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Review article

Licorice (Glycyrrhiza glabra L.) A Unique Herbaceous Plant: Review of its Medicinal Uses

Mohammad Makhmur Ahmad[1,*], *Mohd. Rashid*[2]

[1]Department of Pharmaceutics, College of Dentistry and Pharmacy, Buraydah Private Colleges, Buraydah, Al-Qassim 51418, Kingdom of Saudi Arabia
[2]Department of Pharmacognosy and Phytochemistry, College of Dentistry and Pharmacy, Buraydah Private Colleges, Buraydah, Al-Qassim 51418, Kingdom of Saudi Arabia

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ACADEMIC EDITOR
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[*]CORRESPONDING AUTHOR
Dr. Mohammad Makhmur Ahmad, Assistant Professor (Pharmaceutical Biotechnology)
Department of Pharmaceutics, College of Dentistry and Pharmacy
Buraydah Private Colleges
Buraydah, Al-Qassim 51418, Kingdom of Saudi Arabia.

ABSTRACT

Since the beginning of human civilization numerous plants have been used extensively as an essential medicinal source. The need for natural medications is steadily growing over time. One of the herbal plants that is most frequently used in foods, medicines, and extensive global study is licorice or sweetwood as Glycyrrhiza glabra belongs to family Fabaceae. It was used in traditional and complementary medicine to treat a variety of ailments such as allergies, liver toxicity, gastric ulcer, lung diseases, skin disorders, oral health issues such as tooth decay, and inflammation. The phytochemical constituents of licorice include various essential oils, sugars, inorganic salts, resins, amino acids, and nucleic acids. Licorice active substances such as triterpene, flavonoids, and saponins have been shown to exhibit biological activity. Licorice has been extensively researched in recent years to find its benefits, constituents and mechanism of action. This review summarizes the therapeutic and pharmacological benefits of licorice, as well as its applications in various health-related conditions along with its toxicity and maximum amounts of licorice consumption.

Keywords: *Glycyrrhiza glabra; Herbal medicines; Phytoconstituents; Pharmacological activities*

Introduction

Due to unwanted side effects, symptoms and resistance to pathogenic microorganisms, antibiotics have been limited in many countries [1, 2] despite of prescribing them in a combination therapy. Consequently, research on alternative approach is required on herbal plants that provides modern medicines with many useful active constituents used to manage various diseases. Many Asian and African people are depending on crude plant extract for the treatment of various human and animal diseases [3, 4]. Since many plants have a variety of pharmacological advantages over time, they are frequently utilized as spices and medications. These plants contain many functional properties due to the presence of several bioactive molecules. These plants along with their extracts can be consumed by the human beings as their daily diet [5]. Glycyrrhizin, one of the major ingredients present in licorice which is scientifically the root of Glycyrrhiza glabra. Glycyrrhizin is employed in many traditional plants based medicines, sweetener and additional flavour in candies, drinks and foods in the Asian and European countries [6]. Greek physicist termed licorice plant as "sweet root" due to their sweet taste which is 50 to 100 times sweeter than sucrose [7]. G. glabra is considered as "medicine food homology" herbal medication due to their natural sweetener properties [8]. It is interesting to know that licorice is also used as therapeutic herb to cure many diseases. As far as this medicinal plant's geographical location is concern, it is thought to have originated from Iraq [9] and found in many Asian as

well as European countries [10]. G. glabra is widely distributed in Italy, Spain, Turkey, the Caucasus, western China, and Central Asia. On the other hand, one of the species G. uralensis is found only in Central Asia, China and Mongolia [11]. It is commercially cultivated in India, China, Afghanistan, Italy, Spain, Greece, France, Iran, Iraq, Turkey, Turkmenistan, Uzbekistan, Syria, Azerbaijan, United States and England [12]. Due to the wide range of application in tobacco, cosmetics, food and pharmaceuticals industry, Licorice is one of the most commercially valued plants globally [13]. Qualitative and quantitative analysis of active constituents of Licorice have been studied meticulously in order to be used in the various food and pharmaceutical industry [11, 14-17].

