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•Review•

# Polysaccharides from Chinese herbal medicine: a review on the hepatoprotective and molecular mechanism

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**[ABSTRACT]** Polysaccharides, predominantly extracted from traditional Chinese medicinal herbs such as *Lycium barbarum*, *Angelica sinensis*, *Astragalus membranaceus*, *Dendrobium officinale*, *Ganoderma lucidum*, and *Poria cocos*, represent principal bioactive constituents extensively utilized in Chinese medicine. These compounds have demonstrated significant anti-inflammatory capabilities, especially anti-liver injury activities, while exhibiting minimal adverse effects. This review summarized recent studies to elucidate the hepatoprotective efficacy and underlying molecular mechanisms of these herbal polysaccharides. It underscored the role of these polysaccharides in regulating hepatic function, enhancing immunological responses, and improving antioxidant capacities, thus contributing to the attenuation of hepatocyte apoptosis and liver protection. Analyses of molecular pathways in these studies revealed the intricate and indispensable functions of traditional Chinese herbal polysaccharides in liver injury management. Therefore, this review provides a thorough examination of the hepatoprotective attributes and molecular mechanisms of these medicinal polysaccharides, thereby offering valuable insights for the advancement of polysaccharide-based therapeutic research and their potential clinical applications in liver disease treatment.

**[KEY WORDS]** Polysaccharides; Hepatoprotective; Chinese herbal medicine; Mechanism
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## Introduction

The liver, a pivotal organ in human physiology, is responsible for essential functions including detoxification and metabolism. It metabolizes exogenous substances, often producing toxic metabolites. Differences between the generation of these metabolites and the liver's detoxification processes can precipitate oxidative stress, inflammation, or even apoptosis within liver tissues. Numerous studies have corroborated the significant role of oxidative stress and inflammation in the etiology and progression of liver injury [1, 2]. The increasing prevalence of liver diseases is attributed to various factors, including obesity, drug misuse, excessive alcohol intake, and environmental pollution [3]. Globally, liver diseases are responsible for an estimated 2 million deaths annually [4], with about 300 million affected individuals in China [5]. Left unchecked, liver diseases may progress to chronic injury, fibrosis, and eventually liver cancer [6], highlighting the need for prevention and treatment of liver injury.

Polysaccharides, characterized as complex carbohydrates with a polymerization degree exceeding 10, linked by glycosidic bonds, are widely present in nature [7, 8]. Their structural composition and properties are influenced by the extraction methods used [9], which have evolved to include techniques such as water-boiling and alcohol precipitation, microwave-assisted, hydrolytic-enzymatic-assisted, and vacuum- or ultrasound-assisted extraction [10, 11].

Traditional Chinese herbal medicine, with its rich history extending over two millennia in China, frequently utilizes polysaccharide as principal active ingredients. These polysaccharides, sourced from a variety of herbs or different parts of the same herb, exhibit substantial variation in mono-

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saccharide composition, molecular weight, and biological functionality. However, the monosaccharide composition of these polysaccharides are relatively consistent, mainly composed of glucose, fructose, arabinose, rhamnose, fucose, mannose, xylose, galactose, and galacturonic acid [12]. Herbal polysaccharides are noted for their immunomodulatory, anti-inflammatory, and antioxidant activities, as well as their ease of extraction, low toxicity, and minimal side effects [13, 14]. Up to now, alcohol consumption, and non-alcoholic fatty liver disease (NAFLD) are considered the major causes of liver injury [15]. The incidence of liver diseases caused by various hepatotoxic substances is increasing annually and has become an important problem in modern society as well. The most common liver toxins are alcohol [16], drugs [17], and chemicals [18]. Unmanaged liver injury can escalate to fibrosis and potentially culminate in hepatic sclerosis or hepatocellular carcinoma (HCC) [6]. While existing literature predominantly addresses the mechanisms or diseases associated with polysaccharide-mediated liver protection, there is a paucity of categorized reports and systematic analyses on liver injuries instigated by different etiologies or substances. Therefore, in this paper, the protective effects of herbal polysaccharides against liver injury caused by different causes are classified into six major categories: anti-drug, anti-alcoholic, anti-non-alcoholic, anti-fibrotic combined with anti-HCC, and anti-chemical toxicant activities.

This review comprehensively examines various polysaccharides extracted from Chinese herbal medicines (Fig. 1), monitoring their anti-liver injury activities and elucidating related mechanisms based on scientific findings in recent five years. Our objective is to provide insights into the development of novel hepatoprotective drugs, promote further research into polysaccharides, and enhance the treatment of liver injury.

## Polysaccharides

### *Lycium barbarum polysaccharides (LBPs)*

*Lycium barbarum*, belonging to the Solanaceae family, is widely recognized as the “longevity fruit” and is distinguishable by its fusiform and oval shape (Fig. 1). A key bioactive constituent of this plant is LBPs, which are renowned for their extensive pharmacological properties. XU *et al.* utilized a method that was both straightforward and precise, leading to the discovery that LBPs comprise seven monosaccharides, namely galactose, arabinose, mannose, rhamnose, xylose, ribose, and glucose [19]. This revelation was supported by numerous investigations, which collectively affirm the multifaceted pharmacological impacts of LBPs, particularly its potent anti-liver injury effects.

