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Pharmaceutical, phytochemical, and economical potentials of *Glycyrrhiza glabra* L: a review

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ABSTRACT

Glycyrrhiza glabra L. (Licorice) is one of the most important medicinal plants indigenous to Iran. The main component of this species is a triterpenoid saponin compound called glycyrrhizic acid or glycyrrhizin that is 30-40 times sweeter than sucrose and is used in medicine, food and tobacco industries. Licorice has different therapeutic implications as it is used against Hepatitis c, skin and pulmonary diseases, and heart failures. It also improves the immune system and has anti-inflammatory, antiviral, antimicrobial, antioxidant and anticancer properties. The aim of the present study is to demonstrate the pharmaceutical, phytochemical, and economic potentials of this plant.

KEY WORDS: Therapeutic effects, Licorice, *Glycyrrhiza glabra*, Glycyrrhizic acid, Glycyrrhizin.

1. INTRODUCTION

It has been estimated that the burden of hard curable diseases including diabetes mellitus, atherosclerosis and other cardiovascular diseases, related to oxidative stress, contribute for about 60% of the 56.5 million reported deaths in 2001 (Farnsworth, 2004). Nowadays, a lot of researches focus on identification and preparation of natural compounds for prevention (Bahmani, 2014; Rahnama, 2014; Rafieian-Kopaei, 2014; Delfan, 2014; Asgary, 2013) and treatment (Rafieian-Kopaei, 2014; Gharipour, 2013; Asadi-Samani, 2014; Mirhosseini, 2014) of these diseases. Medicinal plants are a reliable source for preparation of effective drugs (Bahmani, 2014; Khosravi-Boroujeni, 2012; Saki, 2014; Khosravi-Boroujeni, 2013; Karamati, 2014).

Licorice with the scientific name of *Glycyrrhiza glabra* L. (Figure 1) is one of these plants. It is a perennial herb of fabaceae family which possesses a wide range of medicinal and food compounds in its root and rhizome. Licorice is widely used in medicinal, food and also tobacco industries. However, it grows easily so that it decreases products in farms and gardens due to high development of root and rhizome (Chandler, 2000). With regard to increasing value and special position of this plant in new medicinal industries, it is necessary to recognize its various potentials in different areas that is the aim of this review paper.

Figure 1: *Glycyrrhiza glabra*

1.1. Plant name and botanical description: The scientific name of licorice is Glycyrrhiza glabra L. and is known as Licorice or Liquorice. *Glycyrrhiza glabra* is a Greek name and has been derived from two words of glykys meaning sweet and rrhiza means root. Glabra means smooth refers to the fruit of this species which is smooth (Akhundzadeh, 2000).

Licorice is a perennial plant of the Astragaleae family and subfamily of Fabaceae and Faboideae. Height of this plant is different and reaches to 100-200 cm. The plant has mass and excessive leaves. The leaves are alternatively attached to the stem and have 4-7 leaflets and a terminal leaflet. Leaflets are dark green. Flowers are seen irregular and crowded on terminal spikes in yellow, violet or purple colors. Length of flowers reaches to more than 1 cm. Plant flowers late spring and early summer (June-July). Fruit is an oblong pod, 2-3cm long and brown in color. Sides of fruit are thin and become more or less peaked. There are 3-5 brown seeds inside the fruit

that are like bean. Seed layer is thick and steady and weight of one thousand seeds is about 10 gram. Length of root is different between 30-60 cm depending on species of plant and climatic condition of growing place. Length of root in dry regions and light soils reaches to 200 cm. Root and rhizome have medicinal uses. Licorice has different varieties including G. glabra var. glandulifera, G. glabra var, G. glabra var. violacca and G. glabra var. pallid (Ghahraman, 1999). Glycyrrhiza glabra grows in deep valleys with full sun mostly in well-drained soils (Merriam-Webster's, 2007).

1.2. Distribution: Licorice is a Mediterranean plant and is cultivated extremely in south-east of Asia. This plant grows from south of Europe to central Asia between two 30-45°N latitudes. The countries producing liquorice include Iran, Pakistan, Afghanistan, Iraq, China, Turkmenistan, Azerbaijan, Uzbekistan, and Turkey. Licorice is also cultivated in extensive areas in England, Belgium, French, Greece, Italy, and Germany. In Iran, also this plant is frequently found in whole east, west and center of country. Although in many countries this plant is cultivated as a medicinal plant but is considered as a weed in wheat and pea farms of central regions of Iran like Isfahan and Arak and dry farms of Kermanshah, Ilam and Fars provinces (Ghahraman, 1999).

