

Pharmacological perspective of *glycyrrhiza glabra* linn.: a mini-review

Abstract

Glycyrrhiza glabra Linn. (Family: Fabaceae) is a traditional medicinal plant used in various ancient medicine systems and documented across the globe for its ethanopharmacological value to cure varieties of ailments. Glycyrrhizin is the major active constituent obtained from liquorice roots, one of the most widely used in herbal preparations for the treatment and management of chronic diseases. The present mini-review is focused mainly on major secondary metabolites, ethnopharmacology and potential medicinal uses of *Glycyrrhiza glabra*. The sources for the literature search were PubMed, ScienceDirect, SciFinder and Google Scholar. Reported pharmacological activities, characterized secondary metabolites and traditional uses of *Glycyrrhiza glabra* warrants its potential therapeutic uses. However, further scientific validations along with evidence-based studies are still required in support to its traditional uses, to serve as "lead" for development of novel agents and a better drug candidate in future.

Keywords: *glycyrrhiza glabra*, liquorice, glycyrrhizin, traditional uses, medicinal plant

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Ajit Kumar Thakur, Pooja Raj

Centre for Development of Pharmacology and Toxicology, Delhi Pharmaceutical Sciences and Research University, India

Correspondence: Ajit Kumar Thakur, Assistant Professor of Pharmacology, Centre for Development of Pharmacology and Toxicology, Delhi Pharmaceutical Sciences and Research University, Pushp Vihar Sector-III, M.B. Road, New Delhi-110 017, India, Fax -29554423, Email ajitmitpharm@gmail.com

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Introduction

Plants have been major source of medicine in all cultures from ancient times. In the traditional system, various indigenous plants are being used in the diagnosis, prevention and elimination of acute and chronic disease. There is an increasing demand for herbal medicines, health products, pharmaceuticals across the world as herbs have stood the trial of time for their positive safety, efficacy, cultural acceptability and lesser side effect. Medicinal plants have been a part of modern life style and plants are a source of important therapeutic aid for alienating human ailments.¹ *Glycyrrhiza glabra* Linn. (Family: Fabaceae) is a well-known medicinal plant used in traditional medicine across the globe for its ethanopharmacological value to cure varieties of ailments. The roots and rhizomes are the main medicinal parts of liquorice (Figure 1). *Glycyrrhiza glabra* Linn. is also called as Liquorice, Mulaithi or Yashtimadu. Glycyrrhiza is a word derived from the ancient Greek term 'glykos', meaning sweet, and 'rhiza', meaning root.² This plant is generally used as a flavoring agent due to its sweetness. *Glycyrrhiza glabra* plays an important part in Ayurveda and Siddha (Indian Traditional Medicine Systems) arrangement of drug acting as ulcer protective, demulcent, expectorant, anti-tussive and purgative.³ Some marked pharmaceutical formulations containing *Glycyrrhiza glabra* and their indication and therapeutic uses are summarized in Table 1. Among various plants of the Glycyrrhiza genus, *Glycyrrhiza glabra* is the utilized for therapeutic purposes and it is additionally pre-clinically and clinically the most focused one.⁴⁻⁷ In this review, we have illustrated major secondary metabolites, ethnopharmacology and potential medicinal uses.

Biodiversity of liquorice

The Glycyrrhiza genus contains more than 30 species and widely distributed all over the world.⁷ Glycyrrhizagenus plants are wide spread in Mediterranean, Southern and Central Russia and Asia, being minor to Iran. Many species are now grown throughout Europe, Syria, Asia, UK, USA, Italy, France, Germany, Spain, China, Middle East, Central and South Western Asia and the Mediterranean region, which is basin of Africa, in South Europe, Afghanistan and Northern India (Punjab and Sub-Himalayan regions). Large-scale commercial cultivation is available in Spain, Sicily and England.^{8,9}

