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Systematic Review of Anti-Inflammatory and Antiviral Properties of *Glycyrrhiza*

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Abstract *Glycyrrhiza* spp., a commonly used medicinal herb originating from plants of the genus *Glycyrrhiza* spp., exhibits significant anti-inflammatory and antiviral activities. The primary bioactive components of licorice include flavonoids, triterpenoids (including glycyrrhizic acid), polysaccharides, and other secondary metabolites. Many studies have reported that these compounds intervene in inflammation and viral infections through regulating various inflammatory mediators such as TNF-α, IL-1β, IL-6, key signaling pathways such as NF-κB, MAPK, JAK/STAT immune cell functions, and antioxidant and cytoprotective effects. The molecular mechanisms underlying the antiviral activity of licorice against viral replication and invasion have also been systematically explored both in vitro and in vivo. In recent years, critical roles of multi-omics approaches (genomics, proteomics, metabolomics), systems biology, and network pharmacology have been demonstrated in the study of the action mechanism of licorice bioactives, while the application of artificial intelligence and big data provides new instruments in the research of natural products. Licorice has the potential to be used in anti-inflammatory and antiviral therapy, as indicated by clinical studies, although its pharmacokinetics, bioavailability, standardized extraction, and safety need further assessment. The study will systematically summarize the progress, mechanisms, and application prospects of the anti-inflammatory and antiviral activities of licorice, providing theoretical guidance for the development of natural drugs, public health, and clinical use.
Keywords *Glycyrrhiza*; Anti-inflammatory; Antiviral; Flavonoids/triterpenoids; Multi-omics

1 Introduction

Botanically known as *Glycyrrhiza* spp., licorice has been one of the most commonly used traditional medicinal herbs for millennia in Chinese, Ayurvedic, and European medicine due to its sweet flavor and harmonizing properties in herbal formulations, with a wide spectrum of pharmacological effects including anti-inflammatory, antiviral, hepatoprotective, and immunomodulatory activities. Licorice is widely incorporated into traditional prescriptions for the treatment of respiratory, gastrointestinal, and immune-related disorders.

Inflammation and viral infections are central to the pathogenesis of numerous acute and chronic diseases. The role of natural products with dual anti-inflammatory and antiviral properties is of increasing interest because they offer safer alternatives for treatments and multi-target possibilities. Licorice holds immense potential as a source of bioactive compounds for its use in preventive and therapeutic applications, and the known mechanisms of this product lay the basis for drug discovery and clinical translation (Pastorino et al., 2018).

The major bioactive compounds of *Glycyrrhiza* are flavonoids, triterpenoids, especially glycyrrhizic acid, polysaccharides, and many other classes of secondary metabolites. Indeed, recent studies have shown that such compounds modulate key inflammatory mediators, including TNF-α, IL-1β, and IL-6, together with immune cell function, oxidative stress, and viral replication pathways. Although these compounds have recently been identified and their pharmacological effects clarified, comprehensive mechanistic insights into the mode of action and clinical validation remain incomplete and, therefore, require an integrated approach (Bisht et al., 2021; Simayi et al., 2021).

This study provides a comprehensive overview of the anti-inflammatory and antiviral actions of *Glycyrrhiza*, focusing on the key molecular mechanisms, major bioactive components, and translational applications. This study integrates data from multi-omics studies, preclinical experiments, and clinical research in a structured approach: major bioactive compounds; mechanisms of anti-inflammatory activity; mechanisms of antiviral activity; multi-omics and modern technological applications; clinical studies and safety evaluation; research challenges; and concluding perspectives.

2 Major Bioactive Components of *Glycyrrhiza*

2.1 Flavonoids and triterpenoids and their structural characteristics

The major flavonoids present in *Glycyrrhiza* include liquiritin, liquiritigenin, isoliquiritigenin, glabridin, and licochalcone A. They usually contain a C6-C3-C6 skeleton and are usually glycosylated or prenylated; thus, their solubility and bioactivity depend on the nature of the substituent. Flavonoids from *Glycyrrhiza* have shown potent anti-inflammatory, antioxidant, and antiviral activities, with the structural diversity underlying a wide range of biological activities (Frattaruolo et al., 2019; Hasan et al., 2021) (Figure 1).