*Anti-alcoholic liver injury activity*

Utilizing human normal hepatocytes, specifically L-02 cells, notable advancements have been observed. WEI *et al.* stimulated L-02 cells with ethanol in an *in vitro* experiment and found that LBPs mitigated oxidative stress in ethanol-stimulated L-02 cells. Concurrently, LBPs upregulated the expressions of NF-E2-related factor 2 (Nrf2) protein and its downstream proteins HO-1, NQO1, and GCLC in the nucleus [20]. Moreover, a study by WANG *et al*. further showed that LBPs restored the balance between anti-apoptotic protein B-cell lymphoma protein 2 (Bcl-2) and the pro-apoptotic protein Bcl-associated X (Bax) and inhibited the activities of cytochrome C, caspase-3, and caspase-9 in ethanol-stimulated L-02 cells [21]. LI *et al.* investigated the effects of LBPs on alcoholic fatty liver disease (AFLD) in mice. The study revealed that LBPs promoted lipid metabolism and improved the expressions of oxidative stress indicators [malondialdehyde (MDA), glutathione peroxidase (GSH-Px), and superox-

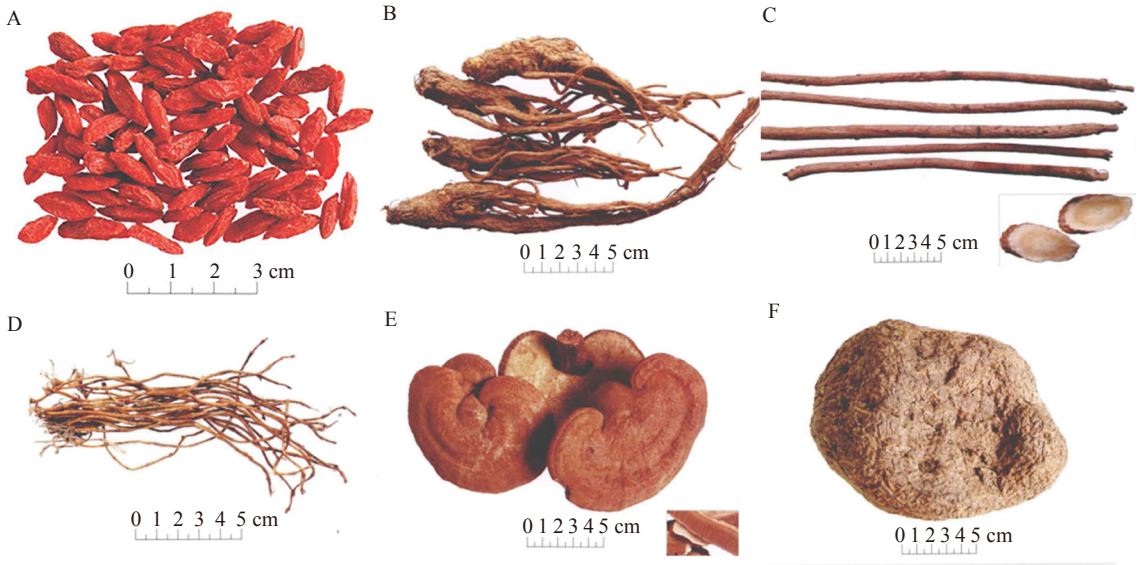


**Fig. 1 Pictures of Chinese traditional herbal medicine with anti-liver injury. (A) *Lycium barbarum*; (B) *Angelica sinensis*; (C) *Astragalus membranaceus*; (D) *Dendrobium officinale*; (E) *Ganoderma lucidum*; (F) *Poria cocos*.**

ide dismutase (SOD)] and inflammatory cytokines [tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and IL-6]. In addition, LBPs regulated liver injury-related metabolism by increasing the AMPK2 mRNA expression and decreasing SREBP-1c, CYP2E1, Toll-like receptor 4 (TLR4), and MyD88 mRNA expressions [22]. Further, WANG *et al.* identified that the expression levels of estrogen and SCD1 could affect the ameliorative effect of LBPs on alcoholic liver injury mice, suggesting that LBPs can interact with estrogen receptor Erα to activate the SCD1-AMPK-CPT signaling pathway [23]. In addition, YAN *et al.* found a synergistic effect of LBPs in combination with $ZnSO_4$ in treating AFLD. This combination was effective in alleviating AFLD by promoting lipid metabolism, reducing oxidative stress, controlling inflammatory responses, and regulating the expression and activity of alcohol-metabolizing enzymes in rats [24].

