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*Original Article*

# Multi-Target Hepatoprotective Mechanisms of *Glycyrrhiza glabra*: Molecular Pathways, Experimental Evidence, and Clinical Translation

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## ABSTRACT

Background: Liver diseases including non-alcoholic fatty liver disease, viral hepatitis, drug-induced liver injury, cholestatic injury, and fibrosis are driven by interconnected mechanisms such as oxidative stress, inflammation, apoptosis, mitochondrial dysfunction, and dysregulated lipid metabolism. *Glycyrrhiza glabra* has long been used in traditional medicine and contains multiple bioactive compounds with potential hepatoprotective activity. Objective: To critically synthesize the phytochemical basis, molecular pathways, experimental evidence, and clinical translational relevance of *Glycyrrhiza glabra* in liver protection. Methods: A structured narrative review was conducted using literature from major biomedical databases and reference screening, with emphasis on liver-specific studies evaluating extracts, isolated constituents, and derivatives of *Glycyrrhiza glabra.* Evidence was organized by phytochemistry, molecular mechanisms, preclinical hepatoprotective models, and clinical relevance. Results: The strongest evidence supports antioxidant and anti-inflammatory effects mediated through Nrf2 activation, NF-κB suppression, modulation of Bax/Bcl-2 and caspase signaling, inhibition of CYP2E1-related toxic bioactivation, and partial attenuation of TGF-β1-associated fibrogenesis. Glycyrrhizin, 18β-glycyrrhetinic acid, glabridin, liquiritigenin, isoliquiritigenin, and magnesium isoglycyrrhizinate were the principal compounds linked to hepatoprotection. Experimental studies consistently reported reductions in ALT, AST, ALP, malondialdehyde, and inflammatory cytokines with restoration of endogenous antioxidant defenses and histological improvement. Clinical evidence suggests biochemical benefit in selected liver disorders, but remains heterogeneous. Conclusion: *Glycyrrhiza glabra* is a promising multi-target hepatoprotective agent, although clinical translation requires standardized formulations, pharmacokinetic optimization, safety monitoring, and well-designed randomized trials. Keywords: *Glycyrrhiza glabra*; glycyrrhizin; hepatoprotection; oxidative stress; inflammation; NAFLD; drug-induced liver injury

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## INTRODUCTION

Liver diseases remain a major global health burden and include a heterogeneous spectrum of disorders ranging from non-alcoholic fatty liver disease (NAFLD), viral hepatitis, drug-induced liver injury (DILI), cholestatic liver disorders, and progressive fibrotic liver disease to cirrhosis and hepatocellular carcinoma. Despite differences in etiology, many of these conditions converge on common pathobiological processes, particularly oxidative stress, inflammatory signaling, mitochondrial dysfunction, dysregulated lipid metabolism, apoptosis, and extracellular matrix remodeling. These interconnected mechanisms drive hepatocellular injury and promote progression from early biochemical disturbance to fibrosis, organ failure, and malignancy. Among these disorders, NAFLD has emerged as one of the most prevalent chronic liver diseases worldwide, with rising burden in both developed and developing countries. In Pakistan, recent evidence indicates a particularly high

prevalence of NAFLD in the general population, with substantially greater rates among individuals with diabetes and obesity, underscoring the need for safe and mechanistically targeted preventive and therapeutic strategies (1-5).

Chronic viral hepatitis also continues to impose a substantial disease burden worldwide, with hepatitis B virus and hepatitis C virus remaining major contributors to cirrhosis, liver failure, and liver cancer. Similarly, DILI and toxicant-induced liver injury remain clinically important because the liver is the central organ for xenobiotic metabolism and is highly vulnerable to oxidative biotransformation, toxic metabolite generation, and immune-mediated injury. Cholestatic liver disorders further compound this problem through bile acid accumulation, membrane injury, inflammatory activation, and progressive fibrosis. Although pharmacological advances have improved outcomes in selected liver diseases, currently available therapies are often disease-specific, incompletely effective, associated with adverse effects, or limited in their capacity to address the multiple overlapping molecular pathways that sustain hepatic injury. This has strengthened interest in multi-target agents capable of simultaneously modulating oxidative, inflammatory, apoptotic, fibrotic, and metabolic pathways relevant to liver protection (1,12-18).

Medicinal plants have long provided structurally diverse bioactive compounds with antioxidant, anti-inflammatory, antiviral, and cytoprotective potential, and they continue to serve as important sources for therapeutic discovery. Among them, *Glycyrrhiza glabra*, commonly known as liquorice, occupies a prominent position in traditional systems of medicine including Traditional Chinese Medicine, Ayurveda, and Middle Eastern medicine, where it has historically been used in disorders involving the digestive, respiratory, and hepatobiliary systems. The roots and rhizomes of *G. glabra* contain a broad spectrum of secondary metabolites, particularly triterpenoid saponins, flavonoids, chalcones, isoflavonoids, and polysaccharides, many of which possess pharmacological properties directly relevant to hepatic protection. Glycyrrhizin and its metabolite 18β-glycyrrhetinic acid are among the best-characterized constituents and have been linked to anti-inflammatory, antiviral, antioxidant, anti-apoptotic, and membrane-stabilizing activities. Other constituents, such as glabridin, liquiritigenin, and isoliquiritigenin, have also demonstrated strong redox-modulating and inflammation-regulating effects in experimental systems, suggesting that liquorice exerts hepatoprotection through coordinated multi-compound and multi-pathway interactions rather than through a single dominant mechanism (8,20,22-25,39-45,63-70).

Experimental studies increasingly support the hepatoprotective potential of *G. glabra* across diverse injury models. In toxic liver injury, liquorice-derived compounds have been shown to reduce serum alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase, attenuate lipid peroxidation, preserve endogenous antioxidant systems, and improve histopathological architecture. Mechanistically, these effects have been associated with activation of the Nrf2-dependent antioxidant response, suppression of NF-κB-mediated inflammatory signaling, modulation of Bax/Bcl-2 and caspase-dependent apoptosis, inhibition of CYP2E1-mediated toxic bioactivation, and attenuation of fibrogenic mediators such as transforming growth factor-β1. Similar benefits have been reported in methotrexate-, cadmium-, amiodarone-, and carbon tetrachloride-induced hepatic injury models, as well as in metabolic models characterized by steatosis and oxidative stress. In addition, certain liquorice derivatives, including magnesium isoglycyrrhizinate, have attracted interest because they appear to retain hepatoprotective efficacy while potentially improving tolerability profiles in clinical use (12,20,35,76-77,87-92,95,97,99-100).

Clinical interest in *G. glabra* and its derivatives is also increasing, particularly in chronic hepatitis, NAFLD, and other inflammatory liver conditions. Glycyrrhizin-containing preparations have been used in parts of Asia for chronic hepatitis, and emerging studies suggest biochemical improvement in liver enzyme profiles and selected pathological features in some patient populations. However, translation from preclinical promise to clinical application remains incomplete. The available literature varies

considerably in terms of plant preparation, constituent standardization, route of administration, dosage, study design, comparator selection, and outcome assessment. Moreover, the safety profile of liquorice-derived compounds requires careful attention, particularly with prolonged exposure or higher doses, because mineralocorticoid-like effects such as sodium retention, hypokalemia, edema, and hypertension may complicate therapeutic use. These translational considerations make it essential to critically distinguish between mechanistic plausibility, preclinical efficacy, and clinically validated benefit rather than treating them as equivalent levels of evidence (12,42-45,67,69,80,84-86).

Although several publications have reviewed the broad phytochemistry and pharmacology of *G. glabra*, the hepatology-focused evidence remains dispersed across phytochemical reviews, disease-specific experimental reports, and clinically oriented summaries. A clear synthesis linking constituent-specific actions with major hepatoprotective molecular pathways and with the translational relevance of experimental and clinical findings is still needed. The present review was therefore undertaken to critically integrate the available evidence on *G. glabra* as a hepatoprotective medicinal plant, with specific emphasis on its principal bioactive constituents, their molecular targets, the major signaling pathways involved in oxidative stress, inflammation, apoptosis, fibrogenesis, and xenobiotic metabolism, and the extent to which these mechanisms are supported by in vitro, in vivo, and clinical studies. By organizing the literature around liver-specific pathobiology and translational relevance, this review aims to clarify the therapeutic promise, limitations, and future research priorities for *G. glabra* in modern hepatology (8,22,25,42,67,69,80,85).

