AUCTORES
Globalize your Research

Journal of General Medicine and Clinical Practice
Muhammad Arshad Ullah *
Open Access

Review Article

Utilization of Licorice - Mulethi (glycyrrhiza glabra l.) As Natural Medical Herb

Muhammad Arshad Ullah

Pakistan Agricultural Research Council, Islamabad, Pakistan.

***Corresponding Author:** Muhammad Arshad Ullah, Pakistan Agricultural Research Council, Islamabad, Pakistan.

Received date: February 25, 2025; **Accepted date:** March 05, 2025; **Published date:** March 10, 2025

Citation: Muhammad A. Ullah (2025), Utilization of Licorice - Mulethi (glycyrrhiza glabra l.) As Natural Medical Herb, *J. General Medicine and Clinical Practice*, 8(3); **DOI:10.31579/2639-4162/257**

Abstract

Licorice commonly known as Y ashthimadhu in Ayurveda is one such plant. Licorice (Glycyrrhiza glabra) symbolises all that is wondrous in nature because, the it is used as traditional medicine for household remedy against various human ailments from antiquity. Licorice is a very well-known herb in Chinese medicine. In China, it is called "gancao" means sweet grass and has been recorded in the Shennong's classic of Materia Medica around 2100 BC. which says that licorice was supposed to have life-enhancing properties. It was used to have the functions of nourishing, alleviating pain, eliminating phlegm, and relieving coughing. The canvas of the pharmacological activities when complied it stands out strongly as a drug of choice in various disorders. Licorice contains more than 20 triterpenoids and nearly 300 flavonoids. Among them, glycyrrhizin (GL), 18-beta-glycyrrhetinic (GA), liquiritigenin (L TG), licochalcone A (LCA, licochalcone E (LCE) and glabridin (GLD) are main active components which possess antimicrobial and anti viral activities.

Antibacterial activity of glycyrrhiza glabra on oral pathogens showed that glycyrrhiza glabra extract showed good antibacterial activity against six bacterias includingStreptococcus mutans, Actinomyces viscous, E coli, Streptococcus aureus and Streptococcus sanguis. Twice daily use of herbal liquorice lollipop significantly reduced, the number and relative percentage of S mutans in high-risk children for 22 days which then stabilized and begin to rebound. An unusual biflavonoid named licoagrodin was isolated from the hairy root cultures of G. glabra along with three prenylatedretrochalcones, licoagrochalcones B, C, D, a prenylatedaurone, licoagroaurone and four known prenylated flavonoids, licochalcone C, kanzonol Y, glyinflanin B and glycyrdione A. From the glycosidic fraction, aisoflavone glycoside, licoagroside A, and a maltol glycoside, licoagroside B were isolated together with four known isoflavone glycosides, two flavone C-glycosides, and three other glycosides. The isoflavonesglabridin and hispaglabridins A and B had antioxidant activity and both glabridin and glabrene possessed estrogen like activity.

In traditional Chinese medicine, the plant is recommended as a common remedy for gastrointestinal problems, cough, bronchitis, and arthritis. In particular, it is still widely used to treat gastritis, peptic ulcers, respiratory infections, and tremors in folk medicine. Commonly, G. glabra root is employed to prepare a tea that is an excellent thirst quencher. The dried root has been described as a tooth cleanser. Actually, the most important industrial use of G. glabra is the production of food additives, such as flavours and sweetening agents. In particular, the root is used as a flavouring agent for American-type tobacco, chewing gum, candies, baked goods, ice cream, and soft drinks. Nutritionally, liquorice is a source of proteins, amino acids, polysaccharides and simple sugars, mineral salts (such as calcium, phosphorus, sodium, potassium, iron, magnesium, silicon, selenium, manganese, zinc, and copper), pectins, resins, starches, sterols, and gums. Oestrogens, tannins, phytosterols (sitosterol and stigmasterol), coumarins, vitamins (B1, B2, B3, B5, E, and C), and glycosides have been reported. A large number of biological compounds have also been isolated, mostly triterpenes, saponins (responsible for the sweet taste), and flavonoids. The main constituent of roots is glycyrrhizin, a triterpenoid sapo-nin that is almost 50 times sweeter than sucrose, being the primary active ingredient. Glycyrrhizin represents about 10% of the liquorice root dry weight, being a mixture of potassium, calcium, and magnesium salts of glycyrrhizic acid that varies between 2% and 25%. After oral administration, glycyrrhizin is metabolized to 18-glycyrrhetic acid 3- omonoglucuronide and glycyrrhetic acid by intestinal bacteria. Liquiritin apioside, an active compound reported in the methanolic extract of liquorice, has the ability to inhibit capsaicin, a compound that induces cough. The effect on sore throat has been compared with that of carbenoxolone, a glycyrrhetinic acid derivative with a steroid-like structure, which stimulates gastric mucus secretion.

Kew Words: sarcoidosis of urinary bladder; vesical sarcoidosis; sarcoidosis of the spine; biopsy; cystoscopy; high index of suspicion; neurogenic bladder; computed tomography scan; contrast-enhancement; urodynamics

Introduction

Another accession, EC-21950, has been identified by All India Coordinated Research Project on Medicinal and Aromatic Plants; this variety is also tolerant to the root rot disease. Other varieties of mulethi are EC-114303 and EC-124587 (Zaidi, 2011). The crop remains in the field for two and a half to three years, every year the same dose has to be applied (Farooqi, 2001). The yield of mulethi depends upon the soil fertility, variety of plant, climatic conditions and method of cultivation. A yield of 5 tons of roots and 14-20 tons of trimming is considered satisfactory. The HM-1 yields 7-8 tons roots with a 7.5 per cent content of glycyrrhizin (Uniyal and Jariyal, 2003). Licorice commonly known as Y ashthimadhu in Ayurveda is one such plant. Licorice (Glycyrrhiza glabra) symbolises all that is wondrous in nature because, the it is used as traditional medicine for household (Korhalkar *et al,* 2014) remedy against various human ailments from antiquity. Licorice is a very well-known herb in Chinese medicine. In China, it is called "gancao" means sweet grass and has been recorded in the Shennong's classic of Materia Medica around 2100 BC. which says that licorice (Wang and Liu, 2015) was supposed to have life-enhancing properties. It was used to have the functions of nourishing, alleviating pain, eliminating phlegm, and relieving coughing. The canvas of the pharmacological activities when complied it stands out strongly as a drug of choice in various (Korhalkar *et al,* 2014) disorders. Licorice contains more than 20 triterpenoids and nearly 300 (Wang and Liu, 2015) flavonoids. Among them, glycyrrhizin (GL), 18-beta-glycyrrhetinic (GA), liquiritigenin (L TG), licochalcone A (LCA, licochalcone E (LCE) and glabridin (GLD) are main active components which (Lingaraj *et al,* 2014) possess antimicrobial and anti viral activities.

Sedighinia et al. (2012) conducted an in vitro study to analyse antibacterial activity of glycyrrhiza glabra on oral pathogens which showed that glycyrrhiza glabra extract showed good antibacterial activity against six bacterias including Streptococcus mutans, Actinomyces viscous, E coli, Streptococcus aureus and Streptococcus sanguis. Sug et al. (2012) conducted an in vitro study to analyze the antimicrobial effects of deglycyrrhizinated licorice root extract (DG-LRE) on streptococcus mutans UA159 in both planktonic and biofilm cultures and concluded that it has strong antimicrobial activity against S mutans in planktonic phase. Peter et al. (2010) concluded that twice daily use of herbal liquorice lollipop significantly reduced, the number and relative percentage of S mutans in high-risk children for 22 days which then stabilized and begin to rebound. Jain et al. (2013) showed that highest number of fall in streptococcus mutans colony counts was observed in ethanolic liquorice group and at the same time palatable by child patients.