The signature compounds of triterpenoid saponins, mainly from *Glycyrrhiza* roots, are glycyrrhizic acid and its aglycone, 18β-glycyrrhetinic acid, both produced by the hydrolysis of glycyrrhizic acid in vivo. These display remarkable anti-inflammatory, antiviral, hepatoprotective, and immunomodulatory activities. These triterpenoids are responsible for the sweetness of licorice (Sharifi - Rad et al., 2021; Yao et al., 2022; Shinu et al., 2023).

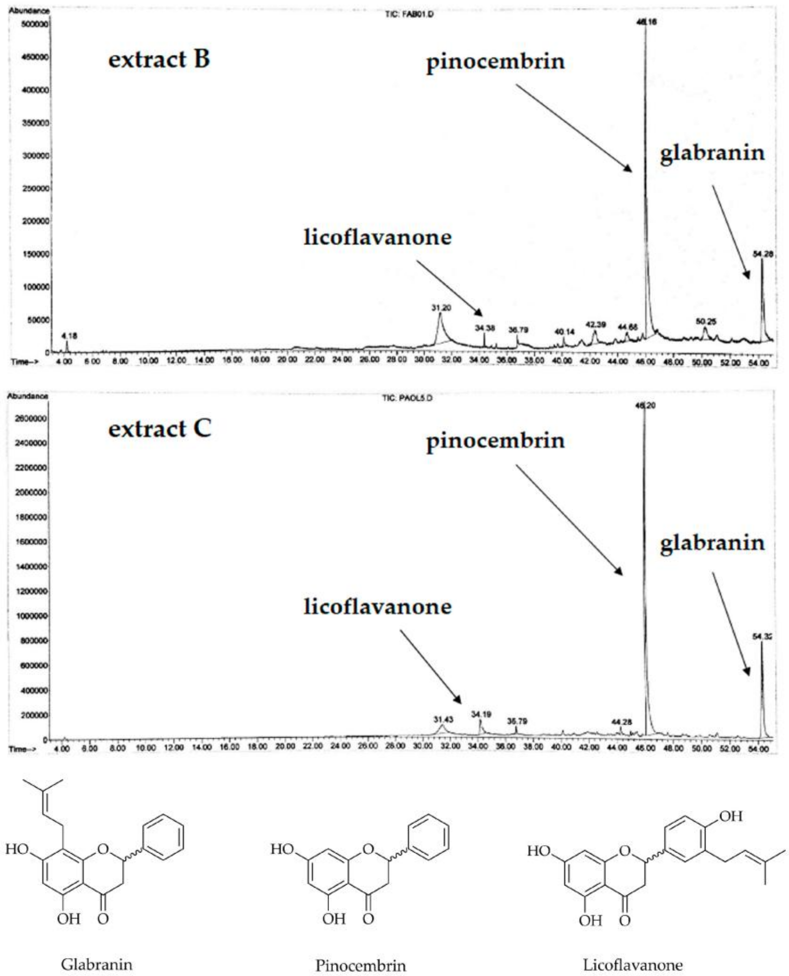

Figure 1 Chemical constituents of licorice and the active constituents of its main extracts and isolated compounds (Adopted from Frattaruolo et al., 2019)

2.3 Polysaccharides and other secondary metabolites

Immunomodulatory and antioxidant effects of polysaccharides, including sugars such as arabinose, glucose, and galactose present in *Glycyrrhiza*, have been identified. Other secondary metabolites involve coumarins and phenolic acids, further adding to the pharmacological profile of this plant (Hasan et al., 2021).

