**Glycyrrhiza glabra - A PLANT FOR THE FUTURE**

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**ABSTRACT**

Objective: A review article on *Glycyrrhiza glabra*, a plant which has lots of medicinal properties. So it may be known as a plant for the future. The present article is an effort to highlight the role of a few major constituents of this plant, which have multifaceted pharmacological actions and could be used as a template for designing new herbal medicines. 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.

Conclusion: *Glycyrrhiza glabra* is an old age plant used in traditional medicine across the globe for its ethnopharmacological value to cure varieties of ailments from simple cough to hepatitis to more complexes like SARS and CANCER. *Glycyrrhiza glabra* is used as a mild laxative, anti-arthritic, anti-inflammatory, anti-biotic, anti-viral, anti-ulcer, anti-tissue, anti-oxidant, anti-diuretic, hypolipidmic agent. It is reported to contain important phytoconstituents such as glycyrrhizin, glycyrrhizic acid, glabrin A&B, triterpene sterols, saponin, and isoflavons.

Key words: *Glycyrrhiza glabra*; pharmacokinetics; glycyrrhizin; anti-oxidant; toxicity; anti-cancer; phytochemistry.

**INTRODUCTION**

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, phenolic compounds [1]. Many of these indigenous medicinal plants are used as spices and food plant. They are also sometimes added to foods meant for pregnant and nursing mothers for medicinal purposes [2, 3]. *Glycyrrhiza glabra* 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. *Glycyrrhiza glabra* belongs to genus *Glycyrrhiza* and is commonly called as licorice which is available in India. A number of traditional healers have claimed the efficacy of *Glycyrrhiza* species for a variety of pathological conditions as a diuretic, choleretic and used as insecticide and indicated in traditional medicine for coughs, colds and painful swellings [4].

**Scientific Classification**

Kingdom: Plantae  
Division: Angiospermae  
Class: Dicotyledoneae  
Order: Rosales  
Family: Leguminosae  
Genus: Glycyrrhiza  
Species: glabra Linn  
Binomial Name: Glycyrrhiza glabra L.
Pharmacy

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Pharmacology [39]

_Glycyrrhiza glabra_ contains the glycoside, glycyrrhizin which has a similar structure and activity as the adrenal steroids. Licorice has an anti-inflammatory activity similar to cortisol 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 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 glycyrrheticin 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 [39].

Biological Activity

The various studies carried out by ethno-botanists, 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:

Anti-tussive & expectorant [40, 41]

The licorice powder and extract was found to be useful for the treatment of sore throat, cough and bronchial catarrh. It is anti-tussive and expectorant loosening and helping to expel congestion in the upper respiratory tract as it accelerates tracheal mucus secretion [40]. The demulcent action is attributed to glycyrrhizin. 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 [41].

Anti-bacterial & Anti-oxidant activity [42]

Hydro-methanolic root extract (crude) of _Glycyrrhiza glabra_ showed presence of many useful secondary metabolites such as; saponins, alkaloids, flavonoids and so on. Because of these components the extract exhibited potent anti-bacterial and anti-oxidant activities. It is able to fight against bacterial infection & scavenging hydroxyl radical. It may be an important drug for prevention of bacterial infection and scavenging of hydroxyl radicals which are generated during carcinogenesis [42].

Anticoagulant [43, 44]

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 Platelet Aggregating Factor (PAF) or Collagen induced agglutination was not affected by glycyrrhizin [43, 44].

Antiviral [45-47]

Glycyrrhizin has a prominent antiviral activity, as it does not allow the virus cell binding. It has been reported as HIV-1, Japanese encephalitis virus and yellow fever virus. Recently antiviral activities of ribavirin, 6-azauridine, pyrazofurin, mycophenolic acid and glycyrrhizin against two clinical isolates of SARS (Severe Acute Respiratory Syndrome) virus (FFM-1 and FMM-2) from patients with SARS, admitted to clinical center of Frankfurt University, Germany were evaluated and 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 [45, 46, 47].

Antulcer [48-49]

Licorice has been used as an antulcer agent since early 1970’s. The extracted glycyrrhizin, Deglycyrrhizinated licorice (DGL) is generally employed for the effective treatment of ulcers. Carbemoxon from licorice roots produce the anti-ulcerogenic effect by inhibiting the secretion of gastrin [48]. Licorice can raise the concentration of prostaglandins in the digestive system that promote mucus secretion from the stomach; it was also reported that licorice prolongs the life span of surface cells in the stomach and has an anti-pepsin effect [49].

Hepato-protective [50-55]

Chronic hepatitis (viral as well as non-viral) is a slowly progressive liver disease that may evolve into cirrhosis with its potential complications of liver failure or hepatocellular carcinoma. Current therapy with the alpha-interferon is directed as viral clearance, but sustained response is only achieved in 20-40% of patients without cirrhosis and is less than 20% in patients with cirrhosis who have greatest need of therapy. In Japan glycyrrhizin has been used for more than 60 years as treatment for chronic hepatitis under the name of Stronger Neo- Minophagen C (SNMC) clinically as an anti-allergic and antihelipase agent [50]. Glycyrrhizin induced a 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 (HBV) surface antigen (HBsAg) [51, 52]. It has been found that glycyrrhetic acid (GA), an aglycone of glycyrrhizin decreases the expression of P450 E1 thereby protecting the liver [53]. GA also prevents the oxidative and hepatic damage caused by aflatoxins by increasing the CYP1A1 and Glutathione-S-transferase (GST) activities and may also contribute to anticarcinogenic activity by metabolic deactivation of the hepatotoxin [54]. 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 [55].

