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Review Article

Pharmaceutics for Effective Drug Dosage

Ethno- Medicinal Properties of Glycyrrhiza Glabra L. (Licorice): A Mini Review

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Abstract: Plants have long been valued for their medicinal properties. The secret to efficient treatment is finding the right herb. The purpose of this review is to provide an updated overview of *Glycyrrhiza glabra* L., "the guardian of herbs" regarding its traditional uses, phytochemistry, and emphasizing the relevance of a few key characteristics of this plant. This review covers a combination of all aspects from an aphrodisiac point of view that were missed by previous articles. This article is presented to include all of the most recent information on its phytochemical and pharmacological effects, which were investigated using a variety of approaches. The plant can be a suitable candidate to manage the long fought erectile dysfunction in men. The extract and the constituents have been found effective in inducing NO signaling pathway that has beneficial effects in initiation and maintenance of erection. It is an age-old plant that belongs to the family Fabaceae. *G. glabra* (Licorice) has been used in folk medicine all over the world for its ethnomedicinal characteristics, and has historically been recognized as a preventative treatment for stomach ulcers, according to pharmacological research. It comprises a wide range of biological actions, including antibacterial, anti-inflammatory, antiviral, antioxidant, as well as others, for which it has been used to treat a variety of disorders ranging from simple cough to hepatitis, as well as more serious conditions like SARS and cancers. This study presents a critical, and thorough assessment of the current understanding of *G. glabra* composition and therapeutic potential. This article concludes that *G. glabra* is actually a potent herb that can cure almost all illnesses.

Keywords : *Glycyrrhiza glabra L.*, Biological activities, Aphrodisiac, Erectile dysfunction, NO signaling

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1. INTRODUCTION

Glycyrrhiza glabra L. is a well-known medicinal herb from the family Fabaceae (Leguminosae). It is a perennial herb. The name "Glycyrrhiza" comes from two Greek words: glykys, which means "sweet," and "rhiza," which means "root." The genus *Glycyrrhiza* has around 30 species worldwide. However, the *glabra* species is exclusively found in Eurasia, Central and South-Western Asia, and the Mediterranean region (Spain, Italy, Turkey, Iran, Iraq), Central Asia, and China's northwest corner.[1,2]. It has tall pinnate leaves with 9–17 leaflets, with purple to pale bluish flowers, and oblong pod-shaped fruits that contain many seeds with stoloniferous roots. It is traditionally the most extensively used herb in Ayurveda, both as a medicine and as a flavoring agent to conceal the unpleasant taste of other medications. This plant's medicinal properties have been known since 500 BC, and it is renowned as the "guardian of herbs."[3] The presence of glycyrrhizin, a bioactive compound of *G. glabra*, makes it 50 times sweeter than sucrose. For its sweetness, it is known by many different local names, such as licorice, sweet wood, mulaithi, yasthimadhu, kanzoh, and ganca. The roots and rhizomes are the crucial attributes of this plant's medicinal value.[4]

1.2. Traditional Uses

Licorice is a versatile medicine, and its compounds have been used to treat throat and bronchial infections for over 2,000 years.[5] The dried rhizome and root of licorice were used as expectorants and carminatives in ancient Egypt, China, Greece, India, and Rome. Traditionally, licorice has been recommended as a prophylactic agent for gastrointestinal ulcers. It is also effective against other ailments such as respiratory problems, epilepsy, fever, sexual disorders, paralysis, rheumatism, leucorrhea, malaria, hemorrhagic diseases, heartburn, paralysis, and jaundice.[5,6] It is also used as a contraceptive, laxative, anti-asthmatic, and antiviral agent. *Glycyrrhiza* roots possess demulcent and purgative properties, making them useful for the treatment of coughs. It can help with anemia, gout, sore throat, tonsillitis, flatulence, sexual debility, hyperplasia, fever, skin disorders, and swellings. It is a mild laxative that helps calm and tones the mucous membranes while also relieving muscle spasms.[7] Licorice extracts have been shown in clinical investigations to be more effective than well-known synthetic substitutes. It is high in flavonoids and is being studied as an antioxidant, cancer preventive, botanical booster, and immunological function booster, including interferon production.[8] Acidity, leucorrhoea, hemorrhage, jaundice, hiccough, hoarseness, bronchitis, vitiated vatadosha disorders, gastralgia, diarrhea, fever with delirium, and anuria are among conditions that licorice can help with.[9] It is a key component of therapeutic oils for rheumatism, hemorrhagic illnesses, epilepsy, and paralysis.[10] According to research conducted over several years, glycyrrhizin breaks down in the gut and has an anti-inflammatory action similar to hydrocortisone and other corticosteroid hormones. It is a great tonic and a demulcent for genitourinary catarrh.[11] It is used in the confectionery and tobacco industries. The root of this plant contains black material. To extract the black material present in licorice, the plant's roots are roasted. After that, the materials are dried and sold. Licorice is also employed as a foaming ingredient in beers and fire extinguishers. The extracts from this plant are used to flavor beer, soft drinks, and pharmaceutical items.[10]

