

Mechanisms and therapeutic potential of glycyrrhizic acid: Insights into key signaling pathways and disease modulation (Review)

JINJIN YU^{1,2}, HUIHENG QU^{3,4}, WEICHENG XU², YIMING FANG², NAN WANG⁴ and WEI SHI²

¹Department of Ophthalmology, Wuxi Affiliated Hospital of Nanjing University of Chinese Medicine, Wuxi, Jiangsu 214000, P.R. China;

²Department of Ophthalmology, Nanjing Hospital Affiliated to Nanjing University of Chinese Medicine,

The First Clinical Medical College of Nanjing University of Chinese Medicine, Nanjing, Jiangsu 210004, P.R. China;

³Department of General Surgery, Jiangnan University Medical Center, Jiangnan University, Wuxi, Jiangsu 214002, P.R. China;

⁴Department of Cancer Biology, Atrium Health Wake Forest Baptist Comprehensive Cancer Center, Winston-Salem, NC 27157, USA

Received August 12, 2025; Accepted February 5, 2026

DOI: 10.3892/mmr.2026.13836

Abstract. Glycyrrhizic acid (GL), a natural extract derived from licorice, has shown notable therapeutic potential across various diseases through complex mechanisms involving key signaling pathways. The present review systematically summarized the primary biological actions of GL, highlighting its role

as an inhibitor of high-mobility group box-1 and regulator of multiple notable pathways, including the nuclear factor- κ B, phosphoinositide 3-kinase/protein kinase B, mitogen-activated protein kinase, Janus kinase/signal transducer and activator of transcription and pyroptosis-related pathways. GL effectively modulates innate and adaptive immune responses, reduces inflammation and exhibits protective effects against liver injury. In oncology, GL has demonstrated anti-proliferative and pro-apoptotic effects by interacting with the tumor microenvironment, suppressing angiogenesis and enhancing chemotherapeutic efficacy as an adjuvant therapy. By synthesizing previous research advancements that elucidate the multifaceted biological mechanisms of GL, the present review aimed to provide a comprehensive foundation for future translational research.

Correspondence to: Professor Wei Shi, Department of Ophthalmology, Nanjing Hospital Affiliated to Nanjing University of Chinese Medicine, The First Clinical Medical College of Nanjing University of Chinese Medicine, 155 Hanzhong Road, Qinhuai, Nanjing, Jiangsu 210004, P.R. China
E-mail: shiwei_1218@163.com

Abbreviations: 11 β -HSDs, 11 β -hydroxysteroid dehydrogenase activity; Akt, protein kinase B, PKB; ASC, apoptosis-associated speck-like protein containing a CARD; C/EBP, CCAAT/enhancer-binding protein; CD134, OX40; CP, cisplatin; CUGBP1, CYG-binding protein1; ERS, endoplasmic reticulum stress; ERK, extracellular signal-regulated kinase; GSDMD, Gasdermin D; GL, glycyrrhizic acid; HCC, hepatocellular carcinoma; HMGB1, high-mobility group box 1; IL-1 β , interleukin1 β ; I/R, ischemia-reperfusion; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MgIG, magnesium isoglycyrrhizinate; MMP, matrix metalloproteinase; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; Nrf2, nuclear factor erythroid 2-related factor 2; p38, p38 mitogen-activated protein kinase; PARP, poly(ADP-ribose) polymerase; PI3K, phosphoinositide 3-kinase; RAGE, receptor for advanced glycation end-products; Smad, SMAD family member; STAT3, signal transducer and activator of transcription 3; TGF- β , transforming growth factor- β ; TLR2, toll-like receptor-2; TLR4, toll-like receptor-4; TNF- α , tumor necrosis factor- α ; YAP, yes-associated protein

Key words: glycyrrhizic acid, signaling pathways, inflammation, HMGB1

Contents

1. Introduction
2. Chemical structure and pharmacokinetics of GL
3. High-mobility group box-1 (HMGB1)
4. Relevant signaling pathways
5. Discussion

1. Introduction

Licorice is a well-known herb that has been widely used in traditional Chinese medicine. According to the Chinese Pharmacopoeia (1), three original plants from the family Leguminosae, *Glycyrrhiza uralensis* Fisch, *Glycyrrhiza inflata* Bat. and *Glycyrrhiza glabra* L. are prescribed as licorice. Numerous studies indicate that the most pharmacologically important bioactive compounds in licorice include ~20 types of triterpenoids, 300 types of flavonoids and various polysaccharides (2,3). Among these, the triterpenoid glycyrrhizic acid (GL) is particularly notable. GL is a sweet-tasting compound extensively used as a flavoring agent in the food industry. Upon hydrolysis, GL yields two molecules of

glucuronic acid and one molecule of glycyrrhetic acid (GA). In the intestines, GL undergoes enzymatic conversion to GA-3-O-mono- β -D-glucuronide, a derivative with enhanced bioavailability and metabolic potential (4).

GL-based therapies, including compound GL tablets and compound GL injections, have been prescribed to treat a number of inflammatory and immune diseases, including viral and autoimmune hepatitis (5). The therapeutic effects of GL have also been validated in diseases such as cirrhosis, eczema, chronic urticaria, psoriasis, and ulcerative colitis (6-8). Furthermore, as an inhibitor of cellular signal transduction molecules that has been demonstrated to suppress angiogenesis and the secretion of tumor-associated cytokines, GL effectively inhibits the migration and invasion of various types of cancer cells (9). Due to its low toxicity and minimal side effects, GL exhibits a wide range of potential therapeutic applications (10).

The present review discusses the effects of GL on intracellular and extracellular inflammatory signaling pathways, aiming to provide a theoretical foundation for the clinical applications of GL and its formulations. Furthermore, the present review highlights emerging therapeutic strategies involving GL, underscoring its potential as a cornerstone for developing new treatments across a spectrum of diseases.

2. Chemical structure and pharmacokinetics of GL

GL, also known as glycyrrhizin, is the principal bioactive component of licorice. This compound is a pentacyclic triterpenoid saponin composed of one molecule of GA conjugated with two molecules of glucuronic acid (11). The molecular formula of GL is $C_{42}H_{62}O_{16}$, with a relative molecular weight of 822.93 kDa, whereas its derivative GA, which has a relative molecular weight of 470.69 kDa, has the molecular formula $C_{30}H_{46}O_4$ (Fig. 1). The structure of GL includes five interconnected rings termed rings A-E, with functional groups present on rings A, C and E; hydroxyl and carboxyl groups are present at the 3rd and 30th carbon positions, respectively. These positions are the primary sites for chemical modification of GL, enabling the synthesis of various GA derivatives with potential therapeutic applications (12).

Following its intake, the aglycone section of GL is hydrolyzed by glucuronidase to form two isomers, 18 α -GA and 18 β -GA (13). The α -form has higher lipophilicity than the β -form, making it more likely to bind to receptor proteins within the body. The conformation of the D and E rings closely resemble that of prednisolone, allowing GA to easily bind to target cells of steroid hormones, which confers its antitoxic effects (14). 18 β -GA, with a structure similar to cortisol, can mimic the activity of cortisol by inhibiting 11 β -hydroxysteroid dehydrogenase activity (11 β -HSDs) (12). This isomer also inhibits the activation of the classical complement pathway and reduces reactive oxygen species (ROS) levels, exerting anti-inflammatory and glucocorticoid hormone-like effects (6).

When administered orally, GL is broken down by β -D-glucuronidase in the intestines to produce GA. Following intravenous administration, GL is metabolized by β -D-glucuronidase in liver lysosomes to produce 3-mono-glucuronic GA, which is subsequently distributed via the enterohepatic circulation. GL is metabolized to GA under the action of gut bacteria and is subsequently reabsorbed through the intestinal wall to exert its pharmacological effects (15).

3. High-mobility group box-1 (HMGB1)

HMGB1 is a nuclear protein that functions as a structural chromatin-binding factor, contributing to the maintenance of nucleosome architecture and the regulation of gene transcription. In response to various stimuli, HMGB1 can be actively secreted by immune and non-immune cells or passively released into the extracellular milieu (16). HMGB1 is a multi-functional regulator: Intracellularly, it acts as an architectural chromatin-binding factor. It can be passively released by damaged or virus-infected cells, or actively secreted by innate immune cells in response to exogenous bacterial products (e.g. endotoxin or CpG-DNA) or endogenous inflammatory stimuli (17). Extracellular HMGB1 mediates the inflammatory response upon binding to inflammation mediators, such as lipopolysaccharide (LPS), DNA or the cytokine interleukin-(IL-) 1β . Once released, HMGB1 can bind to the receptor for advanced glycation end-products (RAGE) in soluble or cell-bound forms and to toll-like receptor-2 (TLR2) and TLR4 (16). This binding induces the production of inflammatory cytokines, chemokines, adhesion molecules and ROS, activating downstream signaling pathways such as the p38 mitogen-activated protein kinase (MAPK) kinase (MEK) (18), c-Jun N-terminal kinase (JNK) (19) and nuclear factor- κ B (NF- κ B) pathways. These pathways, in turn, stimulate the expression and release of other pro-inflammatory cytokines, initiating a positive feedback loop via the NF- κ B signaling pathway, which leads to cellular inflammation, damage and apoptosis. HMGB1 is therefore implicated in the pathogenesis of a variety of chronic inflammatory diseases, autoimmune disorders and malignant tumors (16,20).

In recent years, research on GL has primarily focused on its role as a specific inhibitor of HMGB1 (21,22). Experimental studies have demonstrated that GL can directly bind to both high-mobility group boxes of HMGB1 with a dissociation constant of $\sim 150 \mu$ M, thereby suppressing its chemotactic and mitogenic activities (18,23,24). Previous studies have explored the mechanisms by which GL-mediated inhibition of HMGB1 exerts protective effects in various disease models (25-27). GL effectively suppresses the pro-inflammatory cytokine activity of extracellular HMGB1 and confers protection against ischemia-reperfusion (I/R)-induced injury in the spinal cord, liver, brain and myocardium in animal models (16). For instance, in a rat liver model of I/R, GL administration was shown to reduce HMGB1 expression in Kupffer cells, demonstrating potential as a preventive treatment for I/R injury, particularly with regards to hepatobiliary surgery (28). Furthermore, a study by Zhai *et al* (29) reported that GL alleviated I/R injury in rat myocardium by directly inhibiting the cytokine activity of extracellular HMGB1 and blocking the phosphorylation of the JNK/apoptosis regulator BAX (Bax) pathway.

