
Glycyrrhiza Glabra: Chemistry and Pharmacological Activity

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Abstract

Nature is an attractive source of new therapeutic candidate compounds as a tremendous chemical diversity is found in millions of species of plants, animals, marine organisms, and microorganisms as potential medicinal agents. This chapter of research is an effort to highlight the phytochemical/chemical constituents of an ancient medicinal plant *G. glabra* and their pharmacological importance. *G. glabra* is an old age medicinal plant that belongs to Leguminosae/Fabaceae/Papilionaceae family and commonly known as mullaithi in north India. The chemical composition of *G. glabra* is glycyrrhizin, glycyrrhetic acid, isoliquiritin, isoflavones, etc., and their derivatives have been reported for several pharmacological activities like, expectorant, antedemulcent, antiulcer, anticancer, anti-inflammatory, antidiabetic, etc. These phytochemicals hold strong promise for designing new herbal drugs, and derivatives of these compounds are being generated to evaluate their pharmacological purposes for future drug use. Natural products have been a prime source for the treatment of many forms of ailments, many of which are consumed daily with the diet. They provide significant protection against various diseases and disorders.

Keywords

Chemistry • *Glycyrrhiza glabra* • Licorice • Medicinal plant • Pharmacology

Abbreviations

AP-1	Activator protein-1
Bcl2	B cell lymphoma-2
CCl ₄	Carbon tetrachloride
CYP1A1	Cytochrome P1450A1
DGL	Deglycyrrhizinated licorice
DNA	Deoxyribonucleic acid
GA	Glycyrrhetic acid
GG/G	<i>glabra Glycyrrhiza glabra</i>
GST	Glutathione-S-transferase
H1N1	Hemagglutinin type-1 and neuraminidase type-1
HIV	Human immunodeficiency virus
KK-Ay	Knockout diabetic mice
MAP	Mitogen activated protein
NADH	Nicotinamide adenine dinucleotide (reduced)
PAF	Platelet aggregating factor

Fig. 1 *Glycyrrhiza glabra* plant



SARS	Severe acute respiratory syndrome
SNMC	Stronger neo-minophagen-C
TPA	12- <i>O</i> -tetradecanoylphorbol-13-acetate

1 Introduction

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, etc. Medicinal plants are of great importance to the health of individuals and communities. The medicinal value of these plants lies in some chemical substances that produce a definite physiological action on the human body. The most important of these bioactive constituents of plants are triterpenoid, saponin, flavonoids, tannins, alkaloids, and phenolic compounds [1]. Many of these indigenous medicinal plants are used as spices and food plants. They are also sometimes added to foods meant for pregnant and nursing mothers for medicinal purposes [2, 3].

Glycyrrhiza glabra (Fig. 1) is one of the useful medicinal plants. *Glycyrrhiza* is derived from the ancient Greek term *glykos*, meaning sweet, and *rhiza*, meaning root.

Glycyrrhiza glabra is known as mulaithi in north India. *Glycyrrhiza glabra*, also known as licorice and sweet wood, is native to the Mediterranean and certain areas of Asia. A number of traditional healers have claimed the efficacy of *Glycyrrhiza* species for a variety of pathological conditions as a diuretic, choleric, used as insecticide, and indicated in traditional medicine for coughs, colds, and painful swellings [4, 5].

1.1 Scientific Classification

Kingdom: Plantae
Division: Angiospermae
Class: Dicotyledoneae
Order: Rosales
Family: Leguminosae
Genus: *Glycyrrhiza*
Species: *glabra* Linn

1.2 Binomial Name

Glycyrrhiza glabra Linn.

1.3 Synonyms

Glycyrrhiza glandulifera

1.4 Vernacular Names [4]

Sanskrit: Yashti-madhu, madhuka
Bengali: Jashtimadhu, jaishbomodhu
Gujarat: Jethimadhu
Hindi: Jothi-madh, mulaithi
Kannada: Yastimadhuka, atimaddhura
Malayalam: Iratimadhuram
Marathi: Jeshtamadha
Oriya: Jatimadhu
Tamil: Atimaduram
Telugu: Atimadhuranu, yashtimadhukam
English: Licorice, liquorices, sweet wood
Arab: Aslussiesa
Persia: Ausareha mahaka
France: Boisdoux
Germany: Sussholz

1.5 Origin

The roots are unearthed in the autumn of the fourth season. It is grown in India, Spain, Iran, Russia, China and Italy.