G. glabra is known as an "essential herbal medicine" in Chinese traditional system of medicine and it is believed that nine out of ten formulations contain licorice because when used with other herbal medicines, licorice is one of the most potent herbal remedies for lowering toxicity and boosting efficacy. One of the approximately 30 species of licorice is Glycyrrhiza glabra, considered most extensively used species in feed and food [18]. Licorice contains amino acids, proteins, simple sugars, polysaccharides, mineral salts, pectin, starches, sterols, gums and resins [19]. The most significant medicinal components of licorice are its rhizomes and roots, which have been used either alone or in combination with other herbs to treat a variety of conditions including epilepsy, fever, sexual debility, paralysis, leucorrhoea, psoriasis, prostate cancer, malaria, haemorrhagic diseases, jaundice and digestive disorders like stomach ulcers, hyperdipsia, flatulence and colic. Additionally, it can also be added to tobacco products to flavor them and be utilized as a flavoring agent in foods and beverages [20].

Glycyrrhiza glabra roots contain various active compounds including flavonoids (liquirtin, rhamnoliquirilin, liquiritigenin, prenyllicoflavone A, glucoliquiritin apioside, 1-metho-xyphaseolin, shinpterocarpin, shinflavanone, licopyranocoumarin, glisoflavone, licoarylcoumarin, and coumarin-GU-12) and saponins (glycyrrhizin which is 60-times sweeter than sugarcane). Apart from the above constituents four isoprenoid-substituted phenolic constituents (licoriphenone, 1-methoxyficifolinol, isoangustone A, semilicoisoflavone B), kanzonol R (prenylated isoflavan derivative) and numerous volatile components like tetramethyl pyrazine, pentanol, linalool oxide A, and B, geraniol, hexanol, terpinen-4-ol and terpineol) have also been reported. Earlier it has been reported that propionic acid, 1-methyl-2-formylpyrrole, 2, 3-butanediol, benzoic acid, ethyl linoleate, furfuryl formate, trimethylpyrazie, furfuraldehyde, methyl ethyl ketone, and maltol were isolated from the essential oil using hydrodistillation methods.

The powerful substances found in G. glabra are glycyrrhizin, a saponin molecule, and its aglycone, glycyrrhetinic acid. Licorice root contains naturally occurring calcium and potassium salts of glycyrrhizin, which is made up of glycyrrhetic acid and triterpenoid aglycone and linked to glucuronic acid disaccharide [21,22]. Glycyrrhizin can be metabolized and transformed to glycyrrhetinic acid in humans, therefore its pharmacological actions are similar to glycyrrhetinic acid [23]. Minerals (calcium, phosphorus, sodium, potassium, zinc, and copper) and amino acids (serine, aspartic, glycine, glutamic, threonine, valine, prolinealanine, isoleucine, tyrosine, leucine, lysine, phenylalanine, tyrosine, and histidine) are also present in raw and tea licorice infusions. It's interesting to note that acetic acid, propanoic acid, fumaric acid, citric acid, butyric acid, malic acid, and tartaric acids were all found in the methanolic licorice extract in HPLC analysis [24].

The aim of this article is to provide a concise summary of the therapeutic and pharmacological advantages of licorice, as well as its applications in treating various medical diseases. It will also discuss its toxicity and safe intake limits.

Effects of Licorice on Asthma

Nowadays, asthma is a widespread respiratory condition. In order to reduce inflammation during asthma, corticosteroids are frequently utilized. However, prolonged usage of such medications can have a number of negative impacts on human health. Licorice has traditionally been used to treat bronchial asthma, according to historical records. Lic A, one of licorice's active ingredients, is thought to have anti-asthma properties. The main cause of asthma is a cytokine molecule known as thymic stromal lymphopoietin (TSLP) and its expression can be controlled by a nuclear factor kappa B (NF-kB). Lic A was found to block NF-kB activation mediated by tumor necrosis factor α (TNF α) by suppression of IkB kinase complex activity [25]. The human foetal lung fibroblast line HFL-1's synthesis of eotaxin 1 is downregulated by glycyrrhizin (GL) and its derivatives at the protein or mRNA level [26]. The primary mediator of eosinophilic proliferation and differentiation is interleukin (IL)-5 [27]. Eotaxin attracts eosinophils to allergic inflammatory areas. Researchers frequently employ human lung fibroblast (HFL-1) cells to examine eotaxin release and the workings of eotaxin inhibitors [28-30].

Many researches have demonstrated that flavonoids included in licorice reduce eosinophilic lung inflammation, IgE levels, interleukin (IL)-13, IL-5, IL-3, and boost interferon gamma activity. Another molecule obtained from licorice, ganoderic acid, has an anti-asthmatic action through stressing TNF [31].

