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A Review: Pharmacological Effects of Licorice (Glycyrrhiza glabra) on Human Health

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Abstract

Having been used by human beings for medical purposes since the beginning of written history, licorice is still often used today because of its positive effects thought to be beneficial for human health. The first traces of medical use of licorices go back to Egyptian, Chinese and Indian cultures. It is known that licorice's protective effect against obesity, diabetes, peptic ulcer, cancer and tooth decays; healing quality against asthma and positive effect on lipid profile are rooted in its antioxidant function, antimicrobial features and active substances. However; there are several studies proving that licorice increases the risk of premature birth, hypokalemia and high blood pressure. Additionally, it has high amount of iron (Fe), manganese (Mn) and cobalt (Co) and these chemical elements may lie behind the comprehensive use of licorice in health. This compilation examines chemical structure, using forms, effects on human health, maximum usage dosage and drug interaction.

Key words: Licorice, Glycyrrhiza glabra, glycyrrhizin, health, toxicity.

1.Introduction

The first traces of the documents about the medical use of licorices go back to Egyptian, Chinese and Indian cultures (1). Having a sweet taste, licorice was named "sweet root" by Greek physicist Pedanius Dioscorides (2). The sweet taste of licorice comes from glycyrrhizic acid which is one of its active components (3). There are three herbs defined as licorice: *Glycyrrhiza glabra (G. glabra), Glycyrrhiza uralensis Fisch. (G. uralensis),* and *Glycyrrhiza inflata Bat. (G. inflata)* (2).

One of the most common herbal treatments applied in China, licorice is

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included in more than half of the prescriptions in Chinese medicine (4). Besides its main active component glycyrrhizic acid, licorice also consists of high amount of flavonoids, saponins, triterpenes, isoflavonoids and chalcones (5). Bio-active component of licorice, glycyrrhizic acid is used for herbal treatment of various diseases due to its anti-inflammatory, neuro-protective, anticarcinogenic and antiviral features (6). Isoliquiritigenin (ISL), chalcone and liquiritigenins (LTG's) are the flavonoids in the structure of licorice. While ISL has anti-inflammatory, antioxidant, antitumor activities and liver protective effect against oxidative stress, LTG has oestrogenic effect (7).

Compared to average indexes of other herbs, all organs of licorice contain more Fe, Mn and Co. These chemical elements lie behind the comprehensive use of licorice in health (8).

Various studies have proved that licorice increases insulin sensitivity and treats glucose intolerance (9,10). In addition, there are several studies suggesting that licorice stresses adipose tissue formation, increase energy expenditure and have antimicrobial and anticancer effects (11-14). However, some studies claim that consumption of licorice may have adverse effects such as high blood pressure, hypokalemia and premature birth despite tens of studies demonstrating numerous positive effects of licorice (14-19).

Licorice is widely used in the production of tea and alcoholic beverages, and confectionery, tobacco, pharmaceutical and cosmetics industry (1, 2, 20).

While the production of licorice is higher in the first months of summer, its production decreases in August because of high temperature and humidity (21). G. glabra is widely available in Spain, Italy, Turkey, Iraq, Iran, the Middle Asia and Northeast China. Japan imports very high amount of *G. Glabra* and *G. Inflata* for the production of glycyrrhizin, cosmetics and food additives. As licorice is not cultivated in Japan, it is mostly imported from China, Uzbekistan, Afghanistan, Turkmenistan and Pakistan (20).

This review provides information through a wide perspective from the cultivation of licorice to its consumption forms, from its effects on human health to recommended consumption amounts and from its toxicity level to drug interaction.

2. Licorice's Effects on Human Health

Licorice is used for the prevention and treatment of numerous diseases with various mechanisms (Figure 1).

