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Multifunctionality Interpretation of *Glycyrrhiza glabra* - A Nutraceutical Herb

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Abstract

Glycyrrhiza glabra L., or liquorice, is a perfect example to show how traditional medicine has changed into scientific and evidence-based nutraceutical applications. The current review will combine and cover the whole connection of information concerning the herb's ethnobotanical connection, its chemical and pharmacological properties, and its therapeutic potentials. The roots and rhizomes of the liquorice plant are rich in active substances like glycyrrhizin, liquiritin, glabridin, and many flavonoids that are responsible for the different biological activities of the plant. Modern scientific research has supported the historical use by revealing the plant's antioxidant, anti-inflammatory, antimicrobial, liver-protecting, brain-protecting, and cancer-inhibiting properties. The studies on molecular mechanisms involved show that the plant modulates the key signalling pathways such as NF-κB, MAPK, and Nrf2, regulates oxidative stress and apoptosis. New extraction technologies, analytical standardisation, and nano-technology-based formulation approaches have improved the bioavailability and therapeutic potential. Although the preclinical data are very promising, the standardised clinical trials are still the major requirement for global regulatory acceptance. Biotechnological methods such as metabolic engineering and CRISPR-based techniques may greatly help in increasing the production of secondary metabolites. The present review links traditional knowledge to modern scientific evidence and classifies *G. glabra* as a nutraceutical herb with significant translational potential for the integrative healthcare system.

Major Findings: *Glycyrrhiza glabra* has more than 400 phytochemicals, with glycyrrhizin and flavonoids like glabridin playing a role in antioxidant, anti-inflammatory, antimicrobial, hepatoprotective, neuroprotective, as well as anticancer activities. In practice, glycyrrhizin seems to tune the NF-κB, MAPK, and Nrf2 pathways, while glabridin gives fairly solid antibacterial together with antiviral effects. Even with newer biotech options such as CRISPR that have boosted glycyrrhizin output, taking too much can still lead to hypertension and hypokalemia, mainly because 11β-HSD2 gets inhibited. Still, despite encouraging preclinical and clinical observations, there's no full standardized set of Phase II/III trials, so broad therapeutic approval and clinical translation remain kind of limited.

Keywords: *Glycyrrhiza glabra*, Glycyrrhizin, Nutraceuticals, Phytochemicals, Pharmacological Activities, Traditional Medicine

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1. Introduction

Nutraceuticals, which include bioactive food-based compounds that show health benefits beyond their basic nutritional value, have become essential elements of modern preventive medical practices because the nutrition and pharmacology fields have started to work together. The field has experienced rapid growth since DeFelice

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created the term in 1989 because more consumers want natural solutions, and people now understand the negative effects of synthetic drugs, and the world has returned to investigating traditional medical systems such as *Ayurveda* and *Homeopathy* and *Siddha*[1,2]. The world uses medicinal plants as essential healing resources because they provide the primary medical solutions, which approximately 80% of Indian citizens use and because their uses have spread to different medical practices[3]. *G. glabra* L., known as liquorice or sweet root, belongs to the *Fabaceae* family and has served as an important medicinal plant throughout diverse global ethnopharmacological systems. Indigenous peoples and Mediterranean cultures, and Central Asian and Middle Eastern societies (Figure 1) have cultivated and used this plant for more than 3000 years, with its medicinal properties documented in ancient pharmacopoeias[4]. The plant contains more than 400 chemical compounds, which include its main triterpene saponin, glycyrrhizin, that makes up 2 to 15 per cent of dry root weight, plus flavonoids, liquiritin, isoliquiritin and isoflavonoids glabridin, which together create the plant's various biological functions[5,6]. The sweet compound glycyrrhizin shows a sweetness level which exceeds 50 times that of sucrose and functions as a standalone medicinal substance, while its other components create additional anti-inflammatory, hepatoprotective, gastroprotective, neuroprotective, immunomodulatory and anticancer protection, which scientists have proven through clinical studies and preclinical research studies.

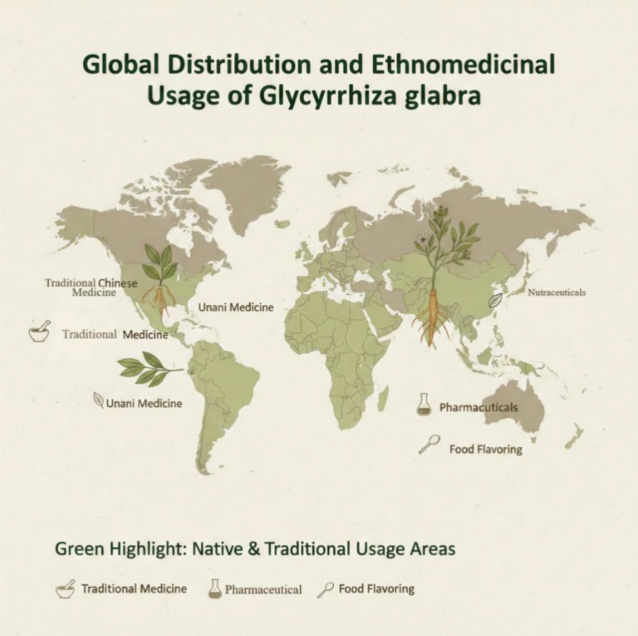


Figure 1. Geographical distribution of *G. glabra*; The green colour indicates countries where the species is available for ethnobotanical use[4].

The map shows how the *G. glabra* (liquorice) plant uses traditional medicine from different parts of the world. The plant exists as a native species throughout Central Asia, the Mediterranean and Western Asia, but its cultivation occurs in China, Iran, India and various European territories. The traditional medical systems that have used liquorice root throughout history include Traditional Chinese Medicine, *Unani* medicine and different Indigenous healing systems. The plant possesses anti-inflammatory properties, which function as expectorants and protect the liver and regulate immune system activity according to these systems. The presence of bioactive compounds, which include glycyrrhizin and flavonoids, enables modern medicine to use these compounds for pharmaceutical development, nutraceutical product creation, and food flavouring purposes. Legend: The green shaded areas on the map show regions where *G. glabra* grows as a traditional crop and is used for various purposes. The icons show different application areas, which include traditional medicine and pharmaceutical products, nutraceuticals and food flavouring.

The multiple reviews which exist about *G. glabra* have studied its phytochemistry and its individual pharmacological activities because researchers have not produced a detailed mechanism-based study which unites all aspects of the plant through its physical structure, its extraction methods, its molecular pharmacology and its safety assessment in the context of developing nutraceutical products. The development of new chromatographic and extraction methods has improved bioactive standardisation and therapeutic potency, yet researchers have not achieved complete synthesis of these new developments with conventional knowledge in a practical research environment.

2. Materials and Methods

The current review presents a complete evidence-backed assessment of *G. glabra,* which serves as a model nutraceutical because it includes information about the plant's characteristics, its chemical makeup, its biological functions, its medical research findings and its safety

assessment requirements. The review connects traditional ethnopharmacological practices with modern biomedical research to create an evidence-based framework which supports the development of liquorice-derived drugs for global preventive healthcare purposes.

2.1 Review Design

The article presents an extensive evidence-based narrative review which follows the SANRA assessment framework to achieve transparent research methods and scientific research validity. We used existing peer-reviewed articles, pharmacopoeial monographs and regulatory documents as our only sources of information for the study. Therefore, the study did not require ethical approval. We completed the design and execution of the review process between January 2024 and March 2025.

2.2 Literature Search Strategies

The authors performed an independent systematic electronic literature search, which examined five major bibliographic databases, including PubMed/MEDLINE, Scopus, Web of Science (WoS), Google Scholar and EMBASE. The search started from the database inception and continued until March 2025 without any geographical boundaries. The search used Boolean operators (AND, OR, NOT) to link controlled vocabulary (MeSH headings where available) and free-text keywords through these Boolean operations. The research used *"Glycyrrhiza glabra"* and "liquorice" and " sweet root" and "*Yashtimadhu*" and "*Gan Cao*" and "*Asl-us-soos*" and "*Mulathi*" as follow primary terms. The research used "nutraceutical" and "phytochemistry" and "glycyrrhizin" and "glabridin" and "licochalcone" and "liquiritin" and "pharmacological activity" and "anti-inflammatory" and "antioxidant" and "antimicrobial" and "hepatoprotective" and "neuroprotective" and "anticancer" and "immunomodulatory" and "gastroprotective" and "molecular mechanism" and "NF-κB" and "MAPK" and "Nrf2" and "clinical trial" and "extraction" and "bioavailability" and "nanoformulation" and "metabolic engineering" and "CRISPR" and "biotechnology" and "toxicology" and "safety" and "ethnobotany" and "traditional medicine" and "*Ayurveda*" and "Traditional Chinese Medicine" as secondary terms which combined with primary terms through AND relationship. The researchers conducted hand searches through the reference lists of all included articles and relevant reviews to find additional sources. The researchers obtained regulatory and safety data from official resources, which included WHO monographs, EMA guidelines and FDA databases and pharmacopoeial monographs (European Pharmacopoeia, United States Pharmacopoeia, Indian Pharmacopoeia).

2.3 Inclusion and Exclusion Criteria

The review process involved two reviewers who independently assessed articles through both title and abstract evaluations and subsequent full-text examinations. The following pre-defined criteria were applied: The study included research articles which had undergone peer review and included original research content, clinical trials, systematic reviews, meta-analyses and book chapters that existed in English. The study included research articles which had undergone peer review and included original research content, clinical trials, systematic reviews, meta-analyses and book chapters that existed in English. The study investigated *G. glabra* and studied its active components, which included glycyrrhizin, glabridin, licochalcones, liquiritin, glycyrrhetinic acid and additional substances. The study used *G. glabra* data to report ethnobotanical information, phytochemical information, pharmacological information, toxicological information, formulation information and biotechnological information. The research study included publications which existed between 1990 and March 2025. The research study included publications which existed between 1990 and March 2025. The study included comparative research between *G. uralensis* and *G. inflata,* which are closely related species. The study excluded the following types of content: (i) conference abstracts and editorials and letters and commentaries which contained no original data; (ii) non-peer-reviewed grey literature; (iii) studies that investigated *Glycyrrhiza* species but did not include *G. glabra* data; (iv) full texts which could not be accessed; (v) articles which had serious deficiencies in their methodological reporting and (vi) duplicate datasets.

2.4 Study Selection and PRISMA-inspired Workflow

The research team employed a four-stage selection process, which used PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) as its basis for conducting their work. The identification stage

required database searches to collect approximately 3200 records, while handsearching discovered 48 extra records, which brought the total record count to approximately 3248. After duplicate records were removed, 2640 distinct records remained available for screening purposes. The two reviewers examined 2640 records through separate title and abstract screening, which led to 420 articles being selected for further eligibility tests. From 420 articles which went through assessment, 343 articles were excluded for multiple reasons, with 89 articles lacking proper methodology details, 74 articles containing non-English content, 112 articles studying different *Glycyrrhiza* species, 43 articles missing full text and 25 articles presenting duplicate datasets. The review process included 57 articles which fulfilled all eligibility requirements for final inclusion.