## MATERIALS AND METHODS

This article was designed as a structured narrative review focused on the hepatoprotective effects of *Glycyrrhiza glabra* and its major bioactive constituents. The review was planned to synthesize mechanistic, experimental, and clinical evidence relevant to liver protection while maintaining a clear emphasis on translational applicability. The scope was restricted to studies examining *G. glabra*, its authenticated extracts, or liver-relevant isolated constituents and derivatives, including glycyrrhizin, glycyrrhizic acid, 18β-glycyrrhetinic acid, glabridin, liquiritigenin, isoliquiritigenin, and magnesium isoglycyrrhizinate, in the context of hepatic oxidative stress, inflammation, apoptosis, fibrosis, steatosis, cholestatic injury, toxic injury, viral hepatitis, or clinically measurable liver outcomes.

The literature was identified through a focused search of major biomedical databases, including PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. Search terms were developed to capture botanical, phytochemical, mechanistic, and clinical dimensions of the topic and included combinations of "*Glycyrrhiza glabra*," "liquorice," "licorice," "glycyrrhizin," "glycyrrhetinic acid," "glabridin," "liquiritigenin," "isoliquiritigenin," "magnesium isoglycyrrhizinate," "hepatoprotective," "liver injury," "NAFLD," "fatty liver," "viral hepatitis," "drug-induced liver injury," "cholestasis," "fibrosis," "oxidative stress," "inflammation," "Nrf2," "NF-κB," "TGF-β," "CYP2E1," and "apoptosis." Reference lists of relevant review articles and primary studies were also screened manually to identify additional eligible literature and reduce the risk of omission of influential studies.

Studies were considered for inclusion if they met at least one of the following criteria: they evaluated the phytochemical composition of *G. glabra* in a way relevant to hepatoprotection; investigated molecular or cellular mechanisms associated with liver protection; assessed biochemical, histological, or mechanistic hepatic outcomes in animal or in vitro models; or reported clinical findings related to liver disease, liver function, or hepatoprotective use of *G. glabra* derivatives. Priority was given to peer-reviewed original studies and high-quality review articles that were directly relevant to hepatic outcomes. Literature focused exclusively on non-hepatic pharmacological actions without a clear mechanistic or translational connection to liver protection was not emphasized in the synthesis. Where multiple reports addressed overlapping themes, preference was given to studies that provided clearer

mechanistic data, disease-specific relevance, stronger methodological detail, or greater translational value.

Data were extracted narratively and organized into four analytic domains: phytochemical constituents relevant to hepatoprotection, molecular pathways involved in hepatic protection, experimental evidence from in vitro and in vivo models, and clinical relevance with translational considerations. For each included study, emphasis was placed on the type of preparation or constituent evaluated, liver injury model or disease context, principal molecular targets or signaling pathways, biochemical and histological outcomes, and key safety or translational observations. Mechanistic interpretation was limited to pathways directly examined or reasonably supported by the reported biomarkers and experimental design, and care was taken to distinguish direct target-level evidence from broader pathway-level inference.

To improve internal validity of the review, the synthesis was structured to compare findings across distinct categories of hepatic injury rather than merging all evidence into a single descriptive narrative. Toxicant-induced injury, metabolic liver injury, inflammatory and fibrotic liver changes, and clinically studied liver disorders were considered separately before being integrated into an overall translational interpretation. Attention was also paid to formulation-related heterogeneity, including differences between crude extracts, standardized preparations, isolated compounds, and semisynthetic or pharmaceutical derivatives, because these differences may influence bioavailability, potency, mechanism attribution, and safety profile. Studies were interpreted cautiously when outcome reporting relied only on liver enzyme changes without histological or mechanistic corroboration.

Because this was a literature-based review and did not involve human participant recruitment, direct patient contact, or access to identifiable personal data, formal institutional ethical approval and informed consent were not required. Reproducibility was supported by use of explicit search concepts, predefined thematic inclusion boundaries, and a transparent evidence-organization framework centered on liver-specific outcomes. The final synthesis was developed to provide a clinically and mechanistically coherent appraisal of the hepatoprotective potential of *Glycyrrhiza glabra* while identifying areas where the current evidence remains preliminary, heterogeneous, or in need of more rigorous clinical validation.

## RESULTS

The revised evidence synthesis supports a predominantly preclinical hepatoprotective profile for *Glycyrrhiza glabra,* with the strongest concentration of evidence in oxidative stress modulation, inflammatory pathway suppression, and attenuation of toxicant- or drug-induced hepatocellular injury. Across the reviewed studies, the most consistently improved biochemical markers were alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, malondialdehyde, and endogenous antioxidant systems including superoxide dismutase, catalase, glutathione, glutathione peroxidase, and glutathione reductase. Histologically, the major reported benefits included reduced necroinflammatory change, lower lipid peroxidation-associated injury, attenuation of apoptosis, and preservation of hepatic architecture in metabolic, toxic, and chemically induced liver injury models. The most frequently implicated pathways were Nrf2-mediated antioxidant activation, NF-κB suppression, modulation of Bax/Bcl-2 and caspase-dependent apoptosis, inhibition of CYP2E1-associated toxic bioactivation, and attenuation of TGF-β1-related fibrogenic signaling.

To improve analytical clarity, the evidence has been reorganized into three publication-oriented synthesis tables. Table 1 summarizes major preclinical hepatoprotective studies by model, intervention, dose, endpoints, and principal findings. Table 2 integrates constituent-level mechanisms with dominant molecular targets and measurable hepatic outcomes. Table 3 consolidates translational relevance, including human use contexts, therapeutic prospects, and major safety considerations. This approach addresses the earlier weakness of overly descriptive narrative synthesis by making the direction, depth, and clinical proximity of the evidence easier to interpret.

*Table 1. Revised Summary of Major Preclinical Hepatoprotective Evidence on Glycyrrhiza glabra*

| Study / Model | Intervention | Dose / Exposure | Principal Outcomes Evaluated | Main Hepatoprotective Findings |
|---|---|---|---|---|
| **Gumpricht et al. (12), bile acid-induced rat hepatocyte toxicity** | Glycyrrhizin and 18β-glycyrrhetinic acid | Experimental in vitro exposure | Hepatocyte cytotoxicity, bile acid-related injury | Both compounds modulated bile acid-induced cytotoxicity and supported hepatocellular protection |
| **Kim et al. (95), steatosis/oxidative injury model** | Liquiritigenin | Experimental exposure | Hepatic steatosis, oxidative injury, Nrf2/LXRα signaling | Reduced steatosis and oxidative injury through Nrf2 activation and inhibition of LXRα-dependent lipogenic signaling |
| **Liang et al. (91), carbon tetrachloride-induced liver injury** | Glycyrrhizic acid | Experimental treatment | Apoptosis, fibrosis, oxidative injury | Reduced hepatocyte apoptosis and fibrosis in $CCl_4$-induced injury |
| **Chauhan et al. (89), methotrexate-induced hepato-renal injury in rats** | *G. glabra* supplementation | 100–400 mg/kg | MDA, GSH, SOD, CAT, peroxidase, glutathione reductase, histology | Lowered lipid peroxidation and normalized antioxidant defenses; strongest protection reported at higher tested dose |
| **Dogra et al. (35), methotrexate-induced liver injury** | Glabridin | Experimental treatment | Oxidative stress, inflammation, apoptosis | Ameliorated methotrexate-induced liver injury via anti-oxidative, anti-inflammatory, and anti-apoptotic mechanisms |
| **Mohamed (90), cadmium chloride-induced toxicity in rats** | Aqueous *G. glabra* extract | Experimental treatment | ROS/TBARS, SOD, CAT, GSH, caspase-3 | Reversed oxidative injury, restored antioxidant enzymes, and reduced apoptosis-related damage |
| **Fadhil et al. (87), amiodarone-induced hepatotoxicity in rats** | *G. glabra* root extract | Experimental treatment | AST, ALT, PLA2, hepatic SOD, GSH, MDA | Reduced aminotransferases and lipid peroxidation while improving antioxidant status |
| **Alrefaei and Elbeeh (88), diabetic male rat model** | *G. glabra* treatment | Experimental treatment | ALT, AST, ALP, MDA, GSH, liver histology | Improved liver enzymes, reduced oxidative stress, and ameliorated histopathological damage |
| **Tan et al. (92), triptolide-induced hepatotoxicity** | Liquorice root extract and magnesium isoglycyrrhizinate | Experimental treatment | Nrf2 pathway, oxidative stress markers, hepatic injury | Activated Nrf2-linked antioxidant defense and reduced hepatotoxicity |
| **Bhatt et al. (77), CYP2E1-targeted hepatotoxicity mechanism** | Glabridin | IC50 = 6.2 μM for CYP2E1 inhibition | CYP2E1 inhibition, toxic bioactivation relevance | Established glabridin as a potent CYP2E1 inhibitor with relevance to toxic liver injury prevention |