*Anti-non-alcoholic liver injury activity*

NAFLD, characterized by excessive hepatic fat deposition unrelated to alcohol consumption, can escalate to non-alcoholic steatohepatitis (NASH) under severe conditions [25, 26]. XIAO *et al.* found that LBPs significantly reduced the expression of inflammatory cytokines and alleviated liver fibrosis in NASH mice. This effect was attributed to the inhibition of the NOD-like receptor family pyrin domain containing 3/6 (NLRP-3/6) inflammasome pathway and nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB), with LBPs administration showing no detrimental effects on hepatic function in mice [27]. At the same time, it was shown that LBPs attenuated the effects of liver injury in NAFLD rats *in vivo* by modulating the indicators related to the lipopolysaccharide (LPS)/TLR4/NF-κB signaling pathway [28]. Moreover, LIU *et al.* found that LBPs also ameliorated liver and intestinal injury in mice with LPS-induced peritonitis *in vivo* [29] by regulating the polarization of macrophages and NF-κB translocation. In a clinical study, LBPs were found to lower alanine transaminase (ALT) concentrations and modulate the zonation properties of gut microbes in NAFLD patients. This is consistent with previous results in rats [28], suggesting that LBPs also exert a hepatoprotective effect by maintaining gut microbiota homeostasis [30]. Additionally, DING *et al.* reported that LBPs attenuated cyclophosphamide (CTX)-induced liver injury in mice through the modulation of the gut microbiota [31]. Collectively, LBPs not only reduce lipid accumulation and inflammatory responses in the liver but also restore the intestinal barrier by maintaining the balance of gut microbiota, thus exerting a hepatoprotective effect.

*Anti-chemical liver injury activity*

Di-(2-ethylhexyl)-phthalate (DEHP), a ubiquitous plasticizer in everyday products, poses significant hepatotoxic risks. After using DEHP to induce hepatotoxicity in rats, LIU *et al.* found that LBPs attenuated oxidative stress in rat liver and further reduced the levels of phase I detoxification enzymes (CYP450, CYP2E1, and CYP3A1) and phase II detoxification enzymes (UGT1 and GST) by downregulating the expression of PXR *in vivo*, thereby attenuating DEPH-induced liver injury [32].

*Anti-hepatic fibrosis activity*

GAN *et al.* investigated the efficacy of LBPs in counteracting carbon tetrachloride ($CCl_4$)-induced liver fibrosis in rats. The research demonstrated that LBPs could alleviate $CCl_4$-induced oxidative damage in the liver. Notably, LBPs suppressed inflammatory responses and inhibited the expression of components in the TLRs/NF-κB signaling pathway, effectively mitigating liver fibrosis in these rats [33]. Meanwhile, CHIANG *et al.* identified that LBPs inhibited caspase-9 and caspase-3 activities in the liver, which alleviated $CCl_4$-induced liver fibrosis in rats by increasing the IL-10/TNF-α ratio and decreasing the expression levels of TGF-β1 and TIMP-1 in liver tissues [34].

In addition, SUN *et al.* found that LBPs ameliorated hypercerebral injury in hepatic encephalopathy (HE) mice *in vivo* by regulating MAPK pathways in the liver and brain, and the pro-inflammatory cytokine may play an important role as communication molecules in this mechanism [35]. Innovatively, SHI *et al.* developed an LBP-based nanosheet (NS), termed L-MMT NSs. The L-MMT nanoparticles were loaded into polyvinyl alcohol (PVA) to form a P-L-MMT hydrogel, which exhibited pronounced hemostatic effects in a mouse liver hemorrhage model and reduced inflammation-induced tissue damage [36].

These studies collectively highlight the multifaceted therapeutic potential of LBPs, not only in liver injury mitigation but also in the treatment of associated diseases. The synergistic effects of LBPs with zinc sulfate ($ZnSO_4$) also suggest a new direction for developing advanced therapeutic strategies for liver diseases.

### *Angelica sinensis polysaccharides (ASPs)*

*Angelica sinensis*, a plant with both medicinal and culinary applications, belongs to the angiosperm family Umbelliferae. Distinctive for its yellowish-brown to brown hue, the plant exhibits characteristic longitudinal wrinkles and lenticel-like protrusions (Fig. 1). ASPs, one of the important bioactive components in *Angelica sinensis*, are heteropolysaccharides composed of glucose, galactose, arabinose, rhamnose, fucose, xylose, and galacturonic acid [37]. The extraction of ASPs predominantly employs hot water and ultrasonic extraction [38]. Additionally, ASPs have exhibited a range of protective effects against liver injury caused by diverse factors.

*Anti-drug liver injury activity*

ZENG *et al.* found that ASPs inhibited the downregulation of apoptosis-associated protetin Bcl-2 and the upregulation of Bax protein in mice induced by the chemotherapeutic drug 5-FU. Additionally, ASPs enhanced the activities of GSH, SOD, and catalase (CAT) in mice, thereby effectively

reducing oxidative stress and lipid metabolism disturbances in the liver caused by 5-FU *via* regulating the Nrf2/Kelch-like ECH-associated protein 1 (keap1) signaling pathway [39]. LI *et al.* further explored the impact of ASPs on hepatotoxicity induced by the anticancer drug Diosbulbin-B (DB). Their findings indicated that ASPs attenuated DB-induced hepatocyte toxicity by upregulating the expressions of Cyclin D1 and CDK2, increasing the intracellular LC3B-II/I ratio and Atg5 content, and decreasing the P62 protein expression. These effects suggest that ASPs mediate autophagy through the activation of the MEK/ERK pathway, contributing to the mitigation of DB-induced hepatotoxicity [40]. Moreover, excessive intake of acetaminophen (APAP), also known as paracetamol, can cause severe liver injury [41]. CAO *et al.* discovered that ASPs ameliorated APAP-induced hepatocyte degeneration and cytoplasmic vacuolization in rats by reducing the expressions of cleaved caspase-3 and Bax and increased the level of Bcl-2 [42].

