

PHARMACOLOGICAL STUDIES ON *GLYCYRRHIZA GLABRA*:

A REVIEW

R. K. Harwansh*¹, K. C. Patra¹, S. K. Pareta¹, J. Singh¹, R. Biswas²

¹*SLT Institute of Pharmaceutical Sciences, Guru Ghasidas Vishwavidyalaya, Bilaspur (C.G.) - 495001, India*

²*Department of pharmaceutical Technology, Jadavpur University, Kolkata -700032, West Bengal, India*

Summary

Glycyrrhiza glabra, also known as liquorice and sweetwood, is native to the Mediterranean and certain areas of Asia. Historically, the dried rhizome and root of this plant were used medicinally by the Egyptian, Chinese, Greek, Indian and Roman civilizations as carminative, expectorant and cough remedies. It is now known that glycyrrhizic acid and its aglycone glycyrrhetic acid present in the root extract are responsible for the biological activities. In modern medicine, liquorice extracts are employed as parenteral preparation for Chronic Hepatitis, Ulcer, viral infection and some common diseases. In Japan, it is used as pharmaceutical preparation since, 1960 years. In the present context glycyrrhizin and its derivative is focus on pharmacological studies, against disease viz. HIV syndrome, Hepatitis, H1N1 flue, cancer and diabetes etc.

Keywords: Liquorice, Glycyrrhizin, Leguminosae, Sweetwood, Traditional

*Correspondence

R. K. Harwansh

Assistant Professor

SLT Institute of Pharmaceutical Sciences,

Guru Ghasidas Vishwavidyalaya, Bilaspur- 495009 (C. G.), India

Email : harwanshranjeet@gmail.com

Introduction

Liquorice is the root and rhizome of the *Glycyrrhiza* plant, which belongs to the family Leguminosae. This plant has been recognized worldwide as an important medicinal herb since ancient times [1, 2, 3]. The main taproot, which is harvested for medicinal use, is soft, fibrous, and has a bright yellow interior [4]. *Glycyrrhiza* is derived from the ancient Greek term *glykos*, meaning sweet, and *rhiza*, meaning root. Glycyrrhizin (GZ) Figure 1, a major component of liquorice (*Glycyrrhiza glabra* L.), is used as a remedy for chronic hepatitis, allergies, and other remedies [5]. It has been reported that liquorice is effective in gastric ulcer treatment [6] and glycyrrhetic acid, the aglycone of glycyrrhizin, has an anti-inflammatory and antiulcer effect [7]. Liquorice constituents also exhibit anti-arthritis, anti-arrhythmic, antibacterial, antiviral, expectorant [8] and 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 [9]. *In vitro* research has also demonstrated glycyrrhizic acid inhibits cyclooxygenase activity and prostaglandin formation (specifically prostaglandin E2), as well as indirectly inhibiting platelet aggregation, all factors in the inflammatory process [9,

10]. It is now known that glycyrrhizic acid and its aglycone glycyrrhetic acid present in the root extract are responsible for the biological activities [2, 11]. Now, it is used extensively in the tobacco, food, confectionery, and pharmaceutical industry, throughout the world [12].

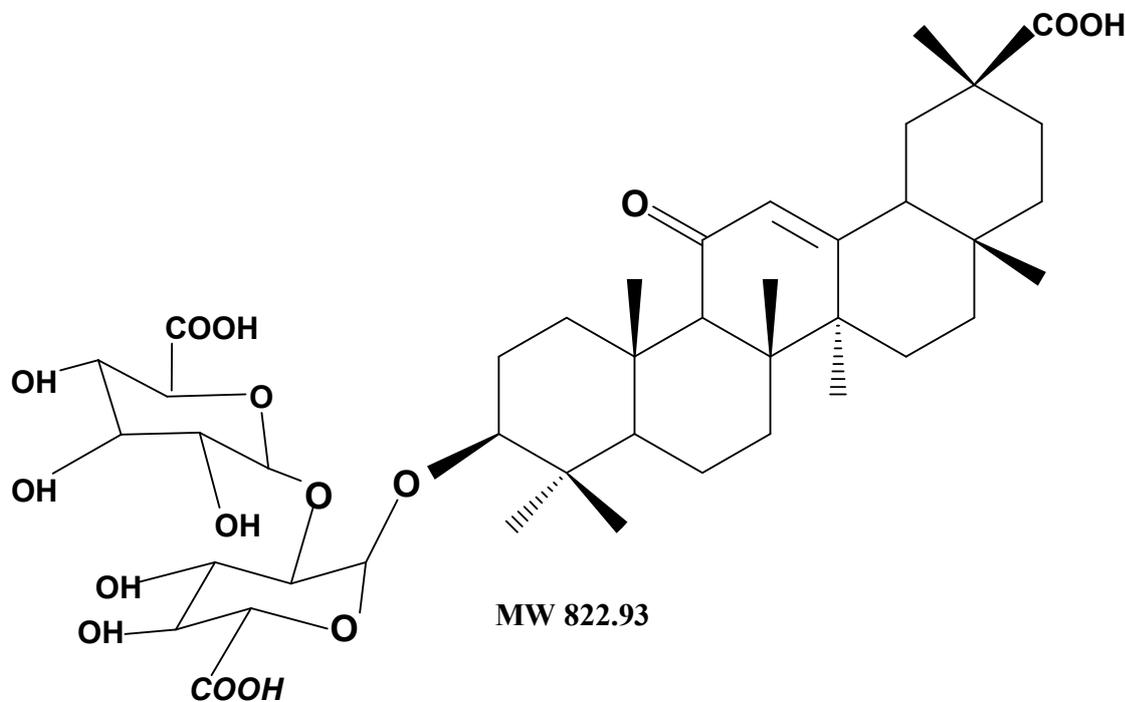


Figure 1- Structure of Glycyrrhizin

Beside these benefit effects, on prolonged use and with higher doses of glycyrrhizin, some side effects may occur such as, mineralocorticoid effects, hypertension, inhibition of the rennin-angiotensin system, hypokalemia, myoglobinuria, lethargy, paraparesis hypertensive encephalopathy, quadriplegia (body paralysis) [8, 13].

