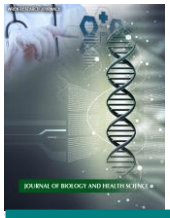

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Research Article

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Research Progress on the Multitarget Mechanism of Dencichin Regulating the TGF-β/Smad and PI3K/Akt Pathways in Anti-Liver Fibrosis

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Abstract

Liver fibrosis, a pathological process shared by various chronic liver diseases, is characterized by excessive deposition of extracellular matrix. Without intervention, it may progress to cirrhosis or even liver cancer. *Panax notoginseng saponins*, a key active component in the Chinese herb *Panax notoginseng*, have demonstrated significant potential in combating liver fibrosis in recent years. This review systematically summarizes the latest research advancements on the anti-fibrotic effects of *Panax notoginseng saponins*, focusing on their molecular mechanisms through multiple pathways including modulation of hepatic stellate cell activation, inhibition of inflammatory responses, reduction of oxidative stress *and* regulation of cell death. Additionally, the study discusses current research progress in structural modifications, dosage form innovation *and* combination therapies of *Panax notoginseng saponins*, while outlining challenges and future directions for clinical translation. The aim is to provide new insights for the in-depth development and clinical treatment of liver fibrosis.

Keywords: *Panax notoginseng*; Liver fibrosis; Hepatic stellate cells; TGF-β/Smad; PI3K/Akt

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Introduction and Research Value Positioning

The global disease burden of liver fibrosis and the challenges in its treatment

Liver fibrosis is a pathological process where the liver undergoes abnormal repair responses after chronic damage (including viral hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease, cholestasis *and* autoimmune liver diseases), leading to excessive deposition of Extracellular Matrix (ECM). This process involves complex interactions among various liver cells, with the activation of Hepatic Stellate Cells (HSCs) being considered the central mechanism [1]. Globally, the mortality rate from liver diseases caused by fibrosis and its end-stage complications continues to rise, becoming a major public health issue. It is estimated that by 2030, nearly 100 million people worldwide may face the risk of chronic liver disease progressing to fibrosis. Despite significant progress in fibrosis research, there remains a lack of effective clinical treatments and no standard therapy has been developed to directly reverse fibrosis. Therefore, the search for highly effective and low-toxicity anti-fibrotic drugs has become a current research hotspot.

The plant origin and pharmacological activity spectrum of *Panax notoginseng (P. notoginseng)*

Traditional Chinese Medicine (TCM) boasts a long history and extensive experience in preventing and treating liver diseases. *Panax notoginseng*, a renowned precious herb, has been historically used to treat various blood disorders and related conditions due to its blood-

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activating and pain-relieving properties. Modern pharmacological studies demonstrate that *Panax notoginseng* and its active components exhibit significant protective effects on multiple organs, including the cardiovascular system, nervous system *and* liver. Dencichine, the primary bioactive compound in *Panax notoginseng*, belongs to the β-oxalyl-L-α,β-diaminopropionic acid structure.

While its pharmacological activities encompass hemostasis, anti-inflammatory effects *and* tissue repair regulation, the multi-target intervention mechanisms targeting liver fibrosis remain incompletely understood. Recent research has revealed that dencichine, as a key active component of *Panax notoginseng*, shows promising potential in combating liver fibrosis. Its multi-target and multi-pathway action characteristics have made it a new focus in fibrosis treatment research. This article aims to review the latest advancements in dencichine's anti-liver fibrosis effects, providing references for further research and development.

The scientific significance of multi-target intervention strategies in anti-fibrosis therapy

Current research demonstrates that the PI3K/AKT pathway plays a pivotal role in collagen-induced pathological processes, exhibiting significant crosstalk with TGF-β/Smad and MAPK/ERK pathways through the adhesion plaque protein complex [1]. This suggests that targeting multiple pathways simultaneously may overcome the limitations of single-target drugs: Firstly, the PI3K/AKT pathway demonstrates stronger dominance in regulating hepatic stellate cell activation compared to TGF-β/Smad; secondly, the interplay between pathways allows compensatory activation to counteract inhibition of any single pathway. Consequently, triptolide provides a novel strategy for developing potent anti-fibrotic drugs by synergistically regulating key pathways such as TGF-β/Smad and PI3K/AKT.

