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Review Article

Glycyrrhiza Glabra [Liquorice] from Botany to Phytochemistry and Pharmacological Insights

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ABSTRACT

Liquorice (Glycyrrhiza glabra) is a perennial herb belonging to the Fabaceae family and is recognized as one of the most widely studied medicinal plants. It holds significant value in traditional systems of medicine as well as in culinary use. The roots and rhizomes are primarily utilized for their healing properties and natural sweetness in various herbal formulations. Historical records from Ayurveda, Traditional Chinese Medicine, Unani, and ancient Greek systems highlight its long-standing use in treating respiratory and digestive disorders. From a pharmacological perspective, liquorice demonstrates a wide range of therapeutic effects. It has been applied in the treatment of liver disorders, allergic conditions, eczema, cardiovascular abnormalities, gastric and peptic ulcers, respiratory ailments, inflammatory joint diseases, kidney issues, low blood pressure, and microbial infections. These diverse therapeutic roles are attributed to its rich phytochemical composition. Phytochemical investigations have revealed the presence of triterpenoid saponins, flavonoids, isoflavonoids, and chalcones as major active constituents. Among these, glycyrrhizic acid (glycyrrhizin) is considered the principal bioactive compound, known for its potent anti-inflammatory, antiviral, and hepatoprotective activities. Flavonoids and is flavonoids are responsible for antioxidant and anti-inflammatory actions, whereas chalcones exhibit antimicrobial and anticancer properties. Recent pharmacological studies emphasize the hepatoprotective, anti-inflammatory, anti-ulcer, antidiabetic, immunomodulatory, laxative, and antidepressant activities of liquorice. In addition, new findings indicate its potential in promoting hair growth, regulating lipid metabolism, aiding weight management, improving mood, and supporting cardiovascular health through anticoagulant and circulatory mechanisms. Overall, Glycyrrhiza glabra remains a versatile medicinal herb that effectively connects traditional knowledge with modern pharmacological science. With glycyrrhizic acid as its core active molecule, supported by various

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phytoconstituents, liquorice continues to gain scientific relevance in the development of evidence-based therapeutic applications.

INTRODUCTION

Licorice roots are usually long, cylindrical, and fibrous, with a wrinkled appearance, growing horizontally beneath the surface [1]. Lately, researchers have been diving into plants that indigenous healers and herbalists have traditionally used to boost liver function and tackle liver-related issues [2]. This study is all about creating an ex situ collection of Glycyrrhiza glabra, using plant material sourced from Bulgarian populations, and assessing the key traits of these cultivated plants to see if they could serve as a viable source for establishing plantations [3]. Among the various populations examined, the one located near the village of Beltsov stood out with the highest glycyrrhizin content [4]. In-depth chemical analyses have revealed that the underground parts of Glycyrrhiza species not only contain glycyrrhizin, a type of triterpene saponin, but also a range of flavonoids, including unique compounds like glabridin that are specific to certain species [5].Since ancient times, people have turned to plants not just for food and shelter, but also for their healing properties. Long before modern pharmaceuticals and technological advancements came into play, traditional societies relied heavily on herbal remedies for their healthcare needs [6]. The exploration of plant biochemistry and their natural compounds has been crucial for centuries and continues to be a key area of global research. The name Glycyrrhiza comes from Greek, meaning “sweet root,”[7] which perfectly captures its distinct flavor. Medicinal plants have always been vital in healthcare, with Glycyrrhiza glabra, part of the Fabaceae (Leguminosae) family, being a standout example. Other related species are also commonly utilized in the food and livestock sectors.[8] Over the years, many drugs have been derived from natural substances found in these medicinal plants. One traditional system, Ayurveda, began in India and is still widely practiced in many developing countries because of its accessibility, affordability, therapeutic benefits, and low side effects.[9] G. glabra is a key component in Ayurvedic remedies[10] and thrives across Asia and Southern Europe.[11] Historical records indicate that liquorice may have first appeared in Iraq,[12] and today, various Glycyrrhiza species are commercially grown in countries like Italy, France, Spain, Greece, Turkey, Turkmenistan, Uzbekistan, Syria, Afghanistan, Azerbaijan, and China. [13]Ancient scholars such as Theophrastus and Dioscorides acknowledged liquorice for its healing properties and categorized it as a medicinal herb. In contemporary cosmetics,[14] G. glabra is often used as a skin-lightening [15] ingredient in topical products, and its dried root has traditionally been used as a natural tooth cleaner.[16] Did you know that tea made from its root is celebrated for its refreshing qualities?[17] Botanically speaking, G. glabra features pinnate leaves that measure between 7 to 15 cm long, each adorned with 9 to 17 leaflets.[18] Its delicate flowers bloom in axillary spikes, showcasing short, bell-shaped calyces that come in shades from pale white-blue to purple.[19] The root system is quite fascinating, consisting of a soft, fibrous taproot with a vibrant yellow core that branches out into secondary roots, which then develop into horizontal woody stolons. These secondary roots are roughly 1.25 cm in diameter, while the main root is notably thick, flaunting reddish or lemon-colored outer layers and a pale yellow interior. The bark of both the roots and rhizomes can range from brownish-green to dark brown.[20,21]On the phytochemical side, liquorice is packed with triterpenoids, saponins, tannins, phenols, flavonoids, and alkaloids, all of which contribute to its wide array of physiological

