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Health perspectives of licorice (*Glycyrrhiza glabra* Linne.)

Sana Noreen*, Bahisht Rizwan, Aiman Ijaz, Muhammad Imran, Sameen Azhar, Tehreem Nisar

University Institute of Diet and Nutritional Sciences, The University of Lahore, Pakistan

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Abstract

Licorice (Malthi) has been used for thousands of years worldwide as a medicinal remedy with several pharmacologic properties in antique medicine and as a sweetening agent in food products. It has various health advantages and is used to combat various diseases and symptoms. The main objective of this study is to demonstrate the therapeutic effects and health perspectives of licorice (*Glycyrrhiza glabra*) for safety. It is a significant source of phytochemicals such as flavonoids, iso-flavonoids, triterpene, saponins and glabridin that exhibits a wide range of biological activities, including hepatoprotective, anticular, anti-inflammatory, antiviral, and anticancer activity. Combined use with licorice derivatives and prescription chemotherapy drugs significantly increases the efficacy of anticancer and decreases the side effects of chemotherapy. In addition, glycirizic acid and glycyrrhetinic acid in licorice have been indicated in drug delivery systems targeted for hepatocellular carcinoma treatment to present liver targeting effects. The licorice extracts controls the inflammation and neurotoxicity that leads to Parkinson's disease. The results indicates that ethanolic extract of licorice is more active in treatment of diabetes, insulin resistance, reducing obesity and ameliorating hypertension, dyslipidemia and suggest that licorice ethanolic extract are effective in preventing and ameliorating the metabolic syndrome. This review aims to outline the current health outlook and medicinal properties and pathways of extract and gain new perspectives for further research and development in licorice.

* **Corresponding Author:** Sana Noreen ✉ sananoreen.rizwan @gmail.com

Introduction

Licorice (*Glycyrrhiza glabra* Linne) is a famed plant having medicinal proprties, cultivated in many areas of Southern Europe and Asia. The industrial crop commonly known as licorice which are extracted from the stoloniferous root of licorice plant and are used in herbal products, tobacco flavoring and nutrient industries (Altay *et al.*, 2016). The potassium and calcium salt of glycyrrhizinic acid and glycrrhizin is 50 times sweeter than sucrose and encourages the production of hydrocortisone. *Glycyrrhiza* consists of 20% starch, up to 6.5% glucose, 2-4% asparagines, 8% fat, resins, mannitol, gum protein, a trace of tannin. Due to its medicinal properties, licorice has been used to control chronic stomach problems like peptic ulcer, arthritis, weight gain issues and psychiatric disorders worldwide (Jain *et al.,* 2016). Scientific proof showed that licorice roots have many therapeutic properties because of the presence of chemical compounds included triterpenes, iso-flavonoids and flavonoids (Karkanis *et al.,* 2018).

Triterpenes contain glycyrrhizic acid (GA) and glycyrrhetinic acid monoglucuronide (GM) that are the most pharmacoactive compounds in licorice extract having antioxidant properties (Pastorino *et al.,* 2018). Licorice contain flavonoids like isoliquiritigenin (ISL), liquiritin (LQ), liquiritigenin and LQ-apioside shows medication, antioxidation, antimicrobial and antiulcer property (Hosseini *et al.,* 2018). It also contains Dehydroglyasperin C (DGC) that is iso-flavonoid gets from the licorice roots facilitate to accelerate detoxification enzymes in hepatic cells (Li *et al.,* 2019). According to many different studies the licorice extract contains refined specific compounds derived from licorice including GA, GM, liquiritigenin and DGC act as a good neuroprotective agents and helps to stops the progress of neurodegenerative syndromes like Alzheimers's disease (AD) and Parkinson's disease (Petramfar *et al.,* 2020). Licorice additionally contains glabridin which is an isoflavon showed repressive impact on adiopogenesis. In liver glabridin supplements efficiently obstruct high-fat diet induced hepatic steatosis through down regulation of gluconeogenesis related to phosphoenolpyruvate carboxykinase and glucose 6- phosphate (Huang *et al.,* 2017). Licorice roots contain many compounds like flavonoids and iso-flavonoid that play a defensive role against chronic diseases like stroke, cancer and chronary heart diseases. Several complex compounds made up of flavonoids family. Isoliquiritigenin (ISL), liquiritigenin, LQ and glabridin are essential flavonoids which are present in licorice (Ahmed *et al.,* 2017).