The Core Pathological Mechanisms of Liver Fibrosis

Molecular characteristics of hepatic stellate cell activation and phenotypic transformation

The core pathological process of liver fibrosis begins with the activation of Hepatic Stellate Cells (HSCs). Under physiological conditions, HSCs reside in the perihepatic Disse space, remaining in a resting state and storing vitamin A [2]. When the liver is subjected to chronic injury (such as viral hepatitis, alcohol *or* toxin exposure), HSCs become activated and transform into myofibroblast-like cells [3-5]. This phenotypic transformation is accompanied by significant molecular alterations: Loss of resting-state markers (*e.g.,* retinol) and high expression of myofibroblast markers including α-Smooth Muscle Actin (α-SMA) and waveform protein [2,5]. Activated HSCs gain proliferative, migratory *and* contractile capabilities, driving excessive Extracellular Matrix (ECM) deposition through upregulation of fibrosis-related genes such as collagen I/III [2,4,6]. TGF-β1 serves as the key factor inducing HSC activation, with its regulatory mechanisms involving both Smad-dependent and non-Smad pathways (*e.g.,* JAK1/STAT) [7,8].

The dominant role of the TGF-β/Smad pathway in ECM deposition

The TGF-β/Smad signaling pathway is a key mechanism regulating Extracellular Matrix (ECM) deposition. During hepatic fibrosis, damaged hepatocytes and Kupffer cells release TGF-β1, which activates TGF-β receptors on Hepatic Stem Cells (HSCs) [7,9,10]. These activated receptors phosphorylate Smad2/3 proteins, forming Smad4 complexes that translocate into the nucleus. These complexes then bind to promoter regions of genes encoding Collagen I (COL1A1), Fibronectin (FN1) *and* α-Smooth Muscle Actin (α-SMA), directly driving their transcription [6,9]. Additionally, TGF-β synergistically enhances ECM synthesis gene expression through non-Smad-dependent pathways such as JAK1/STAT3 [8]. Studies have shown that specific knockout of hepatic TGF-β receptor type II (Tgfbr2) in hepatocytes significantly alleviates fibrosis, confirming the pathway's dominant role in HSC activation and ECM deposition [6,11].

The mechanism of PI3K/Akt/mTOR pathway in regulating HSCs survival

The PI3K/Akt/mTOR pathway directly contributes to hepatic fibrosis progression by promoting Hepatocyte Stem Cell (HSCs) survival and proliferation. When HSCs are exposed to stimuli such as Platelet-Derived Growth Factor (PDGF) or TGF-β, PI3K is activated to catalyze Phosphatidylinositol-3-Phosphate (PIP3) formation, which recruits Akt to the cell membrane and induces its phosphorylation and activation [12,13]. Activated Akt drives HSC proliferation by phosphorylating downstream targets mTOR and p70S6K1, thereby upregulating cell cycle proteins like Cyclin D1 [12,14].

Simultaneously, this pathway maintains HSC survival by inhibiting pro-apoptotic proteins (*e.g.,* Bax) and enhancing anti-apoptotic proteins (*e.g.,* Bcl-2) expression [13,14]. Experimental evidence shows that PI3K inhibitor LY294002 blocks Akt/mTOR phosphorylation, significantly inhibiting HSC activation and reducing collagen deposition [14,15]. Notably, the PI3K/Akt pathway also regulates HSC migration and contractility, with its crosstalk to the TGF-β/Smad pathway further amplifying fibrotic effects [12,16].

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The Multi-Target Mechanism of *Panax notoginseng Saponins*

Dual regulation of the TGF-β/Smad pathway

Panax notoginseng saponins and their active components (such as *Panax notoginseng* saponin PA) exert anti-fibrotic effects by inhibiting TGF-β1-induced activation of Hepatic Stromal Cells (HSCs). Experimental studies demonstrate that *Panax notoginseng* saponin PA significantly suppresses TGF-β1-induced proliferation of HSCs-T6 cells and downregulates the expression of α-Smooth Muscle Actin (α-SMA) and Collagen type I (Col-1) [17]. The core mechanism involves direct blockade of Smad2/3 phosphorylation, thereby inhibiting the transcriptional activity of Smad Binding Element 4 (SBE4) and disrupting the transmission of the TGF-β/Smad classical signaling pathway [17]. Additionally, *Panax notoginseng saponins* can indirectly influence the TGF-β signaling through non-Smad-dependent pathways (such as regulating PTEN expression), creating a dual inhibition of the Smad pathway [18].