1.3. Phytochemistry

The chemical elements present in the roots of this plant are primarily responsible for its medicinal properties. The phytochemical screening of licorice roots generated a large number of different components. The water-soluble, physiologically active compound makes up 40-50 percent of *G. glabra*'s total dry material weight. Starches (30%), pectins, polysaccharides, simple sugars, gums, mucilage (Rhizome), amino acids, triterpene saponin, flavonoids, mineral salts, bitters, essential oil, fat, asparagines, estrogen, tannins, glycosides, protein, resins, sterols, volatile oils, and various other substances are all found in this complex. [12] Glycyrrhizin and its isomer glycyrrhetinic acid are the main components of G. glabra, accounting for 10–25% of the licorice root extract. . The tribasic acid glycyrrhizin can be converted into a variety of salts.It is present in the form of calcium and potassium salts in licorice root.[7] Licorice extracts are used to make the ammoniated salt of glycyrrhizin. The Food Chemicals Codex has developed the standards for this salt form. This salt is utilized in the food industry as a taste enhancer and flavoring agent. [13-15] Among Asian traditional therapies, glycyrrhizin is the most often used anti-inflammatory agent on neutrophil functions, including ROS (reactive oxygen species) generation. Glycyrrhizin thus finds application as a free radical quencher as well as a lipid peroxidation chain reaction blocker. Glycyrrhizin demonstrated chemopreventive, antioxidant, and antiproliferative effects in an animal model.[16] Flavonoids present in licorice roots include liquirtin, rhamnoliquiritigenin, licopyranocoumarin, glisoflavone, licoarylcoumarin, and coumarin-GU-12.[17] Dry roots yield five novel flavonoids: glucoliquiritinapioside, shinflavanone, shinpterocarpin, prenyllicoflavone A, and 1-methoxyphaseolin.[18] The plant's flavonoid concentration gives licorice its yellow color. Glabridin and hispaglabridins A and B are isoflavones with significant antioxidant properties. Glabridin and glabrene both exhibit estrogen-like properties.[19] It also contains four isoprenoid-substituted phenolic compounds (Isoangustone A, semilicoisoflavone B, licoriphenone, and 1-methoxyficifolinol), as well as kanzonol R (prenylatedisoflavan derivative) and several volatile components (pentanol, tetramethylpyrazine, hexanol, terpinen-4-ol, Propionic acid, benzoic acid, furfuraldehyde, 2,3 butanediol, furfurylformate, maltol, 1-methyl-2-formylpyrrole, trimethylpyrazine).[13,14,20] The HPLC examination of the methanolic extract of licorice revealed the presence of several organic acids such as acetic, propanoic, fumaric, malic, butyric, and tartaric acids. Raw licorice and tea licorice infusions also contain a variety of amino acids, minerals, proteins, lipids, fibre, silica, and carbs.[21]

1.4. Pharmacological Activities

Licorice and its derivative compounds have a wide range of pharmacological properties due to their different modes of action. Glycyrrhiza is a known inhibitor of 11 beta-hydroxysteroid dehydrogenases (11-HSD2) that prevents cortisol inactivation and hence increases mineralocorticoid effectiveness, or pseudohyperaldosteronism...[22] Glycyrrhetinic acid has an inhibitory effect on 11HSD2 even at low serum concentrations, but its binding to the mineralocorticoid receptor takes place later after it has accumulated in the blood. Calo et al.[23] used MNL (mononuclear leukocyte) to look into the inflammatory effects of glycyrrhetinic acid and aldosterone. They

discovered that incubating mononuclear cells with glycyrrhetinic acid boosted the expression of two inflammation indicators, PAI-1 and p22phox and that this effect was reversed when they added canrenone to the mixture (canrenone is an aldosterone antagonist). Elevated water and salt reabsorption over potassium excretion occur as a result of increased mineralocorticoid activity, resulting in high blood pressure and the development of edema.[24] Glycyrrhetinic acid and glycyrrhizin, for example, have been shown to inhibit the proliferation of numerous RNA and DNA viruses, including herpes simplex, herpes zoster, and human immunodeficiency virus. They also affect aldosterone hepatic metabolism and block 5-reductase activity, which is responsible for the symptoms of well-known pseudoaldosterone.[24]