1.3. Commercial applications and preparation: Licorice is the dried root of Glycyrrhiza glabra that has valuable chemicals such as glucose, sucrose, asparagine, albomidic substances, resin and essence. Effective substances of this plant have various consumptions in pharmacy, tobacco and confectionary industries (Mirhaidar, 1994; Fenwick, 1990). Licorice has a favorable flavor and taste. Its flavor mainly comes from *anethole.* This compound is also available in anise, fennel, and some other herbs. As a flavoring agent, licorice is used for chewing tobacco, liqueurs and soft drinks. The sweetness of licorice comes mainly from *glycyrrhizic acid* (Fenwick, 1990).

Licorice extract contains approximately *100 calories* per *ounce*. By boiling root of plant and volatizing its main part of water, a black substance is obtained. The most important indexes to determine quality of licorice root are the amount of aqueous extract and the amount of glycyrrhizic acid percentage. Amount of extract should be at least 20% in dried roots of plant 17 and the percentage of glycyrrhizic acid in plant root should be at least 2/5% according to USP pharmacopeia, 22 and 4 % (British Pharmacopeia, 2004) according to BP pharmacopeia. Free glycyrrhizin has been reported 58-60% and up to 98% as salt, in extract. In western countries, this substance is mainly used as sweetener since it is 50 times sweeter than sucrose and also has medicinal properties. Dried root of licorice can be chewed as sweet. Licorice extract is used in various types of sweet condiments (like candy). There are a lot of pharmaceutical products prepared from licorice, worldwide. Some of these products are used in Iran as medicine which are relatively popular and are sold as OTC (over the counter) are listed in table 1.

Table 1: Medicinal products of licorice available in Iran

Row	Drug Name	Medicinal form	Medicinal properties (manufacturer suggestion)	Name of manufacturer
1	Reglis	Pill	Treatment of duodenal and abdominal distension, excess acid secretion	Iran Darouk
2	d-reglis	pill	Inhibiting peptic ulcer in concurrent use with *Non-steroidal anti-inflammatory drugs*	Iran Darouk
3	Licophar	Pill	Anti-inflammatory, anti-cough and mucoactive	Goldaru
4	Gastrine	Pill	Anti-inflammatory, analgesic, accelerating duodenum and stomach ulcers healing	Goldaru
5	Mentazin	Pill	Relief of gastrointestinal pain, treat gastric ulcer and boating, laxative	Ebne-Masuyeh
6	Altadin	Pill	Treatment of inflammation and irritate mucous membranes, mucoactive in stimulated coughs	Dineh
7	Shirinoush	Syrup	Treatment of stomach and duodenum ulcer, gastritis and gastralogy	Goldaru
8	Reglicidin	Pill	Treatment of stomach and duodenum bloating, gastritis and gastralogy	Dineh

Some extracts of licorice are without glycyrrhizin and are called de-glycyrrhizinated licorice. This type of extract does not affect adrenal gland and is useful for people who suffer stomach and duodenum ulcers. This type of extract is used as basic substance in producing drinks.

1.4. Plant cultivation:

1.4.1. Ecological needs: Origin of licorice is Mediterranean areas and needs hot weather and enough sunlight during growth. Licorice species grow in sandy-loam soil and bearing lime compounds. Root of this plant is extensively developed and its performance increase in sandy soils, rich of calcium and pH of 5/5-8/1. Enough

nutrients have main role in increasing root performance and its active ingredients. Licorice favors light and is well grown in 7-25 0C. Enough light, water and nutrients increase active ingredients of root. This plant usually grows in regions where annual rainfall varies from 400 to 1160 mm (British Pharmacopeia, 2004).

Early spring is suitable time to direct planting of grain in the main land 24. Early spring also is suitable time for planting seed in indirect method Suitable rows distance is 30-40cm. licorice seed should be planted to a depth of 2cm. The best time for vegetative reproduction of licorice is fall. Inter-row *spacing* is 60-80 cm and two shrubs are spaced 30-40cm apart in two rows. The suitable depth of planting root pieces is different and depends on soil texture and environment moisture so that the recommended depth in light soils is 15-20cm and 10-12 cm in heavy soils. Vegetative reproduction of licorice is more economical and often this method is used to reproduce this plant. Increasing planting depth from 20-52 cm increases leaf surface and then decrease it. Increasing planting depth and rhizome size increased dry weight. Dry weight of stem in low depths decreased but it increased when rhizome size increased. The highest total weight in planting depth obtained 20cm that was very close to dry weight of 40cm depth. Three-node Rhizome produced the highest dry weight than one-node and two-node rhizome (Waliullahpoor, 2005).

