CHAPTER 6

LICORICE: AN OVERVIEW OF HEALTH BENEFITS AND RISKS

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INTRODUCTION

Wild plants and natural products have been used for centuries. World Health Organization emphasized the necessity of natural products and plant derived drugs in primary health care. Licorice (Glycyrrhiza glabra L. (synonyms: Glycyrrhiza glandulifera Waldst. et Kit; Liquiritae officinalis Moench)) is one of these plants and belongs to Leguminosae (synonyms Fabaceae) family. [1,2] The genus name "Glycyrrhiza" is originated from Greek word for 'sweet root' (Gr. glykos (sweet) + rhiza (root)), which was later Latinized to liquiritia than licorice.[3] It contains more than 20 triterpenoids; aglycone etc. and 300 flavonoids; liquirtin, isoliquertin liquiritigenin and rhamnoliquirilin and five new flavonoids glucoliquiritin apioside, prenyllicoflavone A, shinflavanone, shinpterocarpin and 1-methoxyphaseolin etc. (3-5.)

Gycyrrhiza genus has more than 30 species. Gycyrrhiza Glabra (typically cultivated in Europe, called European licorice), Gycyrrhiza inflata and Gycyrrhiza Uralensis (the two species are generally used in the traditional Chinese medicine and are known as Chinese licorice) are the most important licorice varities.(6)

The root and the juicy extract that obtained by boiling the roots, are mainly consumption types of the plant. Bioavailable components and flavor molecules involved in conical roots and rhizomes of the plant which are the main reasons the common usage of this parts. Main bioactive component of licorice: glycyrrhizin is 50 times sweeter than sugar and widely used as a sweetener in different kinds of products (gums, mouth spray, candies, health products, antacids, chewing tobacco, medicines, some alcoholic beverages, and herbal teas).[1] Furthermore, glycyrrhizin maintains its sweetness after heating and its sweetness remains in the

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mouth longer.[7] Other active constituents of the licorice plant root extract are the enoxolones: glycyrrhetinic acid (GA), its active metabolite glycyrrhizic acid (GE), and the hemi succinate derivative of GA, carbenoxolone.(8)

Licorice was detected in the tombs of Egyptian pharaohs, and it has been a widely used plant for over 3.000 years in the traditional Oriental medicine and in ancient Indian medicine (Ayurveda).[8,9] It was also used in Greek and Roman empires.[3] In traditional medicine, it has been used for treating asthma, hoarseness of voice, cough, and lung diseases and for mouth ulcerations, diseases of liver, and heart burning.[10] Nowadays, licorice is originated from Russia and China however it is also produced in Mediterranean countries, Southeast Europe, and parts of Asia. In Turkey, there is a higher consumption of licorice sherbet in east regions, especially in summer and Ramadan.(11)

Licorice is an important plant with its traditional use since pre-historic times and in commercial products, dietary supplements etc. nowadays. Its health benefits have been well reported, however, its adverse effects should not be ignored. In this article, it was aimed to review all effects of licorice and its bioactive components on health.

METHODS

Literature search was carried out on 4 different databases including "Pubmed", "Web of Science", "The Cochrane Library", "Lilacs" between May 2017-2018 without any time restriction. Search terms applied as "licorice" OR "Gycyrrhiza Glabra" OR "Gycyrrhiza inflata" OR "Gycyrrhiza Uralensis" OR "Gycyrrhiza" AND "health" OR "antiulcer", OR "antioxidan", OR "antiinflammatory", OR "antiatherosclerotic", OR "antiprotozoa", OR "antitumoral", OR "antifungal", OR "hepatoprotective", OR "neuroprotective", OR "adverse effects". Articles evaluated by abstract and title and relevant articles were included for full text examination; whether met the inclusion criteria; written in English, conducted on human and animals, being clinical, randomized controlled, cross-sectional, prospective studies, and reviews.

