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Schisandra chinensis in Liver Disease: Exploring the Mechanisms and Therapeutic Promise of an Ancient Chinese Botanical

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Abstract

Background: *Schisandra chinensis* is a traditional Chinese herbal medicine that has been used for centuries for liver health. The active lignans in *Schisandra*, including schisandrin and gomisins, have exhibited anti-inflammatory, antioxidant, and hepatoprotective properties in preliminary studies. With rising rates of chronic liver diseases globally, there is interest in the potential therapeutic role of *Schisandra*.

Purpose: To comprehensively review the current evidence for *Schisandra chinensis* in treating liver injury and disease and synthesize implications for future human research.

Main body: *Schisandra* extracts decreased inflammatory cytokines and oxidative stress markers and increased endogenous antioxidant activity in animal models, suggesting utility in mitigating liver inflammation and damage. Additional preclinical studies demonstrated attenuated liver enzyme levels, necrosis, and fibrosis progression in chemical-induced hepatotoxicity with *Schisandra* treatment. Enhanced cytochrome P450 activity, glutathione production, and glycogen synthesis were also observed, improving detoxification and regeneration capacity. Small human trials in hepatitis and nonalcoholic fatty liver disease showed improved liver enzymes and symptoms with *Schisandra* supplementation but were limited in quality and sample size.

Conclusion: *Schisandra chinensis* has biologically relevant mechanisms that warrant further human research on its role as a hepatoprotective phytotherapy. Well-designed, large-scale clinical trials are needed to establish efficacy and safety for liver disease applications.

Keywords: *Schisandra chinensis*, Hepatoprotective effects, Liver injury, Liver fibrosis, Oxidative stress, Detoxification, Inflammation

Background

Schisandra chinensis, also known as five-flavor-fruit, is a deciduous woody vine native to northern China and parts of Russia. Fruits from this plant have been used in traditional Chinese medicine for centuries and more recently have been investigated for modern therapeutic applications [1]. The fruit contains over 30 lignans, along with polysaccharides, essential oils, and organic acids. Key bioactive lignans include schisandrin, schisantherin, and gomisins, which have shown anti-inflammatory, antioxidant, and hepatoprotective effects in research studies as depicted in **Table 1**. *Schisandra* fruit is typically prepared as a dried extract powder from the whole fruit [2].

Liver disease remains a major public health concern globally accounting for over 2 million deaths per year. Chronic liver diseases like viral hepatitis, non-alcoholic fatty liver disease,

Table 1. Key Lignans in *Schisandra Chinensis* and Hepatoprotective Mechanisms.

Lignan	Sources	Mechanisms	Effects
Schisandrin	Fruits, stems, leaves	Antioxidant - Anti-inflammatory - Enhances glutathione	Protects liver cells - Reduces liver enzymes - Enhances detoxification
Gomisin A	Fruits, stems	Anti-inflammatory -Antifibrotic	Reduces inflammatory cytokines -Inhibits hepatic stellate cell activation
Deoxyschisandrin	Fruits	Induces cytochrome P450 -Antioxidant	Enhances toxin clearance -Reduces oxidative injury
Schisantherin A	Seeds, fruits	Antioxidant -Stimulates regeneration	Scavenges free radicals - Increases glycogen synthesis

and cirrhosis are increasing, driven by risk factors such as infections, alcohol, obesity, and diabetes. Many patients use complementary medicines like botanical supplements for liver health [3-10]. *Schisandra chinensis* is an important herb in traditional Chinese medicine used for enhancing food flavor and nutrition as well as promoting health. Dried fruits and extracts have shown diverse therapeutic effects in treating cardiovascular, neurological, gastrointestinal, and metabolic disorders. Major active components include dibenzocyclooctadiene lignans such as schisandrin, the most abundant lignan representing 2.2-5.3 mg/g dry weight of fruits [11]. Additionally, *S. chinensis* contains approximately 1.5% sugars like glucose, fructose, galactose, and arabinose; two classes of tannins - hydrolyzable (gallic acid esters) and condensed (proanthocyanidins, catechols); anthocyanin pigments; about 3% essential oils with 75% comprised of sesquiterpenes including α-bergamotene, β-chamigrene and 5% oxygenated mono/sesquiterpenes. Other bioactive compounds consist of triterpenoids like cycloartanes, organic acids (citric, malic acids), phenolic acids (chlorogenic, p-coumaric acids), flavonoids such as quercetin and rutin, vitamins C and E, phytosterols and minerals chromium, copper, calcium, manganese, and zinc as depicted in **Figure 1** [12].