Licorice can be reproduced by seed or vegetative method. Since licorice seed has thick layer and this layer decreases its vegetative power, some scratch should be created in the surface of layer before planting it. Reproduction by seed is performed by two direct and indirect methods. Rhizomes do not germinate in temperature below 6 0C and need at least 154 0C for germination. This temperature has been considered as base temperature for germination of licorice (Nezamabadi, 2006).

1.4.2. Maintenance and care: Licorice growth in the first year is slow so that weeds can develop rapidly. It is necessary to keep weeds under control before planting and also preparing bed without weeds. In the first growth year, weeds should be controlled by hand or mechanically by cultivator. In the spring season in order to develop root, 10-cm long basal stems of licorice should be cut and bring out of land before leaves are fallen (Omidbeigi, 2004).

1.4.3. Product harvest: If licorice is reproduced by vegetative method, 3-4th year after planting its root can be harvested but if reproduction is done by seed its root can be harvested 5-6th year after planting (Ghanbari, 2005). The suitable time to use root is early fall to late winter with regard to specification of growth region that has the highest glycyrrhizin level in this time. To recovery root, furrows are made in land by tractor, axe or shovel at a depth of 50cm and roots are collected by worker. Since effective substance in licorice root are solved in root so roots should be washed rapidly and by flowing water. After cleaning, roots skin should be separated then divided into 10-15 cm pieces and finally dry them. To dry roots, direct light or high temperature should not be used. If electrical dryers are used, the suitable temperature is 40 0C. Dried roots are then cracked. Dried root performance in 3 year old plants reaches to 1.5-2 ton in hectare and ratio of fresh roots to dry roots is 3.5-1 24. It seems that roots with fewer diameters have more side surface for dry weight and can search soil and attract food elements better than thicker roots (Rengel and Graham, 1996). In roots with more diameters, skin and epidermis is destroyed in result of generative layer and one cork tissue is created (Mojtahedi and Lesani, 2015).

1.5. Chemical compounds: Licorice root contains a wide variety of compounds like sucrose (up to 18%), flavonoids, sterols, amino acids, starch, oil essences and saponins. The main triterpene is glycyrrhizic acid or glycyrrhizin (Figure 2) (C_{42} H_{62} O_{16}) that is composed of two molecules of glucuronic acid and one molecule of glycyrrhetinic acid (Jiang, 2004; Montoro, 2011; Blumenthal, 2000; Alan Teck, 2007). Glycyrrhizin salt can be as potassium or calcium (Sabbioni, 2005). This substance as the most important substance in licorice root is about 50 times sweeter than sugar (Hayashi, 1998). The amount of this substance in the root varies with plant variety and climatic conditions of growing place and is between 5-20%. For example, the amount of glycyrrhizic acid in Spanish licorice root is 6-8% and in Russian licorice is about 10-14%. Some researchers believe that Iranian licorice contains the highest level of glycyrrhizic acid (Douglas, 2004). Level of this substance increases following age increase so that root has the highest glycyrrhizic acid in final years. The sweetness of licorice is very different from sugar, being less instant, tart, and in comparison to sugar lasting longer (Somjen, 2000). Study of scientific resources on chemical and physical properties of this compound shows that glycyrrhizic acid decomposes in 120^0C (Ong and Len, 2003). In some resources also softening point has been mentioned 170^0C and melting point 220^0C (Acharya, 1993). Different methods of extracting glycyrrhizic acid from root powder have been studied. Base of these methods often has been Pressurized hot water extraction (PHWE) and using alkalies and acids or both and other chemicals and adding them to hot water or steam to increase extraction use (Acharya, 1993). In Iranian National Standard and Pharmacopeia, the high-performance liquid chromatography has been used to determine glycyrrhizic acid level (Shi and Mei, 2003). Glycyrrhizic acid concentration in licorice root depends on variety, place and time of harvest (Hayashi, 1998).