Glycyrrhizin, an active ingredient in licorice, was studied to see how it affected the histopathologic characteristics of the lung in BALB/c mice. According to the study's findings, all recognized lung histopathologic alterations in the mouse model of asthma were significantly ameliorated in the treatment group receiving glycyrrhizin. Therefore, Lic A and glycyrrhizic acid, the active components of licorice, can be used in the treatment of asthma [32].

Effect of Licorice on Skin Disorders

Due to anti-allergenic, anti-immune-mediated cytotoxicity, antioxidant, and anti-inflammatory, glycyrrhizin has a significant influence on the underlying inflammation of various skin-related disorders. Shaving and UV light-induced erythema have been found to be greatly reduced by the administration of a topical gel containing Lic A, a glycyrrhizin derivative. In a questionnaire-based assessment, the use of Lic A indicated a significant improvement in erythema and quality of life. Glycyrrhizin is also being used to relieve allergic dermatitis. Among 90 patients with atopic dermatitis, licorice gel dose dependently led to a reduction in edema, erythema score, and itching sense (placebo vs treatment group and 1% vs 2% licorice gel, all $P < 0.01$). The topical steroid that is frequently prescribed to individuals with atopic dermatitis has a resistance in some patients. However, the usage of glycyrrhizin resulted in an increase in antibody production, suppression of cortisol-induced stress reactions and inflammation. As a result, glycyrrhizin has the potential to be proposed as an effective treatment for atopic dermatitis because it acts similarly to steroids but with less adverse effects. [33]. Vitiligo is an idiopathic depigmentation condition. Although narrow-band UVB light therapy and oral cortisone or methotrexate has been used to treat active stage vitiligo, these treatment techniques might induce side effects, especially in children. A study examined the effects of UVB alone, glycyrrhizin alone, and a combined therapy of both UVB and glycyrrhizin on active stage vitiligo. All three treatments yielded positive effects, with the combined therapy of glycyrrhizin and UVB being the most successful [34]. In another study, it was discovered that patients with vitiligo exhibit dermal inflammation and increased levels of enzymes IL-1b and IL-18 [35]. Glycyrrhizin has the ability to block the inflammatory cascade. As a result, glycyrrhizin's anti-inflammatory qualities can also explain its beneficial effects in vitiligo. Another skin condition caused by an autoimmune disorder with T-cell involvement is alopecia areata. Histological examination has revealed an increased infiltration of T cells surrounding the affected follicles. Glycyrrhizin functions as an immuno regulator through preventing T cell activation and the release of cytokines produced by CD4+ and CD8+ T cells. A Chinese research study including children aged 2–14 years, showed that both treatments, including glycyrrhizin tablets alone and glycyrrhizin tablets along with total glucosides of paeony capsule, were effective for treating alopecia areata. Another Chinese study found that glycyrrhizin compound combined with topical 2% minoxidil helped patients with alopecia areata [36].

The primary water-soluble component of licorice root is triterpenoid saponin glycoside glycyrrhizic acid (GL or glycyrhizin), and its primary metabolite is 18-glycyrrhetinic acid (GA or glycyrrhetic acid) [37].

The pentacyclic triterpenoids (PTs), which have a basic chemical structure with five rings, have garnered a lot of interest from a biological standpoint because of their pharmacological effects. In light of this, 18-glycyrrhetinic acid (GA) and its derivatives demonstrate an impressively wide range of biological and pharmacological actions [38].

Glycyrrhizin is degraded into two pentacyclic triterpenoids, which are stereoisomers, during metabolism in the plant by glucuronidase or by intestinal bacteria following oral ingestion: 18-glycyrrhetinic acid and 18-glycyrrhetinic acid.

Effect of Licorice on Cancer

The use of natural products and their synthetic analogs as anti-cancer agents is widespread. Flavonoids and triterpene saponins are the primary biologically active components of licorice, and they have a wide range of health benefits, such as antioxidant, anti-inflammatory, and anti-cancer properties. Recent research has revealed that glycyrrhizic acid inhibits the growth of leukemia cells as well as endometrial and breast cancer cells by stressing the AKT/mTOR signal. It has been shown through a wide range of in-vivo and in-vitro studies that specific purified compounds and mixed extracts from licorice have anticancer properties by preventing the proliferation, causing cell cycle arrest, autophagy, differentiation, apoptosis, suppressing metastasis, promoting angiogenesis, and sensitizing chemotherapy or radiotherapy. When clinical chemotherapy drugs combined with licorice compounds, it has resulted a

substantial reduction in the adverse effects of chemotherapeutics and an improvement in the anticancer effects [39].