In spinal cord injury models, GA, the active metabolite of GL, was found to reduce inflammation by inhibiting HMGB1 activity via the p38/JNK signaling pathway (30). Additionally, GL has been shown to reduce the HMGB1-induced apoptosis of hepatocytes via a p38-dependent mitochondrial pathway, further supporting the therapeutic potential of GL in alleviating HMGB1-mediated liver injuries, such as viral hepatitis, liver I/R injury and sepsis-associated liver injury (31).

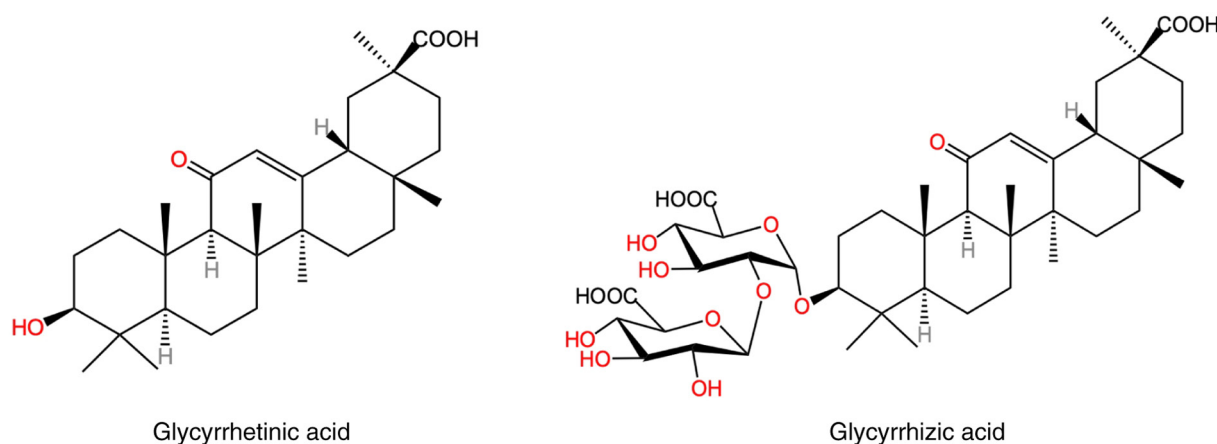


Figure 1. Chemical structures of GL and GA. GL is a glycosylated derivative of GA, formed by the conjugation of GA with two molecules of glucuronic acid. The structural differences between GA and GL contribute to their distinct pharmacological properties and bioavailability. GA, glycyrrhetic acid; GL, glycyrrhizic acid.

The HMGB1 is also stimulates the proliferation of cancer and endothelial cells, activates angiogenesis and induces inflammation formation, which has a negative impact on tumor progression and recurrence (32-34). As a HMGB1 inhibitor, GL hinders tumor regeneration in mice by blocking protein-stimulated cell proliferation and migration, inhibiting HMGB1-mediated angiogenesis, and reducing inflammatory conditions levels (16).

In addition, GL has previously been evaluated as a potential therapeutic agent targeting sepsis. Promising results indicate that GL modulates the serum level and gene expression of HMGB1 and other pro-inflammatory cytokines, thereby maintaining hemodynamic stability and protecting vital organs from LPS-induced endotoxemia in a porcine model (35).

In ophthalmic applications, the topical administration of glycyrrhizinate-genistein micelle-based eye drops has been shown to markedly promote corneal epithelial and nerve regeneration in diabetic mice. This therapeutic effect is likely mediated through the inhibition of HMGB1 signaling via downregulation of HMGB1 and its receptors RAGE and TLR4, as well as the suppression of inflammatory cytokines such as IL-6 and IL-1 β (36). Furthermore, as an inhibitor of HMGB1, GA has been shown to alleviate symptoms of conjunctivitis, blepharitis and dry eye disease by reducing pro-inflammatory protein levels in tear fluid (37).

Additionally, GL provides neuroprotection by inhibiting HMGB1 activity in the nervous system, thereby improving chronic stress-induced depressive behavior. This is achieved via modulation of the kynurenine pathway, which has been linked to stress-induced neuroinflammation and depressive symptoms (38).

4. Relevant signaling pathways

NF- κ B and its signaling pathway. NF- κ B is an important transcription factor responsible for regulating inflammation and immune responses, and is closely associated with immune cell activation, T- and B-lymphocyte development, stress responses and apoptosis (39). Under normal conditions, NF- κ B remains bound to inhibitor of κ B (I κ B) and remains inactive in the cytoplasm. However, when stimulated by upstream factors,

I κ B- α undergoes ubiquitination and degradation. This process releases the NF- κ B p65 subunit from its inhibitory complex with I κ B- α , allowing it to translocate to the nucleus and activate the transcription of various genes (40).

Once activated, NF- κ B promotes the expression of genes that facilitate cell proliferation, inhibit apoptosis and support cancer cell proliferation. In human glioblastoma U251 cells, GL suppresses cell proliferation in a dose- and time-dependent manner. This effect is mediated through the downregulation of p65 expression and inhibition the NF- κ B pathway, demonstrating GL's anti-inflammatory and antitumor properties (41). Additionally, dipotassium glycyrrhizate, a potassium salt of GL, has been shown to exhibit anti-proliferative effects in U251 and U138MG cells by inducing apoptosis and upregulating microRNA (miR)-4443 and miR-3620, which inhibit NF- κ B post-transcriptionally (42). Given that overexpression of NF- κ B is a hallmark of malignant glioma, this transcription factor remains a key target for GL in treating such cancers (43,44). GL has also been found to reduce the ratio of M1-like macrophages in colon. Furthermore, by inhibiting the LPS/HMGB1/NF- κ B signaling pathway, it suppresses the production of C-C motif chemokine 2 and TNF- α in colonic macrophages (45). Furthermore, in hepatocellular carcinoma (HCC) cells, GL induces DNA damage and inactivates NF- κ B, which collectively contribute to G₁-phase arrest. This arrest is mediated through the activation of ataxia-telangiectasia mutated proteins, increased expression of cell cycle inhibitors p21 and p27, and the inhibition of NF- κ B-mediated cyclin D1 expression (46).

GL has also been shown to improve bone loss and trabecular parameters in ovariectomized mice. Bone marrow stromal cells isolated from these mice have been shown to exhibit enhanced receptor activator of NF- κ B-induced osteoclast formation capabilities, a characteristic that GL notably reverses. NF- κ B plays an important role in osteoclastogenesis, yet glycyrrhizin inhibits the NF- κ B signaling pathway in ovariectomized mice, posing GL administration as a potential adjunctive therapy for postmenopausal osteoporosis (47,48).

Furthermore, GL has been shown to alleviate acute lung injury induced by LPS by reducing the production of inflammatory factors, such as IL-1 β , monocyte chemoattractant

protein-1 and cyclooxygenase-2, HMGB1 and adhesion molecules. This effect is mediated by the upregulation of angiotensin-converting enzyme 2 and inhibition of the caveolin-1/NF- κ B signaling pathway (49). In human bronchial epithelial cells treated with toluene diisocyanate-albumin conjugate, GL-mediated inhibition of HMGB1 has been demonstrated to lower nuclear factor erythroid 2-related factor 2 (Nrf2) expression and reduce ROS production, resulting in increased matrix metalloproteinase (MMP) levels and reduced NOD-like receptor pyrin domain-containing 3 (NLRP3) inflammasome activation. As such, GL has been shown to enhance the activation of the NLRP3 inflammasome by modulating the HMGB1-regulated ROS/NF- κ B pathway (50).

In a rat model of isoproterenol-induced myocardial ischemia, GL has been shown to dose-dependently downregulate phosphorylated-(p-)NF- κ B p65 and p-I κ B α levels, enhancing cardiac antioxidant capacity and reducing cardiomyocyte apoptosis (51). Similarly, a mouse model of myocardial fibrosis induced by isoproterenol has demonstrated that inflammatory responses are amplified by NF- κ B-mediated TLR4 activation. However, magnesium isoglycyrrhizinate (MgIG) has been shown to protect against isoproterenol-induced myocardial fibrosis by inhibiting the TLR4/NF- κ B p65 signaling pathway (52).

Additionally, GL has demonstrated renal protective effects in an insulin-resistant rat model of aluminum-induced renal toxicity by inhibiting oxidative stress as well as the TLR4/NF- κ B pathway (53). Cisplatin (CP), a commonly used anti-cancer drug, often causes nephrotoxicity (54). Treatment with GL or 18 β -GA has been shown to restore oxidative homeostasis and reduce inflammation in the kidneys of CP-treated mice to near-normal levels, likely via upregulation of Nrf2 and downregulation of activated NF- κ B (55).

Endothelial dysfunction is an important factor in the pathogenesis of diabetes and its vascular complications. Pre-treatment with GL has been shown to markedly reduce human umbilical vein endothelial cell apoptosis induced by advanced glycation end-products, as well as exhibit protective effects against endothelial dysfunction by inhibiting the RAGE/NF- κ B pathway. These anti-apoptotic, anti-inflammatory and antioxidant activities enable GL to demonstrate potential therapeutic benefits for diabetic vascular complications (56).

In a model of cerebral I/R injury, GL has been shown to inhibit the secretion of inflammatory cytokines, including IL-1 β , IL-6 and TNF- α , in serum and brain tissue. Additionally, GL has been shown to protect against I/R-induced cerebral ischemic disease by inhibiting the expression of the HMGB1-mediated TLR4/NF- κ B pathway (57).

Furthermore, MgIG, a magnesium salt of the 18 α -GA derivative of GL, has been shown to possess liver-protective, anti-inflammatory, antioxidant and antiviral properties (52). These properties underlie its clinical efficacy; for example, MgIG has been shown to markedly ameliorate liver fibrosis by preventing the nucleus translocation of NF- κ B (58).

Phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway. PI3Ks are enzymes that catalyze the conversion of phosphatidylinositol 4,5-bisphosphate into phosphatidylinositol 3,4,5-trisphosphate. These enzymes play notable roles in a number of cellular processes, such as

proliferation, cancer progression and inflammation. Akt is a key player in the PI3K/Akt signaling pathway, which has been implicated in multiple diseases such as cancer, diabetes, cardiovascular diseases and neurological disorders (59–61).