benefits.[22] For nearly four centuries, Glycyrrhiza root has been cherished for both its medicinal properties and its role as a flavoring agent. Its extracts are commonly used to enhance the flavors of baked goods, ice cream, chewing gum, candies, and soft drinks.[23] Beyond its culinary and medicinal applications, Glycyrrhiza also plays a role in biomass production, bioenergy, and pulp manufacturing.[24] Its continued use in Ayurvedic medicine underscores its lasting therapeutic importance.[25].

Scientific Studies

Liquorice is typically sourced from the dried roots of Glycyrrhiza glabra, which naturally contain between 2% and 9% glycyrrhizin—a sweet saponin celebrated for its medicinal benefits. In a clinical trial with forty-two HIV-1 positive patients who also had hemophilia, researchers noted improvements in immune function, liver health, and symptoms like oral candidiasis, lymphadenopathy, and skin rashes.[26] Back in the late 1940s, Dutch physician Revers discovered that glycyrrhizin and its metabolite, glycyrrhetinic acid (GA), played crucial roles in healing ulcers, with GA also demonstrating localized anti-inflammatory properties. Compounds like glycyrrhizin, CB, and deglycyrrhizinated liquorice (DGL) are known for their anti-ulcer effects, primarily by inhibiting gastrin secretion. DGL is a modified version of liquorice where glycyrrhizin is removed to minimize side effects.[27] It's often used in treating peptic ulcers alongside antacids and comes in various forms, such as wafers, capsules, liquids, and lozenges.[28] The wide-ranging pharmacological effects of liquorice and its derivatives stem from unique biochemical processes. [29]For example, glycyrrhetinic acid can inhibit 11β-HSD2 even at low serum levels, while its interaction with mineralocorticoid receptors happens more gradually, allowing it to stay active in the bloodstream.[30].

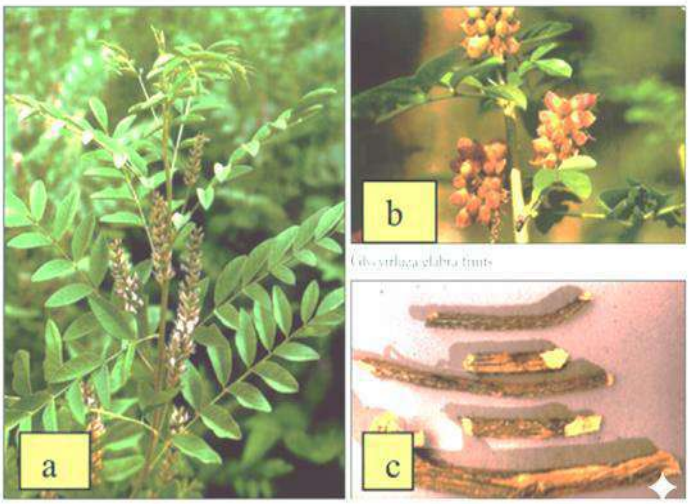

Figure 1: [A] Glycyrrhiza glabra (B) flowers (C) Roots [1]