2.5 Data Extraction

Data were extracted using a standardised template to capture author information, publication year, study design, plant material, extract type, compound, experimental model/population, primary outcomes and methodological limitations. The researchers organised the data into thematic groups matching the main sections of the review.

2.6 Quality Assessment

The evaluation of methodological quality required the use of validated tools which matched the study design of each research project. The study used ARRIVE 2.0 to assess *in vivo* animal studies. The Cochrane Risk of Bias tool (RoB 2.0) assessed randomised controlled trials. The study uses standard quality indicators, which require both authenticated cell lines and positive/negative controls and statistical rigour for their *in vitro* studies. The AMSTAR-2 checklist serves as the evaluation standard for all systematic reviews. The study determined quality ratings to establish weight for each finding, which affected synthesis results and conclusion confidence, yet the results could not be used to exclude findings from the study.

2.7 Evidence Synthesis and Grading

Formal meta-analysis could not be conducted because the research used different study designs, experimental models, and outcome measures. The data were organised into groups which shared common themes, while the authors used narrative storytelling to present their findings. The study results included shared findings from multiple studies, yet the researchers documented contradictory results through critical analysis of factors which explained differences in research findings, such as dose and extract composition, model system and study quality. The assessment of evidence strength for each major pharmacological activity was graded with three categories. The study classified evidence strength according to three categories, which included strong evidence, which required three independent clinical trials or a robust meta-analysis. The study classified evidence strength according to three categories, which included Moderate evidence, which required two or fewer clinical trials together with preclinical data. The study classified evidence strength according to three categories, which included Preliminary evidence, which depended on *in vitro* or animal evidence, together with very little or no clinical evidence. The Results and Discussion section employs this grading system to show how ready each documented activity is for practical application.

3. Historical and Ethnobotanical Background

Glycyrrhiza glabra has a history dating back more than 4000 years, supported by ancient clay tablets and classical Greek medical texts. The discovery of King Tutankhamun's tomb by archaeologists loudly signified the use of liquorice root for ceremonial and medicinal purposes in ancient Egyptian civilisation around 1350 BCE[7]. The Greek physician Hippocrates (460-370 BCE) suggested liquorice for respiratory ailments, while Theophrastus documented its cultivation and therapeutic applications in his botanical treatises.

In *Ayurveda*, *G. glabra* is designated as "*Yashtimadhu*", which means honey-like stick and is classified as a rejuvenative herb possessing *Madhura* (sweet) taste and *Sheeta* (cooling) potency. Classical *Ayurvedic* texts, which include *Charaka Samhita* and *Sushruta Samhita,* document its applications for respiratory disorders (*Kasahara*), digestive complaints (*Agnimandya*), inflammatory conditions, and as a harmonising agent (*Yogavahi*), enhancing the efficacy of other herbal formulations. *Ayurvedic* practitioners traditionally use *G. glabra* for voice enhancement, peptic ulcers, cough, bronchitis, and as a tonic[8].

Traditional Chinese Medicine named liquorice as "*Gan Cao*" (sweet grass) and categorised it among the

fifty fundamental herbs in the Divine Husbandman's Classic of Materia Medica (Shen Nong Ben Cao Jing), 200 CE. Chinese practitioners assign qi-tonifying, heat-clearing, and detoxifying properties to liquorice, prescribing it for spleen deficiency, cough, palpitations, and as a harmonising component in multi-herb formulations. *G. glabra* hence appears in approximately 60% of traditional herbal prescriptions, underscoring its fundamental role in Eastern medicine[9].

In *Unani Tibb*, liquorice is known as "*Asl-us-soos*" or "*Mulathi*" and considered as a *Muqawwi-e-baah* (aphrodisiac), *Mulattif* (demulcent), and *Mohallil-e-waram* (anti-inflammatory) agent together. Among the urinary disorders, throat infections, gastric ulcers, and reproductive health issues, *Unani* doctors usually recommend it. The medieval doctor Avicenna (980-1037 CE) greatly acknowledged the use of liquorice in his Canon of Medicine, where he not only prescribed it for chest problems but also used it as a medium for the delivery of other medicines. Ethnobotanical surveys around the world demonstrate consistent traditional applications correlating with modern pharmacological evidence. Mediterranean populations are advised to consume liquorice for gastrointestinal disorders and respiratory problems. The Orientals utilised it for throat soothing and as a natural sweetener. Native American tribes independently discovered and used indigenous *Glycyrrhiza* species for therapeutic purposes, demonstrating ethnobotanical knowledge in different regions[10].

These ethnopharmacological studies have provided scientific validation to a number of traditional claims. Antitussive and expectorant properties are recognised in *Ayurveda*. The traditional applications as hepatoprotective agents find their justification in current hepatology research in chronic hepatitis. The harmonising concept in TCM fits with the modern notion of pharmacokinetic interaction and synergy. It completes the circle from traditional wisdom to modern science and underlines the values of ethnobotanical knowledge as a footing for evidence-based nutraceuticals development.

4. Botanical Description and Phytochemistry

Glycyrrhiza glabra L. belongs to the family *Fabaceae*, subfamily *Papilionoideae*, and represents one of about 30 species in the genus *Glycyrrhiza*. The species epithet "*glabra*" refers to the leaflets being rather smooth or glabrous compared to hirsute relatives. The morphology is typical for leguminous plants, characterised by a strong taproot system with far-reaching lateral rhizomes; the latter are the organs of medicinal value. Plants reach heights of 1 to 2 meters, with erect, branched aerial stems growing from underground rhizomes. The compound leaves are pinnately arranged, with 9-17 ovate-lanceolate leaflets, 2-5 cm long, that have entire margins and glandular punctations on the abaxial surface secreting sticky resinous exudates. The inflorescence consists of axillary racemes bearing 8-15 papilionaceous flowers with pale purple to whitish-blue corollas typical of *Fabaceae* (Figure 2). The fruit develops as a compressed, oblong legume-pod containing 1-5 reniform seeds. The medicinal rhizomes are cylindrical, longitudinally wrinkled, and typically 15-25 cm long with 1-3 cm diameter; the external colouration is characteristically yellowish-brown, while internally the tissue is fibrous yellow, with a distinctively sweet taste.

The *G. glabra* phytochemical composition represents a complex metabolome, comprising over 400 identified constituents distributed across several major chemical classes (Table 1). The triterpene saponins are the predominant bioactive category, of which the principal component is glycyrrhizin (glycyrrhizic acid or glycyrrhizinate) at 2-15% of root dry weight, depending on its geographical origin, conditions of cultivation and methodology of processing. Glycyrrhizin is presented as a calcium or potassium salt of glycyrrhizinic acid, structurally a triterpenoid aglycone, namely glycyrrhetinic acid, conjugated with two glucuronic acid molecules at the C-3 position.

Figure 3 shows a diagrammatic representation of the diverse pharmacological properties associated with *Glycyrrhiza glabra* (liquorice). The plant contains several bioactive phytochemicals, including glycyrrhizin, glycyrrhetinic acid, flavonoids (liquiritigenin, isoliquiritigenin), chalcones, and isoflavonoids, which collectively contribute to multiple therapeutic effects. These compounds exert antioxidant and anti-inflammatory activities through modulation of oxidative stress pathways and inflammatory mediators. Antimicrobial and antiviral effects have been reported



Representative images showing the key morphological features of *G. glabra* (liquorice), an important medicinal plant belonging to the family *Fabaceae*. (A) The complete plant shows vertical growth patterns together with its pinnate compound leaf structure. (B) The flowering period displays standard papilionaceous flowers, which grow in spike-like flower clusters that are typical of *Fabaceae* family plants. (C) The mature fruit pods hold seeds, which need pollination to develop into seeds that people use to propagate plants. The agricultural industry cultivates the plant to extract its roots, which contain pharmacologically active compounds that include glycyrrhizin, flavonoids and chalcones, which produce therapeutic effects.

Figure 2. Morphological features of *G. glabra*: Plant view (left); Inflorescence with flower buds (middle); Seeds of the plant (right) (SA plants, CC BY-SA 4.0, via Wikimedia Commons).

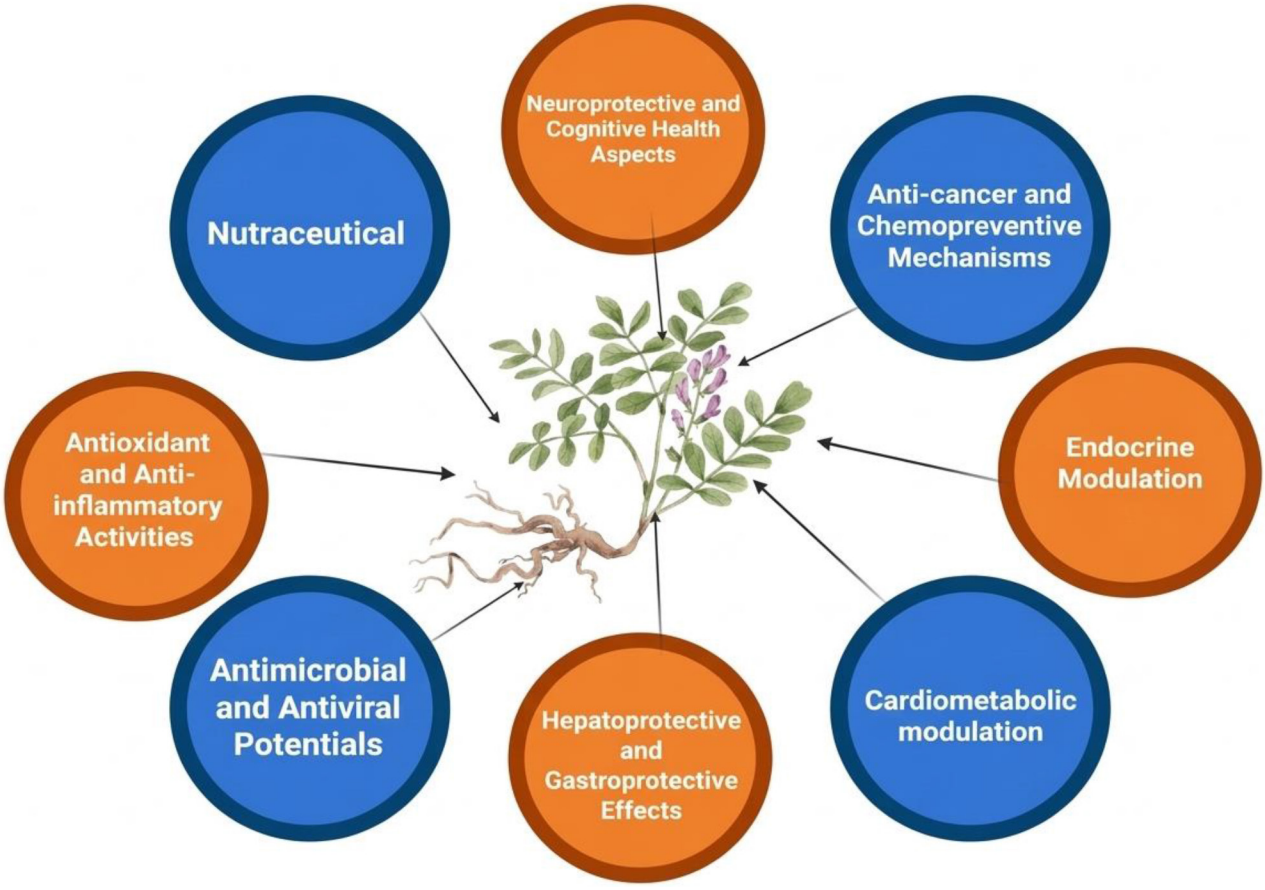


Figure 3. Multifunctionality of *Glycyrrhiza glabra*.