The combination of lignans, triterpenoids, flavonoids and other anti-inflammatory, antioxidant constituents contribute to diverse pharmacological activities. Lignan dibenzocyclooctadienes likely underlie effects on fatigue, mitochondrial function, metabolic disorders. Essential oils may support gastrointestinal and cardiovascular benefits. Phenolic acids, flavonoids and vitamins elicit antioxidant, anti-inflammatory, anti-microbial actions. Minerals and phytosterols provide nutritional value. Thus *S. chinensis* is a valuable medicinal food with chemical complexity underlying its ethnopharmacology [13,14]. *Schisandra chinensis* has historically been used as a tonic in traditional Chinese medicine to help treat liver and kidney disease. Increasing modern research shows *Schisandra* extracts may help protect liver cells from injury and inflammation, enhance detoxification capacity, improve tissue regeneration, and slow progression of fibrosis. These beneficial mechanisms make *Schisandra chinensis* a promising herbal medicine for further research on chronic liver therapies [15].

Anti-Inflammatory and Antioxidant Effects

Schisandra chinensis has demonstrated anti-inflammatory

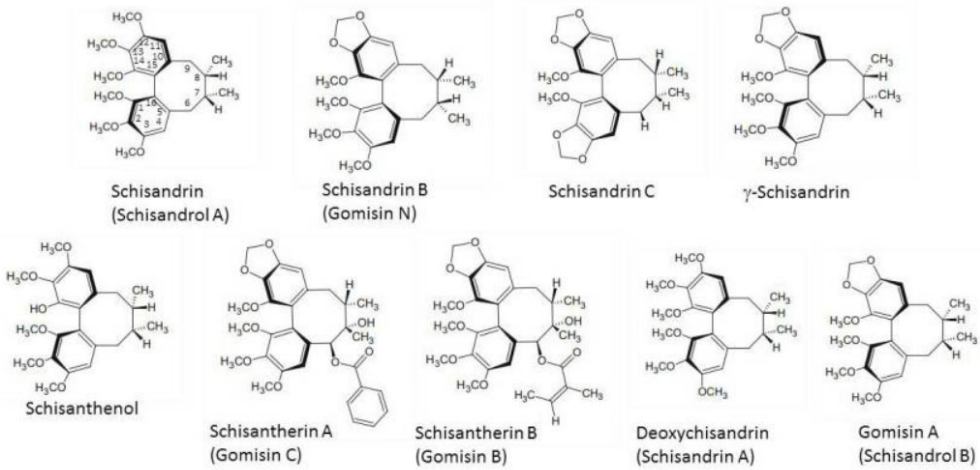

Figure 1. Bioactive Compounds in *Schisandra chinensis* and Associated Health Benefits [12].

and antioxidant properties in preclinical studies that suggest it may help reduce liver inflammation and damage [16]. Several animal studies have shown that *Schisandra* extracts can significantly decrease levels of inflammatory cytokines such as TNF-α, IL-1β, and IL-6 in models of chemically-induced liver injury. Additionally, *Schisandra* treatment attenuated inflammatory cell infiltration and necrosis in liver tissues compared to control groups. The anti-inflammatory effects are thought to be mediated in part by inhibition of NF-κB and MAPK inflammatory signaling pathways [17]. *Schisandra* has also exhibited antioxidant activity by enhancing levels of glutathione, superoxide dismutase, catalase, and other endogenous antioxidant enzymes. Oxidative stress markers like malondialdehyde and reactive oxygen species are reduced in liver cells and tissues treated with *Schisandra* extracts *in vitro* and *in vivo* [18]. The combination of anti-inflammatory and antioxidant effects demonstrated in preclinical *Schisandra* studies suggest it may be able to mitigate excessive inflammation and oxidative damage that contributes to pathogenesis of many liver diseases. By attenuating these processes, *Schisandra* has the potential to reduce hepatocyte injury, necrosis, fibrosis, and other harmful outcomes of uncontrolled inflammation and oxidative stress [19]. The biologically relevant mechanisms underlying the hepatoprotective potential of *Schisandra chinensis* may involve the regulation of the anti-aging gene Sirtuin 1 (SIRT1), which is critical for liver function and regeneration. SIRT1 repression has been implicated in the development of liver diseases, including non-alcoholic fatty liver disease (NAFLD) [20,21]. *Schisandra chinensis* contains potential SIRT1 activators, such as quercetin and rutin, which could activate SIRT1 in the liver, leading to the reversal of liver disease and promoting liver regeneration [22]. This mechanism warrants further investigation to elucidate the therapeutic potential of *Schisandra chinensis* in the context of liver diseases.

