice plant is widely distributed all over the world. The extract from roots of *G. glabra* is inhabited in various countries like Greece, Turkey, Spain, Iraq, Caucasian, Transcasian Russia, India, Italy, Iran and northern China (Lucas, 1976; Lakshami and Geetha, 2011). The foliage of the plant has 3-8 leaflets. It is a perennial plant and leaves come out every year (Lakshami and Geetha, 2011).

BIOACTIVE PHYTOCHEMICALS OF LICORICE

Glycyrrhizin

Glycyrrhizin, extracted from dried roots and stolons of *G. glabra* is used in agricultural, pharmaceutical and confectionery industries (Fenwick et al., 1990; Kinghorn and Compadre, 2001). Sweetness of glycyrrhizin is 200 times more than sucrose and it

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is long lasting (Mizutani et al., 1994). A natural sweetener, mono-ammonium glycyrrhizate (MAG) is made from licorice by using pressurized hot water extraction (PHWE) (Mamata and Panja, 2008). In glycyrrhizin, oleanane-type triterpene saponin is responsible for sweet flavor of this plant (Hayashi and Sudo, 2009). In Japan, it is used as additive for flavoring and sweetening tobacco, candies, chewing gum and toothpaste. Ammonium glycyrrhizate is used as flavoring and foaming agent and generally regarded as safe. Previous phytochemical studies on licorice has shown that two structurally important secondary metabolites are present i.e. triterpenoids (glycyrrhizic acid) and phenolic derivatives (e.g. liquiritigenin) (Kitagawa, 2009; Nomura et al., 2002). Various biological effects are associated with these chemical constituents, such as anti-microbial (Mitscher et al., 1980), anti-oxidant (Vaya et al., 1997), anti-inflammatory, anti-ulcer (Aly et al., 2005), anti-hepatotoxic (Dhiman and Chawla, 2005), cytoprotective and cytotoxic activities (Young et al., 2007).

Chemopreventive agents

Licorice contains chemopreventive agents like chalcone derivative (Wang and Nixon, 2001) and a novel group neolignan lipid esters (Kinghorn and Compadre, 2001). Several chemopreventive agents have been found in root of *Glycyrrhiza uralensis* which can inhibit proliferation of human breast cancer cell. Extract of licorice was modulated with the expression of Bcl-2/Bax family of apoptotic family regulators against human breast cancer (Eun-Hye et al., 2004).

Flavonoids

Five flavonoid compounds from the air-dried roots of *G. glabra* L. collected from Xinjiang province of China include glucoliquiritin apioside (a flavonone bisdesmoside), prenyllicoflavone (a bisprenylflavone) (Kitagawa et al., 1993), shinflavanone (a prenylated pyranoflavanone), shinpterocarpin (Fukai et al., 1998), and 1-methoxyphaseollin (both pyranopterocarpan). Yenesew et al. (2000) extracted eleven flavonoids, eight known saponins and seven flavonoid glycosides from *Erythrina*. Underground parts of *G. uralensis* also contain three minor flavonoids namely, licofuranocoumarin, isotrifoliol and glisoflavanone (Hatano et al., 2000). Flavonoids are found to be associated with various biological activities. Mainly, plants of Leguminosae family (e.g. beans and peas) have these flavonoids. Although the tendency of these compounds is weak but to some extent can suppress diverse diseases like, atherosclerosis, osteoporosis and Alzheimer's disease (Shi et al., 2001; Nomura et al., 2002). Five flavonoids were isolated by purification of *G. uralensis* extract i.e. liquiritin, liquiritigenin, isoliquiritigenin, 7,4-dihydroxyflavone and isoononin (Bolledula et al., 2009). Some compounds of flavonoids have weaker anti-*Helicobacter pylori* activity. These include glycyrrin, gancaonin I, formononetin, 6,8-diprenylorobol, dihydrolicoisoflavone A, isolicoflavonol, glyasperin D, and gancaonol B (Fukai et al., 2002). Hatano et al. (1988) isolated two new flavonoids namely, glycyrrhisoflavanone and glycyrrhisoflavone. Their structure was also elucidated, that is 7,8-dihydroxy-2,2-dimethyl-5-methoxy{3,6-bi-2H-1-benzopyran}4-3H-one, and 3-[3,4-dihydroxy-5-(3-methyl-2-butenyl) phenyl]-5,7-dihydroxy-4H-1-benzopyran-4-one.