Vu Dang et al. (2011) reported that LIAand LC inhibited the secretion of interleukin 6 and chemokine in a dose dependent manner and hence can have potential for the development of novel host modulating Strategies for the treatment of cytokinin and MMP mediated disorders such as periodontitis. Farhad et al. (2013) resulted that the decrease in mean MMP 8 concentration was higher in doxycline and liquorice group in comparison with the placebo group and concluded that licorice extract can prevent the production of MMP by host cell and can be useful as antibiotic like doxicycline to cure peridontitis and other inflammatory diseases, with no side effects. In a study by Geetha and Anitha (2013) on in vitro evaluation of antimycotic activity of ethanolic extract of Glycyrrhiza glabra, the results clearly indicated the antifungal activity of ethanolic extract of glycyrrhiza glabra on organisms like candida albicans, aspergillus fumigates, aspergillus Niger, mucus species and Penicillium marneffei which could be enhanced with purified active components and determined adequate dose for proper administration. An in vitro and in vivo study conducted by Seleem et al. (2016) to check the antifungal activity of Lichochalcone –A against candida albican biofilm. Lichochalcone –Ais a bio active natural compound found in licorice root. The result of the study showed that 625µM Lichochalcone –A significantly reduced biofilm growth compared to control group by reducing colony forming units and reducing activity of proteolytic enzymes. Messeier et al. (2012) in the article on Licorice and its potential beneficial effects in common orodental diseases stated that liquorice and its bioactive ingredients such as glycyrrhizin, glabidin, licochalcone A, licoricidin and licorisoflavan A possesses potential beneficial effects in oral diseases including recurrrent aphthous ulcer. Rafi et al. (2012) stated that novel polyphenols molecule isolated from liquorice root induces apoptosis, G2/M cycle arrest, and BCL-2 phosphorylation in tumor cell lines. Sinha and Sinha (2014) stated that liquorice has shown greater biocompatibility with fibroblast cells compared to calcium hydroxide, which is severely toxic to cells. Hence a mixture of liquorice and Calcium Hydroxide can be used to minimize toxicity to fibroblasts. Kim et al. (2018) conducted a study to analyze the anti-inflammatory effects of licorice and roasted licorice of extracts on 12- O-tetradecanoylphorbol-13-acetate (TP A) induced acute inflammation and collagen induced arthritis in mice and suggested supplementation with licorice extract (LE) and roasted licorice extract (rLE) may be beneficial in preventing and both acute and chronic inflammatory conditions like arthritis.A yield of two tons of roots per acre for bailing, plus 3-4 cwt of trimmings is considered satisfactory (Chopra and Chopra, 2006). Root-T.S showed structure of closely resembling that of stolon except that no medulla was present; xylem tetrarch; usually four principal medullary rays at right angles to each other; in peeled drug cork showed phelloderm and sometimes without secondary phloem; all parenchymatous tissues had abundant, simple oval or rounded starch grains, 2-20µ in length. Glycyrrhizin is a nonhemolytic saponin with foaming property (Vispute and Khopade, 2011). To produce these quantities of active principles, 300 tons of Glycyrrhiza roots will be required. It could be cultivated on waste/marginal lands (Shinwari *et al,* 2003). An unusual biflavonoid named licoagrodin was isolated from the hairy root cultures of G.. glabraalong with three prenylatedretrochalcones, licoagrochalcones B, C, D, a prenylatedaurone, licoagroaurone and four known prenylated flavonoids, licochalcone C, kanzonol Y, glyinflanin B and glycyrdione A. From the glycosidic fraction, aisoflavone glycoside, licoagroside A, and a maltol glycoside, licoagroside B were isolated together with four known isoflavone glycosides, two flavone C-glycosides, and three other glycosides (Li *et al,* 2000). The isoflavonesglabridin and hispaglabridins A and B had antioxidant activity and bothglabridin and glabrene possessed estrogen like activity (Kataria *et al,* 2013). The decoction of the root is a good wash for falling and graying hair (Singh et al., 2006). Large randomized placebo-controlled trials on humans conducted by Upjohn Company for minoxidil, a potassium channel opener, showed efficacy in 54 % of the treated patients compared to 34 % in placebo (control) group. Thus, minoxidil (reference) was a more effective hair growth enhancer than the control group but was inferior to the 2% extract-treated group probably due the fact that G. glabraextract has some estrogenic property (Somjen *et al,* 2004). A recent study on Eclipta albaherb which validate it as a hair growth promoter showed that thepresence of antigen FGF-7 and Shh and absence of BMP4 favoured anagenic state of hair (Dattaa *et al,* 2009). The extracts are currently used in pharmaceutical and food industries, as well as in the manufacture of functional foods and food supple-ments (Hayashi & Sudo, 2009; Herrera *et al,* 2009).

The use of liquorice predates the Greek and Roman empires, hav-ing a long history of traditional medicines and folk remedies. In fact, different geographical areas and periods are linked to different uses (Armanini *et al,* 2002). The first documents can be traced back to ancient Assyrian, Egyptian, Chinese, and Indian cultures. Theophrastus and Pedanius Dioscorides wrote about liquorice as a medicinal plant and described its therapeutic effects

(Armanini *et al,* 2002). In traditional Chinese medicine, for example, the plant is recommended as a common remedy for gastrointestinal problems, cough, bronchitis, and arthritis. In particular, it is still widely used to treat gastritis, peptic ulcers, respiratory infections, and tremors in folk medicine. Commonly, G. glabra root is employed to prepare a tea that is an excellent thirst quencher. The dried root has been described as a tooth cleanser (Armanini et al., 2002). Actually, the most important industrial use of G. Glabra is the production of food additives, such as flavours and sweetening agents (Mukhopadhyay & Panja, 2008). In particular, the root is used as a flavouring agent for American-type tobacco, chewing gum, candies, baked goods, ice cream, and soft drinks (Rizzato *et al,* 2017). With regard to government approval, liquorice extract and glycyrrhizin have been allowed for use in foods by the United States Food and Drug Administration, the Council of Europe, and the Joint FAO/WHO Expert Committee on Food Additives (FAO, 2005). The genus Glycyrrhiza (Fabaceae) consists of about 30 species, such as G. glabra, G. uralensis, G. inflata, G. aspera, G. korshinskyi, or G. eurycarpa. Like the other plants of Fabaceae, G. glabra is able to fix nitrogen, due to symbiosis with bacteria of the genus Rhizobium, at the root level, being suitable for sandy and clay soils, though preferring humid soils. Since the Egyptian age, the therapeutic proper-ties of G. glabra are well documented (Fiore *et al,* 2005). The roots are the most used parts whereas leaves are considered an agrochemical waste. However, in the last years, different authors studied the phytochemical composition of G. glabra leaves, demonstrating that certain compounds present in the roots are also identified in leaves, although in smaller quantities (Hayashi & Sudo, 2009; Siracusa *et al,* 2011).

In the last years, the chemical constituents of liquorice have been extensively investigated by different authors (Hayashi *et al,* 2016; Siracusa *et al,* 2011). Nevertheless, few studies were carried out on the nutritional composition of G. glabra. Nutritionally, liquorice is a source of proteins, amino acids, polysaccharides and simple sugars, mineral salts (such as calcium, phosphorus, sodium, potassium, iron, magnesium, silicon, selenium, manganese, zinc, and copper), pectins, resins, starches, sterols, and gums (Wang *et al,* 2015). Oestrogens, tannins, phytosterols (sitosterol and stigmasterol), coumarins, vitamins (B_1, B_2, B_3, B_5, E, and C), and glycosides have been reported (Wang *et al,* 2015). A large number of biological compounds have also been isolated, mostly triterpenes, saponins (responsible for the sweet taste), and flavonoids (Rizzato *et al,* 2017; Wang *et al,* 2015). The main constituent of roots is glycyrrhizin, a triterpenoid sapo-nin that is almost 50 times sweeter than sucrose, being the primary active ingredient (Yu *et al,* 2015). Glycyrrhizin represents about 10% of the liquorice root dry weight, being a mixture of potassium, calcium, and magnesium salts of glycyrrhizic acid that varies between 2% and 25% (Rizzato et al., 2017). After oral administration, glycyrrhizin is metabolized to 18-glycyrrhetic acid 3- omonoglucuronide and glycyrrhetic acid by intestinal bacteria (Albermann *et al,* 2010).