The effects of GL on the PI3K/Akt pathway vary depending on cellular context, tissue type and disease model. In numerous pathological conditions, GL functions primarily as an inhibitor of PI3K activity (62). As PI3K/Akt signaling acts upstream of the NF- κ B signaling pathway, experimental evidence has demonstrated that GL suppresses IL-1 β -induced phosphorylation of PI3K/Akt and subsequent NF- κ B activation, thereby attenuating the inflammatory response (62) and subsequently mitigating liver injury. Additionally, GL suppresses both inflammation and apoptosis via the inhibition of HMGB1 and the PI3K/mammalian target of rapamycin (mTOR) signaling pathway (63). In LPS-stimulated macrophages, both GL and 18 β -GA have been shown to inhibit the activity of the p110 δ and p110 γ subunits of PI3K, therefore inhibiting subsequent NF- κ B activation. This inhibition has also been shown to result in a dose-dependent reduction in LPS-induced TNF- α , IL-6 and IL-1 β production in RAW264.7 cells (64).

Furthermore, GL has been shown to induce excessive autophagy in HCC cells both *in vitro* and *in vivo*, a process that is regulated by the concurrent inhibition of the Akt/mTOR and extracellular signal-regulated kinase (ERK)1/2 pathways. This has highlighted autophagy-mediated cell death as a potential strategy for tumor suppression (65). A study reported by Tsai *et al.* (66) found that GL markedly inhibited tumor cell growth, invasion and the phosphorylation of ERK, Akt and epidermal growth factor receptor. In HCC cells, GL treatment inhibited anti-apoptotic and metastatic protein expression, thereby promoting caspase-8/9-mediated apoptosis in both *in vitro* and *in vivo* models. In the gastric cancer cell line MGC-803, GL has been shown to induce apoptosis. This effect is accompanied by inhibition of PI3K/Akt, downregulation of the expression of Bcl-1, survivin and p65 expression, upregulation of Bax and promotion of poly(ADP-ribose) polymerase (PARP) (67). A study reported by Niu *et al.* (68) supported the GL-mediated inhibition of HMGB1 both *in vitro* and *in vivo*, which affected the protein brahma homolog 1 and PI3K/Akt/mTOR pathways and suppressed the epithelial-mesenchymal transition in pulmonary fibrosis in mice, ultimately slowing the progression of silicosis.

Furthermore, GL and 18 β -GA have been shown to reduce mitochondrial bioenergetics and activate the PI3K/Akt pathway in PC12 cells, therefore protecting these cells from ischemic injury by modulating the intracellular antioxidant system and reducing mitochondria-induced apoptosis (69).

MAPK signaling pathway. Numerous studies have shown that ROS can activate the MAPK pathway. In mammals, there are three subgroups of MAPKs: ERKs, JNKs and p38 MAPKs. All three MAPK subgroups are involved in regulating cellular growth and apoptosis, which are important for normal cellular function (70). The Ras/Raf/MAPK/MEK/ERK pathway is activated by receptor tyrosine kinase signals from growth factors and cytokines. Once activated, Ras activates Raf, which subsequently activates MEK1/2, ultimately leading to ERK1/2 activation; continuous ERK pathway activation promotes cellular proliferation (71). Furthermore, the JNK pathway is

activated by MEK7 and MEK4, leading to the translocation of activated JNK to the nucleus, where it further activates various transcription factors to regulate cellular proliferation (72).

As an inhibitor of HMGB1, GL reduces inflammation and fibrosis by inhibiting the MAPK and SMAD family member (Smad)3 signaling pathways, respectively (73); this has been shown to alleviate pulmonary toxicity induced by bleomycin, a drug used for treating various tumors (74). Additionally, GL markedly inhibits ROS production, blocking a cascade of events comprising endoplasmic reticulum calcium release, endoplasmic reticulum stress (ERS), MAPK activation and cell death (75). This GL-mediated ROS suppression provides effective photoprotection, offering potential for cosmetic or therapeutic purposes. In human skin fibroblasts (Hs68 cell line), GL protects against UV-B-induced damage by mitigating both Ca^{2+} imbalance, ERS, as well as by suppressing MAPK activation and subsequent apoptosis (70). Furthermore, GL has been shown to exhibit cytotoxic effects, induce apoptosis and promote G_0/G_1 phase cell cycle arrest in the rat pituitary adenoma-derived MMQ and GH3 cell lines. These results indicate that GL promotes cell cycle arrest and apoptosis through a ROS-dependent activation of the MAPK pathway (76).

The p38 MAPK pathway is activated by pro-inflammatory cytokines such as IL-1, IL-6 and TNF- α . Activated p38 MAPK influences downstream transcription factors, including NF- κ B and transcription factor (TF)-1, -2 and -6, in order to regulate cellular proliferation, differentiation and growth processes (77). An experimental study has shown that GL may prevent colitis by reducing the expression of NF- κ B p65 and p38 MAPK (40). Additionally, GL has been shown to modulate the T helper 1/T helper 2 cell balance by suppressing OX40 (CD134)-OX40 ligand signaling and p38 MAPK activity, thus reducing disease severity in ovalbumin-induced asthma models (78). GL also mitigates inflammation following spinal cord injury by regulating the p38/JNK pathway to inhibit HMGB1 expression (30). Furthermore, GL has previously been used as an anti-apoptotic agent due to its inhibition of JNK1/2 and p38 MAPK phosphorylation, as well as its suppression of CCAAT/enhancer-binding protein (C/EBP) homologous protein, resulting in the reduction of ERS (79).

The ERK and JNK signaling pathways are both associated with learning and memory functions (80). A study has demonstrated that GL improves short-term memory by reducing the phosphorylation of ERK and JNK, both of which are important for regulating neuroplasticity and inflammatory responses (81). In vascular endothelial cells, GL has demonstrated the potential to inhibit angiogenesis by suppressing the ROS/ERK signaling axis, potentially slowing the progression of angiogenesis-dependent diseases such as various types of cancer (82).

In a chicken model of *Mycoplasma gallisepticum* infection, GL has been found to suppress the infection-induced expression of MMP2, MMP9 and inflammatory cytokines via the p38 and JNK signaling pathways. *In vivo* histopathological analysis has revealed that GL treatment markedly alleviates tracheal and lung injuries resulting from *M. gallisepticum* infection (83). In a rat model of sepsis-induced kidney injury, GL has been shown to markedly suppress LPS-induced oxidative stress by activating the ERK pathway (84). Furthermore, the C/EBP family plays a core role in regulating adipogenesis within the transcriptional network that controls this process. GL has been shown to inhibit

early-stage adipogenesis in the 3T3-L1 cell line by inhibiting the MEK/ERK-mediated expression of C/EBP β and C/EBP δ (85).

Janus kinase (JAK)/signal transducer and activator of transcription (STAT)3 signaling pathway. JAKs, such as JAK1, JAK2, JAK3 and non-receptor tyrosine-protein kinase TYK2, are transmembrane tyrosine kinases that activate STAT proteins (86). Upon cytokine receptor binding, JAKs become activated and phosphorylate tyrosine residues on the receptor tail. This phosphorylation facilitates the binding of STAT3. The phosphorylated STAT3 then undergoes dimerization and translocates from the cytoplasm to the nucleus, where it regulates target gene expression, including NF- κ B, cyclin D1, survivin, apoptosis regulator Bcl-2 and vascular endothelial growth factor, in order to increase cell proliferation. JAK1 in particular plays a notable role in cytokine signaling pathways that regulate inflammatory cytokine expression (87).

Several studies have shown that phosphorylated non-receptor tyrosine kinases, such as Akt and mTOR, can activate STAT3 proteins (88-90). GL has been shown to suppress the Akt/mTOR/STAT3 signaling pathway, downregulate cyclin D1 and survivin, promote the cleavage of caspase-3 and PARP, and inhibit TF-1 cell proliferation *in vitro*; this inhibition of cell proliferation has resulted in reductions in TF-1 tumor volume *in vivo* (91). A previous study on the non-small cell lung cancer cell line HCC827 has shown that GL inhibits cancer cell migration and invasion by targeting the JAK/STAT/HMGB1 pathway (92).

Additionally, a study reported by Tian *et al* (93) demonstrated that GL ammonium salt reduced hepatocyte apoptosis by suppressing the JAK1/STAT1/interferon regulatory factor 1 signaling pathway, inhibiting oxidative stress, downregulating p-JNK expression and modulating apoptosis-related protein expression, therefore alleviating liver injury and restoring T helper cell balance in the liver. Another study reported by Guo *et al* (94) observed that GL promoted CYG-binding protein 1-mediated activation of the interferon- γ (IFN- γ)/STAT1/Smad7 signaling pathway, which reduced liver fibrosis and suppressed hepatic stellate cell (HSC) activation.

Pyroptosis signaling pathway. Pyroptosis is a regulated form of programmed cell death that is characterized by inflammatory responses. Pyroptotic signaling pathways are primarily categorized into canonical pathways and non-canonical pathways, which are mediated by caspase-1 and caspase-11, respectively. Pyroptotic cell death is marked by the activation of inflammatory caspases, predominantly caspase-1, -4, -5 and -11, and the cleavage of gasdermin family proteins. Cleaved gasdermin proteins subsequently form membrane pores, resulting in cell membrane rupture, the release of inflammatory mediators and cell death (95). The NLRP3 inflammasome is a key regulator of pyroptosis. The inflammasome recruits apoptosis-associated speck-like protein to form an active inflammasome complex that responds to various exogenous and endogenous stressors by secreting inflammatory factors such as IL-1 β or IL-18, leading to inflammation (96).

GL enhances the expression of the tumor suppressor protein p53 and upregulates the levels of caspase-9 and cleaved caspase-3 (97). These results indicated that GL treatment induces apoptosis, which is consistent with previous reports (98-100).