Licoricidin is an isoflavan derivative. Its chemical formula is C₂₅H₃₂O₅ and melting point 161 °C and structure is 3, 6-diisopentenyl-2,4,5-trihydroxy-7-methoxyisoflavan (Shibata and Saito, 1968). *G. aspera* contains flavonoid compounds like: glucoisoliquiritin apioside, 7-O-apioglucosyl, 4-dihydroxyflavone, dihydroglyasperin C, asperopterocarpin and 1-methoxyphaseollidin (Kitagawa et al., 1988). Wang et al. (2004) isolated seven compounds from cultivated licorice for the first time including isoliquiritigenin, enchinatin, licochalcone B, liquiritigenin, 4,7-dihydroxyflavone, liquiritin and isoliquiritin. Multistep chromatographic fractionation from licorice of *G. uralensis* and *G. inflata* contained five flavonoids which include liquiritin, licuraside, isoliquiritin, liquiritigenin, and licochalcone A. These compounds were investigated for anti-tyrosinase activity for applications in food and cosmetic industries (Boqiang et al., 2005). Four known isoflavonoids; 5-O-methylglycyrol, isoglycyrol, 6, 8-di-isoprenyl-5,7,4-trihydroxyisoflavone and gancaonin extracted from *G. uralensis* found to have anti-bacterial activity (Jian et al., 2006). The main flavonoid of *G. uralensis* Fisch. is licoricidin. The hydroxyl groups of flavonoids conjugate with glucuronyl by the action of UDP-glucuronosyltransferase (UGT). Licoricidin incubation with uridine 5'-diphosphoglucuronic acid and NADPH in the microsomes of human liver yields a metabolite monoglucuronyl licoricidin by UGT1A9. Formation of this metabolite in human liver microsomes (HLMs) may be used as a substrate *in vitro* to measure the efficiency of UGT1A9 (Cho et al., 2019).

Phenolic compounds

Licorice contain phenolic compounds like formononetin, glabridin, hemileiocarpin, hispaglabridin B, isoliquiritigenin (Kinghorn and Copadre, 2001), 4-O-methylglabridin, and pratocarpin B (Nomura et al., 2002). Shua et al. (2016) has reported 20 flavonoid glycosides compounds from roots and rhizomes of *G. uralensis*.

Saponins

G. Aspera contains four known saponins (Kitagawa et al., 1988). From dried roots of *G. uralensis* Fisch., a triterpene oligoglycoside named licorice-saponin L3 and a chalcone oligoglycoside (isoliquiritin apioside) were isolated along with licorice-saponins A3, E2, G2, and H2 (Kitagawa et al., 1993). Licorice roots, taken from different origin found to contain 15 types of saponins (Kitagawa et al., 1988). From *G. lepidota* (American licorice) two known saponins are licorice-saponin H2 and macedonoside A (Hayashi et al., 2005).

Sapogenins

G. uralensis roots contain seven triterpene sapogenins; methyl glycyrrhetate, glabrolide, methyl 3 β , 24-dihydroxyolean-11, 13(18)-diene-30-oate, methyl 24-hydroxyglycyrrhetate and 24-hydroxyglabrolide (Shu et al., 1985).

Pterocarpenes

By bioassay-guided fractionation methods two new pterocarpenes; glycyrrhizol A and glycyrrhizol B were isolated from roots of *G. uralensis* (Jian et al., 2006).

Coumestan derivatives

Structures of coumestan derivatives, 2-glycyrol, 5-O-methoxyglycerol and isoglycerol were known half century ago (Saito and Shibata, 1969). Glycyrol coumestan has been extracted from *G. uralensis* (Li et al., 2010; Nehybova et al., 2014).