*Anti-alcoholic liver injury activity*

HE *et al.* developed an AFLD model to assess the impact of ASPs on liver lipid metabolism. They found that ASPs reduced the levels of ACC and FAS in the live, thereby inhibiting lipid synthesis. Moreover, ASPs restored the levels of AMPK-SIRT1 and CD36 to normal, which reversed the ethanol metabolic pathway from CYP2E1 catalysis to ADH catalysis, thus promoting alcohol metabolism [43]. In addition, ASPs can be used as a liver-targeting drug delivery carrier. WANG *et al.* synthesized ASP-chemotherapeutic enzyme microsphere system (CHEMS) conjugates *via* an esterification reaction and prepared ASP-CHEMS self-assembled nanoparticles (ACNPs) and curcumin-loaded ACNPs (CuR/ACNPs) in an aqueous solution. Their research indicated that Cur/ACNPs alleviate oxidative stress, thus providing protection against alcohol-induced liver injury in mice [44].

*Anti-non-alcoholic liver injury activity*

Patients with diabetes frequently experience significant liver complications, including prevalent fatty liver disease. Recent investigations have revealed the efficacy of ASPs in alleviating diabetes-induced hepatic steatosis and liver injury. ZHANG *et al.*'s study on type 2 diabetes mellitus (T2DM) mice unveiled that ASPs significantly improved liver conditions, such as steatosis, cytoplasmic vacuolization, and necrosis, while increasing hepatic glycogen content and decreasing collagen deposition in the liver of T2DM mice [45]. Furthermore, LIU *et al.* isolated a novel homogeneous polysaccharide, APS-1I, from *Angelica sinensis*, and the findings indicated significant amelioration of liver injury and hepatic steatosis, downregulated RAGE expression in HepG2 cells, and inhibited JNK and P38 activation, thereby reducing insulin resistance in a diabetic model rat [46].

*Anti-hepatic fibrosis activity*

WANG *et al.* investigated the therapeutic potential of ASPs in mitigating liver fibrosis. Their research showed that ASPs markedly elevated the IL-22 level in liver tissues. This elevation of IL-22 was associated with the activation of the STAT3 signaling pathway in the liver, which led to the inhibition of hepatic stellate cell (HSC) activation, thus effectively alleviating $CCl_4$-induced chronic liver fibrosis in mice [47].

*Anti-HCC activity*

LIU *et al.* synthesized an angelica polysaccharide-based nanocarrier, which exhibited superior biocompatibility and liver-specific targeting properties, paving the way for synergistic anti-tumor therapies, particularly those inducing ferroptosis [48]. Furthermore, ZHANG *et al.* prepared an amphiphilic conjugate (ASP-DOCA) by the hydrophobic modification of ASPs. This novel conjugate emerged as a promising candidate for liver cancer-targeted drug delivery systems [49].

Beyond its direct therapeutic roles, ASPs have been found to play a critical role in iron metabolism. WANG *et al.* conducted a study examining the impact of ASPs on the hepatic expression of hepcidin, a key regulator of iron homeostasis. They reported that ASPs reduced the hepatic levels of p-STAT3 and p-SMAD1/5/8 by upregulating the expression of iron transporter protein (ferroprotein), leading to an increased iron efflux from the liver to plasma and thus inhibiting the expression of hepcidin in the liver [50].

Therefore, the diverse functionalities of ASPs in the treatment of liver injuries and associated pathologies make it an important focus for future pharmacological research and development.

*Astragalus membranaceus polysaccharides (APSs)*

As shown in Fig. 1, the traditional Chinese herb *Astragalus membranaceus* has been utilized for the treatment of various diseases for centuries. APSs, the predominant and immunologically active in *Astragalus*, are mainly composed of glucose, accompanied by rhamnose, galactose, arabinose, xylose, mannose, glucuronide, and galacturonic acid [51]. APSs are renowned for its pharmacological properties, such as immunomodulatory, anti-inflammatory, and antioxidant effects [52]. Its efficacy in preventing and treating liver injury is multi-dimensional, mainly including the following aspects.

*Anti-drug liver injury activity*

Tilmicosin (TIL), a macrolide antibiotic that is mainly used to treat infectious diseases and has potent immunomodulatory effects [53, 54]. Farage *et al.* investigated the hepatotoxicity of TIL in rats and found that TIL upregulated hepatic heat shock protein 70 (HSP70) mRNA expression and blocked Nrf2/HO-1-mediated responses. Contrastingly, APSs alleviated the hepatotoxic effects induced by TIL [55]. Meanwhile, previous studies have shown that cantharidin (CTD) can be used as an anticancer drug for the treatment of various cancers with significant effects, but CTD has strong toxic side effects, and its use is often restricted [56]. HUANG *et al.* found that APSs can reduce liver injury caused by CTD *via* regulating primary bile acid biosynthesis and glycerophospholipid metabolism in mice [57]. This provides a basis for the

use and development of clinical drugs.

*Anti-alcoholic liver injury activity*

ZHOU *et al.* demonstrated APS's capability to attenuate lipid accumulation, inflammation, and liver fibrosis in the liver and regulate gut flora disorders by inhibiting the keap1/NRF2 pathway and TLR4/MyD88/NF-κB pathway [58].

