

The roles of *Gardenia jasminoides* and its constituents in liver diseases

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Abstract

Gardenia jasminoides extract (GJE), widely used in traditional medicine, contains bioactive compounds such as geniposide, genipin, and crocin with diverse pharmacological effects. This review summarizes its hepatoprotective roles across liver diseases, including acute liver failure (ALF), non-alcoholic fatty liver disease (NAFLD), cholestatic liver disease, fibrosis, and hepatocellular carcinoma (HCC). Preclinical studies demonstrate that GJE reduces mortality and improves liver histology in ALF by suppressing inflammation, oxidative stress, apoptosis, and necroptosis while enhancing endogenous antioxidant defenses. In NAFLD, GJE alleviates hepatic steatosis and fibrosis, downregulates lipogenesis, and restores mitochondrial function. In cholestatic models, it enhances bile flow and modulates bile acid transporters such as FXR, BSEP, and MRP. Additionally, GJE exhibits anti-fibrotic and anti-tumor effects by inhibiting key signaling pathways such as TLR4/NF- κ B, Sonic hedgehog, and Akt/mTOR, while reducing oxidative stress and inflammation and promoting tumor cell apoptosis. Overall, GJE shows promise as a multi-target therapeutic agent, warranting further clinical validation.

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Introduction

Gardenia jasminoides (GJ), a member of the *Rubiaceae* family, is an evergreen shrub with glossy green leaves and aromatic white flowers. *Gardenia* plants are widely distributed in tropical and subtropical regions, including Japan, North Korea, China, and Southeast Asia. *Gardenia* fruits contain over 46 iridoid glycosides, comprising about 3–9% of the dry weight of mature fruits. Bioactive constituents isolated from *Gardenia* fruits possess multiple biological activities that contribute to health promotion, including protective effects on the liver, nervous system, and cardiovascular system, as well as anti-inflammatory, antioxidant, antidiabetic, and antineoplastic properties.¹ More than 281 traditional Chinese medicine preparations contain *Gardenia jasminoides* extract (GJE) as a component. In Chinese medicine, GJE is used to reduce body temperature and irritability, as well as to promote diuresis and bile flow. In addition to their medicinal uses, these fruits are widely utilized in the food and dye industries.² Contemporary pharmacological research has concentrated on the therapeutic potential

of GJE's active constituents, including geniposide, genipin, crocin, and crocetin, on various medical conditions. In this review, we will focus on the effects of GJE and its constituents in liver diseases (summarized in Figure 1 and Table 1).

Phytochemistry, Pharmacokinetics, and Safety of *Gardenia jasminoides* extract

Gardenia jasminoides contains several classes of bioactive molecules, including iridoids, iridoid glycosides, triterpenoids, organic acids, and volatile compounds. The primary bioactive compounds are geniposide, genipin, gardenoside, and crocin (shown in Figure 2).³ Pharmacokinetic studies of *Gardenia* fruits have mainly focused on geniposide. The absorption and metabolism of geniposide vary significantly based on the administration route and biological environment. The absolute bioavailability of geniposide in rats is highest when administered intramuscularly (72.69%), followed by intranasally (49.54%), and is lowest intragastrically (9.74%). It is primarily absorbed through passive diffusion. Once absorbed, geniposide is distributed throughout the body, with the highest concentrations typically found in the kidneys, followed by the spleen and liver. Geniposide is a prodrug that is hydrolyzed into its aglycone, genipin, by β -glucosidase produced by intestinal bacteria.⁴ While *Gardenia* is widely used, high doses can lead to toxicity. *Gardenia* yellow is classified as virtually non-toxic in acute oral studies, with an LD₅₀ greater than 15.0 g/kg bodyweight (bw) in rats. The No Observed Adverse Effect Level (NOAEL) for *Gardenia* yellow in rats is 0.50 g/kg bw/day. At higher doses (1.50 g/kg bw/day or more),

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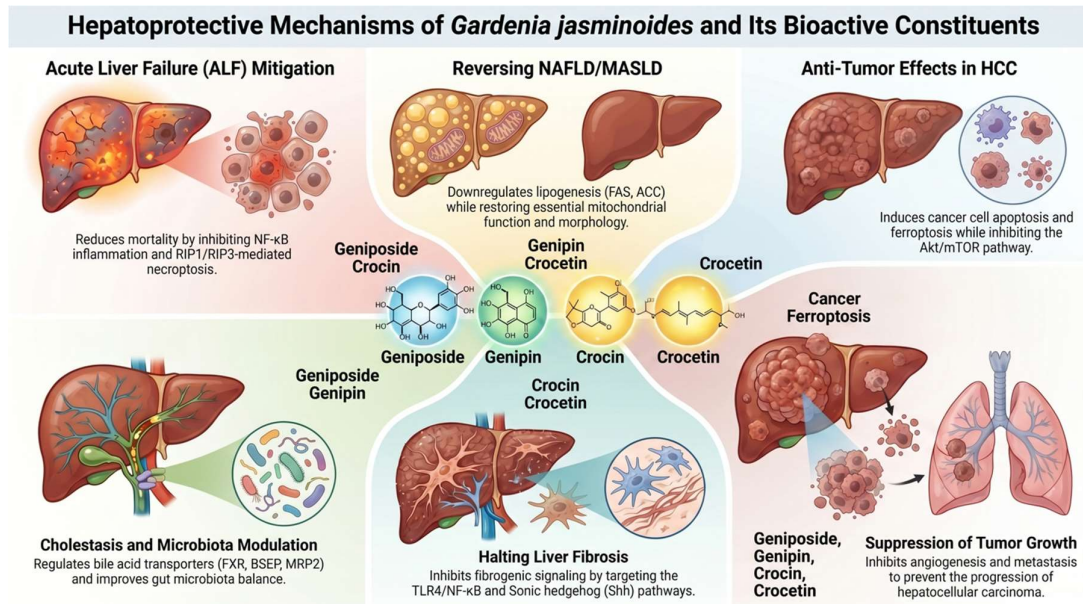


