

Therapeutic and Pharmacological Efficacy of *Glycyrrhiza glabra* L.: An Updated Review

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Article Info

ABSTRACT

Article Type

Review Article

Article History

Received: 15 May 2025

Accepted: 26 August 2025

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Glycyrrhiza glabra (*G. glabra*) or licorice is a medicinal plant used traditionally worldwide. It has a rich phytochemical makeup that contains flavonoids, saponins, and coumarins, providing various therapeutic benefits. It has been utilized as traditional medicine to treat multiple conditions such as liver toxicity, gastrointestinal diseases, skin, and allergic disorders. *G. glabra*, an integral component in Ayurvedic practices, has maintained profound medicinal importance since antiquity. In Ayurveda, it is referred to as "Yashtimadhu," an extraordinary and healing herb known for its effectiveness in treating throat inflammation. *G. glabra* is mentioned as an ancient herbal medicine in "Bhavprakash Nighantu" (an extensive Sanskrit text which has significance in Ayurveda, the ancient medicinal system). It is referred to as Mulethi (Kalintak and Madhulika), characterized by its sweet taste, substantive digestibility, and cooling properties. Additionally, it has been mentioned as a beneficial remedy for hair, skin, and throat issues, to cure ulcers, bleeding disorders, inflammation, and weakness. The presence of active metabolites such as glabridin, liquiritoside, licochalcone, Beta-sitosterol, glabrene, glycyrrhetic acid, glycyrrhizin, glabrone, and isoliquiritigenin enables *G. glabra* to exhibit anti-inflammatory, anticancer, antiulcer, hepatoprotective, neuroprotective, antidiabetic, and antioxidant properties. The data for this review article on licorice were collected from diverse sources, including ancient Ayurvedic books, scientific databases, scholarly journals, published papers, books, and pharmacopoeias. Google Scholar, PubMed, and other scientific data repositories were used to collect ethnopharmacological and clinical properties of the *G. glabra*. This study reviewed traditional uses, phytochemistry, various pharmacological properties, and clinical and scientific evidence of *G. glabra*. Scientific investigation of the metabolites of *G. glabra* for their therapeutic properties, with special emphasis on the mechanism of action, has been reviewed and discussed with suitable scientific references. The study highlights the need for additional research to fully comprehend the mechanisms behind the therapeutic effects of licorice and its promise in modern medicine. This review article thoroughly analyzes the pharmacological and phytochemical characteristics of *G. glabra*, which will serve as a resource for future clinical and fundamental studies.

Keywords: *Glycyrrhiza glabra* L., Traditional Uses, Anti-diabetic, Hepatoprotective, Neurodegenerative diseases

How to cite this paper

Jahan, I., Saxena, A., Alharthi, A., Hazazi, A., Anjum, F., Alotaibi, S., F Aleissi, A., Jaswani, S., Hayatul Islam, M., Khubaib, M. Therapeutic and Pharmacological Efficacy of *Glycyrrhiza glabra* L.: An Updated Review. Journal of Medicinal Plants and By-products, 2026; 15(3): 298-310. doi: 10.22034/jmpb.2026.369492.1970

INTRODUCTION

Owing to developments in the battle against non-communicable and infectious diseases, the past three decades are regarded as a golden age of global health. A wide range of plants and their bioactive metabolites have been thoroughly investigated to treat various communicable and non-communicable diseases. More than 100 plant genera used in traditional medical systems worldwide are found in India. India offers the highest quality and quantity of medicinal plants, and ranks second in exports. It is one of the world's 12 major biodiversity hotspots, with 16 agro-climatic zones

and over 45,000 plants, including 7000 known medicinal herbs [1]. Since the dawn of agriculture, people have been using plants for medical purposes. A frequently used medicinal plant in the *Faba* family, also known as the Legume family, is *G. glabra*. The majority of plants in the genus *Glycyrrhiza* are used as feed and food. The name comes from the Greek words *Glycos* (sweet) and *Rhiza* (root). It is native to the Mediterranean, but *G. glabra* can also be found in China, Russia, and India. Plant extracts are often utilized in the domains of functional foods, medications, food, and nutritional supplements [2]. This herbal remedy, commonly found

in southern Europe and certain regions of Asia, is extensively utilized for its health benefits as well as its applications in the confectionery industry [3].

Historically, licorice was used in traditional and ancient medicine before the Greek and Roman empires. Researchers keep track of this extensive usage history, and it is used for a variety of purposes at different times and places. Licorice was mentioned in texts from China and India that originated in Assyria and Egypt in antiquity. Theophrastus and Pedanius Dioscorides were among the writers who provided tales of the medical benefits of licorice. In traditional Chinese health systems, licorice was used in conjunction with a variety of medicinal plants to treat a variety of diseases, including arthritis, cough, pneumonia, and stomach problems. In traditional medicine, this plant was used to treat pulmonary infections, boost immunity, treat gastritis, stomach ulcers, reduce inflammation, and aid in ulcer healing [4]. It is also used in herbal formulations for asthma and other respiratory conditions. *G. glabra* is primarily used in the food industry to produce flavours and sweeteners. *G. glabra* roots are usually used to season a wide range of products, including chewing gum, chocolate, baked goods, ice cream, soft drinks, and tobacco [5]. Licorice also exhibits antioxidant as well as antimicrobial activities, specifically in reducing oxidative stress in conditions such as HIV/AIDS [6]. The compounds present in *G. glabra* also show anti-depressant activity specifically glycyrrhizin when used with standard drugs adjunctively. The flavonoids such as liquiritin and isoliquiritin exhibit significant antidepressant like effects in animal models. The plant also has applications in skin care, notably for treating atopic dermatitis and inflammation [7].

Root extracts are utilized as foaming agents in beers and fire extinguishers, while root fibers are used as insulation, wallboard, and boxboard materials after being stripped of their flavor and medicinal qualities. For this reason, topical preparations containing *G. glabra* are utilized in the cosmetics industry as a skin depigmentation agent [8]. Additionally, the plant's secondary metabolites, particularly glycyrrhizin and flavonoids, are commercially extracted for use in pharmaceuticals, cosmetics, and nutraceuticals due to their bioactive and therapeutic properties [9]. This review aims to conduct a detailed analysis of the pharmacological and phytochemical properties of licorice, or *G. glabra*, with a focus on the plant's possible medical benefits and applications in complementary and alternative medicine. Employing an extensive examination of current data, this review aims to elucidate the fundamental principles underlying the therapeutic applications of licorice, identify knowledge gaps, and propose future research directions to maximize benefits and minimize risks.

Botanical Properties of *G. glabra*

The plant *G. glabra*, or licorice, is a member of the *Fabaceae* family. Its ancient origins can be traced to Iran, Asia Minor, and the Mediterranean region, including south and central Russia. The plant, which is most known for its sweet root, has long been used by people for both culinary and medicinal purposes. It needs well-drained soil and an orientation that is sunny to semi-shady. It has 9-17 oblong leaflets, each about 2-3 cm in length and 0.5-1 cm in breadth, and pinnate leaves that are 7-15 cm long. Typically purple to pale greenish-blue in hue, the 0.8-1.2 cm long flowers are grouped in a loose inflorescence. The fruit is a lengthy capsule that holds several seeds. Licorice has well-developed roots that consist of a main tap root and several spreading rhizomes. The portion of the stems that tastes sweetest is found underground. Thick, sweet sap is extracted from these stems, and it contains the component

glycyrrhizin, which has a sweetness that can be up to 50 times greater than sugar. This chemical may be the primary bioactive contributor to the therapeutic capabilities, which may include anti-inflammatory, antiviral, and antibacterial actions when combined with other flavonoids and phytoestrogens [2].