1.6 Ecology

Glycyrrhiza glabra enjoys fertile, sandy, and 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.

1.7 Morphology

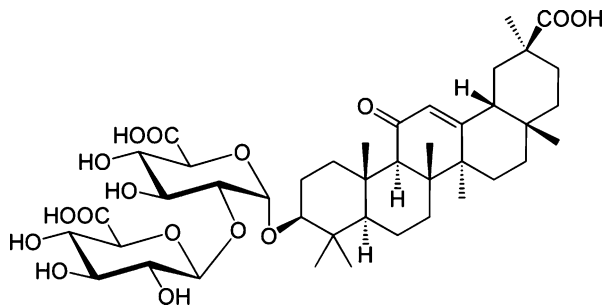
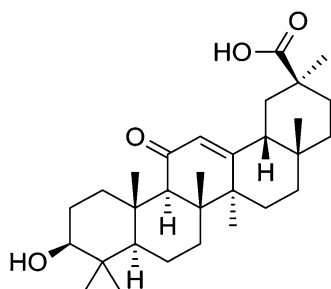
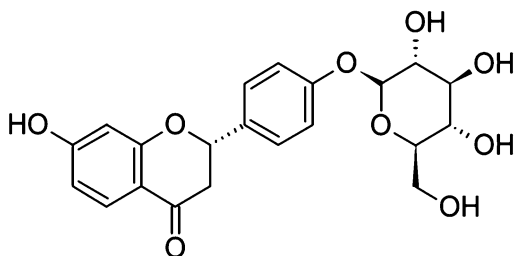
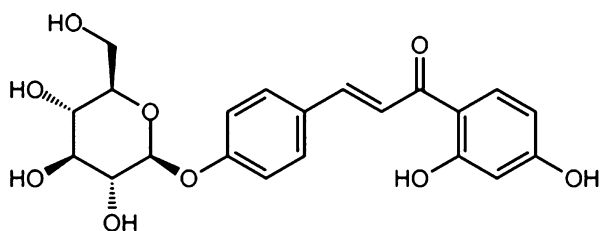
Glycyrrhiza glabra is herbaceous perennial, growing to 1 m in height, with pinnate leaves about 7–15 cm long, with 9–17 leaflets. The flowers are 0.8–1.2 cm long, purple to pale whitish blue, produced in a loose inflorescence. The fruit is an oblong pod, 2–3 cm long, containing several seeds [6]. The *Glycyrrhiza* shrub is a member of the pea family and grows in subtropical climates in rich soil. Below ground, the *Glycyrrhiza glabra* plant has an extensive root system with a main taproot and numerous runners. The main taproot, which is harvested for medicinal use, is soft, fibrous, and has a bright yellow interior [7].

1.8 Medicinal Parts Used

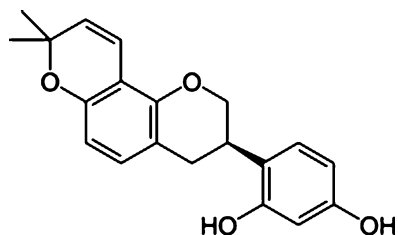
Roots and Rhizome (powder, teas, tonic, extracts, tinctures, decoction).

2 Phytochemistry/Chemistry

A number of components have been isolated from the roots of *Glycyrrhiza glabra*, including a water-soluble, biologically active complex that accounts for 40–50 % of total dry material weight. This complex is composed of triterpene, saponin, flavonoids, polysaccharides, pectins, simple sugars, amino acids, mineral salts, asparagines, bitters, essential oil, fat, female hormone estrogen, gums, mucilage (rhizome), protein, resins, starches, sterols, volatile oils, tannins, glycosides, and various other substances [8, 9]. Glycyrrhizin (Fig. 2), a triterpenoid compound, accounts for the sweet taste of licorice root. This compound represents a mixture of potassium-calcium-magnesium salts of glycyrrhizic acid that varies within a 2–25 % range. Among the natural saponin, glycyrrhizic acid is a molecule composed of a hydrophilic part, two molecules of glucuronic acid, and a hydrophobic fragment, glycyrrhetic acid (Fig. 3) [10]. The yellow color of licorice is due to the flavonoid content of the plant, which includes liquiritin (Fig. 4), isoliquiritin (Fig. 5)

Fig. 2 Glycyrrhizin**Fig. 3** Glycyrrhetic acid**Fig. 4** Liquiritin**Fig. 5** Isoliquiritin

(a chalcone) and other compounds [11]. The isoflavones, glabridin (Fig. 6) and hispaglabridins A and B have significant antioxidant activity [12], and both glabridin and glabrene possess estrogen-like activity [13].