Glabridin is the principal isofla-vone identified, ranging between 0.08% and 0.35% of roots' dry weight (Simmler et al., 2013). The minor phenolic compounds are isoprenoid-substituted flavonoids, chromenes, coumarins, dihydrostilbenes, coumestans, benzofurans, and dihydrophenanthrenes. Furthermore, many volatile components are present in roots, such as geraniol, pentanol, hexanol, terpinen-4-ol, and α-terpineol, conferring the characteristic odour. The essential oil obtained fromG. glabrais also rich in propionic acid, benzoic acid, furfuraldehyde, 2,3-butanediol, furfuryl formate, maltol, 1-methyl-2-formylpyrrole, and trimethylpyrazine (Chouitah *et al,* 2011) The phenolic content is probably responsible for the powerful antioxidant activity observed (Rackova *et al,* 2007). Varsha and Sonam (2013) attributed this activity to flavonoids, whereas Singh et al. (2015) reported that mostly isoflavones, such as glabridin, hispaglabridin A, and 30-hydroxy-4-O-methylglabridin, are the responsible compounds. Biondi et al. (2003) reported a huge antioxidant activity of the dihydrostilbene derivates present inG. Glabra leaves. Also, licochalcones B and D are present in G. glabra, showing a strong scav-enging activity on DPPH radical and the ability to inhibit the micro-somal lipid peroxidation (Biondi *et al,* 2003; Sharma *et al,* 2016). According to Castangia et al. (2015), the topical application of liquorice extract for-mulations may be of value in innovative dermal and cosmetic products as it counteracts oxidative stress damage, maintaining the skin homeo-stasis due to its high antioxidant content.

The anti-inflammatory activity of G. glabraand its use in the treat-ment of inflammatory diseases have been documented since ancient times (Yang *et al,* 2017). Shalaby et al. (2004) evaluated the anti-inflammatory activity of G. glabra in male rats after 4 weeks of food intake. The authors observed a significant decrease in the total cholesterol and triglyceride levels as well as in the levels of serum liver enzymes. Harwansh et al. (2011) reviewed the pos-itive effects of G. glabraon the treatment of the upper respiratory tract and gastric system diseases. These pharmacological effects were due to an increase in the secretion of serotonin and prostaglandins in the stomach that led to a decrease of gastric inflammation (Bahmani *et al,* 2014). Different authors described that the anti-inflammatory action is primary mediated by glycyrrhizin, which in vitro could inhibit factors responsible for inflammation as well as promote the healing of stomach and mouth ulcers (Rackova *et al,* 2007; Yin *et al,* 2017). Furthermore, G. glabra is used in renal and liver complications on the basis of its strong anti- inflammatory effects (Xiao *et al,* 2010). Xiao et al. (2010) reported the inhibition of liver granuloma formation and the inflammatory cytokine production by glycyrrhizin, whereas Wang et al. (2017) described the anti-inflammatory effects on endometriosis. Moreover, Liu et al. (2017) proved the anti-inflammatory activity of glabridin on RAW cells.

The antitussic and expectorant effects of liquorice have been reported by different authors, particularly its useful effects on the treatment of sore throat, cough, and bronchial catarrh (Damle, 2014; Fiore *et al,* 2005). These effects are associated with the presence of glycyrrhizinthat helps to expel congestion in the upper respiratory tract and accel-erates tracheal mucus secretion (Sharma *et al,* 2016). Likewise, liquiritin apioside, an active compound reported in the methanolic extract of liquorice, has the ability to inhibit capsaicin, a compound that induces cough (Kamei *et al,* 2003). The effect on sore throat has been compared with that of carbenoxolone, a glycyrrhetinic acid derivative with a steroid-like structure, which stimulates gastric mucus secretion (Damle, 2014).

The use of G. glabra extract as antiulcerative is widely known. For the gastrointestinal system, it is used in gastric and duodenal ulcers, whereas for the treatment of spasmodic pains of chronic gastritis, it is employed as an adjuvant (Armanini *et al,* 2002). The benefits o f G. Glabra in the treatment of duodenal and peptic ulcers has been reported since the 1970s, and this traditional use is related to the presence of anti- inflammatory saponins (Krausse *et al,* 2004). The major compound responsible for this activity is glycyrrhizin, which can raise the concen-tration of prostaglandins in the digestive tract, promoting stomach mucus secretion (Jafarian & Ghazvini, 2007). In addition, liquorice prolongs the lifespan of stomach surface cells, demonstrating an antipepsin effect (Ram *et al,* 2010). Fur-thermore, deglycyrrhizinated liquorice has shown some effects in the treatment of gastrointestinal ulcers, suggesting the presence of other active ingredients (Zadeh *et al,* 2013). Indeed, carbenoxolone, a glycyrrhetinic acid analogue, is reported to inhibit two important enzymes for the metabolism of prostaglandin, 15-hydroxyprostaglandin dehydrogenase and Δ 13 prostaglandin reductase, raising prostaglandin levels and leading to positive effects in clinical trials for gastric and duodenal ulcers (Damle, 2014). Different authors reported the antimicrobial properties of G. glabra, particu-larly on Gram-positive and Gram-negative bacteria such as Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Candida albicans, and

Bacillus subtilis (Gupta *et al,* 2008; Wang *et al,* 2015). The antibacterial activity observed is due to the presence of secondary metabolites, namely, saponins, alkaloids, and flavonoids (Wang *et al,* 2015).

Glabridin 75 mg/kg In vivo—oral administration to mice Decrease of MIP 1αexpression (Xiao et al., 2010) Glycyrrhizin 1–100μM DPPH, AAPH Protection against lipid peroxidation of liposomal membraneInhibition of ROS(Rackova et al., 2007) 50–200μg/ml LPS inflammatory mediators production (TNF-α,IL-1β,COX-2, PG2) Decrease of endometriosis (Wang, *et al,* 2017) 10, 20, 100 mg/kg In vivo—mice Decrease of LPS inflammatory mediators (Yin *et al,* 2017) ALT: alanine aminotransferase; AST: aspartate aminotransferase; DHV: duck hepatitis virus; FRAP: ferric reducing antioxidant potential; ICR: Institute of Cancer Research; IVF: in vitro fertilization; LDL: low-density lipoprotein; LPS: lipopolysaccharide; MBC: minimum bactericidal concentration; MIC: minimum inhibitory concentration; ROS; reactive oxygen species; SOD: superoxide dismutase B, 40-methylglabridin, and 3-hydroxyglabrol, isolated from G. glabra, are responsible for this activity (Wang *et al,* 2015). The mechanism behind this could be the decrease of bacterial gene expression, the inhibition of bacterial growth, and the reduction of bacterial toxin production (Gupta *et al,* 2008; Wang *et al,* 2015). In 2014, Ahn et al. (2014) demon-strated that liquorice prevents bacterial caries caused byStreptococcus mutans and Streptococcus sobrinus. Likewise, in vitro studies proved that aqueous and ethanolic extracts of liquorice have an inhibitory activity on Streptococcus pyogenes (Fukai *et al,* 2002a, b; Wang *et al,* 2015). On the other hand, the ability to inactivate methicillin-resistant S. Aureus (MRSA) by decreasing the expression of SaeR and Hla, the key virulence genes of MRSA, have also been reported by different authors (Fukai *et al,* 2002a, b; Wang *et al,* 2015). It is also suggested that licochalcone E could be used for chemical synthesis of novel anti-S. aureuscompounds, reduc-ing the production of α-toxin in both methicillin-sensitiveS. Aureus and MRSA (Wang *et al,* 2015). Besides, α-haemolysin is an important exotoxin in the pathogen-esis o f S. ureusi nfections (Berube & Bubeck Wardenburg, 2013). Liquiritigenin, one of the most active compounds of liquorice, demonstrated the capacity to prevent human lung cells (A549) from α-haemolysin-mediated injuries, by decreasing α- haemolysin production (Wang *et al,* 2015). Similarly, glabrin and glycyrrhetinic acid have shown antibacterial activity against S. aureus (Singh *et al,* 2015).