Phytochemistry of *G. glabra*

G. glabra is a plant that is highly valued for its phytochemistry and belongs to the *Leguminosae* family. Its phytochemistry includes a diverse array of bioactive chemicals. Compounds of the *Leguminosae* family's phytochemistry contribute to the usage of *G. glabra* in both conventional and alternative medicine. *G. glabra* roots are a good source of phytochemicals, with flavonoids, saponins, and coumarins being the most significant constituents. Because of their medicinal qualities, they have been the focus of a great deal of scientific investigation. One important naturally occurring triterpenoid saponin present in licorice roots is glycyrrhizin. Glycyrrhizin, the primary active ingredient, gives it a pleasant taste and provides significance to its potent anti-inflammatory, antiviral, and hepatoprotective properties. As glycyrrhizin hydrolyzes, glycyrrhetic acid is produced, which is the main active ingredient that gives glycyrrhizin its anti-inflammatory, anti-ulcer, and antiallergic properties [10]. Recent research has further highlighted glycyrrhizin and its derivatives as a potent arsenal of secondary metabolites, contributing to a broad spectrum of pharmacological effects, including anti-inflammatory, antiviral, hepatoprotective, and immunomodulatory activities [11]. Furthermore, glycyrrhetic acid has specific pharmacological actions, such as modulating corticosteroid activity and strengthening the gastrointestinal tract's mucosal defense mechanisms [12]. Liquiritin and isoliquiritin, along with their aglycones, liquiritigenin and isoliquiritigenin, are other flavonoids found in the plant. The antispasmodic, anti-inflammatory, and antioxidant qualities of licorice are facilitated by these flavonoids. Licorice's flavonoids exhibit strong anti-inflammatory and anti-oxidative properties. Thus, this could result in a decreased vulnerability to long-term conditions, including cancer and cardiovascular disease, among others [13].

Isoflavonoids include substances such as welljson parabol and hispaglabridin A and B. The licorice's bioactive components, known as hispaglabridins A and B, have the potential of glaciroidin to reduce LDL oxidation and hence suggest its role in reducing the risk of atherosclerosis has generated a great deal of interest. In addition, isoflavonoids suggest estrogenic actions that could aid in managing menopausal symptoms and indications to support bone health [14]. Numerous coumarins, including umbelliferone and herniarin, which have antibacterial, anti-inflammatory, and anticoagulant properties, are also found in licorice. Numerous coumarins found in licorice root also have anti-inflammatory properties and aid in circulation, which reduces skin inflammation. According to a study, licorice coumarins aid in the treatment of skin conditions. For instance, this kind of chalcone contains the highly effective antibacterial and anti-inflammatory compounds isoliquiritigenin and licochalcone A, which can also be used to treat malaria. For instance, it has demonstrated the ability to suppress the proliferation of cancer cells, exhibit apoptotic activity, and pique the curiosity of cancer researchers [15]. Beta-sitosterol, the first molecule identified in oil with anti-inflammatory and anti-cancer qualities, is one of the several phytosterols abundant in *G. glabra*. Licorice's polysaccharides have been linked to immunomodulatory activity, boosting the immune system's response, and potential therapeutic applications for autoimmune illnesses [16]. The phytochemical composition of *G. glabra* is compiled in Table 1, highlighting the plant's potential for therapeutic uses in various medical disorders.

Table 1 Phytochemical Composition and Therapeutic Properties of *G. glabra*

Compound type	Examples	Key properties and effects	References
Triterpenoid Saponin	Glycyrrhizin (glycyrrhizic or glycyrrhizinic acid)	Anti-inflammatory, antiviral, hepatoprotective; yields glycyrrhetic acid, which has anti-ulcer, anti-inflammatory, and anti-allergic properties	[17, 18]
Flavonoids	Liquiritin, isoliquiritin, liquiritigenin, isoliquiritigenin	Antioxidant, anti-inflammatory, antispasmodic; helps fight against oxidative stress and inflammation	[19-21]
Isoflavonoids	Glabridin, hispaglabridin A and B	Antioxidant, anti-fungal, anti-inflammatory, exhibits estrogenic activities beneficial for menopausal symptoms and bone health	[14, 22, 23]
Coumarins	Herniarin, umbelliferone	Antioxidant, antimicrobial, anticoagulant; beneficial in treating skin conditions	[24-26]
Chalcones	Isoliquiritigenin, licochalcone A	Anti-inflammatory, antimalarial, antimicrobial; isoliquiritigenin shows potential in cancer research	[15, 27]
Phytosterols	Beta-sitosterol	Anti-inflammatory, anti-cancer	[28]

Pharmacokinetic Studies of *G. glabra*

The pharmacokinetic relationship between the chemotherapy drug paclitaxel and licorice extract was assessed by the researchers. It was discovered that following the initial licorice extract ingestion, there were no effects on the drug's absorption or distribution inside the body. However, the drug's metabolism and clearance were improved starting 14 days earlier. This could be a result of the components of licorice influencing cytochrome P450's glycyrrhizin and glycyrrhetic acid, which in turn trigger enzymes. Glycyrrhizin and Glycyrrhetic acid, the major bioactive compounds of *G. glabra*, are known to modulate hepatic enzyme activity, particularly those involved in drug metabolism, supporting pharmacokinetic interaction [29]. Accordingly, there was no discernible difference in the excretion of paclitaxel between the groups that took licorice for extended or brief periods. A recent investigation showed that the therapeutic effects of paclitaxel will be decreased by prolonged licorice use [30].

The pharmacokinetics (ADME) of licorice extract were determined in a clinical experiment using four distinct probe agents, and the effect of licorice extract on CYP1A2, CYP2C9, CYP3A4/5, and CYP2D6 was also estimated concurrently. This information was presented in another study. According to the acquired results, licorice extract did not significantly affect the probing medicines' absorption, distribution, or excretion; however, it did marginally enhance tolbutamide's metabolism and clearance, which is a marker of CYP2C9 substrate activity. Therefore, the scientists concluded that there were no clinically significant pharmacokinetic interactions between the licorice extract and any of the four major CYP enzymes [31]. Rat plasma was used in research to evaluate the pharmacokinetics of licorice extract and its metabolite, Glycyrrhetic acid 3-O-mono- β -d-glucuronide (GAMG). According to the study, licorice extract was poorly absorbed, while the GAMG component was extracted quickly and throughout a large range. Additionally, they observed that, in the majority of cases, GAMG was the primary product of change to GA. In contrast, in the majority of cases, larger and more widespread levels of GAMG were found in various tissues after licorice extract, mostly in organs and the brain. They found that the GAMG has a lower rate capacity encompassing both metabolism and clearance and a higher rate of stability when compared to the licorice extract [32].

Mano et al. researched how licorice's glycyrrhizin affected the pharmacokinetics of methotrexate (MTX), a drug used to treat cancer in mice. They demonstrated that GL (Glycyrrhizin), either given concurrently or a day after MTX treatment, did not affect the drug's absorption, distribution, or excretion. However, when GL was given in conjunction with MTX or three hours before MTX exposure, they observed that MTX's metabolism and clearance increased likely as a result of MTX metabolism being stimulated by an enzyme. Giving GL six or twenty-four hours before MTX

avoided this interaction. Furthermore, it was noted that the liver-protective impact of GL against MTX damage is predicated on GL's ability to prevent MTX-induced liver damage, as GL's body retention duration should be used to calculate the proper dose interval [33].