Effects on Liver Injury and Fibrosis

Several animal studies have demonstrated that *Schisandra chinensis* extracts can protect against chemically-induced liver injury. In mice with liver injury caused by carbon tetrachloride, *Schisandra* treatment significantly reduced serum aminotransferase levels and decreased hepatocyte necrosis compared to control groups. Additional studies using acetaminophen, alcohol, and other chemical toxins have shown similar hepatoprotective effects, with reduced markers of liver damage with *Schisandra* supplementation [23-27].

Research also indicates *Schisandra* can inhibit processes involved in liver fibrosis. By downregulating TGF-β1 signaling, *Schisandra* extracts suppressed activation of hepatic stellate cells which produce excess collagen during liver fibrosis. *Schisandra* treatment also decreased collagen fiber deposition in rat models of liver fibrosis compared to controls [28-34].

Effects on Liver Detoxification and Regeneration

Schisandra chinensis appears to enhance liver detoxification capacity and support tissue regeneration through several mechanisms. Multiple *in vitro* and animal studies have shown that *Schisandra* extracts and isolated lignans can induce activity of cytochrome P450 liver enzymes including CYP3A and CYP2E1. By modulating xenobiotic-metabolizing enzymes, *Schisandra* may improve hepatic clearance of toxins and drugs [35]. Additionally, Schisandra treatment has been found to increase levels of reduced glutathione and stimulate glutathione synthesis in hepatocytes. As the major intracellular antioxidant, enhanced glutathione status promotes liver detoxification of free radicals and reactive metabolites [36-41].

Schisandra supplementation in rodent models of liver injury has also improved markers of tissue regeneration like hepatic glycogen levels. The extracts appear to stimulate glycogen synthesis and storage, providing energy for liver regeneration. Enhanced cytokine production and protein synthesis also contribute to the hepatoprotective regenerative effects. **Table 2** explores the considerations around incorporating *Schisandra chinensis* into over-the-counter liver health supplements given rising consumer demand - highlighting formulation and regulation challenges but also potential patient access benefits [42-44].

Human Studies on Hepatic Effects

A limited number of human clinical trials have examined the effects of *Schisandra chinensis* on liver function and disease progression, with modest evidence for hepatoprotective effects. **Table 3** provides a framework for designing future clinical trials to rigorously evaluate the potential therapeutic efficacy of *Schisandra chinensis* preparations in improving

Table 2. Implications for Inclusion in Liver Health Supplements.

Formulation Considerations	Rationale
Standardized lignan content	Ensure batch-to-batch consistency; validate biological activity
Enhanced bioavailability	Optimize absorption; consider phytosomes, lipid-bound compounds
Synergistic ingredients	Milk thistle, astragalus, turmeric may amplify effects
Optimal dosing	Balance efficacy and safety; dosing studies still needed
Consumer education	Manage expectations; caution as unproven therapy

Table 3. Clinical Endpoints for Future Human Trials of Schisandra in Liver Disease.

Disease Stage	Primary Endpoints	Secondary Endpoints
Early disease	Histological changes - Disease progression rates	Symptoms - Quality of life
Compensated cirrhosis	Decompensation rates - Transplant-free survival	Hospitalizations - Liver cancer incidence
Decompensated cirrhosis	Transplant-free survival - Overall survival	Complications - Hospitalizations

clinically meaningful endpoints for progressive liver diseases. Outlining key endpoints, inclusion criteria, and analytical considerations will help translate the preclinical promise of *Schisandra* into high-quality human research on patient-centered outcomes [45,46].

In patients with hepatitis B, *Schisandra* treatment for 6-12 weeks reduced liver enzyme levels and improved some symptoms compared to baseline or control groups. However, most studies were of low quality with small sample sizes. Similar liver enzymes and symptom improvement has been shown in trials on *Schisandra* supplementation in hepatitis C [47]. In individuals with nonalcoholic fatty liver disease, one study found *Schisandra* extract for 6 months significantly decreased ALT and AST levels while also improving quality of life indicators. However, the trial lacked a control group for comparison. Most studies demonstrate a reasonable safety profile and minimal adverse effects, though some interactions have been noted with anti-coagulant, anti-diabetic, and CYP3A4-metabolized medications [48-54].

Several *in vitro* studies examined the effects of *Schisandra* extracts and isolated lignans like schisandrin on hepatocyte and stellate cell cultures. The extracts inhibited inflammatory signaling pathways like NF-κB and MAPK, reducing cytokine release. Antioxidant effects were seen by increased antioxidant enzymes and reduced oxidative stress markers. The lignans also suppressed stellate cell activation and collagen production, suggesting anti-fibrotic potential [55,56].