Different authors reported the antibacterial action of G. Glabra against Mycobacterium tuberculosis (Gupta *et al,* 2008), demonstrat-ing that glabridin is the responsible compound for this activity, instead of hispaglabridin B (Simmler *et al,* 2013). The antitubercular phenolic compounds were previously identified as licoisoflavone and licochalcone A (Chakotiya *et al,* 2017). In a mice lung infection model, G. glabrawas therapeutically active against multidrug-resistant strain of P. aeruginosa (Chakotiya *et al,* 2016), and the hydro-alcoholic extract led to a reduction of the micro-bial load in the blood, mainly due to the presence of stigmasterol, ergosterol, licochalcone, and glabridin (Chakotiya *et al,* 2017). The activity of G. glabra against Helicobacter pylorihas been also reported, as mentioned in the previous subsection (Krausse *et al,* 2004). According to Krausse et al. (2004), the compounds responsible for this activity are glabridin and glabrene. Cao et al. (2016) also reported that 18β-glycyrrhetinic acid significantly attenuated the gas-tritis infection caused by H. pylori. Asha et al. (2013) found that the fla-vonoid glabridin exhibits activity against H. Pylori whereas glycyrrhizin did not present activity even at a concentration of 250μg/ml. These flavonoids also showed activity against H. pyloristrains resistant to clarithromycin and amoxicillin (Fukai et al., 2002a, b). The proba-ble mechanism behind these actions is the inhibition of the protein synthesis, DNA gyrase, and dihydrofolate reductase (Fukai *et al,* 2002a, b). Moreover, the liquorice polysaccharides also present activity against Porphyromonas gingivalis adhesion, which is of huge importance because no specific adhesion inhibitors have been described (Chinsembu, 2016). The antifungal activity of G. glabra is also detailed (Sato et al., 2000). Sato et al. (2000) reported that the methanolic extract of liquorice presents fungicidal activity against Arthrinium sacchariandChaetomium funicola, whereas glabridin was found to be the active compound responsible for the observed effects (Sato *et al,* 2000). In fact, isoflavonoids, such as glabridin, glabrol, and their derivatives, are responsible for the in vivo inhibition of Mycobac-terium smegmatis, Shigella, Salmonella, E. coli, S. mutans, and Lactobacillus acidophilus (Ajagannanavar *et al,* 2014). Recently, Chandra and Gunasekaran (2017) also proved the antifungal activity of crude meth-anolic extract of G. Glabra against Aspergillus niger. Different authors reported that C. Albicans is susceptible to liquorice extracts due to their richness in liquiritigenin, liquiritin, licochalcone A, and glabridin (Chandra & Gunasekaran, 2017; Lee *et al,* 2009; Singh *et al,* 2015). Nevertheless, according to Karahan et al. (2016), the antimicrobial activity could be influenced by the environmental conditions that may affect the chemical compound contents and the biological activity. Licochalcone A and glabridin present a therapeutic potential against C. albicans oral infections, whereas glycyrrhizic acid had no effect (Messier & Grenier, 2011; Moazeni *et al,* 2017).

The antiviral activity of G. glabra extracts against different viruses has been reported, including herpes simplex, Varicella zoster, Japanese encephalitis, influenza, and vesicular stomatitis virus (Wang *et al,* 2015). Different studies have demonstrated that two triterpenoids are responsible for the antiviral activity reported: glycyrrhizin and 18β-glycyrrhetinic acid (Wang *et al,* 2015). These compounds have the ability to inhibit virus gene expression and replication, decreasing the adhesion force and stress and reducing HMGB1 binding to DNA (Wang et al., 2015). Also, they can enhance host cell activities by blocking the degradation of IκB enzyme involved in the propagation of the cellular response to inflammation, activating T lymphocyte proliferation, and suppressing host cell apo-ptosis (Wang *et al,* 2015). The antiviral mechanisms of both compounds are similar, inhibiting the adsorption and penetration of the virus in the early steps of the replicative cycle. Nevertheless, Cinatl et al. (2003) reported that these active principles are less effective if added during the adsorption period than after virus adsorption. On the other hand, Soufy et al. (2012) found that glycyrrhizin has excel-lent immunostimulant properties and induces a synergistic effect with duck hepatitis virus (DHV) vaccine by activatingT lymphocyte proliferation. Thus, the treatment with glycyrrhizin alone or in combination with DHV vaccine could lead to an immune stimulation and antiviral effect against DHV (Soufy *et al,* 2012).

Herpes simplex virus (HSV) is one of the most common viruses infecting humans and animals. During HSV infection, the cellular adhe-sion is increased, playing a key role in inflammatory response. Huang et al. (2012) reported that the adhesion force and stress between the cerebral capillary vessel endothelial cells and the poly-morphic nuclear leukocytes were amplified during HSV infection. Glycyrrhizin stimulates the mouse defence system against HSV-1 infection (Sekizawa *et al,* 2001). Furthermore, glycyrrhizic acid was found to have a distinctive effect against Kaposi sarcoma-associated herpes virus (KSHV). It was proved that glycyrrhizic acid could terminate the latent infection of KSHV when all current drugs are ineffective (Damle, 2014). Also, glycyrrhizic aciddown-regulates the expression of latency-associated nuclear antigen in B lymphocytes leading to natural cell death (apoptosis) of the KSHV-infected cells (Damle, 2014). Recently, the antiviral activity of glycyrrhizin against severe acute respiratory syndrome virus was eval-uated (Cinatl et al., 2003). Glycyrrhizin affects the cellular signaling pathways such as protein kinase C, casein kinase II, and transcription factors, namely, activator protein 1 and nuclear factor κB (Cinatl *et al,* 2003). Furthermore, glycyrrhizin and its aglycone, 18β- glycyrrhetinic acid, up-regulate the expression of inducible nitric oxide

synthase and the production of nitric oxide in macrophages (Cinatl *et al,* 2003). Zhang et al. also reported that glycyrrhizin reduces the expression of proinflammatory cytokines affecting coxsackievirus B3-induced myocarditis (Wang *et al,* 2015; Zhang *et al,* 2012). Also, the activity against human immunodeficiency virus (HIV) was evaluated (Sasaki et al., 2002). Glycyrrhizin has been used to treat patients with HIV-1 (Wang *et al,* 2015). The results revealed a low concentration of P24 antigen in patients, probably due to the up-regulation of chemokines (Sabde *et al,* 2011).

Glycyrrhizin, when compared with the placebo, presents clinical interest for the possible treatment of chronic hepatitis C, inducing a significant reduction of the serum aminotransferases and an improvement in the liver histology (Ploeger et al., 2001). Intra-venous glycyrrhizin can be also used for the treatment of acute-onset autoimmune hepatitis (Yasui et al., 2011). Another study shows that glycyrrhizin interferes with highly pathogenic H5N1 influenza A virus replication (Michaelis et al., 2011).Glycyrrhizin can also be used as a novel therapeutic method to control porcine epidemic diarrhoea virus (PEDV) infection, inhibiting the infection of Vero cells (namely, the entry and replication of PEDV) and decreasing the mRNA levels of proinflammatory cytokines (Huan *et al,* 2017). The hepatoprotective activity of glycyrrhizin and 18β-glycyrrhetic acid by inhibition of free-radical generation and lipid peroxidation has been extensively reported (Huo *et al,* 2011). One of these studies indicated that the hydromethanolic root extract ofG. Glabra exhibits a significant protection against hepatotoxicity induced by carbon tetrachloride in the liver tissue of mice (Sharma & Agrawal, 2017). The effects of liquorice on nonalcoholic fatty liver disease have also been investi-gated (Hajiaghamohammadi et al., 2012). According to Rizzato et al. (2017), glycyrrhizin and glycyrrhetinic acids prevent drug-induced liver injury and ensure the disruption of bile acid metabolism in humans.