BIOACTIVE COMPOUNDS OF LICORICE

Phenolic compounds, flavonoid glycosids, and triterpenoid saponins are significant bioactive molecules with their bioactive diversity. Licorice has wide varity of these biological compunds; phenolic compounds (flavonoids (5,8-dihydroxy-flavone-7-O-β-D-glucuronide (glychionide A), 5-hydroxy-8 – methoxyl-flavone-7-O-β-D-glucuronide (glychionide B), galbrene, glabrone, glabraisoflavanone A, glabraisoflavanone B, isoviolanthin, 5,7-dihydroxyflavanone,

rhamnoliquiritin), chalconoids (liquiritigenin, liquiritin, isoliquiritigenin, isoliquiritin, licochalcone A and B (12), coumarins (herniarin and umbelliferone, glycycoumarin(13), licopyranocoumarin(14), glycyrin, glycyrol (15), dipheny-lethanones, flavonoid glycosides, stilbenes (Gancaonin G(16)) and triterpenoid saponins (18β-Glycyrrhetinic acid (17), glycyrrhizic acid (18), licorice saponin A3, licorice saponin G2, licorice saponin J2, licorice saponin C2 (1,4,7,17,19) (Figure 1). Extracts of and compounds of licorice have been well studied. (7) At least 1 phenolic compound, 23 flavonoid glycosides and 35 saponins, have been isolated from G. Uralensis.[14] In a study, 35 phenolic and 11 triterpenoid compunds were identified by high-performance liquid chromatography with diode-array detection (HPLC/DAD), time-of-flight mass spectrometry (HPLC/TOFMS) and quadrupole ion trap mass spectrometry (HPLC/QITMS).(20) In a recent study, 11 new compunds were also detected and named as glycybridins A–K (1–11). (21) These biological compounds are associated with some positive health effects of licorice.[6]

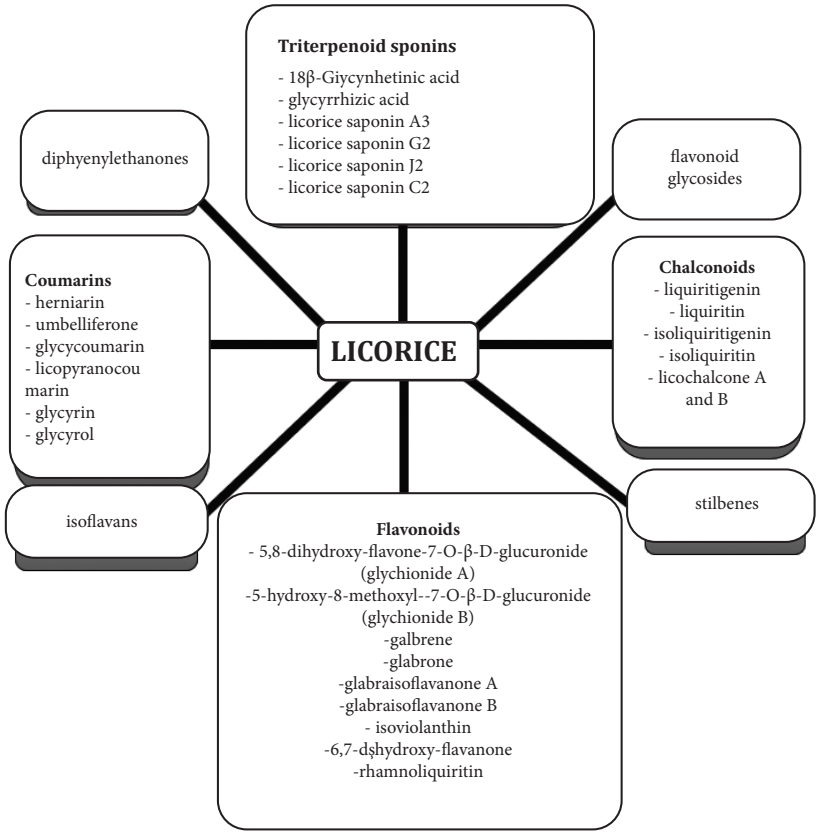

Figure 1. Bioactive compounds of licorice

Among these bioactive compounds, glycyrrhizin (mentioned as glycyrrhizic acid, glycyrrhizinic acid, and 18β-glycyrrhizin in the literature) is an oleanane-type saponin and the most abundant compound of licorice.[6,22] (Figure 2). As tribasic acid, glycyrrhizin comprised of a triterpenoid aglycone, glycyrrhetic acid (glycyrrhetinic acid; enoxolone) conjugated to a disaccharide of glucuronic acid. Glycyrrhetinic acid, associated aglycone and liquiritigenin is other prominent compunds of licorice. Both glycyrrhizin and glycyrrhetic acid can exist in the 18α – and 18β – stereoisomers.(3)