Generally, the therapeutic efficacy of *Glycyrrhiza* can be attributed to synergistic interactions among its constituents. Flavonoids and triterpenoids may exert mutual enhancement in anti-inflammatory and antiviral effects, while polysaccharides can modulate immune responses and improve the bioavailability of other compounds. It is these forms of synergy that form the backbone of the wide-ranging pharmacological activities both in traditional uses and in modern applications (Lu et al., 2021).

3 Anti-inflammatory Effects and Mechanisms of *Glycyrrhiza*

3.1 Regulation of inflammatory mediators

Bioactive compounds such as *Glycyrrhizic* acid, glabridin, and flavonoids, from *Glycyrrhiza*, significantly suppress the production and expression of pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6 in several in vitro and in vivo models. These effects have been seen in LPS-stimulated microglial cells, macrophages, and animal models of inflammatory disease, in which licorice constituents decrease cytokine mRNA and protein levels, as well as other mediators such as COX-2 and iNOS (Frattaruolo et al., 2019; Ko et al., 2021; Cheng et al., 2023).

3.2 Key signaling pathways (NF-κB, MAPK, JAK/STAT)

Anti-inflammatory activities of *Glycyrrhiza* components are mediated predominantly through inhibition of NF-κB and MAPK signaling pathways. Glycyrrhizic acid, licoflavanone, glabridin, and isoliquiritigenin suppress the phosphorylation and nuclear translocation of NF-κB subunits and inhibit the activation of the MAPK pathway, including that of ERK, JNK, and p38. Modulation of the JAK/STAT pathway is supported by some evidence, additionally dampening inflammatory signaling cascades (Sun et al., 2022; Cheng et al., 2025).

3.3 Modulation of immune cell functions

Licorice extracts and their bioactive compounds modulate immune cell activity through the inhibition of inflammatory cell infiltration, suppression of the activation of macrophages and microglia, and control of T cell differentiation. These may be responsible for the attenuation of tissue inflammation, improvement in disease symptoms in models of dermatitis, colitis, and pneumonia, as reported in some current literature (Ko et al., 2021; Sun et al., 2022; Cheng et al., 2023).

3.4 Antioxidant and cytoprotective effects

Both flavonoids and triterpenoids from *Glycyrrhiza* are potent antioxidants, mitigating ROS generation and increasing cellular antioxidant capacity. These effects prevent oxidative stress-related tissue injury and contribute to the anti-inflammatory and cytoprotective activities of licorice (Frattaruolo et al., 2019; Sun et al., 2022).

4 Antiviral Effects and Mechanisms of *Glycyrrhiza*

4.1 Inhibition of viral replication and entry

These compounds have inhibiting actions on viral replication through a mechanism of action that involves the inhibition of key viral enzymes, such as the main protease of SARS-CoV-2, and interference with viral entry into host cells. They can act directly by binding to viral surface proteins-e.g., spike protein of coronaviruses, envelope protein of dengue virus-and, as a result, prevent attachment and fusion with host cell membranes. *Glycyrrhiza*-based carbon dots and polysaccharides interfere with viral invasion and replication and can also stimulate host antiviral responses (Li et al., 2021; Wu et al., 2025).

4.2 Activity against different types of viruses

Glycyrrhiza exhibits anti-viral activity against SARS-CoV-2 and other viruses, including HCoV-OC43, HCoV-229E, dengue virus, pseudorabies virus, porcine reproductive and respiratory syndrome virus, and influenza viruses. In animal models, its efficacy in reducing viral loads and improving clinical outcomes was confirmed both in vitro and in vivo (Tong et al., 2020; Huan et al., 2021; Wu et al., 2025).

4.3 Key targets and signaling pathway regulation

The antiviral mechanism of *Glycyrrhiza* includes direct interaction with viral proteins such as spike protein and main protease, inhibition of virus-host receptor binding-such as ACE2 for SARS-CoV-2-and modulation of host signaling pathways, including the HMGB1/TLR4-MAPK p38 pathway. These mechanisms help in not only blocking viral replication but also suppressing virus-induced inflammation and oxidative stress (Li et al., 2021; Wu et al., 2025).