Traditional Uses of *Glycyrrhiza glabra*

Licorice has been historically noted to treat numerous diseases, including asthma, tonsillitis, sore throat, flatulence, hyperdipsia, epilepsy, fever, sexual debility, stomach ulcers, paralysis, cough, heartburn, colic, rheumatism, swellings, skin disorders, acidity, leucorhea, bleeding, hemorrhagic disorders, and even jaundice. In addition, it was said to have been used as an insecticide, a laxative, an anti-inflammatory, an anti-ulcer, an antibiotic, an anti-arthritis, an antiviral, and a memory stimulator. For these purposes, licorice was claimed to have provided the most effective results when used because it inhibits monoamine oxidase (MAO) inhibitor alongside other compounds such as anticholinergics, antitussives, hypolipidemic, anti-candida, estrogenic, antioxidants, anticancer, and diuretic substances [34].

G. glabra L. has a broad spectrum of traditional uses, ranging from treatment of burns and wounds in combination with butter, promoting lactation with cow milk, an infusion for washing grey hair, and even treating erysipelas with an herbal decoction [35].

In India, the roots of licorice have been made into eye drops for conjunctivitis, licorice powder combined with honey for bloodless conditions, a mixture of *Glycyrrhiza* and Picirrhizakurroa with sugar water used as a cardiotonic, and a treatment for hemorrhage of ground licorice with Sandalwood powder. Hoarseness of voice is treated with a rice milk solution made with *Glycyrrhiza*; oedema is treated with a paste of yashti, milk, and Sesamum indicum combined with butter. As a tonic to increase intelligence, *Glycyrrhiza* combined with honey is taken immediately after milk consumption. It can also be used to cure intrinsic bleeding [36]. The Ayurvedic use of Yashtimadhu in respiratory, digestive, and rejuvenation therapies has also been reported [37]. Glycyrrhizin, a well-known anti-inflammatory ingredient, is regarded as the first plant-based thrombin inhibitor because it has been shown to lengthen the time it takes for thrombin and fibrinogen to coagulate, as well as the amount of time that plasma recalcifies *in vitro*. It was discovered that glycyrrhizin prevented platelet aggregation brought on by thrombin, but it had no effect on agglutination brought on by collagen or platelet-aggregating factor (PAF) [38, 39]. To make liquorice, *G. glabra* roots are dried, and the roots contain a pleasant saponin, Glycyrrhizin, which is typically between 2 to 9% in concentration. It has been researched as a potential treatment for HIV patients. One study examined the effects of Glycyrrhizin on 42 hemophiliacs infected with HIV-1, and the patients' oral candidiasis, lymph node edema, and rash showed signs of improvement alongside the patients' immunological and hepatic symptoms [40]. Furthermore, one other study has shown the long-

term effects of glycyrrhizic acid on 84 patients suffering from chronic hepatitis C [41]. The glycyrrhizic acid content in the Pharmacopoeia Licorice root must be at least 4%, and 20% of water-soluble extractive material must be present at a minimum [40]. The Japanese Pharmacopoeia requires a 25% dilution of the ethanol-soluble extractive. The roots also contain roughly 0.5 to 0.9% of glycyrrhetic acid (GA), which is the aglycone of glycyrrhizin (GL). Flavonoids give the roots their yellow hue. Liquiditin, a primary flavonoid glycoside from roots, transforms into isoliquiritigenin after heating.

Glycyrrhizin and glycyrrhetic acid were investigated as the components responsible for ulcer healing in the late 1940s as a result of a study conducted by a Dutch physician named Revers. GA had local anti-inflammatory properties as well. For the treatment of duodenal and stomach ulcers, the English researchers created carbenoxolone (CB), a semi-synthetic derivative. When cimetidine, the first of the acid inhibitors, became available, its use quickly decreased since it had the same adverse effects as licorice and glycyrrhizin.

In terms of chemistry and pharmacology, CB and GL had certain resemblance in chemistry and pharmacology. CB was endowed with mineralocorticoid characteristics. It had most likely low steroid receptor affinity in tissues, but it was probably working by increasing the action of hormones produced by the body. Some patients reported side effects such as edema, hypertension, and hypokalemia. CB improved the defence by inhibiting adherence of bacteria to injured urothelium. A mouth ulcer was treated with a DGL containing CB gel. DGL is a concentrated licorice extract (soft extract) which contains a maximum of 3% GL; therefore, it was not entirely free of GL [42].

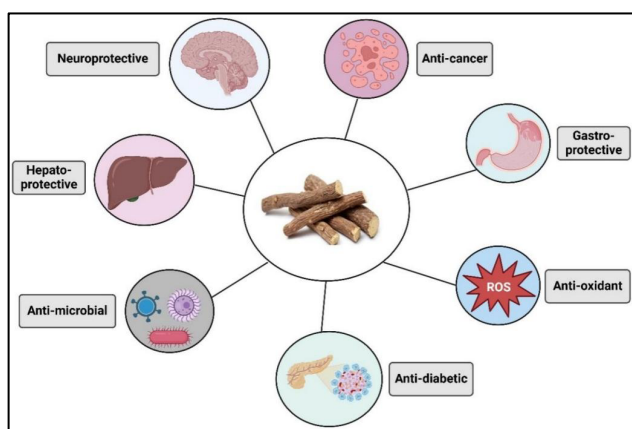


Fig. 1 Traditional ethanopharmacological benefits of *G. glabra* L

Pharmacological Properties of *G. glabra*

Formerly recognized for its potential medical benefits, *G. glabra* has been the focus of numerous studies examining its potential pharmacological activity [43]. Due to its potent anti-inflammatory and antiapoptotic qualities, it may be utilized in clinical settings to treat hepatitis [44]. Furthermore, *G. glabra* has demonstrated its cytotoxic action against malignant cells through testing, indicating that its potential application as a medication at the cellular level is particularly relevant to endometriosis. There are numerous biological categories where 18 β -Glycyrrhetic acid (18 β -GA) is known to have wide activities, including asthma, cancer, diabetes, antiviral, antibacterial, and anti-inflammatory. On the other hand, *G. glabra* has phytochemical substances with a variety of uses, including memory improvement, antibacterial, antioxidant, and

treatment of ulcers [45]. Various pharmacological activities of *G. glabra* have been reported.

Anticancer Activity

G. glabra exhibits significant anticancer properties through cytotoxic effects on various human cancer cell lines and induction of apoptosis and cell cycle arrest. Studies have shown its effectiveness against breast, liver, colon, and lung cancer cells, with certain extracts displaying cytotoxicity comparable to standard chemotherapy. Additionally, licorice compounds inhibit key signaling pathways, enhancing their potential as anti-tumor agents [46, 47].

Cytotoxic Effects on Cancer Cell Lines

Several studies have reported the cytotoxic potential of *G. glabra* against different human cancer cell lines. Ahmad et al. investigated the effect of licorice root extracts obtained from different geographical sources on the viability of four cancer cell lines: MCF-7 (breast), HepG2 (liver), HCT-116 (colon), and A549 (lung). Cell viability was assessed using the MTT assay after 24 hours of exposure to varying concentrations of the extracts [48]. Among the tested samples, the Indian extract exhibited the highest cytotoxicity, with IC₅₀ values ranging from 9.8 to 18.6 μ g/mL across all four cell lines. In contrast, some extracts displayed weak or negligible activity, whereas extracts from Palestine and Iran showed marked cytotoxic effects. The observed cytotoxicity was attributed to the phytochemical composition of licorice root, particularly the presence of flavonoids and chalcones, which were identified as the major bioactive metabolites.