Traditional Uses

Traditional Ayurvedic texts highlight the diverse therapeutic benefits of Glycyrrhiza glabra, commonly known as Yashtimadhu, which is often used in combination with other natural ingredients. For treating anemia, a mix of madhuka powder or its decoction blended with honey was frequently recommended. To boost lactation, Yashtimadhu was taken with cow's milk. In cases of heavy menstrual bleeding, a combination of 10 grams each of madhuka powder and sugar, crushed in

rice water, was advised. For vocal hoarseness, a sweet treat made from rice milk and infused with Yashtimadhu was suggested. Charaka described a tonic that stimulates the brain and acts as an aphrodisiac, consisting of 10 grams of madhuka powder mixed with honey and followed by milk. He also recommended a heart-strengthening formulation that combined liquorice with Picrorhiza kurroa paste dissolved in sugar water, and for cases of vomiting blood, a powdered mix of Yashtimadhu and Santalum album blended with milk was proposed. Sushruta, another prominent figure in Ayurveda, suggested a 10-gram paste of Yashtimadhu to help manage internal bleeding. Additionally, a paste made from liquorice and Sesamum indicum was recommended as a treatment for edema.[31]

Recent Advancements

The authors highlighted the difficulties in assessing complex molecular mixtures like liquorice. They pointed out that the therapeutic benefits of plant extracts usually come from the combined and simultaneous effects of various components, rather than just the action of individual compounds [32]. Research using animal models has demonstrated that Glycyrrhiza uralensis and Sophora flavescens can help ease bronchoconstriction and restore cytokine balance [33]. Liquorice stands out not only for its health benefits but also for its role in sweets, making it a valuable ingredient in the market. However, overindulging in liquorice or its active compounds can sometimes lead to acquired mineralocorticoid excess (AME) syndrome [34]. This plant is known for its wide array of healing properties and is thought to be helpful for a variety of health issues, including respiratory, liver, and heart conditions. Liquorice root is often suggested as a dietary supplement for problems like digestive issues, menopausal symptoms, coughs, and certain bacterial and viral infections [35].

Figure 2: Liquorice extract

Applications

Covid 19: When it comes to COVID-19, licorice shows promise with its anti-inflammatory properties, as it can inhibit pro-inflammatory cytokines and other inflammation mediators. It also interacts with MAPK-related signaling

pathways and boosts immune function during COVID-19 treatment. These actions suggest that licorice might help reduce inflammation and lower the chances of severe immune responses, like cytokine storm syndrome [36].

Dentistry: In the realm of dentistry, a supercritical extract of Chinese licorice (Glycyrrhiza uralensis), along with its key isoflavans, Licoricidin and Licorisoflavan A, has demonstrated the ability to inhibit the growth of P. gingivalis, cut down on the production of volatile sulfur compounds (VSCs), and reduce protease activity. This indicates that licorice could have some real benefits for oral health [37].

Poultry feed: As for poultry, adding licorice extract (LE) to their drinking water at concentrations up to 0.4 g/L has been shown to boost feed intake, enhance immune responses, and improve antioxidant status and lipid profiles. However, more research is needed to fully understand the benefits and potential applications of licorice as a feed supplement for poultry [38].

Eye drops: Glycyrrhizin has shown some promising protective effects against keratitis caused by Pseudomonas aeruginosa [28]. A small clinical pilot study found that 2.5% glycyrrhizin eye drops were generally well tolerated by participants. Moreover, researchers developed a dipotassium glycyrrhizinate (DG)-based nanomicelle ophthalmic solution that encapsulates thymol (DG-THY) using a straightforward thin-film dispersion technique [39].

Cosmetics: Glycyrrhetinic acid (GA) and licorice root extract, with GA being the main component, have proven effective in treating conditions like atopic dermatitis, itching, and acne vulgaris [40]. This extract is commonly found in both pharmaceutical and cosmetic products due to its soothing properties, ability to reduce redness, and gentle effects on the skin [41]. Additionally, GA acts as a tyrosinase inhibitor, helping to diminish UVB-induced pigmentation and redness when applied topically at a concentration of 0.5%.[42] Its skin-lightening benefits make it a sought-after ingredient in whitening cosmetic formulations [43].

Mechanism Of Actions

Antimalarial: Glycyrrhizin (GLR) and its metabolites show their antimalarial properties through two main mechanisms. First, they create a membrane effect that disrupts lipid rafts and sequesters cholesterol. Second, they form stable complexes with HMGB1 proteins, which include both human and Plasmodium HMGB1, enhancing their therapeutic effects [44].