*Anti-hepatic fibrosis activity*

Hamid *et al*. enhanced APS's efficacy through selenization, finding that selenized APS (sAPS) surpassed APSs in counteracting hepatic oxidative stress, inflammation, and fibrosis. sAPS effectively induced apoptosis and cell cycle arrest in HSC and mitigated $CCl_4$-induced liver injury by inactivating Kupffer cells [59, 60].

*Anti-HCC activity*

APSs could inhibit the expression of Notch1 in H22 cells and promote apoptosis in HCC cells by regulating the expression of apoptosis-related genes (*Bcl-2* and *Bax*) and proteases (caspase-3 and caspase-8) [61]. LAI *et al.* further discovered that APSs inhibited the growth of H22 cells and promoted the production of IL-2, IL-6, and TNF-α in the serum of H22 tumor-bearing mice, thus enhancing the anti-tumor activity of the mice [62].

In addition, YAO *et al.* investigated the potential protective effects of APSs against hydrogen peroxide ($H_2O_2$)-induced hepatocyte senescence and found that APSs reduced the expression of senescence markers in mouse hepatocytes, inhibit oxidative stress and apoptosis in mice, maintain the dynamic homeostasis of mitochondria, and promote mitosis through the AMPK/mTOR pathway, thereby delaying hepatocyte senescence [63]. Thus, APSs could be developed as a potential drug for the treatment of liver injury.

*Dendrobium officinale polysaccharides (DOPs)*

*Dendrobium officinale*, a precious traditional Chinese medicinal herb, is often used in the treatment of hepatitis, diabetes, obesity, and rheumatoid arthritis [64]. This herb, notable for its spiral or spring-like appearance and yellowish-green to golden yellow coloration (Fig. 1), primarily comprises polysaccharides, flavonoids, alkaloids, amino acids, and other components [65]. Among these chemical components, DOPs are the focal bioactive components that have attracted much attention in recent years. Recent extraction techniques, particularly the freeze-thawing cold-pressing (FTCP) method, have proved efficacious in isolating DOPs, predominantly constituted of mannose and glucosed [66, 67]. In recent years, several studies on the preventive and curative effects of DOPs on liver injury have been conducted, which confirmed the hepatoprotective activity of DOPs, and its anti-liver injury effects are mainly reflected in the following aspects.

*Anti-drug liver injury activity*

In a case of APAP-induced liver injury, LIN *et al.* found that DOPs significantly ameliorated hepatic necrosis and focal intrahepatic hemorrhage. Notably, DOPs significantly upregulated GSH, CAT, and total antioxidant capacity (T-AOC) levels while downregulating reactive oxygen species (ROS) and MDA levels. These hepatoprotective effects are attributed to the activation of the Nrf2-keap1 pathway, contributing to the mitigation of oxidative stress compared with the APAP group [68].

*Anti-alcoholic liver injury activity*

It has been shown that alcohol-induced liver injury is characterized by a strong inflammatory response. YANG *et al.* firstly reported that DOPs may exert significant hepatoprotective effects by effectively reducing the expression of inflammatory cytokines and inhibiting the TLR4/NF-κB/NLRP3 signaling pathway [69]. Meanwhile, DOPs has been shown to preserve the relative balance of GSH and protect the liver of mice with acute alcoholic liver injury by enhancing the antioxidant system, which could be dynamically assessed by the near-infrared (NIR) fluorescence imaging technique [70].

*Anti-non-alcoholic liver injury activity*

It has been well established that NAFLD is closely related to T2DM and that there is a synergistic effect between the siblings [71]. YANG *et al.* reported that there was significant lipid accumulation in the liver tissue of T2DM rats, and the level of bile acids was significantly increased. Further studies demonstrated that DOPs treatment reduced the level of bile acids and decreased the area of oil red O staining, which markedly alleviated the disorder of liver metabolism in rats [72]. Moreover, DOPs significantly suppressed the glucagon-mediated cAMP-PKA and Akt/Fox O1 signaling pathways, catalyzing hepatic glycogen metabolism [73].

*Anti-hepatic fibrosis activity*

Liver fibrosis, characterized by inflammation-induced HSC activation and proliferation, is one of the common causes of liver dysfunction [74]. WANG *et al.* found that DOPs were able to reduce inflammatory factors by inhibiting the LPS/TLR4/NF-κB signaling pathway and significantly decreased the expressions of *α*-smooth muscle actin (*α*-SMA) and collagen I. Furthermore, DOPs upregulated tight junction protein levels while downregulating Bax and caspase-3 protein levels in the intestine, thereby preserving intestinal mucosal barrier function and alleviating $CCl_4$-induced liver fibrosis [75].

*Anti-HCC activity*

HCC is a high-mortality primary liver cancer that develops from steatosis [76]. In recent years, many polysaccharides have exhibited anti-HCC activity. XING *et al.* further isolated four new polysaccharide fractions (DOP-40, DOP-50, DOP-60, and DOP-70) from DOPs by fractional precipitation using the ethanol method demonstrating significant cytotoxicity against HepG2 cells [77].

