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GLYCYRRHIZA GLABRA: A PHYTOPHARMACOLOGICAL REVIEW

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ABSTRACT: Plants have been one of the important sources of medicines since the beginning of human cultivation. There is a growing demand for plant based medicines, health products, pharmaceuticals, food supplements, cosmetics etc. A review of chemical constituents present in various parts of *Glycyrrhiza glabra* and their pharmacological actions is given in the present article. *Glycyrrhiza glabra* Linn, is a commonly used herb in Ayurvedic medicine. Although the review articles on this plant are already published, this review article is presented to comply all the updated information on its phytochemical and pharmacological activities, which were performed by widely different methods. Studies indicate that *Glycyrrhiza glabra Linn* possesses antibacterial, antioxidant, antimalarial, antispasmodic, anti-inflammatory and anti-hyper glycemic properties. Various other effects like antiulcer, antiviral, antihepatotoxic, antifungal and herpes simplex have also been studies. These results are very encouraging and indicate this herb should be studies more extensively to confirm these results and reveal other potential therapeutic effects. A review of chemical constituents present in various parts of *Glycyrrhiza glabra* and their pharmacological actions is given in the present article.

INTRODUCTION: Since ancient times, several societies have resorted to nature, mainly to plants as medical and health sources. Today, a great percentage of the world population, particular in developing countries, uses plants for facing primary needs of medical assistance [1]. Human beings have used plants for medicinal purposes for centuries. It has been estimated that such use of medicinal plants possibly go back in time to around 3000 years.

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Traditional forms of medicine have existed and still exist in many countries of the world including countries in the Indian sub-continent like India, Pakistan and Bangladesh. The various alternative medicinal systems of India (Ayurveda, Unani, and Siddha) uses more than 7500 plant species [2].

Documentation of these traditional medicinal systems is important as a number of important modern pharmaceuticals have been derived from plants used by indigenous people. Modern drugs like aspirin, atropine, ephedrine, digoxin, morphine, quinine, reserpine and tubocurarine are examples, which were originally discovered through observations of traditional cure methods of indigenous people [3].

There has been an increase in worldwide realization of the use of medicinal plants in various traditional health systems of developing countries. Many reports estimated that about 80% of population in developing countries still relies on traditional medicine for their primary healthcare [4].

Natural products are an important source of new structures leading to drugs in all major disease areas. They represent a pool of privileged structures that are optimized by evolution to interact with proteins and other molecules [5]. The starting materials for about one-half of the medicines we use today come from natural sources. The future of higher plants as sources of medicinal agents for use in investigation, prevention, and treatment of diseases is also very promising. Natural products have provided us some of the important life-saving drugs used in the armamentarium of modern medicine. However, among the estimated 250,000-400,000 plant species, only 6% have been studied for biological activity, and 15% have been investigated phytochemically. This shows a need for planned activity guided phyto-pharmacological evaluation of herbal drugs. This article intends to provide an overview of the chemical constituents present in various parts of *Glycyrrhiza glabra* and their pharmacological actions.

Glycyrrhiza glabra Linn is one of the most widely used herb from the ancient medical history of Ayurveda, both as a medicine and also as a flavoring herb. *Glycyrrhiza glabra* Linn is commonly known as Yashti-madhuh. Madhuka (Sanskrit) Jashtimadhu, Jaishbomodhu (Bengali) Jethimadhu (Gujarat) Jothi-madh, Mulhatti (Hindi) Yastimadhuka, atimaddhura (Kannada) Iratimadhuram (Malayalam) Jeshtamadha (Marathi) Jatimadhu (Oriya) Atimaduram (Tamil) Atimadhuranu, Yashtimadhukam (Telugu) Licorice, Liquorice, Sweet wood (English) [6]. It is found mainly in Mediterranean and certain areas of Asia.

The Liquorice of medicine and commerce is derived from the sweet root of various species of *Glycyrrhiza*, a genus which contains about fourteen species, natives of warmer temperate countries in both the New and Old Worlds, ten of them having roots more or less sweet, but most of them not sufficiently so to be of use. Liquorice is one of the most commonly used herbs in Western herbal medicine. Liquorice has been used in medicine for more than 4000 years.