against a range of bacterial and viral pathogens. The plant also exhibits hepatoprotective and gastroprotective properties through the regulation of liver enzymes and gastrointestinal mucosal protection. Additional reported effects include cardiometabolic modulation, endocrine regulation through interactions with steroid metabolism, neuroprotective actions that support cognitive function, and anticancer and chemopreventive activities mediated by apoptosis induction and inhibition of tumour cell proliferation. Due to this broad spectrum of biological activities, *G. glabra* is widely utilised in nutraceutical formulations and traditional medicine systems.

Table 1 shows the various medicinal effects of *G. glabra,* which is known as liquorice. The plant contains several bioactive phytochemicals, including glycyrrhizin, glycyrrhetinic acid, flavonoids (liquiritigenin, isoliquiritigenin), chalcones, and isoflavonoids, which collectively contribute to multiple therapeutic effects. The compounds show antioxidant and anti-inflammatory effects because they control oxidative stress pathways and inflammatory mediators. The plant shows both antimicrobial and antiviral properties, which target various bacterial and viral pathogens. The plant shows hepatoprotective and gastroprotective effects because it controls liver enzymes and protects gastrointestinal mucosal surfaces. The additional reported effects of the treatment include its effects on cardiometabolic health and the way it controls endocrine functions through its interaction with steroid metabolism, together with its neuroprotective effects, which improve cognitive abilities and its ability to fight cancer and prevent cancer through apoptosis induction and tumour cell growth inhibition. *Glycyrrhiza glabra* has extensive biological functions that lead to its use in both nutraceutical products and traditional medicine practices.

The second large class of phytochemicals is flavonoid glycosides, among which the prevailing flavanone glycoside is liquiritin, a 4'-O-glucoside of liquiritigenin. Its aglycone, along with its positional isomers, isoliquiritin, and isoliquiritigenin, are found in the plant with various pharmacological profiles which include estrogenic, neuroprotective, and antioxidant activities. Among other compounds, the prenylated isoflavonoid glabridin, being highly contained in the hydrophobic fraction, was also shown to exhibit remarkable antioxidant capacity, much higher than vitamin E, and a unique melanogenesis-inhibiting activity of great interest for dermatological applications[11]. The chalcones represent open-chain flavonoids; licochalcone A is amongst the most studied natural compounds for their broad-spectrum antimicrobial, anti-inflammatory, and antiproliferative activities (Figure 3). Other secondary metabolites

Table 1. Major phytochemical classes of *Glycyrrhiza glabra* and their representative compounds, approximate abundance, and biological activities

Chemical Class	Representative Compounds	Approximate Content (% DW)	Primary Activities
Triterpene Saponins	Glycyrrhizin, 18β-glycyrrhetinic acid, glabric acid	2-15%	Anti-inflammatory, hepatoprotective, antiviral
Flavonoids	Liquiritin, liquiritigenin, isoliquiritin, isoliquiritigenin	1-3%	Antioxidant, estrogenic, neuroprotective
Isoflavonoids	Glabridin, glabrol, glabrene, hispaglabridin A and B	0.5-2%	Antioxidant, anti-cancer, skin-whitening
Chalcones	Licochalcone A, B, C, D, echinatin	0.3-1.5%	Antimicrobial, anti-inflammatory, anti-cancer
Phenolic Acids	Ferulic acid, salicylic acid, caffeic acid derivatives	0.2-0.8%	Antioxidant, anti-inflammatory
Coumarins	Herniarin, umbelliferone, glycycoumarin	0.1-0.5%	Antispasmodic, antimicrobial
Essential Oils	Fenchone, linalool, benzaldehyde, β-caryophyllene	0.03-0.2%	Antimicrobial, aromatherapeutic

Note: The above table summarises the principal phytochemical classes identified in *G. glabra* roots along with representative compounds, their approximate concentration expressed as percentage of dry weight (% DW), and their major reported pharmacological activities. These bioactive constituents contribute to the plant's therapeutic effects, including anti-inflammatory, hepatoprotective, antiviral, antioxidant, antimicrobial, estrogenic, neuroprotective, and anticancer activities. DW – Dry Weight.

contributing to supplementary biological activities include phenolic acids, coumarins, and terpenoid constituents. The biosynthesis of these compounds is mediated by the mevalonate pathway for triterpene biosynthesis, whereas flavonoids, isoflavonoids, and chalcones are products of the phenylpropanoid-flavonoid pathway.

Figure 4 presents representative molecular structures of key phytochemicals isolated from *G. glabra* (liquorice), grouped according to their chemical classes. The triterpene saponins include glycyrrhizin, glabric acid, and 18β-glycyrrhetinic acid, which are primarily responsible for the plant's anti-inflammatory, hepatoprotective, and antiviral properties. The flavonoid group comprises compounds such as isoliquiritin, liquiritigenin, liquiritin, and isoliquiritigenin, known for their antioxidant, estrogenic, and neuroprotective

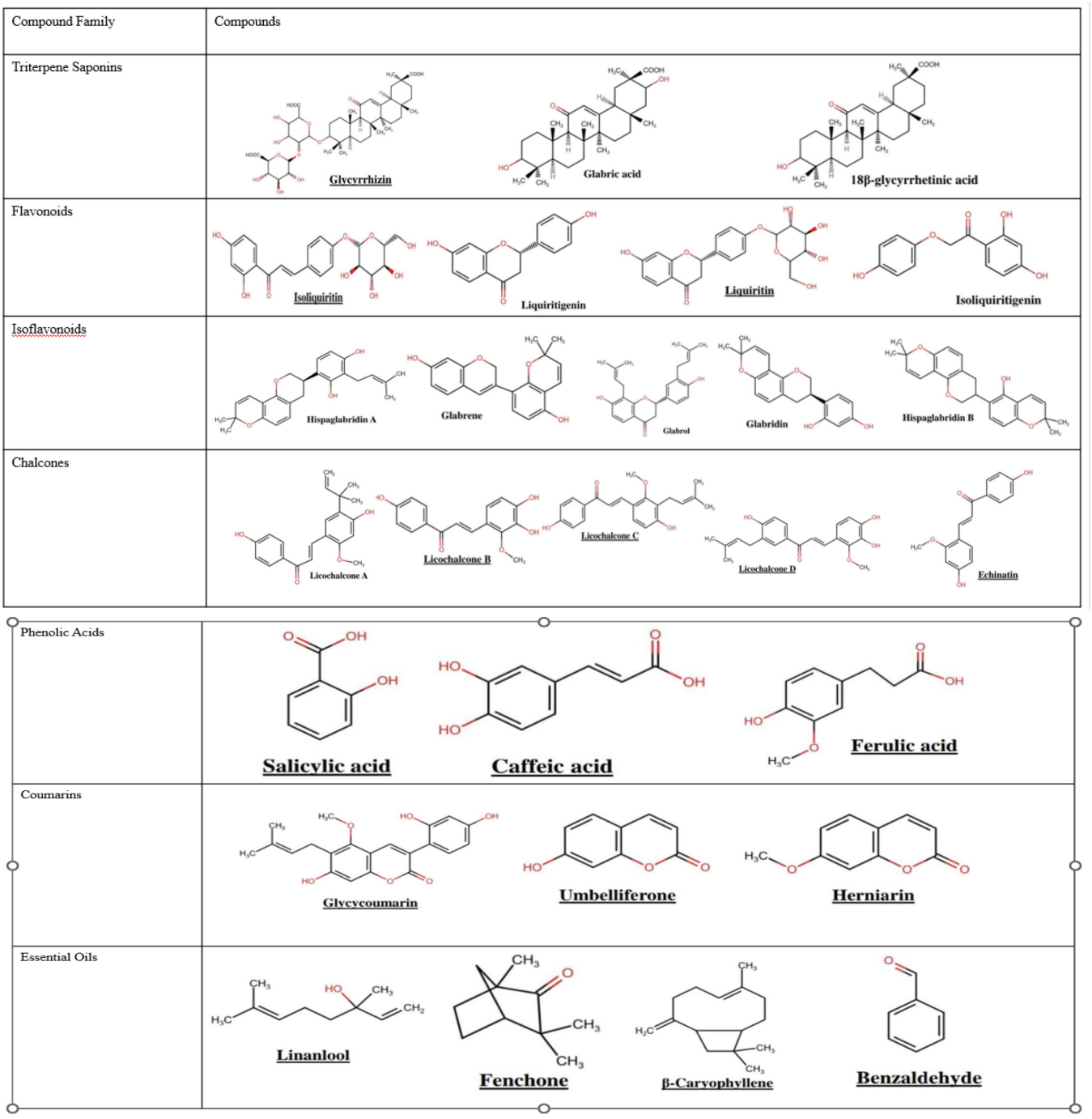


Figure 4. Chemical structures of major bioactive compounds in *Glycyrrhiza glabra.*

activities. Isoflavonoids, including glabridin, glabrol, glabrene, and hispaglabridins A and B, contribute to antioxidant, anticancer, and dermatological effects. Chalcones such as licochalcone A, B, C, D, and echinatin exhibit strong antimicrobial, anti-inflammatory, and chemopreventive activities. These phytochemical constituents collectively underpin the broad pharmacological profile of *G. glabra* and are widely studied for their therapeutic potential. The phenolic acid group includes compounds such as ferulic acid, caffeic acid derivatives, and salicylic acid, which contribute significantly to antioxidant and anti-inflammatory activities through free-radical scavenging and modulation of oxidative stress pathways. The coumarin class comprises molecules such as herniarin, umbelliferone, and glycycoumarin, which are associated with antimicrobial, antispasmodic, and hepatoprotective properties. The essential oil fraction contains volatile constituents, including fenchone, linalool, benzaldehyde, and β-caryophyllene that contribute to antimicrobial activity, aroma, and potential therapeutic effects in respiratory and digestive disorders. These compounds collectively expand the phytochemical diversity of *G. glabra* and contribute to its broad pharmacological and nutraceutical applications.