Antiviral: Various in vitro studies have shown that glycyrrhizic acid (GC) can inhibit HCV by reducing the release of infectious viral particles [45]. It also suppresses HSV (herpes simplex virus) by decreasing cellular adhesion, inhibits the influenza virus by limiting HMGB1's binding to DNA, and disrupts interactions between viral macromolecules and host proteins. Additionally, it prevents HIV replication and helps mitigate H5N1 infection—not by directly disrupting viral replication, but by modulating the proinflammatory gene expression triggered by H5N1 [46].

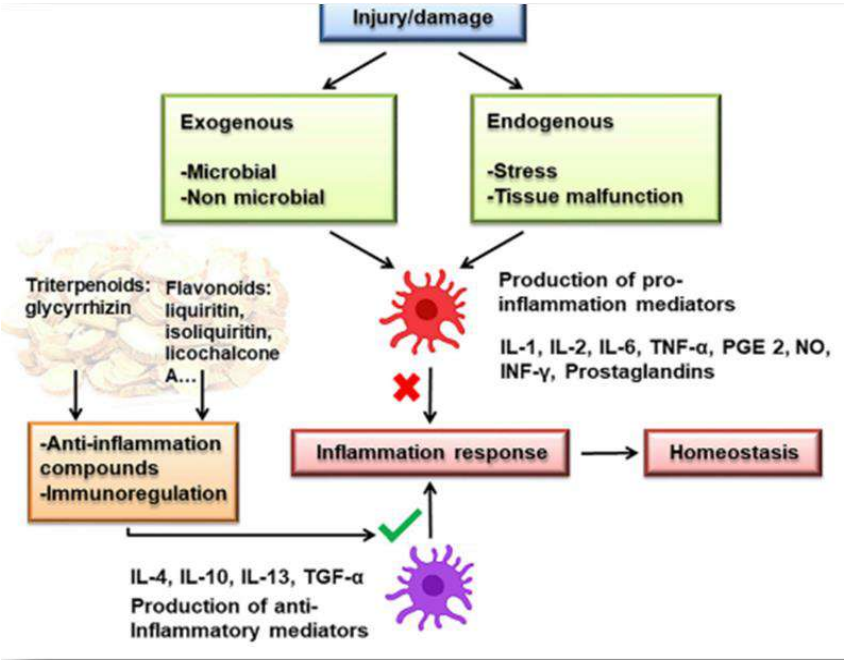

Figure 3: Ant inflammatory action of liquorice [2]

Anti-inflammatory: The monoamine 5-hydroxytryptophan (5-HT or serotonin) is crucial in regulating inflammation. When cells encounter environmental triggers, they release 5-HT into the bloodstream, which increases vascular permeability and promotes inflammation [47]. Tryptophanamide, a substrate of tryptophan aminopeptidase, is enzymatically converted into L-tryptophan, which is then transformed into 5-HT through tryptophan hydroxylase. Research has indicated that licorice flavonoids can lower tryptophanamide levels, which in turn decreases 5-HT production and indirectly reduces PGE2 levels, helping to alleviate inflammation [48].

Antidiabetic: Glycyrrhizin has been found to lower TNFα levels in retinal endothelial cells (REC) that are grown in high-glucose conditions [49]. This suggests it might help protect the diabetic retina by reducing inflammation. Moreover, when glycyrrhizin was given systemically through drinking water, it significantly decreased HMGB1 levels at both the two-month and six-month marks [50]. This further emphasizes its potential in alleviating complications related to diabetes.

Pharmacological Action

Antitusssive: Licorice extract and powder have shown promise in easing bronchial irritation, cough, and throat discomfort by boosting mucus secretion in the trachea [51]. One of the key components, liquiritinapioside, has been found to help suppress coughing triggered by capsaicin exposure [52].

On the anticoagulant front: glycyrrhizin, a well-known anti-inflammatory compound, has recently been recognized as the first plant-derived thrombin inhibitor. It has been demonstrated to extend both thrombin and fibrinogen clotting times and delay plasma recalcification. Glycyrrhizin specifically inhibits platelet aggregation induced by thrombin, while aggregation caused by platelet-activating factor (PAF) or collagen remains unaffected [53,54]. Studies involving populations suggest that the risk of major bleeding is lower when combining Chinese herbal medicines (CHMs) with anticoagulants compared to using

anticoagulants alone [55]. When administered intravenously, glycyrrhizin (GL) led to a dose-dependent reduction in thrombus formation in a venous thrombosis model, with a dose of 180 mg/kg body weight resulting in a remarkable 93% decrease in thrombus mass [56].

