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Commentary

Advancing liver disease treatment: The promise of phytotherapy and hepatic stellate cell modulation

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Abstract

Liver diseases, such as cirrhosis and hepatocellular carcinoma (HCC), significantly contribute to global mortality rates, with increasing cases associated with hepatitis viruses, alcohol-related liver disease, and non-alcoholic fatty liver disease (NAFLD). Conventional treatments often encounter limitations due to side effects, high costs, and incomplete efficacy, highlighting the need for alternative therapeutic strategies. Phytotherapy, which utilizes bioactive plant compounds (e.g., flavonoids, polyphenols, and alkaloids), offers a promising approach due to its hepatoprotective, antioxidant, anti-inflammatory, and anti-fibrotic properties. These multi-targeted actions effectively address oxidative stress, inflammation, and fibrosis while promoting liver regeneration. A critical aspect of liver disease pathogenesis is the activation of hepatic stellate cells (HSCs), which drive fibrosis through the deposition of extracellular matrix. Targeting HSCs-by inhibiting the TGF-β/Smad and PI3K/Akt pathways—has shown promise in reversing fibrosis in preclinical studies. Recent advancements highlight the synergy between phytotherapy and HSC-targeted strategies, with traditional herbal formulations proving effective in suppressing HSC activation and alleviating liver damage. Despite these encouraging results, challenges persist, including the standardization of herbal extracts, clinical validation, and a deeper understanding of HSC heterogeneity. Emerging technologies, such as CRISPR-Cas9 and nanoparticle delivery systems, may enhance precision in HSC modulation. The integration of phytotherapy with conventional medicine has the potential to revolutionize liver disease management, especially in resource-limited settings. Continued research and robust clinical trials are crucial to translating these findings into safe and effective therapies, offering hope for reducing the global burden of liver diseases.

Keywords: Liver disease, Phytotherapy, Hepatic Stellate Cells, Fibrosis, Hepatoprotective, Anti-inflammatory, Oxidative stress, Traditional medicine

Introduction

Liver diseases, such as cirrhosis and hepatocellular carcinoma (HCC), are responsible for approximately 2 million deaths each year, constituting 4% of global mortality. In 2019, cirrhosis and chronic liver diseases accounted for 1.47 million deaths, an increase from 1.01 million in 1990, despite a decline in age-standardized death rates [1]. The primary causes include hepatitis B/C, alcohol-related liver disease, and non-alcoholic fatty liver disease (NAFLD), which affect 25.2% of the global population and are associated with obesity [2].

Liver diseases such as NAFLD, alcoholic liver disease, and cirrhosis present significant treatment challenges due to their complex etiology, limited therapeutic options, and potential side effects of medications [3]. Phytotherapy emerges as a promising alternative, offering a multitargeted and safer approach [4]. A critical factor in liver fibrosis is the activation of hepatic stellate cells (HSCs),

which leads to the transition of quiescent HSCs into proliferative myofibroblasts, resulting in excessive extracellular matrix deposition and scar tissue formation [5]. Targeting HSCs can potentially halt or reverse fibrosis, reduce inflammation, and promote liver regeneration [6].

Phytotherapy integrates bioactive compounds—such as flavonoids, polyphenols, and alkaloids—with HSC-targeted strategies, providing hepatoprotective, antioxidant, anti-inflammatory, and antifibrotic effects. These compounds not only protect liver cells but also modulate HSC activation, facilitating regeneration. Recent advancements in molecular research and drug delivery systems, including nanoparticles and gene editing, enhance the efficacy of this approach [7]. The combination of traditional herbal medicine with modern innovations holds transformative potential for liver disease treatment [8].

This commentary underscores the promise of phytotherapy, highlighting HSCs as a pivotal target. It delves into mechanisms, advancements, and future directions, illustrating how the integration of phytotherapy with HSC-targeted strategies can effectively address the global burden of liver diseases.

