Review Articles

Acupuncture and Herbal Medicine

Research progress on the hepatoprotective effect, pharmacokinetic properties, and hepatotoxicity of geniposide

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Abstract

Liver disease (LD) is a global health problem caused by multiple factors. At present, there are still obvious problems with limited efficacy and strong side effects of drugs used in the clinical treatment of LD. Therefore, it is of great significance to search for effective hepatoprotective drugs from natural products. Geniposide (GS) is a cyclic ether terpenoid compound and a key component in the traditional Chinese medicine *Gardenia jasminoides*. It has a significant inhibitory effect on LD. However, there is currently no literature systematically analyzing its mechanism of action. To adapt to the environment of new drug research and the need for precision medication, this article summarizes the pathways and possible mechanisms of action discovered by GS in the treatment of LD, based on recent research literature: regulating bile stasis, antioxidant and anti-apoptosis, improving amino acid metabolism, improving energy metabolism, regulating lipid metabolism, anti-inflammatory and analgesic effects, etc. It also summarizes the pharmacokinetics of GS *in vivo* and discusses the liver toxicity of GS that is positively correlated with dosage. In addition, the existing problems in current research and possible future development directions were also discussed, to lay the foundation for the clinical development of natural product GS.

Keywords: Geniposide, Hepatotoxicity, Liver disease, Molecular mechanism, Pharmacokinetics

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Introduction

Liver disease (LD) is a major global health problem caused by multiple factors, including (1) exogenous factors, such as alcohol abuse causing alcoholic liver disease (ALD)[1–2], drug-induced liver injury (DILI)[3–4], viral hepatitis (VH)[5–6], etc, and (2) endogenous metabolic abnormalities, such as non-alcoholic fatty liver disease (NAFLD)[7–8], metabolically abnormal fatty liver disease (MAFLD)[9], and autoimmune hepatitis (AIH)[10–11], among others. According to the World Health Organization (WHO), LD causes approximately 2 million deaths annually, of which about 50% are related to cirrhosis or hepatocellular carcinoma[12]. The pathological process of LD usually proceeds in three stages—the acute injury phase, the chronic inflammation phase, and the fibrosis phase—and can eventually develop into irreversible cirrhosis or even liver failure[13]. At present, commonly used hepatoprotective medicine in clinical practice mainly include bile acid modulators (such as ursodeoxycholic acid), insulin sensitizers (such as metformin and semaglutide), antioxidants (such as glutathione), lipid-lowering drugs (such as clopidogrel and atorvastatin), anti-inflammatory agents (such as glucocorticoids), angiotensin receptor antagonists (such as telmisartan), and so on[14]. However, these drugs do not significantly improve liver function or promote liver cell regeneration, and they have significant side effects, such as osteoporosis and muscle toxicity[15–16]. In recent years, research has indicated that some natural products have positive intervention effects on the development of diseases and minimal side effects when used as drugs or dietary supplements. However, determining the most suitable ingredient for the treatment of LDs is still a difficult problem.

Geniposide (GS) is one of the bioactive compounds in the fruit of *Gardenia jasminoides* Ellis (Fructus Gardeniae), which has been used to treat LDs and inflammation (Figure 1)[17]. Fructus Gardeniae is a component

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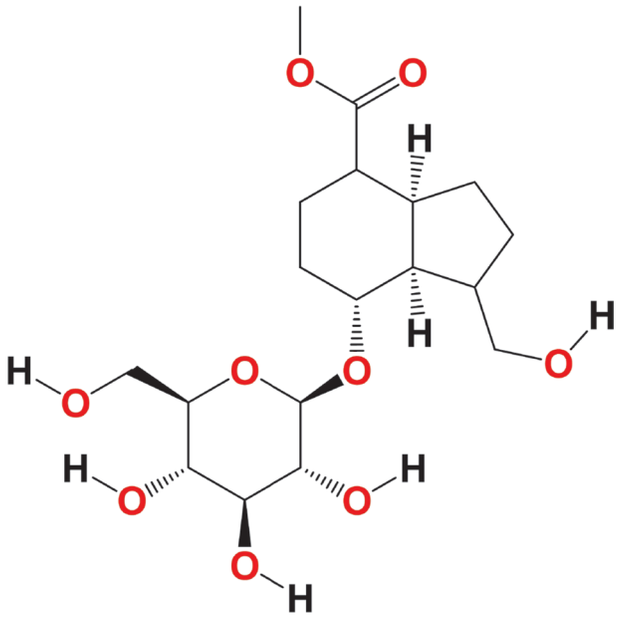


Figure 1. Chemical structural formula of GS. GS: Geniposide.

of Yinchenhao decoction, a famous prescription used in traditional Chinese medicine (TCM) to treat various LDs and jaundice[18]. Yinchenhao decoction can inhibit liver cell apoptosis and promote bile secretion and excretion, and it has the clinical effect of promoting liver regeneration and preventing liver failure[19]. Research has shown that one of the key pharmacological substances in Yinchenhao decoction that plays a crucial role in alleviating LD is GS[20–21]. However, the exact mechanism of action of GS on liver injury is still unclear, and further research is urgently needed. Currently, the efficacy and treatment concepts of TCM are receiving increasing attention from researchers around the world, but there are few systems that can clearly explain its theory and mechanism.