Furthermore, when these authors compared the cytotoxicity of these to several common chemotherapy medications, such as doxorubicin and cisplatin, they discovered that the Indian sample extract had activity that was either the same as or greater than that of some chemotherapy drugs. The study's findings showed that licorice root extract from various sources had varying cytotoxic potentials against human cancer cell lines and that the Indian samples were a good place to look for ideas for new natural products [47, 48].

Another study contrasted the cytotoxic, immunomodulatory, and anti-inflammatory properties of licorice root extracts made using traditional and FMB (fusion, micronization, and bio-activation) procedures against malignant cells. Overall, it was shown that the FMB extract had higher levels of recognized critical components and had improved activity in all bioassays. Consequently, the FMB extract does not cause this kind of toxicity in normal cells. Therefore, the results of this investigation indicated that licorice root extracts may have even greater therapeutic potential when using the FMB approach [49]. *G. glabra*, the plant widely known as licorice, has anti-cancer properties. *Plectranthus amboinicus* Lour. and *G. glabra* are two medicinal plants whose effects were examined in a published study on oral cancer (KB) cells. The plant extracts were produced in ethanolic solutions, and the cell viability (MTT) assay was used to measure the plant extracts' cytotoxicity. Based on the investigations, it was shown that *G. glabra* and *Pl. amboinicus* had IC₅₀ values of 43.6 μ g/ml and 53.0 μ g/ml, respectively. This indicates that the former is more cytotoxic than the latter. Both plants show strong anticancer effects against oral cancer cell lines [50]. Accordingly, it was discovered that the cytotoxicity of *G. glabra* roots in various locations was unceasing against cell lines of liver cancer, lung adenocarcinoma, and human keratinocytes [51].

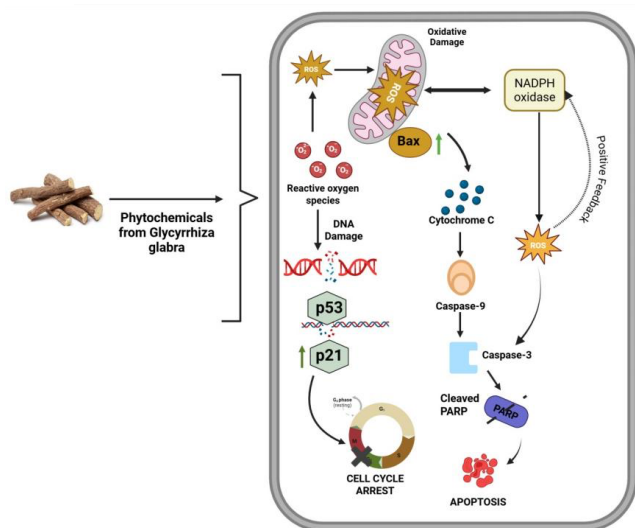


Fig. 2 Phytochemicals from *G. glabra* induce intracellular ROS accumulation, leading to mitochondrial oxidative damage, DNA damage, and p53/p21-mediated cell cycle arrest. ROS promotes cytochrome c release and caspase activation, culminating in apoptosis. ROS also activates NADPH oxidase (NOX), which further amplifies ROS production via a positive feedback loop.

Apoptosis Induction and Cell Cycle Arrest

The antiproliferative effect of licorice root extract (GGE) on the proliferation of prostate cancer (PC-3) cells under co-treatment with adriamycin (ADR) was examined. According to these investigations, GGE causes enhanced cytotoxicity, apoptosis induction, cell-cycle arrest, and DNA damage induction in ADR-treated PC-3 cells (Fig. 2). It also suppresses the production of genes and proteins linked to multi-drug resistance (MDR), which has been connected to resistance to ADRs. The idea that GGE may enhance the effects of ADR in the treatment of prostate cancer was developed by this study [52]. Goel et al. examined 10 drugs against DNA topoisomerase II in C6 glioma cells and screened them against licorice root extract against cytotoxicity. Apoptotic in nature, glabrol, glycyrrhetic acid, and glabridin showed more marked cytotoxicity. These chemicals have the potential to be inhibitors of topoisomerase I and II, which are involved in DNA repair and replication, according to molecular docking studies [53]. In addition to having potent anti-cancer effects, *G. glabra* root extract also dramatically increases apoptosis in HT-29 cells [54]. Compound derived from *G. glabra* has been reported to induce apoptosis, and reduce cancer cell viability, suggesting its potential role in enhancing strategies for cancer prevention and treatment.

Anti-tumor Mechanisms and Pathway Inhibition

The renal protective effect of licorice root extracts in nephropathy caused by cisplatin was investigated using phytochemical analysis. The MTT assay was then used to determine their harmful effect on human cancer cell lines and normal kidney cells. On the one hand, it was discovered that extracts made with FMB exhibited increased cytotoxicity when applied to malignant cells. Normal cells, on the other hand, exhibited no cytotoxicity. According to the study, licorice root extracts can be developed for therapeutic purposes by using the FMB approach [55]. This further resulted in the extraction of three new and eighteen already-known compounds from extracts of licorice roots; the cytotoxicity was then assessed by testing the compounds' bioactivity against four human cancer cell lines. The

research discovered that the substances that produced the most cytotoxicity and death in RKO cells were glycyrol and licopyranol A. Compounds included in licorice root have the potential to be anti-tumor agents since glycyrol is thought to block the Wnt/ β -catenin signaling pathway in colorectal cancer [3]. *G. glabra* root extracts exhibit angiogenesis and VEGF production, which may improve cancer therapy and produce encouraging results when used as an adjuvant source during cancer therapy [23]. The root extract of *G. glabra* stimulates estrogenic activity and fast signaling pathways in breast cancer MCF-7 cells, suggesting that this could be a valuable ingredient in hormone and anti-cancer treatments [56].

Gastroprotective Effects

Licorice root demonstrates substantial gastroprotective effects by modulating gastric barrier functions and reducing inflammation. Its extracts enhance gastric mucosal defense factors and mitigate oxidative stress and inflammation, thus offering protection against gastroduodenal ulcers [57].

Modulation of Gastric Barrier and Inflammatory Responses

Researchers examined the impact of flavonoid-rich extract of *G. glabra* (FREG) on the intestinal epithelium's barrier function *in vivo* and *in vitro* in a study. Based on the current observation, it is determined that FREG administration preserved barrier integrity in Caco-2 cells activated with TNF- α and in rats that developed colitis due to 2,4,6-Trinitrobenzenesulfonic acid (TNBS). Additionally, these metrics showed that FREG altered tight junction proteins, lowering secretory IgA levels and decreasing inflammation. Additionally, researchers believe that FREG protects against leaky gut syndrome [58]. In a different experiment, the researchers calculated the licorice root extract's ability to prevent rats' gastroduodenal ulcers caused by ibuprofen. In other words, the extract decreased inflammation and levels of oxidative stress, tissue damage, and cytokines. The researchers also analyzed and reported the levels of a variety of biochemical, hematological, immunological, and histological markers [59].