Figure 1 Hepatoprotective mechanisms of *Gardenia jasminoides* and its bioactive constituents.

rats exhibited body weight loss, diarrhea, and pigment deposition in vital organ. High doses of geniposide (≥ 574 mg/kg) can induce hepatotoxicity and nephrotoxicity. This toxicity is largely attributed to its metabolite, genipin, which can react with proteins and induce oxidative stress.⁵

Acute Liver Failure

Acute liver failure (ALF) is a life-threatening condition involving multiple organs and associated with high morbidity and mortality, often requiring liver transplantation. Causes include drug/chemical toxicity, viral hepatitis, Wilson disease, ischemia, and autoimmune hepatitis. Despite available medical therapies, mortality can reach 60%, highlighting the urgent need for additional effective treatments.⁶

Preclinical studies investigating GJE and its constituents in acute liver failure models consistently demonstrate significant hepatoprotective effects, including reduced mortality and improved liver histopathology, through several interconnected mechanisms.

A major therapeutic mechanism appears to involve the suppression of inflammatory signaling pathways. In D-galactosamine (GalN) and lipopolysaccharide (LPS)-induced liver failure models, Kim and colleagues demonstrated that genipin reduced serum tumor necrosis factor- α (TNF- α) and nuclear factor- κ B (NF- κ B) expression,⁷ while Ma and colleagues reported that geniposide improved liver histology through the suppression of methyl-CpG binding protein 2 (MeCP2), leading to the inhibition of macrophage-mediated inflammatory responses.⁸ Similarly, in acetaminophen-induced hepatotoxicity, Tangpradubkiat and colleagues showed that GJE reduced inflammatory markers,⁹

whereas Yang et al. demonstrated the suppression of toll-like receptor 4 (TLR4)/NF- κ B signaling by geniposide.¹⁰ Together, these findings suggest that the modulation of inflammatory pathways represents a central upstream mechanism underlying the hepatoprotective effects of GJE and its constituents.

Several studies also highlighted the antioxidative properties of GJE-related compounds. Kim and colleagues observed reductions in hepatic malondialdehyde (MDA) levels following genipin treatment,⁸ while Tangpradubkiat and colleagues similarly demonstrated an attenuation of oxidative stress markers in acetaminophen-induced liver injury.⁹ In addition, Yang et al. proposed that geniposide enhances endogenous antioxidant defenses while inhibiting CYP2E1-mediated the formation of N-acetyl-p-benzoquinone imine (NAPQI), a major toxic metabolite responsible for acetaminophen-induced hepatotoxicity.¹⁰ These findings suggest that the attenuation of oxidative injury may contribute substantially to hepatocellular protection.

The inhibition of hepatocyte cell death pathways also appears to play an important role. Kim and colleagues demonstrated reductions in apoptotic markers, including cytochrome c and caspase-3, following genipin treatment.⁷ Seo and colleagues further showed that genipin suppressed necroptosis-related signaling, including RIP3, phosphorylated RIP1/RIP3, and RIP1/RIP3 necrosome complex formation, comparable to the effects of necrostatin-1.¹¹ Similarly, Yang et al. reported reductions in hepatic necrosis and apoptosis in acetaminophen-induced liver injury following geniposide treatment.¹⁰ These findings indicate that GJE constituents may protect against both apoptotic and necroptotic hepatocyte injury.

Table 1 Summary table detailing the experimental parameters and findings of previous studies