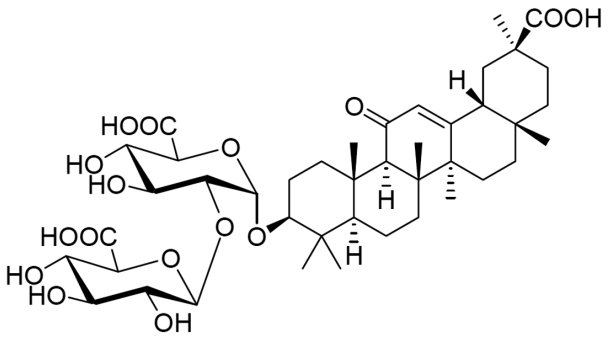

Figure 2. Chemical structure of Glycyrrhizic acid

POSSIBLE HEALTH EFFECTS OF LICORICE

Licorice has been consumed in traditional medicine since Prehistoric Ages due to its several health benefits. There are several clinical studies reported the positive health effects of the plant (Figure 3). According to these study results mentioned below, licorice has antiulcer, antioxidan, antiinflammatory, antiatherosclerotic, antiprotozoal, antitumoral, antifungal, hepatoprotective, neuroprotective effects and has positive effects on dyspepsia. In ancient Chinese medicine and Roman times, licorice was also used in the treatment of sterility in women.(23)