In addition, DOPs also exhibit efficacy in secondary liver injury associated with inflammatory bowel disease (IBD) that can further aggravate and develop into chronic liver disease. LIANG *et al.* found that DOPs reversed the expression levels of inflammatory cytokines and reduced macrophage in-

filtration in liver tissues in a colitis model [78]. Additionally, DOPs regulated the TNF-/Nrf-2 signaling pathway to protect liver tissues against inflammation and oxidative stress induced by dextran sodium sulfate [79]. ZHU *et al.* found that in a mouse D-galactose (D-Gal)-induced aging model, DOPs treated with 50 $w \cdot cm^{-2}$ ultrasound exhibited strong antioxidant activity *in vitro*, reduced the expression of pro-inflammatory cytokines, and ameliorated liver injury by activating the Nrf2/HO-1/NQO1 signaling pathway [80].

Therefore, the multifaceted hepatoprotective activities of DOPs underscore its potential as an effective therapeutic agent for liver injury.

*Ganoderma lucidum polysaccharides (GLPs)*

*Ganoderma lucidum*, commonly known as the "plant of immortality" or Ling-Zhi in traditional Chinese medicine, is highly regarded in Eastern medicinal practices for its capacity to enhance human vitality, promote longevity, and treat various human diseases. The fruiting bodies of *Ganoderma lucidum*, referred to as cysts, are distinguished by their unique morphology, featuring an umbrella-like shape with a hard, corky cap. These caps initially exhibit a shell-yellow color, which gradually deepens into a red-brown hue, and are characterized by a subtly glossy surface (Fig. 1). The extensive historical application of *Ganoderma lucidum* in Asian countries, predominantly for its benefits in health promotion and life extension, is thoroughly documented [81]. GLPs are major bioactive constituents of this mushroom, noted for their immunomodulatory, anti-inflammatory, antioxidant, and antitumor activities [82]. Comprising a stable monosaccharide composition predominantly of D-glucose, D-fructose, D-galactose, D-mannose, D-xylose, L-amylose, L-rhamnose, and L-arabinose, albeit with varying molar ratios [83], GLP's hepatoprotective activities have attracted considerable research interest, particularly in the following areas.

*Anti-nonalcoholic liver injury activity*

Chronic high-fat diet (HFD) consumption induces T2DM and hepatic steatosis in mice [84]. LIANG *et al*. [85] demonstrated that GLPs can reduce the hepatic adipose tissue index in HFD mice. Synthesized GLP-chromium (III) complexes (GLP-Cr) inhibited the accumulation of excessive free fatty acids in the liver [86]. Furthermore, PAN *et al.* revealed that GLPs ameliorated hepatic steatosis in T2DM mice, potentially regulating lipid metabolism disorders in T2DM mice *via* the FAM3C-HSF1-CaM signaling pathway [87]. Meanwhile, some studies indicated that GLPs significantly improved hepatic lipid accumulation and activated the Nrf2/HO-1 signaling pathway thus protecting mice against T2DM-induced hepatic steatosis, oxidative stress, and inflammation [88]. In addition, XU *et al.* obtained ultrasonically degraded GLP (UG) with enhanced antioxidant activity than GLPs, which can reduce the levels of MDA and GSH-Px in serum and increase the SOD activity, thus improving lipid metabolism disorder in the mouse liver [89].

*Anti-chemical liver injury activity*

GLPs demonstrated efficacy in ameliorating $CCl_4$-induced histopathological changes in the liver, decreasing the serum levels of ALT, AST, and MDA, and increasing the serum levels of SOD and CAT in mice [90]. In $CCl_4$- and galactosamine-induced rat hepatocytes, GLPs reduced their GPT values, signifying its essential hepatoprotective role through anti-lipid peroxidation and oxygen radical scavenging activities [91]. GLPS also elevated GSH levels in mouse liver tissues and decreased the serum levels of CYP2E1, NOS, and inflammatory cotyokeins (IL-1β, IL-18, IL-6, and TNF-α), thereby attenuating $CCl_4$-induced liver injury by diminishing NLRP3 activity [92, 93].

*Anti-hepatic fibrosis activity*

The formation of liver fibrosis requires the stimulation and proliferation of HSCs, together with the accumulation of extracellular matrix (ECM), along with the production of α-SMA and type I collagen [94]. CHEN *et al.* found that GLPs significantly mitigated fibrosis and inflammation in a $CCl_4$-induced mouse model *via* the TLR4/NF-κB/MyD88 signaling pathway. In addition, GLPs notably inhibited TGF-β1-induced HSC-T6 cell activation, reducing the expressions of collagen I and α-SMA [95].

*Anti-HCC activity*

YU *et al*. observed that GLPs inhibited the activity of DNA repair-associated proteins in HepG2 cells under radiation conditions and enhanced the radiosensitivity of HCC cells by regulating the Akt signaling pathway [96]. *In vivo* studies have demonstrated that photothermal therapy (PTT) is effective in inducing tumor necrosis in mice with H22 tumors. Additionally, the immunomodulatory, anti-proliferative, pro-apoptotic, and anti-angiogenic properties of GLPs could enhance the distal anticancer impact of PTT in mice with hepatoma [97].

Moreover, the liver is one of the most commonly affected organs in multiple organ dysfunction syndromes (MODS). ZHANG *et al.* [98] conducted research revealing that GLPs enahnced the antioxidant capabilities and reduced the level of inflammatory cytokines in the liver of mice subjected to a MODS model. Complementing this finding, CHEN *et al.* isolated and purified the polysaccharides GLPB2 and GLPC2 from GLPs. Their study indicated that these polysaccharides could alleviate restraint stress by attenuating oxidative stress-induced liver injury in mice [99].