Author	Animal / Cell line	Disease model	Sample size (/ group)	Dosage of Chemical Substance(s)	Control(s)	Main Outcomes
Acute liver failure						
Kim, S.J. ⁷	Male ICR mice	GalN/LPS-induced acute liver failure	n = 15	Genipin (25, 50, 100, 200 mg/kg)	Vehicle group (10% Tween 80-saline)	- Improved survival - Protective against apoptotic liver damage via antioxidant effects and NF- κ B inhibition.
Ma, T.T. ⁸	C57BL/6J mice	CCl4-induced acute liver injury	n = 10	Geniposide (200 mg/kg)	Vehicle group (oil)	Alleviated inflammation and injury by suppressing MeCP2 and the Hedgehog signaling pathway.
Tangpradubkiat, P. ⁹	Male ICR mice	Acetaminophen-induced acute liver injury	n = 6	Low-dose GJE (0.44 g/kg/dose, containing geniposide 100 mg/kg/dose) High-dose GJE (0.88 g/kg/dose, containing geniposide 200 mg/kg/dose)	Vehicle group (corn oil)	Reduced hepatocyte damage by suppressing inflammation (TNF- α , IL-6) and oxidative stress (MDA).
Yang, S. ¹⁰	Male C57 mice	Acetaminophen-induced acute liver injury	n = 6	Geniposide (10, 30, 100 mg/kg)	Vehicle group (0.5% carboxymethylcellulose sodium)	Alleviated hepatocyte necrosis and apoptosis by downregulating CYP2E1 expression and inhibiting the TLR4/NF- κ B signaling pathway
Seo, M.J. ¹¹	Mice	GalN/LPS-induced acute liver failure	n = 8–10	Genipin (25, 50, 100 mg/kg); Necrostatin-1 (1.8 mg/kg)	Vehicle group (10% Tween 80-saline)	- Improved survival rate - Suppressed necroptosis and necroptosis-mediated inflammasome signaling (NLRP3, caspase-1).
NAFLD						
Chen, S.D. ¹³	Male Sprague Dawley rats	HFD-induced NAFLD	n = 7	<i>Fructus Gardeniae</i> decoction (1 mL/100g weight)	Normal feed group; HFD model group	- Improved liver histology - Reduced hepatic triglyceride/FFA and FAS/ACC levels - Increased AMPK - Inhibited TNF- α and P- $\text{I}\kappa$ B inflammatory signaling.
Chen, C. ¹⁴	C57BL/6J mice	HFD-induced NAFLD	n = 10	Geniposide (90 mg/kg); Chlorogenic acid (1.34 mg/kg); Geniposide (90 mg/kg) + Chlorogenic acid (1.34 mg/kg)	Normal diet group; HFD group	- Combination therapy significantly reduced hepatic fat deposition, hepatic triglyceride, total cholesterol, FFA, and liver enzymes compared to either treatment alone - Main mechanism: suppressed SCD-1 expression.
Liang, H. ¹⁵	Wistar male rats	HFD-induced NAFLD	n = 7–10	Chlorogenic acid (15 mg/kg) + Gardenia glycosides (45 mg/kg); Chlorogenic acid (30 mg/kg) + Gardenia glycosides (90 mg/kg); Chlorogenic acid (45 mg/kg) + Gardenia glycosides (30 mg/kg); Chlorogenic acid (60 mg/kg) + Gardenia glycosides (75 mg/kg); Chlorogenic acid (75 mg/kg) + Gardenia glycosides (15 mg/kg); Chlorogenic acid (90 mg/kg) + Gardenia glycosides (90 mg/kg)	Regular diet group; model group (HFD + water)	- Determined 1:1 ratio (90mg each) as optimal for reducing hepatic triglyceride, FFA, and ALT/AST while reducing MDA/increasing SOD.
Xu, Z. ¹⁶	- Zebrafish embryos - L02 cells	- TAA-induced NAFLD - FFA-induced lipid accumulation	n = 3–10	Crocin (1, 1.3, 3, 10 μ M for zebrafish; 2.5, 5, 10 μ M for cells)	Fish water (zebrafish); DMSO (cells)	Reduced intracellular lipid accumulation and liver enzymes by the restoration of mitochondrial functions (increased ATP concentration, $\Delta\Psi_m$, and activities of SOD, catalase, and cytochrome C oxidase)
Suttawong, N. ¹⁷	Male Sprague-Dawley rats	HFHF diet-induced NASH with fibrosis	n = 6	GJE extract (0.119, 0.239 g/kg)	Standard diet; HFHF diet group (NF)	Alleviated NASH and fibrosis by modulating NF- κ B and fibrogenic signaling (MMP-12, IL-13, and TGF- β 1).

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Table 1 (Continued)