The earliest record of its use in medicine is found in 'code Humnubari' (2100 BC). It was also one of the important plants mentioned in Assyrian herbal (2000BC). Hippocrates (400BC) mentioned its use as a remedy of ulcers and quenching of thirds. The drug was also mentioned by Theophrastus and Dioscorides. In traditional Siddha system of medicine, liquorice is used as a demulcent, expectorant, anti-tussive, laxative and sweetener[7].

Morphology: *Glycyrrhiza glabra* Linn is a perennial shrub, attaining a height upto 2.5 m. The leaves are compound, imparipinnate, alternate, having 4-7 pairs of oblong, elliptical or lanceolate leaflets. The flowers are narrow, typically papilionaceous, borne in axillary spikes, lavender to violet in color. The calyx is short, campanulate, with lanceolate tips and bearing glandular hairs. The fruit is a compressed legume or pod, upto 1.5 cm long, erect, glabrous, somewhat reticulately pitted, and usually contains, 3-5 brown, reniform seeds.

The taproot is approximately 1.5 cm long and subdivides into subsidiary roots, about 1.25 cm long, from which the horizontal woody stolons arise. They may reach 8 m and when dried and cut, together with the root, constitute commercial licorice. It may be found peeled or unpeeled. The pieces of root break with a fibrous fracture, revealing the yellowish interior with a characteristic odor and sweet taste. Licorice enjoys fertile, sandy or clay soil near a river or stream where enough water is available for the plant to flourish in the wild, or under cultivation where it can be irrigated [8].

Traditional uses [9]:

1. A decoction of madhuka or its powder was prescribed with honey in anemia.
2. Yashti mixed with cow's milk was prescribed for promoting lactation.
3. 10g madhuka powder mixed with 10g sugar, pounded with rice water was prescribed in men-metrorrhagia.
4. A confection of rice milk, prepared with Yashtimadhu, was prescribed in hoarseness of voice.
5. Charaka prescribed 10 g madhuka powder mixed with honey, followed by intake of milk, as an aphrodisiac and as an intellect-promoting tonic.
6. Charaka also prescribed paste of licorice and *Picirrhiza kurroa* with sugar water as cardio-tonic.
7. Charaka also prescribed Yashtimadhu and *Santalum album*, powdered with milk in haematemisis.
8. Sushrata prescribed the paste of Yashti madhu 10g in intrinsic haemorrhage.
9. In oedema, paste of licorice and Sesamum indicum, milk mixed with butter is prescribed.
10. Warm clarified butter mixed with licorice, was applied topically on wounds, bruises and burns.
11. A decoction of madhuka was applied on erysipelas.
12. A decoction of the root is a good wash for falling and greying of hair.
13. Yashti is an important ingredient in Narikelanjana eye drops, prescribed in both acute & chronic conjuctivities.

Medicinal uses: This plant species are reported in the literature for its biological activities such as: anti-inflammatory and expectorant, controls coughing and has hormonal effects. It detoxifies and protects the liver. Medicinally, it is used internally for Addison's disease, Asthma, Bronchitis, Peptic ulcer, Arthritis, Allergic complaints and steroid therapy [10].

Externally, liquorices are used for Eczema, Herpes and Shingles. Liquorice decreases serum testosterone level in women and is beneficial in aplastic anemia. Since, liquorice extract is used in auto-immune conditions and has therapeutic benefit in immunodeficiency conditions like AIDS. Components of licorice root have both estrogenic and anti-estrogenic activity.

It is thus, an important herb for treating hormone-related female problems. It is used as an energy tonic, particularly for the spleen and stomach, and the root is added to many formulae. Roots of *Glycyrrhiza glabra* being tonic, demulcent laxative emollient are used in genito-urinary diseases.

It is reported to have antiviral, anticancer, anti-ulcer, anti-diabetic, anti-oxidant, anti-thrombic, anti-malarial, anti-fungal, anti-bacterial, immunostimulant, antithrombotic, anticonvulsant, anti-allergenic and expectorant activities[11,12]. Its roots were also demonstrated to have antidepressant, hypotensive heptoprotective, spasmolytic, memory strengthening activity. Licorice roots are used for its demulcent property.