Fig. 6 Glabridin

3 Pharmacological Activity

The various studies carried out by ethnobotanists, phytochemists, and experimental pharmacologists on its bioactivities revealed that the plant may be a source of new drugs, and therapeutic agents for the treatment of a variety of diseases and ailments could be manufactured. Report of various activities is given here.

3.1 Antitussive and Expectorant

The licorice powder and extract was found to be useful for the treatment of sore throat, cough, and bronchial catarrh. It has antitussive, demulcent, and expectorant loosening activities which may attribute due to presence of glycyrrhizin and helping to expel congestion in the upper respiratory tract as it accelerates tracheal mucus secretion [14]. It has been recently found that liquiritin apioside is an active compound present in the methanolic extract of liquorice. The compound inhibits capsaicin-induced cough [15].

3.2 Antimicrobial

Multidrug-resistant microorganisms pose a serious infestation in clinical medicine today due to the rapid spread as well as chronic infections caused by them. Each species of the genus *Glycyrrhiza* Linn is characterized by isoprenoid phenols, which have selective antimicrobial activity. Recent research has shown antibacterial effects of hydromethanolic root extract of *G. glabra* against some gram-positive and negative pathogens [16]. A number of components isolated from *Glycyrrhiza* include glabridin, gabrin, glabrol, glabrene, hispaglabridin A, hispaglabridin B, 40-methylglabridin, and 3-hydroxyglabrol have exhibited potential in vitro antimicrobial activity [17, 18]. Glycyrrhizinic acids have been used to cure atopic dermatitis, pruritis, and cysts due to parasitic infestations of skin [19, 20].

3.3 Anticoagulant and Memory Enhancing Activity

Glycyrrhizin, an already known anti-inflammatory compound, has also been found as the first plant-based inhibitor of thrombin. It prolonged the thrombin and fibrinogen clotting time and increased plasma recalcification duration. The thrombin-induced platelet aggregation was found to be inhibited by the action of glycyrrhizin, but PAF (platelet aggregating factor)- or collagen-induced agglutination was not affected by glycyrrhizin [21, 22]. One of the laboratory-based research has shown memory enhancing activity of *G. glabra* in experimental animals [23].

3.4 Antiviral

Glycyrrhizin has a prominent antiviral activity, as it does not allow the virus cell binding. Recently antiviral activities of ribavirin, 6-azauridine, pyraziofurin, mycophenolic acid, and glycyrrhizin against two clinical isolates of SARS (severe acute respiratory syndrome) virus, i.e., FFM-1 and FFM-2 were evaluated. It was observed that glycyrrhizin was the most effective in controlling viral replication and could be used as a prophylactic measure. Glycyrrhizin has been previously used to treat patients suffering from HIV-1 and chronic hepatitis C virus [24–26].

3.5 Antioxidant and Anti-inflammatory

Hydromethanolic root extract of *Glycyrrhiza glabra* exhibited marked antioxidant activity in a test tube system [16]. *Glycyrrhiza* (root) have a plenty of polyphenolic components as a potential source of antioxidants. Licochalcones B and D exhibit a potential activity by inhibiting the microsomal lipid peroxidation. Retrochalcones exhibit mitochondrial lipid peroxidation and prevent red blood corpuscles from oxidative hemolysis. Isoflavones like glabridin, hispaglabridin A and 3'-hydroxy-4-O-methylglabridin present in *Glycyrrhiza glabra* were found to have potential antioxidant activity. More recently, dehydrostilbene derivatives like α -dihydro-3,5,4-trihydroxy-4,5-diiodopentenylstilbene have been isolated and reported as free radical scavengers [27–29]. Research shows that on being broken down in the gut, glycyrrhizin exerts an anti-inflammatory action similar to hydrocortisone and other corticosteroid hormones.

3.6 Antiulcer Activity

Licorice has been used as an antiulcer agent since early 1970s. The extracted glycyrrhizin, DGL (deglycyrrhizinated licorice) is generally employed for the effective treatment of ulcers. Carbenoxolone from liquorice roots produce the antiulcerogenic effect by inhibiting the secretion of gastrin [28]. Liquorice can raise the concentration of prostaglandins in the digestive system that promote

mucus secretion from the stomach. It was also reported that liquorice prolongs the life span of surface cells in the stomach and has an antipepsin effect [29].