Author	Animal / Cell line	Disease model	Sample size (/ group)	Dosage of Chemical Substance(s)	Control(s)	Main Outcomes
Cholestasis						
Chen, H. ¹⁹	Male Sprague-Dawley rats	ANIT-induced acute cholestasis	n = 8	Geniposide acid (25, 50, 100 mg/kg); UDA (100 mg/kg)	Blank control (olive oil)	<ul style="list-style-type: none"> - Improved liver histology - Increased bile flow rate - Decreased serum total bile acid - Upregulated FXR, BSEP, and MRP2 expression
Fang, S. ²⁰	Male C57BL/6 mice	ANIT-induced cholestatic liver injury	n = 10	GJE polysaccharides (50, 100, 200, 400 mg/kg); UDCA (100 mg/kg)	Pure water (Vehicle)	<ul style="list-style-type: none"> - Reduced hepatocyte necrosis and inflammation - Reduced hepatic bile acid levels - Increased expression of FXR, PXR, BSEP, MRP2, MRP4, OST-α - Improved gut microbiota dysbiosis - Inhibited the TLR4/NF-κB pathway
Wang, L. ²¹	Sprague-Dawley rats	ANIT-induced cholestasis	n = 8	Geniposide (25, 50, 100 mg/kg); UDCA (60 mg/kg)	Vehicle group	<ul style="list-style-type: none"> - Reduced bile duct epithelial damage and portal inflammatory cell infiltration - Improved bile flow - Regulated transporters (BSEP, OATP2, MRP2) and synthesis enzymes (CYP7A1, CYP8B1, and CYP27A1) via FXR/PXR
Liver fibrosis						
Chen, Y.H. ²²	Male Sprague-Dawley rats	Bile duct ligation (BDL)-induced liver fibrosis	n = 8	GJE (25, 50, 100 mg/kg)	Sham-operated rats; ddH ₂ O treatment control	<ul style="list-style-type: none"> - Improved liver fibrosis - Decreased serum ALT/AST and liver hydroxyproline - Suppressed TGF-β1/Smad2 signaling and collagen expression
Lin, X. ²⁴	Male Kunming mice	CCl ₄ -induced liver fibrosis	n = 25	Geniposide (50, 100, 150 mg/kg); Colchicine (0.1 mg/kg)	Normal saline group	<ul style="list-style-type: none"> - Improved liver fibrosis - Reduced markers of fibrosis (α-SMA and Col I a1) - Inhibited Sonic hedgehog (Shh) signaling
Ma, X. ²⁵	Male C57 mice	CCl ₄ -induced chronic liver fibrosis	n = 10	Polysaccharide GJE0.2-2 (50, 100 mg/kg); obeticholic acid (30 mg/kg)	Olive-induced blank group	Alleviated fibrosis by inhibiting the TLR4/NF- κ B signaling pathway.
Yang, L. ²⁶	Male C57BL/6 mice	CCl ₄ -induced liver fibrosis	n = 10	Geniposide (50 mg/kg)	Saline-treated group	<ul style="list-style-type: none"> - Improved liver fibrosis - Reduced oxidative stress (increased SOD and GSH-Px, and decreased MDA), inflammation (decreased IL-6, IL-1β, and TNF-α), and apoptosis (decreased expression of Bax, Caspase 3, and Caspase 9, and increased expression of Bcl-2) - Modulated glycerophospholipid, arginine, protein, and arachidonic acid metabolism
Oh, S.H. ²⁷	Male C57BL/6 mice	HFD-induced obesity and fibrosis	n = 5	Geniposide (50, 100 mg/kg)	Normal chow group; HFD control	<ul style="list-style-type: none"> - Reduced hepatic steatosis and fibrosis - Reduced inflammation - Improved insulin resistance by activating the INSR-IRS2-Akt pathway and AMPK expression.

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Table 1 (Continued)

Author	Animal / Cell line	Disease model	Sample size (/ group)	Dosage of Chemical Substance(s)	Control(s)	Main Outcomes
Hepatocellular carcinoma						
Amin, A. ²⁷	Male albino Wistar rats	DEN/2-AAF-induced hepatocarcinogenesis	n = 8	Crocin (100 and 200 mg/kg) – administered before and after DEN/2-AAF induction	Distilled water and single dose saline	- Reduced hepatocarcinogenesis through the inhibition of inflammatory pathway (NF- κ B1, CCL20) and HDAC, and induction of cancer cell apoptosis.
Luo, M. ³⁰	Huh 7 and HepG2 cells (<i>in vitro</i>) BALB/c nude mice (<i>in vivo</i>)	Subcutaneous xenograft tumor model	n = 5	Geniposide (200 mg/kg); - administered after the tumor has reached 5 mm in size	Vehicle control (ddH ₂ O)	Reduced cell viability and migration, and tumor size through DUOX1-mediated ferroptosis.
Yao, C. ³¹	HepG2 and HCCLM3 (<i>in vitro</i>)	Hepatocellular carcinoma cell model	N/A (Cell lines)	Crocin (various concentrations)	Untreated cells	Induced autophagic apoptosis in HCC cells by inhibiting Akt/mTOR activity.
Eisherbiny, N. ³²	Male Sprague Dawley rats	TAA-induced hepatocarcinogenesis	n = 8-10	Crocin (10 mg/kg, i.p.) – given 2 weeks along with TAA injection and 2 weeks after cessation of TAA injection	Saline (i.p.) control	Attenuated cancerous lesions by modulating oxidative stress (Nrf2, HO-1, KEAP-1), and apoptotic signaling (JNK, p53, TRAIL, caspase-8, BAX, and Bcl-2).
Zhang, C. ³³	Athymic nude mouse	Orthotopic HCC implantation	n = 5	Geniposide (30 mg/kg) – given 7 days after HCC implantation	Geniposide + single i.p. injection of LPS	Suppressed HCC proliferation, angiogenesis, and lung metastasis via inhibition of the TLR4/MyD88 pathway leading to the suppression of STAT3/Sp1-dependent VEGF overexpression.