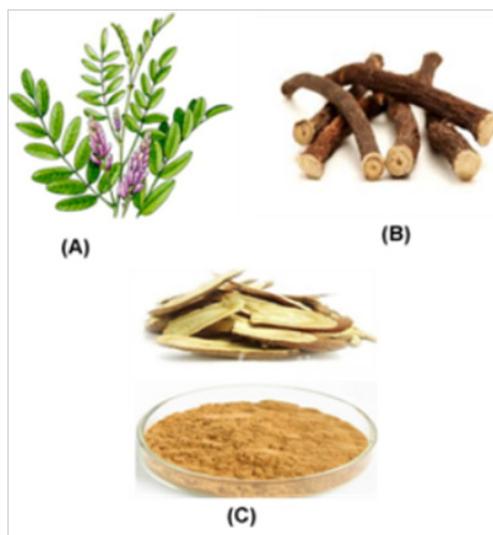


Figure 1 (A) Flowering (aerial part) plant parts of *Glycyrrhiza glabra* Linn. (B) Root of the plant, and (C) powdered form of the plant root used in traditional system of medicines.

Secondary metabolites of liquorice

A number of studies have been reported describing the different secondary metabolites of the *Glycyrrhiza* species. *Glycyrrhiza glabra* contains more than 20 triterpenoids and nearly 300 flavonoids.⁶ Major secondary metabolites of *Glycyrrhiza glabra* are shown in Figure 2. The secondary metabolites are triterpenoid saponin, glycosides, glycyrrhizin, prenylated bioaurone, licoagron, 7-acetoxy-2-methyl-isoflavone, 7-methoxy-2-methylisoflavone, and 7-hydroxy-2 methyl isoflavone, 4-methyl coumarin, liqcoumarin, glyzylglabrin, quercetin, quercetin-3-glucoside, liquiritigenin, isoliquiritigenin. Other constituents reported include a flavanone rhamnoglucoside, isoliquiritin, licuraside, liquiritoside, liquoric acid, liquiritic acid, isoglabrolide, 18 α -hydroxy glycyrrhetic acid, glabrolide, glycyrrhizic acid, glabridin, glabrol, liquiritin, glycyrrhetic acid; licoisoflavonol, glyzarin, glyzylglabrin, licoisoflavones A, B and licoisoflavon.^{6,7}

Glycyrrhizin and glycyrrhetic acid are the main components of *Glycyrrhiza glabra*. The metabolic processes in human being can convert glycyrrhizin to glycyrrhetic acid. Therefore, the pharmacological effects of glycyrrhizin are similar to glycyrrhetic acid.¹⁰

Table 1 Pharmaceutical preparations containing *Glycyrrhiza glabra* with their indication and therapeutic uses

Sl. No.	Name of drug/ cosmetics/ supplement	Manufacturer/ supplier/ marketing	Contents/ Composition	Indication/ therapeutic uses
1.	<i>Glycyrrhiza glabra</i> IX	Dr. Willmar Schwabe	<i>Glycyrrhiza glabra</i> extract	Irritating cough without wheeze, anti-tussive, Sore throat, Chronic inflammatory condition of air passage and cough of non-specific origin
2.	GutGard®	Natural Remedies	<i>Glycyrrhiza glabra</i> extract (>10% flavanoids content)	Support a normal and healthy gastrointestinal tract, sooth heartburn, antioxidant support
3.	Licorice Root 500mg	Pure Science Supplements	10% <i>Glycyrrhiza glabra</i> extract of root, deglycyrrhizinated Licorice	Supports digestive & respiratory function, expectorant and demulcent
4.	Health Aid Licorice (GG 50ml)	Health Aid	Each 1ml Licorice Liquid contains (average): Licorice Extract 1:3 (equivalent of 330mg of Licorice herb)	Dry cough and promotes clear and comfortable breathing
5.	Solaray Licorice 450mg. - 100 Capsules	Nutraceutical	Licorice (<i>Glycyrrhiza glabra</i>) (root), Gelatin and and magnesium stearate	Health Supplement
6.	Nature's sunshine licorice roots	Nature's Sunshine	Licorice root 792 mg	Supports the glandular system, specifically the adrenal glands and liver
7.	Brefus <i>Glycyrrhiza glabra</i> L., 0.2ml/ml	Brefus	<i>Glycyrrhiza glabra</i> L. 0.2ml/ml	Expectorant in cases of pharyngitis, acute and chronic bronchitis, intense coughing and/or secretion, relieve coughs
8.	Chewable DGL Licorice tablets	Nature's Garden	Deglycyrrhizinated Licorice 380 mg (<i>Glycyrrhiza glabra</i>) (root), L-Glycine 50mg	Health Supplement
9.	Himalaya pure herb-licorice	Himalaya Herbal Healthcare	Organic licorice root 250mg (Standardized extract 25% glycyrrhizin-62.5mg). Organic licorice root powder 350 mg (3% glycyrrhizin-10.5mg)	Gastric support, soothes the mucous membranes, balances excess acidity in the stomach lining, and supports comfortable digestion
10.	Banyan botanicals licorice root powder	Banyan Botanicals	<i>Glycyrrhiza glabra</i> extract	Natural expectorant and demulcent, dry cough and promotes clear and comfortable breathing, reproductive system, balanced adrenals, and proper function of the kidneys,
11.	The Nature Republic Cotton Armpit Cream	Nature Republic	<i>Glycyrrhiza glabra</i> root extract as one of the component	Claims to whiten, brighten and deodorize your underarm areas with its calming, powdery scent
12.	Illuminate clean face cleanser	Younique	Made with Garden chrysanthemum, Aloe vera, and Licorice root	Face cleanser for oily skin
13.	Himalaya clear complexion whitening face wash	Himalaya	Pomegranate, saffron, liquorice, white dammer	Removes dark spots, cleanses and clarifies impurities
14.	Liquorice extract –resist barrier repair moisturizer with retinol	Seattle	Retinol, liquorice	Anti-aging cream and removes wrinkles