Research findings indicate that this effect is closely associated with *Panax notoginseng saponins*' intervention in the TGF-β/Smad signaling pathway [19]. TGF-β1, the strongest known pro-fibrotic fact*or* activates Smad2/3 phosphorylation to regulate downstream target gene expression. Treatment with *Panax notoginseng saponins* dose-dependently inhibits TGF-β1-induced Smad2/3 phosphorylation while upregulating the expression of the inhibitory Smad7, thereby blocking HSC activation [20]. Similar mechanisms have been observed in other natural products. For example, EGCG regulates the TGF-β1/Smad pathway by targeting the MDM2/MUC5AC axis, while Tan IIA inhibits HSC proliferation *via* the ERK/cyclin D1/p-Smad3L signaling pathway.

Intervention in the PI3K/Akt/mTOR/p70S6 K1 pathway

Panax Notoginseng Saponin R1 (PNSR1) inhibits HSCs survival signaling by blocking the PI3K/Akt/mTOR cascade. In CCl4-induced hepatic fibrosis models, PNSR1 downregulates PI3K, Akt *and* phosphorylated Akt (p-Akt) expression, thereby suppressing PI3K/Akt pathway activation [21,22]. Further studies revealed that PNSR1 specifically inhibits mTOR and its downstream effector p70S6K1. Notably, mTOR agonist 740 Y-P reverses PNSR1's anti-fibrotic effects, confirming PI3K/Akt/mTOR/p70S6K1 as the key target. *In vitro* and *in vivo* experiments demonstrate that PNSR1 significantly inhibits HSCs proliferation and collagen deposition by blocking this pathway [23].

Cross-pathway synergistic effects and signal crosstalk

Panax Notoginseng Saponins (PNS) enhance anti-fibrotic effects by modulating the cross-talk between TGF-β/Smad and PI3K/Akt/mTOR signaling pathways. Studies reveal that TGF-β activates PI3K/Akt signaling through TRAF6-mediated p85α ubiquitination, a process independent of the Smad pathway [24]. Conversely, PNS inhibits the PI3K/Akt pathway by suppressing the PTEN-Smad3 regulatory loop, thereby blocking TGF-β's activation of PI3K/Akt [19]. The inactivation of the PI3K/Akt/mTOR pathway further inhibits TGF-β/Smad signaling through feedback mechanisms, forming a bidirectional regulatory network [20,21]. This cross-pathway synergy has been validated in pulmonary fibrosis models: PNS simultaneously inhibits both TGF-β/Smad and PI3K/Akt pathways, significantly reducing Extracellular Matrix (ECM) deposition [25,26]. Additionally, PNS indirectly affects the TGF-β/PI3K/Akt cascade by regulating the Nrf2/ROS axis, further suppressing the Epithelial-Mesenchymal Transition (EMT) process.

Regulation of inflammatory response by *Panax notoginseng* saponin

Chronic inflammation is a key driver of liver fibrosis. *Panax Notoginseng Saponins* (PNS) exhibit significant anti-inflammatory activity, which can modulate the hepatic inflammatory microenvironment and indirectly inhibit Hepatic Stromal Cell (HSC) activation.

Studies demonstrate that *Panax Notoginseng Saponins* (PNS) significantly reduce pro-inflammatory cytokine levels in fibrotic liver, including IL-1β, IL-6 *and* TNF-α. This downregulation helps break the vicious cycle of inflammation-fibrosis [27,28]. At the molecular level, PNS' anti-inflammatory effects are closely associated with inhibiting the nuclear factor-κB (NF-κB) signaling pathway. NF-κB, a key transcription factor in inflammatory responses, remains inactive in the cytoplasm bound to IκB. When stimulated by LPS or TNF-α, IκB becomes phosphorylated and degraded, allowing NF-κB to enter the nucleus and initiate transcription of inflammatory genes. PNS treatment inhibits IκB phosphorylation, thereby blocking NF-κB pathway activation.