Indeed glycyrrhetinic acid has been reported as anti-inflammatory and hepatoprotective compound (Yin *et al,* 2017). In addition, it prevents the oxidative and hepatic damage caused by aflatoxins through increasing CYP1A1 and glutathione-S- transferase activity, contributing to the anticarcinogenic activity by metabolic deactivation of the hepatotoxin (Yang *et al,* 2017). Mahmoud et al. (2017) reported that the treatment with 18β-glycyrrhetinic acid significantly reduced the serum enzymes, bilirubin, and proinflammatory cytokines in the liver, decreasing the expression of P450 E1. This activity is due to the 18β-glycyrrhetinic and glycyrrhizic acids that induce mitochondrial permeability transition, leading to the apoptosis of tumour cells (Lee et al., 2008). Lee et al. (2008) demon-strated the toxic effect of G. glabraagainst the human cervix and uterus tumour cell line SiHa cells. The hydromethanolic root extract of G. glabra also exhibited antimutagenic potential by sup-pressing micronuclei formation and chromosomal aberration in bone marrow cells of albino mice (Sharma *et al,* 2014). Glycyrrhizin and glycyrrhetinic acids are effective compounds in gastric cancer treatment, whereas glycyrrhizin suppresses throm-boxane A2 in lung cancer cell with low toxicity (Deng, *et al,* 2017). According to Wang et al. (2017), 18β- glycyrrhetinic acid has antitumour activities in breast and ovarian can-cer, gastric tumours, and leukaemia. In liver cancer, the compound inhibits the proliferation of HepG2 cells without affecting the normal liver cell line. In particular, 18β-glycyrrhetinic acid increases the forma-tion of reactive oxygen species, nitric oxide production, and loss of the mitochondrial membrane potential (Hasan *et al,* 2016).

Glycyrrhetinic acid derivatives have also presented promising cytotoxicity on human breast cancer cell lines (MCF-7, MDA-MB- 231; Li et al., 2016). Also, the anticancer activity in human leukaemia, by inducing the apoptosis of HL-60 cells through the activation of extrinsic and intrinsic apoptotic pathways, was proved by. Huang et al. (2016). Recently, licochalcone E, when compared with well-known antitumour agents, licochalcone A and isoliquiritigenin, exhibited the most potent cytotoxic effect (. Xiao *et al,* 2011; Yu *et al,* 2017). Xiao et al. (2011) explored the licochalcone. A mechanism of action in MKN-28, AGS, and MKN-45 gastric cancer cells and human gastric epithelial immortalized cells (Park *et al,* 2015; Xiao *et al,* 2011). The results indicated that licochalcone A inhibits gastric cancer cells growth in a dose-dependent way, by blocking cell cycle progression at the G2/M transition, inducing apo-ptosis. In addition, licochalcone A induced apoptosis by its effects on the expression of PARP, caspase-3, Bcl-2, and Bax (Xiao *et al,* 2011). Kanazawa et al. (2003) and Jung et al. (2006) showed that isoliquiritigenin inhibits the cell growth by G2/M cell cycle arrest inbreast and prostate tumour cells.

Different studies demonstrated that isoliquiritigenin suppresses pulmonary metastasis in mice (Yamazaki *et al,* 2002) and human hep-atoma cells (Hsu et al., 2005). Apoptosis was primarily mediated through mitochondrial death cascade, as shown by loss of mitochon-drial membrane potential, release of cytochromec, and activation of caspase-9. A possible explanation is that cell growth was arrested through up-regulation of p53 and p21 and down-regulation of cdk2, cyclin E, and E2F-1 while apoptosis was induced by increasing Bax protein expression and activating caspase-7 (Sharma *et al,* 2012). Glabridin exhibited antitumour properties in various human cancer cells (Jiang et al., 2016). The results revealed that glabridin induced apoptosis in dose dependently in Huh7 cells through caspase-3, caspase-8, and caspase-9 activation and PARP cleavage (Hsieh *et al,* 2016).

The effects of G. glabra on learning and memory were investigated in mice (Dhingra & Sharma, 2006; Parle *et al,* 2004). In 2004, Parle et al. (2004) administered the extract of G. glabraorally to mice during 7 days at different concentrations (75–300 mg/kg). Chakravarthi and Avadhani (2013) and Dhingra and Sharma (2006) studied the effects of G. glabra root aqueous extract on the learning and memory of 1-month-old male Wistar albino mice at doses between 75 and 300 mg/kg, orally administered during six successive weeks. Both studies demonstrated a significant improvement of learning and mem-ory in mice, but the exact mechanism behind this action remains unknown (Chakravarthi & Avadhani, 2013; Dhingra & Sharma, 2006).

References

1. Ahn SJ, Cho RJ, Kim HJ, Park SM, Lim YK, ET ALL., (2012) The antimicrobial effects of degycyrrhizinated licorice root extract on Streptococcus mutans UA159 in both planktonic and biofilm cultures. *Anaerobe* Dec;18(6):590-596.
2. Ahn, J., Lee, H., Jang, J., Kim, S., & Ha, T. (2013). Anti-obesity effects of glabridin-rich supercritical carbon dioxide extract of licorice in high- fat-fed obese mice. *Food and Chemical Toxicology,* 51, 439–445.
3. Ahn, S.-J., Song, Y.-D., Mah, S.-J., Cho, E.-J., & Kook, J.-K. (2014). Determi-nation of optimal concentration of deglycyrrhizinated licorice root extract for preventing dental caries using a bacterial model system. *Journal of Dental Sciences*, 9(3), 214–220.
4. Ajagannanavar, S. L., Battur, H., Shamarao, S., Sivakumar, V., Patil, P. U., ET ALL., (2014). Effect of aqueous and alcoholic licorice (Glycyrrhiza glabra) root extract against Streptococcus mutans and Lactobacillus acidophilusin comparison to chlorhexidine: An in vitro study. Journal of International Oral Health, 6(4), 29–34.
5. Albermann, M. E., Musshoff, F., Hagemeier, L., & Madea, B. (2010). Determination of glycyrrhetic acid after consumption of liquorice and application to a fatality. *Forensic Science International,* 197(1), 35–39.
6. Armanini, D., Fiore, C., Mattarello, M. J., Bielenberg, J., & Palermo, M. (2002). History of the endocrine effects of licorice. *Experimental and Clinical Endocrinology & Diabetes,* 110(06), 257–261.