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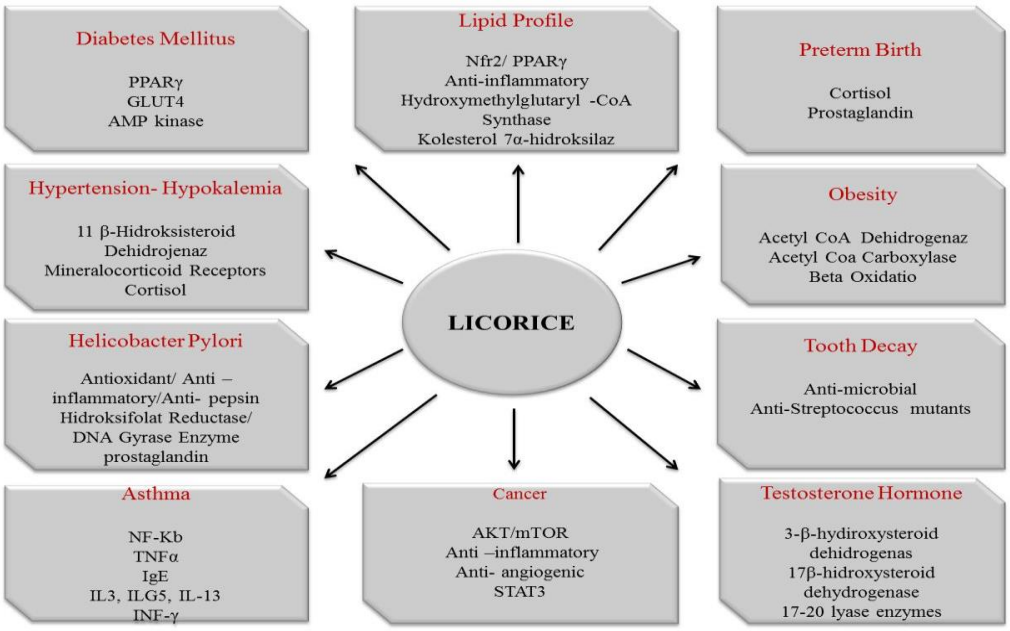

Figure 1. Possible health effects and related to mechanisms of licorice

2.1. Antidiabetic effect of licorice

Herbs have been used for the prevention and treatment of diabetics since old ages. Licorice is one of the oldest herbs which are used for herbal treatment in Chinese medicine due to its wide pharmacological features (7). There are several studies suggesting that chalcone and amorfrutin, which are active components of licorice, have antidiabetic effects by stimulating the activation of PPARγ's which has key roles in carbohydrate and lipid metabolism and adipocyte differentiation (7, 10, 22). It is stated that glabridin increases glucose intake and prevents glucose intolerance through the mechanism which enables the translocation of GLUT4 by means of adenosine monophosphate protein kinase (AMPK) (9).

In the study conducted by Weidner and his colleagues (2012) obese rats were subjected to high-fat diet for 12 weeks and cured for 23 days with 100 mg/kg/day amorfrutin which was considered to have any toxic effect on PPARγ and to have antidiabetic effect. It was found out that amorfrutin cured glucose tolerance at an important level (22%) and increased insulin sensitivity (21%) (10). In another study, including the rats whose blood glucose level is 200 mg/dL and more, researchers applied citrate buffer to the control group rats and 1 g/kg/day licorice essence to the second group. At the end of 8 week experiment, it was found out that the group which was applied licorice essence had considerably lower blood glucose level (22). In a study conducted on diabetic rats, the results showed that

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Licochalcone E (Lic E), isolated from licorice, increased the population of small adipocytes by enhancing PPARγ activation and had positive impacts on adipocyte-oriented diabetics (23).

2.2. *Anti-obesity effect of licorice*

It is stated that glabridin-enriched licorice essence decreased adipose tissue amount by reducing activity of acetyl-CoA carboxylase and increasing acetyl-CoA dehydrogenase activity of licorice flavonoid oil (LFO) and stressing adipose tissue formation in 3T3-L1 cells (13). Another potential mechanism is that LFO increased energy consumption by raising beta-oxidation and caused decrease in body fat and fat mass by prohibiting lipogenesis (11). A study conducted on healthy people proved that application of one-dose of 600 mg LFO can increase energy consumption by causing a rise in thermogenesis on the skin (24). In addition, it is suggested that LFO consumption stresses abdominal fat tissue increase in C57BL/6J rats fed with high-fat diet. (25). Another study demonstrated that LFO has very little effect on weight control of fat and obese individuals (26).

The inconsistencies between these studies may have resulted from the differences such as dietary intake and nutritional habits, physical activity levels, age, body-mass index (BMI) and ethnic roots of individuals and the amount and type of licorice used in the studies and application duration (27).