The ratio of CC50 against human normal oral cells was used to test the licorice's anti-tumor activity, and the findings showed that, when compared to normal cells, the flavonoid-rich portion of the licorice exhibits cytotoxic effects on human oral squamous carcinoma cell lines. Licorice was found to stop tumor cell growth and angiogenesis in an in-vivo experiment. The ethanol extract of licorice caused G1 cell cycle arrest and apoptosis in MCF-7 human breast cancer cells. Glycyrrhizin and the ethanolic extract have dose-dependent antiproliferative effects against MCF-7. When compared to other well-known anti-cancer agents, Lic E, an active ingredient derived from licorice roots, was found to have the most powerful cytotoxic effects [40]. Many compounds derived from licorice, including "topazolite, gancaonin P, gancaonin O, Lic B, and glyasperin A," exhibited augmented cytotoxic activity against human oral squamous carcinoma cell line HSC-2. Through the induction of phase II enzymes like quinone reductase-1 in murine hepatoma cells, isoliquiritigenin also inhibited the growth of prostate cancer and is a significant cancer chemopreventive agent. Lic A, an active component in licorice, has demonstrated a remarkable inhibitory effect on the proliferation of cancer cells as well as the suppression of cellular oxidation. As a result, numerous studies have indicated that licorice's bioactive compounds can be used as powerful anti-cancer and antiproliferative agents [41].

Licorice inhibits the growth of non-small cell lung cancer (NSCLC) via controlling several immune-related signalling pathways and targets, affecting cell cycle progression, and other mechanisms. Licorice's active components have been found to target a wide range of tumor-related signalling pathways, including cell cycle, inflammation, and migration, according to research. Licorice inhibits the CDK4-Cyclin D1 complex, which arrests the G0/G1 phase and raises the expression of PD-L1 in lung cancer cells. However, we also discovered that licorice increased antigen presentation and CD8+ T cell infiltration while significantly reducing the tumour volume of in-vivo mouse models of NSCLC [42].

Effect of Licorice on Memory Enhancement and Antidepressant

The mouse immobility test was clearly demonstrated the effectiveness of licorice in memory enhancement and as an antidepressant agent. Several metabolites of G. uralensis, particularly liquiritin, have been found to have anti-depressant effects on prolonged stress, according to studies done on depressed rats. In a study on mice, isoliquiritin and liquiritin were found to have antidepressant effects. It was suggested that the mode of action of these substances may be related to an increase in norepinephrine and 5-hydroxytryptamine in the hippocampus, cortex, and hypothalamus of mice. In a research study, the anti-depressant activity of liquiritin and isoliquiritin has been reported in forced swimming test and tail suspension test in mice. The results found an increase in the levels of 5-hydroxytryptamine and norepinephrine in the hypothalamus, hippocampus and cortex of mice, which is responsible for the mechanism of action of these compounds [43]. Glabridin and 2, 2, 4-trihydroxychalcone isolated from licorice was found to be most effective compounds to improve memory and learning. They also antagonize scopolamine-induced amnesia. It was reported that this compound also plays a preventive role in the prevention of diabetes-induced deleterious effects on learning and memory [44] when experiments were conducted on rats. A study was carried out to look into the effects of licorice aqueous extract on the dendritic morphology of hippocampal cornu ammonis region 3 neurons. (CA3). By administering 225 mg/kg body weight and 150 mg/kg body weight of the treatment extract, the findings showed an apparent increase in dendritic intersections and dendritic arborization in hippocampal pyramidal neurons. This clearly establishes the neuronal dendritic growth stimulation properties of licorice aqueous extract [45]. The memory-enhancing effects of licorice may be helped by its anti-inflammatory and antioxidant qualities. It is probable that liquorice's favourable impact on memory and learning was caused by the facilitation of cholinergic-transmission in the mouse brain because liquorice corrected scopolamine-induced amnesia. Laboratory models used has demonstrated the potential of Glycyrrhiza glabra as a memory-improving substance [46]. Liquorice extract may have antidepressant-like effects by restoring levels of brain monoamines including norepinephrine and dopamine. Liquorice's primary chemical, glycyrrhizin, exhibited MAO inhibition [47].