5. Extraction Techniques and Standardisation Approaches

The extraction method greatly affects phytochemicals, composition, and biological activity of *G. glabra* preparations. Traditional extraction methods like maceration, percolation, Soxhlet extraction, and decoction have been used over the years and have utilised different polarity solvents according to the targeted class of phytochemicals (Figure 4). Glycosides and saponins are preferentially extracted in aqueous and hydroalcoholic extracts, while organic solvents (ethyl acetate, chloroform and n-hexane) recover the lipophilic constituents, including prenylated isoflavonoids and chalcones[12].

The modern extraction technologies have significantly improved the efficiency, selectivity, and environmental sustainability. The UAE applies the acoustic cavitation method to break down the plant's cells, thus lessening the extraction duration from several hours to only a few minutes, and at the same time, 15-30% more of the product is obtained in comparison to the traditional methods. The MAE technique uses electromagnetic radiation for very rapid heating and breaking down of the cell walls, which leads to better extraction of both glycyrrhizin and flavonoids. SFE, with carbon dioxide, is a non-polar and selective extraction that is primarily directed towards heat-sensitive compounds and essential oils. There are other green chemistry processes, like the pressurised liquid extraction and the enzyme-assisted extraction[13].

Analytical characterisation and standardisation are essential for the control of quality, reproducible results, and the meeting of regulatory requirements. At present, high-performance liquid chromatography with UV or PDA detection is regarded as the gold standard for the quantitative determination of glycyrrhizin, liquiritin, and other phenolic compounds. Liquid chromatography combined with mass spectrometry (LC-MS and LC-MS/MS) provides higher sensitivity and the capability of structural elucidation, thereby facilitating a thorough metabolomics profiling. Gas chromatography-mass spectrometry can be applied to volatile components, while non-volatile ones necessitate suitable derivatisation treatments.

The standardisation procedures usually set the minimum glycyrrhizin percentage, which is 3-5% for raw materials and 20% for concentrated extracts, as the main marker compound, and the measurement of liquiritin as a secondary marker compound is added to the content of glycyrrhizin. Regulatory monographs are present in the European Pharmacopoeia, United States Pharmacopoeia, Chinese Pharmacopoeia, and Indian Pharmacopoeia, which determine their quality standards such as marker compound content, heavy metal limits, thresholds for microbial contamination, and organoleptic characteristics. DNA barcoding using ITS and matK regions grants molecular authentication against substitution or mixing with other morphologically similar but chemically different *Glycyrrhiza* species. Quality control has never been just about chemical standardization but the authentication of botanicals, determination of geographical origin through stable isotope analysis, and contaminant screening for pesticide residues, aflatoxins, and heavy metals are also aspects involved. Adherence to GACP and GMP assures uniform product quality from the cultivation

stage through processing to formulation, which is a necessity for regulatory approval and consumer safety.

6. Pharmacological and Therapeutic Potential

6.1 Antioxidant and Anti-inflammatory Activities

Oxidative stress and chronic inflammation represent the fundamental pathophysiological mechanisms in different degenerative diseases, metabolic disorders, and ageing processes, to mention a few. *G. glabra* exerts a powerful antioxidant capacity by complementary mechanisms: direct free radical scavenging, metal ion chelation, and upregulation of endogenous antioxidant defence systems (Figure 3). Isoflavonoid glabridin shows even higher antioxidant activity than vitamin E and efficiently neutralises ROS such as superoxide anion, hydroxyl radical, and peroxyl radicals (Figure 3)[14,15]. Liquiritin and liquiritigenin show a significant 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity and ferric reducing antioxidant power (FRAP).

The anti-inflammatory properties include the inhibition of important inflammatory mediators and signalling cascades. Glycyrrhizin and glycyrrhetinic acid inhibit Nuclear factor kappa B (NF-κB), a master transcriptional regulator that regulates the expression of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. Glycyrrhizin acts mechanistically in disrupting the high-mobility group box 1 protein, a DAMP molecule, which has been implicated in amplifying inflammatory reactions. Licochalcone A brings down the production of prostaglandin E2 and nitric oxide by inhibiting the expression of COX-2 and iNOS in activated macrophages, respectively. *G. glabra* extracts have shown comparable effectiveness to traditional non-steroidal anti-inflammatory drugs (NSAIDs) in animal models of both acute and chronic inflammation without related gastric toxicity. Carrageenan-induced paw oedema experiments show a dose-dependent decrease in inflammatory exudate and tissue swelling. Adjuvant-induced models of arthritis show suppression of systemic inflammatory markers, bone erosion, and joint inflammation. Regulation of mitogen-activated protein kinase (MAPK) pathways, including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK, which control inflammatory gene transcription, characterises the anti-inflammatory processes.

6.2 Antimicrobial and Antiviral Potentials

Against Gram-positive and Gram-negative bacteria, fungi, and viruses, *G. glabra* shows broad-spectrum antibacterial activity. Addressing major antibiotic resistance issues, the prenylated isoflavonoid glabridin shows strong antibacterial action against Methicillin-Resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE). With Minimum Inhibitory Concentrations (MIC) of 12.5–50 μg/mL[4], licochalcone A shows antibacterial action against *Helicobacter pylori*, the causative agent of peptic ulcers and gastric carcinoma. Membrane disturbance, quorum-sensing interference, and inhibition of bacterial efflux pumps all form part of the antimicrobial mechanisms.

Antifungal characteristics include activity against agricultural fungal pathogens as well as against opportunistic pathogens, including *Candida albicans, Aspergillus* species, and dermatophytes, including *Trichophyton* and *Microsporum*. Glabridin interferes with ergosterol synthesis pathways and destroys the integrity of the fungal cell membrane. Particularly with respect to respiratory viral diseases, the antiviral properties have attracted considerable interest. Through several mechanisms, including inhibition of viral adsorption, suppression of replication, and immunomodulation, glycyrrhizin demonstrates antiviral action against influenza virus, Respiratory Syncytial Virus (RSV), Herpes Simplex Virus (HSV), Human Immunodeficiency Virus (HIV), and hepatitis viruses.

The COVID-19 pandemic accelerated intensive research on *G. glabra* compounds against SARS-CoV-2. Computational docking studies identified glycyrrhizin and glabridin as potential inhibitors of viral spike protein, main protease, and RNA-dependent RNA polymerase. *In vitro* studies showed that glycyrrhizin inhibits SARS-CoV-2 replication in cell culture models at therapeutically achievable concentrations. *In vitro* studies demonstrated that glycyrrhizin inhibits SARS-CoV-2 replication in cell culture models at concentrations potentially achievable therapeutically; however, these findings have not yet been replicated in controlled human trials. The proposed antiviral mechanisms interfere with viral entry,

inhibition of replication machinery, and modulation of host immune responses, including attenuation of cytokine storms, remain mechanistically plausible but clinically unconfirmed[16].

6.3 Hepatoprotective and Gastroprotective Effects

The hepatoprotective properties of *G. glabra* are among the most well- known traditional uses, being supported by a significant amount of clinical evidence. Glycyrrhizin is the active pharmaceutical agent present in Stronger Neo-Minophagen C (SNMC), an injectable drug formulation approved in Japan since 1974 for treating chronic hepatitis. Clinical studies on SNMC treatment show that glycyrrhizin therapy reduces serum levels of ALT and AST in patients with chronic hepatitis B and C, improves histological hepatic inflammation scores, and lowers the incidence of hepatocellular carcinoma[17]. The hepatoprotective mechanisms consist of several synergistic pathways. Glycyrrhizin has a membrane-stabilising effect on the liver cells and therefore protects them from injuries caused by chemicals like carbon tetrachloride, acetaminophen, alcohol, and many other substances. This, in turn, activates the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, and consequently, phase II detoxification enzymes like glutathione S-transferase, NAD(P)H quinone oxidoreductase 1, and heme oxygenase-1 are produced in larger amounts. Glycyrrhizin inhibits the activation of liver stellate cells and the accumulation of collagen, which, in turn, reduces the progression of fibrosis in patients with chronic liver disease. There is also an immunomodulatory action, with modulation of the T-helper cell balance, suppression of hepatic inflammation, and without immunosuppression.

Gastroprotective properties validate traditional applications for peptic ulcer disease. The extracts speed up the healing process of gastric ulcers by several mechanisms, such as increasing mucus secretion and mucosal prostaglandin synthesis, improving mucosal blood flow, and inhibiting pepsin activity. Carbenoxolone, a synthetic derivative of glycyrrhetinic acid, was used as an anti-ulcer drug before the discovery of proton pump inhibitors. The flavonoid fraction has selective anti-*H. pylori* activity, complemented by cytoprotective effects. Clinical evidence suggests efficacy comparable to conventional therapies in uncomplicated peptic ulcer disease, with a better tolerability profile and lower recurrence rates if given in association with conventional treatment[18].

6.4 Neuroprotective and Cognitive Health Aspects

There is emerging evidence supporting neuroprotective potential relevant to neurodegenerative diseases and cognitive decline. Extracts of *G. glabra* protect against oxidative stress-induced neuronal injury in cellular and animal models for Alzheimer's disease, Parkinson's disease, and cerebral ischemia. Isoflavonoid isoliquiritigenin thus shows neuroprotection by activating estrogen receptors and phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) survival-promoting pathways[19,20]. Glabridin prevents β-amyloid-induced neurotoxicity and tau hyperphosphorylation, pathognomonic features of Alzheimer's disease[21]. Various reports have identified several phenolic compounds from *G. glabra* that exert neuroprotective actions by inhibiting ATP depletion and caspase 3/7 activation in cellular models for Parkinson's disease[19].

Mechanisms include antioxidant defence enhancement in neuronal tissue, anti-inflammatory effects in microglia, and neurotransmitter system modulation. Glycyrrhizin diminishes neuroinflammation through inhibition of HMGB1 and suppression of microglial activation. Recent studies in 2024 have shown that it is effective in preventing surgery-induced cognitive impairment and ischemic stroke by modulation of HMGB1/TLR4/NF-κB and Keap1/Nrf2 pathways. Animal studies demonstrate an improvement in spatial learning and memory in the scopolamine-induced amnesia model of animals administered with *G. glabra*. Active ingredients increase acetylcholine levels by inhibiting acetylcholinesterase and facilitating hippocampal neurogenesis. Neuroprotective effects also extend to peripheral neuropathy, with glycyrrhizin showing efficacy in diabetic neuropathy models. Although limited, clinical investigations have shown some potential cognitive benefits. One small, unregistered randomised controlled trial (study design, sample size, and trial registration details not reported in the source citation) found that *G. glabra* supplementation improved cognitive function scores and decreased oxidative stress markers among elderly subjects with mild cognitive impairment. At the preclinical level, a 2025 cell and animal model study reported synergistic

neuroprotective effects when combining *G. glabra* with curcumin in models of Alzheimer's disease, drastically lowering inflammatory markers and improving cognitive outcomes significantly[22]. Its monoamine oxidase inhibitory activity suggests possible antidepressant effects. Animal behavioural studies also point to such a possibility, showing reduced depression- and anxiety-like behaviours. However, comprehensive clinical trials are needed to prove therapeutic efficacy in human neurodegenerative conditions.