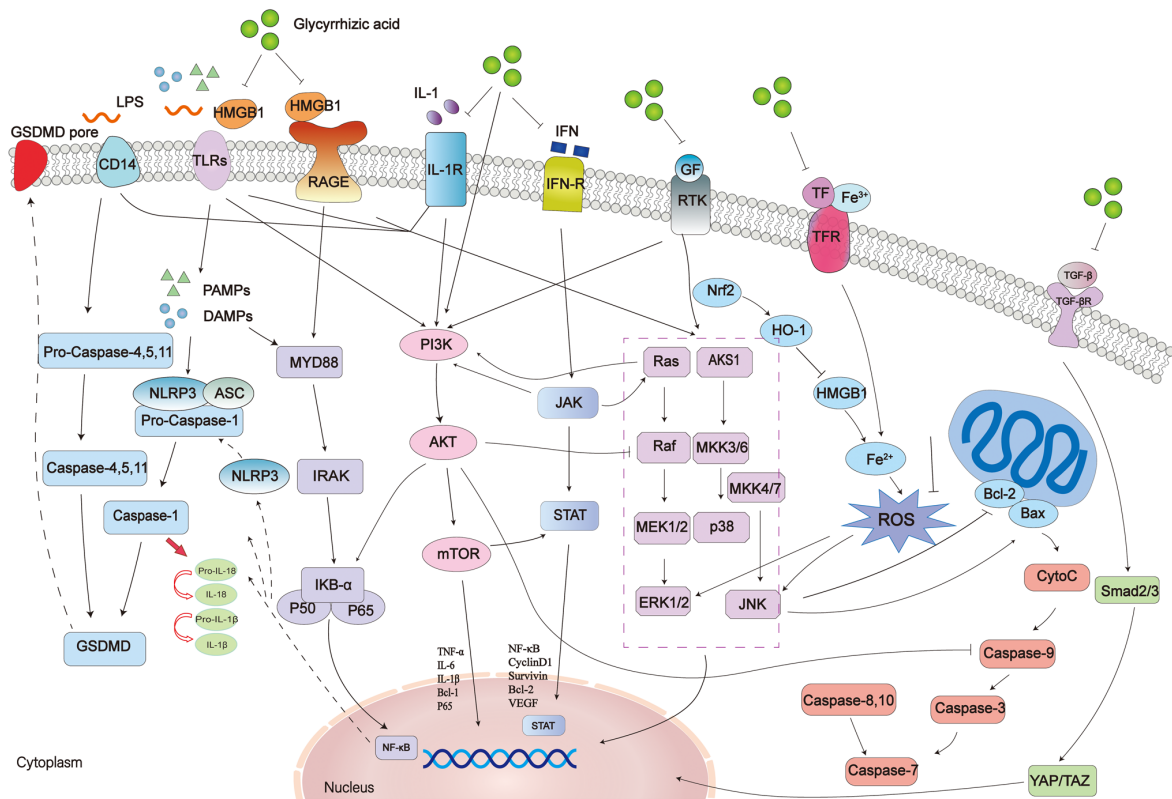


Figure 2. Mechanisms and signaling pathways of GL. GL, a bioactive compound derived from licorice roots, exhibits various pharmacological effects by modulating multiple signaling pathways. GL plays an important role in anti-inflammatory, antioxidant and antitumor processes by targeting key molecular pathways such as the PI3K/Akt/mTOR, MAPK and NF- κ B signaling pathways. GL inhibits inflammation by suppressing HMGB1, resulting in reduced NF- κ B activation and cytokine release. GL also regulates apoptosis via modulation of caspase activation, the Bcl-2/Bax ratio and mitochondrial oxidative stress. Additionally, GL has been shown to induce autophagy by inhibiting the Akt/mTOR pathway. The protective effects of GL extend to various conditions, including neurodegenerative diseases, cardiovascular disorders and immune-related conditions, primarily through the reduction of oxidative stress and inflammation. This schematic provides a comprehensive overview of the role of GL in disease modulation through its interactions with cellular signaling pathways. The dashed box indicates the three major branches of the MAPK signaling pathway. GL, glycyrrhizic acid; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; mTOR, mechanistic target of rapamycin; MAPK, mitogen-activated protein kinase; NF- κ B, nuclear factor κ B; HMGB1, high mobility group box 1; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein.

Additionally, caspase-11 acts as an LPS receptor, mediating ferroptosis, coagulopathy and lethality in endotoxemia and bacterial sepsis. GL treatment has been shown to markedly suppress caspase-11-dependent immune responses in endotoxemia and experimental sepsis models, resulting in reduced coagulopathy, organ damage and mortality (101). Furthermore, GL treatment has been shown to inhibit liver I/R injury and promote pyroptosis in Kupffer cells through gasdermin D-mediated cell death (102).

Other related signaling pathways. In HSCs, GL exerts anti-fibrotic effects by inhibiting the expression of Smad2, Smad3 and Smad7, all of which are activated by transforming growth factor- β (TGF- β)1-activated signaling pathway (103). A previous study in a rat model of liver fibrosis found that combined administration of GL and aspartate aminotransferase notably reduced Smad3 mRNA levels and the protein levels of p-Smad2/3, Smad3 and TGF- β 1. These findings further support the inhibitory effect of GL on the TGF- β 1/Smad signaling pathway (104). GL has also been shown to alleviate gefitinib-induced liver injury by inhibiting the p53/p21 pathway, thereby promoting cell-cycle progression (105).

Furthermore, GL has been shown to regulate the Hippo/yes-associated protein (YAP) pathway, a key modulator of cell proliferation and apoptosis, by inhibiting YAP

nuclear translocation, thus preventing myocardial I/R injury (106). Additionally, GL alleviates steroid-induced femoral head necrosis in both *in vivo* and *in vitro* models by activating the Wnt/ β -catenin pathway. The activation of this pathway reduces oxidative stress, enhances osteogenic differentiation and suppresses the adipogenic differentiation of mesenchymal stem cells. These combined effects restore osteogenic homeostasis in the femoral head, thereby mitigating necrosis (107). A study reported by Lai *et al* (108) demonstrated that GL protected against myocardial I/R injury by mitigating inflammation and cell death, potentially through the inhibition of ERS. Furthermore, GL administration has been demonstrated to alleviate fibrosis and inflammation caused by high glucose levels in glomerular podocytes by upregulating the AMP-activated protein kinase pathway and its associated regulatory factors (109). In both *in vitro* and *in vivo* models of acute liver failure, GL treatment has been shown to markedly inhibit ferroptosis by reducing oxidative stress (110). Co-administration of glycyrrhizin mitigates triptolide (TPL)-induced nephrotoxicity. This protection is achieved through the repair of TPL-damaged tight junction structures in renal tubules, mediated via the RhoA/Rho-associated kinase-1/myosin light chain signaling pathway (111) (Fig. 2).

Table I. Summary of the major mechanisms and therapeutic applications of GL.

Mechanistic category	Key molecular actions of GL	Representative therapeutic effects	(Refs.)
HMGB1 inhibition	Directly binds HMGB1 and blocks its interaction with the RAGE/TLR2/TLR4 receptor axis, thereby suppressing the downstream release of inflammatory mediators.	Reduces inflammation and tissue injury; protects the liver, cornea and neural tissues.	(28,30,31, 36,38)
NF- κ B pathway suppression	Inhibits NF- κ B p65 activation and decreases TNF- α , IL-1 β and IL-6 levels.	Exerts anti-inflammatory and antioxidant effects; inhibits tumor proliferation; confers cardiopulmonary and renal protection.	(41-46, 49-55)
PI3K/Akt/mTOR pathway regulation	Primarily inhibits PI3K/Akt signaling; downregulates cyclin D1 and survivin; promotes autophagy and apoptosis. Promotion the PI3K/Akt pathway in PC12 cells.	Suppresses tumor growth and metastasis; ameliorates inflammatory and fibrotic diseases. Protecting these cells from ischemic injury by modulating the intracellular antioxidant system and reducing mitochondria-induced apoptosis.	(66-69)
MAPK pathway modulation	Inhibits ERK, JNK and p38 activation; reduces oxidative and ER stress.	Exerts anti-fibrotic and cytoprotective effects; protects lung, skin and neural tissues.	(70,74,76)
JAK/STAT3 pathway inhibition	Blocks the phosphorylation JAK1 and STAT3; downregulates proliferation- and survival-related genes.	Suppresses tumor cell proliferation and invasion; reduces immune-mediated liver injury.	(91-94)
Regulation of pyroptosis activity	Inhibits caspase; reduces gasdermin D-mediated pyroptosis.	Protects against liver injury; Inhibits tumor cell proliferation.	(97-100,102)
TGF- β /Smad pathway inhibition	Blocks Smad2/3 activation.	Exerts anti-fibrotic effects in liver tissues.	(104)
Hippo/YAP pathway modulation	Inhibits YAP nuclear translocation.	Reduces myocardial ischemia-reperfusion injury.	(106)
Wnt/ β -catenin pathway activation	Enhances osteogenic differentiation via the Wnt/ β -catenin pathway.	Prevents osteonecrosis and maintains bone homeostasis.	(107)

GL, glycyrrhizic acid; HMGB1, high mobility group box 1; RAGE, receptor for advanced glycation end products; TLR, Toll-like receptor; NF- κ B, nuclear factor κ B; TNF- α , tumor necrosis factor α ; IL, interleukin; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; mTOR, mechanistic target of rapamycin; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3; NLRP3, NOD-like receptor family pyrin domain containing 3; ASC, apoptosis-associated speck-like protein containing a CARD; GSDMD, gasdermin D; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; TGF- β , transforming growth factor beta; YAP, Yes-associated protein.

5. Discussion

GL, a natural triterpenoid compound, exhibits a range of biological activities, including anti-inflammatory, antioxidant and antitumor effects. These pharmacological properties are mediated through multiple signaling pathways, including the NF- κ B, PI3K/Akt, MAPK, JAK/STAT3 and pyroptotic pathways (Table I).

GL has also been shown to attenuate oxidative stress and mediate the activation of inflammatory signaling cascades. For example, GL inhibits the ERK, JNK and p38 MAPK pathways, resulting in the reduced secretion of pro-inflammatory cytokines. Furthermore, GL negatively regulates the JAK/STAT3 pathway by suppressing STAT3 phosphorylation (112), leading to reduced cellular proliferation

and inflammatory responses. Through inhibition of the PI3K/Akt/mTOR pathway, GL modulates cell survival and apoptosis, downregulates the expression of cell cycle-related proteins, such as cyclin D1 and survivin, and promotes tumor cell apoptosis (9). In fibrosis-associated disorders, GL has been shown to exert anti-fibrotic effects primarily through inhibition of the TGF- β /Smad signaling axis, resulting in reduced HSC activation. Additionally, GL has been shown to modulate the Hippo/YAP pathway, thus mitigating myocardial I/R injury, and to activate the Wnt/ β -catenin pathway, which contributes to the maintenance of osteogenic homeostasis and ameliorates steroid-induced femoral head necrosis. The anti-oxidative and anti-inflammatory actions of GL have also been demonstrated in models of high glucose-induced podocyte injury, acute liver failure and neuroinflammation. Notably, GL

Table II. Signaling pathways of glycyrrhizic acid in disease as organized by disease or organ.