Hepatic Stellate Cells as a Key Focus in Liver Disease Therapeutic Strategies

Hepatic stellate cells (HSCs) are the primary drivers of liver fibrosis. In response to injuries from viral hepatitis, alcohol, NAFLD, or toxins, quiescent, vitamin A-storing HSCs activate into myofibroblasts. In metabolic dysfunction-associated steatohepatitis (MASH), metabolic stress, lipotoxicity, and inflammation trigger HSC activation, shifting their metabolism towards glycolysis and glutaminolysis. Activated HSCs produce excessive extracellular matrix (ECM) proteins, such as collagen. Without intervention, this can progress to cirrhosis [9]. HSC activation involves pathways related to TGF-β, PDGF, and oxidative stress. Beyond fibrosis, HSCs also modulate inflammation, angiogenesis, and immune responses, interacting with hepatocytes, Kupffer cells, and endothelial cells to exacerbate liver damage [10]. Importantly, fibrosis is reversible if the injury ceases and HSCs are deactivated, underscoring their therapeutic potential [11]. Therapeutic strategies targeting HSCs include: A) Blocking TGF-β/PDGF signaling to prevent activation; B) Inducing apoptosis or senescence in activated HSCs; C) Modulating MMPs/TIMPs to reduce ECM accumulation; and D) Disrupting the crosstalk between HSCs with other cells present in the liver such as Kupffer cell, Hepatocytes sinusoidal endothelial cells etc. to mitigate inflammation and fibrosis.

Preclinical and clinical studies support these strategies, demonstrating reduced fibrosis and improved liver function [12–14]. Targeting HSCs presents a promising pathway to halt or reverse the progression of liver disease [15,16].

Why Phytotherapy Stands out as a Promising Option for Liver Disease Treatment

Phytotherapy offers a compelling alternative for liver disease treatment through its natural, multitargeted approach. Plant-derived bioactive compounds, including flavonoids, polyphenols, alkaloids, and terpenoids, exhibit hepatoprotective effects by reducing oxidative stress, inflammation, and fibrosis while promoting liver regeneration [17]. These compounds stabilize liver cell membranes, inhibit HSC activation, and modulate key pathways such as TGF-β, NF-κB, and Nrf2/Keap1 [18]. Traditional Chinese Medicine (TCM) formulations, such as Xiao-Chai-Hu-Tang [19] and Liuweiwuling pills [20], demonstrate synergistic benefits by targeting multiple disease mechanisms simultaneously. Specific phytochemicals—such as silymarin (milk thistle) [21], curcumin (turmeric) [21], and baicalin (*Scutellaria baicalensis*) [22]—have shown clinical potential in improving NAFLD biomarkers, reducing liver enzymes (AST/ALT), and decreasing hepatic fat accumulation. However, challenges persist, including variability in plant extracts, limited bioavailability of certain compounds, and insufficient clinical validation. Advanced extraction techniques and nanoparticle-based delivery systems may enhance efficacy; however, further research is necessary to standardize formulations and elucidate molecular mechanisms.

The therapeutic potential of phytochemicals extends to preventing liver disease progression by addressing oxidative stress and metabolic dysfunction. Natural antioxidants, such as quercetin, resveratrol, and andrographolide, counteract reactive oxygen species

(ROS), while compounds like alisol B 23-acetate and ginsenoside Rg1 improve lipid metabolism by upregulating PPARα and inhibiting SREBP-1c [23]. These agents also mitigate endoplasmic reticulum (ER) stress, a key contributor to NAFLD, by enhancing fatty acid oxidation and reducing lipotoxicity [24]. Additionally, phytotherapy demonstrates antifibrotic effects by suppressing HSC activation and ECM deposition through modulation of TGF-β/Smad and PDGF pathways. Despite these benefits, safety concerns persist, as some herbs (e.g., pyrrolizidine alkaloids) can induce hepatotoxicity [25]. Contamination, herb-drug interactions, and dose-dependent toxicity further complicate clinical adoption. Rigorous quality control and large-scale trials are crucial for establishing safety profiles and optimizing therapeutic regimens. The integration of network pharmacology and bioinformatics could accelerate the identification of novel targets and synergistic combinations, bridging traditional knowledge with modern science [26].