3.7 Anticarcinogenic and Antimutagenic Activity

The aqueous extract of *G. glabra* inhibits in vivo and in vitro proliferation of Ehrlich ascites tumor cells and inhibits angiogenesis in in vivo assay, peritoneal and chorioallantoic membrane assay [30]. On the other hand, there are many reports about the anticancer effects of several derivatives of its components both in in vivo and in vitro studies. Glycyrrhetic acid could trigger the proapoptotic pathway by inducing mitochondrial permeability transition, and this property may be useful for inducing apoptosis of tumor cells [31, 32]. The licorice extract induced the Bcl2 phosphorylation and G2/M cycle arrest in tumor cell lines, and 70 % methanol soluble fraction of licorice acetone extract was found to induce apoptosis in human monoblastic leukemia U937 cells. The compound was identified to be licocoumarone also responsible for antioxidant and antimicrobial activity [33]. The hydromethanolic root extract of *G. glabra* also exhibited antimutagenic potential by suppressing micronucleus formation and chromosomal aberration in bone marrow cells of albino mice [34, 35]. It was found that glycyrrhizin induced AP-1 (activator protein-1) activity in untreated cells whereas inhibited TPA (12-*O*-tetradecanoylphorbol-13-acetate) induced AP-1 activity in TPA treated cells. This mechanism could serve as a model for development of new chemoprotective agents [36]. Recently licochalcone E, a new retrochalcone from the roots of *G. inflata*, exhibited the most potent cytotoxic effect compared with the known antitumor agents, licochalcone A and isoliquiritigenin [37].

3.8 Hepatoprotective Activity

Chronic hepatitis (viral as well as nonviral) is a slowly progressive liver disease that may evolve into cirrhosis with its potential complications of liver failure or hepatocellular carcinoma. In Japan, glycyrrhizin has been used for more than 60 years as treatment for chronic hepatitis under the name of SNMC (stronger neo-minophagen-C) clinically as an antiallergic and antihepatitis agent [38]. Glycyrrhizin induced significant reduction in serum aminotransferases and improved the liver histology when compared with the placebo. It has also been implicated that long-term usage of glycyrrhizin prevents development of hepatocellular carcinoma in chronic hepatitis C. In vitro studies have indicated that glycyrrhizin modifies the intracellular transport and suppresses hepatitis B virus surface antigen [39, 40]. It has been found that 18 β -glycyrrhetic acid (GA), an aglycone of glycyrrhizin decreases the expression of P450 E1 thereby protecting the liver [41]. GA also prevents the oxidative and hepatic damage caused by aflatoxins by increasing the CYP1A1 and GST (glutathione-S-transferase) activities and may also contribute to anticarcinogenic activity by metabolic deactivation of the hepatotoxin [42]. One of the researches indicated that the hydromethanolic root

extract of *G. glabra* exhibited significant protection from hepatotoxicity induced by CCl_4 (carbon tetrachloride) in liver tissue of experimental mice [43]. It has also been experimentally investigated that glycyrrhizin and its analogues have a mitogenic effect via epidermal growth factor receptors subsequently stimulating the MAP (mitogen activated protein) kinase pathway to induce hepatocyte DNA synthesis and proliferation [44].

3.9 Antidiabetic

Type 2 (noninsulin dependent) diabetes mellitus, an insulin resistant syndrome, is a growing health concern in the modern society. PPAR's (peroxisome proliferation activated receptors) are ligand-dependent transcriptional factors regulating the expression of a group of genes that play an important role in glucose and lipid metabolism. The PPAR receptors are classified as PPAR- α , PPAR- γ , and PPAR- δ . The PPAR- α is found in liver, muscle, and kidney. PPAR- γ is associated with adipose tissue, adrenals, and small intestine whereas PPAR- δ is expressed ubiquitously. PPAR- γ serves as a predominant target for insulin sensitizing drugs like pioglitazone and rosiglitazone. Ethyl acetate extract of licorice using GAL-4-PPAR- γ chimera assay exhibited a significant PPAR- γ binding activity which was attributed to seven phenolic compounds, viz., dehydroglyasperin, glyasperin B, glyasperin D, glycoumarin, glycyrin, glycyrol, and isoglycyrol. Pioglitazone and glycyrin were found to suppress the increased blood glucose level in mice after sucrose loading during the oral sucrose tolerance test. Pioglitazone, a potent PPAR- γ agonist ameliorated the insulin resistance and type 2 diabetes mellitus. Similarly, glycyrin also exhibited a potent PPAR- γ ligand binding activity and therefore reduces the blood glucose level in KK-Ay (knockout diabetic mice). This finding is of much significance as licorice has also been traditionally used as an artificial sweetening agent and could be helpful in insulin resistance syndrome prevalent in the modern society [45].