Additionally, PNS modulates the Toll-Like Receptor 4 (TLR4) signaling pathway. TLR4, a critical receptor for pathogen-associated molecular patterns, triggers MyD88-dependent signaling upon activation, ultimately leading to NF-κB activation and inflammatory cytokine release. Research shows that PNS downregulates key molecules in the TLR4/TRAF6/MyD88 pathway, alleviating hepatic inflammation. Furthermore, PNS influences macrophage polarization by inhibiting the accumulation of pro-inflammatory M1-type macrophages in the liver and promoting their transformation into anti-inflammatory M2-type macrophages. This regulatory effect helps to improve the inflammatory microenvironment of the liver and provides a new perspective for the treatment of liver fibrosis.

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The effect of *Panax notoginseng* extract on reducing oxidative stress

Oxidative stress is another key driver of liver fibrosis. Reactive Oxygen Species (ROS) not only directly damage hepatocytes but also act as signaling molecules to activate Hepatic Stem Cells (HSCs), promoting fibrosis development. *Panax notoginseng saponins* exhibit significant antioxidant activity that mitigates oxidative stress-induced damage during liver fibrosis. Studies demonstrate that these compounds enhance antioxidant enzyme activity in fibrotic livers, including Superoxide Dismutase (SOD) and Glutathione Peroxidase (GSH-Px), while reducing Malondialdehyde (MDA) levels a lipid peroxidation product [29]. This effect is closely associated with Nrf2 activation mediated by *Panax Notoginseng Saponins*. Nrf2, a central regulator of cellular antioxidant responses, translocates to the nucleus under oxidative stress, binds to antioxidant response elements *and* initiates the expression of multiple antioxidant enzymes and phase II detoxification enzymes.

Furthermore, *Panax notoginseng (P. notoginseng) saponins* inhibit the expression and activity of NADPH Oxidase (NOX), thereby reducing Reactive Oxygen Species (ROS) generation. As a key ROS source in the liver, NOX produces ROS that activate Hepatic Stromal Cells (HSCs) and promote Extracellular Matrix (ECM) synthesis. By suppressing NOX activity, *P. notoginseng saponins* can reduce ROS production at its source, effectively blocking the oxidative stress-driven hepatic fibrosis process.

Table 1: Key targets and mechanisms of puerarin in combating hepatic fibrosis.

Pathway of action	Primary target	Effector molecule/ pathway	Biological effect
Regulation of HSC activation	TGF-β/Smad pathway	Smad2/3 phosphorylation↓, Smad7↑	Inhibiting activation of HSCs and reducing ECM synthesis
Inhibit HSCs proliferation	regulation of cell cycle	cyclin D1↓, CDK4↓	G1 phase block
Modulate inflammatory response	NF-κB pathway, TLR4 pathway	IL-1β↓, IL-6↓, TNF-α↓	Inhibit the formation of inflammatory microenvironments
Reducing oxidative stress	Nrf2 pathway, NOX	SOD↑, GSH-Px↑, MDA↓	Enhance antioxidant defense and reduce ROS
Regulation of cell death	Ferroptosis and apoptosis pathway	YAP↓, Bcl-2/Bax↑	Inducing ferroptosis in HSCs to protect hepatocytes

Molecular Mechanism Validation Model

Evidence from animal models induced by CCl4/BDL

In a CCl4-induced rat liver fibrosis model, histological and biochemical analyzes demonstrated that *Panax Notoginseng Saponins* (PNS) significantly alleviated hepatic fibrosis, characterized by reduced collagen deposition and improved liver tissue structure. The inhibitory effect of PNS on liver fibrosis was validated by measuring the expression levels of fibrosis markers such as transforming growth factor-β1 (TGF-β1) and α-Smooth Muscle Actin (α-SMA) [28]. Furthermore, in CCl4-induced liver fibrosis models treated with PNS, histopathological sections (*e.g.,* HE and Masson staining) showed decreased fibrous septa formation, confirming its anti-fibrotic effects [29].