A, Glioblastoma		
Signaling pathways	Model	(Refs.)
NF- κ B	U251 glioblastoma cell line.	(41,42,44)
B, Liver		
NF- κ B	HCC cells.	(46)
	Rat hepatic stellate cells.	(58)
PI3K/Akt	Human liver macrophages; LPS-induced acute liver injury in C57/B6J mice.	(63)
	HCC cells.	(65)
	SK-Hep1 and Hep3B cells; SK-Hep1/luc2 bearing mice.	(66)
JAK1/STAT1/IRF1	Concanavalin A-induced liver injury in BALB/c mice.	(94)
IFN- γ /STAT1/Smad7	CCl ₄ -induced liver fibrosis in C57/B6J mice; human LX-2 cells and primary hepatic stellate cells.	(95)
TGF- β /Smad	Rat hepatic stellate cells.	(103)
TGF- β 1/Smad	Ligation-induced (BDL) and dimethylnitrosamine-induced liver fibrosis in Wistar rats; mice hepatic stellate cells.	(104)
p53/p21	AML-12 normal mouse liver cells, CRL-2254; male Institute of Cancer Research mice.	(105)
C, Bone		
NF- κ B	Bone marrow monocytes or macrophages; ovariectomized mice.	(47,48)
Wnt/ β -catenin	LPS with methylprednisolone-induced osteonecrosis of the femoral head in SD rats; C3H10T1/2 murine mesenchymal stem cells.	(107)
D, Colon		
NF- κ B	Colonic macrophages.	(45)
Pyroptosis	1,2-dimethylhydrazine-induced precancerous lesions in Wistar rats.	(97)
E, Lung		
NF- κ B	HUVECs; LPS-induced acute lung injury in mice.	(49)
	Human bronchial epithelial cells.	(50)
PI3K/Akt	Human non-small cell lung cancer cells, A549 cells; C57BL/6N mice intratracheally instilled with a sterile SiO ₂ dust suspension.	(68)
MAPK	Bleomycin-induced pulmonary toxicity in BALB/c mice.	(73)
	OVA-induced asthma in 48 BALB/c mice.	(79)
	Chicken primary alveolar type II epithelial cells.	(84)
F, Cardiac		
NF- κ B	ISO-induced myocardial cardiotoxicity in SD rats.	(51)
	ISO-induced myocardial cardiotoxicity in Kunming mice.	(52)
Hippo/YAP	H9c2 cells; I/R rat model.	(106)
G, Kidney		
NF- κ B	Aluminum and fructose-induced renal injury in Wistar rats.	(53)
	Cisplatin-induced nephrotoxicity in BALB/c mice.	(55)
MAPK	LPS stimulated rat mesangial cells (HBZY-1); septic rat models.	(85)

Table II. Continued.

H, Vascular system		
Signaling pathways	Model	(Refs.)
NF- κ B	HUVECs.	(56)
MAPK	BALB/c mice.	(83)
I, Cerebral		
NF- κ B	I/R injury in SD rats.	(57)
MAPK	Scopolamine-induced cognitive impairment in mice.	(82)
J, Gastric cancer		
PI3K/Akt	Gastric cancer cell lines, MGC-803 cells, BGC-823 cells and SGC-7901) cells.	(67)
K, Neurodegenerative disease		
PI3K/Akt	Rat pheochromocytoma cell line PC12	(68)
L, Skin		
MAPK	Human skin fibroblast Hs68 cells.	(70)
M, Intestine		
NF- κ B and MAPK	Methotrexate-induced enteritis in SD rats.	(40)
N, Spine		
p38/JNK	Highly aggressively proliferating immortalized rat microglia cells.	(30)
NF-κB, nuclear factor κB; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; DMN, dimethylnitrosamine; DMH, dimethylhydrazine; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; NQO1, NAD(P)H quinone dehydrogenase 1; JAK1, Janus kinase 1; STAT1, signal transducer and activator of transcription 1; IRF1, interferon regulatory factor 1; IFN-γ, interferon γ; TGF-β, transforming growth factor β; Smad, mothers against decapentaplegic homolog; p53, tumor protein p53; p21, cyclin-dependent kinase inhibitor 1A; Wnt, wntless/integrated signaling pathway; Hippo, Hippo signaling pathway; YAP, Yes-associated protein; HCC, hepatocellular carcinoma; HUVECs, human umbilical vein endothelial cells; LX-2, human hepatic stellate cell line; LPS, lipopolysaccharide; OVA, ovalbumin; ISO, isoproterenol; I/R, ischemia/reperfusion; BDL, bile duct ligation; CCl₄, carbon tetrachloride; SD rats, Sprague Dawley rats.		

has been shown to suppress NLRP3 inflammasome-mediated pyroptosis by inhibiting the HMGB1/TLR4/NF- κ B signaling pathway, reducing inflammatory damage and demonstrating notable neuroprotective and anticonvulsant effects in kainic acid-induced status epilepticus mouse model (113). In models of endotoxemia and sepsis, GL has been shown to alleviate immune dysregulation by suppressing caspase-11-dependent coagulation abnormalities and mitigating organ damage, demonstrating notable systemic protective effects.

Recent studies support the expanding pharmacological relevance of GL and related triterpenoids. Network pharmacology and molecular docking analyses have revealed that GA exerts its effects in diabetic nephropathy by targeting

multiple key pathways involved in inflammation and fibrosis, providing additional mechanistic evidence for the reno-protective potential of licorice-derived compounds (114). A recent review highlighted the therapeutic potential of glycyrrhizin in neuroinflammatory and neurodegenerative diseases, emphasizing its ability to modulate oxidative stress, apoptosis and HMGB1-related signaling within the central nervous system (115). Furthermore, a recent study has examined the efficacy of traditional and nanotechnology-based delivery approaches for GL, underscoring the importance of advanced formulations, such as improved nanotechnology, for enhancing drug bioavailability and clinical utility (116). These findings have complemented

the discussion of the present review by demonstrating that GL-associated compounds modulate broader pathological process (such as inflammation) across organ systems, and that the clinical administration may benefit from innovative delivery strategies.

The present review systematically summarized the signaling networks involved in the pharmacological actions of glycyrrhizin across diverse disease models (Table II) (30,40,41,42,44-53,55-57,58,63,65-70,73,79,82-85,94,95,97,103-107). A thorough understanding of the complex crosstalk among signaling pathways modulated by GL is important for informing the design of rigorous, multicenter, large-scale randomized controlled trials.

Notably, the biological activity of GL exhibits context-dependent variability, which is influenced by cell type, tissue environment and disease state. Elucidating the primary signaling mechanisms regulated by GL in each pathological context is important for optimizing targeted therapeutic strategies. Given the limited oral bioavailability of GL, previous research have focused on the development of novel strategies, such as combination therapies and nanocarrier-based delivery systems, to enhance its pharmacokinetic properties and reduce adverse effects in patients (117-119). Mechanistic insights into GL-mediated signaling regulation will facilitate the rational design of synergistic drug combinations and advanced delivery systems for GL-based therapies, therefore maximizing their therapeutic efficacy.

The present review extended the existing literature regarding GL activity by adopting a pathway-oriented perspective that integrated molecular mechanisms with disease relevance. While a previous review by Semwal *et al* (120) comprehensively summarized the pharmacological activities of glycyrrhizin, the present review placed greater emphasis on the organization of available evidence according to key signaling axes. HMGB1 inhibition was highlighted as a central upstream event linking inflammatory, oncological and fibrotic processes. Additionally, downstream pathways, such as the NF- κ B, PI3K/Akt, MAPK, JAK/STAT3 and pyroptotic pathways, were discussed in a unified framework. To facilitate the interpretation of these complex interactions, concise mechanistic summary tables have been provided with the aim of improving accessibility for readers from diverse scientific backgrounds (Tables I and II).

In conclusion, GL exerts multifaceted biological effects in various pathologies through the modulation of diverse signaling pathways, highlighting its potential as a promising therapeutic agent for inflammatory diseases, oxidative stress-related disorders, tumor progression and fibrosis. Continued mechanistic exploration and pathway-specific studies are required to provide a solid theoretical foundation for the clinical translation of GL.

Acknowledgements

Not applicable.

Availability of data and materials

Not applicable.

Authors' contributions

JY drafted and reviewed the manuscript. WX and YF independently performed literature searches. HQ and NW reviewed the information of the selected literature. WS was responsible for supervision and conceptualization, as well as writing, reviewing and editing the manuscript. JY, WX, YF, NW and WS contributed to manuscript revision. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Chinese Pharmacopoeia Commission. Pharmacopoeia of the People's Republic of China. China Medical Science Press. <https://ydz.chp.org.cn/#/main>. Accessed February 14, 2026.
2. Seki H, Sawai S, Ohyama K, Mizutani M, Ohnishi T, Sudo H, Fukushima EO, Akashi T, Aoki T, Saito K and Muranaka T: Triterpene functional genomics in licorice for identification of CYP72A154 involved in the biosynthesis of glycyrrhizin. *Plant Cell* 23: 4112-4123, 2011.
3. Zhu Z, Tao W, Li J, Guo S, Qian D, Shang E, Su S and Duan JA: Rapid determination of flavonoids in licorice and comparison of three licorice species. *J Sep Sci* 39: 473-482, 2016.
4. Zuo J, Meng T, Wang Y and Tang W: A review of the antiviral activities of glycyrrhizic acid, glycyrrhetic acid and glycyrrhetic acid monoglucuronide. *Pharmaceuticals (Basel)* 16: 641, 2023.
5. Gao W, Zhao Y, Guo L, Wang Y, Gong H, Zhang B and Yan M: Comparative effectiveness of glycyrrhizic acid preparations aimed at improving liver function of patients with chronic hepatitis B: A network meta-analysis of 53 randomized controlled trials. *Phytomedicine* 116: 154883, 2023.
6. Bi X, Yang L, Lin Y, Deng W, Jiang T, Zhang L, Lu Y, Yi W, Xie Y and Li M: Efficacy and safety of glycyrrhizic acid in treatment of autoimmune hepatitis. *Am J Chin Med* 51: 391-405, 2023.
7. Chen S, Cao W, Xiao X, Wang L, Wan R, Zou Z, Yang Q and Li Y: A systematic review and meta-analysis of efficacy and safety of compound glycyrrhizin combined with second-generation non-sedated antihistamine for the treatment of chronic urticaria. *J Dermatolog Treat* 35: 2299597, 2024.
8. Li M, Xiang L and Li Y: Efficacy and safety of compound glycyrrhizin in patients with alopecia areata: A systematic review and meta-analysis. *Ann Med* 57: 2491659, 2025.
9. Zhang Y, Sheng Z, Xiao J, Li Y, Huang J, Jia J, Zeng X and Li L: Advances in the roles of glycyrrhizic acid in cancer therapy. *Front Pharmacol* 14: 1265172, 2023.
10. Su X, Wu L, Hu M, Dong W, Xu M and Zhang P: Glycyrrhizic acid: A promising carrier material for anticancer therapy. *Biomed Pharmacother* 95: 670-678, 2017.
11. Mohammed EAH, Peng Y, Wang Z, Qiang X and Zhao Q: Synthesis, antiviral, and antibacterial activity of the glycyrrhizic acid and glycyrrhetic acid derivatives. *Russ J Bioorg Chem* 48: 906-918, 2022.
12. Chen K, Yang R, Shen FQ and Zhu HL: Advances in pharmacological activities and mechanisms of glycyrrhizic acid. *Curr Med Chem* 27: 6219-6243, 2020.
13. Ploeger B, Mensinga T, Sips A, Seinen W, Meulenbelt J and DeJongh J: The pharmacokinetics of glycyrrhizic acid evaluated by physiologically based pharmacokinetic modeling. *Drug Metab Rev* 33: 125-147, 2001.