Protective Mechanisms in Gastric Mucosa

Linnaeus glabra L. In animal models of stomach ulcers, hydroalcoholic extract also shows an antiulcerogenic effect, potentially as a result of an elevation in gastric mucosal defense factor [60]. In one study, rats were used to examine the anti-ulcer properties of 3-hydroxyimino derivatives of minor licorice triterpenoids. These compounds demonstrated dose-dependent gastroprotection of the stomach mucosa against indomethacin and orthopnea damage. The most active chemical was discovered to be 3-hydroxyimino-11-deoxoglycyrrhetic acid, which completely replaces the conventional carbenoxolone. In the meantime, research has shown that the 3-hydroxyimino substitution increases the licorice triterpenoids' antiulcer action [18]. In a model of ethanol-induced stomach ulcer (US), researchers examined the gastroprotective properties of licorice flavonoid (LF). According to the study, the application of LF had a protective effect due to a decrease in oxidative stress and inflammation, which was followed by tissue damage and cytokines in the stomach mucosa. Furthermore, LF was able to alter the gut microbiota's synthesis of short-chain fatty acids (SCFA) for mucus secretion and cell division.

Further results also signaled that LF activated the PI3K/Akt pathway and, as such, acted to slow down apoptosis of the gastric epithelium. That way, the results coincide with the fact that LF exerts gastroprotective and regenerative effects [20]. The study investigates the gastroprotective effects of licorice flavonoid (LF), a key compound extracted from licorice roots, against ethanol-induced gastric ulcers (GU). While licorice has a long history in traditional medicine, this study aims to elucidate the underlying mechanisms by using an integrated approach that combines metabolomics, network pharmacology, and molecular analysis. In a rat model of gastrointestinal damage caused by ethanol, LF showed a significant protective effect. Metabolomics analysis identified 25 metabolic biomarkers associated with LF treatment, mainly involving amino acid and carbohydrate metabolism. Furthermore, the "component target metabolite" network revealed six key goals linked to GU treatment (HSP90AA1, ACT1, MAPK1, EGFR, ESR1, and PIK3CA). PI3K/Aktweg has been highlighted as an important method of the anti-ulcer effect of LF, and molecular docking confirmed a strong affinity between the LF components and these targets. The results were verified by RT-QPCR and Western blotting. This indicates that LF can reverse the expression of the identified target, activate PI3K/Aktweg, and reduce apoptosis, ultimately providing therapeutic benefits against ethanol-induced gastric ulcers. This study emphasized LF's potential to improve metabolism and suppress apoptosis as part of its gastroprotective mechanism [20].

Anti-oxidant properties

Licorice root is rich in compounds with potent antioxidant properties, such as glycyglabrone and licochalcone C, which effectively scavenge free radicals. These antioxidant effects contribute to the protection against oxidative stress-induced damage, enhancing the activity of antioxidant enzymes and reducing markers of oxidative damage [61].

Scavenging Free Radicals

The stem extract contained a higher number of flavonoids than the root extract. Both the extracts were good at antioxidant, scavenging of nitrite, and protective effects on H₂O₂-injured PC12 cells [62]. Glycyglabrone and licochalcone C, both new compounds found in *G. glabra* roots, exhibit potent free radical scavenging activity [15]. Root extract, particularly in methanol, shows strong free-radical scavenging activity, making it a potential natural antioxidant for health benefits [63]. *G. glabra* L. roots exhibit strong antioxidant effects due to their capacity to scavenge free radicals, reduce potential, and inhibit nitric oxide, making them potential candidates for developing antioxidant-based drug therapy [64].

Protection Against Oxidative Stress-Induced Damage

The extract's content was most likely glabridin, liquiritin, and glycyrrhizin, although it also may have had antioxidant properties. Researchers used a rat model of splenic damage caused by aniline to assess the antioxidant potential of licorice root extract. They claimed that greater Aniline-induced splenic damage was associated with elevated levels of oxidative stress, lipid peroxidation, nitric oxide, and protein carbonyl, which the extract reduced to almost normal levels, regaining the spleen's normal structure and function. Moreover, the extract might increase the levels of antioxidant enzymes like glutathione peroxidase, superoxide dismutase, and catalase. This result stemmed from a theory that licorice root extract, via aniline, protects against spleen damage [65]. Conversely, found that the ethanolic root extract of *G. glabra* had strong efficacy against antioxidant human

lipoproteins in the oxidative system. *G. glabra*'s extraction techniques show that its extracts are rich in compounds that are biologically active and have strong antioxidant activity [66]. According to Rakshanda and Shriniwas (2023), the extract obtained from the methanolic Soxhlet extraction exhibited the highest level of antioxidant activity when tested using the 2, 2'-Azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) technique. Additionally, the molecule can demonstrate the antioxidant and antibacterial properties present in the extract samples, which may be attributed to the presence of flavonoids and polyphenolic components [67]. *G. glabra* root extract showed great promise for nephroprotection, maybe as a result of its antioxidant activity [55].

Anti-diabetic Potential

Licorice root exhibits significant anti-diabetic potential through mechanisms such as enhancing insulin sensitivity and reducing blood glucose levels. Flavonoids in licorice improve lipid metabolism and decrease insulin resistance in type 2 diabetic models. Additionally, licorice compounds modulate glucose metabolism, further contributing to its hypoglycemic effects [68].

Hypoglycemic Effects and Insulin Sensitization

Licorice exhibits hypoglycemic properties by increasing insulin synthesis and expression, improving glucose uptake, and decreasing α -glucosidase activity [69]. Research indicates that licorice therapy enhances insulin resistance and lowers fasting blood glucose [70]. Researchers Luo et al. observed notable improvements in insulin resistance, blood glucose levels, serum lipids, and oral glucose tolerance in mice with type 2 diabetes mellitus (T2DM) generated by a high-fat diet and streptozotocin when they investigated the impact of licorice root flavonoid, licochalcone A (LicA). By up-regulating IRS-2/PI3K/AKT in the liver and pancreas, LicA also enhanced gut microbiota and pancreatic and liver function. These findings raise the possibility of LicA serving as a nutritional supplement for the treatment of type 2 diabetes [71]. In diabetic rats, Álvarez-Almazán et al. improved insulin resistance, blood glucose, serum lipids, and gut microbiota by inhibiting PTP1B and α -glucosidase enzymes. They also produced two derivatives of glycyrrhetic acid (GA), FC-114 and FC-122, and demonstrated their antidiabetic effect by doing so. The study investigates the effects of prenylated flavonoid fractions (PFFs) from *G. glabra* on insulin resistance (IR) and glucose metabolism in insulin-resistant HepG2 (IR-HepG2) cells. In this study, PFFs were isolated from *G. glabra*, and their chemical structures were identified. These compounds, similar to glabridin (GLD), a known active component of *G. glabra*, were found to increase Glucose consumption and translation of glucose transporter 4 (GLUT4) into the plasma membrane of IR-HEPG2 cells. Additionally, while the activity of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase was reduced, the activity of enzymes involved in glucose metabolism, such as glycogen synthase, glucosinase, and pyruvate kinase was improved. Moreover, PFFs activated the PI3K/Akt signaling pathway and suppressed the ERK/IRS-1 pathway, mechanisms that contribute to alleviating glucose metabolism disorders and insulin resistance [72].

Modulation of Glucose Metabolism

Glycyrrhizic acid supplementation alleviates high-calorie diet-induced glucose and lipid metabolic dysregulations by reducing stress hormones, normalizing gluconeogenic enzyme activities, and elevating muscular lipid uptake [73]. *G. glabra* extract contains

compounds like glycosylated flavanones and triterpene saponins, which may modulate glucose metabolism [74].