1.4.1. Hepatoprotective Activity

G. glabra is used to treat disorders such as hepatitis B, hepatitis C, liver fibrosis, and cirrhosis.[25] *G. glabra* has been proven in bile duct ligation-induced rats to reduce inflammation, collagen deposition, and hydroxyproline levels, as well as control hepatic fibrous tissue hyperplasia.[26] An aqueous extract of licorice is found effective in reducing cadmium-induced serum transaminases. It also reduces liver cell edema and necrosis.[27]As observed in hepatic mice, experimentally induced plasma ALT is effectively inhibited by flavonoids present in licorice. It might imply that those flavonoids could be used to treat fatty liver disease.[28]

1.4.2. Anti-Inflammatory Activity

Licorice and its phytochemical constituent, glycyrrhetic acid (GA), exert an anti-inflammatory effect through various pathways. GA suppresses glucocorticoid metabolism by inhibiting 11b-HSD (11 beta hydroxysteroid hydroxylase).[29] Because GA is a strong inhibitor of 11b-HSD, it causes a buildup of glucocorticoids with anti-inflammatory properties.[30] When GA or glycyrrhizin is administered orally, the results are confirmed. Because of its powerful anti-inflammatory properties, *G. glabra* is used to treat renal and hepatic disorders.[31] The researchers found that glycyrrhizin inhibits the formation of liver granulomas and the production of inflammatory cytokines. Whereas Wang et al.[32] found that it has anti-inflammatory effects on endometriosis. In the in vitro study, glycyrrhizin inhibits neutrophils from producing reactive oxygen species, which are a potent mediator of tissue inflammation[33,34] Glycyrrhizin has been demonstrated to improve dendritic cell activity, increase allogeneic T cell proliferation and production of IFN-gamma and IL-10, and decrease IL-4 production.[34]

1.4.3. Gastrointestinal Tract Effect

The methanolic extract of the root of *G. glabra* has potent antiulcer effect. The antiulcer effect may be exerted by suppressing the endogenous stomach acid output provoked by acetylcholine and histamine.[35] It has mucosal safeguarding properties because of which secretin could be a potential mediator of licorice's antiulcer effects.[36] In an HCl/ethanol-induced ulcer, the hydroalcoholic extract of *G. glabra* (50-200 mg/kg) was found to have an antiulcerogenic effect that could be linked to an elevation in gastric mucosal defense factors.[37] Liquiritigenin, one of the active components in licorice, was found to have the strongest antispasmodic effect.[38]

1.4.4. Endocrine Gland Effect

For menopausal women, licorice and its extracts are widely accessible as dietary phytoestrogens, as a natural alternative to hormone replacement therapy to relieve menopausal symptoms. In competitive radiometric binding tests, liquiritigenin and ILG exhibit similar affinities to ER, with IC50 values of 7.5 and 7.8 M, respectively. ILG binds to ER with an IC50 of 16 M, whereas liquiritigenin binds to ER with a weak affinity (200 M).[24] However, a study found that licorice-derived components such as liquiritigenin and glyasperin C, shows a more than a 10-fold preference for ERβ.[39] This finding might imply that licorice extract could prove to be beneficial to menopausal women due to moderate estrogenic activity and ERβ selectivity.

1.4.5. Effect on Cardiovascular System

In Chinese medicine, Zhigancao decoction (roasted licorice decoction), which contains licorice, is a traditional and common prescription for practically any type of arrhythmia. In clinic participants with premature ventricular contractions, Zhigancao decoction appears to have beneficial effects on enhancing the total effective rate and treating several ventricular premature beats.[40] Roasted licorice extract prevents ventricular fibrillation, lowers heart rate, and extends the Q-T interval in electrocardiogram data.[41] Strophanthin G, aconitine, digoxin, and calcium chloride have all been shown to cause heart rhythm abnormalities, with roasted licorice injection being able to counteract this.[42] Flavones and triterpenes, which are active components of licorice, have been studied for their ability to protect the cardiovascular system and prevent endothelial dysfunction.[43,44]

