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Glycyrrhiza glabra- A PLANT FOR THE FUTURE

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ABSTRACT

Objective: A review article on *Glycyrrhiza glabra*, A plant which have lots of medicinal properties. So it may be known as 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* Linn is an old age plant used in traditional medicine across the globe for its ethanopharmacological value to cure varieties of ailments from simple cough to hepatitis to more complexes like SARS and CANCER. *Glycyrrhiza glabra* Linn used as a mild laxative, anti-arthritic, anti-inflammatory, anti-biotic, anti-viral, anti-ulcer, anti-tissive, anti-oxidant, estrogenic, anti-diuretic, hypolipidmic agent. It is reported to contain important phytoconstituents such as glycyrrhizin, glycyrrhizinic acid, glabrin A&B, triterpene sterols, saponin, and isoflavons.

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

INTRODUCTION [1-4]

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 a 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 numbers 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.

Figure 1: Foliage of *Glycyrrhiza glabra*.

Figure 2: Leaves and Pods of *Glycyrrhiza glabra*.

Figure 3: Roots of *Glycyrrhiza glabra.*

Medicinal Parts used

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

Phytochemistry / Bioactive constitutes [5-8]

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 percent of total dry material weight. This complex is composed of triterpene saponin, flavonoids, polysaccharides, pectin's, simple sugars, amino acids, mineral salts, asparagines, bitters, essential oil, fat, female hormone estrogen, gums, mucilage(Rhizome), protein, resins, starches(30%), sterols, volatile oils, tannins, glycosides, and various other substances [5, 6]. Glycyrrhizin, 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 percent 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 [7]. The yellow color of licorice is due to the flavonoid content of the plant, which includes liquiritin, isoliquiritin (a chalcone), and other compounds [8].

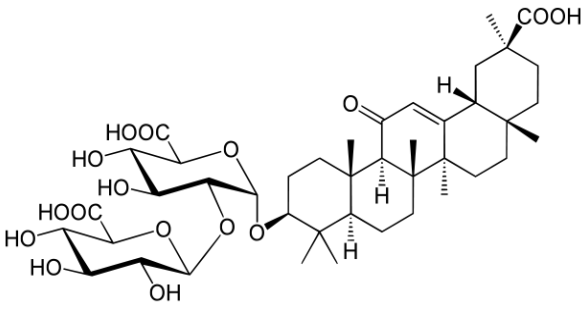

Figure 4: Chemical structure of glycyrrhizin

Quantitative standards [9, 10]

Total ash =Not more than 7%, Acid insoluble ash=Not more than 2%, Sulfated ash= Not more than 10%, Water soluble extractive=Not less than 20%, Diluted alcohol-soluble extract= Not less than 25%, Moisture=5.25%, Ether extracts=16.85%, Albuminoids=37.00% (containing nitrogen5.92%), Soluble carbohydrates=31.00%, Woody fiber=5.05%, Ash=4.80% (containing sand 0.25%).

Traditional Uses [11-18]

Traditionally the plant has been recommended as a prophylaxis for gastric and duodenal ulcers and dyspepsia as an anti-inflammatory agent during allergenic reactions [11]. In folk medicine, it is used as a laxative, emmenagogue, contraceptive, galactagogue, anti-asthmatic drug and antiviral agent [12]. *Glycyrrhiza* roots are used for its demulcent and expectorant property [13]. It is useful in anemia, gout, sore throat, tonsillitis, flatulence, sexual debility, hyperdypsia, fever, coughs, skin diseases, swellings, acidity, leucorrhoea, bleeding, jaundice, hiccough, hoarseness, bronchitis, vitiated conditions of vata dosha, gastralgia etc [14]. It is an important ingredient in medicinal oils for the epilepsy, paralysis, rheumatism, hemorrhagic diseases and also used in the treatment of diarrhea, fever with delirium and anuria [15]. Research shows that on being broken down in the gut, glycyrrhizin exerts an anti-inflammatory action similar to hydrocorticosone and other corticosteroid hormones. It stimulates production of hormones by adrenal glands and reduces the breakdown of steroids by the liver and kidneys. Glycyrrhizin also proved effective in the treatment of chronic hepatitis and liver cirrhosis [16]. For relieving pain, discomfort and other symptoms caused by acrid matter in the stomach, *Glycyrrhiza glabra* is considered as one of the best remedies. It seems to remove the irritating effects of acids in a better way than alkalies [17]. It is used by practitioners of the indigenous systems as tonic, as a demulcent in catarrh of the genitor-urinary passages and as a mild laxative [18].