7. Bahmani, M., Rafieian-Kopaei, M., Jeloudari, M., Eftekhari, Z., Delfan, B., et all., (2014). A review of the health effects and uses of drugs of plant licorice (Glycyrrhiza glabraL.) in Iran.Asian Pacific Journal of Tropical Disease, 4, S847–S849.
8. Biondi, D. M., Rocco, C., & Ruberto, G. (2003). New dihydrostilbene derivatives from the leaves ofGlycyrrhiza glabraand evaluation of their antioxidant activity. Journal of Natural Products, 66(4), 477–480.
9. Cao, D., Jiang, J., You, L., Jia, Z., Tsukamoto, T., Cai, H., Cao, X. (2016). The protective effects of 18β-glycyrrhetinic acid on Helicobacter pylori-infected gastric mucosa in Mongolian gerbils. BioMed Research International, 4943793, 2016,1–8. Chakotiya, A. S., Tanwar, A., Srivastava, P., Narula, A., & Sharma, R. K. (2017). Effect of aquo-alchoholic extract ofGlycyrrhiza glabraagainst Pseudomonas aeruginosain mice lung infection model. Biomedicine & Pharmacotherapy, 90, 171–178.
10. Chandra, J. H., & Gunasekaran, H. (2017). Screening of the phytochemical, antimicrobial and antioxidant activity ofGlycyrrhiza glabraroot extract. *Journal of Environmental Biology*, 38(1), 161–165.
11. Chinsembu, K. C. (2016). Plants and other natural products used in the management of oral infections and improvement of oral health. *Acta Tropica*, 154,6–18.
12. Chopra RN and Chopra IC (2006). Chopra´s indigenous drugs of India. Academic Publishers. Kalkata. p.185.
13. Chouitah, O., Meddah, B., Aoues, A., & Sonnet, P. (2011). Chemical compo-sition and antimicrobial activities of the essential oil fromGlycyrrhiza glabraleaves. Journal of Essential Oil-Bearing Plants, 14(3), 284–288.
14. Cinatl, J., Morgenstern, B., Bauer, G., Chandra, P., Rabenau, H., & Doerr, H. W. (2003). Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. The Lancet, 361(9374), 2045–2046.
15. Damle, M. (2014). Glycyrrhiza glabra(liquorice)—A potent medicinal herb. International Journal of Herbal Medicine, 2(2), 132–136.
16. Dattaa K, Singha TA, Mukherjee A, Bhata B, Ramesh B, Burmana AC. Eclipta alba extract with potential for hair growth promoting activity. J Ethnopharmacol 2009; 124: 450–456.
17. Deng, Q. P., Wang, M. J., Zeng, X., Chen, G. G., & Huang, R. Y. (2017). Effects of glycyrrhizin in a mouse model of lung adenocarcinoma. Cellu-lar Physiology and Biochemistry: International Journal of Experimental Cellular Physiology, Biochemistry, and Pharmacology, 41(4), 1383–1392.
18. Dhingra, D., & Sharma, A. (2006). Antidepressant-like activity of Glycyrrhiza glabraL. in mouse models of immobility tests. Progress in Neuro-Psycho-pharmacology and Biological Psychiatry, 30(3), 449–454.
19. FAO (2005). Evaluation of certain food additives. InSixty-third report of the Joint FAO/WHO Expert Committee on Food Additives. Singapore: World Health Organization.
20. Farhad SH, Aminzadeh A, Mafi M, Barekatain M, Nagheney M, Ghafr MR. The effectof adjunctive low dose doxycycline and licorice therapy on gingival crevicular fluid MMP 8 levels in chronic periodontitis. Dent Res J 2013 Sep-Oct;10(5):624-29.
21. Farooqi, A. A., Sreemaru, B. S. (2001). Cultivation of Medicinal and Aromatic Crops, Hyderabad: University Press (India) Limited.
22. Fiore, C., Eisenhut, M., Ragazzi, E., Zanchin, G., & Armanini, D. (2005). A history of the therapeutic use of liquorice in Europe. Journal of Ethnopharmacology, 99(3), 317–324.
23. Fukai, T., Marumo, A., Kaitou, K., Kanda, T., Terada, S., & Nomura, T. (2002a). Anti-Helicobacter pyloriflavonoids from licorice extract. Life Sciences, 71(12), 1449–1463.
24. Fukai, T., Marumo, A., Kaitou, K., Kanda, T., Terada, S., & Nomura, T. (2002b). Antimicrobial activity of licorice flavonoids against methicil-lin-resistantStaphylococcus aureus. Fitoterapia, 73(6), 536–539.
25. Geetha R , Roy A. In vitro evaluation of antimycotic activity of ethanolic extract of glycyrrhiza glabra. Asian J Pharm Clin Res 2013;6(3):205-207.
26. Gupta, V. K., Fatima, A., Faridi, U., Negi, A. S., Shanker, K., Kumar, J. K.,… Khanuja, S. P. S. (2008). Antimicrobial potential ofGlycyrrhiza glabra roots.Journal of Ethnopharmacology, 116(2), 377–380.
27. Hajiaghamohammadi, A. A., Ziaee, A., & Samimi, R. (2012). The efficacy of licorice root extract in decreasing transaminase activities in non-alco-holic fatty liver disease: A randomized controlled clinical trial. Phytotherapy Research, 26(9), 1381–1384.
28. Harwansh, R. K., Patra, K. C., Pareta, S. K., Singh, J., & Biswas, R. (2011). Pharmacological studies ofGlycyrrhiza glabra: A review. Pharmacology, 2, 1032–1038.
29. Hasan, S. K., Siddiqi, A., Nafees, S., Ali, N., Rashid, S., Ali, R.,…Sultana, S. (2016). Chemopreventive effect of 18β-glycyrrhetinic acid via modula-tion of inflammatory markers and induction of apoptosis in human hepatoma cell line (HepG2). Molecular and Cellular Biochemistry, 416(1–2), 169–177.
30. Hayashi, H., & Sudo, H. (2009). Economic importance of licorice. Plant Bio-technology, 26(1), 101–104.
31. Hayashi, H., Tamura, S., Chiba, R., Fujii, I., Yoshikawa, N., Fattokhov, I., & Saidov, M. (2016). Field survey ofGlycyrrhizaplants in Central Asia (4). Characterization ofG. glabraandG. bucharicacollected inTajikistan. Biological & Pharmaceutical Bulletin, 39(11), 1781–1786.
32. Herrera, M., Herrera, A., & Ariño, A. (2009). Estimation of dietary intake of ochratoxin A from liquorice confectionery.Food and Chemical Toxicol-ogy, 47(8), 2002–2006.
33. Hsieh, M. J., Chen, M. K., Chen, C. J., Hsieh, M. C., Lo, Y. S., Chuang, Y. C., Yang, S. F. (2016). Glabridin induces apoptosis and autophagy through JNK1/2 pathway in human hepatoma cells. Phytomedicine, 23(4), 359–366.
34. Hsu, Y.-L., Kuo, P.-L., & Lin, C.-C. (2005). Isoliquiritigenin induces apoptosis and cell cycle arrest through p53-dependent pathway in Hep G2 cells. Life Sciences, 77(3), 279–292.
35. Huan, C. C., Wang, H. X., Sheng, X. X., Wang, R., Wang, X., & Mao, X. (2017). Glycyrrhizin inhibits porcine epidemic diarrhea virus infection and attenuates the proinflammatory responses by inhibition of high mobility group box-1 protein.Archives of Virology, 162(6), 1467–1476.
36. Huang, W., Chen, X., Li, Q., Li, P., Zhao, G., Xu, M., & Xie, P. (2012). Inhibi-tion of intercellular adhesion in herpes simplex virus infection by glycyrrhizin.Cell Biochemistry and Biophysics, 62(1), 137–140.
37. Huang, Y. C., Kuo, C. L., Lu, K. W., Lin, J. J., Yang, J. L., Wu, R. S.,…Chung, J. G. (2016). 18α-Glycyrrhetinic acid induces apoptosis of HL-60 human leukemia cells through caspases-and mitochondria-dependent signaling pathways.Molecules, 21(7).
38. Huo, H. Z., Wang, B., Liang, Y. K., Bao, Y. Y., & Gu, Y. (2011). Hepatopro-tective and antioxidant effects of licorice extract against CCl(4)- induced oxidative damage in rats. International Journal of Molecular Sci-ences, 12(10), 6529–6543.
39. Jafarian, M. M., & Ghazvini, K. (2007). In vitro susceptibility of Helicobacter pylorito licorice extract.Iranian Journal of Pharmaceutical Research, 6(1), 69–72.
40. Jain E, Pandey RK, Khanna R. Liquorice root extracts as potent cariostatic agents in pediatric practice. J Indian Soc Pedod Prev Dent 2013 Jul-Sep;31(3):146-52.\