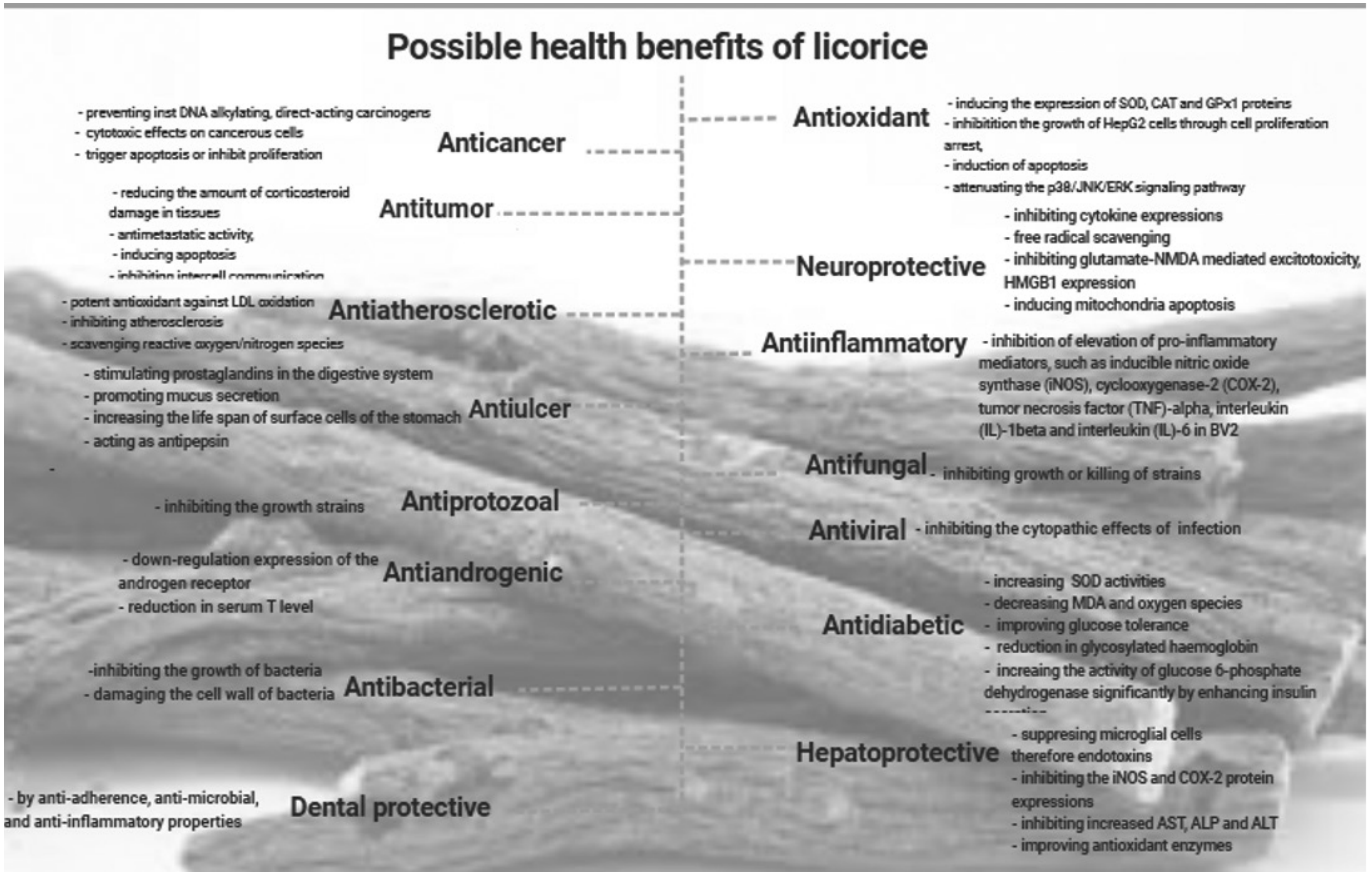

Figure 3. Possible health benefits of licorice

Antioxidant Effects

D'angelo et al. reported the antioxidant properties of licorice in their study which gave results about that pretreatment of Caco-2 cells with licorice polyphenolic extracts provided a remarkable protection against oxidative damage induced by H_2O_2.(9) In another study, glycyrrhizic acid was found to protect against aflatoxin-induced oxidative stress in human hepatoma cell line.(24) Chen et al. (2017) conducted an in vivo study and reported that Licochalcone A (LCA) is a phenolic chalcone compound and a characteristic chalcone of licorice, induce the expression of SOD, CAT and GPx1 proteins; inhibits the growth of HepG2 cells through cell proliferation arrest and the subsequent induction of apoptosis, attenuated the p38/JNK/ERK signaling pathway in a dose-dependent manner.(2) These study present significant data about effects of licorice on oxidative stress and oxidative stress-related disease including cancer.

Anticancer Effects

As well as its antioxidant effects, licorice also may protect agains mutagenic acitivities via different mechanisms. Eight purified components from Glycyrrhiza, namely glabridin, glycyrrhetinic acid, glycyrrhizin, licochalcone A, licoricesaponin H_2, licoricesaponin G_2, liquiritigenin and liquiritin were found to be against DNA alkylating, direct-acting carcinogens.(25) In a study with conducted with G. pallidiflora from Russian Far East, which has been rarely studied, results were in line with previous findings that supporting cytotoxic activity of the plant.(26) Furthermore, G. glabra and glycyrrhizin possess selective cytotoxic effects on cancerous cells.(10)

Licochalcone A (LCA) is a characteristic chalcone of licorice, which is the root of Glycyrrhiza inflata Batalin, was also reported as anticancer according to some study results which indicated that LCA can trigger apoptosis or inhibit proliferation.(27,28.)

Antitumor

Study results indicated the positive effects of licorice and on tumor growth.(29) They have demonstrated that compounds of licorice inhibit tumor growth, probably, by reducing the amount of corticosteroid damage in tissues and show antimetastatic activity, induce apoptosis, inhibit intercell communication.(29) Fukuchi et al. found clear support for the neoisoliquiritin apioside had the highest anti-tumor activity.(29)

Antiatherosclerotic Effects

Licorice has shown to affect cardiovascular properties. In one study, carotid inti-

ma-media thickness (CIMT) was evaluated which is an important indicator for cardiovascular disease.(30) They reported a decrease in mean CIMT, total cholesterol, LDL levels, and blood pressure after following 1 year of licorice consumption. However, Carmeli et al. (2009) did not found any significant decrease in hypercholesterolemic, and normal lipidemic human.(31)

Neuroprotective Effects

Some natural show neuroprotective effects by enhancing the survival of neurons by preventing their death and apoptosis.(32) In a study, 450 and 900 mg/d licorice extract or placebo capsules were given to 75 patients three times daily for 7 days in the neurology emergency department. In licorice treatment groups, there is a statistically signficant decrease in National Institute of Health Stroke Scale (NIHSS) and Modified Rankin Scale (MRS) scores which were assessed before initiation of therapy and 3 months after treatment compared to control group.(33) In an in vitro study, glycyrrhizin was reported as anti-Alzheimer agent.(34)

Antiulcer Effects

Licorice is widely known due to its effects on gastric system. Moreover, carbenoxolone which is a pharmaceutical ajan for gastric ulcers, is derived from glycyrrhetic acid.(3) Licorice stimulates prostaglandins in the digestive system which promote mucus secretion. Licorice may also increase the life span of surface cells of the stomach and acts as antipepsin which are the possible mechanism of licorice's anti-ulcer effect.(35)