Pharmaco-kinetic Study [19-22]

After oral administration of *Glycyrrhiza glabra* in humans, the main constituent, glycyrrhizic acid, is hydrolyzed to glycyrrhetic acid by intestinal bacteria possessing a specialized (beta)-glucronidase [19, 20]. Glycyrrhetic acid is 200-1,000 times more potent inhibitor of 11-(beta)-hydroxysteroid dehydrogenase (involved in corticosteroid metabolism) than glycyrrhezic acid; therefore, its pharmacokinetics after oral intake are more relevant. After oral dosing, glycyrrhetic acid is rapidly absorbed and transported via carrier molecules to the liver. In the liver it is metabolized to glucuronoid and sulfate conjugates, which are subsequently rehydrolyzed to glycyrrhetic acid. Glycyrrhetic acid is then reabsorbed, resulting in a significant delay in terminal clearance from plasma [21]. After oral administration of 100mg glycyrrhizin in healthy volunteers, no glycyrrhizin was found in the plasma but glycyrrhetic acid was found at <200mg/ml. In the 24-hours period after oral administration, glycyrrhizin was found in urine, suggesting it is partly absorbed as an intact molecule [22].

Mechanism of action [23-38]

The beneficial effect of *Glycyrrhiza glabra* 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 [23] & C [24,25], herpes zoster [26], HIV[27,28], herpes simplex [29, 30], and CMV [31]. 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 mineral-corticoid and gluco-corticoid activity of glycyrrhizic acid [32]. *Glycyrrhiza glabra* constituents also exhibit steroid-like anti-inflammatory activity, similar to the action of hydrocortisone. This is due, in part, to inhibition of phospolipase A2 activity, an enzyme critical to numerous inflammatory processes [33]. *In vitro* research has also demonstrated glycyrrhizic acid inhibits cycloxygenase activity and prostaglandin formulation as well as indirectly inhibiting platelet aggregation, all factors in the inflammatory process [33, 34]. *Glycyrrhiza glabra* 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 [35, 36]. *In vitro* studies have demonstrated licorice isoflavones, hispaglabridin A & B, inhibit (Fe.sup.3)-induced mitochondrial lipid per-oxidation in rat liver cells. Other research indicates glycyrrhizin lowers lipid peroxide values in animal models of liver injury caused by ischemia reperfusion [37]. *Glycyrrhiza glabra* constituents also exhibit hepatoprotective activity by lowering serum liver enzyme levels and improving tissue pathology in hepatitis patients [38].

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 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 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 [39].

Biological Activity

The various studies carried out by ethno-botanists, phyto-chemists 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, pyraziofurin, mycophenolic acid and glycyrrhizin against two clinical isolates of SARS (Severe Acute Respiratory Syndrome) virus (FFM-1 and FFM-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].

Antiulcer [48-49]

Licorice has been used as an antiulcer agent since early 1970's. The extracted glycyrrhizin, Deglycyrrhizinated licorice (DGL) is generally employed for the effective treatment of ulcers. Carbenoxolon from liquorice roots produce the anti-ulcerogenic effect by inhibiting the secretion of gastrin [48]. 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 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 antihepatitis 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 uppresses hepatitis B virus (HBV) surface antigen (HbsAg) [51, 52]. It has been found that 18β-glycyrrhetinic 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 choreoallantonic membrane assay [56]. Also the ethanol extract of *G. uralensis* root 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. inflate*, 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) 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 Roziglitazone. 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, glyasperin B, glyasperin D, glycycoumarin, glycyrin, glycrol and isolglycyrol. 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 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].

Immuno-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 a virus that is mediated by stopping the virus replication. Glycyrrhizic 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 entroheptic 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 extract have been of immense importance in phytotherapeutic. 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 thrououtput methods help in generating newer version 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 folds 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 antiulcer and hepatoprotective action. There are ample chances of arriving 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 believes 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 antidepssant like: memory-enhancing activities and produce anti-thrombotic effects

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