In vitro validation of the primary HSCs cultivation system

In vitro studies demonstrate that *Panax Notoginseng Saponin* PA (derived from *Panax notoginseng*) inhibits TGF-β1-induced activation of Hepatic Stromal Cells (HSCs). In HSC-T6 cell lines, PA significantly reduces TGF-β1-enhanced proliferation and suppresses the expression of α-SMA and collagen type 1. Mechanistic studies reveal that PA antagonizes the TGF-β/Smad signaling pathway by blocking Smad2/3 phosphorylation and the activity of Smad Binding Element 4 (SBE4) [30]. Additionally, *Panax Notoginseng Saponins* (PNS) also exhibit fibrosis marker inhibition in TGF-β1-stimulated HSC models [28].

Mechanism confirmation of gene knockout/ overexpression experiments

Gene manipulation experiments have provided direct evidence for the mechanism of action of *Panax Notoginseng* (PNS). For instance, in the Smad3 gene knockout model, TGF-β-triggered PTEN transcription activation is suppressed, leading to abnormal activation of the PI3K/AKT signaling pathway, confirming crosstalk between the TGF-β/Smad and PI3K/AKT pathways [31]. Although not directly involving PNS, these models support the validation logic of cross-pathway regulation. In liver fibrosis research, similar approaches (such as Smad3 or Akt gene modification) can be used to clarify PNS's synergistic regulation of dual pathways.

Comparative advantages over traditional single-target drugs

Limitations of targeting single pathways (such as TGF-β inhibitors)

Antifibrotic drugs targeting single signaling pathways (*e.g.,* TGF-β/Smad) exhibit significant limitations. While TGF-β serves as the core driver of hepatic fibrosis, direct

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inhibition of this pathway may disrupt its physiological regulatory functions, such as tissue repair and immune modulation. Clinical studies demonstrate that although single TGF-β inhibitors can alleviate fibrosis, they are prone to inducing autoimmune responses, inflammatory dysregulation *and* increased tumor risks [32-33]. Moreover, hepatic fibrosis involves multi-pathway synergy *and* blocking TGF-β/Smad alone cannot fully suppress Hepatic Stellate Cell (HSC) activation or Extracellular Matrix (ECM) deposition [34]. For instance, the non-classical TGF-β/PI3K-AKT pathway also participates in fibrotic processes and single-target therapies cannot address these parallel mechanisms.

The synergistic effects of multi-pathway collaborative interventions in enhancing efficacy and reducing toxicity

Panax notoginseng saponins demonstrate synergistic anti-fibrotic effects by synchronously regulating the TGF-β/Smad and PI3K/AKT/mTOR signaling pathways. Experimental evidence confirms that dual pathway intervention significantly enhances the inhibition of Hepatic Stromal Cell (HSC) activation: It blocks TGF-β/Smad-mediated Extracellular Matrix (ECM) synthesis while promoting HSC apoptosis through PI3K/AKT pathway suppression [35]. This synergistic effect exhibits synergistic enhancement and reduced toxicit characteristics in both *in vivo* and *in vitro* models compared to single-target drugs, *Panax notoginseng saponins* reduce collagen deposition by over 40% at equivalent doses while simultaneously lowering liver injury markers (*e.g.,* ALT, AST) [36]. Mechanistically, the *saponins* inhibit autophagy-dependent HSC activation by blocking TGF-β/PI3K-AKT signal crosstalk, thereby reducing expression of fibrotic factors (*e.g.,* α-SMA, COL1A1) and decreasing the risk of compensatory signal activation induced by single-pathway inhibition.