14. Wagle A, Seong SH, Zhao BT, Woo MH, Jung HA and Choi JS: Comparative study of selective in vitro and in silico BACE1 inhibitory potential of glycyrrhizin together with its metabolites, 18 α - and 18 β -glycyrrhetic acid, isolated from *Hizikia fusiformis*. *Arch Pharm Res* 41: 409-418, 2018.
15. Shetty AV, Thirugnanam S, Dakshinamoorthy G, Samykutty A, Zheng G, Chen A, Bosland MC, Kajdacsy-Balla A and Gnanasekar M: 18 α -glycyrrhetic acid targets prostate cancer cells by down-regulating inflammation-related genes. *Int J Oncol* 39: 635-640, 2011.
16. Musumeci D, Roviello GN and Montesarchio D: An overview on HMGB1 inhibitors as potential therapeutic agents in HMGB1-related pathologies. *Pharmacol Ther* 141: 347-357, 2014.
17. Yang H, Antoine DJ, Andersson U and Tracey KJ: The many faces of HMGB1: Molecular structure-functional activity in inflammation, apoptosis, and chemotaxis. *J Leukoc Biol* 93: 865-873, 2013.
18. Mollica L, De Marchis F, Spitaleri A, Dallacosta C, Pennacchini D, Zamai M, Agresti A, Trisciuglio L, Musco G and Bianchi ME: Glycyrrhizin binds to high-mobility group box 1 protein and inhibits its cytokine activities. *Chem Biol* 14: 431-441, 2007.
19. Fu Y, Zhou E, Wei Z, Song X, Liu Z, Wang T, Wang W, Zhang N, Liu G and Yang Z: Glycyrrhizin inhibits lipopolysaccharide-induced inflammatory response by reducing TLR4 recruitment into lipid rafts in RAW264.7 cells. *Biochim Biophys Acta* 1840: 1755-1764, 2014.
20. Arumugam T, Ramachandran V, Gomez SB, Schmidt AM and Logsdon CD: S100P-derived RAGE antagonistic peptide reduces tumor growth and metastasis. *Clin Cancer Res* 18: 4356-4364, 2012.
21. Su L, Zhu Y, Li X, Wang D, Chen X, Liu Z, Li J, Zhang C and Zhang J: Topical adhesive spatio-temporal nanosystem co-delivering chlorin e6 and HMGB1 inhibitor glycyrrhizic acid for in situ psoriasis chemo-phototherapy. *Acta Pharm Sin B* 15: 1126-1142, 2025.
22. Gadanec LK, Andersson U, Apostolopoulos V and Zulli A: Glycyrrhizic acid inhibits high-mobility group box-1 and homocysteine-induced vascular dysfunction. *Nutrients* 15: 3186, 2023.
23. Sha X, Wang C, Liu Y, Zhong N, Lu Y, Zhang Q, Lu S, He D, Jin Y, Tang Y and Wang S: Multifunctional glycyrrhizic acid-loaded nanoplateform combining ferroptosis induction and HMGB1 blockade for enhanced tumor immunotherapy. *J Nanobiotechnology* 23: 224, 2025.
24. Li Y, Wu J, Du F, Tang T, Lim JCW, Karuppiath T, Liu J and Sun Z: Neuroprotective potential of glycyrrhizic acid in ischemic stroke: Mechanisms and therapeutic prospects. *Pharmaceuticals (Basel)* 17: 1493, 2024.
25. Lin YT, Ho CY, Sun GC, Wong TY, Hsiao M, Tseng CJ and Cheng PW: Targeting acetylated high mobility group box 1 protein (HMGB1) and toll-like receptor (TLR4) interaction to alleviate hypertension and neuroinflammation in fructose-fed rats. *Br J Pharmacol* 183: 171-188, 2026.
26. Yu C, Xiang Y, Zhang M, Wen J, Duan X, Wang L, Deng G and Fang P: Glycyrrhizic acid alleviates semen strychni-induced neurotoxicity through the inhibition of HMGB1 phosphorylation and inflammatory responses. *J Neuroimmune Pharmacol* 19: 21, 2024.
27. Sun Q, Li L, Li J, Li J, Li SY, Zhang Y, Chen XS, Liu SS and Hua ZY: Glycyrrhizin alleviates brain injury in necrotizing enterocolitis model mice by suppressing HMGB1/TLR4 pathway. *Int Immunopharmacol* 150: 114294, 2025.
28. Ogiku M, Kono H, Hara M, Tsuchiya M and Fujii H: Glycyrrhizin prevents liver injury by inhibition of high-mobility group box 1 production by Kupffer cells after ischemia-reperfusion in rats. *J Pharmacol Exp Ther* 339: 93-98, 2011.
29. Zhai CL, Zhang MQ, Zhang Y, Xu HX, Wang JM, An GP, Wang YY and Li L: Glycyrrhizin protects rat heart against ischemia-reperfusion injury through blockade of HMGB1-dependent phospho-JNK/Bax pathway. *Acta Pharmacol Sin* 33: 1477-1487, 2012.
30. Wu Z, Wang Z, Xie Z, Zhu H, Li C, Xie S, Zhou W, Zhang Z and Li M: Glycyrrhizic acid attenuates the inflammatory response after spinal cord injury by inhibiting high mobility group box-1 protein through the p38/Jun N-terminal kinase signaling pathway. *World Neurosurg* 158: e856-e864, 2022.
31. Gwak GY, Moon TG, Lee DH and Yoo BC: Glycyrrhizin attenuates HMGB1-induced hepatocyte apoptosis by inhibiting the p38-dependent mitochondrial pathway. *World J Gastroenterol* 18: 679-684, 2012.
32. Wang S and Zhang Y: HMGB1 in inflammation and cancer. *J Hematol Oncol* 13: 116, 2020.
33. Chen R, Zou J, Zhong X, Li J, Kang R and Tang D: HMGB1 in the interplay between autophagy and apoptosis in cancer. *Cancer Lett* 581: 216494, 2024.
34. Sims GP, Rowe DC, Rietdijk ST, Herbst R and Coyle AJ: HMGB1 and RAGE in inflammation and cancer. *Annu Rev Immunol* 28: 367-388, 2010.
35. Wang W, Zhao F, Fang Y, Li X, Shen L, Cao T and Zhu H: Glycyrrhizin protects against porcine endotoxemia through modulation of systemic inflammatory response. *Crit Care* 17: R44, 2013.
36. Hou Y, Xin M, Li Q and Wu X: Glycyrrhizin micelle as a genistein nanocarrier: Synergistically promoting corneal epithelial wound healing through blockage of the HMGB1 signaling pathway in diabetic mice. *Exp Eye Res* 204: 108454, 2021.
37. Burillon C, Chiambaretta F and Pisella PJ: Efficacy and safety of glycyrrhizin 2.5% eye drops in the treatment of moderate dry eye disease: Results from a prospective, open-label pilot study. *Clin Ophthalmol* 12: 2629-2636, 2018.
38. Wang B, Lian YJ, Dong X, Peng W, Liu LL, Su WJ, Gong H, Zhang T, Jiang CL, Li JS and Wang YX: Glycyrrhizic acid ameliorates the kynurenine pathway in association with its antidepressant effect. *Behav Brain Res* 353: 250-257, 2018.
39. Yu HJ, Park HJ, Lee B and Hahm DH: The bidirectional interaction between NF- κ B and glucocorticoid receptor: Underlying mechanisms of chronic stress-induced pathology. *J Immunol Res* 2025: 5517840, 2025.
40. Wang YM and Du GQ: Glycyrrhizic acid prevents enteritis through reduction of NF- κ B p65 and p38MAPK expression in rat. *Mol Med Rep* 13: 3639-3646, 2016.
41. Li S, Zhu JH, Cao LP, Sun Q, Liu HD, Li WD, Li JS and Hang CH: Growth inhibitory in vitro effects of glycyrrhizic acid in U251 glioblastoma cell line. *Neurol Sci* 35: 1115-1120, 2014.
42. Bonafé GA, Dos Santos JS, Fernandes AMAP, Ziegler JV, Marson FAL, Rocha T, Carvalho PO and Ortega MM: Anti-migratory effect of dipotassium glycyrrhizinate on glioblastoma cell lines: Microarray data for the identification of key MicroRNA signatures. *Front Oncol* 12: 819599, 2022.
43. Staudt LM: Oncogenic activation of NF-kappaB. *Cold Spring Harb Perspect Biol* 2: a000109, 2010.
44. Li W, Liu X, Zhang B, Qi D, Zhang L, Jin Y and Yang H: Overexpression of candidate tumor suppressor ECRG4 inhibits glioma proliferation and invasion. *J Exp Clin Cancer Res* 29: 89, 2010.
45. Qiu M, Huang K, Liu Y, Yang Y, Tang H, Liu X, Wang C, Chen H, Xiong Y, Zhang J and Yang J: Modulation of intestinal microbiota by glycyrrhizic acid prevents high-fat diet-enhanced pre-metastatic niche formation and metastasis. *Mucosal Immunol* 12: 945-957, 2019.
46. Wang WS, Chen YS, Kuo CY, Tsai JJ, Hsu FT, Chung JG and Pan PJ: DNA damage and NF- κ B inactivation implicate glycyrrhizic acid-induced G₁ phase arrest in hepatocellular carcinoma cells. *J Food Biochem* 46: e14128, 2022.
47. Yin Z, Zhu W, Wu Q, Zhang Q, Guo S, Liu T, Li S, Chen X, Peng D and Ouyang Z: Glycyrrhizic acid suppresses osteoclast differentiation and postmenopausal osteoporosis by modulating the NF- κ B, ERK, and JNK signaling pathways. *Eur J Pharmacol* 859: 172550, 2019.
48. Tang Y, Lv XL, Bao YZ and Wang JR: Glycyrrhizin improves bone metabolism in ovariectomized mice via inactivating NF- κ B signaling. *Climacteric* 24: 253-260, 2021.
49. Chen Y, Qu L, Li Y, Chen C, He W, Shen L and Zhang R: Glycyrrhizic acid alleviates lipopolysaccharide (LPS)-induced acute lung injury by regulating angiotensin-converting enzyme-2 (ACE2) and caveolin-1 signaling pathway. *Inflammation* 45: 253-266, 2022.
50. Jiao B, Guo S, Yang X, Sun L, Sai L, Yu G, Bo C, Zhang Y, Peng C, Jia Q and Dai Y: The role of HMGB1 on TDI-induced NLRP3 inflammasome activation via ROS/NF- κ B pathway in HBE cells. *Int Immunopharmacol* 98: 107859, 2021.
51. Yang J, Shi Y, Chen H, Wang X, Chen Y and Yang B: Glycyrrhizic acid attenuates myocardial injury: Involvement of RIP140/NF- κ B pathway. *Biomed Pharmacother* 95: 62-67, 2017.
52. Ma D, Zhang J, Zhang Y, Zhang X, Han X, Song T, Zhang Y and Chu L: Inhibition of myocardial hypertrophy by magnesium isoglycyrrhizinate through the TLR4/NF- κ B signaling pathway in mice. *Int Immunopharmacol* 55: 237-244, 2018.
53. Emara NA, Mahmoud MF, El Fayoumi HM and Mahmoud AAA: The renoprotective effect of glycyrrhizic acid in insulin-resistant rats exposed to aluminum involves the inhibition of TLR4/NF- κ B signaling pathway. *Naunyn Schmiedeberg Arch Pharmacol* 394: 863-872, 2021.