Prevention and Treatment of Diabetes Complications

The usage of licorice has been shown to have anti-diabetic effects, improving both diabetes and diabetic nephropathy (DN). Bioactive components found in licorice, such as glycyrrhizin, liquiritigenin, liquiritin, and glycyrrhetic acid, provide defense against harmful effects and agents in various human organs [75]. Moreover, it possesses anti-inflammatory, anti-apoptotic, and antioxidant qualities that protect against the consequences of diabetes [76]. Flavonoids from licorice showed activity in inhibiting abdominal fat deposition and increasing blood glucose levels in obese diabetic mice, potentially due to PPAR-gamma activation [21]. The ethanolic extract of licorice shows protective and therapeutic effects against diabetes, abdominal obesity, and hypertension, demonstrating its potential in preventing and/or therapeutically addressing metabolic syndrome [77]. Licorice flavonoids, including glabridin, licochalcone A, and its derivatives, exhibit inhibitory activity against α -glucosidase and PTP1B enzymes, suggesting their potential as functional dietary ingredients for the management and prevention of type 2 diabetes mellitus [78]. Licorice root extracts have been shown by Tiwari and Alim to have antidiabetic and antioxidant qualities. The methanolic extract has been shown to have high free radical scavenging activity, while the aqueous extract has been shown to inhibit alpha-amylase strongly. Flavonoids, saponins, glycosides, terpenoids, and other secondary metabolites are present in the extracts [79].

Antimicrobial Activity

Licorice root has demonstrated broad-spectrum antimicrobial activity against various bacteria and fungi. Extracts show significant antibacterial effects against pathogens like *Escherichia coli* and *Pseudomonas aeruginosa*, with methanol extracts showing the highest efficacy. Glycyrrhizic acid from licorice also targets microbial membrane permeability and biofilm formation, enhancing its antimicrobial potential [25].

Action against Bacteria and Fungi

There have been reports of antibacterial properties for *G. glabra*. According to recent research, extracts from *G. glabra* have antibacterial properties against *Candida albicans*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Bacillus subtilis* [80, 81]. The Soxhlet-extracted methanol crude extract has the strongest antibacterial activity. Similarly, a zone of 10.8 to 16.1 mm growth inhibition against the tested bacteria indicated the extract's antibacterial activity. Flavonoids and polyphenolic chemicals found in *G. glabra* have been linked to antibacterial action [66, 82]. Saeed and colleagues evaluated the antibacterial and antioxidant properties of licorice root extracts using methanol and water as solvents. Except for *Ps. aeruginosa*, the majority of the examined microorganisms were more susceptible to the antibacterial activity of the methanol extract than that of water. Furthermore, the methanolic extract outperformed the aqueous extract in the DPPH experiment in terms of antioxidant activity. Licorice root extracts could be useful as precursors for use in the food and pharmaceutical industries, according to this discovery [26].

Mechanisms of Antimicrobial Effects

G. glabra and its compound glycyrrhizic acid effectively inhibit *Ps. aeruginosa* growth and target its membrane permeability, efflux activity, and biofilm formation, offering a potential alternative to antibiotics [83]. Through bioactivity-guided phytochemical analysis, *G. glabra* demonstrates potent antimicrobial activity,

particularly against *Mycobacterium tuberculosis* strains. Glabridin, a component identified in licorice, is notably effective against both Gram-positive and Gram-negative bacteria, highlighting its broad-spectrum antimicrobial potential [28].

The mechanism studies revealed that glabridin could induce reactive oxygen species accumulation, the loss of mitochondrial membrane potential, and cell membrane destruction by affecting the expression levels of phosphatidylserine decarboxylase that exerted its fungicidal activity. These findings indicated that glabridin exhibited pronounced fungicidal activities against *S. sclerotiorum* and could serve as a potential fungicidal candidate [84]. Flavonoids from licorice, particularly glabrol, target and disrupt the cell membrane of MRSA, leading to increased membrane permeability and dissipation of the proton motive force, effectively killing the bacteria with low resistance development and minimal cytotoxicity to mammalian cells [85].

Potential Therapeutic Applications

G. glabra roots have shown antimicrobial activity against Gram-positive and Gram-negative bacteria and also could be an antitubercular agent. Furthermore, they contain an active component, glabridin, said to exhibit antifungal activity against yeast and filamentous fungi, and activity modulating resistance against its drug-resistant mutants [22]. 18- β glycyrrhetic acid (GA) from *G. glabra* root has antimicrobial activity against *Ca. albicans* strains, which makes it a viable substitute for the topical therapy of vulvovaginal candidiasis that recurs frequently [86].

Hepatoprotective Effects

Licorice root exhibits hepatoprotective effects through its antioxidative and anti-inflammatory properties. Studies have shown that licorice extracts can protect against liver injury by reducing oxidative stress and inflammation, thereby improving liver function and reducing hepatic steatosis. Licorice polysaccharides have also been found effective in treating fatty liver disease without adverse effects [87].

Mechanisms of Liver Protection

Glycyrrhiza polysaccharide (GPS) demonstrated strong evidence against 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) ability to protect against liver injury in Jian carp, indicating its effective application in hepatoprotection and antioxidation. Lithospermate B has been demonstrated *in vitro* and *in vivo* to decrease apoptosis induction through extrinsic/intrinsic routes and decrease hepatocellular carcinoma metastasis [88]. With no negative side effects and a considerable reduction in hepatic steatosis, the aqueous extract of *G. glabra* is thought to help treat fatty liver disease in rats [89]. As a result, the *G. glabra* roots' aqueous extract demonstrated improved liver functions and a restorative effect on hepatic tissue, making it a viable option for curative therapy for hepatic tissue problems [90]. Moreover, it has been documented that the root extract of *G. glabra* exhibited promise in hepatoprotection against carbon tetrachloride-induced hepatotoxicity in rats caused by oxidative stress [91].

Antioxidative and Anti-inflammatory Actions

According to study reports, *G. glabra* has been investigated for its potential to protect the liver. One study found that, in addition to its hepatoprotective properties, the plant may also provide several other mechanisms, such as anti-inflammatory and antiapoptotic, which could be useful in preventing liver damage [92]. In addition, antioxidant activity plays a part in lowering oxidative stress and safeguarding the liver [55].

Clinical Implications in Liver Disease Management

These compounds in *G. glabra* may be the cause of the plant's hepatoprotective benefits. Moreover, it was discovered to offer protection against liver damage brought on by large dosages of methotrexate. For *G. glabra*, however, the dosing interval should be taken into account to ensure no unfavourable herb interaction that would lessen the hepatoprotective effect. According to recent studies, the rhizome of *G. glabra* inhibits the development of pro-inflammatory, pro-apoptotic, and oxidative stress pathways in rats' hepato-renal damage caused by methotrexate [93]. According to a study, pretreatment with hepatocyte-specific glycyrrhetic acid 5a-c could help mice with CCl₄-induced liver damage return to normal liver lobular architecture and cell structure [94].

The study explores the hepatoprotective effects of *G. glabra* against amiodarone-induced hepatotoxicity in rats. In the experiment, thirty rats were divided into five groups, with one control group and others receiving amiodarone alone or pretreated with *G. glabra* extract in varying doses (200, 400, and 800 mg) before amiodarone administration. Results showed that amiodarone caused significant liver damage, evidenced by elevated liver enzymes (AST and ALT) and decreased serum phospholipase A₂ (PLA₂). Pretreatment with *G. glabra* significantly reduced these liver enzyme levels and restored PLA₂. The extract also enhanced antioxidant activity by increasing superoxide dismutase (SOD) and glutathione (GSH) levels while reducing malondialdehyde, a marker of oxidative stress. Additionally, *G. glabra* reduced serum TNF levels, indicating its anti-inflammatory effects [95].