Therapeutic potentials and traditional uses

Research have come up with many therapeutic activities of licorice, a recent review paper summarized the pharmacological activities and discussed potential uses of *Glycyrrhiza glabra* for antitumor, antimicrobial, antiviral, anti-inflammatory, immunoregulatory, and several other activities that contribute to the recovery and protection of the nervous, alimentary, respiratory, endocrine, and cardiovascular systems.⁶ The reported potential therapeutic activities and traditional uses of *Glycyrrhiza glabra* Linn. are summarized in Figure 3. Glycyrrhizin, a triterpene glycoside from root of *Glycyrrhiza*

glabra, has positive effects on inhibition of hepatic apoptosis and necrosis by suppression of TNF- α and caspase-3, an important cytokine, which is a key mediator of hepatic apoptosis and necrosis in LPS/D-GaAlN-induced liver failure.¹¹ and down-regulation of matrix metalloproteinase-9 in lipopolysaccharide/D-galactosamine-induced liver injury.¹² Hydro-methanolic root extract of *Glycyrrhiza glabra* exhibit potent anti-bacterial activity due to the presence of secondary metabolites such as alkaloids, flavonoids, saponins and so on. Various *in-vitro* studies have been proved that aqueous, methanolic or ethanolic extract of *Glycyrrhiza glabra* show inhibitory

activity against various species of bacteria. The *in-vitro* inhibitory activity of *Glycyrrhiza glabra* extract against *Salmonella typhi*, *S. paratyphi B*, *S. flexneri*, *Shigella sonnei* and enterotoxigenic *E. coli* was investigated using well and disc diffusion method. It was found that all the strains were inhibited by *Glycyrrhiza glabra* extract at concentration higher than 7.5% thus proved that *Glycyrrhiza glabra* extract could be used as an alternative herbal antibacterial agent.¹³ The *in-vitro* anti-bacterial activity of ethanolic extract of *Glycyrrhiza glabra* against oral microbes such as, *Streptococcus mutans*, *S. sanguis*, *S. salivarius*, *S. mitis* and *Lactobacillus acidophilus* using disc diffusion method concluded that ethanolic extract of *Glycyrrhiza glabra* (500µg/disc) was more effective with high zone of inhibition among various bacterial species in comparison to aqueous extract of *Glycyrrhiza glabra*. This inferred that extract of *Glycyrrhiza glabra* can be used in herbal treatment in dentistry and oral infections.¹⁴ The *in-vitro* antibacterial activity of aqueous and methanolic root extract of *Glycyrrhiza glabra* against *Streptococcus aureus* and *Streptococcus agalactiae* were also defined.¹⁵ Recently, researchers have demonstrated the anti-bacterial activity of root and leaf extract of *Glycyrrhiza glabra* against *E. coli*, *Pseudomonas aeruginosa*, *Enterobacter cloacae* and *Klebsiella* sp. using well and disc method showing that both extracts were ineffective against *Enterobacter cloacae* and *Klebsiella* sp. while strong anti-bacterial activity against *E. coli* and *Pseudomonas aeruginosa*. Therefore, *Glycyrrhiza glabra* might be useful in the treatment of diarrhea caused by rotavirus infection.¹⁶ Antifungal activity of liquorice extract is due to its active compound identified as glabridin (3-(2',4'-dihydroxyphenyl)-8-dimethylpyrano[8,7-e]chroman) which also demonstrates the resistance modifying activity against drug resistant mutants *Candida albicans* and *Aspergillus niger*.¹⁷ The *in-vitro* and *in-vivo* anti-malarial activity of 18-β-glycyrrhetic acid an active constituent of *Glycyrrhiza glabra* was also found to be effective.¹⁸