Health perspectives of licorice

Licorice polyphenols show anticancer, antidiabetic and antiobesity property. Triterpenes which are present in licorice roots contain alpha and beta-liquiritic acid (GA) as shown in Fig. 1.

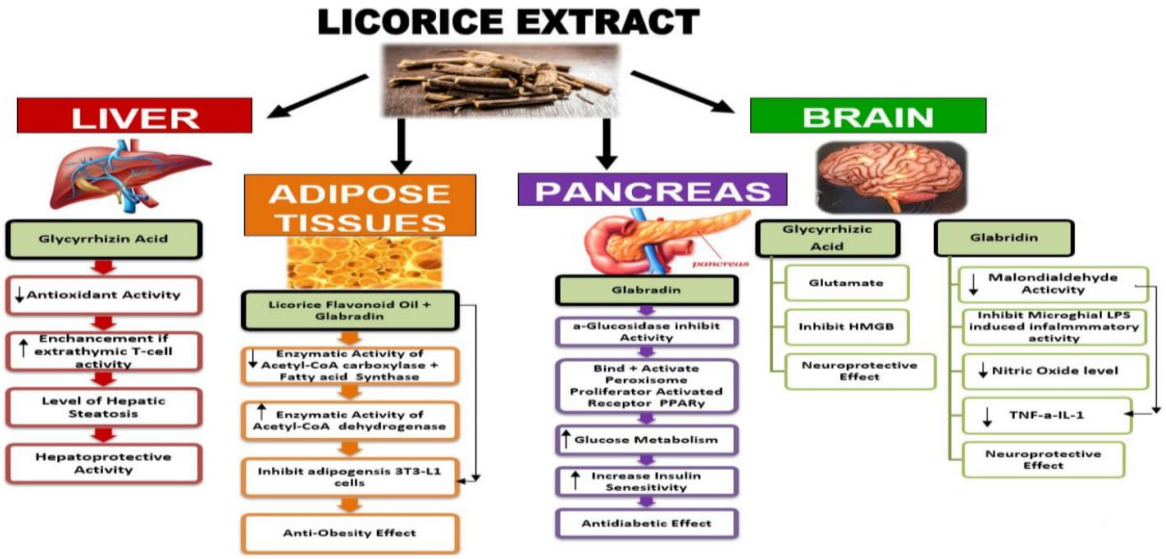

Fig.1. Health Prespectives mechanism of licorice extract.

Licorice and neuroprotective

With the help of experimental studies it has been studied that raw licorice extract contain higher concentration of glycyehetinic acid which performs neuroprotective role with the aid of inhibition of glutamate-mediated excitotoxicity in neural tissues (Wang *et al.,* 2011). A study was done in which intravenous GA was injected to rats having temporary blockage of the middle cerebral artery and the consequences presented significantly smaller size of infraction area of brain (Dastagir *et al.,* 2016) Same results was also found about GA as neuroprotective effect may inhibit the pathway of HMGB (Yang *et al.,* 2013).