54. Arany I and Safirstein RL: Cisplatin nephrotoxicity. *Semin Nephrol* 23: 460-464, 2003.
55. Wu CH, Chen AZ and Yen GC: Protective effects of glycyrrhizic acid and 18 β -glycyrrhetinic acid against cisplatin-induced nephrotoxicity in BALB/c mice. *J Agric Food Chem* 63: 1200-1209, 2015.
56. Feng L, Zhu MM, Zhang MH, Wang RS, Tan XB, Song J, Ding SM, Jia XB and Hu SY: Protection of glycyrrhizic acid against AGEs-induced endothelial dysfunction through inhibiting RAGE/NF- κ B pathway activation in human umbilical vein endothelial cells. *J Ethnopharmacol* 148: 27-36, 2013.
57. Yan S, Fang C, Cao L, Wang L, Du J, Sun Y, Tong X, Lu Y and Wu X: Protective effect of glycyrrhizic acid on cerebral ischemia/reperfusion injury via inhibiting HMGB1-mediated TLR4/NF- κ B pathway. *Biotechnol Appl Biochem* 66: 1024-1030, 2019.
58. Qu Y, Chen WH, Zong L, Xu MY and Lu LG: 18 α -Glycyrrhizin induces apoptosis and suppresses activation of rat hepatic stellate cells. *Med Sci Monit* 18: BR24-BR32, 2012.
59. Leng T, Zhao J, Xiao Z, Hao S, Xie W and Nie Q: The impact of the PI3K/AKT pathway on arrhythmia: Mechanisms of action and therapeutic potential. *J Mol Histol* 57: 60, 2026.
60. Rana N, Deval, Singh H, Garg A, Monika, Tiwari R and Sharma S: Current landscape and recent developments of PI3K/AKT/mTOR targeted inhibitors for breast carcinoma. *Bioorg Chem* 170: 109430, 2026.
61. Haque MA, Poullikkas T, Kaisar FMA, Khan A, Haque S, Mollik M, Mowa MJ, Khatun MH, Mamun A and Bithy MBA: Targeting tumorigenic coactivators in the PI3K/AKT signaling pathway: A novel approach for cancer treatment. *Cancer Med* 14: e71304, 2025.
62. Jiang RH, Xu JJ, Zhu DC, Li JF, Zhang CX, Lin N and Gao WY: Glycyrrhizin inhibits osteoarthritis development through suppressing the PI3K/AKT/NF- κ B signaling pathway in vivo and in vitro. *Food Funct* 11: 2126-2136, 2020.
63. Shen CH, Ma ZY, Li JH, Li RD, Tao YF, Zhang QB and Wang ZX: Glycyrrhizin improves inflammation and apoptosis via suppressing HMGB1 and PI3K/mTOR pathway in lipopolysaccharide-induced acute liver injury. *Eur Rev Med Pharmacol Sci* 24: 7122-7130, 2020.
64. Wang CY, Kao TC, Lo WH and Yen GC: Glycyrrhizic acid and 18 β -glycyrrhetinic acid modulate lipopolysaccharide-induced inflammatory response by suppression of NF- κ B through PI3K p110 δ and p110 γ inhibitions. *J Agric Food Chem* 59: 7726-7733, 2011.
65. Zhang X, Zhang H, Yue S, He G, Qu S, Zhang Z, Ma B, Ding R, Peng W, Zhang H, *et al.*: The mTOR inhibition in concurrence with ERK1/2 activation is involved in excessive autophagy induced by glycyrrhizin in hepatocellular carcinoma. *Cancer Med* 6: 1941-1951, 2017.
66. Tsai JJ, Pan PJ, Hsu FT, Chung JG and Chiang IT: Glycyrrhizic acid modulates apoptosis through extrinsic/intrinsic pathways and inhibits protein kinase B- and extracellular signal-regulated kinase-mediated metastatic potential in hepatocellular carcinoma in vitro and in vivo. *Am J Chin Med* 48: 223-244, 2020.
67. Wang H, Ge X, Qu H, Wang N, Zhou J, Xu W, Xie J, Zhou Y, Shi L, Qin Z, *et al.*: Glycyrrhizic acid inhibits proliferation of gastric cancer cells by inducing cell cycle arrest and apoptosis. *Cancer Manag Res* 12: 2853-2861, 2020.
68. Niu Z, Lin J, Hao C, Xu X, Wang C, Dai K, Deng X, Deng M, Guo Y and Yao W: Glycyrrhizic acid attenuates pulmonary fibrosis by inhibiting the interaction between HMGB1 and BRG1 through PI3K/Akt/mTOR pathway. *Int J Environ Res Public Health* 19: 8743, 2022.
69. Kao TC, Shyu MH and Yen GC: Neuroprotective effects of glycyrrhizic acid and 18beta-glycyrrhetinic acid in PC12 cells via modulation of the PI3K/Akt pathway. *J Agric Food Chem* 57: 754-761, 2009.
70. Farrukh MR, Nissar UA, Kaiser PJ, Afnan Q, Sharma PR, Bhushan S and Tasduq SA: Glycyrrhizic acid (GA) inhibits reactive oxygen species mediated photodamage by blocking ER stress and MAPK pathway in UV-B irradiated human skin fibroblasts. *J Photochem Photobiol B* 148: 351-357, 2015.
71. Parker MI, Nikonova AS, Sun D and Golemis EA: Proliferative signaling by ERBB proteins and RAF/MEK/ERK effectors in polycystic kidney disease. *Cell Signal* 67: 109497, 2020.
72. Meng Q and Xia Y: c-Jun, at the crossroad of the signaling network. *Protein Cell* 2: 889-898, 2011.
73. Zhu ZH, Li X, He LF, Cai HF, Ye B and Wu ZM: Glycyrrhizic acid, as an inhibitor of HMGB1, alleviates bleomycin-induced pulmonary toxicity in mice through the MAPK and Smad3 pathways. *Immunopharmacol Immunotoxicol* 43: 461-470, 2021.
74. Gederas OA, Sharma A, Mbarak S, Sporsheim B, Høgset A, Bogoeva V, Slupphaug G and Hagen L: Proteomic analysis reveals mechanisms underlying increased efficacy of bleomycin by photochemical internalization in bladder cancer cells. *Mol Omics* 19: 585-597, 2023.
75. Wang D, Wong HK, Feng YB and Zhang ZJ: 18beta-glycyrrhetinic acid induces apoptosis in pituitary adenoma cells via ROS/MAPKs-mediated pathway. *J Neurooncol* 116: 221-230, 2014.
76. Jain R, Hussein MA, Pierce S, Martens C, Shahagadkar P and Munirathinam G: Oncopreventive and oncotherapeutic potential of licorice triterpenoid compound glycyrrhizin and its derivatives: Molecular insights. *Pharmacol Res* 178: 106138, 2022.
77. Prickett TD and Brautigan DL: Cytokine activation of p38 mitogen-activated protein kinase and apoptosis is opposed by alpha-4 targeting of protein phosphatase 2A for site-specific dephosphorylation of MEK3. *Mol Cell Biol* 27: 4217-4227, 2007.
78. Wu Q, Tang Y, Hu X, Wang Q, Lei W, Zhou L and Huang J: Regulation of Th1/Th2 balance through OX40/OX40L signalling by glycyrrhizic acid in a murine model of asthma. *Respirology* 21: 102-111, 2016.
79. Tsai JJ, Kuo HC, Lee KF and Tsai TH: Glycyrrhizin represses total parenteral nutrition-associated acute liver injury in rats by suppressing endoplasmic reticulum stress. *Int J Mol Sci* 14: 12563-12580, 2013.
80. Peng S, Zhang Y, Zhang J, Wang H and Ren B: ERK in learning and memory: A review of recent research. *Int J Mol Sci* 11: 222-232, 2010.
81. Ban JY, Park HK and Kim SK: Effect of glycyrrhizic acid on scopolamine-induced cognitive impairment in mice. *Int Neurourol J* 24 (Suppl 1): S48-S55, 2020.
82. Kim KJ, Choi JS, Kim KW and Jeong JW: The anti-angiogenic activities of glycyrrhizic acid in tumor progression. *Phytother Res* 27: 841-846, 2013.
83. Wang Y, Wang L, Luo R, Sun Y, Zou M, Wang T, Guo Q and Peng X: Glycyrrhizic acid against *Mycoplasma gallisepticum*-induced inflammation and apoptosis through suppressing the MAPK pathway in chickens. *J Agric Food Chem* 70: 1996-2009, 2022.
84. Zhao H, Liu Z, Shen H, Jin S and Zhang S: Glycyrrhizic acid pretreatment prevents sepsis-induced acute kidney injury via suppressing inflammation, apoptosis and oxidative stress. *Eur J Pharmacol* 781: 92-99, 2016.
85. Yamamoto M, Nagasawa Y and Fujimori K: Glycyrrhizic acid suppresses early stage of adipogenesis through repression of MEK/ERK-mediated C/EBP β and C/EBP δ expression in 3T3-L1 cells. *Chem Biol Interact* 346: 109595, 2021.
86. Yin Q, Wang L, Yu H, Chen D, Zhu W and Sun C: Pharmacological effects of polyphenol phytochemicals on the JAK-STAT signaling pathway. *Front Pharmacol* 12: 716672, 2021.
87. Spinelli FR, Colbert RA and Gadina M: JAK1: Number one in the family; number one in inflammation? *Rheumatology (Oxford)* 60 (Suppl 2): ii3-ii10, 2021.
88. Li L, Zhou D, Zheng Y and Xie W: Expression and functions of the STAT3-SCLIP pathway in chronic myeloid leukemia cells. *Exp Ther Med* 12: 3381-3386, 2016.
89. Chen B, Chen Q, Lu M, Zou E, Lin G, Yao J, Wang L, Gan Y, Chen B, Chen G and Wu L: Hypocrellin A against intrahepatic Cholangiocarcinoma via multi-target inhibition of the PI3K-AKT-mTOR, MAPK, and STAT3 signaling pathways. *Phytomedicine* 135: 156022, 2024.
90. He Y, Wang H, Lin S, Chen T, Chang D, Sun Y, Wang C, Liu Y, Lu Y, Song J, *et al.*: Advanced effect of curcumin and resveratrol on mitigating hepatic steatosis in metabolic associated fatty liver disease via the PI3K/AKT/mTOR and HIF-1/VEGF cascade. *Biomed Pharmacother* 165: 115279, 2023.
91. He SQ, Gao M, Fu YF and Zhang YN: Glycyrrhizic acid inhibits leukemia cell growth and migration via blocking AKT/mTOR/STAT3 signaling. *Int J Clin Exp Pathol* 8: 5175-5181, 2015.
92. Wu X, Wang W, Chen Y, Liu X, Wang J, Qin X, Yuan D, Yu T, Chen G, Mi Y, *et al.*: Glycyrrhizin suppresses the growth of human NSCLC cell line HCC827 by downregulating HMGB1 level. *Biomed Res Int* 2018: 6916797, 2018.
93. Tian X, Liu Y, Liu X, Gao S and Sun X: Glycyrrhizic acid ammonium salt alleviates Concanavalin A-induced immunological liver injury in mice through the regulation of the balance of immune cells and the inhibition of hepatocyte apoptosis. *Biomed Pharmacother* 120: 109481, 2019.
94. Guo M, Wang Z, Dai J, Fan H, Yuan N, Gao L, Peng H and Cheng X: Glycyrrhizic acid alleviates liver fibrosis in vitro and in vivo via activating CUGBP1-mediated IFN- γ /STAT1/Smad7 pathway. *Phytomedicine* 112: 154587, 2023.