Multiple research studies and analyses have been conducted to characterize the pathogenesis of LD and explore the therapeutic pathways of GS for LD. Most phenotypes of LD include the accumulation of reactive oxygen species (ROS) and lipid peroxidation (LPO) in the liver, as well as bile acid stasis and inflammation[22–24]. To date, through in-depth research on the pathogenesis of LD, a series of potential therapeutic targets and pathways for LD have been widely studied, including the gut microbiota, cell apoptosis, oxidative stress, amino acid metabolism, and the tricarboxylic acid (TCA) cycle, all of which are considered to be related to the treatment of LD[25–29]. With the continuous deepening of research, GS is considered one of the most promising natural products for treating LD[30–31]. The possible molecular mechanism is shown in Figure 2. In addition, a large number of animal experiments have shown that GS not only has hepatoprotective effects but also causes significant liver toxicity when used in excess. Therefore, specific analyses of the liver toxicity of GS are necessary.

GS may exert hepatoprotective effects by activating glucagon-like peptide-1 receptor (GLP-1R)[32]: (1) inhibition of oxidative stress through nuclear factor E2-related factor 2 (Nrf2) pathway: research shows that Nrf2 is a key factor mediating the upregulation of antioxidant enzyme heme oxygenase-1 (HO-1)[33], GS can promote Nrf2 nuclear translocation and the expression of enzymes such as HO-1, inhibit ROS accumulation, and thus reduce Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and generation of inflammatory factors[34–36]; (2) inhibit apoptosis through multiple ways: ① activate protein kinase B (PKB) and protein kinase B (AKT) by increasing the level of phosphoinositide 3-kinase (PI3K), thereby inhibiting glycogen synthase kinase-3β (GSK-3β). Furthermore, it controls the AMP-activated protein kinase (AMPK) signaling pathway and mechanistic target of rapamycin (mTOR) to inhibit cell apoptosis[37–38]; ② regulating the TCA cycle through miR-144-5p: The TCA cycle is the foundation of mitochondrial energy production, and GS can regulate key enzymes IDH1 and IDH2 in the TCA cycle by controlling miR-144-5p, increasing ATP content in cells and slowing down liver cell damage[29];③ reduce Fas-mediated cell apoptosis and inhibit caspase-3 activity[28,39]; (3) inhibiting bile acid secretion by activating FXR and reducing CYP7A1 activity[29,40–41].

Based on this, this article summarizes and generalizes the possible protective mechanisms, pharmacokinetics, and liver toxicity of GS in the treatment of LD, providing theoretical support for its clinical application in the treatment of LD and new ideas for the development of TCM drugs using GS as the active ingredient.

Possible protective mechanism of GS on LD

The successful establishment of an animal model of LD is a crucial step in exploring the therapeutic mechanism of GS in the later stage. Depending on the damage mechanism, modeling methods can be mainly divided into the following categories: (1) CCl_4-induced model: CCl_4 is metabolized by CYP450 into trichloromethyl-free radicals, which cause LPO and liver cell necrosis and are suitable for studying liver oxidative stress and fibrosis mechanisms[42]; (2) ethanol-induced model: ethanol metabolites directly cause toxicity and oxidative stress, suitable for ALD[43]; (3) lipopolysaccharide (LPS) combined with D-galactosamine (D-GalN) model: an intraperitoneal injection of LPS and D-GalN induces explosive hepatitis[44]; (4) a high-fat diet or gene-deficiency model: high-fat diet (60% fat)-fed or ob/ob or db/db mice are suitable as an NAFLD model[45]; (5) a bile acid stasis model: bile duct ligation and ANIT gavage cause bile duct epithelial injury, suitable for a bile stasis liver injury model[46–47]. Accumulating evidence suggests that GS has a mitigating effect on LD both *in vitro* and *in vivo*. Currently, GS is considered a multi-target drug that can antagonize LD.