It is also useful in gout, asthma, sore throat, tonsillitis, flatulence, sexual debility, epilepsy, hyperdypsia, fever, coughs, skin diseases, swellings, acidity, leucorrhoea, bleeding, jaundice, hiccough, hoarseness, and vitiated conditions of vata dosha, gastralgia, cephalalgia, ophthalmopathy and pharyngodnia.

Licorice is an important ingredient in medicinal oils for epilepsy, paralysis, rheumatism, haemorrhagic diseases. It is also used in the treatment of diarrhoea, fevers, fever with delirium and anuria.

They are also used as food in the confectionery industry such as sweets, alcohol free drinks etc. and in the tobacco industry. Economically, the roots are boiled to extract the familiar black substance used in liquorice confectionery and this is sold dried to eat. Liquorice is also the basis for most proprietary laxatives and its extracts flavors beer, soft drinks and pharmaceutical products, and is used as a foaming agent in beers and fire extinguishers.

Phytochemistry: The roots of *Glycyrrhiza glabra* Linn contain glycyrrhizin, which is a saponin that is 60 times sweeter than cane sugar; Flavonoid rich fractions include liquirtin, isoliquertin liquiritigenin and rhamnoliquirilin and five new flavonoids-glucoliquiritin apioside, prenyllicoflavone A, shinflavanone, shinpterocarpin and 1-methoxyphaseolin isolated from dried roots[13]. Isolation and structure determination of licopyranocoumarin, licoarylcoumarin, glisoflavone and new coumarin-GU-12 also isolated. Four new isoprenoid-substituted phenolic constituents – semilicoisoflavone B, 1-methoxyficifolinol, isoangustone A, and licoriphenone isolated from roots.

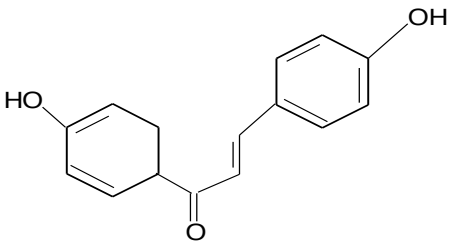
A new prenylated isoflavan derivative, kanzonol R was also isolated [13]. The presence of many volatile components such as pentanol, hexanol, linalool oxide A and B, tetramethyl pyrazine, terpinen-4-ol, α-terpineol, geraniol and others in the roots is reported. Presence of propionic acid, benzoic acid, ethyl linoleate, methyl ethyl ketine, 2, 3-butanediol, furfuraldehyde, furfuryl formate, 1-methyl-2-formylpyrrole, trimethylpyrazie,maltol and any other compounds is also isolated from the essential oil [13].

The Indian roots show various 2-methyliso - flavones, and an unusual coumarin, C liquocoumarin, 6 - acetyl- 5, hydroxy- 4 - methyl coumarin. Asparagine is also found. Glycyrrhizin (glycyrrhizic acid; glycyrrhizinate) constitutes 10–25% of licorice root extract and is considered the primary active ingredient. Glycyrrhizin is a saponin compound comprised of a triterpenoid aglycone, glycyrrhetic acid (glycyrrhetinic acid; enoxolone) conjugated to a disaccharide of glucuronic acid.

Both glycyrrhizin and glycyrrhetic acid can exist in the 18α and 18β stereoisomers. As a tribasic acid, glycyrrhizin can form a variety of salts and occurs naturally in licorice root as the calcium and potassium salts.

The ammoniated salt of glycyrrhizin, which is manufactured from licorice extracts, is used as a food flavoring agent and specifications for this salt form have been established in the Food Chemicals Codex. Carbenoxolone (18-βglycyrrhetinic acid hydrogen succinate), an analog of glycyrrhetic acid, is used in the treatment of some alimentary tract ulcerative conditions, such as peptic ulcers [14, 15].