95. Wei S, Feng M and Zhang S: Molecular characteristics of cell pyroptosis and its inhibitors: A review of activation, regulation, and inhibitors. *Int J Mol Sci* 23: 16115, 2022.
96. Coll RC, Schroder K and Pelegrin P: NLRP3 and pyroptosis blockers for treating inflammatory diseases. *Trends Pharmacol Sci* 43: 653-668, 2022.
97. Khan R, Khan AQ, Lateef A, Rehman MU, Tahir M, Ali F, Hamiza OO and Sultana S: Glycyrrhizic acid suppresses the development of precancerous lesions via regulating the hyperproliferation, inflammation, angiogenesis and apoptosis in the colon of Wistar rats. *PLoS One* 8: e56020, 2013.
98. Hibasami H, Iwase H, Yoshioka K and Takahashi H: Glycyrrhizin induces apoptosis in human stomach cancer KATO III and human promyelotic leukemia HL-60 cells. *Int J Mol Med* 16: 233-236, 2005.
99. Han Y, Sheng W, Liu X, Liu H, Jia X, Li H, Wang C, Wang B, Hu T and Ma Y: Glycyrrhizin ameliorates colorectal cancer progression by regulating NHEJ pathway through inhibiting HMGB1-induced DNA damage response. *Sci Rep* 14: 24948, 2024.
100. Bian F, Niu FH, Qu PY, Gong F and Yan JZ: Glycyrrhizic acid inhibits DNA damage repair and enhances cisplatin-induced apoptosis of melanoma cells. *Chem Biol Drug Des* 103: e14536, 2024.
101. Wang Z, Yang X, Wang X, Liang F and Tang Y: Glycyrrhizin attenuates caspase-11-dependent immune responses and coagulopathy by targeting high mobility group box 1. *Int Immunopharmacol* 107: 108713, 2022.
102. Hua S, Ma M, Fei X, Zhang Y, Gong F and Fang M: Glycyrrhizin attenuates hepatic ischemia-reperfusion injury by suppressing HMGB1-dependent GSDMD-mediated kupffer cells pyroptosis. *Int Immunopharmacol* 68: 145-155, 2019.
103. Dong L, Sun JY, Fang GT, Jiang LD and Wang JY: Effects of glycyrrhizin on TGF β 1 stimulated hepatic stellate cell signaling transduction. *Zhonghua Gan Zang Bing Za Zhi* 13: 828-831, 2005 (In Chinese).
104. Zhou Y, Tong X, Ren S, Wang X, Chen J, Mu Y, Sun M, Chen G, Zhang H and Liu P: Synergistic anti-liver fibrosis actions of total astragalus saponins and glycyrrhizic acid via TGF- β 1/Smads signaling pathway modulation. *J Ethnopharmacol* 190: 83-90, 2016.
105. Li M, Peng S, Bu J, Quan S, Liu L, Yue Z, Wang L and Li Y: Glycyrrhizic acid alleviates gefitinib-induced liver injury by regulating the p53/p21 pathway and releasing cell cycle arrest. *Food Chem Toxicol* 200: 115405, 2025.
106. Cheng X, Liu Y, Qi B, Wang Y, Zheng Y, Liang X, Chang Y, Ning M, Gao W and Li T: Glycyrrhizic acid alleviated MI/R-induced injuries by inhibiting Hippo/YAP signaling pathways. *Cell Signal* 115: 111036, 2024.
107. Xu H, Fang L, Zeng Q, Chen J, Ling H, Xia H, Ge Q, Wu C, Zou K, Wang X, *et al*: Glycyrrhizic acid alters the hyperoxidative stress-induced differentiation commitment of MSCs by activating the Wnt/ β -catenin pathway to prevent SONFH. *Food Funct* 14: 946-960, 2023.
108. Lai T, Shen Y, Chen C, Huang B, Deng T, Zhao Z, Zhang Z, Huang Z and Pan X: Glycyrrhizic acid ameliorates myocardial ischemia-reperfusion injury in rats through inhibiting endoplasmic reticulum stress. *Eur J Pharmacol* 908: 174353, 2021.
109. Zhao TQ, Li Y, Zhang M, Zhao MC, Cao X and Hou SZ: Glycyrrhizic acid protects glomerular podocytes induced by high glucose by modulating SNARK/AMPK signaling pathway. *Curr Med Sci* 43: 696-707, 2023.
110. Wang Y, Chen Q, Shi C, Jiao F and Gong Z: Mechanism of glycyrrhizin on ferroptosis during acute liver failure by inhibiting oxidative stress. *Mol Med Rep* 20: 4081-4090, 2019.
111. Zhou L, Yang Y, Fu X, Xia B, Li C, Lu C, Qi Y, Zhang H and Liu T: The protective effect and molecular mechanism of glycyrrhizic acid glycosides against Tripterygium glycosides induced nephrotoxicity based on the RhoA/ROCK1 signalling pathway. *J Ethnopharmacol* 319: 117100, 2024.
112. Fang L, Wang X and Guan W: Glycyrrhizic acid ameliorates sepsis-induced acute lung injury through suppression of endoplasmic reticulum stress. *Discov Med* 37: 841-849, 2025.
113. Wei L, Ou S, Meng Y, Sun L, Zhang L, Lu Y and Wu Y: Glycyrrhizin as a potential disease-modifying therapy for epilepsy: Insights into targeting pyroptosis to exert neuroprotective and anticonvulsant effects. *Front Pharmacol* 15: 1530735, 2025.
114. Meng FD, Yuan L, Xu DJ, Che MY, Hou SZ, Lu DD, Liu WJ and Nan Y: Exploring the targets and molecular mechanism of glycyrrhetic acid against diabetic nephropathy based on network pharmacology and molecular docking. *World J Diabetes* 14: 1672-1692, 2023.
115. An J, Han M, Chen P, Wang L, Gao L, Zhou Z, Huang S, Du J and Peng F: Therapeutic potential of glycyrrhizin in nervous system diseases. *Chin Med J (Engl)* 139: 457-459, 2026.
116. Gupta J, Kumar D, Gupta R, Kumar S and Kumar M: Emerging trends in the pharmacological and therapeutic potential of ginger: From traditional medicine to nanotechnological innovations. *Curr Pharm Des* 31: 2995-3016, 2025.
117. Li Q, Deng Y, Han X, Dong Y, Wu X, Zhu W and Yan M: Naringenin nanosuspensions embedded glycyrrhizin-based hydrogel ameliorates cholestatic liver injury in mice by inhibiting oxidative stress and HMGB1-mediated inflammation. *Colloids Surf B Biointerfaces* 261: 115466, 2026.
118. Cui Q, Song X, Zhou L, Dong J, Wei Y, Liu Z and Wu X: Fabrication of resveratrol-loaded soy protein isolate-glycyrrhizin nanocomplex for improving bioavailability via pH-responsive hydrogel properties. *Int J Biol Macromol* 258: 128950, 2024.
119. Sun Z, Zhang M, Wei Y, Li M, Wu X and Xin M: A simple but novel glycymicelle ophthalmic solution based on two approved drugs empagliflozin and glycyrrhizin: In vitro/in vivo experimental evaluation for the treatment of corneal alkali burns. *Biomater Sci* 11: 2531-2542, 2023.
120. Semwal DK, Kumar A, Semwal RB, Dadhich NK, Chauhan A and Kumar V: Glycyrrhizin (glycyrrhizic acid)-pharmacological applications and associated molecular mechanisms. *Drugs Drug Candidates* 4: 44, 2025.



Copyright © 2026 Yu et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.