Regulating cholestasis

Regulating bile acids

When the liver is damaged, it can easily lead to bile stasis, causing secondary damage to the liver[48]. Bile acids are important components of bile and play a crucial role as signaling molecules and metabolic regulators in regulating lipid, glucose, and energy metabolism in the liver[49–50]. In the liver, taurine combines with bile acids to form taurocholic acid, which can increase the solubility of lipids and cholesterol, increase bile flow, and alleviate inflammation[51–52]. Experiments have shown that after

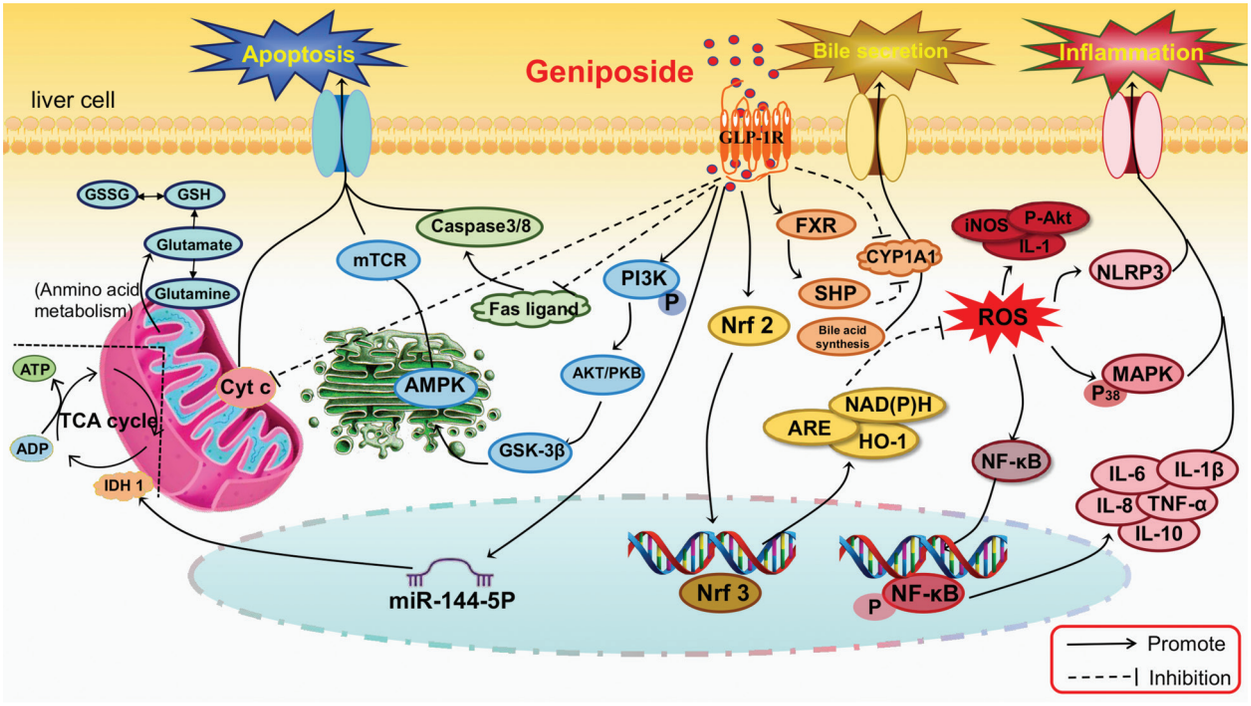


Figure 2. Possible mechanism of GS in the treatment of LD. AKT: Protein kinase B; AMPK: AMP-activated protein kinase; ARE: Antioxidant response element; FXR: Farnesol X receptor; GLP-1R: Glucagon-like peptide-1 receptor; GS: Geniposide; GSH: Glutathione; GSK-3β: Glycogen synthase kinase-3β; GSSG: Oxidized glutathione; HO-1: Heme oxygenase; IDH: Isocitrate dehydrogenase; IL: Interleukin; iNOS: Inducible nitric oxide synthase; LD: Liver disease; MAPK: Mitogen-activated protein kinase; mTOR: Mechanistic target of rapamycin; NAD(P)H: Nicotinamide adenine dinucleotide (phosphate)—reduced form; NLRP3: NLR family pyrin domain-containing 3; Nrf2: Nuclear factor E2-related factor 2; PI3K: Phosphoinositide 3-kinase; PKB: Protein kinase B; ROS: Reactive oxygen species; SHP: Small heterodimer partner; TCA: Tricarboxylic acid cycle; TNF: Tumor necrosis factor.

administering 11.25 mg/100 g GS to ALD model mice for 14 consecutive days, an increase in taurocholic acid levels can be observed in the mice, indicating that GS alleviates the decrease in taurocholic acid levels in the model mice by improving abnormal bile acid biosynthesis pathways and inhibiting inflammation in the body[29].