According to these studies, licorice and a number of compounds found in its extract can be used as a therapeutic medication to treat dementia, memory loss, learning disabilities, and a few other neurodegenerative diseases.

Effects of Licorice on Different Health Disorders

Recent research has demonstrated the beneficial benefits of licorice and its active ingredients, including

glycyrrhizin, licoricidin, Lic A, and glabridin, on dental caries and oral health. Since licorice has antibacterial properties, it is primarily used in this context. Certain food products contain ingredients that are immune to Streptococcus mutans. Only glycyrrhizin-free licorice is being used for various studies because human intestinal bacteria convert glycyrrhizin into a severe hypertensive substance and glycyrrhizic acid may also induce hypertension [48]. One common symptom of hemodialysis patients is xerostomia/dryness in mouth). Along with dental health, it also has an impact on patients' quality of life. In a trial, patients receiving hemodialysis had their mouthwash interventions of pure water and licorice compared for their effects. The findings demonstrated that licorice mouthwash was superior to pure water in terms of alleviating mouth dryness and boosting saliva flow [49].

Antiulcer Effects of Licorice

Helicobacter pylori (H. pylori) is the most common cause of infections, oxidative stress, peptic ulcers, and stomach ulcers. Antacids, histamine antagonists, and/or proton-pump inhibitors can be used to treat these conditions, but they have a number of side effects, such as arrhythmias, hypertension, asthenia, and specific liver disorders. Due to its antimicrobial effects and pharmacological properties, licorice is the most frequently used therapeutic agent. As a result, using natural medicinal herbs is typically chosen for treatment. Licorice is primarily used to cure peptic ulcers due to its anti-inflammatory, antioxidant, and prostaglandin formation-boosting properties [50]. Licorice extracts that are flavonoid-rich inhibit the action of H. pylori by stressing the synthesis of proteins and two enzymes, hydroxyl-folate reductase and DNA gyrase. Additionally, some licorice compounds have been shown to prolong the life of cell surfaces and increase mucus secretion in the gastrointestinal tract, both of which have an anti-pepsin effect in the stomach. Licosio-flavan B, licochalcone A, glabridin, licoricidin, and glabrene were found to inhibit H. pylori reproduction. Licorice can therefore be said to have anti-helicobacter pylori properties [51].

Hepatoprotective Effects of Licorice

Licorice is being used as a traditional medicinal herb in the treatment of liver diseases. The secondary metabolites derived from licorice can cause a reduction in the levels of serum liver enzyme and leads to progress in tissue pathology of hepatitis patients [52]. In a research study, several compounds isolated from G. glabra including glabridin, hispaglabridin B, isoflavan derivatives, hispaglabridin A, 3′-hydroxy-4′-O-methylglabridin, and 4′-O-methylglabridin were being investigated for their property of protecting mitochondria of the liver against oxidative stress. It was demonstrated through studies that glycyrrhizic acid caused a significant decrease in levels and an improvement in the liver histology. A study revealed that even a dose of 2 mg/kg body weight per day of Glycyrrhizin glabra aqueous extract greatly improved liver functions in acute liver disease [53]. Liver damage induced by retrorsine and carbon tetrachloride hepatotoxicity was protected by glycyrrhetinic acid. Glycyrrhizin is widely used for the preparation of medicines for the treatment of liver cirrhosis, hepatitis B, liver fibrosis, and hepatitis C. In various studies of in -vivo animal models, the protective effects of glycyrrhizin against carbon tetrachloride induced liver injuries have been observed. Additionally, glycyrrhizin protects against Xanthium-induced liver cirrhosis and hepatotoxicity. The effects of licorice on chronic alcohol-induced fatty liver injury, which is mediated by oxidative stress and inflammation, were examined in different research. The findings indicated that licorice showed a positive response in chronic fatty liver injury caused by alcohol, owing primarily to licorice's enhanced antioxidant defence [54].