1.4.6. Antiviral Activity

Antiviral activity of *G. glabra* extracts has been demonstrated against a number of viruses, including herpes simplex, varicella-zoster, Japanese encephalitis, influenza, and vesicular stomatitis virus.[45] Glycyrrhizin and 18 glycyrrhetinic acids, two triterpenoids, have been found to have antiviral properties in several studies.[45] These compounds can inhibit virus gene expression and replication, diminish HMGB1 binding to DNA, and lower forces of attraction and stress.[45,46] They can also increase host cell activity by limiting the breakdown of the IB enzyme, which is necessary for the amplification of the physiological inflammatory process, increasing T lymphocyte multiplication, and suppressing host cell apoptosis.[45] Nonetheless, Cinatl et al.[47] found that adding these active principles during the adsorption stage is less efficient than adding them after virus adsorption. Glycyrrhizin has strong immune-stimulating properties and causes a synergistic effect with the duck hepatitis virus (DHV) vaccine. Thus, glycyrrhizin treatment, either alone or in combination with the DHV vaccine, may result in immune activation and antiviral activity against DHV.[48] Glycyrrhizin boosts the immune system of mice in the presence of HSV-1 infection.[49] Furthermore, glycyrrhizic acid was found to have a noticeable effect on the Kaposi sarcoma-associated herpesvirus (KSHV). After all other therapies have failed; glycyrrhizic acid was reported efficacious in terminating the persistent infection of KSHV.[7] Almost for 20 years, intravenous glycyrrhizin has been used to relieve severe hepatitis in Japan.[50] It also prevents hepato-cellular carcinoma in chronic hepatitis C patients.[51] Glycyrrhizin can also be administered

intravenously to treat autoimmune hepatitis.[52] Antiviral activities of Ribavirin, 6 – Azauridine, Pyraziofurin, Mycophenolic acid, and glycyrrhizin were recently tested against two clinical isolates of SARS virus (FFM -1 and FFM - 2) from SARS patients admitted to Frankfurt University's clinical center, and it was discovered that glycyrrhizin was effective in controlling viral replication.[47]

1.4.7. Antimicrobial Activity

G. glabra extracts and its constituent compounds possess antimicrobial properties. Secondary metabolites, including saponins, alkaloids, and flavonoids, are responsible for the antibacterial activity.[45,53] Glabridin, Glabrol, Glabrene, Hispaglabridin A, hispaglabridin B, methylglabridin, and 3-hydroxyglabrol, all identified from *G. glabra*, are the active compound having antimicrobial activity.[45] Gupta et al.[54] suggest a decrease in bacterial gene expression, inhibition of bacterial growth, and a reduction in bacterial toxin production with the use of *G. glabra*. Licochalcone E found in *G. glabra* could be employed in the chemical synthesis of new anti-Staphylococcus *aureus* compounds, reducing toxin production in methicillin-resistant *S. aureus* and MRSA.[45] The antibacterial activity of *G. glabra* against *Mycobacterium tuberculosis*, was due to glabridin, , which was reported to be the main component for this activity.[55] Licoisoflavone and licochalcone A were previously found as antitubercular phenolic compounds.[56] Because liquorice extracts are high in liquiritigenin, liquiritin, licochalcone A, and glabridin, *Candida albicans* is vulnerable to them.[57-59] Nonetheless, according to Karahan et al.[60], environmental conditions can influence antibacterial action by affecting chemical component concentrations and biological activity.

1.4.8. Sedative Activity

Anesthetics, neuroleptics, anxiolytics, and anticonvulsant drugs all target GABA receptors since GABA is the most common inhibitory neurotransmitter in the central nervous system.[55] *G. glabra* works as a GABA receptor modulator, causing sedative and anxiolytic effects.[61] GABA responses in acutely isolated dorsal raphe neurons of a rat were used to assess Glabridin. Glabridin potentiated GABA-induced responses by positive regulation of GABA receptors, resulting in sedative and hypnotic effects.[62] Glabridin, which can pass the blood-brain barrier, may also contribute to the hypnotic effect.[55]