Collectively, these studies underscore the potential of GLPs as a therapeutic agent for various forms of liver injury, suggesting its potential as an effective treatment method in the future.

*Poria cocos polysaccharides (PCPs)*

*Poria cocos*, a renowned traditional East-Asian medicinal fungus, has its epidermis (Fu-Ling in Chinese) utilized as a diuretic. Classified under Basidiomycota and Agaricomycetes, *Poria cocos* exhibits a white, downy mycelium with a pale brown or dark brown epidermis. The sclerotium is tuber-shaped, featuring a granular interior composed of dense mycelium layers Fig. 1. PCPs, constituting different types of polysaccharides, consisted of glucose, fucose, arabinose, xyl-

ose, mannose, and galactose, accounting for 84% of the dry weight of the sclerotium [100, 101]. PCPs have been recognized for their wide-ranging pharmacological effects, including antioxidant, anti-apoptotic, immunomodulatory, and anti-cancer properties [102]. In recent years, there is increasing evidence that PCPs have the hepatoprotective activity against liver injury, which is mainly reflected in the following aspects.

*Anti-drug liver injury activity*

WU *et al.* found that PCPs ameliorated APAP-induced inflammatory infiltration and cell death in mouse liver tissues. This protective effect was evidenced by an increased count of AKR7A, c-Jun, and Bcl-2-labeled positive cells, alongside a reduction in the number of Bax-labeled cells in the liver. Additionally, PCPs also downregulated the expression of NF-κB p65 and IκB-α in hepatocytes [103]. Their study further revealed that PCPs reduced the number of cleaved-caspase-3, cleaved-PARP, and Hsp90-labeled positive cells in the liver. *In vitro*, PCPs promoted AML12 cell growth, increased the number of proliferating cell nuclear antigens (PCNA)- and P38 mitogen-activated protein kinase (MAPK)-labeled positive cells. In addition, PCPs inhibited the biological activity of HSP90 [104].

*Anti-alcoholic liver injury activity*

JIANG *et al.* established that PCPs ameliorated histopathological liver injury in an ALD mouse model. This effect was accompanied by a notable reduction in the number of liver macrophages. Furthermore, PCPs were observed to attenuate oxidative stress and inflammatory damage in mice by regulating the expression of CYP2E1 and inhibiting the expression of TLR4/NF-κB pathway-related proteins [105]. Meanwhile, PCP-1C, a purified derivative of PCPs, exhibited a potent anti-inflammatory effect in ALD mice by inhibiting the TLR4/NF-κB signaling pathway. In addition, PCP-1C reduced serum biochemical parameters, ameliorated liver steatosis in mice, and improved hepatocyte apoptosis through the CYP2E1/ROS/MAPK signaling pathway [106].

*Anti-nonalcoholic liver injury activity*

NAFLD is associated with gut microbiota-induced inflammation, and protecting the integrity of the intestinal barrier can mitigate the progression of NAFLD. It has been shown that PCPs can enhance the immunomodulatory effects of macrophages [107]. YE *et al.* reported that PCPs alleviated hepatic steatosis in mice and reduced the HFD-induced disruption of the gut-vascular barrier and translocation of endotoxins. Additionally, PCPs regulated PARP-1 to suppress the pyrogenesis of small intestinal macrophages, thereby maintaining the integrity of the intestinal barrier in response to an HFD challenge [108]. Furthermore, PCPs alleviated lipid metabolism in NAFLD mice through the metabolic pathways of fatty acid metabolism, bile acid metabolism, and tricarboxylic acid cycle [109]. This finding broadens the understanding of PCP's mechanistic action against NAFLD, although the specific role of macrophages in this disease context warrants further investigation. In a related study, TAN *et al*. investigated the role of PCPs in NASH mice. Their findings revealed that PCPs regulated the intestinal microbiota and downregulated the expression of related factors in the NF-κB/CCL3/CCR1 axis, which attenuated liver injury in NASH mice [110].

*Anti-HCC activity*

QIN *et al.* identified PCPs as potential inhibitors of ALB and VEGFA proteins in HepG2 cells. Molecular docking analysis highlighted these proteins as effective pharmacological targets of PCPs. Moreover, the study identified a range of critical PCPs targets in HCC cells, including ALB, VEGFA, TNF, CASP3, SRC, EGF, CXCR4, STAT3, HRAS, HSP90AA1, MMP9, BCL2L1, FGF2, and PTPRC [111].

In addition, in $CCl_4$-induced liver injury, CHENG *et al.* found that PCP-1C reduced the expressions of CAR and CYP2E1 in liver tissues and attenuated oxidative stress and inflammatory responses in mice [112].

These studies collectively highlight the therapeutic potential of PCPs in protecting against liver injury caused by various factors, which provides a new direction for the development of anti-liver disease drugs in the future.

*Other polysaccharides of Chinese traditional herbal medicine*

In addition to the aforementioned polysaccharides, numerous other polysaccharides derived from traditional Chinese herbal medicine exhibit hepatoprotective properties. These are collated in Supporting Information Table S1, summarizing research conducted over the past five years.