In a mice model with HCl/ethanol-induced ulcer, Glycyrrhiza glabra Linn administration (50, 100, 150 and 200 mg/kg) showed antiulcer activity.(36) In another animal model Gut Gard (Licorice Extract Capcule) reduced gastric content, total acidity, ulcer index, and increased pH of gastric fluid.(37) In a human study, Aly et al. (2005) found that licorice is as effective as anti-ulcer drug.(35) In their study, thirty-six male albino rats divided into 6 groups; negative control group received 0.2 mL of sesame oil, positive control group was injected intramuscularly with diclofenac sodium (10 mg/kg), treated group 1 was injected intramuscularly with glycerrhitinic acid (100 mg/kg), treated group 2 was injected intramuscular (IM) with aqueous licorice extract (250 mg/kg), treated group 3 was injected IM with a combination of GA and diclofenac sodium (DS) (100 mg/kg and 10 mg/kg, respectively), treated group 4 was injected IM with a combination of aqueous licorice extract and diclofenac sodium (250 mg/kg and 10 mg/kg, respectively). After the investigation, it was found that licorice had similar properties with famotidine. Combination of them showed higher anti-ulcer activity. Study results support the positive effects of licorice on ulcer treatment.

Antiinflammatory Effects

Licorice has been shown to have significant antioxidant properties according to some study results.(2,35) In a study, six flavonoids, 5-(1,1-dimethylallyl)-3,4,40-trihydroxy-2-methoxychalcone, licochalcone B, licochalcone A, echinatin, glycycoumarin and glyurallin B were isolated from the extracts of licorice and were evaluated by antioxidant and anti-inflammatory properties. Two of the flavonoids; 5-(1,1-dimethylallyl)-3,4,40-trihydroxy-2-methoxychalcone and glyurallin B were first reported as antioxidant and anti-inflammatory.(38) In a mice model, licorice especially roasted licorice extract compared to unroasted licorice extract prevent ear edema with phorbol ester, which induces acute inflammation due to the increased activity of TNF-α and IL-1β.(27) In an in vivo study on lipopolysaccharide-stimulated microglial cell model, glycyrrhizic acid, liquiritin and liquiritigenin inhibited elevation of pro-inflammatory mediators, such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), tumor necrosis factor (TNF)-alpha, interleukin (IL)-1beta and interleukin (IL)-6 in BV2 (mouse brain microglia) cells.(32)

Antiprotozoal Effects

Protozoan parasites cause diseases such as malaria which is an endemic infection caused by genus Plasmodium.(39) The burden of Malaria is getting worse, mainly due to the increasing resistance of Plasmodium falciparum against the widely available antimalarial drugs.(5) Therefore, alternatives therapies are getting attention. Plants have been reported to show antiplasmodial activity in different studies.(40,41) Licorice roots was also found to reduce parasitemia in vivo in female Swiss albino mice at a dose of 400 mg/kg 42 and 18β-Glycyrrhetinic acid was found to be protective against Plasmodium falciparum.(39) Positive effects of licorice on toxoplasma have also been studied (43)

Antifungal Effects

Licorice was counted among Ayurvedic medicinal plants which have antifungal activities. (44) In a study evaluating effects of licochalcone A, glabridin and glycyrrhizic acid on growth, biofilm formation and yeast-hyphal transition of C. Albicans, the most important agent involved in human candidiasis and associated with denture stomatitis, researchers found that especially glabridin and licochalcone A showed antifungal activity on C. albicans while glycyrrhizic acid do not. Their synergystic effects with the drug, nystatin, was also confirmed.(45) Fatima et al. also supported the previous study results about glabridin in their study. They found that glabridin which was isolated through bioactivity guided fractionation of the licorice root extract, was found to be most potent against amphotericin B resistant C. Albicans culture.