Another study was done based predicted on preischemia treatment of rats with ISL for several days the results of the study showed that neurological deficit and more minuscule infraction volume after two hours of the middle cerebral artery obstruction compared to untreated controls (Yu *et al.,* 2008) and the result of the study presented a paramount increase in brain endogenous antioxidants like superoxide dismutase, glutathione peroxidase and catalase activity and minimization in malonialdehyde content (Ravanfar *et al.,* 2016). the neuroprotective effect of ISL was identified and stated that glutamate-induced cell damage in HT22 hippocampal neuronal cell is efficiently inhibited by ISL. Licorice root contain other flavonoids like LQ and liquiritigenin and have both been found efficacious in neuroprotection through inhibition of glutamate-induced neurotoxicity. The result of this study was additionally concluded that LQ significantly stimulates overgrowth of neurite which is a main process in axonal regeneration and neural tissue repair (Srinivasan *et al.,* 2015). Glabridin is also another effective flavonoid present in licorice which also has neuroprotective effects such as ISL that decrease staurosporin induced damage to malondialdehyde activity and postischemic infarction in neural cultured tissue. It also prevent significantly microglial LPS-induced inflammatory activities which leading to low nitric oxide, TNF-α and IL-1 development (Lawrence *et al.,* 2009). Parkinson's disease, like other neurodegenerative disease is a long term degenerative disorder, in which the nerve cells damages dopamine. An experimental study was conducted to analyze the ISL effects extracted from licorice on the toxicity induced by 6-hydroxydopamine (6-OHDA) in dopaminergic neurons and the results showed that ISL reduced ROS and nitric oxides level. ISL may also inhibit the deposition of species of α-synuclein fibrils that are responsible for inflammation and neurotoxicity leads to Parkinson's disease (Lee *et al.,* 2012).

Licorice and Obesity

Licorice flavonoid oil (LFO), contains hydrophobic flavonoids may have a property of anti-obesity. An experimental study was conducted to observe LFO activity on diet-induced obese rats and the study results showed that by adding of 2 percent LFO in a high fat diet, abdominal adipose tissues and plasma triglycerides are expressively reduced (Ahn *et al.,* 2010). It has also been noted that LFO has decreased the enzymatic activity of acetyl-CoA carboxylase and fatty acid synthase while it develops the enzymatic activity of acyl-CoA dehydrogenase in the liver fatty acid oxidative pathway (Sasakawa *et al.,* 2017). LFO has been found to reduce the hypertrophy of white adipose tissue and the thickness of fat cells. LSC supplementation effectively reserved high fat diet-induced hepatic steatosis through down regulation of gluconeogenesis related phosphoenolpyruvate carboxykinase and glucose 6-phosphate and up regulation of the β-oxidation related carnitine palmitoyltransferas (Namazi *et al.,* 2017). Glabridin in the extract of licorice (LSC) shows anti-obesity effects. In 3T3-L1 cells glabridin effectively reduced adipogenesis. In fact, LSC has shown dose dependent inhibitory effects on adipogenesis. The inhibitive effects of LSC derived from inhibiting the induction CCAAT enhancer transcriptional factors that bind protein ά and peroxisomes proliferator-activated receptor γ (Luis *et al.,* 2018).

Licorice and diabetes

Glabridin is the most essential bioactive compound found in licorice. A study conducted which measure the glucose lowering effect of glabridin obtained through licorice in rats model of diabetes mellitus.

Glabridin (10, 20 and 40mg/kg) was administered in rats of diabetes mellitus. However each of the treatment be persistent on a daily basis about 28 days. The result illustrated that glabridin considerably raised the glucose activity and superoxide dismutase (SOD) and decrease fasting blood glucose (FBG) levels and Malondialdehyde (MDA) levels in the different organs such as liver, kidney and pancreas. Conclusion revealed that glabridin contains glucose lowering effect it may be because of a-glucosidase hindrance, in addition to its capacity to combine and stimulate peroxisome proliferator-activated receptor (PPAR) (Luis *et al.,* 2018). A phytoestrogen glabridin derived from licorice roots and endorsed the loss of estradiol-vascular protection. Additionally, glabridin safeguarded paraoxonase 2's anti-atherogenic capacity and controlled the production as well inducible nitric oxide synthase, thus averted vascular dysfunction associated with diabetes mellitus (Hatano *et al.,* 2017).

A study conducted on the complications of diabetes mellitus to establish the beneficial role of licorice extract. Kidney disorders in diabetic induced mice were taken. Licorice extract of standard oral consumption (about 1g/kg of total body weight) intended for 60 days in diabetic nephropathy. Extracts from licorice improves glucose levels, re-established renal activity, reduces body-weight and restores overall antioxidant efficiency. The biochemical and histological findings suggested that because of its antioxidant and hyperglycemic qualities, licorice has important medicinal properties for diabetes (Wu *et al.,* 2013).