Chemical Structures:



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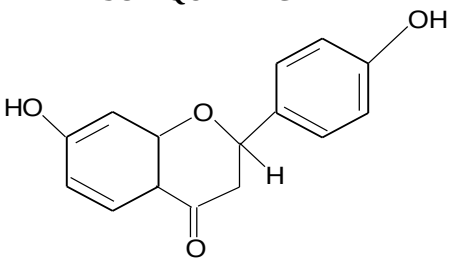

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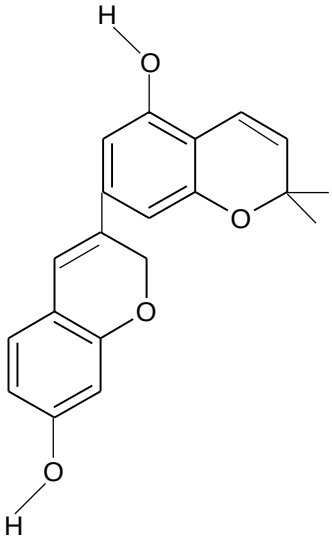
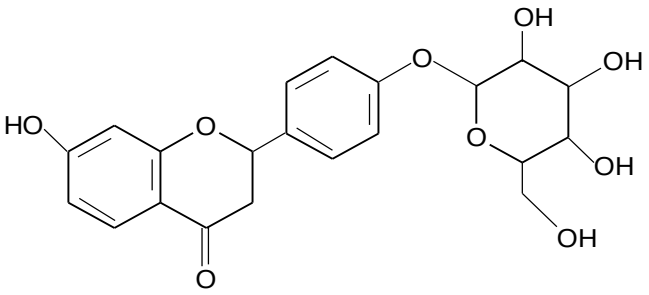
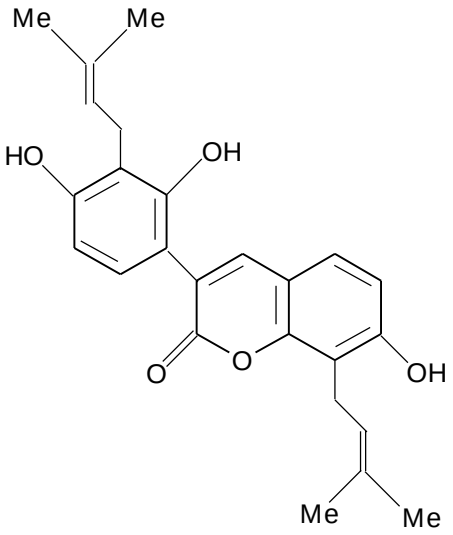


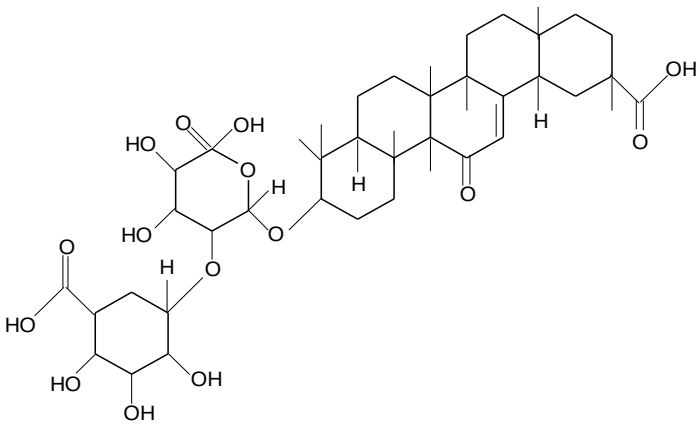
GLABRENE



LIQUIRITIN



LICOCAUMARIN



GLYCYRRHIZIN

Mechanism of action: The beneficial effects of licorice can be attributed to a number of mechanisms. Glycyrrhizin and glycyrrhizic acid have been shown to inhibit growth and cytopathology of numerous RNA and DNA viruses, including hepatitis A and C[16] herpes zoster, HIV, Herpes simplex [17, 18] and CMV[19]. Glycyrrhizin and its metabolites inhibit hepatic metabolism of aldosterone and suppress 5-[beta]-reductase, properties responsible for the well-documented pseudoaldosterone syndrome. The similarity in structure of glycyrrhetic acid to the structure of hormones secreted by the adrenal cortex accounts for the mineralocorticoid and gluco-corticoid activity of glycyrrhizic acid. Licorice constituents also exhibit steroid-like anti-inflammatory activity, similar to the action of hydrocortisone. This is due, in part, to inhibition of phospholipase A2 activity, an enzyme critical to numerous inflammatory processes. In vitro research has also demonstrated glycyrrhizic acid inhibits cyclooxygenase activity and prostaglandin formation as well as indirectly inhibiting platelet aggregation, all factors in the inflammatory process.