41. Jung, J. I., Lim, S. S., Choi, H. J., Cho, H. J., Shin, H.-K., Kim, E. J.,…Park, J. H. (2006). Isoliquiritigenin induces apoptosis by depolarizing mitochon-drial membranes in prostate cancer cells.The Journal of Nutritional Biochemistry, 17(10), 689–696.
42. Kanazawa, M., Satomi, Y., Mizutani, Y., Ukimura, O., Kawauchi, A., Sakai, T., Miki, T. (2003). Isoliquiritigenin inhibits the growth of prostate can-cer. European Urology, 43(5), 580–586.
43. Karahan, F., Avsar, C., Ozyigit, I. I., & Berber, I. (2016). Antimicrobial and antioxidant activities of medicinal plant Glycyrrhiza glabra var. glandulifera from different habitats. Biotechnology & Biotechnological Equipment, 30(4), 797–804.
44. Kataria, R, Hemraj, G. Singh, A. Gupta, S. Jalhan and A. Jindal (2013). Pharmacological activities on Glycyrrhiza glabraa review. Asian J. Pharm. Clinical Res., 6(1): 6.
45. Kim KR, Jeong CK, Park KK, Choi JH, Park JY, Lim SS et al.Anti-inflammatory Effects \of Licorice and Roasted Licorice extracts on TPA induced Acute Inflammation and Collagen induced Artheritis in Mice. J Biomed Biotechnol 2010. Available from: http://dx.doi.org/10.1155/2010/709378. Accessed March 7, 2018
46. Korhalkar A, Deshpande M, Lele P , Modak M. Antimicrobial activity Of Yasthimadhu (glycyrrhiza glabra L.)-A review . Int J Curr Microbiol App Sci 2014;3(1):329-336
47. Krausse, R., Bielenberg, J., Blaschek, W., & Ullmann, U. (2004). In vitro anti- Helicobacter pyloriactivity of extractum liquiritiae, glycyrrhizin and its metabolites.Journal of Antimicrobial Chemotherapy, 54(1), 243–246.
48. Kuo, K. K., Chang, J. S., Wang, K. C., & Chiang, L. C. (2009). Water extract of Glycyrrhiza uralensis inhibited enterovirus 71 in a human foreskin fibroblast cell line.American Journal Chinese Medicine, 37(2), 383–394.
49. Lee, C. S., Kim, Y. J., Lee, M. S., Han, E. S., & Lee, S. J. (2008). 18β- Glycyrrhetinic acid induces apoptotic cell death in SiHa cells and exhibits a synergistic effect against antibiotic anti-cancer drug toxicity. Life Sciences, 83(13–14), 481–489.
50. Li W, Asada Y and Yoshikawa T (2000). Flavonoid constituents from Glycyrrhiza glabrahairy root cultures. Phytochem., 55(5):447-56
51. Lingaraj S, Battur H, Shamarao S, Sivakumar V , Patil PU, Shanavas P . Effects of Aqueous and alcoholic licorice root extract against S mutans and L acidophilus in comparison to Chlorhexidine: An in vitro study. J Int Oral Health 2014 Jan; 6(4):29-34.
52. Liu, K., Pi, F., Zhang, H., Ji, J., Xia, S., Cui, F.,…Sun, X. (2017). Metabolomics analysis to evaluate the anti-inflammatory effects of polyphenols: Glabridin reversed metabolism change caused by LPS in RAW 264.7 cells.Journal of Agricultural and Food Chemistry, 65(29), 6070–6079.
53. Mahmoud, A. M., Hussein, O. E., Hozayen, W. G., & Abd El-Twab, S. M.(2017). Methotrexate hepatotoxicity is associated with oxidative stress, and down-regulation of PPARgamma and Nrf2: Protective effect of 18β-glycyrrhetinic acid.Chemico-Biological Interactions, 270,59–72.
54. Messeier C, Epifano F, Genovesa S, Grenier D. Licorice and its potential beneficial effects in common orodental diseases. Oral diseases 2012 Jan;18(1):32-39.
55. Messier, C., & Grenier, D. (2011). Effect of licorice compounds licochalcone A, glabridin and glycyrrhizic acid on growth and virulence properties of Candida albicans. Mycoses, 54(6), e801–e806.
56. Michaelis, M., Geiler, J., Naczk, P., Sithisarn, P., Leutz, A., Doerr, H. W., & Cinatl, J. (2011). Glycyrrhizin exerts antioxidative effects in H5N1 influenza a virus-infected cells and inhibits virus replication and pro- inflammatory gene expression. PLoS One, 6(5), e19705.
57. Moazeni, M., Hedayati, M. T., Nabili, M., Mousavi, S. J., Abdollahi Gohar, A., & Gholami, S. (2017). Glabridin triggers over-expression of MCA1 and NUC1 genes inCandida glabrata: Is it an apoptosis inducer? Journal de Mycologie Medicale, 27(3), 369–375.
58. Mukhopadhyay, M., & Panja, P. (2008). A novel process for extraction of natural sweetener from licorice (Glycyrrhiza glabra) roots. Separation and Purification Technology, 63(3), 539–545.
59. Park, M. R., Kim, S. G., Cho, I. A., Oh, D., Kang, K. R., Lee, S. Y.,…Kim, J. S. (2015). Licochalcone-A induces intrinsic and extrinsic apoptosis via ERK1/2 and p38 phosphorylation-mediated TRAIL expression in headand neck squamous carcinoma FaDu cells. Food and Chemical Toxicology, 77,34–43.
60. Parle, M., Dhingra, D., & Kulkarni, S. K. (2004). Memory-strengthening activity of Glycyrrhiza glabra in exteroceptive and interoceptive behavioral models.Journal of Medicinal Food, 7(4), 462–466.
61. Peter MC, Tallman JA, Braun TM, Jacobson JJ. Clinical reductionof S mutans in preschool children using a novel licorice root extract lollipop: A pilot study. Eur Arch Paediatr Dent 2010; 11(6):274-79.
62. Ploeger, B., Mensinga, T., Sips, A., Seinen, W., Meulenbelt, J., & DeJongh, J. (2001). The pharmacokinetics of glycyrrhizic acid evaluated by physio-logically based pharmacokinetic modeling. Drug Metabolism Reviews, 33(2), 125–147.
63. Rackova, L., Jancinova, V., Petrikova, M., Drabikova, K., Nosal, R., Stefek, M., Kovácová, M. (2007). Mechanism of anti-inflammatory action of liquorice extract and glycyrrhizin. Natural Product Research, 21(14), 1234–1241.
64. Rafi M, Vastano BC, Zhu N, Ho CT, Ghai G, Rosen R et al. Novel polyphenol molecule isolated from licorice root induces apoptosis, G2/M cell cycle arrest and Bcl2 phosphorylation in tumor cell lines. J Agric. Food Chem. 2002;50(4):677-84.
65. Ram, H. N. A., Lachake, P., Kaushik, U., & Shreedhara, C. S. (2010). Formu-lation and evaluation of floating tablets of liquorice extract. Pharmacognosy Research, 2(5), 304–308.
66. Rizzato, G., Scalabrin, E., Radaelli, M., Capodaglio, G., & Piccolo, O. (2017). A new exploration of licorice metabolome. Food Chemistry, 221, 959–968.
67. Sabde, S., Bodiwala, H. S., Karmase, A., Deshpande, P. J., Kaur, A., Ahmed, N., Singh, I. P. (2011). Anti-HIV activity of Indian medicinal plants. Journal of Natural Medicines, 65(3), 662–669.
68. Sasaki, H., Takei, M., Kobayashi, M., Pollard, R. B., & Suzuki, F. (2002). Effect of glycyrrhizin, an active component of licorice roots, on HIV replication in cultures of peripheral blood mononuclear cells from HIV-seropositive patients. Pathobiology: Journal of Immunopathology, Molecular and Cellular Biology, 70(4), 229–236.Sato, J., Goto, K., Nanjo, F., Kawai, S., & Murata, K. (2000). Antifungal activ-ity of plant extracts against Arthrinium sacchari and Chaetomium funicola. Journal of Bioscience and Bioengineering, 90(4), 442–446.
69. Sedighinia F, Safipor A, Soleimanpour S, Zarif S, Asili S, Ghazvini K. Antibacterial activity of glycyrrhiza glabrglabra on oral pathogens: an in vitro study. Avicenna J Phytomed 2012;2(3):118-124.
70. Sekizawa, T., Yanagi, K., & Itoyama, Y. (2001). Glycyrrhizin increases survival of mice with herpes simplex encephalitis. Acta Virologica, 45(1), 51–54.
71. Seleem D, Benso B, Noguti J, Pardi V , Murata RM. In vitro and in vivo antifungal act i vi t y of Li chochal cone-a agai nst candi da al bi cans bi ofil ms. PLos One 2016;11(6): e0157188. Available from: http://www.ncbi.nlm.nih.gov/ pmc/articles/ PMC4902220. Acccessed April 3,2018