Neuroprotective Activity

Licorice root has shown promising neuroprotective effects, particularly in reducing neurodegenerative symptoms and improving cognitive functions. Glycyrrhizin, a major component, has been found to protect against neurobehavioral deficits, oxidative stress, and inflammation in models of Huntington's disease and other neurological disorders. Licorice compounds also exhibit anti-inflammatory and antioxidant activities, which contribute to their neuroprotective potential [96].

Protection against Neurodegenerative Diseases

Studies have indicated that licorice, or *G. glabra*, has neuroprotective properties. It was discovered, in particular, to be associated with a decrease in the negative consequences of Huntington's illnesses, as it enhanced neurobehavioral impairments and decreased inflammation, apoptosis, and oxidative stress. In the meantime, the weight loss was reversed [17]. Certain bioactive components, such as licorice's glycyrrhizin, have been demonstrated to suppress the protein known as high mobility group box 1 (HMGB1). This suggests that they may find application in the treatment of conditions such as multiple sclerosis, neuroinflammation, Alzheimer's disease, Parkinson's disease, and traumatic brain injury [96]. The study on *G. glabra*, a well-known medicinal plant, explores its neuroprotective potential, particularly focusing on isolated phenolic compounds. Previous research has documented various pharmacological properties of *G. glabra*, including neuroprotection, but this study is unique in identifying the neuroprotective effects of specific phenolic compounds for the first time. Chromatographic analysis of the plant's methanolic extract revealed 22 compounds, including naringenin 4'-O-glucoside, isoliquiritin, and glabridin. In an *in vitro* model using SH-SY5Y cells, several compounds (1, 7, 11, 16, and 20) demonstrated neuroprotective effects by inhibiting ATP depletion

and reducing caspase 3/7 activities induced by MPP⁺ toxicity, which are key markers of neurodegeneration in Parkinson's Disease (PD). Interestingly, other compounds, such as glabrol and abyssinone, exhibited cytotoxicity, which could have implications for cancer research. The study highlights the potential of these phenolic compounds as novel therapeutic agents for PD treatment. However, a key limitation is that the findings are based solely on cell line studies [97].

Anti-Inflammatory and Antioxidant Mechanisms in Neuroprotection

It has also been evidenced to significantly improve learning and memory in mice, though apparently its anti-inflammatory and antioxidant activities [27]. Glycyrrhizin, found in licorice roots, effectively protects neurons from kainic acid-induced neuronal death in the mouse hippocampus by suppressing inflammation and excitotoxic effects. Proinflammatory indicators (COX-2, INOS, and TNF- α) were incited and gliosis was inhibited in conjunction with the GL-mediated neuroprotection. Primary cortical cultures treated with LPS and primary cortical cultures treated with NMDA or KA demonstrated that GL has anti-inflammatory and anti-dense toxic effects [98]. Glycyrrhizin, a component of licorice, has an anti-inflammatory effect on microglia cells, potentially reducing inflammation and promoting healing in inflammatory diseases by inhibiting the production of TNF- α in BV-2 cells [99].

Potential for Cognitive Enhancement and Memory Improvement

Glycyrrhizic acid (GA), among other substances, has been shown to influence neuroprotection by preventing immuno-involution and age-related cognitive issues while simultaneously enhancing cerebral blood flow and immune system-related gene expression. This indicates that because of its anti-inflammatory, antioxidant, and neuroprotective properties, licorice is a prospective therapy candidate for several degenerative neurological diseases. In the rat brain model, studies have shown that glycyrrhizin may be sufficient to restore the neuronal damage caused by fusaric acid. It is a result of that injury since, in both kinds of celiac neurons, it typically regenerates the neurobiochemical parameters and the regenerative capacities of neurons [100]. Furthermore, by inhibiting HMGB1 secretions, glycyrrhizic acid (GL) can also secrete neuroprotective effects in postischemic brains. This will result in a dose-dependent reduction in infarct volumes, protecting against neurological deficits and motor dysfunction [96]. Thus, the results suggest that glabridin from the roots of *G. glabra* may help improve memory and reduce brain cholinesterase activity in mice, which is encouraging for the application of this extract in the treatment of Alzheimer's disease [101]. Through NF- κ B activation and apoptotic suppression, glycyrrhizic acid may protect against glutamate neurotoxicity. This suggests that glycyrrhizic acid may have therapeutic value in preventing brain damage caused by glutamate [102]. Subsequent research examined the impact of glycyrrhizic acid, a licorice root component, on oxidative stress and memory in mice whose brains had been damaged by scopolamine. According to the findings, glycyrrhizic acid dramatically decreased acetylcholinesterase activity while also improving memory function in the mice as measured by the Y-maze test. However, it has been discovered that glycyrrhizic acid increases the activity of antioxidant enzymes and restores the equilibrium of signaling molecules, including superoxide dismutase and catalase, in the elicitation of neuroprotection [103].

Table 2 Pharmacological Activities of *G. glabra* with special emphasis on mechanism of action