In vivo studies utilized rodent models of chemically-induced liver injury. Mice and rats treated with *Schisandra* extracts showed significantly lower levels of liver enzymes like ALT and AST compared to controls, indicating reduced hepatocellular damage. Histological analysis revealed less inflammation, necrosis, and collagen deposition in the livers of *Schisandra*-treated animals. The extracts also enhanced hepatic glycogen storage as a marker of regenerative capacity [57].

Mechanistic studies focused on the role of *Schisandra* in boosting Phase I and II detoxification pathways. Treatment led to higher activity of cytochrome P450 enzymes like CYP3A and CYP2E1 that metabolize xenobiotics. Increased glutathione levels and synthesis were also observed, enhancing free radical scavenging. These findings suggest *Schisandra* may improve the liver's capacity to eliminate toxins and reactive metabolites [58].

The multi-pronged pharmacological effects demonstrated in rigorous preclinical models are promising. *Schisandra* exhibits anti-inflammatory, antioxidant, anti-fibrotic, and pro-regenerative properties that could mitigate pathways driving chronic liver diseases. The ability to induce detoxification mechanisms may also protect hepatocytes from injury [59,60]. These biological activities provide a strong rationale for further clinical research on *Schisandra* as a potential hepatoprotective therapy.

Conclusions

Schisandra chinensis is an herbal medicine that has shown hepatoprotective potential through multiple biological mechanisms in preliminary research, including anti-inflammatory, antioxidant, antifibrotic, and liver regenerative effects. Animal models demonstrate attenuated markers of liver injury and disease progression with *Schisandra* treatment. Small human trials report improved liver enzymes and symptoms in certain hepatic conditions but are limited in quality and sample size. Overall, while initial data is promising, there is currently insufficient clinical evidence from well-designed, large scale human trials to support *Schisandra* as an effective phytotherapy for liver diseases. Further rigorous research is still needed to conclusively determine the therapeutic efficacy and safety of *Schisandra chinensis* in humans. If effectiveness is established, *Schisandra* could provide a valuable botanical supplement to help prevent and manage common chronic liver diseases driven by rising rates of obesity, diabetes, and other risk factors.

Recommendations

Based on the biological mechanisms and preclinical data, there is a strong rationale to continue investigating *Schisandra chinensis* as a potential treatment for liver diseases. **Table 4** outlines important areas for additional study to facilitate translation of the promising preclinical findings with *Schisandra chinensis* into evidence-based clinical applications for liver diseases. Guiding further research will help determine its place in therapy. Large, high-quality placebo-controlled randomized trials should be conducted to evaluate efficacy and safety of standardized *Schisandra* extracts in patients with chronic liver injury and fibrosis. Studies should assess clinically-relevant endpoints including histological changes, long-term prognosis, morbidity, and mortality, rather than just biochemical markers. Dose-response trials are also necessary to establish optimal therapeutic dosing. Subgroup analyses based on disease stage and etiology may also reveal

Table 4. Key Areas for Additional Research.

Research Needs	Rationale
Dose-response trials	Determine optimal doses for liver disease efficacy and safety
Pediatric research	Safety and appropriate doses not established in children
Explore novel delivery systems	Enhance bioavailability; validate pharmacokinetics
Head-to-head drug trials	Compare efficacy to first-line medications
Combination therapy trials	Evaluate synergistic effects with other botanicals/nutrients
Nutritional synergies	Assess potentiation of effect with dietary adjustments
Genetic and genomic analyses	Identify genotype-specific responses; precision medicine applications

differential responses to *Schisandra* therapy. If effectiveness and safety are established, *Schisandra chinensis* could provide a cost-effective complementary approach to support liver health and slow progression of chronic liver diseases globally.

List of Abbreviations

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; CYP: Cytochrome P450; IL: Interleukin; MAPK: Mitogen-Activated Protein Kinase; MDA: Malondialdehyde; NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells; ROS: Reactive Oxygen Species; TGF-β: Transforming Growth Factor beta; TNF-α: Tumor Necrosis Factor alpha

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data and sharing, as well as publication, are available.

Competing Interests

The authors hereby declare that they have no competing interests.

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Authors' contributions

All authors completed the study protocol and were the primary organizers of data collection and the manuscript's draft and revision process. Tamer A. Addissouky wrote the article and ensured its accuracy. All authors contributed to the discussion, assisted in designing the study and protocol, and engaged in critical discussions of the draft manuscript. All authors reviewed and confirmed the final version of the manuscript.

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