2.3. *Licorice's effect on birth weight*

It is stated that 7-45 % of pregnant women in Europe, America and Australia consume herbal products during pregnancy (28). However, it is quite important to search the effects of these herbal products on pregnancy process and the newborn. There are several studies searching the effect of licorice consumption during pregnancy on low birth weight and premature birth (18, 19).

Glycyrrhizin inhibits the break of cortisol in placenta locally and the increase in cortisol levels may be effective on prostaglandin levels. Therefore, it is suggested that with this effect mechanism licorice consumption may cause preterm births by creating premature spasms by increasing prostaglandin level in uterus (18, 19).

Surveys including detailed questions about licorice consumption were conducted with 95 women who gave premature birth and 107 women who gave normal birth and glycyrrhizin intake of participants was calculated. Participants were separated into 3 groups according to their glycyrrhizin consumption; low (<250 mg/week), moderate (250-499 mg/week) and high (>500 mg/week, >about 250 g licorice). It was found out that preterm birth risk of the group consuming highest amount of licorice doubles the group

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consuming lowest amount of licorice (18). The study conducted by Choi and his colleagues included 370 pregnant women who were carrying only one fetus and did not receive any herbal or teratogenic treatment during their pregnancy and 187 women who were also carrying only one fetus but consumed licorice during their pregnancy. The study found no relation between licorice consumption and plenty of negative parameters with regard to the newborn but suggested that licorice consumed during pregnancy may increase the risk of miscarriage (19).

2.4. Licorice's hypertensive and hypokalemic effect

The fact that consuming high amount of licorice for a long time may cause hypokalemia, hypertension and metabolic alkalosis became a current issue in 1950's (15). In hypokalemia cases, it is very important to consider secondary causes of hypokalemia such as drugs and herbal complexes (16). Active component of licorice, glycyrrhizic acid inhibits renal 11-beta hydroxysteroid dehydrogenase enzyme which inactivates cortisol. It is claimed that inhibition of this enzyme by licorice may cause excessive active cortisol formation. Excessive cortisol may cause hypertension, renal potassium loss, high bicarbonate and metabolic alkalosis by stimulating mineralocorticoid receptors (14-17).

In a case presentation, hypokalemic effect of licorice was recorded through a research conducted on a 55 years old male individual consuming 25 g/day licorice for one year after quitting smoking (14). In another case presentation, it was found out that blood pressure of a 66 years old male patient coming to a hospital because of hypertension was high and hypokalemic and this resulted from the fact that the patient consumed average 160 licorice pastille (240 g licorice contains 288 mg glycyrrhizin) per day. Hypertension and hypokalemia were attributed to the excessive consumption of licorice pastille and it was recorded that 7 weeks after quitting licorice pastille consumption, findings of the patient became normal again (15). It was stated that the severity and beginning of symptoms depend on the duration and dosage of licorice consumption as well as individual sensitivities (14).

2.5. Licorice's antimicrobial effect on tooth decays

Tooth decay is the most common oral-contagious disease and growth of decays is also affected from diet components working with the activity of pathogens. Many antimicrobial agents do not allow *Streptococcus mutants* to grow and stick on its surface, and inhibit bio-film formation. Therefore; they are used to avoid tooth decays. Recent studies have shown that

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licorice and its active components glycyrrhizin, glabridin, licochalcone A and licorisidin have positive effect on tooth decays and oral health (28-31). One of positive effects of licorice on human health is its antimicrobial effect (12). Some foodstuff (apple, red grape seeds, red wine, small coconut, chicory, mushroom, cornelian cherry, garlic extract, cacao extract, bee resin and licorice) have components which are resistant to pathogen *Streptococcus mutants* (32). Glycyrrhizin is transformed by human intestinal bacteria into severe hypertension and glycrrhizic acid that may cause hypertension. Therefore, only the licorice extracts which do not contain any glycyrrhizin content have been used in studies (33).

Different studies proved that 16 µg/mL of glycyrrhizin-free licorice extract inhibited the growth of UA159 *Streptococcus mutants* and bio-film formation (12, 30). Additionally, data show that 18β-glycyrrhetinic acid which is one of the active components of licorice, enhanced the effect of current antibiotics against drug resistant bacteria (31). In the light of these data, it is fair to suggest that glycyrrhizin-free licorice extract can be used in oral-hygiene products such as gargle solution and toothpaste (12).