## Future Perspective

Multiple liver injury diseases, involving complex pathways such as inflammation, oxidative stress, and apoptosis, have garnered widespread attention. At present, there is an urgent need for effective hepatoprotective therapies. The biological activity of polysaccharides derived from traditional Chinese herbal medicine is closely related to their chemical structures. In recent years, these herbal polysaccharides, known for their low toxicity and significant biological activity, have increasingly become a focal point of research. Demonstrating hepatoprotective activity both *in vitro* and *in vivo*, they are emerging as a promising avenue for treating liver diseases. Traditional Chinese herbal polysaccharides can mitigate hepatocyte apoptosis by affecting liver function, regulating immunity and enhancing antioxidant capacity, thereby contributing to liver protection. As depicted in Fig. 2, we summarized the relevant pathway mechanisms, underscoring the complex role and indispensable role of these polysaccharides in addressing liver injury.

Although traditional Chinese herbal polysaccharides have shown promising therapeutic effects on various liver injuries, research on their molecular mechanisms requires further development. Nowadays, most structural analyses of these polysaccharides focus primarily on their basic chemical structure, with the fine structure still needing exploration. A comprehensive understanding of the structure-activity of polysaccharides is crucial for grasping their anti-liver injury efects, highlighting the importance of advanced structural

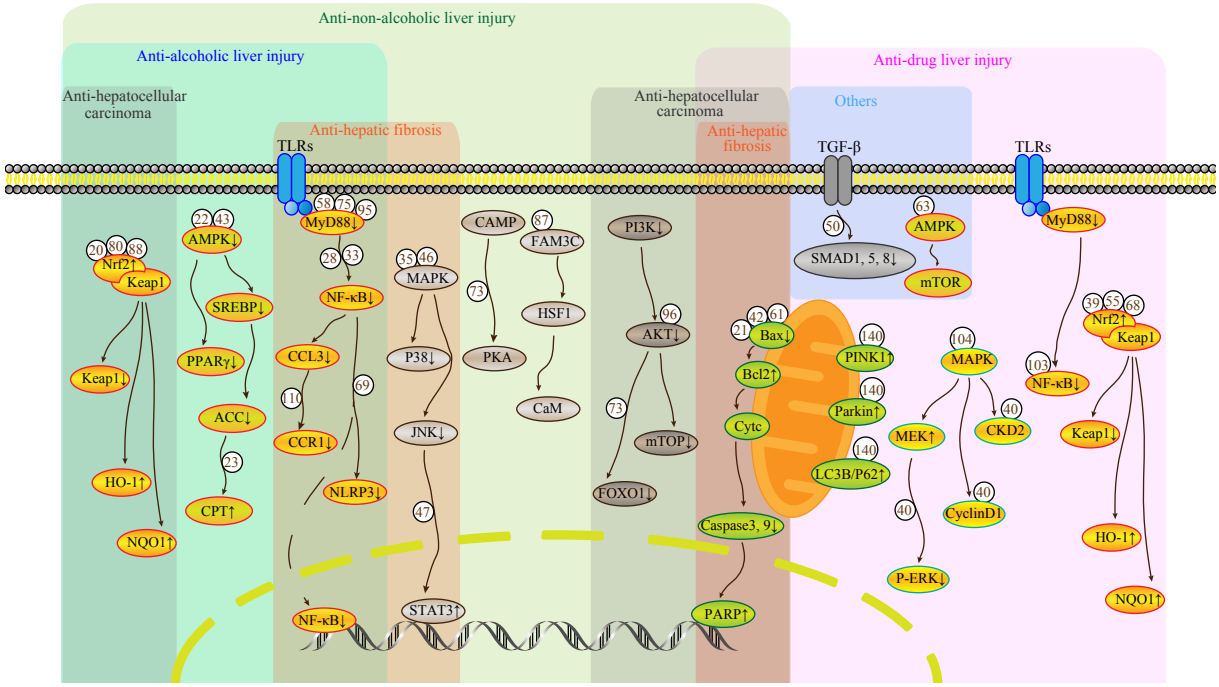


**Fig. 2 Schematic illustration of polysaccharides in liver injury and potential molecular targets. The references number indicates the potential target of polysaccharides.**

analysis techniques. Furthermore, although there are numerous methods for preparing polysaccharides in traditional Chinese medicine, the yield from many extraction processes remains low. Most studies on liver injury use only crude polysaccharides, so refining extraction and purification methods is essential. In addition, chemical modification methods like phosphorylation and selenization can enhance the biological activity of these polysaccharides, yet research in this area is limited and presents another potential research focus. Clinical research on the hepatoprotective activity of herbal polysaccharides also warrants more attention. While current experiments primarily use cell and animal models, the effects on humans may differ. Several studies have indicated that herbal polysaccharides can reduce drug-induced hepatotoxicity. However, it is crucial to investigate any potential toxic side effects of the polysaccharides themselves. Therefore, future research should not only seek robust evidence supporting the efficacy and safety of traditional Chinese herbal polysaccharides in clinical applications but also delve deeper into their mechanisms and clinical applications, incorporating advanced technologies. This approach will ensure safer and more effective application in treating various types of liver injury in patients.

## Supporting Information

Supporting information of this paper can be requested by sending E-mails to the corresponding authors.

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