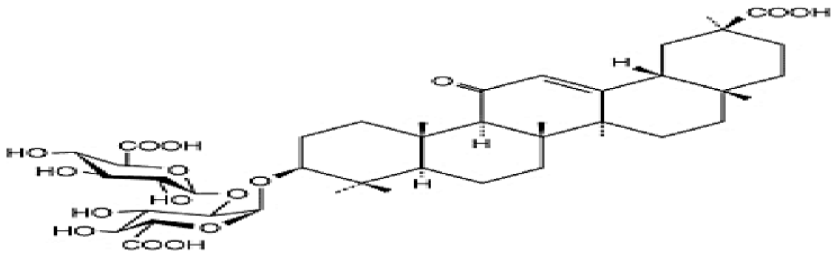

Figure 2. Structure of Glycyrrhizic acid

Results of determining Glycyrrhizic acid and aqueous extract of samples collected from different regions of Iran have shown that plant grown in Kermanshah, Fars and Kerman border, has been the best product and has high export value. In addition to mentioned compounds, licorice root contains acid-2-beta-glycyrrhizic, glucuronic acid, glycyrrhetinic acid (enoxolone), tannic acid, asparagine, resins, volatile oils, flavonoids such as liquiritigenin, liquiritin, isoliquiritigenin, and coumarin compounds, such as herniarin and umbelliferone with medicinal values (Li, 2000). Licorice also has phytoestrogens such as glabren and grlabridin (Alan Teck, 2007).

Licorice root contains triterpene saponins, flavonoids, isoflavonoids and chalcones, coumarins, stilbenoids, as well as miscellaneous compounds as biologically active components. Most of them have antioxidant activities. The dehydroglyasperin D (DGD), isoangustone A (IsoA) and phenylflavonoids dehydroglyasperin C (DGC) have been derived from licorice and identified as major antioxidants of this plant (Figure 3) (Alan Teck, 2007). Among them DGC possesses the highest free radical scavenging capacity. All of these three compounds and the other components with antioxidant activity suppress lipid peroxidation in rat tissues as well as H_2O_2-induced free radical production in hepatoma cells (Hyo- Jung, 2012).

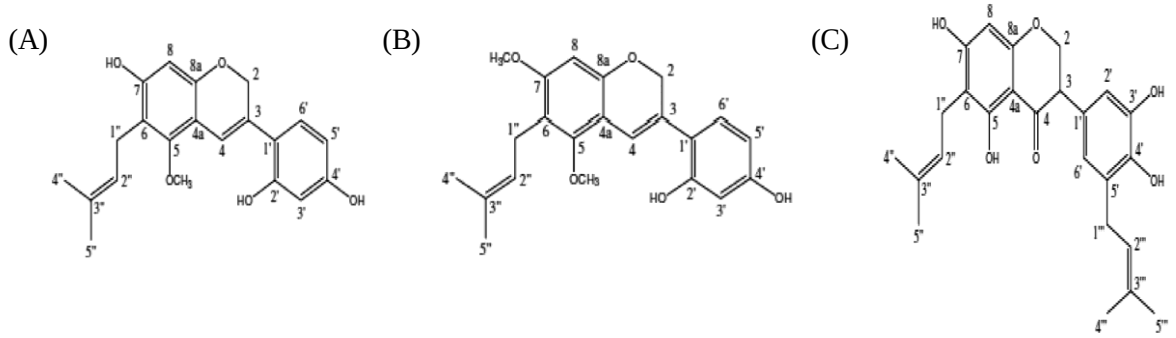

Figure.3: Molecular structures of dehydroglyasperin C(A), dehydroglyasperin D(B), Isoangustone A(C).

1.6. Pharmacological and medicinal properties: It is more than 4000 years that the root and rhizome of licorice has been used as medicine. It is recorded in pharmacopeia of different countries like America, China and other countries. In traditional medicine of Asia and Europe, Licorice is used to treat gastritis, respiratory infections and peptic complications (Bahmani, 2014). It is also used to treat hepatitis, tuberculosis, and other viral or microbial infections, as well as cancer, cough and heart diseases (Li, 2011). Glycrrizzinic acid has ability to inhibit Helicobacter pylori bacterium (Li, 2011) and so it is effective in the treatment of gastric ulcer and gastric mucosal problems (Csuk, 2010; Fukai, 2002). Licorice influences body endocrine gland system and its consumption can decrease testosterone level in blood. Also it has been demonstrated that Licorice is able to increase serotonin and prostaglandin secretion in stomach (Colalto, 2010). Commission E (The Complete German Commission E) has approved the use of licorice for gastric or duodenal ulcers as well as for catarrhs of the upper respiratory tract (Hayashi, 1998). Today also licorice extract is considered as one of ingredients of cough syrup (Hayashi, 1998). Extract of this plant also inhibits simulation of HIV virus in patients with AIDS (Alan Teck, 2007). Presence of lipid-lowering compounds and flavonoids with strong antioxidant activity and the positive effects of the extract on prevention of atherosclerosis have been approved in rabbit (Bahmani, 2014). However, studies have not yet reported that extract of this plant prevents and treats this disease in human (Fiore, 2008). Liquorice has been shown promising effects on skin dieasese, especially against atopic dermatitis and hyperpigmentation as well as dental carries and neurodegenerative disorders (Gazzani, 2012; Messier, 2012).