2-Arylobenzofuran derivative

From xibei (seihoku kanzo) which is a commercial licorice, 2-arylbenzofuran derivative named licocoumarone was isolated. 3-arylcoumarin derivative, glycy coumarin was also derived from xibei licorice. By spectroscopic and chemical studies, structure of licocoumarone was determined. Licocoumarone had both antimicrobial and antioxidant activity while glycy coumarin had only antimicrobial activity (Demizu et al., 1988).

Acidic constituents

Zuo et al. (1994) has reported 42 compounds isolated from *G. pallidiflora* by using various separation methods. For the first time, three new compounds homopterocarpin, soyasapogenol B and glypallidifloric acid (2 β -hydroxy-oleana-11, 13(18)-diene-30-dioic acid) were isolated by spectroscopic and chemical methods. Yong et al. (2009) has extracted licorice content using simultaneous distillation extraction and analyzed with gas chromatography-mass spectrometry (GC-MS). Total 128 volatile components were separated. 108 components constituted 92.2% of total and among these 30.6% was caproic acid, 13.55% hexadecanoic acid, 3.99% ethyl hexanoate, 3.93% ethyl linoleate, 2.84% 11-hexadecanal, 2.09% 3-methyl-cyclopentol, 1.82% 2-pentnyl-furan and 1.76% 1-hexanol. Licorice extract was also investigated to reduce the irritation of cigarette smoke. These components were found useful and sweetness of smoke was improved.

MECHANISM OF ACTION

Licorice has proper mechanism of action for the prevention of diseases. In liver, glycyrrhizic acid can inhibit the metabolism of aldosterone, and suppress the activity of 5-(beta)-reductase which is responsible for pseudoaldosterone syndrome. It can perform the functions of mineralocorticoid and glucocorticoid due to the structural similarity (Armanini et al., 1983). Licorice can inhibit phospholipase A2 enzyme (which is responsible for inflammation) because it has steroid like anti-inflammatory action. Glycyrrhizic acid can inhibit all the inflammatory processes and enzymes like cyclooxygenase, and prostaglandin, it can inhibit the platelet aggregation also (Okimasu et al., 1983). It can inhibit the growth of DNA and RNA bacteria, which are responsible for herpes zoster (Baba and Shigeta, 1987), Hepatitis A (Crance et al., 1990), and Hepatitis C (Rossum et al., 1999). Licorice can lower the lipid peroxide value in liver of rat by the help of licorice isoflavones, hispaglabridin (Nagai et al., 1991). At the site of inflammation, Glycyrrhizin and glabridin can inhibit the production of reactive oxygen species (ROS) by the help of neutrophils (Akamatsu et al., 1991; Wang and Nixon, 2001). Licorice is used for inhibiting DNA gyrase in *H. pylori* which stop its growth and replication (Chatterji et al., 2001).

BIOLOGICAL ACTIVITIES

Licorice from Russian and Xinjiang origin has been investigated for anti-microbial and anti-oxidant activity. Glabrene, glabridin, and licochalcones A and B were found to be active ingredients (Okada et al., 1989). The biologically important components of licorice have anti-viral, anti-bacterial, anti-inflammatory, anti-oxidative, anti-allergy, anti-cancer, anti-depressive, anti-diabetic and cardioprotective effects (Asl and Hosseinzadeh, 2008; Fiore et al., 2008). It is used for tonifying stomach, eliminating phlegm, relieving cough, removing heat, detoxifying, peptic ulcer, hepatic disease, cancer, and for viral infections (Li et al., 2011; Qiao et al., 2014).