6.5 Anti-cancer and Chemopreventive Mechanisms

In addition, the antiproliferative and chemopreventive properties of *G. glabra* constituents show promise in diverse types of cancers through various mechanisms. Licochalcone A exerts selective cytotoxicity toward human cancer cell lines such as breast, prostate, colon, gastric, and oral squamous carcinoma cells with no significant effects on normal cells. Detailed mechanisms have been proposed for the induction of cell cycle arrest at G2/M phase, apoptosis via mitochondrial and death receptor pathways, and inhibition of invasion and metastasis of cancer cells. Glabridin exhibits estrogenic activity along with SERM properties and thus has proved to be of potential in hormone-dependent cancers. It triggers apoptosis in cancerous cells of the breast via caspase activation and modulation of the Bcl-2 family proteins. Isoliquiritigenin displays antiangiogenic action via inhibition of vascular endothelial growth factor signalling, which is very important in vascularisation and tumour growth. This compound also activates AMPK, which is a metabolic sensor that controls cellular energy homeostasis and is implicated in cancer metabolism[23]. Glycyrrhizin increases chemotherapeutic efficacy and simultaneously decreases toxicity in combination therapy protocols. *In vitro* studies reported in 2023 demonstrated that glycyrrhizin sensitises human ovarian cancer cell lines to cisplatin-induced cytotoxicity via synergistic mechanisms, including modulation of apoptotic pathways. These findings are confined to cell culture models and have not been evaluated in clinical oncology settings. Similarly, reversal of P-glycoprotein-mediated doxorubicin resistance and attenuation of chemotherapy-induced hepatotoxicity and nephrotoxicity have been documented exclusively in preclinical (*in vitro* and animal) models. Critically, no Phase I, II, or III clinical trial has yet investigated any *G. glabra* constituent as part of a combination oncology protocol; the entire synergy evidence base must therefore be graded as Preliminary per the evidence-grading criteria defined in Section 2.7 of this review. Its immunomodulatory properties can support immune surveillance against tumour development. The chemopreventive properties include the inhibition of carcinogen activation, enhancement of detoxification enzyme expression, and suppression of tumour promotion through anti-inflammatory mechanisms. Animal models of chemical carcinogenesis show that *G. glabra* pretreatment lowers the incidence, multiplicity, and tumour burden in colon, skin, and liver carcinogenesis protocols. Very few human studies have gone beyond observational data and small pilot trials; large-scale clinical investigations have yet to be conducted to fully establish anti-cancer efficacy and define optimal therapeutic protocols.

6.6 Cardiometabolic and Endocrine Modulation

The cardiometabolic effects and endocrine impacts of *G. glabra* L. exist because its main bioactive compound, glycyrrhizin, produces these effects. The active substance glycyrrhizin blocks the function of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which serves to transform active cortisol into its inactive cortisone form within peripheral body regions. The substance glycyrrhizin blocks the process through which this enzyme converts cortisol, leading to the situation where excess cortisol binds with mineralocorticoid receptors in the body, which produces effects that resemble aldosterone, a medical condition known as pseudoaldosteronism[24]. The body requires this mechanism to create sodium and water retention while producing potassium excretion that leads to hypokalemia and results in increased blood pressure. The relationship between these effects and glycyrrhizin intake shows that they develop after people consume more than 100 mg daily for multiple weeks. People who already suffer from hypertension, heart failure or kidney problems should limit their consumption of liquorice products because they belong to a high-risk group[24].

Research shows that *G. glabra* contains specific flavonoids, which include glabridin and liquiritin that demonstrate cardioprotective properties by their capacity to decrease oxidative stress through their antioxidant

functions and their ability to regulate lipid metabolism while blocking the NF-κB and MAPK pathways that lead to inflammation. The findings illustrate that *G. glabra* functions as a pharmacologically varied herb that provides therapeutic benefits for cardiometabolic disorders, while its excessive use leads to known dangers. The medical community requires standardised clinical trials to determine safe dosage limits and test treatment effectiveness for human cardiometabolic diseases[24].

7. Molecular Mechanisms of Action

The therapeutic versatility of *G. glabra* thus indicates the modulation of fundamental cellular signalling pathways and molecular targets controlling inflammation, oxidative stress, apoptosis, and cellular metabolism. The principal bioactive constituents interact with multiple molecular effectors to produce coordinated biological responses through network pharmacology principles, as illustrated in Figure 3.

7.1 NF-κB Signalling Pathway

The activation of NF-κB is inhibited in multiple ways by glycyrrhizin and glycyrrhetinic acid. They inhibit the phosphorylation of IKK, thus preventing the degradation of IκB and subsequent nuclear translocation of NF-κB. Besides, glycyrrhizin binds to HMGB1 and blocks its interaction with TLRs and RAGE, thereby attenuating the downstream activation of NF-κB. This pathway inhibition decreases the transcription of inflammatory cytokines, chemokines, adhesion molecules, and pro-inflammatory enzymes[25].

7.2 MAPK Signalling Cascades

The three major MAPK pathways, such as ERK1/2, JNK, and p38 MAPK, are modulated by the constituents of liquorice. Licochalcone A suppresses the phosphorylation of these kinases in response to inflammatory stimuli, thereby decreasing the AP-1 transcriptional activity. The differential modulation of the pathway depends on the cell type and stimulus; while most show inhibition, some contexts reveal pathway activation, particularly ERK in neuroprotection.

7.3 Nrf2-ARE Pathway

Glycyrrhizin activates the Nrf2-antioxidant response element (ARE) pathway, a master regulator of cellular antioxidant defences. As a result of the dissociation of Nrf2 from Keap1, Nrf2 migrates into the nucleus to induce the expression of cytoprotective genes encoding HO-1, NQO1, GSTs, and GCL. This pathway enhances cell resistance against oxidative stress and xenobiotic insults.

7.4 Apoptotic Machinery (Intrinsic and Extrinsic Pathways)

The anticancer effects induce modulation of the apoptotic pathways through both intrinsic mitochondrial and extrinsic death receptor mechanisms. Licochalcone A and isoliquiritigenin induced mitochondrial membrane permeabilisation, release of cytochrome c, and activation of caspase-9 and caspase-3. They regulate Bcl-2 family proteins through the mechanism of downregulating the anti-apoptotic ones, i.e., Bcl-2 and Bcl-xL, while the pro-apoptotic ones, i.e., Bax and Bad, are upregulated. The activation of the death receptor pathway accounts for the upregulation of Fas and death receptor 5 (DR5), which leads to the initiation of apoptosis through the caspase-8 pathway[26].

7.5 Context-Dependent PI3K/Akt Pathway Modulation

Glabridin and liquiritigenin are two compounds that can influence this essential survival and metabolism pathway oppositely, depending on the situation. In cases where neuroprotection is needed, these two compounds are able to trigger the phosphorylation of Akt, which in turn results in the survival of neurons. Conversely, in cases of cancer, some of the compounds created through the process of herbal medicine inhibit the pathway, thus leading to a decrease in the proliferation of cancer cells and also promoting the process of autophagy by the suppression of mTOR, the mammalian target of rapamycin. The modulation of the pathway results in the alteration of the downstream effectors that consist of glycogen synthase kinase-3β (GSK-3β), forkhead box O (FOXO) transcription factors, and p53, among others.

7.6 Estrogen Receptor Signalling

Among isoflavonoids, glabridin and glabrene have been recognised as possessing SERM (Selective Estrogen Receptor Modulator) activity through their interaction with ERα and ERβ. Such interaction takes place in a

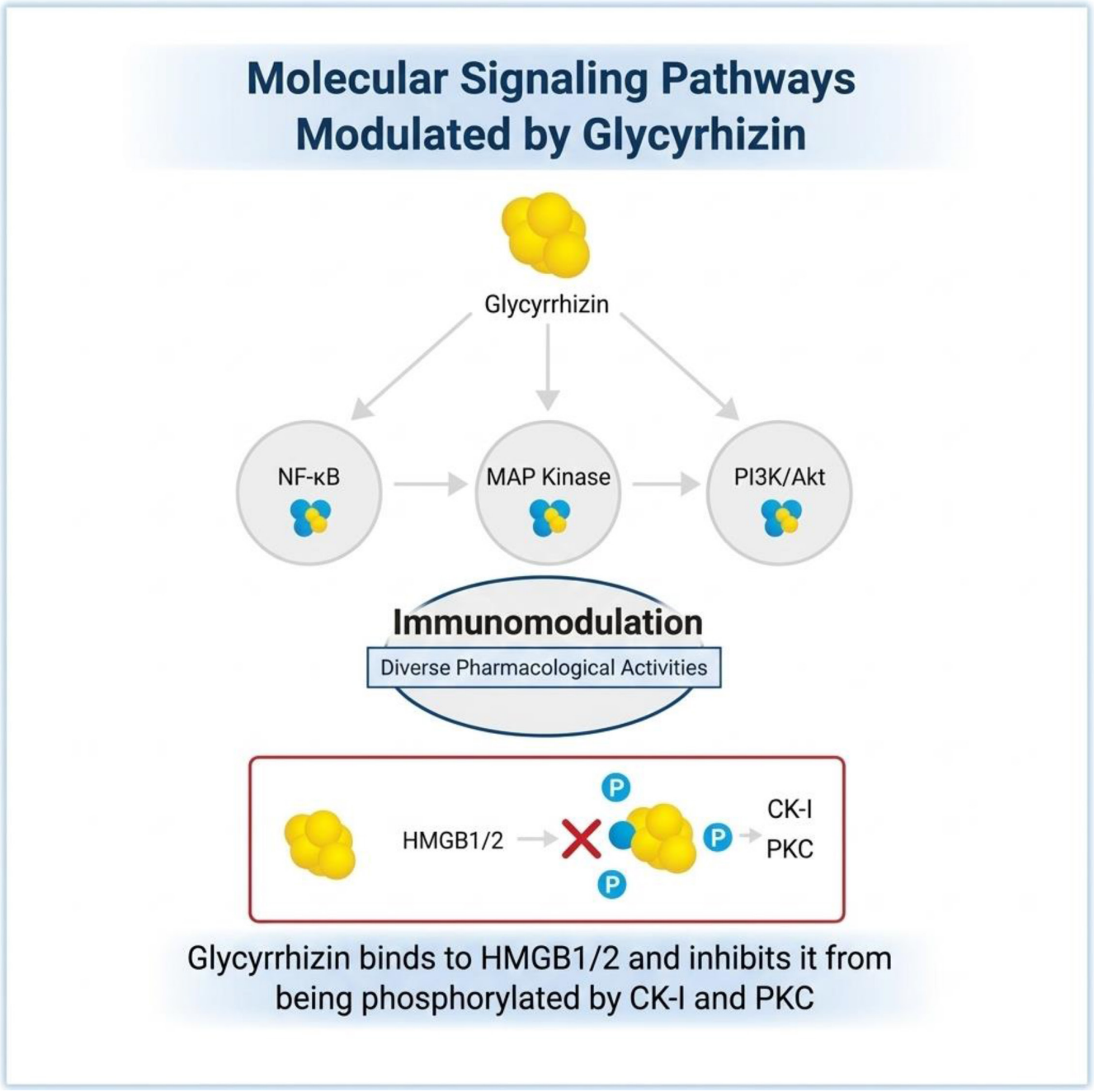


Figure 5. Molecular signalling pathways modulated by *Glycyrrhiza glabra* constituents.

manner that affinity varies, and hence, the effects are tissue-specific. Already, estrogenic activity has been deemed responsible for the qualities of neuroprotection, bone health, and cardiovascular health. On the contrary, it is not very clear where hormone-dependent cancers are concerned. The molecular selectivity is such that it involves different camps of co-regulators being recruited, as well as changes in the receptor's structure taking place.