Antiviral Effects

In Japan licorice extracts have been used for more than 60 years in the treatment of viral disesases; human immunodeiciency virus (HIV), cytomegalovirus (CMV), and Herpes simplex.(5) Fukuchi et al. obtained results about antiviral effects of licorice that licorice root flavonoids, especially liquiritin apioside, isoliquiritin apioside, lucurzid, isoliquiritin, showed higher anti-HSV activity than other polymethoxyflavonoids and low molecular weight polyphenols.(29)

Antiandrogenic Effects

Prostate cancer, hirsutism, acne, androgenic alopecia, and benign prostatic hyperplasia are androgen-mediated diseases.(46) Data so far have revealed the antiandrogenic properties of licorice in animals.(46) Androgens also have functions in the regulation of bone metabolism. (47) It is important to normalize hormonal fluctations for treatment of complications and diseases.

Antidiabetic Effects

In recent years, traditional Chinese medicine has become important in the therapy of diabetes and its complications.(48) Kalaiarasi et al. revealed that oral administration of 18β glycyrrhetinic acid (50, 100, or 200 mg/kg/body weight) or glibenclamide (600 μg/kg/body weight) in 5% dimethyl sulfoxide, for 45 days to streptozotocin-diabetic rats prevented the changes related to diabetes.(49) In another animal study, Male Kunming mice were divided into six groups (10 per group): normal control, diabetic control, diabetic + low-dose glabridin treatment (glabridin, 10 mg/kg), diabetic + medium-dose glabridin treatment (glabridin, 20 mg/kg), diabetic + high-dose glabridin treatment (glabridin, 40 mg/kg) and diabetic + glyburide treatment group (glyburide, 4 mg/kg). After 28 days examination, glabridin significantly increased body weight, glucose tolerance and SOD activities in the liver, kidney, and pancreas.(48)

Antibacterial Effects

Listeria monocytogenes, Campylobacterjejuni and Escherichia coli are foodborne pathogens which are some often responsible factors for food contamination. In one study which was conducted on effects of licorice antibacterial activiy; eight species of Gram-negative and Gram-positive bacteria, including Listeria monocytogenes, Listeria innocua, Staphylococcus aureus, Enterococcus faecalis and Bacillus subtilis were screened. Bacteria were grown in the presence of licorice extract at range of concentrations, and it was found that 50 μg ml-1 was sufficient to inhibit the growth of bacteria. Doses of 12.5 μg ml-1 and 50 μg ml-1 were prepared and growth was monitored. The extract only affected the growth of

Gram positive bacteria and Gram positive bacteria tested showed normal levels of growth. For the Gram-positive bacteria, at 50 μg ml-1 growth was completely inhibited, whereas at 12.5 μg ml-1 growth rate was reduced but some growth was still detected.(50) In another study, Gut Gard (Licorice Extract Capcule), standardized extract of Glycyrrhiza glabra (The extract is standardized to contain glabridin (≥3.5% w/w), glabrol (≥0.5%w/w), eicosanylcaffeate (≥0.1%w/w), docosyl caffeate (≥0.1%w/w) and total flavonoids (≥10%w/w)) was found to have positive effects on Helicobacter pylori. GutGard exhibited superior activity against Helicobacterpylori whereas glycyrrhizin did not have activity even at 250 mg/ml concentration.(51) Inhibition of protein synthesis, DNA gyrase and dihydrofolate reductase was reported as possible mechanism in the prevention of Helicobacter pylori action. However, it should not be rule out that some natural medical reagents lead to side effects resulting in other diseases or cancers in the cancer treatment.(2)

Hepatoprotective Effects

Liver is in the core of metabolism and excretion, and it is often exposed to a variety xenobiotics and therapeutic agents.(52) Licorice has shown to protect liver due to its antioxidant proterties. In a study, licorice extract high in Glycyrrhizin showed hepato-protective effects by supressing liver enzymes.[22] In another study, licorice extract inhibited increased AST, ALP and ALT activities and the decreased total protein, albumin and globulin levels caused by CCl_4 intoxication, enhanced liver super oxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), glutathione reductase (GR), glutathione S-transferase (GST) activities and glutathione (GSH) level, decreased malondialdehyde (MDA) level [52]. Al-Qarawi et al. also reported the hepatoprotective effect of Glycyrrhizin glabra on CCI_4 induced acute hepatotoxicity in rats.(53)