The silencing regulatory protein SIRT1 has been reported to regulate the activity of the farnesol X receptor (FXR), which is now known as a bile acid nuclear receptor and plays a core regulatory role in bile acid metabolism, lipid homeostasis, glucose metabolism, and liver protection[53–54]. Studies have shown that after 2 weeks of administration of 25/50 mg/kg GS, the NLR family pyrin domain-containing 3 (NLRP3) inflammasome was significantly inhibited and liver fibrosis was significantly improved in bile duct-ligated mice. Further research has shown that GS exerts its hepatoprotective effect by activating SIRT1 and deacetylating FXR[55].

Regulating the hepatic intestinal circulation of bile acids

The hepatic intestinal circulation of bile acids plays a crucial role in the absorption, distribution, and balance of nutrients in the human body[56–57]. LD can impair the circulation of bile acids between the intestine and liver, preventing bile acids from flowing back to the liver and leading to elevated levels of bile acids in the blood, resulting in a series of adverse reactions, such as liver failure[58]. Research has shown that if the key enzyme in bile acid synthesis, cholesterol 7α-hydroxylase (CYP7A1), is inhibited and sterol 12α- hydroxylase (CYP8B1) is upregulated, the content of bile acids in liver cells decreases, and bile acid stasis can be effectively alleviated[59–61]. In addition, FXR plays an important regulatory role in inhibiting cholesterol 7α-hydroxylase (CYP7a1). The activation of FXR indirectly inhibits CYP7A1 by inducing small heterodimer partners (SHPs), thereby reducing bile acid secretion and lowering bile acid levels[62–67]. Experiments have shown that after the oral administration of GS (25, 50, and 100 mg/kg) for 7 days, GS can reduce the concentration of bile acids in liver cells by inhibiting CYP7A1 and upregulating FXR activity, inducing liver cells to reabsorb bile acids from the intestine, thereby reducing the concentration of bile acids in the intestine and blood. At the same time, the model rats showed decreased levels of serum markers of bile stasis, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), and direct bilirubin (DBIL), indicating that GS alleviated bile acid stasis[68]. As a key component of Yinchenhao decoction, GS plays an irreplaceable role in the treatment of bile stasis with Yinchenhao decoction[69]. In addition, after oral administration of 21 and 42 mg/kg of GS for 5 days, GS could also alleviate ANTI-induced cholestasis by upregulating CYP8B1 and promoting bile acid excretion[70].

FXR is also an important factor in improving the hepatic intestinal circulation of bile acids. Molecular mechanism studies have shown that GS can promote hepatic bile acid synthesis by inhibiting the FXR-mediated negative feedback regulation of bile acids, thereby enhancing the reverse transport and catabolism of cholesterol. It can also reduce FXR-dependent ileal bile acid reabsorption and increase bile acid excretion[71]. In addition, after administering 90 mg/kg of GS and 1.34 mg/kg of chlorogenic acid to NAFLD mice for

4 consecutive weeks, it was found that GS could induce FXR signaling, that is, regulate the expression of SHP in the liver tissue of mice, and this effect could be reversed by antibiotics. This indicates that GS can improve bile stasis through gut microbiota and bile acid signaling[20].

Antioxidant and cell apoptosis

Improve oxidative stress

Although many organisms have evolved complex antioxidant systems to alleviate oxidative stress, there are still many factors that can cause elevated levels of ROS, leading to cell and tissue damage[72–73]. The liver is the main organ attacked by ROS, and high levels of ROS can lead to LPO, resulting in liver damage and fibrosis[74–75]. Oxidative stress has been confirmed as a key pathological mechanism of liver injury induced by various pathogenic factors, such as alcohol, drugs, viral infections, environmental pollutants, and dietary components. It can cause enzyme activity disorders in liver tissue and consume high levels of enzyme removers, such as glutathione peroxidase (GSH-PX), ultimately affecting collagen metabolism in liver tissue[76–77]. As a widely present "free radical scavenger" in the body, GSH binds with ROS to produce oxidized glutathione (GSSG), which protects cells. The value of GSH/GSSG is usually constant but also changes accordingly when cellular function is impaired. A decrease in this ratio, to some extent, indicates a decrease in antioxidant capacity[78]. Research has shown that after administering GS to ALD mice, GSH levels significantly increased, the GSH/GSSG ratio slightly increased, malondialdehyde (MDA, an important marker of cell membrane LPO) levels decreased, CuZn superoxide dismutase (SOD) and catalase (CAT) levels increased, and oxidative stress and ethanol-induced liver injury were alleviated[29]. In addition, gastric administration of 20, 40, or 80 mg/kg of GS can significantly reverse the excessive elevation of ALT/AST and hepatic LPO levels induced by alcohol in rats and increase the liver mRNA expression of CuZn SOD and CAT, indicating that GS can protect against acute alcohol-induced liver injury by upregulating the expression of major antioxidant enzymes[79]. There is also evidence to suggest that GS can increase the activity of SOD and GSH-PX in the liver and alleviate the oxidative stress response in mice with liver fibrosis[80].