2.6. Licorice's effect on lipid profile

Although the mechanisms of licorice enhancing lipid profile are not completely clear, there are different potential mechanisms. One of the potential mechanisms is that licorice can have afore-said effect via the liquiritigenin which is one of the active flavonoid components of licorice and able to activate the effect mechanism peroxisome proliferator-activated receptor-γ (PPARγ) through nuclear erythroid 2-related factor 2 (Nfr2). Other potential mechanisms reduces hepatic cholesterol levels by stressing hidroxymetilglutaril-CoA synthase of LFO and increasing cholesterol 7α-hydroxylase activity or enhances lipid profile by effecting insulin resistance, liver function, oxidative and anti-inflammatory condition or gene expressions (28,32). However, it should not be ignored that the enhancement in lipid profile may originate from the reduction in body weight and fat mass.

In a case control study held in Japan on rats, the rats were separated into two groups including control group (high-fat diet) and experimental group (high fat diet + 2% LFO). At the end of the experiment held for 21 days, plasma total cholesterol, very low-density lipoprotein (VLDL), low-density lipoprotein (LDL) cholesterol and LDL/high-density lipoprotein (HDL) cholesterol rates of the rats in experimental group were found to be considerably lower than that of the rats in control group (28). In addition, a study conducted on humans showed that the total cholesterol and LDL-C

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levels of the people who were given 900 mg LFO per day for 8 weeks were remarkable lower compared to control group (11). In the study conducted by Fogelman and his colleagues, participants of the experiment were separated into two groups including experimental group (n: 59) and control group (n: 51). While the participants in experimental group were given 0.2 g ethanol extract of licorice every day, participants of control group were given placebo for 365 days. The experiment proved that ethanol extract of licorice may help the prevention of cardiovascular diseases by creating positive effects of plasma lipoproteins (34). The results suggest that licorice consumption has a healer effect of lipid profile. However; it is required to conduct more studies to determine the mechanisms and necessary dosage and period for licorice consumption to get positive results for lipid profile.

2.7. Licorice's interaction with helicobacter pylori, peptic-gastric ulcer

Helicobacter pylori is one of the most common reasons of infections and oxidative stress gastric and peptic ulcer (35). The curative agents such as anti-acids, proton-pump inhibitors and histaminic antagonists are used to cure this disease. However, it is known that these agents may have side effects such as hypertension, arrhythmia, liver disorders and asthenia. Therefore, scientists search natural products that can be used in the treatment of peptic ulcer. Licorice is one of the oldest medical herbs used in the treatment of peptic ulcer (36).

Anti-inflammatory, antioxidant and prostoglandin formation booster effects of licorice are considered to be the mechanisms which create anti-peptic ulcer effect (36). According to another potential mechanism, flavonoid-enriched licorice extract causes helicobacter pylori activity by stressing protein synthesis, hydroxy-folate reductase enzyme and DNA gyrase enzyme (37). Moreover, licorice components create anti-pepsin effect by increasing mucus secretion in alimentary canal and extending the life time of cell surfaces in stomach (38). A study demonstrated that glabridin, glabrene, licochalcone A, licoricidin and licoiso-flavan B act as inhibitors against the reproduction of helicobacter pylori. It may be considered to involve licorice components in the structure of anti-helicobacter pylori (39).

2.8. Licorice's effect on cancer

Today's chemotheraphy-related approaches cannot lead us success at a satisfactory level because of serious toxic side effects, existence drug resistance and frequent re-deteriorations. Therefore, it is vital to discover and develop new anticancer agents. Most anticancer agents are produced from natural products or their synthetic analogs (40).

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Currently is has been reported that glycyrrhizic acid stresses AKT/mTOR signal on endometrial and breast cancer cells and inhibits the proliferation of these cancer cells (41). There are several studies suggesting that licorice has anticarcinogenic features because of its anti-inflammatory, apoptotic, angiogenic and oestrogen-like effects (33, 42). The results of the study, which examined glycyrrhizic acid's effects on the proliferation of leucemia cells and the mechanism lying under anticancer activity of glycyrrhizic acid, showed that glycyrrhizic acid inhibits the proliferation of leucemia cells and their migration by stressing AKT/ mTOR and STAT3 signal (41). The study conducted in China proved that the extract taken from alkaline extract of *Glycyrrhiza inflata* roots stresses proliferation of SCC-25 oral cancer cells on the basis of dosage by means of apoptosis (43). In a study conducted by Lee et al. it was found out that licorice extract considerably stressed tumor proliferation in BALB/C rats injected with CT-26 colon cancer cells. The other results of the experiment showed that use of licorice extract with cisplatin reduced cisplatin-based toxicity and licorice extract increased antitumor activity remarkably (44). These synthetic analogs are examined as a brand new branch of anticancer drugs (45).