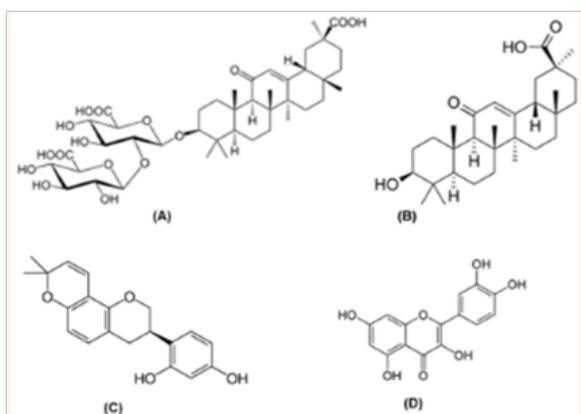


Figure 2 Major secondary metabolites of *Glycyrrhiza glabra* Linn. (A) Glycyrrhizin, (B) Glycyrrhetic acid, (C) Glabridin, and (D) Quercetin.

Researchers have evaluated the cytotoxicity of polyphenol molecule extracted from *Glycyrrhiza glabra* which is used for the treatment of breast and prostate cancer,¹⁹ head and neck cancer cell lines and non-malignant primary mucosal cells,²⁰ and against different cancer cell lines such as Immortal Human Keratinocyte (HaCaT), Lung Adenocarcinoma (A549), and Liver Carcinoma (HepG2) cell lines.²¹ *Glycyrrhiza glabra* possess immunomodulatory effects at 100µg/ml concentration proved by various *in-vitro* studies. It increases fabrication of TCD69N lymphocytes and macrophages from human granulocytes. According to *in-vivo* studies, *Glycyrrhiza glabra* was found to keep the ascent for complexes related to autoimmune disease.

The antihyperlipidemic and antihyperglycemic effects of ethanolic extract of *Glycyrrhiza glabra* against streptozotocin and high fat diet induced diabetic rats has been explored out. Various physical, biochemical and histomorphological parameters were evaluated to study the antihyperlipidemic effects.²² In an independent study, oral dose of 100mg/kg of 18-β-glycyrrhetic acid possess a suitable the anti-hyperglycemic effect in streptozotocin (40mg/kg of body weight) induced diabetic rats that is comparable with glibenclamide.²³

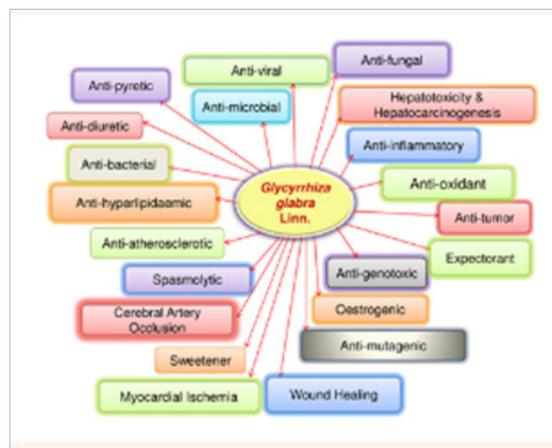


Figure 3 Potential therapeutic activities and traditional uses of *Glycyrrhiza glabra* Linn.