Anti-apoptosis mechanism

Along with oxidative stress, cell apoptosis also occurs in liver tissue, and apoptosis inhibition has become an effective strategy to combat LD[81–84]. Caspase-3 is a terminal cleavage enzyme in the process of cell apoptosis and has become a key biomarker for determining apoptosis. Its high expression is closely related to cell apoptosis[85]. Terminal deoxynucleotide transferase-mediated dUTP nick end labeling (TUNEL) is a method of examining cell apoptosis using fluorescence microscopy. In this method, apoptotic cells are labeled as positive cells, and the larger the area and density of positive cells, the higher the degree of cell apoptosis[86]. In our study, we found that the model group rats had higher caspase-3 activity and larger and more obvious positive cell areas. However, treatment with GS reversed caspase-3 overexpression, and the area and density of TUNEL-positive cells decreased, indicating that GS can be used as an anti-apoptotic agent to protect the liver of rats with ALD[29]. In addition, studies have shown that the daily administration of 50 mg/kg GS to mice with liver fibrosis for four consecutive weeks can increase the activity of SOD and GSH-PX in the liver while reducing the level of MDA. Furthermore, GS treatment leads to a decrease in the concentrations of interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF)-α in liver tissue homogenate. TUNEL staining further shows that GS is able to reduce the apoptosis of liver cells in mice with liver fibrosis[80].

Another noteworthy factor is the methylation/demethylation of anti-apoptotic genes, which can have a profound impact on gene expression[87]. B-cell lymphoma 2 (BCL-2) is a key protein regulating apoptosis and belongs to the core member of the anti-apoptotic protein family (BCL-2 family). Overexpression of BCL-2 may prevent apoptosis and protect tissues[88]. Research has shown that GS can reduce specific DNA methylation levels in the BCL-2 promoter region during the H_2O_2-induced regulation of the human liver cell line L-02, inhibit cell apoptosis, and protect human liver cells[89].

Regulation of amino acid metabolism

Except for branched-chain amino acids, the liver is the main organ for the metabolism of a vast majority of amino acids in the body[90–91]. When the liver is damaged or liver function is impaired, amino acid metabolism becomes insufficient, leading to an increase in the concentration of amino acids to be metabolized in the blood and a lack of amino acids in the body[92]. The excessive concentration of phenylalanine in the blood can lead to mental disorders, phenylketonuria, albinism, and damage to the liver[93–94]. Glutamine is a rich and versatile amino acid in the body, which is easily converted into glutamate and produces the antioxidant glutathione[95–97]. It can also generate an arginine precursor through citrulline transport. Arginine is crucial for cardiovascular function, skeletal muscle, and fat metabolism and participates in the ornithine cycle, which promotes growth hormone release and immune system maintenance[98–99]. Ornithine is further converted into proline, which helps balance the redox state, reduce oxidative stress, regulate protein synthesis, and more[100–101].

Metabolomics studies have shown that GS can improve liver damage caused by high levels of phenylalanine and enhance phenylalanine metabolism by regulating the biosynthesis of phenylalanine, tyrosine, and tryptophan in the liver and the metabolic pathways of phenylalanine. In addition, GS can promote the metabolism of arginine, ornithine, and proline in the liver, thereby reducing the concentrations of arginine, ornithine, and proline in ALD model mice, as well as increasing the level of glutamine in mice and improving amino acid metabolism disorders and hepatic fat accumulation[29]. In addition, after 19 potential biomarkers of type II diabetes were identified using mass spectrometry-based fecal metabolomics technology, GS was found to regulate phenylalanine metabolism, tryptophan metabolism, and the diabetes-induced secondary bile acid biosynthesis pathway in type II diabetes rats, which also confirms its ability to protect the liver and intestine by improving amino acid metabolism[102].

Improve energy metabolism

Relieve mitochondrial dysfunction

Abnormal energy metabolism in liver cells occurs after LD and is one of the important causes of liver damage[103–105]. Mitochondria are the main structures that provide energy to liver cells. They perform cellular biological oxidation and provide ATP to liver cells so that they can maintain their normal biological activity[106]. Damage to the liver can cause changes in mitochondrial dynamics and impaired adaptability and flexibility, directly leading to a decrease in ATP synthesis[107–109]. Our experiment showed that after being exposed to alcohol for 24 hours, liver cells treated with 0.9 μg/mL GS had significantly increased mitochondrial respiratory capacity and ATP content[110]. There is also evidence to suggest that gastric administration of GS can significantly alleviate mitochondrial dysfunction: GS has a significant protective effect on mitochondrial dysfunction in APP/PS1 mice by inhibiting oxidative damage processes in mitochondria, increasing mitochondrial membrane potential, and enhancing cytochrome C oxidase activity[111].