3.10 Immunomodulator Activity

Swine flu is a highly contagious respiratory disease of pigs with low mortality (1–4 %), is species-specific in nature, and outbreak usually occurs once in a year with an upsurge in autumn and winter in temperate zones. One such virus, namely, influenza A H1N1 virus has evolved the capacity to cross species barrier (i.e., pig to humans) and has spread widely among humans. Polysaccharide fractions obtained from *Glycyrrhiza glabra* stimulate macrophages and hence elevate and assist immune stimulation [46]. *N*-acetylmuramoyl peptide is glycyrrhizin analogue having potential in vitro immune-stimulating properties, [47] also animal studies have revealed its efficacy against the influenza virus that is mediated by stopping the virus replication. Glycyrrhizic acid present in the plant inhibits virus growth and inactivates virus particles is a potential source of immunomodulator [48].

4 Side Effects and Toxicity

Everything on the earth has a purpose whether they are plants, animals, or microbes, but there is a limit for consumption because it is well known that anything can be harmful or poisonous after a limit. The most common reported side effect with licorice supplementation is elevated blood pressure. This is thought to be due to the effect of licorice on the rennin-angiotensin-aldosterone system. It is suggested licorice saponins are capable of potentiating aldosterone action while binding to mineral-corticoid receptors in the kidneys. In addition to hypertension, patients may experience hypokalemia and sodium retention, resulting in edema. All symptoms usually disappear with discontinuation of therapy. Many studies report no side effects during the course of treatment [27, 28]. Generally the onset and severity of symptoms depend on the dose and duration of licorice intake, as well as individual susceptibility. The amount of licorice ingested daily by patients with mineral-corticoid excess syndromes appears to vary over a wide range, from as little as 1.5 g daily to as much as 250 g daily [5, 29].

5 Future Aspects

In ancient Indian literature, it is mentioned that every plant on this earth is useful for human beings, animals, and other plants. *G. glabra* is an herbal plant which has lots of medicinal properties such as antimicrobial, antioxidant, anti-inflammatory, antitussive, antidiabetic, antiviral, anticancer, antimutagenic, antiulcer, and hepatoprotective. The phytochemicals present in *G. glabra* have been of immense importance in phytotherapeutics. Thus there is an immense need to modify the natural *Glycyrrhiza* constituents to reduce these side effects thereby generating the advanced versions of the bioactive compounds to be used as drugs in future. There are so many bioactive compounds that have been isolated from *G. glabra* like glycyrrhizin, glycyrrhetic acid, glabridin, liquiritin, isoliquiritigenin, isoflavones, etc. and have been assessed for medicinal potential which showed that these compounds hold a strong promise in designing future drugs. Derivatives of these compounds are being generated to evaluate their pharmacological purposes for future drug use. There are ample chances of arriving to pharmacophores with least toxic side effects using combinatorial chemistry.

6 Conclusion

Glycyrrhiza glabra (GG) is a plant with strong ethnobotanical history. The root and rhizome parts of this plant are used as a folk medicine both in Europe and eastern countries. *G. glabra* extracts have been shown to possess lot of medicinal properties like antitussive, antimicrobial, antioxidant, anti-inflammatory, antiulcer, anticancer, etc. due to presence of so many bioactive components, triterpene, saponins, flavonoids, alkaloids, glycyrrhizin, glycyrrhetic acid, glabridin, liquiritin, etc. *G. glabra* is one of those ancient plants, which have been used in the traditional pharmacopoeias

for its multifaceted activities against variety of systematic and nonsystematic ailments. The chemical foundations of *G. glabra* have been discovered in the last era. The chemical constituents of *G. glabra* hold a strong promise for providing new molecules, which could be of immense medicinal applications in the drug discovery process for the development of new drugs present era.

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