Antioxidative Activity: Compounds found in Glycyrrhiza show impressive antioxidant properties.[57] For instance, glabridin, an isoflavone derivative from Glycyrrhiza glabra, has been shown to reduce lipid peroxidation in rat liver microsomes and safeguard mitochondrial integrity from oxidative harm. Moreover, glabridin has exhibited robust antioxidant effects against the oxidation of low-density lipoprotein (LDL) in both laboratory and live studies.[58]

Anticancer Activity: The ethanol extract from Chinese licorice root (Glycyrrhiza uralensis) has been studied for its estrogen-like effects and its ability to curb cell growth in the MCF-7 human breast cancer cell line. [59]. These findings suggest that the extract not only mimics estrogen but also has anticancer properties. Additionally, using licorice (Glycyrrhiza species) in patients with hepatitis C has been associated with a protective effect against liver cancer and shows promise in treating stomach cancer.[60]

Table: Pharmacological Actions of Licorice

Pharmacological Action	Mechanism of Action	Dose	Description/Reference
Antitussive and Expectorant	Promotes mucus secretion in trachea via glycyrrhizin; Liquiritinapioside suppresses capsaicin-induced cough.	Not specified	Licorice extract relieves cough, throat discomfort, and bronchial irritation. [51,52]
Anticoagulant Activity	Glycyrrhizin inhibits thrombin, prolongs clotting times, delays plasma recalcification, and suppresses thrombin-induced platelet aggregation.	180 mg/kg (i.v. in animal model)	93% reduction in thrombus mass in venous thrombosis model; inhibited thrombus formation in arteriovenous shunt. [53,54,56]
Antioxidative Activity	Isoflavone derivatives like glabridin inhibit lipid peroxidation, protect mitochondria, and prevent LDL oxidation.	Not specified	Glabridin shows strong antioxidant properties in vitro and in vivo. [57,58]
Anticancer	Ethanolic extract of G. uralensis shows estrogen-like activity and inhibits proliferation of MCF-7 cells; liver and stomach	Not specified	Licorice extract inhibits breast cancer cell growth, prevents liver cancer in hepatitis C patients, and shows stomach cancer potential. [59,60]

Toxicological Study

Licorice and its main active ingredient, glycyrrhizin, can have some pretty serious side effects that fall into a few different categories: general toxicity, potential for mutagenic and genotoxic effects, cancer risk, developmental toxicity, cytotoxic reactions, reported side effects, and interactions with medications.[61] To assess skin toxicity, researchers applied glycyrrhetinic acid at a concentration of 100 mg/mL (about 0.5 cc) directly onto both healthy and damaged skin on

the backs of rabbits, following the method outlined by Eaton and Gilbert in 2013.[62] In another experiment, mice were given 0.4% ammoniated glycyrrhizin in their drinking water for four days before being subjected to prolonged cold stress (8 hours at 5 °C).[63] The mice that received the treatment had shorter survival times compared to those that didn't.[64] Likewise, rats that were given the same concentration for a week showed increased sensitivity during a 48-hour fasting period, leading to significant hypoglycemia.[65] Additionally, sub-acute administration of Glycyrrhiza glabra and its glycyrrhizin derivatives has been shown to suppress adrenal-pituitary axis activity and lower liver iron levels.[66] Hypokalemia caused by licorice has been associated with a higher risk of digoxin toxicity, as low potassium levels can amplify the drug's harmful effects on the heart. Natural killer (NK) cells, which are essential for eliminating virus-infected cells, are usually activated by immune signals like interferon-γ and interleukin-2. However, clinical studies suggest that regular consumption of glycyrrhizin can lead to a condition known as pseudohypercorticosteroidism, which mimics the effects of having too much corticosteroid in the body.[67]In a study, administering licorice extract at a dose of 2.5 g/kg/day was found to slightly inhibit body weight gain in experimental animals [68]. Researchers have also looked into the cytoprotective properties of Glycyrrhiza glabra root extract (GRE) against both apoptotic and non-apoptotic cell death triggered by cadmium (Cd) exposure [69]. Notably, among its components, liquiritigenin showed a more significant protective effect against the heightened cytotoxicity resulting from the combined exposure to cadmium and sulfhydryl depletion, compared to the effects of cadmium toxicity on its own [70].