Anti-ulcer and anti-*Helicobacter pylori* activity

Helicobacter pylori is the gram negative S shaped flagellated bacterium which has infected half of mankind worldwide and is considered causative agent of peptic ulcer (Gorden et al., 1994; Hunt et al., 2011; Mannanthendil et al., 2013). Extract of licorice has been used for the treatment of peptic ulcer. Flavonoids from licorice were expected to show more anti-*H. pylori* activity because kaempferol (4',5,7- trihydroxyflavonol) exhibited antibacterial action in *H. pylori*-infected Mongolian gerbils (Kataoka et al., 2001). Among the flavonoids, licoricone, 1-methoxyphaseollidin, vestitol and gancaonol C also show anti-*H. pylori* activity against clarithromycin amoxicillin-resistant and sensitive strains. Ethanol extract of *G. uralensis* contains three isoflavonoids (3-arylcoumarin, pterocarpan, isoflavan) and 15 known flavonoid compounds. In *H. pylori*-infected individuals, these compounds may prove as effective chemopreventive agents of gastric and peptic ulcer (Fukai et al., 2002). Licorice also has anti-ulcer agent glycyrrhizic acid, which is responsible for raising the prostaglandin concentration that increase rate of mucous secretion and cell proliferation in stomach. *In vitro* activity of some components of licorice [Extractum liquiritiae (EL), Glycyrrhizic acid (GL), glycyrrhetic acid (GA), novel lipophilic derivative of glycyrrhetic acid monoglucuronide (GAMG), and acetylated GAMG (aGAMG)] against 29 *H. pylori* strains has been studied. The minimum inhibitory concentration (MIC) of each compound was measured through agar dilution method, and brain heart infusion method was used for measuring the killing kinetics (Dhiman and Chawla, 2005). GA can inhibited 79.3% of the strains and found as a most potent component of licorice against ulcer bacterium (Kim et al., 2009; Tsai and Chen, 1991). Licorice root extract contain polysaccharide which inhibit *H. pylori* adhesion with gastric mucosa (Wittschier et al., 2009). In 2012, antibiotic resistance of clarithromycin and amoxicillin increased in *H. pylori* (An et al., 2013). Licorice is used for production of secretin for protection of mucosal cells (Hajiaghahmohammadi et al., 2016).

Hepatoprotective and anti-hepatitis activity

Licorice protect liver by resisting the change in cell membrane permeability, and inhibit the phospholipase A2 (Dhiman and Chawla, 2005; Kim et al., 2009). Glycyrrhizin have components which are active against hepatitis B and C. It decreases the serum alanine aminotransferase concentration which give stability to virus, and also inhibit the replication of HCV (Hepatitis C virus) RNA genome (Van Rossum et al., 1999; Orlent et al., 2006; Stickele

and Schuppan, 2007; Manns et al., 2012). *G. uralensis* and *G. glabra* also inhibit HCV genome replication, and is used in folk medicine to treat liver diseases (Asl and Hosseinzadeh, 2008; Sekine-Osajima et al., 2009; Wang et al., 2013). Real-time PCR is used for analyzing the effects of *Glycyrrhiza* species on HCV RNA genome (Deng et al., 2011; Wahyuni et al., 2013). The component of *G. uralensis* like glabridin, liquiritigenin, glycycomarin, glycyrrin and glycyrol; all of these are potent agents against hepatitis C (Adianti et al., 2014).

Anti-inflammatory activity

Triterpen glycyrrhizin is the most potent anti-inflammatory agent extracted from licorice (Kiso et al., 1984). Glycyrrhizin is not only the scavenger of ROS (reactive oxygen species) but it also inhibits formation of ROS by neutrophils (Akamatsu et al., 1991). Licorice can resist formation of ROS and inhibit peroxidation of lipid in cell membrane. It increases formation of natural antioxidants in the body like super oxide dismutase (Rackova et al., 2007). Several workers have reported that *G. glabra* has anti-inflammatory effect (Aly et al., 2005; Dong et al., 2007; Zore et al., 2008).