Several studies have been reported for the beneficial effects of *Glycyrrhiza glabra* Linn. in co-morbidities associated with central nervous system. High phenolic content compounds present in *Glycyrrhiza glabra* Linn. is responsible for its strong antioxidant activity due to free radical scavenging, metal ion chelating, hydrogen-donating, anti-lipid peroxidative and reducing activities. Studies have reported that liquorice flavonoids have 100 times strong antioxidant activity when compared with antioxidant activity of vitamin E.²⁴ The aqueous and ethanolic extract of *Glycyrrhiza glabra* also shows dose dependent oxidative scavenging activity and have potential for protective effect against the human lipoprotein oxidative system.²⁵ In this reported study, antioxidant activity of aerial part and root of *Glycyrrhiza glabra* Linn. was also compared. Aqueous and ethanolic extract of roots and bark of *Glycyrrhiza glabra* were evaluated using various *in-vitro* antioxidant assays such as DPPH scavenging activity, total antioxidant activity, Fe³⁺-Fe²⁺ and Cu²⁺-Cu⁺ reducing abilities H₂O₂ and metal chelating activities.²⁶ The *Glycyrrhiza glabra* has shown promising effect as a memory-enhancing agent on learning and memory animal models in rodents.²⁷⁻²⁹ The root extract of *Glycyrrhiza glabra* proved to have an antidepressant and anti-stress activity in rodents. Antidepressant-like effect of liquorice extract might be through the restoration of brain monoamines, like norepinephrine and dopamine levels. Glycyrrhizin, the main constituent of liquorice, showed MAO inhibiting activity.^{30,31} Aqueous extract of *Glycyrrhiza glabra* was also depicted to increase animal resistance to stress and play a role for adaptogenic activity. Researchers investigated the effect of hydro alcoholic extract of *Glycyrrhiza glabra* Linn. on behavioral alteration in mice induced by chronic fatigue stress.³² In an ongoing research from our laboratory, *Glycyrrhiza glabra* extract was found to be beneficial in stress-induced psychopathologies and co-morbidities (*unpublished data*) like other adaptogenic herbal drugs.^{33,34} The anticonvulsant activity of ethanolic extract of roots and rhizomes of *Glycyrrhiza glabra* various dose of extract (10, 30, 100 and 500mg/kg) delayed the onset of convulsions caused by pentyltetrazole and lithium pilocarpine.³⁵ The aqueous extract

of *Glycyrrhiza glabra* promoted the locomotor activity by decreasing the level of brain enzymes such as dopamine & glutamate and decreased AchE activity. Lipid peroxidation was also restored by extract of *Glycyrrhiza glabra*. Thus anti-oxidant and neurotransmitter modulating activity explain the potential cerebroprotective effect of *Glycyrrhiza glabra* in hypoxic rat [36]. Scientists also investigated the antinociceptive activity of aqueous and ethanolic extracts of *Glycyrrhiza glabra* by using different pain models like acetic acid induced abdominal constrictions, formalin induced hyperalgesia and tail flick method in Swiss albino mice. The ability of glycyrrhizin to inhibit inflammatory events, such as oedema, apoptosis, iNOS expression and NFκB, was reported and marked in various studies.^{37,38}

Concluding remarks

This review summarized the distribution, ethnobotany, major secondary metabolites, ethnopharmacology and potential medicinal uses of *Glycyrrhiza glabra*. Furthermore, the clinical efficacy and toxicity studies of *Glycyrrhiza glabra* need to be explored and discussed. As the herbal drug characterization is a major controversial, therefore secondary metabolites must be identified and analytically characterized in the extracts of *Glycyrrhiza glabra*. Since, herbal drugs showed drug-drug and drug-food interactions hence, extracts of *Glycyrrhiza glabra* must be experimentally validated for its drug-food-extract interactions in clinical setup. Moreover, advances in experimental research work along with high-throughput experimentations and DNA microarrays may provide a suitable platform for research and development of drugs from natural products.

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None.

Conflicts of interest

There is no conflict of interest to declare.

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