7.7 Gene Expression and Epigenetic Regulation

Among the new findings is the involvement of epigenetic mechanisms, which take the form of DNA methylation and histone modification. Glycyrrhizin is an example of the expression of microRNAs (miRNAs) being changed that bear a relationship with inflammation, fibrosis, and cancer progression. The miRNAs being referred to include miR-122 (for liver

metabolism), miR-21 (for fibrosis and cancer), and miR-155 (for inflammation). Some of the compounds in question have been associated with activity that inhibits HDAC, which in turn has a consequence of changing chromatin remodelling and consequently the patterns of gene transcription.

Glycyrrhizin, the main triterpenoid saponin found in *G. glabra*, activates different cellular pathways which control inflammation and immune system function. The compound affects three essential pathways, which include nuclear factor-kappa B (NF-κB), mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), to control cytokine production and cell survival and immune responses. The compound glycyrrhizin binds to high mobility group box proteins (HMGB1/2) and damage-associated molecular patterns (DAMP), which start the process of inflammatory signalling. The binding of glycyrrhizin stops casein kinase I (CK-I) and protein kinase C (PKC) from phosphorylating HMGB proteins, which leads to decreased HMGB-mediated inflammatory responses that result in the compound's immunomodulatory and anti-inflammatory effects. NF-κB – Nuclear factor kappa-B; MAPK – Mitogen-activated protein kinase; PI3K – Phosphoinositide 3-kinase; Akt – Protein kinase B; HMGB – High mobility group box protein; CK-I – Casein kinase I; PKC – Protein kinase C.

The major signalling molecule, Glycyrrhizin, brings about diverse pharmacological activities through various cell signalling pathways such as NF-κB, MAP kinase, PI3K/Akt (Figure 5). One of such major activities is immunomodulation. Glycyrrhizin binds to HMGB1/2 and inhibits it from being phosphorylated by CK-I and PKC[27]. The multitargeting aspect is reminiscent of the network pharmacology model of traditional medicine in which the synergistic modulation of interconnected pathways leads to therapeutic effects that are usually unavailable to single-target treatments. The molecular complexity involved requires the use of systems biology techniques to provide a full understanding of the mechanisms.

8. Nutraceutical Formulations and Functional Food Applications

The use of *G. glabra* in nutraceutical and functional food products has been dazzlingly growing due to the consumers' demand for natural health products and the validated bioactive ingredients. All commercial applications had dietary supplements, herbal formulations, functional beverages, confectionery, and cosmeceuticals as the fields of application. Each application had its own special formulation considerations regarding stability, bioavailability, and organoleptic properties, and thus, they were all very different from each other.

8.1 Dietary Supplements

Glycyrrhiza glabra is used in single-herb and combination dietary supplements that are targeted at digestive, respiratory, hepatic, immune-enhancing, and adrenal support. Standardised extracts with specific glycyrrhizin content are used in the commercial preparations, and their range is usually from 12 to 20%, and they are available as capsules, tablets, or liquid extracts. DGL is a product that is made by partial elimination of glycyrrhizin, and its use is limited to the gastrointestinal area because it has minimal mineralocorticoid activity. DGL, on the other hand, does have flavonoids and other active components in it and is used for treating peptic ulcer disease and gastroesophageal reflux disease without any reports of causing hypertensive side effects[10]. Relying on herbal beverages, traditionally liquorice-based drinks are still the most consumed ones in the Mediterranean and Middle Eastern regions. *G. glabra* extracts are now widely used as sweeteners and in modern formulations of functional drinks due to their bioactive properties. Its overwhelming sweetness, which is about 50-fold that of sucrose, permits the reduction of the public's need for the health benefits offered in beverages. Liquorice root is frequently employed in herbal tea formulations for flavour blending and healing power pairing. The application of *G. glabra* in sports and energy drinks would be for electrolyte management and adrenal support, but the mineralocorticoid impact must be weighed in.

8.2 Concerning Bioavailability Enhancement Strategies

The development of advanced delivery systems has been the consequence of the relatively low oral bioavailability of some lipophilic constituents, especially glabridin and licochalcones. Nanoformulations such as liposomes, solid lipid nanoparticles, nanoemulsions, and polymeric nanoparticles are included in the category of advanced delivery systems that improve bioavailability, stability,

and targeted delivery. Research has revealed that nanoparticles laden with glabridin boost bioavailability 3-5 times when compared to common extracts. Cyclodextrin complexation increases the water solubility of non-polar constituents while preventing degradation. This means that the absorptive power of the phospholipid complexes or phytosomes is doubled by the fact that they become compatible with the lipid membrane[28].

8.3 Synergistic Herbal Formulations

Glycyrrhiza glabra is considered to be a synergist and harmoniser throughout the herbal traditions, and is usually found in multi-herb formulations. Among *Ayurvedic* medicines, *Triphala, Chyawanprash*, and many others are made with *Yashtimadhu* to not only mask but also to elevate the therapeutic effect. In Traditional Chinese Medicine, *Gan Cao* is used in approximately 60% of formulas to harmonise, lessen toxicity, and adjust pharmacokinetics. Recent research substantiates the synergistic interactions, reporting greater effectiveness and lower toxicity when combined[26].

8.4 Regulatory Status and Safety Considerations

The root and extracts of *G. glabra* are generally recognised as safe (GRAS) for use as flavouring agents at certain levels in the United States. The EFSA and several national agencies have published acceptable daily intake limits for glycyrrhizin, generally up to 100 mg/day for adults, with mineralocorticoid activity as a critical endpoint. Monographs from the Council of Europe and WHO also set limits on safe use and discuss contraindications. Nutraceutical preparations should be manufactured according to GMPs; their labelling should include the declared content of glycyrrhizin and safety warnings related to certain populations sensitive to the ingredient[29] (Table 2).

8.5 Cosmeceutical Applications

Skincare product incorporation is driven by the skin-whitening, anti-inflammatory, and antioxidant properties. Glabridin acts by inhibiting tyrosinase activity and melanin synthesis and is used in the treatment of hyperpigmentation and skin-lightening formulations (Table 2). Anti-inflammatory and antimicrobial properties of licochalcone A have applications in formulations for acne and rosacea. Antioxidant constituents protect against photoaging and UV-induced damage. Commercial cosmeceutical products include creams, serums, masks, and cleansers incorporating standardised *G. glabra* extracts at concentrations from 0.5 to 5%[30].

Table 2. Commercial, nutraceutical and therapeutic formulations of *Glycyrrhiza glabra* with typical dosage, applications, and standardisation parameters

Product Category	Formulation Type	Typical Dosage	Primary Applications	Standardization
Dietary Supplements	Capsules/Tablets	380-760 mg extract (1-3×/day)	Digestive health, immune support	12-20% Glycyrrhizin
DGL Products	Chewable tablets	300-400 mg (before meals)	Peptic ulcer, GERD	Glycyrrhizin Removed
Liquid Extracts	Tinctures/Syrups	1-4 mL (1-3×/day)	Respiratory support, Cough	1:5 or 1:1 Concentration
Herbal Teas	Tea bags/loose herb	1-5 g root (1-3 cups/day)	General wellness, Digestion	Whole herb
Functional Foods	Beverages, confections	Variable	Sweetening, health benefits	Natural Sweetener
Topical Products	Creams, serums	0.5-5% extract	Skin whitening, anti-ageing	1-10% glabridin

Note: The table presents information about common nutraceutical and herbal products, which include dietary supplements, deglycyrrhizinated liquorice (DGL) products, liquid extracts, herbal teas and functional foods and topical products which are derived from *Glycyrrhiza glabra* (liquorice). The package provides information about standard dosage ranges, main medical uses and the standardisation methods which manufacturers use to create their products. DGL products are processed to remove glycyrrhizin to minimise mineralocorticoid-related side effects such as hypertension and hypokalemia while maintaining the gastroprotective properties of flavonoids. DGL – Deglycyrrhizinated Licorice.

9. Synergistic Interactions and Combination Therapy

The concept of synergy, where the combined components result in effects that are more than the sum of the individual parts, is a fundamental principle of both ancient and modern herbal medicine. *G. glabra* is a classic example of a plant whose components have a strong synergistic effect both among themselves and with other plants or pharmaceuticals, and therefore is a plant that has been considered a harmonizer[31].

9.1 Intra-plant Synergy

Highly diversified phytochemicals of *G. glabra* display mutualistic interactions between the ingredients that affect the same and adjacent molecular paths. The cellular anti-inflammatory effect of glycyrrhizin and the antioxidant effect of flavonoids are so interdependent that they give overall cellular protection. Antimicrobial chalcones and immunomodulatory saponins together are creating an anti-infective effect that is more impressive than that of the isolated compounds. Pharmacokinetic synergy results from the action of flavonoids; they increase the bioavailability and tissue distribution of glycyrrhizin through the inhibition of metabolic enzymes and transporters[31].

9.2 Herb-herb Interactions

Traditional formulations are the combinations that offer the best medicinal effects. For example, in Traditional Chinese Medicine, the mixture of *G. glabra* with *Paeonia lactiflora* (*Shakuyaku-kanzo-to*) has been even more efficient in treating muscle cramps and spasms than each herb given separately. The same is true for ginger and *G. glabra,* where the latter's anti-inflammatory and gastroprotective effects are enhanced thanks to the complementary inhibition of COX-2 and LOX pathways. *Ayurvedic* formulations combine *Yashtimadhu* with *Terminalia chebula, Emblica officinalis*, and *Terminalia bellirica* in *Triphala*, a synergistic combination of antioxidants and immunomodulators[32].