*Table 2. Revised Constituent-to-Mechanism Evidence Matrix for Hepatoprotection*

| Constituent / Preparation | Dominant Molecular Targets | Core Mechanistic Axis | Key Hepatic Biomarker Direction | Functional Hepatic Relevance |
|---|---|---|---|---|
| **Glycyrrhizin / glycyrrhizic acid** | NF-κB, HMGB1, inflammatory mediators, Nrf2 | Anti-inflammatory + antioxidant | ↓ ALT, ↓ AST, ↓ inflammatory cytokines, ↓ oxidative stress | Useful in inflammatory and viral-associated liver injury contexts |
| **18β-Glycyrrhetinic acid** | CYP2E1, NF-κB, apoptosis regulators | Toxic bioactivation control + anti-inflammatory + anti-apoptotic | ↓ toxic metabolite burden, ↓ lipid peroxidation, ↓ apoptosis | Relevant to chemical and drug-induced hepatotoxicity |
| **Glabridin** | Nrf2, NF-κB, CYP2E1 | Antioxidant + anti-inflammatory + metabolic enzyme modulation | ↑ SOD, ↑ CAT, ↑ GSH, ↓ MDA | Strong relevance in methotrexate and oxidative liver injury models |
| **Liquiritigenin** | Nrf2, LXRα-linked lipid pathways | Anti-steatotic + antioxidant | ↓ steatosis, ↓ oxidative injury | Particularly relevant to NAFLD-like metabolic injury |
| **Isoliquiritigenin** | Nrf2, inflammatory mediators | Antioxidant + cytokine suppression | ↓ ROS, ↓ inflammatory signaling | Supports oxidative and inflammatory injury control |
| **Magnesium isoglycyrrhizinate** | Nrf2, NF-κB, oxidative stress pathways | Hepatoprotective derivative with improved tolerability profile | ↓ oxidative damage, ↓ inflammation | Translationally relevant derivative in hepatotoxic injury settings |
| **Crude / aqueous / root extracts** | Multi-compound, multi-target actions | Integrated redox-inflammatory-cytoprotective effect | ↓ ALT/AST/ALP, ↓ MDA, ↑ GSH/SOD/CAT | Broad-spectrum protection in diverse animal injury models |

*Table 3. Revised Clinical Translation and Safety Synthesis*

| Translational Domain | Current Evidence Position | Clinical Relevance | Key Limitation |
|---|---|---|---|
| **Chronic hepatitis use of glycyrrhizin-containing preparations** | Supportive but heterogeneous | Biochemical improvement in liver enzymes has been reported in clinical use settings | Variable formulations, routes, and study design quality |
| **NAFLD / steatosis-related application** | Mechanistically plausible and preclinically supported | Anti-steatotic, antioxidant, and anti-inflammatory actions align with disease biology | Need for controlled trials with standardized endpoints |
| **Drug-induced liver injury** | Strong preclinical rationale, including CYP2E1 and Nrf2-linked protection | Candidate supportive therapy for toxic injury settings | Human confirmatory data remain limited |
| **Fibrosis modulation** | Supported in selected preclinical models | Potential value in slowing progression of chronic injury | Anti-fibrotic evidence is less extensive than antioxidant evidence |
| **Standardization of preparations** | Major translational requirement | Essential for reproducibility, dose selection, and regulatory acceptance | Crude extracts and derivatives differ substantially in pharmacology |
| **Safety and tolerability** | Important clinical constraint | Mineralocorticoid-like adverse effects may limit prolonged or high-dose use | Requires monitoring for hypertension, edema, sodium retention, and hypokalemia |

Table 1 shows that the most substantial preclinical evidence clusters around 10 principal studies spanning toxic, metabolic, and chemically induced liver injury. Among these, at least 4 studies directly evaluated drug- or toxin-related hepatotoxicity, including methotrexate, amiodarone, cadmium chloride, and triptolide models, while 2 studies specifically addressed metabolic or steatotic injury contexts. Across these models, the repeated pattern was reduction of aminotransferase elevation, attenuation of malondialdehyde or related lipid peroxidation products, and recovery of antioxidant defenses such as glutathione, superoxide dismutase, and catalase. Dose-explicit evidence was available in the methotrexate study, where *G. glabra* extract was tested across 100–400 mg/kg and the strongest protection was reported at 400 mg/kg, strengthening the case for a dose-responsive hepatoprotective effect in that model.

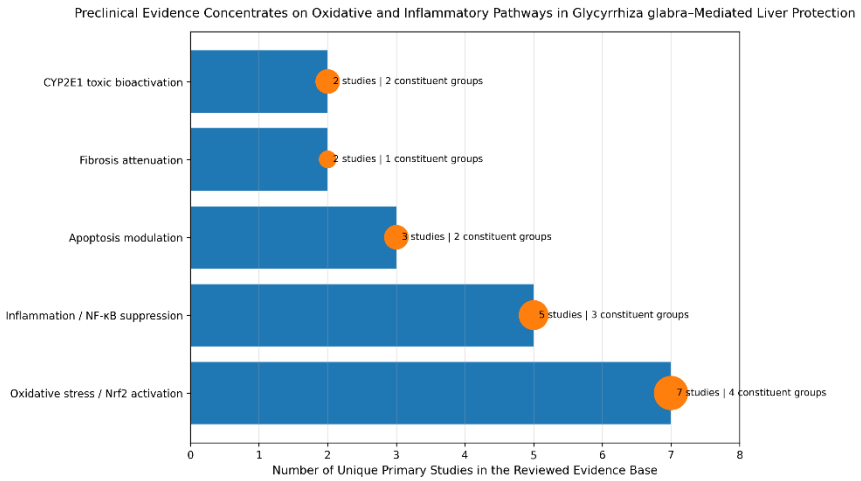


*Figure 1 Preclinical evidence concentration across major hepatoprotective pathways of Glycyrrhiza glabra.*

Table 2 clarifies that hepatoprotection is not attributable to a single compound-pathway pair. Instead, at least 6 constituent or preparation categories map onto 5 major mechanistic axes. Glycyrrhizin and glycyrrhizic acid are most closely linked with inflammatory suppression and antioxidant stabilization, 18β-glycyrrhetinic acid with toxic bioactivation control and apoptosis modulation, glabridin with both redox regulation and CYP2E1 inhibition, and liquiritigenin with anti-steatotic signaling through Nrf2 and LXRα-related pathways. This pattern supports the revised interpretation that *G. glabra* functions as a multi-target hepatoprotective system rather than a plant with a single dominant hepatic mechanism.