In Summary, GJE and its constituents confer significant hepatoprotective effects in various models of acute liver failure and liver injury, including GalN/LPS-, CCl₄-, and acetaminophen-induced models. Their mechanisms of action are primarily mediated through the suppression of inflammatory signaling pathways, particularly TNF- α /NF- κ B- and TLR4/NF- κ B-associated pathways, which appear to serve as central upstream mechanisms driving liver injury. The inhibition of these inflammatory cascades subsequently attenuates downstream oxidative stress, apoptotic signaling, macrophage activation, and necroptosis-related inflammasome activation. In acetaminophen-induced liver injury, additional upstream protection may arise from CYP2E1 inhibition, leading to reduced NAPQI generation and subsequent attenuation of oxidative and inflammatory damage.

Non-Alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD), now also referred to as metabolic dysfunction-associated steatotic liver disease (MASLD), is one of the most common liver diseases worldwide, affecting approximately 30–40% of the global population. In this manuscript, we use the term NAFLD/NASH (non-alcoholic fatty liver disease/non-alcoholic steatohepatitis) to align with the historical terminology used in the cited studies. NAFLD is considered the hepatic manifestation of metabolic syndrome and is associated with increased risks of both liver-related and non-liver-related mortality. Currently, there are limited medications approved by the U.S. Food and Drug Administration for NAFLD, and these are primarily indicated for patients with at least F2 fibrosis.¹² Lifestyle modification and weight loss remain the mainstay of treatment for NAFLD; however, they are often difficult to achieve and sustain. Therefore, alternative therapies for NAFLD are urgently needed.

Studies investigating the effects of GJE and its constituents in NAFLD/NASH models consistently demonstrate improvements in hepatic steatosis, inflammation, and fibrosis through several interconnected mechanisms. Regarding hepatic lipid metabolism, Chen and colleagues showed that gardenia fruit treatment reduced hepatic steatosis and downregulated key lipogenic genes, including fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC), in a rat model of NASH.¹³ Similarly, chlorogenic acid combined with gardenia glycosides suppressed stearoyl-CoA desaturase 1 (SCD1) expression, suggesting the inhibition of *de novo* lipogenesis.¹⁴ Consistent with these findings, another study demonstrated dose-dependent reductions in hepatic triglyceride and free fatty acid (FFA) levels following treatment with chlorogenic acid and gardenia glycosides.¹⁵

Several studies also highlighted the antioxidative properties of GJE-related compounds. Chlorogenic

acid combined with gardenia glycosides reduced oxidative stress, as evidenced by decreased MDA levels and increased SOD activity.¹⁵ Likewise, crocetin decreased MDA levels while increasing antioxidant enzyme activities, including SOD and catalase (CAT), in FFA-induced L02 cells.¹⁶ These antioxidative effects may contribute to the attenuation of hepatocellular injury and metabolic dysfunction.

Mitochondrial protection appears to be another important mechanism underlying the beneficial effects of GJE constituents. *In vitro*, crocetin restored mitochondrial function in FFA-induced L02 cells, as demonstrated by increased ATP production, improved mitochondrial membrane potential ($\Delta\Psi_m$), enhanced cytochrome c oxidase (COX IV) activity, and the normalization of mitochondrial morphology on transmission electron microscopy.¹⁶ Together, these findings suggest that the restoration of mitochondrial integrity may represent an important downstream mechanism contributing to reduced lipid accumulation and oxidative injury. In addition to metabolic effects, Suttawong and colleagues demonstrated that GJE improved NASH histology and fibrosis while reducing inflammatory and fibrotic marker expression in a rat model of NASH with fibrosis.¹⁷

Collectively, the available evidence suggests that the primary mechanisms underlying the beneficial effects of GJE and its constituents in NAFLD/NASH involve the regulation of hepatic lipid metabolism and the suppression of *de novo* lipogenesis, as reflected by the reduced expression of lipogenic genes, together with decreased hepatic triglyceride and FFA accumulation. These upstream metabolic effects are likely accompanied by secondary downstream mechanisms, including the attenuation of oxidative stress, the restoration of mitochondrial function, and the suppression of inflammatory and fibrotic signaling pathways. Improvements in antioxidant defenses and mitochondrial integrity may contribute to reduced hepatocellular injury and metabolic dysfunction, ultimately leading to improvements in hepatic inflammation, fibrosis, and overall NASH histopathology.

Cholestatic Liver Disease

Cholestatic liver diseases encompass a heterogeneous group of conditions defined by impaired bile flow. Although their underlying pathophysiological mechanisms differ, they share the common feature of cholestasis, which may progress to fibrosis and eventually end-stage liver disease requiring liver transplantation. The principal cholestatic liver diseases include primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC), and IgG4-related cholangitis (IgG4-C). Therapeutic options for cholestatic liver diseases are limited, and most lack definitive treatments to halt progression. Consequently, identifying effective therapies has become a key focus of recent hepatology research.¹⁸

GJE has traditionally been used in Chinese medicine to enhance bile flow, making it a promising alternative therapy for cholestatic liver diseases.