Licorice constituents possess significant antioxidant and hepatoprotective properties. Glycyrrhizin and glabridin inhibit the generation of reactive oxygen species (ROS) by neutrophils at the site of inflammation [20, 21].

In vitro studies have demonstrated licorice isoflavones, hispaglabridin A and B, inhibit [Fe.sup.3]- induced mitochondrial lipid peroxidation in rat liver cells. Other research indicates glycyrrhizin lowers lipid peroxide values in animal models of liver injury caused by ischemia reperfusion [22]. Licorice constituents also exhibit hepatoprotective activity by lowering serum liver enzyme levels and improving tissue pathology in hepatitis patients [23].

Pharmacology: Licorice contains the glycoside, glycyrrhizin which has a similar structure and activity as the adrenal steroids. Licorice has an anti-inflammatory activity similar to cortisone and has been found useful for arthritis and allergies. In addition licorice has been used for mild Addison's disease and other adrenal insufficiencies, such as hypoglycemia. Licorice also acts like the hormone, ACTH, causing sodium retention, potassium depletion, and water retention.

Excess consumption of licorice can lead to the classic symptoms of hypertension, with edema, increased blood pressure, potassium loss, and muscular weakness. The Deglycyrrhizinated form is most often used to avoid the hypertensive side effects of the glycyrrhetinic acid in whole Licorice. Licorice and DGL have a mild laxative effect and can protect the intestinal lining by increasing the production of mucus, thus alleviating heartburn and ulcers. Licorice and DGL also have a demulcent action and have been used for coughs [24].

TABLE 1: PHARMACOLOGICAL ACTIVITIES REPORTED FROM *GLYCYRRHIZA GLABRA*:

Sr. No	Activity	Part/Extract	Animal models & cell lines
1.	Immunomodulatory activity	Aqueous extract	*In vivo* phagocytosis, determination of cellular immune response haemagglutination antibody titre & plaque forming cell assay using sheep RBCs [25]
2.	Antitussive activity	Ethanol extract	SO_2 gas induced cough in experimental animals. Mice showed an inhibition of 35.62% in cough on treatment with G.glabra extract [26]
3.	Anti-inflammatory activity	Hydroalcoholic extract	Carrageenan induced rat paw oedema at dose levels of 100,200,300 mg/Kg. The extract showed a maximum of 46.86% inhibitory action [27]
4.	Chronic fatigue stress	Hydroalcoholic extract	The extract showed the protective effect on mice on exposure to chronic fatigue stress [28]
5.	Antinociceptive activity	Ethanol extract	Different pain models in Swiss albino mice. Activity was evaluated at 50-200 mg/Kg ip in mice using various pain models like acetic acid induced abdominal constrictions, formalin induced hyperalgesia & tail flick method [29]
6.	Antiulcer activity	Aqueous, acetone, ethanolic extracts of leaves	Micro-organism used: *Helicobacter pylori* by agar well diffusion method [30]
7.	Hepatoprotective activity	Aqueous extract of roots	PCM induced rats hepatocytes damage *in vivo*. Rabbit models with acute liver injury induced by CCl_4 [31]
8.	Memory enhancing activity	Aqueous extract of roots	Three month old Wistar albino rats. Elevated -plus maze and Morris water –maze test were conducted [32]
10.	Anticonvulsant activity	Hexane, ethanol,methanol extract of leaves	Fractions were evaluated intraperitoneallyin mice using maximal electroshock (MES) & pentylene tetrazol (PTZ) seizure tests [33]
11.	Antistress activity	Alcoholic & aqueous extract	Reduce stress in *Drosophila melanogaster* induced by Methotrixate at different conc. [34]
12.	Antioxidant activity	Methanol extract	The method based on scavenging activity & reduction capability of 1,1-diphenyl-2-picrylhydrazyl radical; Also against nitric oxide & superoxide radicals [35]
13.	Testicular toxicity	Aqueous extract	Carbendazim induced testicular toxicity in albino rats [36]
14.	Cytotoxic activity	$CHCl_3$, methanol & aqueous extract	*In vitro* cytotoxic actovity using two different cell lines MCFT-cancerous & Vero-normal cell line [37]
15.	Enzyme inhibiting activity	Methanolic extract	Invitro inhibition of tyrosinase enzyme[38]
16.	Antihyperglycemic activity	--------	Male albino rats of Wistar strain [39]
17.	Antimalarial activity	Alcoholic extract	Micro-organism used: *Plasmodium falciparum; Plasmodium yoelii* [40]
18.	Antiviral activity	Aqueous extract	Herpes simplex 1 & vesicular stomatitis virus[41]
19.	Anticancer activity	Licorice extract	Ames test, Trp-p-1, Trp-p-2 in *S.typhimurium* TA 98 reverants [42]
20.	Estrogenic activity	Alcoholic extract	Mouse
21.	Antimycobacterial activity	Methanolic extract	Micro-organisms used: *Mycobacteriaum tuberculosis* H37Ra & H37Rv strain
22.	Antidyslipidaemic activity	Ethanol extract	Fractions significantly brought down LDL and VLDL in the HFD fed hamsters to various degrees
23.	Antimicrobial activity	Ether, Chloroform, acetone	Micro-organisms used: *E. coli, B. subtilis, P. aerogenosa, S. aureus* [43]