Regulating the TCA cycle

The TCA cycle is the basis for mitochondrial energy production and can directly reflect the functional status of mitochondria[112]. One of the key enzymes guiding the TCA cycle is isocitrate dehydrogenase (IDH), which catalyzes the oxidative decarboxylation of isocitrate and maintains cellular homeostasis[113]. IDH exists in the cytoplasm in the form of IDH1, while in mitochondria, it exists in the form of IDH2. IDH1 and IDH2 mutations can cause TCA cycle dysfunction, and multiple researchers have discovered IDH1 and IDH2 mutants in various cancers[114–117]. Research has shown that MiR-144-5p is highly involved in the regulation of IDH1/IDH2 and oxoglutarate (key organic enzymes in the TCA cycle) in the TCA cycle. Through the study of proteomics and metabolomics data, we found that GS can regulate IDH1/IDH2 and oxoglutarate in the TCA cycle by reducing MiR-144-5p levels, thereby improving the TCA cycle and promoting the recovery of liver cells affected by alcohol[113]. In addition, there is evidence to suggest that after a systematic analysis of the therapeutic effect of GS on liver injury using biochemistry, metabolomics, and proteomics, it was found that the TCA cycle is one of the nine therapeutic differentiation metabolites, and the identified differential proteins are also related to energy metabolism, indicating that the molecular therapeutic mechanism of GS on liver injury rats is closely related to regulating energy metabolism[118].

Regulating lipid metabolism

Improve lipid breakdown

The liver plays a central role in regulating systemic lipid circulation. LD can affect the liver TCA cycle and reduce fatty acid oxidation, and if accompanied by a high-fat diet, it can easily lead to hyperlipidemia and exacerbate liver steatosis[119–121]. Research has shown that lipid accumulation and the loss of insulin function can lead to an increase in TCA oxidation flux, accelerating the formation of fatty liver[122–123]. In our experiment, we found that after the administration of GS, the levels of citric acid, isocitric acid, and D-glucose involved in the TCA cycle and starch, sucrose, and acetaldehyde metabolism increased in ALD model mice, alleviating symptoms such as loss of appetite and hypoglycemia[110]. In addition, evidence suggests that GS can inhibit lipid accumulation in the rat liver by activating peroxisome proliferator-activated receptor α (PPAR α) and regulating the AMPK/mTOR complex signaling pathway[124–126]. There are also studies showing that GS can control cholesterol synthesis in the liver by inhibiting HMG CoA reductase (HMGCR, the rate-limiting enzyme for cholesterol synthesis), steroid regulatory element binding protein 1c (SREBP-1c), and their downstream target genes, thereby inhibiting lipid synthesis in the liver[127–128]. The above evidence indicates that GS can reduce the risk of liver steatosis by regulating lipid metabolism.

Adjust the content of lysophosphatides

Glycerol phospholipid (GP) is the most common phospholipid in the body. In addition to forming biofilms, it is also one of the components of membrane surfactants, with functions such as transporting substances and acting as receptors. Phosphatidylcholine has a good protective effect on liver damage caused by toxic effects and is an important nutrient in the liver. The changes in the content and metabolic pathways of one of the metabolites of glycerophospholipids, lysophosphatidylcholine (LysoPC), are the focus of many disease studies[129–131]. Research has shown that rapid updates of phosphatidylcholine in the early stages of liver damage are associated with LysoPC[132]. In our study, the levels of LysoPC (15:0) and LysoPC (16:0) in ALD model mice treated with GS tended to be normal, indicating that GP metabolism in mice improved after treatment with GS and the GP metabolic pathway was improved. At the same time, it was found in the study that the serum levels of sphingolipids in ALD model mice were significantly increased, and sphingolipids are considered highly diverse lipids with multiple biological activities. Therefore, sphingolipids are also suspected to affect the pathogenesis of ALD[110].

Anti-inflammatory and analgesic

Arachidonic acid (AA) is a liquid essential omega-6 fatty acid, which only accounts for a small portion in the human body[133], it is important for the production of prostaglandins, thromboxanes, and leukotrienes, as well as for infant brain development[134]. The main effect of AA in the body is to stimulate inflammation[135–137]. AA is a precursor form of bioactive derivatives of cyclododecanoic acid such as prostaglandins and thromboxanes, which play important roles in lipoprotein metabolism, vasodilation, coagulation enhancement, and regulation of body temperature[138]. As a central metabolic organ, when the liver is damaged, it can lead to impaired AA metabolism and elevated levels of AA in the body, resulting in increased levels of active derivatives such as prostaglandin E2. Prostaglandin E2 can cause vasodilation and increased permeability, leading to redness,

fever, swelling, and pain[139], and this is closely related to liver pain in ALD patients in clinical practice, and experiments have also shown that the levels of AA and prostaglandin E2 in ALD model mice are higher, and the inflammatory response is obvious. Treatment with GS can alleviate these symptoms, indicating that the effect of GS on inflammation may be related to regulating AA metabolism[110].