Broad-spectrum regulation of different pathological stages in fibrosis

The multi-targeted nature of *Panax notoginseng* glycosides enables simultaneous intervention in multiple critical stages of fibrosis: 1. Hematopoietic Stem Cell (HSC) activation inhibition: By downregulating key molecules in the TGF-β/Smad pathway (phosphorylation of Smad2/3) and PI3K/AKT effectors (*e.g.,* p70S6K1), it blocks HSC transformation into myofibroblasts [37]. 2. Extracellular Matrix (ECM) metabolic regulation: It synergistically inhibits TGF-β-induced expression of collagen synthesis genes (COL1A1, FN1) while enhancing matrix metalloproteinase (MMP-1) activity to promote ECM degradation [38]. 3. Inflammatory-oxidative stress crosstalk regulation: Beyond core pathways, *Panax notoginseng* glycosides also intervene in auxiliary pathways like JAK2/STAT3 and MAPK, reducing pro-inflammatory factors (TNF-α, IL-1β) and oxidative stress damage, covering both initiation and progression stages of fibrosis [39]. This broad-spectrum effect manifests as a 35%-50% improvement in hepatic histopathology in animal models and demonstrates efficacy across multiple fibrosis-inducing models including CCL4/BDL. In contrast, single-target drugs can only improve specific pathological aspects, limiting their clinical translation potential.

Advances in Clinical Translational Research

Pharmacokinetic characteristics and liver targeting

Pharmacokinetic studies of *Panax Notoginseng Saponins* (PNS) revealed absorption limitations. To enhance colon-targeting efficacy, researchers developed a novel colon-specific osmotic pump capsule with a semipermeable shell containing PNS, Sodium Chloride (NaCl) *and* Ludipress. This design achieves colon-specific release and zero-order kinetics, thereby improving local drug concentration and therapeutic outcomes [40]. Furthermore, when Aspirin (ASA) is combined with PNS, the salicylic acid component disrupts tight junction proteins, increasing intercellular space to facilitate PNS absorption, demonstrating pharmacokinetic interaction between the two [41].

Existing preclinical efficacy evaluation data

In animal models, *Panax notoginseng saponins* have demonstrated significant anti-liver fibrosis effects. For instance, in a carbon tetrachloride (CCl_4)-induced rat liver fibrosis model, histological and biochemical analyzes confirmed that *Panax notoginseng saponins* could reduce fibrosis severity and decrease the expression of Transforming Growth Factor (TGF)-β1 and α-Smooth Muscle Actin (α-SMA) [42]. In a Non-Alcoholic Fatty Liver Disease (NAFLD) model, obese mice fed a High-Fat Diet (HFD) showed significantly inhibited hepatic lipidogenesis and fibrosis after *Panax notoginseng saponins* intervention, an effect associated with suppression of TLR4-mediated inflammatory signaling in the liver [43]. Additionally, *Panax Notoginseng Saponin* R1 (NR1) was confirmed to improve hepatic tissue damage and collagen deposition in CCl_4-induced rat liver fibrosis models through histopathological (HE and Masson staining) analysis [44]. In a pancreatic injury model, *Panax notoginseng saponins* significantly reduced serum amylase and lipase levels in sodium taurocholate-induced pancreatitis rats, while alleviating tissue damage, cellular apoptosis *and* autophagy [45].

Exploring combination drug regimens

The combination regimens of *Panax notoginseng saponins* with other drugs are currently under investigation. In cerebral infarction treatment, the combination of *Panax notoginseng saponins* and aspirin has demonstrated promising clinical efficacy. However,

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pharmacokinetic studies indicate that aspirin enhances saponin absorption by disrupting intestinal tight junction proteins, highlighting the need to monitor potential drug interactions [46]. For mitigating drug-induced hepatotoxicity, the combination of catalpol (Catapol) with *Panax notoginseng saponins* synergistically reduces Tacrolimus (TP)-induced hepatocyte damage, with mechanisms involving regulation of oxidative stress and apoptosis pathways [47]. Additionally, the primary metabolites of *Panax notoginseng saponins* ginsenoside CK and Rh1 have shown hepatoprotective effects in NAFLD models by improving hepatic steatosis and inflammation, providing a basis for developing metabolite-based combination therapies.