TABLE 2: CHEMICAL CONSTITUENTS RESPONSIBLE FOR THE BIOACTIVITY:

Sr. No	Activity	Chemical constituent	Class
1.	Antiulcer activity	Glabridin, glabrene, glycyrrhizinic acid	Flavonoid, isoflavan, saponin glycoside
2.	Antimycobacterial activity	Glabridin	Flavonoid
3.	Analgesic & uterine relaxant	Isoliquiritigenin	Flavonoid
4.	Antioxidant activity	Licochalcone, glabridin, isoliquiritigenin, licocoumarin	Chalcone, flavonoid
5.	Memory enhancer	Glabridin	Flavonoid
6.	Corticosteroid activity	18-β-glycyrrhetinic acid	Triterpenoid saponin glycoside
7.	Antiallergic activity	Glycyrrhizin, 18-β-glycyrrhetinic acid, liquiritigenin	Triterpenoid saponin glycoside, flavanone
8.	Hepatoprotective activity	Glycyrrhizin	Triterpenoid saponin glycoside
9.	Anti-inflammatory activity	Glycyrrhetic acid, liquiritoside, Licochalcone a	Chalcone
10.	Anticancer activity	Glycyrrhetic acid, Glycyrrhizin	Triterpenoid saponin glycoside
11.	Antimalarial activity	Licochalcone A	Chalcone
12.	Antiviral activity	Glycyrrhizin, licochalcones, glycyrrhetinic acid	Triterpenoid saponin glycoside
13.	Antihyperglycemic activity	18-β-glycyrrhetinic acid, glycyrrhizin	Triterpenoid saponin glycoside
14.	Hepatocellular carcinoma	Glycyrrhizin	Triterpenoid saponin glycoside
15.	Antitussive activity	Glycyrrhizin	Triterpenoid saponin glycoside
16.	Antithrombin activity	Glycyrrhizin, isoliquiritigenin	Triterpenoid saponin glycoside, flavanoid
17.	Immunostimulating	Glycyrrhetinic acid	Triterpenoid
18.	Anti HIV	Glycyrrhizin	Triterpenoid saponin glycoside
19.	Chronic hepatitis C	Glycyrrhizin	Triterpenoid saponin glycoside
20.	Spasmolytic	Liquiritin	Flavonoid
21.	Muscle relaxant	Rhamnoglucoside	Flavanone
22.	Antimycobacterial activity	Glabridin	Flavonoid
23.	Estrogenic activity	Glabrene, liquiritigenin	Isoflavan, flavanone

CONCLUSION: There has been an increase in demand for the phytopharmaceuticals all over the world because of the fact that the allopathic drugs have more side effects. This forms a good basis for the selection of plant for further phytochemical and pharmacological investigation. The pharmacological and clinical studies reported in the present review confirm the therapeutic value of *Glycyrrhiza glabra.*

Presence of chemical compounds indicates that the plant could serve as "lead" for development of novel agents for disorders in the coming years. In this regard, further studies need to be carried out to explore *Glycyrrhiza glabra* Linn for its potential in preventing and treating diseases.

So, the present review gives a direction for future investigators to carry out research on the plant so that they could get some medicinally important drugs.

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