4.4 In vitro and in vivo experiments and pharmacological validation

Extensive in vitro studies of *Glycyrrhiza* extracts and isolated compounds have shown the inhibition of viral infection, replication, and cytopathic effects in cell cultures. In vivo studies have also been performed in mouse models of coronavirus and dengue virus infection. This resulted in reduced viral titers, alleviated symptoms, and improved survival after treatment with compounds from *Glycyrrhiza*, further supporting their pharmacological potential as antiviral agents (Tong et al., 2020; Li et al., 2021).

5 Multi-omics Approaches and Modern Technological Applications in *Glycyrrhiza* Research

5.1 Application of genomics in bioactive component research

Through a comparative genomics approach between *Glycyrrhiza* species, key genes and structural variations accounting for the biosynthesis of glycyrrhizin and characteristic flavonoids were pinpointed. High-quality genome assemblies and analyses of gene function have identified key transcription factors and biosynthetic enzymes involved in the production of pharmacologically active compounds, supporting molecular breeding and synthetic biology applications (Li et al., 2025; Zhou et al., 2025).

5.2 Insights from proteomics and metabolomics

The integration of metabolomics and transcriptomic analyses led to several thousand metabolites being identified, including flavonoids and terpenoids, and their association with gene expression patterns across the species of *Glycyrrhiza*. Proteomics and metabolomics have also been put into application in species differentiation and elucidation of the mechanisms behind some pharmacological effects (Yan et al., 2022; Lu et al., 2025).

5.3 Systems biology and network pharmacology approaches

Network pharmacology and systems biology approaches, facilitated by metabolomics, have thereby delineated the multi-target and multi-pathway actions of bioactive compounds in *Glycyrrhiza*. The hub genes, key signaling pathways, and protein-protein interaction networks associated with different diseases can be exposed using these approaches, which can shed light at the systems level and explain the therapeutic effect of *Glycyrrhiza* (Sharma and Yadav, 2022).

5.4 Potential of artificial intelligence and big data in natural product research

Artificial intelligence, including machine learning and semantic technologies, currently has an increased application to multi-omics data integration, target prediction, and drug-likeness screening. Such tools extend data visualization, predictive modeling, and the discovery of new bioactive compounds, thereby accelerating natural product research and applications in personalized medicine (Toussaint et al., 2023; De Filippis et al., 2025).

6 Clinical Research and Applications of *Glycyrrhiza*: Anti-Inflammatory and Antiviral Effects

6.1 Progress in clinical studies on anti-inflammatory and antiviral effects

Clinical trials and translational studies have revealed the remarkable anti-inflammatory and antiviral activities of *Glycyrrhiza* extracts and glycyrrhizin. More importantly, a randomized clinical trial of nebulized glycyrrhizin/enoxolone in COVID-19 patients modulated inflammatory cytokines, especially IL-17A, and improved antiviral immune responses without any serious side effects, highlighting safety and efficacy in acute viral infection, as evidenced by Zendejas-Hernandez et al. (2024). Glycyrrhizin is given intravenously for chronic hepatitis and acute autoimmune hepatitis, resulting in improved liver function and reducing the progression to hepatocellular carcinoma, according to Pastorino et al. (2018); Batiha et al. (2020). Antiviral activities of *Glycyrrhiza* extracts have been determined against herpes simplex, influenza virus, and dengue virus, thus displaying broad-spectrum activity through the action mode related to virus replication inhibition and host immune response modulation (Sun et al., 2019; Stecanella et al., 2021; Shi et al., 2023) (Figure 2).