Table 3 highlights a clear translational asymmetry. The antioxidant and inflammatory evidence base is relatively dense, but the fibrosis and clinical translation domains remain thinner. Preclinical support appears strongest for oxidative and inflammatory injury control, whereas direct human evidence

remains more heterogeneous in formulation, route, and endpoint selection. The table also makes the safety signal more visible: therapeutic use cannot be interpreted independently of the mineralocorticoid-like adverse-effect profile, which remains one of the main barriers to uncritical clinical adoption.

Figure 1 showed evidence map shows that oxidative stress regulation is the most densely supported pathway, represented by 7 unique primary studies and 4 constituent groups, followed by inflammatory pathway suppression with 5 studies and 3 constituent groups. Apoptosis modulation is supported by 3 studies, whereas fibrosis attenuation and CYP2E1-linked toxic bioactivation control are each supported by 2 studies. This distribution indicates that the strongest current mechanistic foundation for *G. glabra* lies in redox-inflammatory protection, while anti-fibrotic and toxicokinetic mechanisms remain promising but comparatively less developed. Clinically, this pattern suggests that the most immediate translational value may lie in liver disorders dominated by oxidative stress and inflammatory injury rather than advanced remodeling alone.

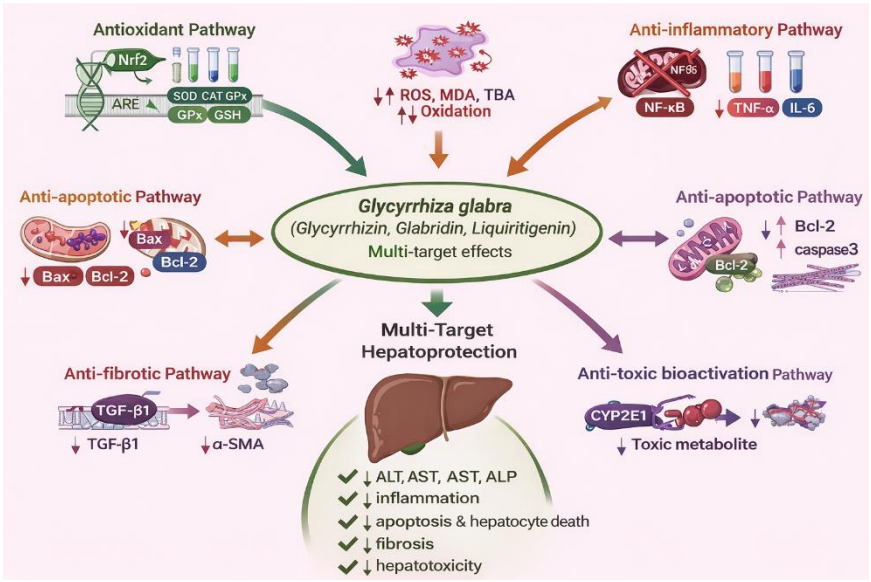


*Figure 2 Multi-target hepatoprotective mechanisms of Glycyrrhiza glabra.*

This schematic illustrates the principal molecular pathways through which *Glycyrrhiza glabra* and its major bioactive constituents (glycyrrhizin, glabridin, and liquiritigenin) exert hepatoprotective effects. The extract enhances antioxidant defense primarily through activation of the Nrf2 pathway, leading to increased expression of endogenous antioxidant systems including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and reduced glutathione (GSH), which collectively decrease reactive oxygen species (ROS) and lipid peroxidation markers such as malondialdehyde (MDA) and thiobarbituric acid–reactive substances (TBARS). In parallel, anti-inflammatory activity is mediated through suppression of NF-κB signaling and downregulation of pro-inflammatory cytokines including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). The plant also exerts anti-apoptotic effects by modulating mitochondrial apoptotic regulators, reducing Bax expression while increasing Bcl-2 levels and limiting caspase-3 activation, thereby protecting hepatocytes from programmed cell death. Anti-fibrotic activity occurs through inhibition of transforming growth factor-β1 (TGF-β1) signaling and reduced α-smooth muscle actin (α-SMA) expression, which limits hepatic stellate cell activation and fibrogenesis. Additionally, inhibition of CYP2E1-mediated toxic bioactivation decreases formation of reactive toxic metabolites. Collectively, these coordinated mechanisms result in reduced hepatocellular injury, reflected by decreased serum liver enzymes (ALT, AST, ALP), attenuation of inflammation and oxidative damage, prevention of apoptosis, and mitigation of hepatic fibrosis, culminating in overall hepatoprotection.

## DISCUSSION

The available evidence indicates that *Glycyrrhiza glabra* exerts hepatoprotective effects through a genuinely multi-target pharmacological profile rather than through a single dominant pathway. The strongest and most reproducible signal across the reviewed literature lies in the reduction of oxidative stress and the restoration of intracellular antioxidant defense systems. In multiple toxic, metabolic, and chemically induced liver injury models, liquorice preparations and constituent compounds reduced malondialdehyde, reactive oxygen species, and related markers of lipid peroxidation while restoring glutathione, catalase, superoxide dismutase, glutathione reductase, and glutathione peroxidase activity. This redox-stabilizing pattern is biologically coherent with current understanding of liver injury, in which oxidative imbalance is both an initiating insult and an amplifier of inflammatory, apoptotic, and fibrogenic signaling. The repeated linkage of glycyrrhizin, glabridin, liquiritigenin, and magnesium isoglycyrrhizinate with Nrf2-associated antioxidant activation further supports the view that reinforcement of endogenous cytoprotective machinery is one of the central mechanisms underlying the hepatic benefit of *G. glabra* (35,76,87-97).

A second major finding of this review is the consistent anti-inflammatory activity of *G. glabra* in liver-relevant systems. Across the experimental literature, hepatoprotection was frequently accompanied by suppression of NF-κB signaling, reduced tumor necrosis factor-α and interleukin-6 expression, decreased prostaglandin-related inflammatory activity, and attenuation of inflammatory cell infiltration in hepatic tissue. This is particularly important because oxidative stress and inflammation in chronic liver disease are not parallel but mutually reinforcing processes. Oxidative injury activates inflammatory transcription pathways, while cytokine signaling further drives mitochondrial dysfunction, hepatocyte damage, and stellate cell activation. The reviewed data therefore suggest that *G. glabra* may interrupt this injury cycle at more than one level. Glycyrrhizin and 18β-glycyrrhetinic acid appear especially relevant in this regard, while glabridin and liquorice flavonoids broaden the anti-inflammatory spectrum through additional effects on prostaglandin production, redox-sensitive transcription factors, and related mediator systems (12,35,43-45,76,97,99-101).

The evidence for anti-apoptotic and anti-fibrotic activity is promising but less extensive than the antioxidant and inflammatory evidence. In selected models, glycyrrhizic acid and related constituents improved the Bax/Bcl-2 balance, reduced caspase-3 activation, and preserved hepatocellular architecture, indicating that cytoprotection extends beyond biochemical normalization to include structural preservation of liver tissue. Similarly, attenuation of transforming growth factor-β1-driven fibrogenesis and reduction of fibrosis-associated markers have been reported in carbon tetrachloride and related models. These findings are mechanistically important because apoptosis and fibrosis are more proximal to long-term disease progression than isolated changes in aminotransferases. However, the anti-fibrotic literature is still narrower in volume and model diversity, and the current evidence does not yet justify strong claims that *G. glabra* is an established anti-fibrotic therapy. At present, the anti-fibrotic potential should be regarded as plausible and supported by early preclinical data rather than clinically confirmed (12,91,97).