Major Challenges

The quality of medicinal herbs, like licorice, often suffers because of a lack of genuine plants, the economic downsides of careless farming practices, and outdated testing methods.[71] These issues really hold back the growth of the herbal industry. Research shows that cultivating licorice could bring significant ecological, economic, and social benefits to Uzbekistan.[72] Given the country's environmental hurdles—such as the drought of the Aral Sea, soil salinity, climate change, sandstorms, and water shortages—licorice farming is crucial for alleviating these ecological pressures.[73] This resilient plant has a deep root system that can reach up to 17 meters, making it especially useful for reclaiming and managing saline soils. However, many of its mechanisms for tolerating stress are still not well understood, which points to the need for more research. Some studies even suggest that the reduction of soil salinity might be connected to licorice roots' ability to absorb salts while producing glycyrrhizic acid, which helps in soil remediation.[74]

Therapeutic Benefits

Licorice and Its Health Benefits: Licorice is packed with secondary metabolites that offer a range of health perks.[75] The compounds found in licorice roots have been linked to helping treat conditions like cancer, tuberculosis, atherosclerosis, gastric ulcers, immunodeficiency, hepatitis, and bacterial infections. Lately, there's been a surge of interest in how it can help manage oral health issues.[76] Plus, licorice has a long history of being used for ailments such as epilepsy, fever, sexual debility, rheumatism, paralysis, psoriasis, and jaundice. Licorice showcases a variety of pharmacological effects.[77] It works as a monoamine oxidase inhibitor and has anticholinergic, antitussive, hypolipidemic, antifungal, antioxidant, and anticancer properties. Traditionally, it's also been used for its anti-

inflammatory, anti-ulcer, antibiotic, anti-arthritic, antiviral, laxative, and memory-boosting effects.[78] In Traditional Chinese Medicine, licorice is seen as a "guiding medicine" that helps with respiratory issues, viral coughs, viral hepatitis, and more, appearing in over half of both traditional and modern prescriptions.[79] When it comes to oral health, licorice plays a role in keeping teeth, gums, and oral tissues healthy, and it can help tackle common dental problems like cavities, gum disease, bad breath, oral thrush, and recurring mouth ulcers. However, overindulging in licorice-flavored sweets or dark foods might lead to temporary staining of the teeth and tongue, especially if you also smoke.