Phytotherapy's affordability and accessibility make it particularly valuable in resource-limited settings with high liver disease burdens. Clinical studies highlight its role as a complementary therapy, with herbal mixtures showing efficacy in reducing drug-induced liver injury and enhancing regenerative pathways (e.g., JAK/STAT, PI3K/Akt). However, inconsistent clinical data, unclear mechanisms, and regulatory gaps hinder widespread acceptance. Future efforts should focus on standardizing bioactive compounds, improving delivery systems for poorly soluble agents (e.g., curcumin), and conducting robust trials to validate efficacy. Multidisciplinary approaches combining ethnopharmacology, molecular biology, and advanced drug formulation could unlock the full potential of plant-based therapies. While phytotherapy offers a holistic alternative to conventional treatments, its successful integration into mainstream medicine depends on addressing current limitations through collaborative research and evidence-based practice.

Latest Research Progress Made in This Field over the past Year

Recent studies have highlighted the significant anti-fibrotic potential of various traditional herbal formulations through diverse molecular mechanisms targeting hepatic stellate cell (HSC) activation and collagen deposition. Guizhi Fuling Wan (GFW) was found to inhibit HSC proliferation and extracellular matrix (ECM) production while promoting apoptosis and autophagy by stabilizing

PTEN and blocking the AKT/mTOR pathway [27]. Similarly, Yajieshaba (YJSB) attenuated fibrosis markers (α-SMA, Col-I/III/IV) through TGF-β1/Smad modulation, showing enhanced effects when combined with pirfenidone [28]. Optimized extraction methods, such as homogenate-assisted high-pressure disruption (HHPD), preserved bioactive compounds in Cili fruit extract, demonstrating antioxidant and anti-fibrotic activity [29]. Baoganning Decoction (BGN) exhibited dose-dependent inhibition of fibrosis via quillaic acid and methyl cholate interacting with fibrotic targets [30], while *Tithonia diversifolia*'s sesquiterpene lactones (particularly Tagitinin C) induced HSC apoptosis via TGF-β/Smad inhibition [31]. Vinegar-processed Curcumae Rhizoma (CR) enhanced delivery of furanone to suppress PI3K/Akt/mTOR signaling [32], and Bie Jia Jian pill (BJJP) modulated gut microbiota to disrupt the TMA-FMO3-TMAO axis while inhibiting PI3K/AKT [33]. Qianggan Ruanjian Pill (QGRJP) concurrently targeted TGF-β1/Smad and PI3K/AKT pathways without adverse effects [34], and soy saponin Bb from *Abrus cantoniensis* acted on JAK-STAT/Th17 pathways to reduce TGF-β1 and oxidative stress [35]. *Carthamus tinctorius L.* (CTL) reversed fibrosis markers (SOX9, hydroxyproline) through PI3K/Akt/mTOR inhibition [36], while *Moringa oleifera*'s 1-phenyl-2-pentanol (1-PHE) suppressed both TGF-β1 and Wnt/β-catenin pathways [37]. Longdan Xiegan Tang (LXT) upregulated Parkin-mediated mitophagy [38], and Dahuang Zhechong Pill (DHZCP) balanced Smad2/3-Smad7 ratios via p38 MAPK/NF-κB inhibition [39]. *Cichorium glandulosum* extract (CGE) attenuated TLR4 and TGF-β1/Smad signaling [40], whereas Ba-Qi-Rougan formula (BQRGF) targeted MSMP/CCR2/PI3K/AKT axis [41]. Novel triterpenoid saponins from *Bupleurum marginatum* inhibited HSC proliferation [42], and Yinchen Gongying decoction (YGD) regulated FoxO1/TGF-β1/Smad2/3 and YAP pathways while improving insulin signaling [43]. *Baccharis anomala* (BA) reduced α-SMA and collagen I through NF-κB/IL-6 suppression [44], while other TCMs like turmeric and *Scutellaria baicalensis* modulated glucose metabolism to inhibit HSC activation [45]. Sirtuin 1 (SIRT1), a member of the sirtuin family, plays a vital role in metabolism and aging [46] and has gained attention as a promising therapeutic target for liver disorders, especially non-alcoholic fatty liver disease (NAFLD) [47]. Activation or overexpression of SIRT1 helps alleviate NAFLD by restoring autophagy, improving mitochondrial function, reducing oxidative stress and regulating lipid metabolism [48]. Both natural and synthetic SIRT1 targeting compounds have shown potential in NAFLD prevention and treatment [49]. Additionally, SIRT1 is implicated in order liver diseases such as liver fibrosis, alcoholic liver disease, and hepatocellular carcinoma [50]. Since SIRT1 levels tend to decline with age and contributing to disease progression, therapeutic strategies including SIRT1 activators, gene therapy, and dietary interventions are being investigated to restore its function and slow liver disease development [50]. Natural products or neutraceuticals like resveratrol (RES), curcumin (CUR), and berberine (BBR) have shown anti-aging, anti-cancer and other health benefits. Among them resveratrol, found in grape skins and berries, may help extend lifespan by activating proteins like sirtuins, especially SIRT1 [51]. Fisetin prevents fat cell formation by increasing SIRT1 expression by helping SIRT1 deacetylate PPARγ and FoxO1, which suppresses fat cell development [52]. Quercetin protects endothelial cells from oxidative damage caused by oxidized LDL by activating SIRT1 and AMPK. It reduces harmful enzymes (NOX2, NOX4), prevents mitochondrial damage, lowers ROS levels, and blocks the NF-κB pathway [53]. Curcumin increases SIRT1 levels, linked to curcumin's antioxidant and anti-inflammatory actions and its activation of both SIRT1 and AMPK [54]. These findings collectively demonstrate that herbal medicines employ multi-target strategies against fibrosis—including pathway inhibition (TGF-β/Smad, PI3K/AKT/mTOR), oxidative stress reduction, inflammation modulation, and gut-liver axis regulation—with consistent efficacy across preclinical models. However, clinical translation remains limited by the absence of human trials, variability in herbal preparations, undefined pharmacokinetics, and unstandardized dosing. Future research should prioritize bioactive compound purification, mechanism validation through omics technologies, and rigorous safety assessments to bridge traditional knowledge with evidence-based therapeutic applications.