Glycyrrhiza glabra extract against streptozotocin has been tested for the anti-hyperlipidemic and an antihyperglycemic activity of diabetic rats caused by high fat diet. For test the antihyperlipidemic effects different biochemical as well as histomorphological specfication was estimated. A research was conducted in which oral dosage of 100mg/kg of 18-β glycirrhetic acid acquires an appropriate diabetes lowering effect in streptozotocin (40mg/kg body weight) persu ades rats having diabetes comparable to glibenclamide (Yang *et al.,* 2016). Furthermore, glycyrrihinzine derived from licorice is 50 times sweeter than saccharose and is commercially available. Natural sweeteners such as glycyrrhizine, nonsaccharide, have low caloric value and can solve the industrial sweetener issues and it is useful sugar substitute for diabetic patients and in other cases of calorie restrictions (Rebhun *et al.*, 2015).

Licorice and Hepatoprotective

Licorices played a remarkable role in control of oxidative damage through free radical production to kidneys, inhibit toxins or carcinogenesis induced by the hormone, and also has a hepatoprotective activity effect. *Glycyrrhiza glabra* (GA) is the most essential active ingredient extracted from the root of licorice, and it has various therapeutic and pharmacological properties (Kataya *et al.*, 2011). GA (Glycyrrhetinic Acid) has been formulated as an anti-allergic and anti-inflammatory medicine for heptic disease in China or Japan in association with glycyrrhinitic acid and 18-beta-glycyrrotic acid. Pharmacological effects of GA include both hepatic apoptosis and necrosis inhibition; immune regulatory activity; antiviral; and antitumor properties (Shamim *et al.*, 2016). It is commonly used in the treatment of liver disorders or other illnesses due to GA medical applications. Glycyrrhizin, a triterpene glycoside extracted from *Glycyrrhiza glabra*, comprise a positive role on the obstruction of liver apoptosis and necrosis by blocking of TNF-α and caspase-3, a major liver apoptosis and necrosis mediator in LLPs/GaAIN-induced liver failure (Li *et al.*, 2014). In another study the researcher scrutinize the impact of licorice in fatty liver injury mediated by chronic alcohol consumption, mediated by inflammation and oxidative damage to the liver. Raw licorice was collected, and its components were analyzed quantitatively and qualitatively using LC-MS/MS. For four weeks rats were taken and were fed with diet containing liquid alcohol with or without licorice (Jung *et al.*, 2015).

Recent researches on hepatoprotective effects of licorice imply that it decrease liver injury through increasing anti-inflammatory in addition antioxidant capacity. Alcohol intake increased the activity of

serum alanine aminotransferase, aspartate aminotransferase activities and triglycerides levels and tumor necrosis factor (TNF)-α level. Accumulation of lipid in liver was evident, however decreased levels of glutathione and the production of TNF-α caused by alcohol were effectively prevent by licorice treatment (Abd-Al-Sattar *et al.*, 2016). Clinical studies have concluded that fatty liver caused by alcohol intake has a major pathogenic role in liver disease. In addition, inflammations as well as oxidative stress are considered as second important factors in the progression of disease from simple fat accumulation to hepatic disease. Among the groups of *G. glabra* significantly reduced level of ALP, AST, ALT, GGT, cholesterol, LDL, triglyceride, conjugated bilirubin, glucose, total protein, albumin, grouped HDL, , and SOD to the untreated in comparison (Goorani *et al.*, 2019). In addition, *Glycyrrhiza glabra* decreased the level of hepatic steatosis contrasted with control group *Glycyrrhiza glabra* aqueous extracts were used on mice to treat fatty liver disease that does not cause any side effects (Haflidadottir *et al.*, 2014).