72. Shalaby, A. M., Ibrahim, H. S., Mahmoud, E. M., & Mahmoud, A. F. (2004). Some effects of Glycyrrhiza glabra (liquorice) roots extract on male rats. Egyptian Journal of Natural Toxins, 1,83–94.
73. Sharma, G., Kar, S., Palit, S., & Das, P. K. (2012). 18β-Glycyrrhetinic acid induces apoptosis through modulation of Akt/FOXO3a/Bim pathway in human breast cancer MCF-7 cells. Journal of Cellular Physiology, 227(5), 1923–1931.
74. Sharma, V., & Agrawal, R. C. (2017). In vivo antioxidant and hepatoprotec-tive potential of Glycyrrhiza glabraextract on carbon tetra chloride (CCl4) induced oxidative-stress mediated hepatotoxicity. International Journal of Research in Medical Sciences, 2(1), 7.
75. Sharma, V., Agrawal, R. C., &Shrivastava, V. K. (2014). Assessment ofmedian lethal dose and anti-mutagenic effects ofGlycyrrhiza glabraroot extract against chemically inducedmicronucleus formation in Swiss albinomice. International Journal of Basic & Clinical Pharmacology, 3(2), 292–297.
76. Sharma, V., Katiyar, A., & Agrawal, R. C. (2016). Glycyrrhiza glabra: Chemis-try and pharmacological activity. In J.-M. Merillon, & K. G. Ramawat (Eds.), Sweeteners: Pharmacology, biotechnology, and applications (pp. 1–14). Cham: Springer International Publishing.
77. Shinwari ZA, Khan AA, and Nakaike T (2003). Medicinal and other useful plants of district swat, Pakistan. Al Aziz Communications, Peshawar, Pakistan. pp.121-122.
78. Simmler, C., Pauli, G. F., & Chen, S.-N. (2013). Phytochemistry and biolog-ical properties of glabridin. Fitoterapia, 90, 160–184.
79. Singh J, Tripath, A, Gandhi R, Singh S.C, Jain S.P, Sharma A, Khanuja SPS Traditional uses of Glycyrrhiza glabra (mulethi/yastimadhu). J Med Aromatic Plant Sci 2006; 28(2): 263-269
80. Singh, V., Pal, A., & Darokar, M. P. (2015). A polyphenolic flavonoid glabridin: Oxidative stress response in multidrug-resistantStaphylococ-cus aureus. Free Radical Biology and Medicine, 87,48–57.
81. Sinha D, Sinha A. Natural medicaments in dentistry. An international quarterly journal of research in Ayurveda 2014;35(2):113-18
82. Siracusa, L., Saija, A., Cristani, M., Cimino, F., D'Arrigo, M., Trombetta, D., Ruberto, G. (2011). Phytocomplexes from liquorice (Glycyrrhiza glabra L.) leaves—Chmical characterization and evaluation of their antioxidant, anti-genotoxic and anti-inflammatory activity. Fitoterapia, 82(4), 546–556.
83. Somjen D , Knoll E, Jacob V , Naftali S, Tamir S .Estrogen-like activity of licorice root constituents:glabridin and glabrene, in vascular tissues in vitro and in vivo. J Steroid Biochem Mol Biol 2004; 91: 147–155.
84. Somjen, D., Katzburg, S., Vaya, J., Kaye, A. M., Hendel, D., Posner, G. H., & Tamir, S. (2004). Estrogenic activity of glabridin and glabrene from lic-orice roots on human osteoblasts and prepubertal rat skeletal tissues. Journal of Steroid Biochemistry and Molecular Biology, 91(4–5), 241–246.
85. Soufy, H., Yassein, S., Ahmed, A. R., Khodier, M. H., Kutkat, M. A., Nasr, S. M., & Okda, F. A. (2012). Antiviral and immune stimulant activities of glycyrrhizin against duck hepatitis virus. African Journal of Traditional, Complementary, and Alternative Medicines, 9(3), 389–395.
86. Uniyal, M., G. S. Jariyal (2003). Aushadiya Podhpon Ka Vyavasayik Krishikaran, New Delhi: Indian Society of Agribusiness Professionals.
87. Varsha, A. R., & Sonam, P. (2013). Phytochemical screening and determina-tion of anti-bacterial and anti-oxidant potential ofGlycyrrhiza glabra root extracts. Journal of Environmental Research and Development, 7(4A), 1552–1558.
88. Vispute S and Ashlesha K (2011). Glycyrrhiza glabraLinn. "Klitaka": A review. Int. J. Pharma & Biosci., 2(3): 45.
89. Vu Dang La, Tanabe S, Bergeron C, Gafner S, Grenier D. Modulation of Matrix metalloproteinase and cytokine production by licorice isolates Licoricidin and Licorisoflavin A: potential therapeutic approach for periodontitis. J Periodontol 2011 Jan;82(1):122-128.
90. Wang L, Liu C. The antiviral and antimicrobial activities of licorice, a widely used Chinese herb. Acta Pharm Sin B. 2015 July; 4:310-15.
91. Wang, L., Yang, R., Yuan, B., Liu, Y., & Liu, C. (2015). The antiviral and anti-microbial activities of licorice, a widely-used Chinese herb. Acta Pharmaceutica Sinica B, 5(4), 310–315.
92. Wang, Q., Qian, Y., Wang, Q., Yang, Y.-f., Ji, S., Song, W., Ye, M. (2015). Metabolites identification of bioactive licorice compounds in rats. Journal of Pharmaceutical and Biomedical Analysis, 115, 515–522.
93. Wang, S., Shen, Y., Qiu, R., Chen, Z., Chen, Z., & Chen, W. (2017). 18β- Glycyrrhetinic acid exhibits potent antitumor effects against colorectal cancer via inhibition of cell proliferation and migration. International Journal of Oncology, 51(2), 615–624.
94. Wang, X. R., Hao, H. G., & Chu, L. (2017). Glycyrrhizin inhibits LPS-induced inflammatory mediator production in endometrial epithelial cells. Microbial Pathogenesis, 109, 110–113..
95. Xiao, X. Y., Hao, M., Yang, X. Y., Ba, Q., Li, M., Ni, S. J., du, X. (2011). Licochalcone A inhibits growth of gastric cancer cells by arresting cell cycle progression and inducing apoptosis. Cancer Letters, 302(1), 69–75.
96. Yang, R., Yuan, B. C., Ma, Y. S., Zhou, S., & Liu, Y. (2017). The anti-inflam-matory activity of licorice, a widely used Chinese herb. Pharmaceutical Biology, 55(1), 5–18.
97. Yang, Y., Yang, L., Han, Y., Wu, Z., Chen, P., Zhang, H., & Zhou, J. (2017). Protective effects of hepatocyte-specific glycyrrhetic derivatives against carbon tetrachloride-induced liver damage in mice. Bioorganic Chemistry, 72,42–50.
98. Yasui, S., Fujiwara, K., Tawada, A., Fukuda, Y., Nakano, M., & Yokosuka, O. (2011). Efficacy of intravenous glycyrrhizin in the early stage of acute onset autoimmune hepatitis. Digestive Diseases and Sciences, 56(12), 3638–3647.
99. Yin, X., Gong, X., Zhang, L., Jiang, R., Kuang, G., Wang, B., Wan, J. (2017). Glycyrrhetinic acid attenuates lipopolysaccharide-induced fulminant hepatic failure in d-galactosamine-sensitized mice by up-regulating expression of interleukin-1 receptor-associated kinase-M. Toxicology and Applied Pharmacology, 320,8–16.
100. Yu, J. Y., Ha, J. Y., Kim, K. M., Jung, Y. S., Jung, J. C., & Oh, S. (2015). Anti- inflammatory activities of licorice extract and its active compounds, glycyrrhizic acid, liquiritin and liquiritigenin, in BV2 cells and mice liver. Molecules, 20(7), 13041–13054.
101. Yu, S. J., Cho, I. A., Kang, K. R., Jung, Y. R., Cho, S. S., Yoon, G., Kim, J. S. (2017). Licochalcone-E induces caspase-dependent death of human pharyngeal squamous carcinoma cells through the extrinsic and intrin-sic apoptotic signaling pathways. Oncology Letters, 13(5), 3662–3668.
102. Zadeh, J. B., Kor, Z. M., & Goftar, M. K. (2013). Licorice (Glycyrrhiza glabra Linn) as a valuable medicinal plant. International Journal of Advanced Biological and Biomedical Research, 1(10), 1281–1288.
103. Zaidi. T. H. (2011). Development and Spread of Medicinal and Aromatic Plants in Haryana: A Geographical Study, Ph.D. thesis submitted to the Department of Geography, Jamia Millia Islamia, New Delhi.

104. Zhang, H., Song, Y., & Zhang, Z. (2012). Glycyrrhizin administration amelio-rates coxsackievirus B3-induced myocarditis in mice. The American Journal of the Medical Sciences, 344(3), 206–210.

DOI:10.31579/2639-4162/257