9.3 Herb-drug Interactions

The herb *G. glabra* shows interactions with drug agents that are of clinical significance and that require monitoring and modification of the dose. The mineralocorticoid effects increase the risk of hypokalemia resulting from the use of thiazide and loop diuretics, which requires the drugs to be avoided or closely monitored. Glycyrrhizin increases the action of corticosteroids through 11β-HSD2 inhibition, possibly allowing for the reduction of corticosteroid doses in proper cases. The anticoagulant warfarin is less potent when taken together with liquorice because of the complex effects on vitamin K metabolism. The modulation of the CYP450 enzyme, particularly the CYP3A4 inhibition by glabridin, has the consequence of affecting the metabolism of numerous pharmaceutical substrates, such as, but not limited to, statins, calcium channel blockers, and immunosuppressants.

9.4 Synergistic Therapeutic Applications

The clinical and preclinical evidences are towards supporting the combination therapy approaches. The combination of Glycyrrhizin and traditional interferon therapy has been shown to give rise to greater efficacy in chronic hepatitis C engagement, along with sustained virological response rates getting improved. The mixture of *G. glabra* and NSAIDs results in much stronger anti-inflammatory properties and also less NSAID-induced gastropathy. In cancer therapy, the products of liquorice cause the cancer cells to become sensitive to the action of chemotherapeutic agents and at the same time protect the normal tissues from the toxicity due to the chemotherapy, thus it is called therapeutic synergy with improved safety profiles.

9.5 Case Study Examples

A clinical trial conducted by Raveendra *et al.,*[18] found that the addition of *G. glabra* extract to *Glycyrrhiza inflata* yielded better results in functional dyspepsia than the placebo response, with 56% of the patients achieving symptom resolution compared to only 7% in controls. Many formulations from traditional Japanese Kampo medicine include *G. glabra*: *Shakuyaku-kanzo-to* has evidence-based efficacy for muscle cramps in dialysis patients and athletes, and the multi-herb formulation *Yokukansan* has been demonstrated to be effective in the treatment of behavioural and psychological symptoms in dementia, likely due to synergistic modulation of the NMDA receptor-serotonin pathway. Understanding such synergistic interactions will provide the rationale for formulation design to maximise therapeutic benefits and reduce

adverse effects; this represents a new frontier in evidence-based integrative medicine.

10. Toxicological Profile and Safety Evaluation

Although *G. glabra* has a millennia-long history of safe traditional use, scientific toxicological assessment identifies dose-dependent adverse effects, which can be mainly attributed to glycyrrhizin-induced pseudoaldosteronism. Proper safety assessment has to cover acute, subchronic, and chronic toxicity studies, reproductive and developmental toxicity, genotoxicity testing, and the documentation of clinical adverse events.

10.1 Acute and Subchronic Toxicity

Animal studies show low acute toxicity, with oral LD_{50} values above 5,000 mg/kg body weight in rodents. Subchronic toxicity (90-day dosing) animal studies determine a no-observed-adverse-effect level (NOAEL) of around 100 mg glycyrrhizin/kg body weight/day in rats, approximately equivalent to 7 grams daily for a 70 kg human. Greater amounts cause mineralocorticoid side effects such as hypokalemia, sodium retention, and increased blood pressure. Histopathological examination shows no significant organ toxicity at moderate dosages, although thymic atrophy does occur at extremely high dosages, reflecting immunomodulatory effects[29].

10.2 Glycyrrhizin-induced Pseudoaldosteronism

It is characterised by the inhibition of the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which normally converts cortisol into an inactive cortisone in renal tubular cells. Inhibition allows cortisol to activate mineralocorticoid receptors, thus exerting aldosterone-like effects, including sodium retention, potassium excretion, hypertension, and oedema with suppression of the renin-aldosterone axis. There is marked individual variation in susceptibility depending on genetic polymorphisms in 11β-HSD2, baseline blood pressure, renal function, and concomitant medications. Clinical manifestations typically arise in persons consuming in excess of 100 mg glycyrrhizin daily (equivalent to about 50 grams of liquorice candy or 100-200 mL concentrated extract) on a chronic basis, over several weeks to months. Severe cases are associated with hypertensive crisis, severe hypokalemia (K+ <2.5 mEq/L), muscle weakness, rhabdomyolysis, and cardiac arrhythmias. The European Scientific Committee on Food established a safety limit of 100 mg glycyrrhizin daily for extended consumption, though sensitive individuals may experience effects at lower doses[24].

10.3 Contraindications and Special Populations

Glycyrrhiza glabra is contraindicated in patients with hypertension, cardiac disease, renal disease, hypokalemia, liver cirrhosis with ascites, and pregnancy. Concomitant use with potassium-wasting diuretics-thiazides, loop diuretics, corticosteroids, cardiac glycosides, and some antiarrhythmic agents-should be avoided or closely monitored medically. Pregnancy is contraindicated due to associations with prematurity, although causality has not been clearly established. There are limited data on the potential for androgenic effects in male infants exposed in utero[33].

10.4 Reproductive and Developmental Toxicity

Animal studies show no teratogenic effects at moderate doses, though high doses produce maternal toxicity and secondary fetal effects. Epidemiological studies suggest associations between heavy liquorice consumption during pregnancy and adverse outcomes, including preterm birth, though confounding factors complicate interpretation. Glycyrrhizin crosses the placenta and may affect fetal hypothalamic-pituitary-adrenal axis development. Breastfeeding safety remains inadequately studied, prompting cautious recommendations.

10.5 Genotoxicity and Carcinogenicity

Standard tests on genotoxicity, such as the Ames test, chromosomal aberration, and micronucleus, indicate no mutagenic and clastogenic potential either for *G. glabra* extracts or purified constituents at relevant concentrations. Long-term carcinogenicity studies in rodents have evidenced no tumorigenic effects; on the other hand, chemopreventive activities suggest potential anti-cancer properties. Weak estrogenic activities are identified by some studies in isoflavonoids, theoretically relevant to hormone-dependent cancers, even though epidemiological data do not indicate increased risk of cancer after moderate consumption[34].

10.6 Clinical Adverse Event Profile

Systematic reviews of clinical trials report that adverse events occur mainly at high doses or with long duration. Common adverse effects include headache, fatigue, hypertension, hypokalemia, and oedema. Serious but less common adverse events are hypokalemic myopathy, rhabdomyolysis, hypertensive encephalopathy, and Posterior Reversible Encephalopathy Syndrome (PRES). Deglycyrrhizinated preparations minimise mineralocorticoid-related adverse effects while retaining therapeutic efficacy for gastrointestinal uses (Table 3).

10.7 Risk Mitigation Strategies

Safe use involves attention to recommended dosages; 200-800 mg extract standardised to 20% glycyrrhizin daily for <4-6 weeks, monitoring of blood pressure and serum potassium in vulnerable patients, along with avoidance in contraindicated populations are necessary. It is crucial to recognise drug interactions. The use of DGL formulations is a safer choice for long-term treatment of gastrointestinal disorders. Patient care in terms of telling about the presence of liquorice in candies and drinks helps to prevent unintentional overconsumption[35] (Table 3).

11. Biotechnological and Genomic Insights

The biotechnological interventions are seen as the most effective and possibly the only way to get the most out of the *G. glabra* plant's sustainability, the potency of the phytochemicals, and the biosynthetic pathways of the therapeutic metabolites being driven backwards for understanding. The revelations brought about by the advanced plant tissue culture, molecular biology, genomics, and metabolic engineering are changing the picture of traditional cultivation, giving rise to precision biomanufacturing systems.

11.1 *In Vitro* Culture and Micropropagation

It is the plant tissue culture technologies that make it possible for the *G. glabra* plant to be propagated quickly, conserved as germplasm, and the production of secondary metabolites to be controlled without being affected by seasons or other environmental limitations. Established protocols for *G. glabra* include callus induction, shoot multiplication using axillary bud proliferation, adventitious shoot organogenesis, and somatic embryogenesis. Murashige and Skoog medium supplemented with appropriate auxins like 2,4-dichlorophenoxyacetic acid, indole-3-acetic acid, and cytokinins such as benzylaminopurine and kinetin support optimal growth and morphogenesis. High content of secondary metabolites has been obtained in cell suspension cultures and hairy root cultures elicited by *Agrobacterium rhizogenes* transformation. Elicitation approaches based on methyl jasmonate, salicylic acid, chitosan, and fungal elicitors enhanced the production of glycyrrhizin and flavonoids 2-5 fold or more over that seen in control cultures. Bioreactor-based production systems should make it possible to manufacture

Table 3. Safety profile, toxicological parameters, and risk assessment of *Glycyrrhiza glabra*

Parameter	Finding	Clinical Significance
Acute Toxicity (LD_{50})	>5,000 mg/kg (oral, rodents)	Low acute toxicity risk
NOAEL	~100 mg glycyrrhizin/kg/day	Safe margin at therapeutic doses
Primary Adverse Effect	Pseudoaldosteronism	Dose and duration-dependent
Threshold Dose	>100 mg glycyrrhizin/day (chronic)	Individual variation significant
Common Side Effects	Hypertension, hypokalemia, oedema	Monitoring recommended
Contraindications	Hypertension, cardiac/renal disease, pregnancy	Absolute in severe cases
Drug Interactions	Diuretics, corticosteroids, cardiac glycosides	Requires monitoring/avoidance
Genotoxicity	Negative	No mutagenic concern
Carcinogenicity	No evidence	Long-term safety supported

Note: The table shows essential toxicological and safety data which show how *G. glabra* (liquorice) and its main bioactive component glycyrrhizin impact human safety. The study presents data which includes acute toxicity levels, the no-observed-adverse-effect level (NOAEL), the most significant adverse effects, the threshold dose for toxicity, the drug interactions and the genotoxicity/carcinogenicity results. High glycyrrhizin consumption over an extended period results in pseudoaldosteronism through its effects on 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which leads to mineralocorticoid excess and hypertension, hypokalemia and fluid retention. $LD_{50,}$ which represents median lethal dose and NOAEL, which stands for no observed adverse effect level.

standardised phytochemical preparations on a large scale under controlled conditions with uniform quality, an important advantage over field-grown material.