Nonalcoholic fatty liver disease is a predictive factor of fatality from various diseases due to this reason a research was done to explore the protective role of glycyrrheic acid (GA), on a high-fat diet (HFD) - induced NAFLD in mice, moreover elucidating GA defense mechanisms (Yu *et al.,* 2014). Treatment with GA prominently decreased relative liver weight, serum ALT, AST activities, serum lipid, blood sugar, with insulin levels. GA suppresses lipid accumulation of liver. More analysis of the mechanism revealed that GA decreased liver lipogenesis by decreasing expression of SREBP-1c, FAS and SCD1, elevated oxidation of fatty acid by raising PPARα, CPT1α, ACADS and facilitated metabolism of triglyceride by promoting activity of LPL (Tester, 2016).

In addition, GA decreased gluconeogenesis by suppressing PEPCK and G6Pase, and improved glycogen production by activation of PDase and GSK3β gene expression. Glycyrrhetinic Acid also raised insulin sensitivity by increasing phosphorylation of IRS-1 and IRS-2.

It also synthesis beneficial effects against NAFLD, by the regulation of genes implicated in lipid, glucose homeostasis, along with insulin sensitivity (Sun *et al.,* 2017).

Licorice and Asthma

Asthma is an airway chronic inflammatory condition marked by cough, wheeze, and tightness in the lungs and difficulties in the breathing. Eosinophil is the major inflammatory cells involved in the asthma development and is usually found in high percentage of uncontrolled asthmatic patients in the blood and sputum, so eosinophil is important for assessing asthma patients and determining the degree of asthma control. Inhaled corticosteroids are believed to decrease the number of eosinophils in the blood by inhibiting their proliferation, and thus, blood eosinophils in the blood may be considered an important measure of the efficacy of steroidal therapy. Allergic asthma is also the most common type of allergy that has become ever more widespread all over the world. An important feature of allergic asthma is the eosinophilic inflammation of the airways (Khambu *et al.*, 2018).

It is a chronic respiratory tract disorder manifest by erratic obstruction of the airway with progressive inflammation and remodeling, linked with high smooth muscle mass (ASM). Licochalcone A is the major characteristic chalcone in licorice root. It is noticed that licochalcone A stop the ASM cell proliferation which is caused by the vascular endothelial growth factor (VEGF) and induced cell cycle detention. Moreover, VEGF-induced ASM cell proliferation was down regulated via inhibition of extracellular signal-regulated kinase 1/2 (ERK1/2) activity, but not that of Akt (Anandan *et al.*, 2010).

Licochalcone A treatment inhibited VEGF-induced activation of VEGF receptor 2 (VEGFR2) and ER. It blocked the down regulation of caveolin-1 in a concentration-dependent manner. These all findings proposed that licochalcone an inhibited VEGF-induced ASM cell proliferation by suppressing VEGFR2 and ERK1/2 activation and down regulating caveolin. Some studies suggested that potential anti-inflammatory impact pathways could be accomplished by which the production of

pro-inflammatory mediators that motivates eosinophil, basophils and mast cells to release cytokines for the differentiation of T helper cells into Th2 cells to secrete interleukins.

In addition, certain transcription factors such as NF-κB, STAT6 and HDAC2 go with anti-asthmatic activity modulation. Glycyrrhizin is potentially a good natural medication with the lowest adverse effects for managing asthma (Vos *et al.*, 2015). Another study was done on eighty patients with asthma were chosen for research and divided into control and interventional group.

A placebo group was given inhaled corticosteroids, long acting beta agonist and starch tablets and inhaled corticosteroids, LABA and licorice extract were given to treatment group twice a day. Result showed that there was an improvement in forced vital capacity (FVC) and forced expiratory volume (FEV) in the addition of licorice extract to the interventional group (Farahani *et al.,* 2014).

Conclusion

Licorice is a well-known herb due to its pharmacological and nutraceutical properties. It has many bio active components which provides additional health benefits beyond the basic needs. The licorice extracts controls the inflammation and neurotoxicity that leads to Parkinson's disease. The results indicates that licorice ethanolic extract is effective in preventing diabetes, insulin resistance, reducing abdominal obesity and ameliorating hypertension, dyslipidemia and suggest that licorice ethanolic extract are effective in preventing and ameliorating the metabolic syndrome.

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Conflict of interest

There is no conflict of interest

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