1.4.9. Antidepressive Effect

Licorice extract is a useful remedy for depression. Licorice extract has been found in recent research to have antidepressant effects in mice during forced swim tests (FST) and tail suspension tests, TST.[63] In the FST model, mice were forced to swim in a small space and were induced to exhibit a typical immobility behavior. This condition reveals a depressed state. The TST model also causes a state of immobility that is said to mimic human depression. Both models are commonly used to evaluate antidepressant medications. The exact processes through which licorice extract exerted this effect are unknown. The extract may, however, interact with 1 adrenoceptors and dopamine D2 receptors, boosting norepinephrine and dopamine levels in the mice brain.[63]

1.4.10. Neuro-Protective Activity

Alzheimer's disease (AD) is a neurodegenerative disease caused by a genetic mutation that causes amnesia and cognitive impairments such as depression, apathy, and psychosis, all of which are detrimental to daily living.[64]Different Glycyrrhiza species were studied for their clinical effectiveness against neurodegenerative disorders. The study revealed licorice extracts were beneficial against degenerative disorders like tautopathies and Alzheimer's disease. This property is expected because of the antioxidant property of licorice.[65] 1-methyl-4-phenylpyridinium, a neurotoxic substance that interferes with mitochondrial oxidative phosphorylation, causes ROS generation, cytotoxicity, and glutathione downregulation (GSH), a critical component of the brain's antioxidative system, which is inhibited by glycyrrhizin and *G. inflata* extract.[66,67] Increased oxidative stress in dementia is mostly caused by decreasing GSH levels.[68] Isoliquiritigenin's influence on mitochondrial activity may be linked to the effect of glycyrrhiza extract on oxidative stress.[69]

1.4.11. Anti-Cancer Activity

Licorice extract is utilized in herbal formulations to treat malignancies such as prostate cancer. In tumor cell lines, this extract triggered Bcl2 phosphorylation and cell cycle arrest, similar to the therapeutically utilized anti-microtubule drug paclitaxel.[70] It was also discovered to trigger apoptosis in human monoblastic leukemia U937 cells. Lico coumarone , a chemical with antioxidant and antibacterial properties, was found.[71] The transcription factor Activator Protein 1 (AP1) is present in the nucleus. Blocking AP-1 activity caused by the tumor promoter could be employed to stop the induced cellular transformation. Inhibited TPA induced AP-1 activity in TPA treated cells, but glycyrrhizin induced AP1 activity in untreated cells.[72] This mechanism could be used as a paradigm for the creation of new cancer-fighting chemoprotective agents.

1.4.12. Aphrodisiac Activity

Aphrodisiac property of G. glabra is worth mentioning. This plant extract has been shown to be effective in treating male sexual problems. The spray-dried amorphous solid dispersion of tadalafil using glycyrrhizin was assessed for its efficacy towards male rats and found a significantly improved aphrodisiac activity of tadalafil. Sexual behavior was found to be increased compared to the control counterpart. Tadalafil, which is insoluble in water, was found to be significantly soluble using this technique.[73] There are also observations that *G. glabra* aqueous extract could significantly enhance mount frequency and intromission frequency in male rats. The extract could reduce mount latency and intromission latency.[74]

1.4.13. Expectorant Activity

The use of liquorice powder and extract to treat sore throats, coughs, and bronchial catarrh was found to be effective. The ethanolic extract of *G. glabra* has been shown to be an effective candidate for the treatment of cough. The experiment was carried out in albino mice by experimentally inducing cough using sulphur dioxide gas.[75]

2. CONCLUSION

The medicinal properties of *Glycyrrhiza glabra*, as well as the phytochemical substances derived from the plant, are discussed in this paper. Glycyrrhizic acid, 18-glycyrrhetinic acid, glycyrrhizin, and licochalcones are the main chemicals found in *G. glabra* preparations. This plant species is known for antibacterial, antiviral, antitussive, immunostimulant, antioxidant, anti-inflammatory, and anticancer activities. They also possess anti-inflammatory, and antispasmodic properties. Apart from these properties, *G. glabra* is well established as natural aphrodisiac. Consumption of the dried roots, extract, or the constituent compounds of this plant could escalate sexual wellness. Comsumption of this plant could also help cure cough. More research is needed into the mechanisms of action of extracts and compounds, as well as the evaluation of effective doses, interactions, and side effects.

3. AUTHORS CONTRIBUTION STATEMENT

Queen Saikia gathered the data and wrote the manuscript, Ajit Hazarika and Jogen C kalita aided in writing, conceptualized and reviewed the manuscript. All authors contributed to the final manuscript.

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5. CONFLICT OF INTEREST

Conflict of interest declared none.

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