Dental Health

Licorice might have positive effects on dental health. Jain et al. conducted a study on the effects of licorice and chlorhexidine on plaque-induced gingivitis.(54) Participants diagnosed with chronic generalized gingivitis, were selected, and randomly divided into two groups. First group received chlorhexidine mouthwash and second group licorice mouthwash. After the examination, both chlorhexidine and licorice mouthwash were effective to decrease plaque, gingival index scores, and bleeding on probing. However, the improvement in plaque and gingival index scores were better in chlorhexidine group than herbal mouthwash. They reported the chlorhexidine as a gold standard in reducing plaque, gingivitis, and bleeding on probing. In a review about licorice and peri-dental diseases, it was

also stated that licorice extracts and bioactive ingredients; glabridin, licoricidin, licorisoflavan A, licochalcone A, and glycyrrhizin are useful in oral diseases with their anti-adherence, anti-microbial, and anti-inflammatory properties.(55)

POSSIBLE ADVERSE EFFECTS OF LICORICE

Licorice has been reported about some adverse effects as well as health benefits, (Figure 4). Licorice began to use in Pontefract, United Kingdom in 1562 and George Dunhill, a local chemist, added sugar to it and called it Pontefract cake. Severe cases of hypokalemia, rhabdomyolysis and tetraparesis have been reported due to the consumption of these cakes.(56) According to following case reports, long term consumption of licorice is associated with hypertansion, hypopotasemia, muscle weakness, and edema. Ay et al. (2014), reported a case who were admitted with respiratory failure and marked muscle weakness of all extremities that progressed to paralysis after excessive intake of licorice syrup.(11) Plasma potassium concentration of the patient was 1.4 mmol/L. They reported that the patient's complications recovered after potassium replacement. In another case report, a 65-year-old woman with previously well controlled hypertension applied with symptomatic hypertension with blood pressures running 200s/140s which is caused by Snaps licorice which uses its original 1930s recipe including licorice granules.(57) Licorice may have adverse effects due to its glycyrrhizin content. Ottenbacher et al. explained the licorice-related hypertension with type 2 isoenzyme of 11 beta-hydroxysteroid dehydrogenase (11 β – HSD). This enzyme prevents local inactivation of cortisol and increase mineralocorticoid activity or pseudohyperaldosteronism which result in similar complications with primary aldosteronism.

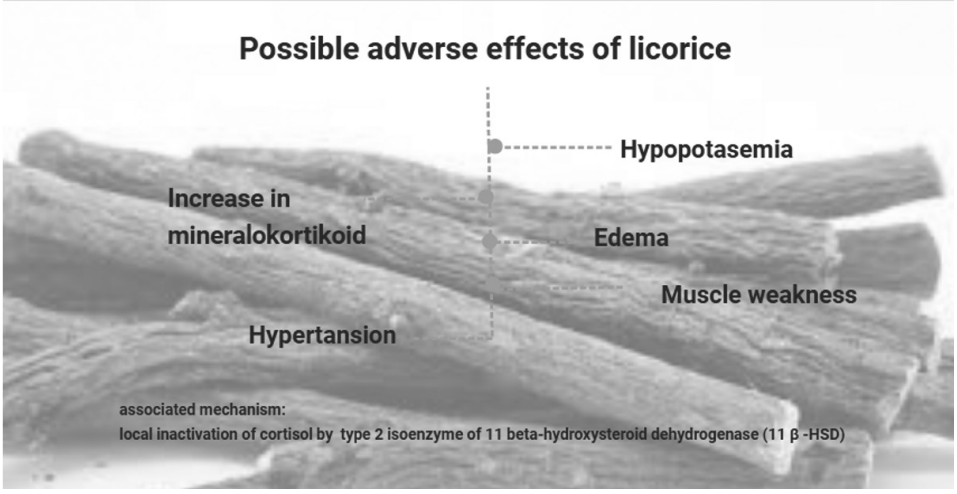

Figure 4. Possible adverse effects of licorice

Licorice-induced edema is rarely described. (8,58) Hendrickson et al. presented a case with generalized edema and prehypertension caused using chewing tobacco for over 6 months after cessation of cigarette smoking. Edema and prehypertension were explained with inhibition of renal 11-OHSD 2 by GA, the active metabolite of licorice present in the chewing tobacco. (8)

Licorice might interact with the metabolism of some drugs. Especially, Midazolom which is a typical subtract of CYP3A4 are inhibited by licorice root. Besides, glycyrrhizin and glycyrrhetic acid are potent inhibitors of 5α-, 5β-reductase and 11β-dehydrogenase. The inhibition of these enzymjes may decrease steroids.(59) The pharmacokinetics and pharmacodynamics of many medications may be altered when used concurrently with GZ or GA. For this reason, related products should be taken with caution when taken with additional medications due to the possible drug interactions.(60) Additonally, Nazari et al. (2017) pointed that licorice's adverse effects incrased by anorexia nervosa, old age, and female sex and it should be use with caution during pregnancy.