6.2 Safety and toxicological evaluations

Glycyrrhiza and its main constituent, glycyrrhizin, are GRAS in foods and pharmaceuticals, respectively, and are widely used clinically for many years. Recent research supports their safety profile: low toxicity, both in vivo and clinically, has been reported lately (Zendejas-Hernandez et al., 2024). Clinical side effects following excessive or chronic consumption include hypertension, hypokalemia, and interactions with cytochrome P450 enzymes. It therefore requires very careful dosing and monitoring, particularly in at-risk populations (Pastorino et al., 2018; Husain et al., 2021). Toxicity testing of various *Glycyrrhiza* extracts demonstrated their good tolerability and biocompatibility, with below-detection limits for heavy metals and contaminants (Semenescu et al., 2024).

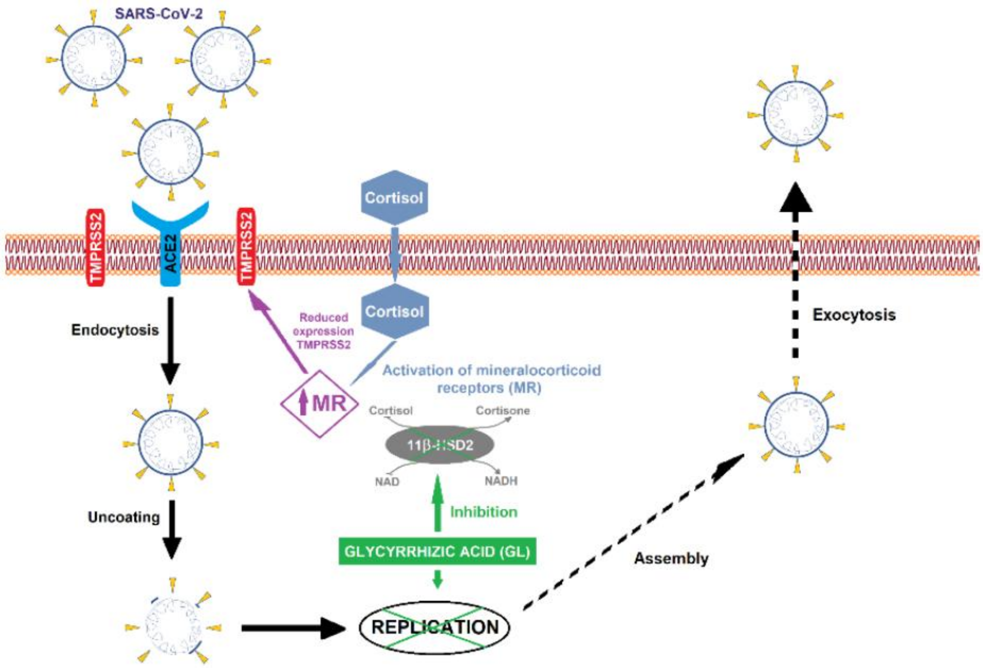

Figure 2 Schematic diagram of the effect of oxalic acid on viral replication (Adopted from Stecanella et al., 2021)

6.3 Applications in functional foods, natural drugs, and pharmaceutical development

Glycyrrhiza finds broad applications as a functional food ingredient, natural drug, and in pharmaceutical formulations due to its sweetening properties and health benefits. Extracts of the plant are used in the preparation of nutraceuticals, herbal medicines, and adjuvants in antiviral and anti-inflammatory therapies (Pastorino et al., 2018; Liu et al., 2025). These are enabled by drug delivery improvements-for example, nanoparticles that use glycyrrhizin as a basis-improving bioavailability and therapeutic efficacy, in particular, for antiviral and anti-inflammatory applications (Stecanella et al., 2021; Zhao et al., 2021). The wide pharmacological profile and safety of the plant justify the further development of the plant for food and pharmaceutical industries (Sharifi‐Rad et al., 2021; Liu et al., 2025).