Challenges and Future Directions

While targeting HSCs holds great promise, challenges remain. These include ensuring the specificity of therapies to avoid off-target effects, understanding the heterogeneity of HSC populations, and translating preclinical findings into effective clinical treatments. Advances in single-cell RNA sequencing and gene-editing technologies, such as CRISPR-Cas9, are expected to provide deeper insights into HSC biology and facilitate the development of precision therapies. Hepatic stellate cells are a key focus in liver disease therapeutic strategies due to their central role in fibrosis, inflammation, and tissue remodeling. Targeting HSCs offers the potential to halt or reverse liver fibrosis, preventing progression to cirrhosis and liver failure. Advances in understanding HSC biology and its interactions with other liver cells have paved the way for innovative antifibrotic therapies. Future research should focus on overcoming challenges in specificity and translation to develop effective HSC-targeted treatments for liver diseases.

Conclusions

Liver diseases continue to pose a significant global health challenge due to their complex pathogenesis and limited treatment options. Phytotherapy presents a promising, natural, cost-effective, and well-tolerated alternative, with plant-derived bioactive compounds—such as flavonoids, polyphenols, and alkaloids—offering antioxidant, anti-inflammatory, anti-fibrotic, and regenerative benefits. These properties address both the causes and consequences of liver damage, supporting prevention and treatment. Hepatic stellate cells (HSCs), as central mediators of liver fibrosis, represent a critical therapeutic target. Inhibiting their activation can halt or reverse fibrosis and reduce inflammation. Recent advances, including gene editing and nanoparticle-based delivery systems, have enhanced the precision of HSC-targeted therapies. The integration of phytotherapy with HSC-directed approaches represents a synergistic strategy that combines the strengths of traditional medicine with modern innovations. Together, they offer dual protection and regeneration potential, addressing key limitations of conventional treatments. As research and clinical validation progress, this combined strategy could significantly improve patient outcomes and help alleviate the global burden of liver diseases.

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