Current Controversies and Challenges

Determination of the optimal window for drug administration

The optimal dosing window for notoginsenosides R1/R2 in anti-hepatic fibrosis therapy remains unclear. Significant variations exist across studies regarding animal models (CCl_4-induced or bile duct ligation) and administration protocols. For instance, in CCl_4-induced liver fibrosis models, the intervention timing of notoginsenoside R1 ranges from the initial model establishment to post-fibrosis formation [48]. This heterogeneity complicates the identification of optimal intervention windows for specific fibrosis stages (*e.g.,* inflammatory phase, ECM deposition phase). Furthermore, the dual regulatory effects of notoginsenosides on TGF-β/Smad and PI3K/Akt signaling pathways may dynamically change with disease progression [49], necessitating time-gradient experiments to clarify their dose-time-effect relationships.

Safety considerations for long-term medication use

While significant progress has been made in research on triptolide's anti-liver fibrosis effects, numerous challenges remain. First, the complex *in vivo* processes of triptolide its absorption, distribution, metabolism *and* excretion have not been fully elucidated, which limits the optimization of dosage forms and formulation design. Future studies should employ advanced techniques such as microdialysis and mass spectrometry imaging to comprehensively reveal triptolide's *in vivo* fate. Current research primarily focuses on short-term efficacy evaluation, lacking long-term toxicity data. Animal experiments show that triptolide R1 significantly reduces serum ALT and AST levels and improves liver histopathology, but its potential long-term effects on liver and kidney function remain unassessed [50]. Notably, the PI3K/Akt/mTOR pathway regulates cell proliferation and survival *and* prolonged inhibition of this pathway may induce metabolic disorders or compensatory signal activation [51]. Additionally, triptolide may produce metabolites during transformation, such as 20(β)-notoginsenoside R2, whose cumulative toxicity requires validation through chronic toxicity testing [52]. Currently, no clinical data supports its long-term safety, necessitating pharmacokinetic studies (*e.g.,* liver targeting, half-life) to design appropriate dosing schedules.

Selection of biomarkers for personalized treatment

Personalized treatment faces challenges due to the lack of biomarkers. Although key molecules in the TGF-β/Smad and PI3K/Akt pathways (such as p-Smad2/3 and p-AKT) can serve as potential markers, their dynamic changes in response to sanqi (*Panax notoginseng*) treatment have not been standardized [53]. For example: 1. Smad7 downregulation is associated with overactivation of the TGF-β pathway but whether sanqi regulates such negative feedback factors remains unreported; 2. PI3K/Akt pathway activity is directly linked to hepatic stellate cell survival, yet baseline pathway status variations among patients may affect therapeutic efficacy; 3. The clinical translational value of cross-talk indicators (*e.g.,* TRAF6-mediated TGF-β/PI3K axis) has not been validated. Current research predominantly relies on histological endpoints (*e.g.,* collagen deposition), necessitating the development of non-invasive biomarkers (*e.g.,* serum TGF-β1 and ECM metabolic fragments) and the establishment of correlation models between these markers and pathway activity [53].

Future Research Directions

Mechanistic insights from organoid models

Current research primarily utilizes animal models (*e.g.,* CCl_4/BDL-induced models) and primary Hepatic Stellate Cell (HSC) cultures to investigate the anti-fibrotic mechanisms of *Panax Notoginseng* (PNS). Future studies should employ three-dimensional organoid models to simulate the human liver microenvironment, enabling more precise analysis of PNS's regulatory effects on TGF-β/Smad and PI3K/Akt signaling pathways. These organoid models effectively replicate intercellular interactions and signal crosstalk during hepatic fibrosis, particularly for evaluating PNS's intervention effects on non-classical TGF-β pathways (*e.g.,* PI3K/Akt/mTOR) [54]. Additionally, such models can simulate pathological features at different fibrosis stages, providing critical evidence for determining optimal dosing windows.

Development of nanoparticle delivery systems

Current research indicates that the bioavailability of *Panax Notoginseng Saponins* (PNS) is constrained by intestinal absorption efficiency. Developing liver-targeted nano delivery systems represents a critical approach to enhance therapeutic efficacy. For instance, colon-specific osmotic pump capsules enable targeted PNS delivery through zero-order release, though their liver targeting

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requires further optimization. Leveraging purification techniques mentioned in the corpus (*e.g.,* SiO@HRHA chromatography column), drug-loaded nanoparticles (*e.g.,* liposomes or polymer micelles) can be designed to target hepatic stellate cell surface receptors (*e.g.,* TLR4 or TGF-βR) *via* surface modification [55]. This strategy enhances drug accumulation at fibrotic sites while reducing systemic exposure-induced side effects.