Antidiabetic Effects of Licorice

Many herbs have been used for thousands of years to avoid and cure diabetes, and one of the oldest herbs, licorice, is also used in Chinese medicine for herbal treatment due to its various pharmacological properties. Licorice inhibits certain changes caused by D-galactose, such as oxidative stress, insulin resistance, and free radical damage, resulting in a substantial delay in the progression and development of diabetes [55]. Many licorice components, including glabridin, liquiritigenin, licochalcone (Lic) A, glycyrrhizin, Lic E, glycyrrhetinic acid, isoliquiritigenin, and some flavonoids, have been shown to have anti-diabetic properties. Several studies have suggested that the active components of licorice, amorfrutin, and chalcone have anti-diabetic effects by activating "peroxisome proliferator-activated receptor gamma (PPAR's)," which plays a key role in adipocyte differentiation and carbohydrate and lipid metabolism. Furthermore, glabridin increases glucose consumption and prevents glucose intolerance by facilitating the translocation of glucose transporter type 4 via adenosine monophosphate protein kinase [56]. In a research study, rats with blood glucose levels of 200 mg/dl were given 1g/kg/day licorice, while the control group received citrate buffer. The results revealed that rats given licorice had lower blood glucose levels after 8 weeks. Another study on diabetic rats found that Licochalcone E (Lic E), a compound isolated from licorice, increased

the levels of small adipocytes by increasing PPAR activation and had a beneficial effect on adipocyte-oriented diabetics [57]. Another research on streptozotocin-diabetic rats revealed that aglycone and 18-glycyrrhetinic acid had antihyperglycemic effects. There was an increase in plasma glucose and glycosylated hemoglobin, Hemoglobin A1c (HbA1c), but a decrease in plasma insulin and hemoglobin (Hb). The results concluded that administering 18glycyrrhetinic acid (50, 100, or 200 mg/kg/body weight) or glibenclamide (600 g/kg/body weight) orally for 45 days can result in a gradual improvement in diabetics [58]. The effect of licorice extracts on albino rodents was also investigated. Glycyrrhiza glabra has anti-lipidemic and anti-hyperglycemic properties at low doses, according to the research. Licorice extract may be useful in preventing and treating diabetic nephropathy caused by mesangial fibrosis and glomerulosclerosis by inhibiting Akt activation and change of growth factor-b signaling [59]. The studies stated above show that licorice can be used as a beneficial therapeutic agent for diabetic treatment.

Anti-obesity Effects of Licorice

Glabridin-enriched licorice reduced adipose tissue formation by decreasing the activity of acetyl-CoA carboxylase and increasing the activity of acetyl-CoA dehydrogenase in licorice flavonoid oil (LFO), causing stress in the formation of adipose tissue in 3T3-L1 cells. Another mechanism implicated in the relationship between licorice consumption and anti-obesity effects says that licorice flavonoid oil increases energy consumption by increasing beta-oxidation, which causes a decrease in fat mass and body fat by inhibiting lipogenesis. A study found that giving 600 mg of LFO to healthy individuals increased their energy consumption by increasing the phenomenon of thermogenesis on their skin. A study on "C57BL/6J rats fed a high-fat diet" found that LFO consumption causes stress in the increase of abdominal fat tissue [60]. According to one study, LFO has a positive effect on weight management in people who are overweight, obese, or both. The effects of licorice on weight management could be attributed to a variety of factors, including age, dietary intake, BMI, levels of physical activity, ethnic roots of people and type, and the quantity of licorice used in the research study. Another research looked at the effects of frozen dried powder of ethanolic licorice extract on rats fed a high fat diet and induced with obesity and hyperlipidemia. According to the findings, licorice powder had anti-obesity effects similar to orlistat, a pancreatic lipase inhibitor. The effects of licorice powder on obesity appeared to be mediated by a decrease in dietary fat absorption from the intestine, as a dose of licorice powder reduced the rise in serum triglyceride levels and increased fat excretion in faeces [61,62].

Conclusion

Due to higher number of side effects of modern medication/allopathic medicine the use of phytopharmaceuticals has increased throughout the world. This has led the scientist to investigate for plant phytoconstituents and their pharmacological activity. In this review we aim to further investigate the phytochemical properties as well as pharmacological properties. The studies witnessed the observation of therapeutic values of licorice. Glycyrrhiza glabra has numerous health benefits which include their role as antidiabetic, anti-depressant, anti-obesity, antioxidant, anti-inflammatory, anti-allergic, anti-cancerous, anti-ulcer, liver protective properties and many others. The chemical components of licorice could act as "lead molecules" in the treatment of a variety of diseases and upcoming disorders. Therefore, this review presents a pathway for future investigative research study on licorice to produce medicinally vital drugs candidates.

Compliance with Ethical Standards

Not applicable.

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Conflict of Interest

The author declares no conflict of interest.

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