2.9. Licorice's effects on asthma

A chronic airway inflammation, asthma is the most common respiratory disorder (46). Corticosteroid drugs are taken into trachea during respiration to inhibit and stress inflammation in case of asthma. However, using corticosteroid drugs for a long time may cause a number of side effects (47). In medicine, licorice has been used in the treatment of bronchial asthma for quite a long time in the history. It is considered that anti-asthma activity originates from Licochalcone A which is one of the active components of licorice (48). The cytokine called thymic stromal lymphopoietin (TSLP) is one of the major factors causing asthma. Excitable expression of TSLP can be controlled by nuclear factor kappa B (NF-kB). It was found out that licochalcone A can inhibit NF-kB activation, caused by TNFα, by inhibiting IkB kinase complex activation (48). There are a large number of studies suggesting that licorice flavonoids stress eosinophilic lung inflammation, IgE levels and IL-3, IL-5, IL-13 levels and increase INF- γ activity (2, 46, 49). Another effect mechanism creates anti-asthma effect by stressing TNF-α of the ganoderic acid isolated from licorice (49).

Ma and et al. (2013) examined glycyrrhizic acid's effects on asthma with a study conducted on 6 groups of rats with asthma resulting from ovalbumin [control group, model group, dexamethasone (2 mg/kg),

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glycyrrhizic acid group 1, 2 and 3 (10 mg/kg, 20 mg/kg, 40 mg/kg)]. It was found out that IgE, IL-4,IL-5, IL-13 levels of all experimental groups exposed to glycyrrhizic acid were stressed remarkably and IFNγ level increased considerably compared to model group (49). Therefore, it is fair to consider using licochalcone A and glycyrrhizic acid which are active components of licorice in the treatment of asthma. However, further studies are required for its use for clinical purposes.

2.10. Licorice consumption's effect on testosterone hormone

Having been used for the treatment of numerous diseases for thousands of years, licorice was a recommended herb for the treatment of infertile women in Chinese and Roman medicine. Licorice blocks the activity of 3-β-hydroxysteroid dehydrogenase, 17β-hydroxysteroid dehydrogenase and 17-20 lyase enzymes taking role in the metabolism and synthesis of androgen and oestrogen (50). It is claimed that licorice extract reduces serum testosterone hormone by stressing 17β-hidroxysteroid dehydrogenase enzyme which catalyzes the transformation of androgenic steroids into testosterone hormone (51).

Nine healthy women ranging in age from 22 to 26 were given 3.5 g of commercial licorice preparate including 7.6 % glycyrrhizin every day and it was found out that total serum testosterone level decreased from 27.8±8.2 to 19.0±9.4 in the first month and to 17.5±6.4 mg/dL in the second month. The use of licorice in the treatment process of the women suffering from hyperandrogenism can be considered on the condition that its hypokalemic and hypertensive effects are taken into consideration (50).

3. Toxicity and Maximum Level of Licorice Consumption

Consumption of licorice and its derivatives among foodstuff is included in generally recognized as safe (GRAS) list. Acceptable daily intake (ADI) of glycyrrhizic acid was discussed in Joint Expert Committee for Food Additives (JECFA) meeting (2005) and 100 mg glycyrrhizic acid consumption per day was found to be acceptable as a maximum limit for the majority of population although the meeting could not determine an exact ADI (52). The use of glycyrrhizin ammonium salt as a flavorer has been included in GRAS list (53).

Maximum consumption dosage was notified to be 3 mg/kg/day for extract, 5 g/day in powder form and 125 mg/kg for glycyrrhizin (54). In a study examining glycyrrhizin content of licorice tea, it was reported that licorice tea contains 126 mg/L of glycyrrhizin in average.