11.2 Genomic and Transcriptomic Insights

Whole genome sequencing of the closely related species *Glycyrrhiza uralensis* and ongoing genomic projects in *G. glabra* reveal a genome size of approximately 4.1 Gb, with complex polyploid characteristics. Recent studies in comparative genomics and phylogenomics, using complete chloroplast genomes, have increased the resolution of *Glycyrrhiza* species evolution and genetic relationships in 2024. Comparative transcriptome studies among different tissues and developmental stages have identified tissue-specific gene expression patterns, including highly expressed genes encoding enzymes of triterpene and flavonoid biosynthesis pathways in roots. RNA-sequencing studies have been performed to characterise differentially expressed genes under abiotic and biotic stress and elicitor treatments, thus providing information on regulatory networks that control secondary metabolism[36]. Key identified biosynthetic genes include β-amyrin synthase (bAS), the committed enzyme in glycyrrhizin biosynthesis, catalysing cyclisation of 2,3-oxidosqualene to β-amyrin. Successive oxidations converting β-amyrin to glycyrrhetinic acid are catalysed by cytochrome P450 monooxygenases represented by CYP88D6 and CYP72A154. Glycosylation reactions yielding glycyrrhizin from glycyrrhetinic acid are catalysed by UDP-glucuronosyltransferases. Flavonoid and isoflavonoid biosynthesis is governed by chalcone synthase, chalcone isomerase, and various tailoring enzymes, including prenyltransferases. Transcription factors from the MYB, bHLH, and WRKY families regulate coordinate expression of biosynthetic genes[37].

11.3 Metabolomic Profiling

LC-MS-, GC-MS-, and NMR-based integrated metabolomics have identified more than 400 metabolites in *G. glabra*, uncovering chemotype variations among geographical accessions and cultivars. Very recently, in 2024, glycyrrhizic acid and glabridin-rich genotypes were identified from cultivated Iranian liquorice populations. The content of glycyrrhizic acid varied from 5.00 to 23.13 mg/g dry weight in the tested different genotypes[38]. mQTL mapping in segregating populations identifies genetic determinants that underscore the phytochemical composition. Metabolic pathway modelling points to bottleneck enzymes in limiting glycyrrhizin accumulation and thus delineates metabolic engineering. Environmental metabolomics provides a visualisation of the influence of cultivation conditions, format, water supply, temperature, and light-on phytochemical profiles and therefore enables the application of optimised agronomic practices[38].

11.4 Metabolic Engineering and Synthetic Biology

Genetic modification methods are directed towards either the enhancement of the production of important metabolites or the setting up of heterologous production systems. Overexpression of biosynthetic rate-limiting enzymes, such as β-amyrin synthase and CYP450s, in transgenic *G. glabra* hairy roots has enhanced glycyrrhizin content by 40-70%. Introduction of transcription factors that control secondary metabolism enhanced coordinate expression of entire biosynthetic pathways. This method of redirecting metabolic flux towards the desired products involves RNA interference (RNAi) silencing of competing pathways[39-41]. Such metabolites have heterologous production in microbial hosts like *Saccharomyces cerevisiae* and *Escherichia coli* and plant chassis like tobacco and Arabidopsis. The fermentation-based production of glycyrrhizin via the reconstitution of its complete biosynthetic pathway in engineered yeast faces optimisation challenges for competing metabolic demands and product toxicity. It is believed that modular pathway assembly and genome-scale metabolic modelling may improve the production efficiency of such metabolites through synthetic biology approaches[42].

11.5 CRISPR-based Genome Editing

The CRISPR/Cas9 approach allows for the precise manipulation of genes involved in *G. glabra* secondary metabolism, development, and responses to stresses. Targeted knockout of negative regulatory genes or competitive pathway branches may redirect carbon flux toward glycyrrhizin biosynthesis. Multiplex editing allows the simultaneous modification of several genetic targets for pathway optimisation. Base editing and prime editing allow nucleotide substitutions without double-strand breaks, thus providing a means to introduce advantageous alleles from wild germplasm or de novo designed superior variants of enzymes[43].

11.6 Marker-assisted Selection and Genomic Breeding

The identification and development of molecular markers, such as SSRs and SNPs, associated with high glycyrrhizin content, along with disease resistance and agronomic traits, accelerates traditional plant breeding. With Genome-Wide Association Studies (GWAS), it will be easy to identify genetic variants concerned with desirable traits. Genomic selection through the use of genome-wide marker information projects a path to predict breeding values to enable the selection of superior genotypes at the seedling stage. These strategies could reduce the breeding cycle from 8-10 years to 4-5 years and preserve genetic diversity for further long-term improvement and adaptation under the changing climate.

11.7 Conservation Biotechnology

The established cryopreservation protocols for the germplasm of *G. glabra* offer the possibility of the long-term storage of the genetic material and thus the preservation of the genetic resources to some extent; however, other ways, such as habitat loss and over-exploitation, still lead to genetic erosion. The application of DNA barcoding and phylogenetic analysis has been an important part of the process of determining conservation priorities since it allows the identification of genetically distinct populations and even the discovery of cryptic species that need safeguarding through these methods. The technology of synthetic seeds that utilise the combination of somatic embryos and encapsulation matrices opens up possibilities not just for the exchange of germplasm but also for field propagation.

12. Future Prospects and Research Gaps

Although there has been remarkable scientific development to support conventional uses, the background knowledge areas and research prospects are still major factors that hinder the realisation of the medicinal power of *G. glabra* and its sustainable use.

12.1 Clinical Translation Obstacles

The bulk of the pharmacological data is derived from laboratory and animal experiments; no properly executed clinical trials that correspond to the current standard of evidence-based medicine have been conducted. In fact, the regulatory approval and the adoption into clinical guidelines necessitate the conducting of phase II and III trials that are randomised, double-blind, placebo-controlled and very rigorous. The research areas that are most likely to reap the benefits of clinical studies are hepatitis and non-alcoholic fatty liver disease, peptic ulcer disease, COVID-19 and respiratory infections, neurodegenerative diseases, and metabolic syndrome. The testing should be carried out with recognised extracts that have clear qualitative and quantitative phytochemical composition, with a proper number of participants, using suitable comparators, and employing outcome measures that are validated[44].

12.2 Standardisation and Quality Control

The huge difference in phytochemical content among the different products on the market makes it difficult to achieve both consistency and therapeutic reliability. The creation of extensive quality standards that comprise several marker compounds in addition to glycyrrhizin, authentication techniques to prevent adulteration, and contamination tests guarantees the uniformity of the product. Pharmacopeial standards need to be updated to reflect current analytical capabilities and safety knowledge. The unification of standards on an international level benefits both global market access and consumer safety[45].

12.3 Mechanistic Understanding

Even though significant pathways have been revealed, a complete molecular-level examination has not yet been done. Networks of cell-level responses can be revealed, and new targets can be identified with the help of transcriptomics, proteomics, and metabolomics pharmacology. The utilisation of studies about the relationship between structure and activity (SAR) aids the refining of the main compounds for their effectiveness and specificity[46], recommends the investigation of pharmacokinetics profiles, which include the absorption, distribution, metabolism, and excretion (ADME) of a drug to come up with the best formulation and dosing strategies.

12.4 Personalised Medicine Approaches

Genetic variations in metabolic enzymes (CYP450s, UGTs, 11β-HSD2) and drug transporters impact

the response of each individual to *G. glabra*. Pharmacogenomic investigation will reveal the therapeutic efficacy and adverse event susceptibility biomarkers, thereby prescribing even more precise recommendations about the treatment. The interoperability with classic medicine constitutional types, like *Ayurvedic doshas* and TCM patterns, can create comprehensive and individualised approaches that may be worth further scientific validation[47].

12.5 Sustainable Production and Conservation

The pressure placed on *G. glabra* wild populations in their habitats where they originally grew is due to the ever-increasing demand. Sustainable harvesting is the practice with nature, and it includes the use of organic farming, water-saving irrigation practices, and preventive pest control, among others. The breeding of high-yield and disease-resistant plants through either traditional or biotechnological methods can reduce the pressure exerted on wild populations. The genetic resources will be preserved for the long term through protected areas, community-based conservation, and germplasm banks[48].

12.6 Novel Therapeutic Applications

The nanoparticles will assist in the targeted drug delivery, the combined therapy with the conventional medicines will be run, the semi-synthetic derivatives with better pharmacological profiles will be developed, and there will be an exploration of the poorly studied biological activities, such as antimalarial, antileishmanial, wound healing, and microbiome-modulating, that are related to the gut-brain axis and metabolic health. The role of *G. glabra* in regenerative medicine, especially in developing tissue engineering and stem cell differentiation, is opening up new areas[49].

12.7 Regulatory Harmonisation

Differences between the regulatory regimes of different countries are a major reason for international trade and clinical development being difficult. Working together towards the establishment of the same safety and efficacy standards, accepting the evidence of traditional medicine along with that of conventional clinical trials, and the provision of expeditious approval channels for plant-derived drugs are all measures that make it easier for products to enter markets. Unambiguous regulatory guidance on products made of more than one ingredient, modern formulations, and therapeutic claims not only allows but also encourages innovation while at the same time safeguarding public health[50-52]. The integration with conventional medicine refers to interdisciplinary collaboration among the stakeholders involved in traditional medicine, pharmacists, doctors, and regulators who will be able to create evidence-based guidelines for the inclusion of *G. glabra* into standard medical care. Development of safe and effective integrative care relies on standardised algorithms, monitoring protocols for herb-drug interactions, and practitioner education programs. Pragmatic trials and registry studies that document real-world effectiveness complement the efficacy data coming from controlled trials[53,54].

12.8 Economic and Social Dimensions

Analysis of the value chain, revealing the weaknesses in the steps of growing, changing, and selling, gives a guide on how to help the small farmers and native people. Fair trade and sharing of gains are the ways the benefits of the economy are made more equal. Consumers who know the quality signs, the right way to use the product, and the possible dangers are the ones who can make the most of their purchases. The combination of *G. glabra* growing with agroforestry and traditional farming can be a source of income to the farmers, and at the same time, the culture will not be lost[55-57].

13. Conclusion

The case of *G. glabra* is very characteristic of the way the world's traditional medicinal plant knowledge can be seen through the lens of modern scientific validation and finally presented as a multi-purpose herbal plant that can function as a medication or dietary supplement and has a broad spectrum of uses in therapy. The plant's vast phytochemical composition, which includes glycyrrhizin, flavonoids, isoflavonoids, and chalcones, results in its being able to affect many different physiological mechanisms at the same time by modulating the basic cellular pathways that are controlling inflammation, oxidative stress, and cellular homeostasis. A great deal of the preclinical studies

done on this plant have both confirmed the traditional uses and opened up new therapeutic areas, particularly in terms of liver protection, enhancing the immune response against viruses, protecting the nervous system, and controlling metabolism. When the different healing practices like traditional and complementary medicine come together with the backing of modern medicine based on evidence, then *G. glabra* will surely be one of the best examples that will tell us how old herbal remedies can still find their way into modern therapeutic innovation if they are not just scientifically but also biotechnologically researched thoroughly.

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Author Contribution

Vaishnavi Amit Herekar: Writing – original draft, visualisation, validation, methodology, literature review, formal analysis, data curation; Dr. Ullas Prasanna Sadarhalli: Writing – review and editing, validation, supervision, resources, project administration, conceptualization for the work carried out; Dr. T.H. Anantha Krishna: Writing – review and editing, validation, supervision, resources, project administration, conceptualization for the work carried out. All authors have read and agreed to the published version of the manuscript.