In addition, the level of inflammatory factors can also indicate the fact. Studies show that the levels of IL-1 β, IL-6, and TNF-α in diabetes db/db mice are significantly inhibited after the administration of GS. Western blot results show that the expression levels of proinflammatory proteins such as serine kinase ROK1/2 and p-NF-κB p65 are reversed, indicating that GS has a good inhibitory effect on diabetes hepatitis[140].

Pharmacodynamics

While the aforementioned mechanisms elucidate GS's therapeutic potential at the molecular level, its clinical efficacy is inherently constrained by its pharmacokinetic behavior *in vivo*. A thorough understanding of GS's absorption, distribution, metabolism, and excretion (ADME) properties is critical for optimizing dose regimens, mitigating off-target effects, and tailoring individualized therapeutic strategies for LD. First, the absorption of GS after entering the body is a complex process. In a rat model, after oral administration of GS, a bimodal phenomenon and the first-pass effect were observed, which may be related to the hepatic intestinal circulation and water solubility of GS[141]. In the intestine, the absorption of GS exhibits first-order kinetic characteristics, especially in the duodenum and jejunum, where the absorption effect is better[142]. In addition, GS also has transdermal absorption properties, and pathological conditions may affect its absorption in the body[143]. There are certain differences in the distribution of GS among various tissues in the body. Research has shown that the GS content is highest in the kidneys, followed by the spleen, liver, heart, lungs, and brain. This indicates that GS has a certain tissue-specific distribution *in vivo*[144]. It is worth noting that after oral administration of GS for 0.5 hours, Cmax (0.46 ± 0.26 μg/mL) appeared in the liver, and area under the curve (AUC) 0.58 ± 0.21 μg·h/mL, indicating that GS can rapidly accumulate in liver tissue at significant levels, consistent with GS exerting multiple effects in protecting the liver, including enhancing liver antioxidant capacity, improving lipid metabolism disorders, and eliminating inflammatory reactions. This specific distribution and significant pharmacological activity provide a solid pharmacokinetic basis for its development as a novel hepatoprotective drug. However, GS cannot penetrate the blood–brain barrier. To improve its poor brain-targeting ability, researchers have prepared GS in liposomes to prolong its half-life or used borneol to promote its transfer to the hippocampus, thereby transporting GS to the brain[145–146]. Regarding the metabolic process, the pathway of GS metabolism in the body is relatively complex and currently not fully understood. Previous studies have shown that GS may be metabolized through steps such as deglycosylation of iridoid glycosides, glucuronidation, and ring cleavage to produce compounds such as sulfates or glucuronic acids. In addition, GS is also converted into genipin in the body, which is also a part of its metabolic process[147–151], as shown in Figure 3. Finally, the process of GS excretion in the body has not been fully elucidated. However, based on its distribution and metabolic characteristics, it can be inferred that GS may be excreted from the body through pathways such as urine and feces. It should be noted that the pharmacokinetic properties of GS may be influenced by various factors, such as the administration route, dosage, individual differences, etc. Therefore, in practical applications, the appropriate administration method and dosage need to be chosen according to the specific situation to ensure its safety and effectiveness.

In summary, the pharmacokinetic study of GS is of great significance in guiding its rational use as a drug. However, the current research on its metabolism and excretion is insufficient, and further research is needed to improve its pharmacokinetic properties.

Hepatotoxic effects and coping strategies of GS

Although GS exhibits significant multi-target effects in LD protection, its potential hepatotoxicity still needs to be carefully evaluated. Existing studies have shown