Bioactive constituents

The major component in the roots and stolons of *Glycyrrhiza* plants that imparts a sweet flavor glycyrrhizin is an oleanane-type triterpene saponin. This compound represents a mixture of potassium-calcium-magnesium salts of glycyrrhizic acid that varies within a 2-25 percent range. Among the natural saponins, glycyrrhizic acid is a molecule composed of a hydrophilic part, two molecules of glucuronic acid, and a hydrophobic fragment, glycyrrhetic acid [14]. The yellow color of licorice is due to the flavonoid content of the plant, which includes liquiritin, isoliquiritin (a chalcone), and other compounds [15]. The isoflavones glabridin and hispaglabridins A and B have significant antioxidant activity [16] and both glabridin and glabrene possess estrogen-like activity [17].

Pharmacological studies

Traditionally the plant has been recommended as a prophylaxis for gastric and duodenal ulcers and dyspepsia as an anti-inflammatory agent during allergenic reactions [18]. In folk medicine, it is used as a laxative, emmenagogue, contraceptive, galactagogue, anti-asthmatic drug and

antiviral agent [19]. 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:

Antitussive and expectorant

The liquorice powder and extract was found to be useful for the treatment of sore throat, cough and bronchial catarrh. It is antitussive and expectorant loosening and helping to expel congestion in the upper respiratory tract as it accelerates tracheal mucus secretion [20]. 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 [21].

Anticoagulant

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 [22, 23].

Antiulcer

Liquorice 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 [23, 24]. 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 [25].

Antimicrobial

Multi drug 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. A number of components isolated from *Glycyrrhiza* include glabridin, gabrin, glabrol, glabrene, hispaglabridinA, hispaglabridin B; 40-methylglabridin and 3-hydroxyglabrol have exhibited potential *in vitro* antimicrobial activity [26, 27]. Glycyrrhizinic acids have been used as a cure to atopic dermatitis, pruritis and cysts due to parasitic infestations of skin [28, 29].

Antiviral

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 [30, 31, 32].

Antioxidant and Antiinflammatory

Extract of glycyrrhiza has exhibited a marked hepatoprotective action by antioxidant activity of liver against ascorbic acid dependent oxidation of endogenous polyenic lipids in rat liver. 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 mitochondria lipid peroxidation and prevent red blood corpuscles from oxidative hemolysis. Isoflavones like glabridin, hispaglabridin A and 3'-hydroxy-4-O-methylglabridin present in glycyrrhiza were found to have a very potential antioxidant activity NADH dependent peroxidation injury. More recently dehydrostilbene derivatives like α , α -Dihydro-3, 5, 4- trihydroxy-4, 5- diiodopentenylstilbene have been isolated and reported as antioxidant activity [33, 24, 25].

Antidiabetic

Type 2 (non- insulin dependent) diabetes mellitus, an insulin resistant syndrome, is a growing health concern in the modern society. Peroxisome 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 Rosiglitazone. Ethyl acetate extract of liquorice 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, glycy coumarin, glycyrin, glycol 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 knockout diabetic mice (KK- A^y). 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 [34].

Hepatoprotective

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 [35]. 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) [36, 37]. It has been found that 18 β - glycyrrhetic acid (GA), an aglycone of glycyrrhizin decreases the expression of P450 E1 thereby protecting the liver [38]. 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 anti-carcinogenic activity by metabolic deactivation of the hepatotoxin [39]. 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 [40].

Anticancer

G. glabra extract has been used in herbal formulations for combating cancers like PC-SPES, a polyherbal composition used for prostate cancer. The licorice extract induced the Bcl2 phosphorylation and G2/M cycle arrest in tumour cell lines as done by clinically used anti-microtubule agent Paclitaxel. 1-(2,4-dihydroxyphenyl)-3-hydroxy-3-(4'-hydroxyphenyl)propanone (β -hydroxy-DHP) was identified in the licorice extract, which induced Bcl2 phosphorylation in breast and prostate tumour cells, G2/M cell cycle arrest, apoptosis demonstrated by Annexin V and TUNEL assay, decreased cell viability demonstrated by tetrazolium (MTT) assay, and altered microtubule structure⁴⁴. 70% Methanol soluble fraction of licorice acetone extract was found to induce apoptosis in human monocytic leukaemia U937 cells. The compound was identified to be licocoumarone also responsible for antioxidant and antimicrobial activity [41]. Activator protein-1 (AP-1) is a nuclear transcription factor. Blocking of tumour promoter induced AP-1 activity could be used to arrest the induced cellular transformation. It was found that Glycyrrhizin induced AP-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 chemo-protective agents [42].

Immunomodulator (H1N1 Flue)

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 [43]. N-acetylmuramoyl peptide (MDP) is glycyrrhizin analog having potential in vitro immunostimulating properties [44] 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 [45] is a potential source of immunomodulator.

Conclusion

Glycyrrhiza glabra is one of the most important ancient medicinal plant, according to traditional pharmacopeia its therapeutic value has been proved like antitussive, antidiabetic, hepatoprotective, antimicrobial, antiulcer, antiviral, anticancer etc. it indicates that it has diverse biological activity. But further investigation is needed for formulation of new chemical entities (NCE) with novel and controlled drug delivery systems for exploration of novel anticancer, antidiabetic, antiviral (HIV virus, H1N1 flu) agent etc. for effective treatment and management.

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