Studies investigating the effects of GJE and its constituents in cholestatic liver disease consistently demonstrate improvements in bile flow, liver histology, and biochemical markers through modulation of bile acid metabolism, bile acid transport pathways, intestinal homeostasis, and fibrogenic signaling.

A major therapeutic mechanism appears to involve regulation of bile acid transporters and nuclear receptor signaling. Chen and colleagues demonstrated that pretreatment with geniposidic acid improved bile flow and reduced intrahepatic cholestasis in α -naphthylisothiocyanate (ANIT)-induced rats, accompanied by increased expression of farnesoid X receptor (FXR), bile salt export pump (BSEP), and multidrug resistance-associated protein 2 (MRP2).¹⁹ Similarly, Fang and colleagues showed that GJE dose-dependently improved liver histology and biochemical markers in ANIT-treated mice while increasing the expression of hepatic FXR, pregnane X receptor (PXR), BSEP, MRP2, MRP4, organic solute transporter α (OST α), and CYP3a11.²⁰ These findings suggest that modulation of bile acid transporter networks and nuclear receptor signaling represents a central mechanism underlying the anti-cholestatic effects of GJE and its constituents.

Several studies also highlighted the role of GJE in regulating bile acid metabolism and reducing hepatic bile acid toxicity. Wang and colleagues demonstrated that geniposide reduced the hepatic accumulation of toxic bile acids through multiple coordinated mechanisms, including the suppression of bile acid synthesis via the downregulation of CYP7A1, CYP8B1, and CYP27A1, inhibition of bile acid uptake through the repression of organic anion transporting polypeptides 2 (OATP2), and the enhancement of bile acid secretion via BSEP and OST β .²¹ Together, these findings indicate that GJE and its constituents may restore bile acid homeostasis by simultaneously reducing bile acid production and promoting bile acid elimination.

Emerging evidence further suggests that gut microbiota modulation may contribute to the hepatoprotective effects of GJE in cholestatic liver disease. Fang and colleagues demonstrated that GJE ameliorated gut microbiota alterations and improved intestinal barrier function in ANIT-treated mice. Importantly, fecal microbiota transplantation (FMT) using feces from GJE-treated mice improved liver histology and biochemical markers in recipient ANIT-treated mice, supporting a potential role of the gut–liver axis in mediating the beneficial effects of GJE.²⁰ The proposed mechanism by which GJE improves gut dysbiosis and cholestasis likely involves the degradation of GJE polysaccharides into short-

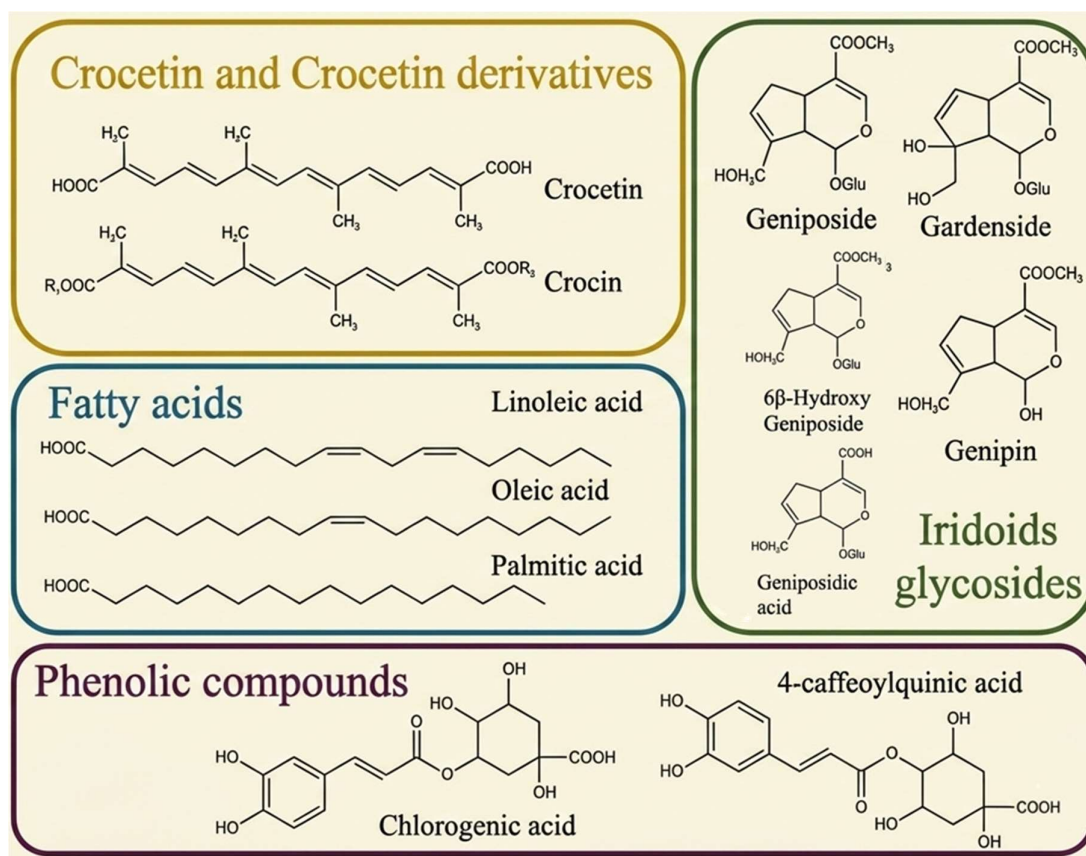


Figure 2 Components of *Gardenia jasminoides* and chemical structures.

chain fatty acids, which enhance intestinal integrity, promote the growth of beneficial bacteria, reduce bacterial and gut toxin translocation, and attenuate hepatic inflammation. Moreover, gut microbiota have previously been shown to regulate secondary bile acid metabolism and inhibit bile acid synthesis, which may further contribute to the improvement in cholestasis.