In the study conducted on rats to determine toxic dosage of glycyrrhizic

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acid, the rats were separated into four groups to be given glycyrrhizic acid with different dosages (0.5, 1, 1.5, 2 g/kg glycyrrhizic acid) and it was reported that glycyrrhizic acid could be well tolerated until the dosage of 1.5 g/kg but 2 g/kg of glycyrrhizic acid could be fatal (52).

US Food and Drug Administration has declared restrictions for the use of licorice and its derivatives in food (Table 1).

Table 1. US Food and Drug Administration Restrictions for the use of licorice and its derivatives in food (Isbrucker and Burdock, 2006).

Food Category	Maximum allowable levels in foods as % glycyrrhizin content	Functional Use
Baked products	0.05	1, 2
Alcoholic beverages	0.1	1, 2, 3
Soft drinks	0,15	1, 2, 3
Gums	1,1	1, 2
Candies	16,0	1, 2
Soft candies	3,1	1, 2
Medicinal herbs and spice	0,15	1, 2
Herbal protein products	0,15	1, 2
Vitamin or mineral supplements	0,5	1, 2
All other food except sugar substitutes	0,1	1, 2

1: flavor enhancer, 2: flavoring agent, 3: surface-active agent

Food and Drug Administration (FDA) reports that consumption of 40-50 g black licorice for 14 days or more may cause arrhythmia, hypokalemia hypertension, edema or lethargy (55). In a recorded case, it was reported that as a result of the examination on a 45 years old woman who came to the hospital with skin erythema, headache and sweating complaints, the woman had hypertensive and hypokalemic findings. The answers given by the sick woman about her food consumption showed that the women consumed 6 cups of licorice tea every day and the symptoms of the disorder vanished two weeks after the end of licorice tea consumption (56). It is indicated that consumption of licorice extract more than 3 g for 8 weeks may cause hypertensive and hypokalemic effects.

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Therefore, the individuals suffering from hypertension, heart and kidney diseases should restrict the consumption of licorice (57). Licorice consumption in the same dosage may create different results in different people depending on various factors. For example; out of two individuals who consume same dosage of licorice, the one who has lower BMI most probably has less amount of blood glycyrrhizic acid (58).
It is possible to come to the conclusion that licorice cannot reach fatal dose at all; however, licorice consumption should be taken under control for the individuals who are suffering from especially hypertension and/or cardiovascular disorders and pregnant women (15, 16, 18, 19, 52).

4. Licorice and Drug Interactions
Licorice is able to reduce the elimination of prednisolone. Using these drugs along with licorice for a long time may increase the side effects of the drugs (59). The results of the study conducted by Liu et al. (2015) showed that active components of licorice may create positive results for the treatment of asthma by stressing the production of TNF-α and boost the efficacy of corticosteroids used for the treatment of asthma (60). Glycyrrhizin, which is one of the active components of licorice and has potential anti-inflammatory effect, is considered to be used with isoniazid antibiotic for the treatment of tuberculosis (59). In addition, glycyrrhizic acid an active component of licorice inhibits renal 11-beta hydroxysteroid dehydrogenase enzyme which inactivates acid cortisol. Inhibition of this enzyme by licorice causes over-active cortisol formation. Excessive cortisol causes hypertension and renal potassium loss by stimulating mineralocorticoid receptors (25-27, 61). Therefore, consumption of licorice with these drugs triggers the risk of hypokalemia (59).

5. Conclusions and Recommendations
The people suffering from hypertension, heart failure, diabetics etc. and pregnant women should be informed about the possible health problems that may be caused by licorice consumption. Glycyrrhizin should not be consumed more than 100 mg per day which is the ADI and powder licorice should not be taken more than 5 per day. Consumption of licorice extract more than 3 g per day for a long time or drinking 6 cups of licorice tea every day may cause hypertensive and/or hypokalemic effects. Licorice can be consumed due to its antiobesity, antidiabetic, antimicrobial and anticarcinogenic effects and positive effects on lipid profile, peptic ulcer and hyperandrogenism. However, it can be claimed that licorice may have positive/negative effects on human health in many areas. Therefore, it is not possible to reach accurate conclusions

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about the consumption of licorice and further research is required. As a conclusion, licorice can be used for medical purposes under doctors' supervision, in proper dosages, by acceptable patients and under proper conditions.

Conflict of interest

The authors have no relevant interests to declare.

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