One of the more translationally relevant aspects of the reviewed evidence is the role of *G. glabra* in toxic and drug-induced liver injury. The inhibition of CYP2E1 by glabridin and the reduction of oxidative injury in methotrexate-, amiodarone-, cadmium-, and triptolide-associated hepatotoxicity suggest that liquorice-derived compounds may have particular value in settings where hepatic injury is driven by reactive metabolite formation, mitochondrial stress, and inflammatory amplification. This is clinically attractive because drug-induced liver injury remains difficult to prevent and often lacks targeted adjunctive options. At the same time, this apparent advantage must be interpreted cautiously. Most of the evidence is derived from controlled experimental models with defined toxin exposure, uniform dosing, and relatively short intervention windows. Human DILI is substantially more heterogeneous, involving variable comorbidities, polypharmacy, timing of exposure, genetic susceptibility, and immune-

mediated components that are not fully reproduced in animal models. The current literature therefore supports mechanistic rationale and preclinical feasibility rather than immediate clinical generalization (35,77,87,89,90,92).

The relevance of *G. glabra* to metabolic liver disease, particularly NAFLD, is also biologically compelling. NAFLD is characterized by a convergence of hepatic steatosis, oxidative stress, inflammatory signaling, lipotoxicity, and progressive fibrogenesis, all of which overlap with pathways modulated by liquorice-derived compounds. Liquiritigenin, in particular, appears notable because it links antioxidant activation with suppression of lipogenic signaling, thereby positioning *G. glabra* not only as a cytoprotective agent but also as a potential metabolic modulator. This dual activity is important because a hepatoprotective intervention in NAFLD should ideally do more than reduce enzyme leakage; it should also address steatosis-driving mechanisms and limit progression toward steatohepatitis and fibrosis. However, despite the strength of this mechanistic fit, the translational evidence remains incomplete. Clinical claims in NAFLD currently rest more on plausibility, limited biochemical improvement, and derivative-specific observations than on large, well-controlled randomized trials with standardized histological or imaging endpoints (1-5,95).

A key strength of *G. glabra* as a candidate hepatoprotective agent is the breadth of its constituent pharmacology. Unlike a single-target synthetic compound, liquorice contains triterpenoid saponins, flavonoids, chalcones, isoflavans, and polysaccharides that may act additively or synergistically across oxidative, inflammatory, apoptotic, and metabolic pathways. This multi-constituent architecture may partly explain why crude or standardized extracts sometimes perform well in complex disease models. At the same time, it creates one of the major barriers to clinical translation: mechanistic attribution becomes difficult when extracts differ in phytochemical composition, extraction method, solvent system, geographic origin, and degree of standardization. In several studies, the intervention is described broadly as root extract, aqueous extract, or liquorice extract without precise phytochemical quantification, which limits reproducibility and complicates dose comparison across studies. For this reason, future research should more consistently distinguish whole extracts from purified constituents and from pharmaceutical derivatives such as magnesium isoglycyrrhizinate, because these are not interchangeable therapeutic entities (22,42,63-70,78,80,85).

Safety remains one of the most important considerations in the therapeutic positioning of *G. glabra*. Although the hepatoprotective literature is generally favorable, liquorice-derived compounds are not pharmacologically neutral. Glycyrrhizin and glycyrrhetinic acid may produce mineralocorticoid-like effects through inhibition of 11β-hydroxysteroid dehydrogenase type 2, leading to sodium retention, potassium loss, hypertension, edema, and pseudoaldosteronism, particularly with chronic exposure or higher doses. This adverse-effect profile is not a minor footnote; it is one of the central translational constraints on long-term clinical use. The growing interest in derivative formulations, especially magnesium isoglycyrrhizinate, reflects an effort to preserve hepatoprotective benefit while improving tolerability and therapeutic control. Even so, safety monitoring, treatment duration, cumulative dose, formulation standardization, and interaction with concurrent medications remain insufficiently addressed in much of the reviewed clinical literature. Any future clinical development pathway should therefore integrate efficacy and safety from the outset rather than treating toxicity as a secondary issue (42,43,69,80,84-86,92).

The current evidence base also has important methodological limitations. A large proportion of the available data comes from animal models or mechanistic cell studies, and positive findings are often based on surrogate outcomes such as aminotransferase levels, oxidative stress markers, and histological scoring. These are informative but do not always translate directly into meaningful human outcomes. The clinical literature is comparatively sparse, heterogeneous in design, and variable in formulation quality, comparator choice, and endpoint definition. Moreover, some published reports emphasize biochemical improvement without sufficiently integrating histological, imaging, virological, or long-

term clinical outcomes. This imbalance between mechanistic richness and clinical validation explains why *G. glabra* can currently be described as a promising hepatoprotective candidate but not yet as an evidence-established broad-spectrum liver therapy. A more mature evidence base will require constituent-specific pharmacokinetic studies, rigorous dose-finding work, standardized extract characterization, and randomized controlled trials tailored to distinct disease phenotypes such as NAFLD, chronic viral hepatitis, cholestatic liver disease, and defined forms of DILI (12,20,42,67,69,80,85,86).

Taken together, the revised synthesis supports a more measured but stronger conclusion than the earlier draft. The value of *G. glabra* does not lie merely in traditional use or generalized antioxidant reputation, but in the convergence of phytochemistry and liver pathobiology across several experimentally supported mechanisms. The most convincing current evidence supports redox stabilization, inflammatory suppression, and mitigation of toxic hepatocellular injury, while the anti-fibrotic and clinically translatable domains remain promising but less mature. This distinction is important for preventing overstatement. The next phase of research should move beyond repeating general hepatoprotective observations and instead prioritize target validation, formulation standardization, pharmacokinetic optimization, and disease-specific clinical trials using robust endpoints. With such refinement, *G. glabra* may advance from a broadly promising phytotherapeutic agent to a more precisely defined adjunct or lead compound platform in hepatology (20,35,76,77,87-92,95,99-101).

## CONCLUSION

*Glycyrrhiza glabra* is a pharmacologically rich medicinal plant with substantial hepatoprotective promise supported by convergent preclinical evidence showing antioxidant, anti-inflammatory, anti-apoptotic, anti-steatotic, and partially anti-fibrotic effects mediated through pathways including Nrf2, NF-κB, Bax/Bcl-2, TGF-β1, and CYP2E1. Its principal constituents, particularly glycyrrhizin, 18β-glycyrrhetinic acid, glabridin, liquiritigenin, isoliquiritigenin, and magnesium isoglycyrrhizinate, collectively support the concept of multi-target liver protection across toxic, metabolic, and inflammatory injury settings. Nevertheless, the current evidence remains weighted toward mechanistic and animal studies, while clinical translation is limited by heterogeneity of formulations, incomplete standardization, insufficient pharmacokinetic characterization, and the need to carefully manage mineralocorticoid-like adverse effects. Future progress will depend on rigorously standardized preparations, constituent-specific translational studies, and well-designed randomized clinical trials with clinically meaningful hepatic endpoints.

## REFERENCES

1. Cotter TG, Rinella M. Nonalcoholic fatty liver disease 2020: the state of the disease. Gastroenterology. 2020;158(7):1851-64.

2. Hassan F, Farman M, Khan KA, Awais M, Akhtar S. Prevalence of nonalcoholic fatty liver disease in Pakistan: a systematic review and meta-analysis. Sci Rep. 2024;14(1):19573.

3. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology. 2004;40(6):1387-95.

4. Zaharia OP, Strassburger K, Strom A, Bönhof GJ, Karusheva Y, Antoniou S, et al. Risk of diabetes-associated diseases in subgroups of patients with recent-onset diabetes: a 5-year follow-up study. Lancet Diabetes Endocrinol. 2019;7(9):684-94.

5. Targher G, Lonardo A, Byrne CD. Nonalcoholic fatty liver disease and chronic vascular complications of diabetes mellitus. Nat Rev Endocrinol. 2018;14(2):99-114.

6. Batiha GES, Beshbishy AM, Tayebwa DS, Adeyemi OS, Yokoyama N, Igarashi I. Evaluation of the inhibitory effect of ivermectin on the growth of Babesia and Theileria parasites in vitro and in vivo. Trop Med Health. 2019;47(1):42.

7. Batiha GES, Beshbishy AA, Tayebwa DS, Shaheen MH, Yokoyama N, Igarashi I. Inhibitory effects of Uncaria tomentosa bark, Myrtus communis roots, Origanum vulgare leaves and Cuminum cyminum seeds extracts against the growth of Babesia and Theileria in vitro. J Vet Parasitol. 2018;17:1-13.