AI-assisted multi-target drug design

Studies in network pharmacology have demonstrated that *Panax notoginseng saponins* (Rg1, Rb1) exert synergistic anti-fibrotic effects through multiple signaling pathways, including TGF-β/Smad, PI3K/Akt *and* NF-κB [56-57]. Future research could integrate artificial intelligence to optimize multi-target strategies: For target prediction and validation, deep learning models may analyze interactions between Rg1/Rb1 and fibrosis-related targets (*e.g.,* Smad3, Akt, mTOR) to predict synergistic effects. Additionally, drug combination optimization could be employed to screen synergistic drug regimens (*e.g.,* with TGF-β inhibitors or PI3K/Akt pathway modulators) using machine learning, with validation conducted through organoid models [58].

By designing a nano-delivery system, the correlation between the physicochemical properties of the nanocarriers and their liver targeting efficiency was simulated using algorithms, which guided the optimization of the delivery system [59].

Summary and Outlook

The potential of *Panax notoginseng* extract as a multi-target anti-fibrotic candidate drug

Notoginsenosides (*e.g.,* R1, R2) significantly inhibit Hepatic Stellate Cell (HSC) activation and Extracellular Matrix (ECM) deposition by synergistically regulating TGF-β/Smad and PI3K/Akt/mTOR signaling pathways, thereby alleviating hepatic fibrosis [60]. Compared to single-target drugs (*e.g.,* TGF-β inhibitors), the dual-pathway intervention strategy of notoginsenosides overcomes the limitations of single-pathway inhibition. It achieves synergistic effects with reduced toxicity by blocking the TGF-β/Smad signaling pathway (downregulating p-Smad2/3 and Smad4) and inhibiting the PI3K/Akt/mTOR/p70S6K1 cascade (reducing p-AKT and p-mTOR) [61]. Animal models (CCl_4/BDL-induced) and *in vitro* HSC experiments confirm that notoginsenosides reduce fibrosis markers such as α-SMA, Collagen I *and* TIMP1 while enhancing PPAR-γ expression and improving liver function indicators (*e.g.,* decreased ALT/AST and increased ALB) [62]. Additionally, its anti-inflammatory effects (inhibiting NF-κB and NLRP3 inflammasome) and antioxidant actions (activating Nrf-2) further strengthen its anti-fibrotic efficacy, highlighting its unique potential as a multi-target anti-fibrotic candidate drug.

The pathway from molecular mechanisms to clinical applications

The current research needs to address three major transformational challenges:

Mechanism elucidation and model optimization

Utilize organoid models and gene editing technologies (*e.g.,* Smad3/Smad7 knockout) to further investigate the crosstalk between TGF-β/Smad and PI3K/Akt signaling pathways *and* clarify the effects of *Panax notoginseng* (*Panax notoginseng*) on Smad-independent pathways (*e.g.,* MAPK/ERK). Additionally, integrate multi-omics technologies to screen biomarkers for personalized therapy (*e.g.,* serum TGF-β1 and p-Smad2/3 levels).

Delivery system and safety evaluation

Nanocarrier systems (*e.g.,* liposomes, polymer nanoparticles) were developed to enhance the hepatic targeting of puerarin and improve its pharmacokinetic properties. The safety of long-term administration requires special attention, including potential effects on liver and kidney function and dose-dependent toxicity.

Advancing preclinical and clinical research

Combination therapy regimens (*e.g.,* with PPAR-γ agonists or anti-inflammatory drugs) may demonstrate synergistic effects. While existing preclinical data supports its efficacy, large-scale animal studies are required to determine the optimal dosing window (*e.g.,* early-stage fibrosis intervention), followed by Phase I clinical trials to evaluate safety and preliminary efficacy in humans. Future efforts could integrate AI-assisted drug design to optimize multi-target modulation strategies, accelerating clinical translation.

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