Type of study	Mechanism of action	References
Cytotoxicity	Evaluated effects of licorice root extracts on MCF-7, HepG2, HCT-116, and A549 cell lines. The Indian sample showed the highest cytotoxicity, possibly due to its flavonoid and chalcone content. Compared cytotoxicity with standard anticancer drugs.	[48]
	The FMB extract showed higher levels of essential trace elements and better cytotoxicity, immunomodulatory, and anti-inflammatory effects, with no toxicity in normal cells.	[49]
	The FMB method-prepared extract showed higher cytotoxicity towards cancer cells and no toxicity towards normal cells. Suggests FMB technique enhances therapeutic potential.	[55]
	Isolated compounds were evaluated for cytotoxicity against four human cancer cell lines. Licopyranol A and glycyrol showed high cytotoxicity and induced apoptosis in RKO cells. Glycyrol may inhibit the Wnt/ β -catenin signaling pathway in colorectal cancer.	[3]
Anti-ulcer	FREG protected barrier integrity in TNF- α stimulated Caco-2 cells and TNBS induced colitis rats, modulated tight junction proteins, reduced inflammation, and increased secretory IgA levels.	[104]
	Demonstrated potential antiulcerogenic properties through increased gastric mucosal defensive factors in mouse models of gastric ulcers.	[60]
	Reduced inflammation, oxidative stress, tissue damage, and cytokine levels in rat models.	[59]
	Protected gastric mucosa from ulceration in rat models, with 3-hydroxyimino-11-deoxoglycyrrhetic acid showing superior activity to carbenoxolone.	[18]
Anti-oxidant	LF reduced inflammation, oxidative stress, tissue damage, and cytokine levels, modulated gut microbiota, increased SCFA production, enhanced mucus secretion and cell regeneration, and activated the PI3K/AKT pathway to inhibit apoptosis in the gastric epithelium.	[20]
	Different extraction methods yielded extracts with high antioxidant activity; Soxhlet extraction with methanol showed the greatest activity via the ABTS method.	[66, 105]
	Presence of polyphenolic compounds and flavonoids contributed to antibacterial and antioxidant activities.	[67]
	Significant nephroprotective potential attributed to antioxidant effects, supported by bioactive constituents like glycyrrhizin, glabridin, and liquiritin.	[55]
Anti-cancer	Restored normal structure and function of the spleen, decreased oxidative stress markers, and increased antioxidant enzymes in rats with aniline-induced spleen damage.	[65]
	Leaf extract has higher flavonoid content than root extract, exhibiting antioxidant, protective barrier and nitrite scavenging on H ₂ O ₂ -injured PC12 cells.	[62]
	Ethanollic root extract showed considerable antioxidant activity and protective effects.	[15]
	<i>G. glabra</i> showed higher cytotoxicity against oral cancer cells than <i>Pl. amboinicus</i> .	[50]
Anti-diabetic	Enhanced the cytotoxicity of ADR, induced apoptosis, cell cycle arrest, and DNA damage; reduced expression of MDR genes and proteins.	[52]
	Glycyrrhetic acid, glabrol, and glabridin showed high cytotoxicity and induced apoptosis; compounds could inhibit topoisomerase I and II.	[53]
	Demonstrates promise as a supplementary source for cancer therapy by suppressing angiogenesis and VEGF production.	[23]
	Activates MCF-7 cells via rapid signaling pathways and estrogenic activity.	[56]
Anti-microbial	Variation in cytotoxicity against immortal human keratinocyte, lung adenocarcinoma, and liver carcinoma cell lines.	[51]
	Glycyrrhizin reduces cervical cancer cell viability and promotes apoptosis.	[47]
	Inhibits colon cancer cell growth and induces apoptosis in HT-29 cells.	[54]
	Contains bioactive components contributing to protective effects against toxins in various organs.	[75]
Hepatoprotective	Decreased fasting blood glucose levels and enhanced insulin resistance.	[106]
	Stimulated insulin secretion and expression, improved glucose utilization, and inhibited α -glucosidase activity.	[69]
	Contributed to protective effects against diabetic complications.	[76]
	Potential through activation of PPAR- γ .	[21]
Neuro-protective	Effective in prevention and alleviation of diabetes, obesity, and hypertension.	[77]
	Potential functional food ingredient for the prevention and treatment of type 2 diabetes mellitus.	[78]
	Improved insulin resistance, blood glucose levels, serum lipids, and oral glucose tolerance by regulating the insulin signaling pathway.	[107]
	Aqueous extract inhibited alpha-amylase, and methanolic extract displayed significant scavenging activity of free radicals.	[79]
Anti-microbial	Inhibited PTP1B and α -glucosidase enzymes, improved insulin resistance, blood glucose levels, serum lipids, and gut microbiota in diabetic rats.	[108]
	Demonstrated antibacterial antibacterial properties against <i>Ca. albicans</i> , <i>Ba. subtilis</i> , <i>Ps. aeruginosa</i> , and <i>Escherichia coli</i> . Soxhlet extraction with methanol showed the highest antimicrobial activity.	[24, 66, 105]
	Against both Gram-positive and Gram-negative bacteria, roots demonstrated antibacterial action.	[28]
	Glabridin showed antifungal activity against yeast and filamentous fungi, including drug-resistant mutants of <i>Ca. albicans</i> .	[22]
Hepatoprotective	Methanolic extract displayed higher antibacterial activity against most tested bacteria except <i>Ps. aeruginosa</i> , and greater antioxidant activity, suggesting potential applications in food and pharmaceutical industries.	[26]
	Anti-inflammatory, antiapoptotic, and hepatoprotective mechanisms; reduce oxidative stress.	[55, 92]
	Alleviates methotrexate-induced hepato-renal damage by reducing oxidative stress and inhibiting pro-apoptotic and pro-inflammatory pathways.	[93]
	<i>Glycyrrhiza</i> polysaccharide (GPS) protects against liver damage caused by TCDD, acting as a hepatoprotective and antioxidant agent.	[109]
Neuro-protective	Induces apoptosis through extrinsic/intrinsic pathways and reduces metastatic potential.	[88]
	Effective in treating fatty liver disease, improving liver function and reducing hepatic steatosis without adverse effects.	[89]
	Hepatocyte-specific glycyrrhetic acid derivatives restore normal liver lobular architecture and cell structure.	[94]
	Aqueous extract improves liver functions and restores hepatic tissue in acute liver injury models.	[90]
Neuro-protective	Root extract possesses hepatoprotective potential against carbon tetra chloride-induced hepatotoxicity.	[91]
	Improved neurobehavioral deficits, reduced oxidative stress, apoptosis, and inflammation, and reversed body weight reduction.	[17]
	Inhibited HMGB1, showing potential for neurological disorders including traumatic brain injury, neuroinflammation, Alzheimer's, Parkinson's, and multiple sclerosis.	[96]
	Prevented age-related immune involution and cognitive disorders, improved cerebral blood flow, modulated gene expression, and immune function.	[69]

Continue Table 2		
	Restored neurobiochemical parameters and neuronal regenerative capacity in fusaric acid-induced damage in rats.	[100]
	Demonstrated significant improvement in learning and memory in mice, likely due to anti-inflammatory and antioxidant properties.	[27]
	Inhibited HMGB1 secretion, reduced infarct volumes, and improved motor impairment and neurological deficits.	[96]
	Suggested potential for Alzheimer's disease management through memory improvement and reduced brain cholinesterase activity.	[101]
	Suppressed apoptosis and inhibited NF-kappaB activity, suggesting therapeutic value against cerebral damage caused by glutamate.	[102]
	Prevented rotenone-induced energetic stress by restoring the mTORC1-AMPK1 axis, averting dysregulation of the citric acid cycle and impairment of autophagy.	[110]
	Enhanced memory performance, curtailed acetylcholinesterase activity, augmented antioxidant enzyme activity, and modulated neuroprotective signaling molecules.	[103]

CONCLUSION

This comprehensive review underscores the significant pharmacological and therapeutic potential of *G. glabra*, commonly known as licorice. Through extensive research, it is evident that licorice exhibits a wide range of beneficial properties, including anticancer, gastroprotective, antioxidant, anti-diabetic, antimicrobial, hepatoprotective, and neuroprotective effects. The bioactive compounds, particularly glycyrrhizic acid, flavonoids, saponins, and coumarins, are primarily responsible for these therapeutic benefits. Studies have demonstrated licorice's ability to induce apoptosis in cancer cells, protect the gastric mucosa, scavenge free radicals, enhance insulin sensitivity, inhibit microbial growth, shield the liver from oxidative damage, and protect neuronal cells from neurotoxicity. Furthermore, the pharmacokinetics of licorice extracts suggests minimal adverse interactions, enhancing its potential as a safe therapeutic agent. Despite these promising findings, further clinical studies are necessary to fully elucidate the mechanisms of action and to validate the efficacy and safety of licorice in human populations. This review highlights the need for continued research to optimize the therapeutic applications of *G. glabra*, ensuring its integration into modern medicine as a natural, effective treatment for various ailments. The profound therapeutic potential of licorice solidifies its relevance in both traditional and contemporary medical practices.

Funding Sources

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRedit Authorship Contribution Statement

Ishrat Jahan: Conceptualization, Investigation, Resources, Writing-Original draft, Ayush Saxena: Writing-Review & Editing, Resources; Afaf Alharthi: Writing-Review & Editing, Ali Hazazi: Review and Editing, Farah Anjum: Validation, Resources, Sarah Alotaibi: Formal Analysis and Visualization, Awad F Aleissi: Formal analysis, Validation; Samridhhi Jaswani: Writing- Review & Editing; Mohammad Hayatul Islam: Conceptualization, Validation, Resources, Visualization Mohd Khubaib: Visualization, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

Acknowledgment

The authors express their gratitude towards Integral University, Lucknow, for providing the necessary facilities and a Manuscript Communication Number (IU/R&D/2024- MCN0003073).

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