8. Batiha GES, Beshbishy AM, El-Mleeh A, Abdel-Daim MM, Devkota HP. Traditional uses, bioactive chemical constituents, and pharmacological and toxicological activities of *Glycyrrhiza glabra* L. (Fabaceae). Biomolecules. 2020;10(3):352.

9. Beshbishy AM, Batiha GES, Adeyemi OS, Yokoyama N, Igarashi I. Inhibitory effects of methanolic Olea europaea and acetonic Acacia laeta on growth of Babesia and Theileria. Asian Pac J Trop Med. 2019;12(9):425-34.

10. Batiha GES, Beshbishy AM, Tayebwa DS, Shaheen HM, Yokoyama N, Igarashi I. Inhibitory effects of Syzygium aromaticum and Camellia sinensis methanolic extracts on the growth of Babesia and Theileria parasites. Ticks Tick Borne Dis. 2019;10(5):949-58.

11. Shah SL, Wahid F, Khan N, Farooq U, Shah AJ, Tareen S, et al. Inhibitory effects of *Glycyrrhiza glabra* and its major constituent glycyrrhizin on inflammation-associated corneal neovascularization. Evid Based Complement Alternat Med. 2018;2018:8438101.

12. Gumpricht E, Dahl R, Devereaux MW, Sokol RJ. Liquorice compounds glycyrrhizin and 18β-glycyrrhetinic acid are potent modulators of bile acid-induced cytotoxicity in rat hepatocytes. J Biol Chem. 2005;280(11):10556-63.

13. Alrefaei AF, Elbeeh ME. Hepatoprotective effects of *Glycyrrhiza glabra* in diabetic male rats: addressing liver function, oxidative stress, and histopathological changes. Biology (Basel). 2025;14(3):307.

14. Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends—an update. Cancer Epidemiol Biomarkers Prev. 2016;25(1):16-27.

15. Alsaleh M, Leftley Z, Barbera TA, Sithithaworn P, Khuntikeo N, Loilome W, et al. Cholangiocarcinoma: a guide for the nonspecialist. Int J Gen Med. 2018;11:13-23.

16. Ghouri YA, Mian I, Rowe JH. Review of hepatocellular carcinoma: epidemiology, etiology, and carcinogenesis. J Carcinog. 2017;16:1.

17. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2018;67(1):358-80.

18. Bosetti C, Turati F, La Vecchia C. Hepatocellular carcinoma epidemiology. Best Pract Res Clin Gastroenterol. 2014;28(5):753-70.

19. Xiong X, Gu L, Wang Y, Luo Y, Zhang H, Lee J, et al. Glycyrrhizin protects against focal cerebral ischemia via inhibition of T cell activity and HMGB1-mediated mechanisms. J Neuroinflammation. 2016;13(1):241.

20. Stecanella LA, Bitencourt AP, Vaz GR, Quarta E, Silva Junior JO, Rossi A. Glycyrrhizic acid and its hydrolyzed metabolite 18β-glycyrrhetinic acid as specific ligands for targeting nanosystems in the treatment of liver cancer. Pharmaceutics. 2021;13(11):1792.

21. Schmittgen TD, Livak KJ. Analyzing real-time PCR data by the comparative CT method. Nat Protoc. 2008;3(6):1101-8.

22. Deng TM, Peng C, Peng DY, Yu NJ, Chen WD, Wang L. Research progress on chemical constituents and pharmacological effects of Glycyrrhizae Radix et Rhizoma and discussion of Q-markers. Zhongguo Zhong Yao Za Zhi. 2021;46(11):2660-76.

23. Qin J, Chen J, Peng F, Sun C, Lei Y, Chen G, et al. Pharmacological activities and pharmacokinetics of liquiritin: a review. J Ethnopharmacol. 2022;293:115257.

24. Mohammed EAH, Peng Y, Wang Z, Qiang X, Zhao Q. Synthesis, antiviral, and antibacterial activity of the glycyrrhizic acid and glycyrrhetinic acid derivatives. Russ J Bioorg Chem. 2022;48(5):906-18.

25. Ramalingam M, Kim H, Lee Y, Lee YI. Phytochemical and pharmacological role of liquiritigenin and isoliquiritigenin from Radix Glycyrrhizae in human health and disease models. Front Aging Neurosci. 2018;10:348.

26. Parlar A, Arslan SO, Çam SA. Glabridin alleviates inflammation and nociception in rodents by activating BK(Ca) channels and reducing NO levels. Biol Pharm Bull. 2020;43(5):884-97.

27. Ye Q, Zhang Q, Yao H, et al. Active-ingredient screening and synergistic action mechanism of shegan mixture for anti-asthma effects based on network pharmacology in a mouse model of asthma. Drug Des Devel Ther. 2021;15:1765-77.

28. Belinky PA, Aviram M, Mahmood S, Vaya J. Structural aspects of the inhibitory effect of glabridin on LDL oxidation. Free Radic Biol Med. 1998;24(9):1419-29.

29. Belinky PA, Aviram M, Fuhrman B, Rosenblat M, Vaya J. The antioxidative effects of the isoflavan glabridin on endogenous constituents of LDL during its oxidation. Atherosclerosis. 1998;137(1):49-61.

30. Goel B, Sharma A, Tripathi N, Bhardwaj N, Sahu B, Kaur G, et al. In-vitro antitumor activity of compounds from *Glycyrrhiza glabra* against C6 glioma cancer cells: identification of natural lead for further evaluation. Nat Prod Res. 2021;35(23):5489-92.

31. Modarresi M, Hajialyani M, Moasefi N, Ahmadi F, Hosseinzadeh L. Evaluation of the cytotoxic and apoptogenic effects of glabridin and its effect on cytotoxicity and apoptosis induced by doxorubicin toward cancerous cells. Adv Pharm Bull. 2019;9(3):481-9.

32. Islam R, Parves MR, Paul AS, Uddin N, Rahman MS, Mamun AA, et al. A molecular modeling approach to identify effective antiviral phytochemicals against the main protease of SARS-CoV-2. J Biomol Struct Dyn. 2021;39(9):3213-24.

33. Azizsoltani A, Piri K, Behzad S, Soleimani M, Nekouei M, Mahmoudi Z, et al. Ethyl acetate extract of liquorice root (*Glycyrrhiza glabra*) enhances proliferation and osteogenic differentiation of human bone marrow mesenchymal stem cells. Iran J Pharm Res. 2018;17(3):1057-67.

34. Wang G, Sun G, Wang Y, Yu P, Wang X, Zhou B, et al. Glabridin attenuates endothelial dysfunction and permeability, possibly via the MLCK/p-MLC signaling pathway. Exp Ther Med. 2019;17(1):107-14.

35. Dogra A, Gupta D, Bag S, Ahmed I, Bhatt S, Nehra E, et al. Glabridin ameliorates methotrexate-induced liver injury via attenuation of oxidative stress, inflammation, and apoptosis. Life Sci. 2021;278:119583.

36. Park SH, Kang JS, Yoon YD, Lee K, Kim KJ, Lee KH, et al. Glabridin inhibits lipopolysaccharide-induced activation of a microglial cell line, BV-2, by blocking NF-κB and AP-1. Phytother Res. 2010;24 Suppl 1:S29-34.

37. Ahn J, Lee H, Jang J, Kim S, Ha T. Anti-obesity effects of glabridin-rich supercritical carbon dioxide extract of liquorice in high-fat-fed obese mice. Food Chem Toxicol. 2013;51:439-45.

38. Wu F, Jin Z, Jin J. Hypoglycemic effects of glabridin, a polyphenolic flavonoid from liquorice, in an animal model of diabetes mellitus. Mol Med Rep. 2013;7(4):1278-82.

39. Shakya A, Kumar K. Critical review on phytoconstituents and pharmacological activity of *Glycyrrhiza glabra*. Pharmacogn Res. 2025;17(3).