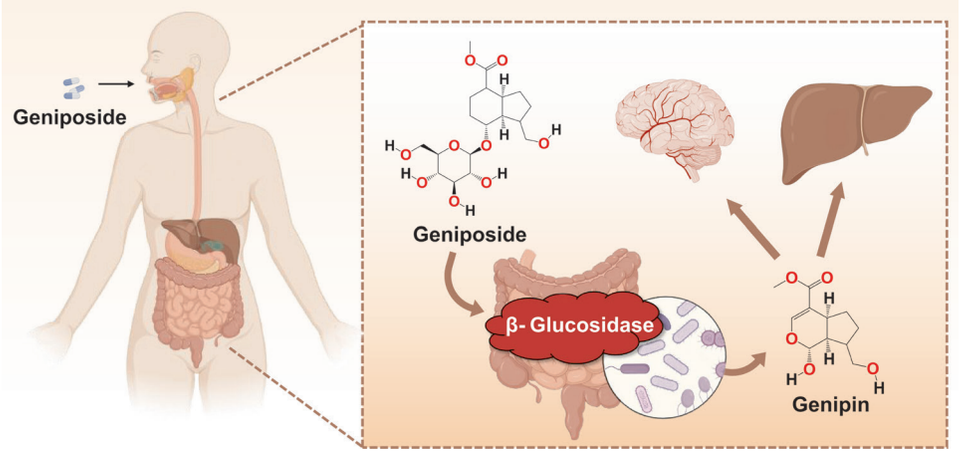


Figure 3. Metabolism of GS. GS: Geniposide.

that the hepatotoxicity of genipin is closely related to its metabolic processes: after oral administration, genipin is hydrolyzed by intestinal microbiota β-glucosidase to produce the active metabolite genipin, which can induce LD through various pathways[152]. First, genipin can covalently bind with glutathione (GSH), significantly reducing the level of GSH in liver cells and weakening the antioxidant defense ability of cells[153]. Second, genipin can also activate apoptosis-related signaling pathways, such as caspase-3 and Bax/Bcl-2 pathways, to induce hepatocyte apoptosis[154]; and according to positive tests for *in vitro* micronuclei and chromosomal aberrations, genipin has genetic toxicity[155]. It is worth noting that these toxic effects exhibit a clear dose and time dependence, particularly significant in long-term high-dose administration[156–159].

However, it is not rational to completely deny the hepatoprotective value of GS due to its potential toxicity. From the perspective of drug development, almost all effective drugs have certain toxic side effects, and the key is how to control risks and exert therapeutic effects through scientific means. For GS, there are at least the following strategies that can significantly reduce its liver toxicity risk: in terms of dose control, adopting a low-dose divided administration regimen (such as <50 mg/kg/d) can effectively avoid toxic reactions; In terms of structural optimization, chemical modification of hydroxyl or sugar groups can reduce the intestinal production rate of genipin. In terms of combination therapy, combining with antioxidants (such as N-acetylcysteine) or hepatoprotective drugs (such as silymarin) can significantly reduce their adverse reactions. More importantly, the unique pharmacological mechanism of GS, including regulating FXR-mediated bile acid metabolism, inhibiting NF-κB inflammatory pathway, activating Nrf2 antioxidant pathway, etc, gives it irreplaceable advantages in the treatment of LD.

Conclusion

The liver, as the largest metabolic organ in the human body, plays multiple important physiological functions. The prevention and treatment of LD is not only related to the health of a single organ but also the fundamental guarantee for maintaining overall life activities. GS is a natural product with various pharmacological activities as a cyclic terpenoid glycoside. Improving LD is one of the important pharmacological activities. GS, as a candidate drug for treating liver injury, has enormous potential as it can alleviate symptoms from the root. Due to the water-soluble nature of GS, it is easily converted into GS and absorbed by the intestine when taken orally, making it easier to exert its pharmacological effects. Despite the risk of liver toxicity, with scientific utilization, it can still exert the maximum effect of liver protection. This review is based on existing research progress and summarizes the possible mechanisms by which GS improves LD. At the same time, the pharmacokinetics of GS *in vivo* are systematically reviewed, and the mechanism of its liver toxicity is elucidated and solutions are proposed.

Although there are many studies on the alleviation of LD by the natural product GS, there are still many challenges waiting to be overcome. At present, most research is still in the primary stage of animal experiments, with limited clinical data support. In the future, appropriate clinical trials should be conducted to ensure the safety of GS in large-scale applications. In addition, current research mainly focuses on searching for LD biomarkers and possible pathways but neglects the verification process. In the future, research should focus on targeted studies of biomarkers and pathways to demonstrate their reliability. Moreover, the mechanism of action of GS in alleviating LD remains not clearly explained at present, although metabolomics research has made considerable efforts in this area. In the future, we can try to combine metabolomics with multi-omics and use multiple methods, such as mass spectrometry imaging and magnetic resonance imaging, to identify specific mechanisms through a "point-to-point" approach.

In summary, GS has great potential for development and research as a new drug for treating LD.

Conflict of interest statement

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Author contributions

Songyuan Tang analyzed the data and wrote the manuscript. Guangli Yan, Ling Kong, Hui Sun, Chang Liu, Ying Han, and Xijun Wang revised the manuscript. All the authors read and approved the final manuscript.

Ethical approval of studies and informed consent

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Data availability

All data generated or analyzed during this study are included in this published article.

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