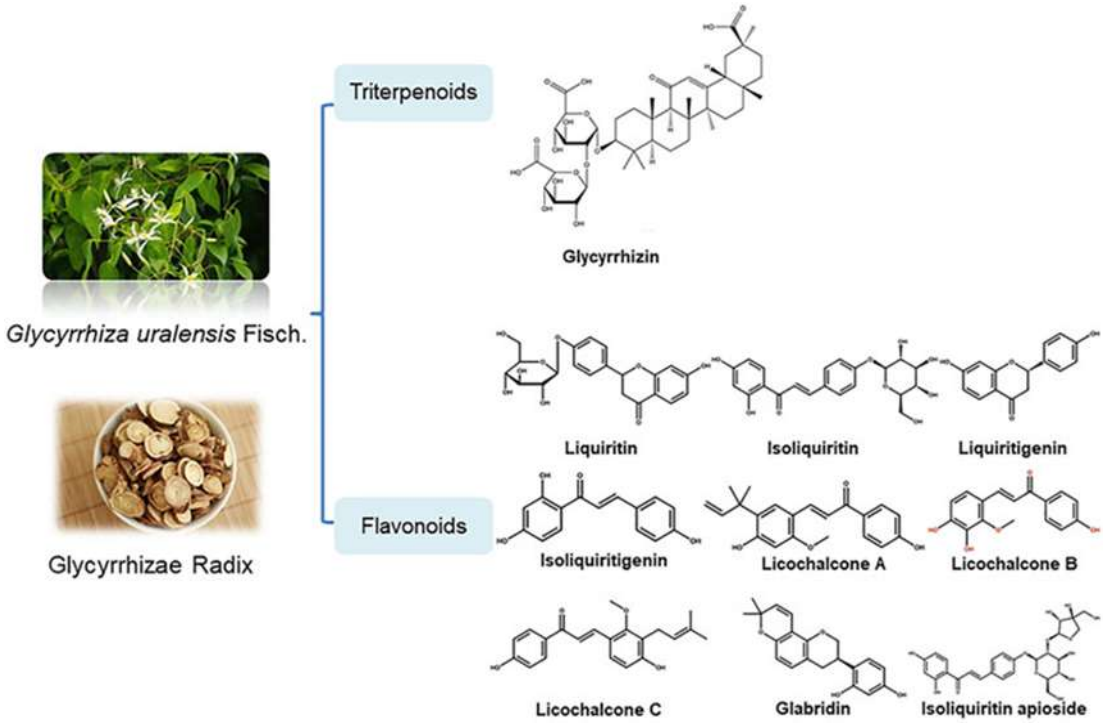

Figure 4: Chemistry of liquorice

Table 2: Phytochemical Screening Tests of liquorice

Phytochemical	Test	Observation	Inference
Alkaloids	Mayer's Test	Cream or white precipitate	Presence of alkaloids
Alkaloids	Dragendorff's Test	Orange brown precipitate	Presence of alkaloids
Alkaloids	Wagner's Test	Reddish-brown precipitate	Presence of alkaloids
Carbohydrates	Molisch's Test	Violet ring at junction	Presence of carbohydrates
Glycosides	Keller–Killiani Test	Reddish-brown ring at junction	Presence of glycosides
Saponins	Foam Test	Formation of stable foam	Presence of saponins
Tannins	Ferric Chloride Test	Blue-black or green color	Presence of tannins

Flavonoids	Lead Acetate Test	Yellow precipitate	Presence of flavonoids
Steroids	Salkowski Test	Reddish-brown color at interface	Presence of steroids
Terpenoids	Libermann–Burchard Test	Deep green color	Presence of terpenoids

DISCUSSION

The roots of different Glycyrrhiza species, like G. glabra var. typica, G. glabra var. glandulifera, and G. uralensis, are cherished not just as traditional herbal remedies but also as popular natural sweeteners and flavor enhancers in cooking and medicine [81]. If you consume licorice root in amounts over 3 grams a day for more than six weeks, or take glycyrrhizin in doses higher than 100 mg daily, you might face some negative side effects, such as water retention, high blood pressure, and low potassium levels [82]. In clinical studies involving HIV patients, a special intravenous formulation called Stronger Neo-Minophagen C (SNMC) has been used, which includes 0.2% glycyrrhizin, 0.1% cysteine, and 2.0% glycine mixed in physiological saline [83]. Moreover, the ethanolic extract from licorice leaves showed the strongest ability to inhibit Gram-positive bacteria [84]. However, taking it for a long time at higher doses can lead to issues like high blood pressure, low potassium, and symptoms that mimic excess mineralocorticoids, thanks to the aldosterone-like effects of glycyrrhetinic acid [85].

RESULT

Research on Glycyrrhiza glabra highlights its remarkable medicinal properties, thanks to bioactive compounds like glycyrrhizin, flavonoids, saponins, and isoflavonoids. Pharmacological studies have shown a variety of benefits, including anti-inflammatory, antitussive, antioxidant, anticoagulant, and anticancer effects. Experimental models also reveal its potential in treating ulcers, respiratory issues, microbial infections, and immune-related disorders. However, it's important to note that toxicological studies suggest that long-term or excessive use can lead to negative effects such as hypertension, low potassium levels, and pseudohyperaldosteronism. So, while licorice shows great promise in both pharmacological and nutraceutical fields, it's crucial to regulate doses carefully to ensure safe clinical use.

CONCLUSION

Liquorice is an important therapeutic herb with extensive applications in both traditional and modern medicine. Its rich phytochemical profile underpins a variety of pharmacological actions, making it effective in managing gastrointestinal, respiratory, cardiovascular, and dermatological disorders. However, the potential for toxicity from prolonged or high-dose consumption underscores the importance of controlled dosing and careful clinical monitoring. Future research should prioritize the development of standardized formulations and the exploration of novel drug delivery systems to enhance therapeutic efficacy while minimizing adverse effects.

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