40. Batiha GES, Beshbishy AM, El-Mleeh A, Abdel-Daim MM, Devkota HP. Traditional uses, bioactive chemical constituents, and pharmacological and toxicological activities of *Glycyrrhiza glabra* L. (Fabaceae). Biomolecules. 2020;10(3):352.

41. Hasan MK, Ara I, Mondal MSA, Kabir Y. Phytochemistry, pharmacological activity, and potential health benefits of *Glycyrrhiza glabra*. Heliyon. 2021;7(6):e07240.

42. Wahab S, Annadurai S, Abullais SS, Das G, Ahmad W, Ahmad MF, et al. *Glycyrrhiza glabra* (liquorice): a comprehensive review on its phytochemistry, biological activities, clinical evidence and toxicology. Plants (Basel). 2021;10(12):2751.

43. Leite CDS, Bonafé GA, Carvalho Santos J, Martinez CAR, Ortega MM, Ribeiro ML. The anti-inflammatory properties of liquorice (Glycyrrhiza glabra)-derived compounds in intestinal disorders. Int J Mol Sci. 2022;23(8):4121.

44. Bisht D, Rashid M, Arya RKK, Kumar D, Chaudhary SK, Rana VS, et al. Revisiting liquorice (*Glycyrrhiza glabra* L.) as anti-inflammatory, antivirals and immunomodulators: potential pharmacological applications with mechanistic insight. Phytomedicine Plus. 2022;2(1):100206.

45. Shakya A, Kumar K. Critical review on phytoconstituents and pharmacological activity of Glycyrrhiza glabra. Pharmacogn Res. 2025;17(3).

46. Osonga FJ, Akgul A, Miller RM, Eshun GB, Yazgan I, Akgul A, et al. Antimicrobial activity of a new class of phosphorylated and modified flavonoids. ACS Omega. 2019;4(7):12865-71.

47. Ozgen S, Kilinc OK, Selamoğlu Z. Antioxidant activity of quercetin: a mechanistic review. Turk J Agric Food Sci Technol. 2016;4(12):1134-8.

48. Magar RT, Sohng JK. A review on structure, modifications and structure-activity relation of quercetin and its derivatives. J Microbiol Biotechnol. 2020;30(1):11-20.

49. Hooda H, Singh P, Bajpai S. Effect of quercetin impregnated silver nanoparticle on growth of some clinical pathogens. Mater Today Proc. 2020;31:625-30.

50. Hooda H, Singh P, Bajpai S. Effect of quercetin impregnated silver nanoparticle on growth of some clinical pathogens. Mater Today Proc. 2020;31:625-30.

51. Yin J, Peng X, Lin J, Zhang Y, Zhang J, Gao H, et al. Quercetin ameliorates Aspergillus fumigatus keratitis by inhibiting fungal growth, toll-like receptors and inflammatory cytokines. Int Immunopharmacol. 2021;93:107435.

52. Abid R, Ghazanfar S, Farid A, Sulaman SM, Idrees M, Amen RA, et al. Pharmacological properties of 4′,5,7-trihydroxyflavone (apigenin) and its impact on cell signaling pathways. Molecules. 2022;27(13):4304.

53. Imran M, Aslam Gondal T, Atif M, Shahbaz M, Batool Qaisarani T, Hanif Mughal M, et al. Apigenin as an anticancer agent. Phytother Res. 2020;34(8):1812-28.

54. Moslehi M, Rezaei S, Talebzadeh P, Ansari MJ, Jawad MA, Jalil AT, et al. Apigenin in cancer therapy: prevention of genomic instability and anticancer mechanisms. Clin Exp Pharmacol Physiol. 2023;50(1):3-18.

55. Hostetler GL, Ralston RA, Schwartz SJ. Flavones: food sources, bioavailability, metabolism, and bioactivity. Adv Nutr. 2017;8(3):423-35.

56. Chen YH, Wu JX, Yang SF, Yang CK, Chen TH, Hsiao YH. Anticancer effects and molecular mechanisms of apigenin in cervical cancer cells. Cancers (Basel). 2022;14(7):1824.

57. Gęgotek A, Skrzydlewska E. Ascorbic acid as antioxidant. Vitam Horm. 2023;121:247-70.

58. Sies H, Jones DP. Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. Nat Rev Mol Cell Biol. 2020;21(7):363-83.

59. Jenab M, Riboli E, Ferrari P, Sabate J, Slimani N, Norat T, et al. Plasma and dietary vitamin C levels and risk of gastric cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST). Carcinogenesis. 2006;27(11):2250-7.

60. Lin XJ, Zou XL, Zhao ZY, Wang J, Yang Z, Ni X, et al. Effect of high dose vitamin C on proliferation and apoptosis of acute myeloid leukemia cells. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2020;28(3):833-41.

61. Khazaei S, Nilsson L, Adrian G, Tryggvadottir H, Konradsson E, Borgquist S, et al. Impact of combining vitamin C with radiation therapy in human breast cancer: does it matter? Oncotarget. 2022;13:439-49.

62. Nibbe P, Schleusener J, Siebert S, Borgart R, Brandt D, Westphalen R, et al. Oxidative stress coping capacity (OSC) value: development and validation of an in vitro measurement method for blood plasma using electron paramagnetic resonance spectroscopy (EPR) and vitamin C. Free Radic Biol Med. 2023;194:230-44.

63. Sawant BS, Alawe JR, Rasal KV. Pharmacognostic study of *Glycyrrhiza glabra* Linn-a review. Int Ayurvedic Med J. 2016;4(10):3989-93.

64. Avula B, Bae JY, Chittiboyina AG, Wang YH, Wang M, Zhao J, et al. Chemometric analysis and chemical characterization for the botanical identification of Glycyrrhiza species (*G. glabra*, G. uralensis, G. inflata, G. echinata and G. lepidota) using liquid chromatography-quadrupole time of flight mass spectrometry (LC-QTof). J Food Compos Anal. 2022;112:104679.

65. Liu HM, Sugimoto N, Akiyama T, Maitani T. Constituents and their sweetness of food additive enzymatically modified liquorice extract. J Agric Food Chem. 2000;48:6044-7.

66. Schmid C, Dawid C, Peters V, Hofmann T. Saponins from European liquorice roots (*Glycyrrhiza glabra*). J Nat Prod. 2018;81:1734-44.

67. Pastorino G, Cornara L, Soares S, Rodrigues F, Oliveira MBPP. Liquorice (*Glycyrrhiza glabra*): a phytochemical and pharmacological review. Phytother Res. 2018;32:2323-39.

68. Wang D, Liang J, Zhang J, Wang Y, Chai X. Natural chalcones in Chinese materia medica: liquorice. Evid Based Complement Alternat Med. 2020;2020:3821248.

69. Husain I, Bala K, Khan IA, Khan SI. A review on phytochemicals, pharmacological activities, drug interactions, and associated toxicities of liquorice (Glycyrrhiza sp.). Food Front. 2021;2(4):449-85.

70. Li W, Asada Y, Yoshikawa T. Flavonoid constituents from *Glycyrrhiza glabra* hairy root cultures. Phytochemistry. 2000;55(5):447-56.

71. Bai L, Li X, He L, Zheng Y, Lu H, Li J, et al. Antidiabetic potential of flavonoids from traditional Chinese medicine: a review. Am J Chin Med. 2019;47(5):933-57.

72. Wang H, Zhang D, Ge M, Li Z, Jiang J, Li Y. Formononetin inhibits enterovirus 71 replication by regulating COX-2/PGE2 expression. Virol J. 2015;12(1):35.

73. Zhang Z, Yang L, Hou J, Tian S, Liu Y. Molecular mechanisms underlying the anticancer activities of liquorice flavonoids. J Ethnopharmacol. 2021;267:113635.

74. Sultana S, Haque A, Hamid K, Urmi KF, Roy S. Antimicrobial, cytotoxic and antioxidant activity of methanolic extract of *Glycyrrhiza glabra*. Agric Biol J N Am. 2010;1:957-60.