Anti-tumor activity

Licorice root extract contain beta-hydroxy-DHP component that induce apoptosis and arrest G2/M cell cycle in breast and prostate cancer (Rafi et al., 2002). *G. uralensis* extract of root in DMSO (Dimethyl sulfoxide) is used in treating estrogen related breast cancer. However, this depends on the extract of root and its specific concentration. It arrests cell cycle at moderate concentration, otherwise it increases cell proliferation (Hu et al., 2009). *G. uralensis* components have anti-tumor characteristics (Miraj, 2016). Glycyrrhizin can increase immune response by increasing anti-tumor cytokine-IL-7 proliferation and maturation which is important in cancer diagnosis (Ayeka et al., 2016). Ethanolic extract of *G. aspera* has anti-tumor property against N-methyl-N-nitrosourea (MNU) showing direct anti-tumor effect against DNA alkylation (Inami et al., 2017).

Anti-hyperlipidemic and anti-cardiovascular toxin activity

Triterpenoid components of licorice are effective in reducing triglycerides and cholesterol level in blood and give protection against cardiovascular disease and atherosclerosis (Jiao et al., 2007). Glycyrrhizic acid is similar in structure with mineralocorticoids and glucocorticoids. So, it can be used as analogue in steroid metabolism. It prevents the action of LOX (lipid peroxidase) and COX (cytochrome oxidase) and decrease the level of VLDL (very low density lipoprotein) in plasma and prevent heart from various diseases (Churchill, 2013).

Anti-stroke activity

Glabridin is the component of licorice extract which has property against stroke formation and prevents brain by inhibiting super oxide production in cortical neuron (Yu et al., 2008).

Anti-cough and immunomodulator activity

Licorice is an efficient compound used for treatment of cough and cold. It has various components that are glycyrrhizin, glycyrrhethinic acid, flavonoids, isoflavonoids and chalcones. Glycyrrhethinic acid increases INF γ (interferon gamma) and IgE (immunoglobulin E) which improve rate of immunity in individuals (Gulati et al., 2016). Aqueous extract of roots of licorice is used as immunomodulator. It increases cellular immune response by increasing antibody concentration in body (Salarzaei et al., 2017).

Anti-herpes activity

Glycyrrhizic component of licorice can be used in the form of gel on lesions which entrap DNA, RNA of virus and reduce the recurrence of herpes (Pizzorno et al., 2016).

Anti-plasmodial activity

Root extract of *G. glabra* is used for production of resistance for all malarial diseases. Attempts have been made to use total root extract for creating new anti-malarial drug from plant source (Sangian et al., 2013; Haddad et al., 2017; Ramazani et al., 2018).

Anti-hypermineralocorticoid activity

Licorice with the aid of intact adrenals leads to hypertension, as it causes sodium retention. One of its components, glycyrrhethinic acid was suggested to cure Addison's disease as it causes hyperaldosteronism, because the activity and structure of this constituent are similar to steroid hormones cortisol and aldosterone (Conn et al., 1968; Elizabeth and Morris, 1991). Glycyrrhizic acid component of licorice can be used in steroid metabolism to stop the production of mineralocorticoid, but this property requires fixed concentration of licorice intake. Otherwise it can oppose this effect (Isbrucker and Burdock, 2006).

CONCLUSION

Licorice is a medicinal herb which has fewer side effects and more potency to treat diseases by controlling their natural pathways; for example, in cancer it modifies immune system to destroy abnormal cells, in ulcer it decreases ammonia coat around bacterium to facilitate its killing, it increases natural antioxidant to prevent free radical formation. So, it has importance due to less side effect and fast response. Main phytochemical which was found in licorice extract was flavonoid. Root extract of *G. uralensis* is being investigated as breast cancer inhibitor. The genus *Glycyrrhiza* consists of about 30 species, including *G. pallidiflora*, *G. lepidota*, *G. aspera*, *G. uralensis*, *G. glabra*, *G. inflata*, *G. eurycarpa*, and *G. korshinskyi*. These have been investigated for their biochemical constituents and biological activities by different investigators and found effective against numerous diseases from digestive problems to cancers. There is need to explore the biochemical constituents and biological activities of the remaining twenty-two species of the magical *Glycyrrhiza* herb and there are chances that the remaining species could be effective against some other diseases. It is also suggested to investigate the antimicrobial

activity of licorice for the treatment of animal and plant diseases.

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