1.7. Side effects: The United States FDA has anouced that foods containing liquorice or glycyrrhizin is safe if not consumed excessively. However, glycyrrhizin and enoxolone, the major components licorice inhibiting effects on cortisol degradation, Licorice may cause hypokalemia, hypertension, edema and weight gain or loss (Douglas,

2004; Somjen, 2000). No more than 100mg to 200mg of glycyrrhizin per day has been suggested, which is equivalent to about 70 to 150g of liquorice (Omar-Hesham, 2015).

Irregular and excessive consumption of licorice or other its products has been inhibited due to irritation of adrenal gland and excess secretion of aldosterone hormone. This state causes some effects like disorder in metabolic activities and high blood pressure. It has been reported that eating more than 20g per day or more probably causes undesirable effects. Excessive use of licorice is also harmful for spleen. Excessive use of licorice may lead to presence of hypertension and also heart stroke. Some people who use high doses of licorice feel myalgia and some other leg and hand swelling. High use of it increases weight (Maha, 2012).

Licorice use must be avoided in cases of hypertension or renal, heart and liver problems. Using this plant and its products has been inhibited for women in pregnancy or lactation periods. Of course these problems can be prevented if recommended doses of it are used. If long-term use of licorice is necessary, it is better to combine it with tragacanth (Maha, 2012).

2. DISCUSSION AND CONCLUSION

Licorice has been recognized as important medicinal plant through world. Different uses of this plant in pharmaceutical and food industries are reason of its significant commercial value in the world. Licorice possesses a wide variety of phytochemicals, having pharmacological and therapeutic properties. Licorice root contains triterpene saponins, flavonoids, isoflavonoids and chalcones, coumarins, stilbenoids, as well as miscellaneous compounds as biologically active components. Most of them have antioxidant activities (Hyo, 2012).

It is well known that under stressful conditions free radicals are over-produced. Oxidative stress occurs due to an imbalance between free radical formation and antioxidant defense capacity (Bahmani, 2014; Delfan, 2014; Nasri, 2014; Rafieian-Kopaei, 2013; Madihi, 2013). The result of this oxidative stress would be the induction of chronic hard curable diseases such as diabetes (Asgary, 2014; Rafieian-Kopaei, 2014; Rafieian-Kopaei, 2014; Nasri, 2014; Asgary, 2013), hypertension (Baradaran, 2014; Sadeghi, 2014), cardiovascular (Asgary, 2013; Madihi, 2013; Sarrafzadegan, 2013) cancer (Shirzad, 2009; 2011; 2013), cognitive diseases (Baradaran, 2012; Rabiei, 2013; Baradaran, 2012; Rabiei, 2014), and pain (Bahmani, 2014; Saki, 2014; Bahmani, 2014; Delfan, 2004) or exacerbation of some other diseases like infectious disorders (Asadbeygi, 2014; Bagheri, 2013; Bahmani, 2014; Bagheri, 2013; Bahmani, 2014; Amirmohammadi, 2014; Bahmani, 2014).

Synthetic antioxidants, in contrast to their natural counterparts, have been shown to produce side effects such as toxicity. Hence, it is important to prepare natural products with antioxidant activities that are able to prevent and treat free radical-associated diseases (Rahimian, 2014; Baradaran, 2014; Nasri, 2014; Nasri, 2014). A lot of plant constituents are known to have antioxidant activities (Nasri, 2014; Rafieian-Kopaei, 2014; Baradaran, 2014; Baradaran, 2014; Ghaed, 2014; Nasri, 2014; Bahmani, 2014; Nasri, 2013).

These plants have drawn much attraction because they have protective or curative properties against most of hard curable diseases such as cognitive deficit, memory impairment, cancer, and cardiovascular diseases (Taghikhani, 2014; Heidarian, 2013; Taghikhani, 2012; Roohafza, 2013; Parsaei, 2013; Asadi, 2013; Gharipour, 2013; Nasri, 2013; Gharipour, 2014; Gholami-Ahangaran, 2012; Bahmani, 2012; Gholami-Ahangaran, 2012; Bahmani, 2014; Bahmani, 2012; Bahmani, 2013; Eftekhari, 2013; Bahmani, 2012).

Hence, the therapeutic effects of licorice which has antioxidant activity on inflammation, malaria, cardiovascular disease, peptic ulcers, hepatitis C, and pulmonary, skin diseases, and so on might be, at least in part, attributed to its antioxidant activity. In this regard, there is ample evidence showing the ability of licorice is closely related to its antioxidant activities.

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