75. Rodino S, Butu A, Butu M, Cornea PC. Comparative studies on antibacterial activity of liquorice, elderberry and dandelion. Dig J Nanomater Biostruct. 2015;10:947-55.

76. Zhang J, Wu X, Zhong B, Liao Q, Wang X, Xie Y, et al. Review on the diverse biological effects of glabridin. Drug Des Devel Ther. 2023;17:15-37.

77. Bhatt S, Kumar V, Dogra A, et al. Amalgamation of in-silico, in-vitro and in-vivo approach to establish glabridin as a potential CYP2E1 inhibitor. Xenobiotica. 2021;51(6):625-35.

78. Husain I, Bala K, Khan IA, Khan SI. A review on phytochemicals, pharmacological activities, drug interactions, and associated toxicities of liquorice (Glycyrrhiza sp.). Food Front. 2021;2(4):449-85.

79. Yu Y, Shen M, Song Q, Xie J. Biological activities and pharmaceutical applications of polysaccharide from natural resources: a review. Carbohydr Polym. 2018;183:91-101.

80. Dang L, Jin Y, Yuan Y, Shao R, Wang Y. Liquorice: comprehensive review of its chemical composition, pharmacodynamics, and medicinal value. Acupunct Herb Med. 2024;4(1):136-50.

81. Pan LC, Zhu YM, Zhu ZY, Xue W, Liu CY, Sun HQ. Chemical structure and effects of antioxidation and against α-glucosidase of natural polysaccharide from Glycyrrhiza inflata Batalin. Int J Biol Macromol. 2020;155:560-71.

82. Wu Y, Zhou H, Wei K, Zhang T, Che Y, Nguyễn AD, et al. Structure of a new Glycyrrhiza polysaccharide and its immunomodulatory activity. Front Immunol. 2022;13:1007186.

83. Zhang CH, Yu Y, Liang YZ, Chen XQ. Purification, partial characterization and antioxidant activity of polysaccharides from Glycyrrhiza uralensis. Int J Biol Macromol. 2015;79:681-6.

84. Thakur AK, Raj P. Pharmacological perspective of *Glycyrrhiza glabra* Linn: a mini-review. J Anal Pharm Res. 2017;5(5):00156.

85. Wahab S, Annadurai S, Abullais SS, Das G, Ahmad W, Ahmad MF, et al. *Glycyrrhiza glabra* (liquorice): a comprehensive review on its phytochemistry, biological activities, clinical evidence and toxicology. Plants (Basel). 2021;10(12):2751.

86. Muslikh FA, Priatna PA, Ekasari W. Pharmacological effects of *Glycyrrhiza glabra* L. as antihepatitis and hepatoprotective for children. J Farmasi dan Ilmu Kefarmasian Indonesia. 2023;10(1):1-7.

87. Fadhil AFSA, Kamal YM, Waheed HJ. The hepatoprotective effect of *Glycyrrhiza glabra* roots extract against amiodarone induced hepatotoxicity in male rats. Iraqi J Pharm Sci. 2024;33(2):190-6.

88. Alrefaei AF, Elbeeh ME. Hepatoprotective effects of *Glycyrrhiza glabra* in diabetic male rats: addressing liver function, oxidative stress, and histopathological changes. Biology (Basel). 2025;14(3):307.

89. Chauhan P, Sharma H, Kumar U, Mayachari A, Sangli G, Singh S. Protective effects of *Glycyrrhiza glabra* supplementation against methotrexate-induced hepato-renal damage in rats: an experimental approach. J Ethnopharmacol. 2020;263:113209.

90. Mohamed NES. Effect of aqueous extract of *Glycyrrhiza glabra* on the biochemical changes induced by cadmium chloride in rats. Biol Trace Elem Res. 2019;190(1):87-94.

91. Liang B, Guo XL, Jin J, Ma YC, Feng ZQ. Glycyrrhizic acid inhibits apoptosis and fibrosis in carbon-tetrachloride-induced rat liver injury. World J Gastroenterol. 2015;21(17):5271-80.

92. Tan QY, Hu Q, Zhu SN, Jia LL, Xiao J, Su HZ, et al. Liquorice root extract and magnesium isoglycyrrhizinate protect against triptolide-induced hepatotoxicity via up-regulation of the Nrf2 pathway. Drug Deliv. 2018;25(1):1213-23.

93. Ma Q. Role of Nrf2 in oxidative stress and toxicity. Annu Rev Pharmacol Toxicol. 2013;53:401-26.

94. Ulven SM, Dalen KT, Gustafsson JÅ, Nebb HI. LXR is crucial in lipid metabolism. Prostaglandins Leukot Essent Fatty Acids. 2005;73(1):59-63.

95. Kim YW, Kim YM, Yang YM, Kay HY, Kim WD, Lee JW, et al. Inhibition of LXRα-dependent steatosis and oxidative injury by liquiritigenin, a liquorice flavonoid, as mediated with Nrf2 activation. Antioxid Redox Signal. 2011;14(5):733-45.

96. Sies H. Oxidative stress: a concept in redox biology and medicine. Redox Biol. 2015;4:180-3.

97. Alrefaei AF, Elbeeh ME. Hepatoprotective effects of *Glycyrrhiza glabra* in diabetic male rats: addressing liver function, oxidative stress, and histopathological changes. Biology (Basel). 2025;14(3):307.

98. Bhattacharjee M, Manoharan S, Sathisaran U, Tamatam A, Perumal E. MAO inhibiting phytochemicals from the roots of *Glycyrrhiza glabra* L. J Biomol Struct Dyn. 2024;42(8):3887-905.

99. Chauhan P, Sharma H, Kumar U, Mayachari A, Sangli G, Singh S. Protective effects of *Glycyrrhiza glabra* supplementation against methotrexate-induced hepato-renal damage in rats: an experimental approach. J Ethnopharmacol. 2020;263:113209.

100. Yang R, Yuan BC, Ma YS, Zhou S, Liu Y. The anti-inflammatory activity of liquorice, a widely used Chinese herb. Pharm Biol. 2017;55(1):5-18.

101. Yu X, Bao Y, Meng X, Wang S, Li T, Chang X, et al. Multi pathway integrated adjustment mechanism of liquorice flavonoids presenting anti inflammatory activity. Oncol Lett. 2019;18(5):4956-63.

102. Alrefaei AF, Elbeeh ME. Hepatoprotective effects of *Glycyrrhiza glabra* in diabetic male rats: addressing liver function, oxidative stress, and histopathological changes. Biology (Basel). 2025;14(3):307.

103. Kim JH, Kim OK, Yoon HG, Park J, You Y, Kim K, et al. Anti-obesity effect of extract from fermented Curcuma longa L. through regulation of adipogenesis and lipolysis pathway in high-fat diet-induced obese rats. Food Nutr Res. 2016;60(1):30428.

104. Rana SV, Pal R, Vaiphei K, Sharma SK, Ola RP. Garlic in health and disease. Nutr Res Rev. 2011;24(1):60-71.

105. Alrefaei AF, Elbeeh ME. Hepatoprotective effects of *Glycyrrhiza glabra* in diabetic male rats: addressing liver function, oxidative stress, and histopathological changes. Biology (Basel). 2025;14(3):307.

106. Chauhan P, Sharma H, Kumar U, Mayachari A, Sangli G, Singh S. Protective effects of *Glycyrrhiza glabra* supplementation against methotrexate-induced hepato-renal damage in rats: an experimental approach. J Ethnopharmacol. 2020;263:113209.

107. Fadhil AFSA, Kamal YM, Waheed HJ. The hepatoprotective effect of *Glycyrrhiza glabra* roots extract against amiodarone induced hepatotoxicity in male rats. Iraqi J Pharm Sci. 2024;33(2):190-6.

108. Mohamed NES. Effect of aqueous extract of *Glycyrrhiza glabra* on the biochemical changes induced by cadmium chloride in rats. Biol Trace Elem Res. 2019;190(1):87-94.