In addition to its anti-cholestatic effects, GJE also appears to exert anti-fibrotic activity in cholestatic liver injury. Chen and colleagues demonstrated that GJE ameliorated liver fibrosis in a bile duct ligation rat model through the inhibition of TGF- β 1-induced Smad2 phosphorylation.²² Collectively, these findings suggest that GJE and its bioactive constituents improve cholestatic liver disease through integrated regulation of bile acid metabolism and transport, gut microbiota homeostasis, intestinal barrier integrity, and fibrogenic signaling pathways.

Liver Fibrosis and Hepatocellular Carcinoma

Primary liver cancer was the sixth most common cancer and the third leading cause of cancer-related mortality worldwide in 2022, with hepatocellular carcinoma (HCC) accounting for the majority of cases and occurring predominantly in patients with cirrhosis.²³ Given the limited preventive options and a lack of effective chemoprotective agents—particularly for patients with established cirrhosis—there is a critical need for safe, affordable therapies that can both prevent HCC and slow fibrosis progression, alongside early detection and treatment to improve survival. GJE and its constituents have demonstrated promising effects on fibrosis regression and HCC prevention in preclinical studies.

Effects of GJE and its constituents on liver fibrosis

Studies investigating the effects of GJE and its constituents on liver fibrosis consistently demonstrate anti-fibrotic activity through the modulation of hepatic stellate cell activation, inflammatory signaling, oxidative stress, apoptosis, and metabolic pathways.

A major anti-fibrotic mechanism appears to involve the suppression of hepatic stellate cell activation and fibrogenic signaling pathways. An *in vitro* study demonstrated that geniposide inhibited the proliferation of activated HSC-T6 cells by inducing G2/M cell cycle arrest, likely through the suppression of the Sonic hedgehog (Shh) signaling pathway.²⁴ Similarly, Ma and colleagues showed in both *in vitro* and *in vivo* models that GJE reduced liver fibrosis and fibrogenic gene expression through inhibition of TLR4/NF- κ B signaling, likely mediated by direct binding of GJE to TLR4.²⁵ These findings suggest that inhibition of stellate cell activation and inflammatory fibrogenic pathways represents a central upstream mechanism underlying the anti-fibrotic effects of GJE and its constituents.

Several studies also highlighted the antioxidative and anti-inflammatory properties of GJE-related compounds. In a CCl₄-induced liver fibrosis model, Yang and colleagues demonstrated that geniposide improved fibrosis, collagen deposition, and α -SMA expression while reducing oxidative stress markers (MDA) and inflammatory cytokines, including IL-6, IL-1 β , and TNF- α .²⁶ Geniposide also attenuated hepatocyte apoptosis, as evidenced by reductions in Bax, cleaved caspase-3, and cleaved caspase-9 expression.²⁶ These findings indicate that the suppression of oxidative stress, inflammation, and apoptosis likely contributes to the downstream attenuation of fibrogenesis.

Emerging evidence further suggests that metabolic regulation may contribute to the anti-fibrotic effects of GJE constituents. Metabolomic analysis demonstrated that geniposide modulated glycerophospholipid metabolism, arginine and proline metabolism, and arachidonic acid metabolism in fibrotic liver tissue.²⁶ In addition, Oh and colleagues showed that geniposide improved hepatic steatosis and liver fibrosis in a high-fat diet-induced NAFLD model through the amelioration of insulin resistance via the activation of the insulin receptor (INSR)–insulin receptor substrate 2 (IRS-2)–protein kinase B (AKT1) pathway and the improvement of glucose and lipid metabolism through the activation of AMP-activated protein kinase (AMPK).²⁷ Together, these findings suggest that the restoration of metabolic homeostasis may represent an additional mechanism contributing to fibrosis improvement.

Collectively, the available evidence suggests that the primary anti-fibrotic mechanisms of GJE and its constituents involve the suppression of hepatic stellate cell activation and the inhibition of fibrogenic signaling pathways, particularly Shh and TLR4/NF- κ B signaling. Secondary mechanisms include the attenuation of oxidative stress, inflammation, hepatocyte apoptosis, and metabolic dysfunction, which together contribute to reduced collagen deposition and liver fibrosis.

Effects of GJE and its constituents on HCC

Studies investigating the effects of GJE and its constituents in HCC models consistently demonstrate anti-tumor activity through the modulation of apoptosis, ferroptosis, proliferation, angiogenesis, inflammation, autophagy, and oncogenic signaling pathways.