Anti-tumor [56-60]

The aqueous extract or _G. glabra_ inhibits in vivo and in vitro proliferation or Ehrlich ascites tumor cells and inhibits angiogenesis in in vivo assay, peritoneal and choleoarantion metastatic murine assay [56]. Anti-tumoral ethanolic extracts of roots has induced apoptosis and G1 cell cycle arrest in MCF-7 human breast cancer cells [57]. On the other hand, there are many studies about the anti-cancer effects of several derivatives of its components both in in vivo and in vitro studies. Glycyrrhetic acid could also trigger the pro-apoptotic pathway by inducing mitochondrial permeability transition and this property may be useful for inducing apoptosis of tumor cells [58, 59]. Recently licochalcone E, a new retrochalcone from the roots of _G. inflata_, exhibited the most potent cytotoxic effect compared with the known antitumor agents, lichochalcone A and isoliquiritigenin [60].

Anti-diabetic [61]

Type 2 (non-insulin dependent) diabetes mellitus, an insulin resistant syndrome, is a growing health concern in the modern society. Per-oxisome proliferation activated receptors (PPAR’s) and insulin 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 Rozigilazone. Ethyl acetate extract of licorice using GAL-4-PPAR-γ chimera assay, exhibited a significant PPAR-γ binding activity which was attributed to six phenolic compounds, viz. dehydroglyasperin, glycyasperin B, glycyasperin D, glycycoumarin, glycyrrhizin, glycol and isoglycyrol. Pioglitazone and Glycyrin were found to suppress the concentration of prostaglandins in the digestive system that promote mucus secretion from the stomach; it was also reported that licorice prolongs the life span of surface cells in the stomach and has an anti-pepsin effect [49].
the oral sucrose tolerance test. Pioglitazone, a potent PPAR-γ agonist ameliorated the insulin resistance and type-2 diabetes mellitus. Similarly glycinrin also exhibited a potent PPAR-γ ligand binding activity and therefore reduces the blood glucose level in knockout diabetic mice (KK-Ay). 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 [61].

Immmuno-modulator (H1N1 Flue) [62-64]
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 amongst humans. Polysaccharide fractions obtained from Glycyrrhiza glabra stimulate macrophages and hence elevate and assist immune stimulation [62]. N-acetylmuramoyl peptide (MDP) is glycyrrhizin analog having potential in vitro immunostimulating properties [63] also animal studies have revealed its efficacy against the influenza virus that is mediated by stopping the virus replication. Glycyrrhizin acid present in the plant inhibits virus growth and inactivates virus particles [64] is a potential source of immune-modulator.

Side Effects and Toxicity [65-67]
One of the most common reported side effects 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. The phenomenon is known as "pseudo-aldosteronism." In addition to hypertension, patients may experience hypokalemia (potassium loss) 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 [65-66]. Generally the onset and severity of symptoms depend on the dose and duration of licorice intake, as well as individual susceptibility. Patients with delayed gastrointestinal transit time may be more susceptible to these side effects, due to enterohepic cycling and re-absorption of licorice metabolites. The amount of licorice ingested daily by patients with mineral-corticoid excess syndromes appears to vary over a wide range, from as little as 1.5g daily to as much as 250g daily [67].

Future approaches [68, 69]
The vast range of biological effects like anti-inflammatory, anti-allergic, anti-oxidant, anti-viral of the phyto-chemicals present in licorice have been of immense importance in phytotherapy. Thus there is an immense need to modify the natural Glycyrrhiza constituents like glycyrrhizin to reduce these side effects thereby generating the advanced versions of the bioactive compounds to be used as drugs in future. High throughput methods help in generating new variety of a natural product template and generate a library of compound or analogues which could be further screened for a particular activity, safety and toxicology. The screening for a particular activity can be achieved using automated high throughput assay system to arrive to a "lead" molecule suitable for the development into a new drug [68]. Glycyrrhizin, glycyrrhetinic acid, glabridin and isoliquiritigenin hold a strong promise in designing future drugs. Derivatives of these compounds are being generated to evaluate their pharmacological purposes for future drug use. Glycyrrhizin sulfate has been synthesized and investigated for anti-HIV activity in comparison with the parent compound glycyrrhizin. Glycyrrhizin sulfate was found to have nearly four fold of the potential anti-viral activity in MT-4 cells compare to glycyrrhizin in molar terms [69]. Penta-O- cinnamate of glycyrrhizin is the basic structure for the preparation of Niglizin which has a pronounced anti-inflammatory activity combined with antilucuer and hepatoprotective action. There are ample chances of deriving to pharmacophors with least toxic side effects using combinatorial chemistry. The advances in drug discovery with tools like the high throughput system, proteomics, genomics and informatics (Bio/chem. and pharmaco) have further enhanced the evaluation of these newly generated compounds for their future medical applications.

CONCLUSION
Glycyrrhiza glabra (GG) (Licorice, Fabaceae/Papilionaceae) is a plant with a rich ethnobotanical history. The roots are used as a folk medicine both in Europe and eastern countries. The main components are the triterpene saponins, glycyrrhizin and glycyrrhetic acid, which are believed to be partly responsible for anti-ulcer, anti-inflammatory, anti-diuretic, anti-epileptic, anti-allergic and anti-oxidant properties of the plant as well as their ability to ‘fight’ low blood pressure. Furthermore, GG extracts have been shown to possess antidepressant like: memory-enhancing activities and produce anti-thrombotic effects.

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