7 Research Hotspots and Challenges

7.1 Challenges in mechanistic studies and complex component interactions

In fact, though many bioactive compounds were elucidated in *Glycyrrhiza*, the elucidation of their precise modes of action has always been complicated by their chemical composition. A combination of several flavonoids, triterpenoids, polysaccharides, and minor metabolites may be synergetic or antagonistic, hindering attempts at dissection of specific molecular pathways. The respective interplay among its components and their combinatory mode of action against inflammatory mediators, immune responses, and viral replication are not fully explained; it thus requires integrative approaches involving biochemical assays, network pharmacology, and systems biology (Bakr et al., 2022).

7.2 Pharmacokinetics and bioavailability of active components

Most compounds of *Glycyrrhiza*, like glycyrrhizic acid and catechins, have low oral bioavailability, rapid metabolism, or poor tissue distribution. These limit the pharmacokinetic translation of in vitro efficacy to in vivo therapeutic potential. Absorption, metabolism, distribution, and excretion need to be taken into consideration to optimize the dosage forms and enhance systemic efficacy. Prodrugs, nanocarriers, or chemical modification are being used to enhance the bioavailability, yet the thorough pharmacokinetic profiling is incomplete (Sharifi‐Rad et al., 2021).

7.3 Standardized extraction and quality control issues

Such factors as cultivation conditions, time of harvest, extraction methods, and processing strongly influence the composition and concentration of active compounds in *Glycyrrhiza*. Indeed, poor standardization of extraction and unsatisfactory quality control compromise study reproducibility and clinical applicability. For this purpose, the development of fingerprints based on reliable chemicals, standardization based on the guidance of bioactivity, and establishment of regulatory frameworks are the basic steps toward research and therapeutic application (Batiha et al., 2020).

7.4 Future research directions and technological opportunities

Future research needs to be focused on integrating multi-omics approaches-genomics, transcriptomics, proteomics, metabolomics-with computational modeling and artificial intelligence to decipher complex component interactions and predict biological effects. Recent advances in high-throughput screening, single-cell analyses, and organ-on-chip models offer opportunities to study pharmacokinetics, toxicity, and mechanisms under physiologically relevant conditions. Further well-designed clinical trials are needed to provide a bridge from traditional usage to evidence-based therapeutic applications by validating efficacy and safety.

8 Concluding Remarks

In the last few decades, studies have established *Glycyrrhiza* as a rich source of bioactive compounds, including flavonoids, triterpenoids, and polysaccharides, having significant anti-inflammatory and antiviral properties. Experimental studies have indicated that these compounds modulate key inflammatory mediators, regulate immune cell functions, and impede viral replication in a wide range of pathogens. The mechanistic studies identified critical signaling pathways like NF-κB, MAPK, and JAK/STAT as central targets of *Glycyrrhiza* bioactives. Overall, a recurring pattern is the multi-targeted and synergistic action of its complex chemical constituents, pointing toward its potential as a holistic therapeutic agent.

To illustrate the molecular basis of *Glycyrrhiza*'s pharmacological effects fully, integrating genomics, transcriptomics, proteomics, metabolomics, and network pharmacology is very important. Such multi-omics approaches could systematically map the interactions of components and targets, pathway crosstalk, and synergistic mechanisms that cannot be done in single-component or single-pathway studies. Their integration with advanced computational modeling for the identification of novel bioactive molecules and understanding their precise roles in anti-inflammatory and antiviral responses is crucial, along with necessary experimental validation.

Most of the bioactivities documented for *Glycyrrhiza* provide a sound scientific basis for the development of natural therapeutics, functional foods, and complementary medicines. The development of effective treatments depends on enhancing bioavailability, standardizing extraction methods, and carrying out appropriate clinical trials. Moreover, its potential role in the management of viral outbreaks, chronic inflammatory conditions, and immune-related disorders places it within a very important context with regard to public health. Future studies should focus on translating mechanistic insights into clinical applications in order to maximize the therapeutic and preventive potentials of the compounds derived from *Glycyrrhiza*.

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Conflict of Interest Disclosure

The authors affirm that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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