Even though, hypokalemia is listed as adverse effects of licorice, some literature handles it as a therapetic agent in especially patients with kidney disease accompanying by hyperkalemia. Farese et al. report that inhibition of the enzyme 11β-hydroxysteroid dehydrogenase type 2 by glycyrrhetinic acid, the active compound of licorice, reduces serum potassium concentration.(61) Ferrari et al. pointed those future studies would be necessary to determine whether inhibition of 11 HSD2 by licorice will reduce the incidence not only of hyperkalemia, but also of associated cardiac events in hemodialysis patients.(62)

CONSUMPTION

Licorice is used in the industry as sweetener in gums, mouth spray, candies, health products, antacids, chewing tobacco, medicines, some alcoholic beverages, herbal teas, and toothpaste.(3) Other sources of intake may be chewing dried Glycyrrhiza roots or chewing or smoking tobacco products.(63)

People use licorice root also as a dietary supplement for digestive problems, menopausal symptoms, cough, and bacterial and viral infections, However, taking licorice root containing glycyrrhizinic acid with medications reducing potassium levels such as diuretics might be cause heart-related problem.(64) Usually, Europe origined G. glabra is used as a dietary supplement.(21)

RECOMMENDATIONS

There are several reports about licorice and its ingredients listed below. The usage of licorice extract and glycyrrhizin in foods was approved by the U.S. Food and Drug Administration (FDA), the Council of Europe, and the Joint FAO/WHO Expert Committee on Food Additives (JECFA).(65,66) Licorice and its derivatives are also listed at GRAS and accepted as safe. Glycyrrhizinic acid has been given Generally Recognized as Safe (GRAS) status in the USA in 1985.(63)

The Nordic Council of Ministers concluded that individuals' adverse effects occur at a regular daily intake of about 100 mg glycyrrhizinic advocated an acceptable daily intake (ADI) for glycyrrhizinic acid of 1-10 mg/person/day by applying an uncertainty factor of 10 to the above mentioned lowest-observed-adverse-effect level (LOAEL) in 1993.(67)

In 1991, the European Union stated a dosage for ingestion of glycyrrhizin (approximately the amount found in 60–70 g licorice) as 100 mg/d. The *Scientific Committee on Food* (SCF) also declared the upper intake of glycyrrhizin as 100 mg/d.(63) World Health Organization also declared the upper intake as 100 mg/d (2 mg/kg).(65) Besides, FDA declared that licorice constitues risk for people who are 40 or older, eating 2 ounces of black licorice a day for at least two weeks could cause irregular heart rhythm or arrhythmia.(66) However, there is no data for licorice consumption for pregnant, children and adolescents (<18 years).

The European Committee considered that the NOAEL obtained in the study by Bijlsma.(63) They conducted a study on 10 healthy female volunteers received orally 0, 1, 2 or 4 mg of pure glycyrrhizinic acid/kg/day for 8 weeks and they obtained a NOAEL value as 2 mg/kg/d. They confirmed the ADI as 0.2 mg/kg by applying safety factor '10'.

In line with the literature mentioned at 'adverse effects' section, it would be benefical to inform people with TV commercials, newspapers, internet sites, magazines and product labels regarding the upper limit of ingestion about possible adverse effects of licorice which especially occur with the high intakes.(56)

CONCLUSIONS

In conclusion, licorice has a wide usage of in traditional medicine, food industry as a sweetener, and as sherbet in some cultures. Licorice has some health benefits such as antiulcer, antioxidan, antiinflammatory, antiatherosclerotic, antiprotozoal, antitumoral, antifungal, and neurprotective based upon its bioactive properties. However, some adverse effects such as hypertansion, hipopotasemia, muscle weakness, and edema were also reported in case presentations because of higher amounts and long-term consumptions. For this reason, it is important not to exceed its upper recommended intake level especially in the populations who has a common consumption habit of licorice. It seems to be there is a consensus between organizations and committees about maximum intake of glycyrrhizin as 100 mg/d. Furthermore, animal, and in vitro studies seem to domain the literature. For this reason, human studies would be benefical to extend the current knowledge and specific recommendations for people.

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