A major anti-cancer mechanism appears to involve induction of tumor cell apoptosis and suppression of proliferation. In HepG2 cells, GJE reduced cancer cell viability without affecting normal hepatocytes and increased the expression of pro-apoptotic mediators, including caspase-3, caspase-8, caspase-9, Bax, Fas, and TNF-related apoptosis-inducing ligand (TRAIL), while decreasing anti-apoptotic proteins such as Bcl-2, Bcl-xL, X-linked inhibitor of apoptosis protein (XIAP), cellular inhibitor of apoptosis protein-1 (cIAP-1), cIAP-2, and

survivin.²⁸ GJE also increased the expression of the tumor suppressor genes p53 and p21.²⁸ Similarly, Amin and colleagues demonstrated that crocin induced G2 cell cycle arrest and exerted anti-proliferative and pro-apoptotic effects in HepG2 cells.²⁹ Together, these findings suggest that activation of apoptotic pathways and inhibition of tumor cell proliferation represent central anti-tumor mechanisms of GJE constituents.

Several studies also highlighted the importance of ferroptosis and autophagy-related pathways. Luo and colleagues demonstrated that geniposide inhibited HCC cell viability and migration while inducing apoptosis through dual oxidase 1 (DUOX1)-mediated ferroptosis, findings that were further confirmed in xenograft mouse models.³⁰ In addition, crocin induced autophagy preceding apoptosis in HCC cells, as evidenced by increased LC3 puncta and LC3-II accumulation.³¹ Mechanistically, crocin suppressed Akt/mTOR signaling, and the restoration of Akt activity attenuated both autophagy and apoptosis, indicating an Akt/mTOR-dependent mechanism.³¹ These findings suggest that the regulation of ferroptosis and autophagy may function as important interconnected downstream pathways contributing to tumor suppression.

Anti-inflammatory and antioxidative effects also appear to contribute substantially to the anti-HCC activity of GJE constituents. Elsherbiny and colleagues demonstrated that crocin attenuated thioacetamide-induced liver precancerous lesions and fibrosis while activating the nuclear factor erythroid 2-related factor 2 (Nrf2)/ heme oxygenase-1 (HO-1) antioxidant pathway and modulating apoptosis-related signaling.³² Similarly, Amin and colleagues reported reductions in inflammatory mediators, including COX-2, iNOS, NF- κ B, TNF- α , and p-TNF-R1, while network analysis identified NF- κ B as a key regulatory hub.²⁹ These findings suggest that suppression of inflammatory and oxidative stress pathways may contribute to the attenuation of hepatocarcinogenesis.

The inhibition of angiogenesis and metastasis represents another important anti-tumor mechanism. Zhang and colleagues demonstrated that geniposide suppressed HCC proliferation, invasion, angiogenesis, and lung metastasis in orthotopic mouse models through the inhibition of TLR4/MyD88 and STAT3/Sp1-dependent vascular endothelial growth factor (VEGF) production, thereby reducing endothelial migration and tumor vascularization. These effects were reversible by lipopolysaccharide, further supporting the role of TLR4 signaling in mediating the anti-tumor effects of geniposide.³³

Collectively, current evidence suggests that the anti-HCC effects of GJE and its bioactive constituents are primarily mediated through the suppression of inflammatory and oncogenic signaling pathways, particularly TLR4/MyD88-, NF- κ B-, STAT3/Sp1-, and Akt/mTOR-associated pathways, which regulate

tumor proliferation, survival, angiogenesis, and metastasis. The modulation of these pathways subsequently promotes downstream anti-tumor effects, including apoptosis, cell cycle arrest, ferroptosis, and autophagy, while the attenuation of oxidative stress and inflammatory mediators further contributes to the suppression of hepatocarcinogenesis. Together, these findings support an integrated anti-cancer mechanism in which the regulation of inflammatory and oncogenic signaling serves as the central upstream event, leading to coordinated downstream inhibition of HCC progression.

Conclusion and Future Perspectives

In summary, accumulating preclinical evidence suggests that GJE and its major bioactive constituents, including geniposide, genipin, and crocin, exert broad hepatoprotective effects across acute liver failure, NAFLD/MASLD, cholestatic liver disease, liver fibrosis, and hepatocellular carcinoma. These effects are mediated through multiple mechanisms, including the suppression of inflammation, oxidative stress, apoptosis, necroptosis, and fibrogenic signaling, as well as the modulation of bile acid metabolism, mitochondrial function, angiogenesis, and tumor progression pathways. Despite these promising findings, current evidence remains limited to animal and *in vitro* studies, and further clinical validation is required to establish efficacy and translational relevance in humans. Future studies should also address important challenges related to safety, toxicity, pharmacokinetics, optimal dosing, bioavailability in humans, and inconsistencies in extract standardization across studies, while further elucidating the complex molecular interactions underlying the therapeutic potential of GJE in liver diseases.

Conflict of Interest

The author declares no conflicts of interest.

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