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Review Article

Exploring the Therapeutic Potential of TGF-β Inhibitors for Liver Fibrosis: Targeting Multiple Signaling Pathways

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Abstract

Liver fibrosis is a pathological process resulting from various chronic liver injuries that lead to the formation of liver fibrous scars. It can further progress to cirrhosis and even liver cancer. Currently, there are no effective drugs specifically approved for the treatment of liver fibrosis; etiological therapy remains the main treatment strategy. Therefore, it is necessary to develop anti-fibrotic drugs targeting different pathways involved in liver fibrosis. Transforming growth factor-beta (TGF-β) is a key driver of fibrosis, and targeting TGF-β can effectively reduce liver fibrosis. In this review, we discussed the anti-liver fibrosis effects of TGF-β inhibitors through different signaling pathways, including the application of certain active ingredients from Traditional Chinese Medicine.

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Introduction

Liver fibrosis is usually caused by various chronic liver injuries,[1] including viral hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease, and autoimmune liver disease.[2] The pathological features of liver fibrosis include fibroblast proliferation and differentiation, inflammatory cell infiltration, abnormal extracellular matrix (ECM), and fibrous scar formation in the liver. Hepatic stellate cell (HSC) activation is the main cause of fibrous scarring in liver fibrosis.[3]

The central feature of liver fibrosis is the accumulation of excess collagen and ECM components in liver tissue.[2] This abnormal ECM deposition leads to severe disruption of liver structure and function.[4] Although potentially reversible, uncontrolled fibrosis can progress to end-stage cirrhosis and hepatocellular carcinoma (HCC).[5] Due to the complex progression of liver fibrosis, no satisfactory anti-fibrotic drugs have been developed to date.

The transforming growth factor-beta (TGF-β) superfamily includes TGF-βs and bone morphogenetic proteins (BMPs).[3,6] These proteins are involved in cell growth, differentiation, immunomodulation, and tissue repair.[4] There are three TGF-β homologs: TGF-β1, TGF-β2, and TGF-β3, all of which bind to TGF-β receptor II (TGF-βRII) as dimers. TGF-βRII then recruits and activates the type I receptor kinase (TGF-βRI, also known as activin receptor-like kinase (ALK) 5). After activation, TGF-βRI phosphorylates its substrates, thereby activating downstream signal transduction pathways and regulating various cellular activities.[6–8]

The liver comprises parenchymal cells (hepatocytes) and diverse non-parenchymal cells, including liver sinusoidal endothelial cells, HSCs, Kupffer cells, intrahepatic lymphocytes, and liver-resident dendritic cells. All non-parenchymal cell populations constitutively synthesize TGF-β, whereas hepatocytes primarily absorb and store this cytokine.[9] In hepatocytes, TGF-β primarily inhibits proliferation, induces apoptosis, promotes epithelial-mesenchymal transition (EMT), and contributes to fibrogenesis.[10,11] Research indicates that even small amounts of TGF-β can strongly suppress hepatocyte proliferation.[12] TGF-β further promotes liver fibrosis by increasing ECM component synthesis and inhibiting ECM degradation. It regulates the balance of matrix metalloproteinases (MMPs) and their inhibitors.

TGF-β can not only induce hepatocyte apoptosis but also regulate fibroblast proliferation. Collectively, these factors promote the formation and progression of fibrosis.[13] TGF-β can stimulate the activation of HSCs, which are normally quiescent. Activated HSCs transform into myofibroblasts and begin secreting large amounts of collagen and other ECM components.[14] Therefore, activated HSCs are mainly responsible for the excessive synthesis and deposition of ECM in the liver interstitium, leading to fibrosis.[15] TGF-β also regulates HSC autophagy, senescence, metabolism, reactive oxygen species production, epigenetic modifications, and circadian genes, all of which amplify the fibrogenic response.[16]

TGF-β promotes fibrosis by regulating immune cells through complex signaling pathways that recruit and activate multiple immune cell types, particularly macrophages, T cells, and neutrophils. These immune cells are critical for

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initiating and sustaining the fibrotic response. TGF-β induces macrophages to secrete cytokines such as PDGF and TGF-β itself, which, in turn, activate HSCs and enhance collagen deposition.[11] TGF-β can also polarize macrophages to an M2 phenotype, which, while suppressing excessive inflammation, secretes fibrogenic mediators (including TGF-β itself) that further activate HSCs.[11] Concurrently, TGF-β reprograms effector T cells (Th1/Th17) into regulatory T cells, establishing a positive feedback loop that perpetuates fibrosis.[17] Therefore, TGF-β is considered the main factor accelerating liver fibrosis and even regulating liver carcinogenesis.[18]

Despite its pro-fibrotic actions, TGF-β is indispensable for peripheral immune tolerance: Tgfb1 knockout mice succumb to multifocal inflammation within three weeks.[19] Deficiency of TGF-β1 in humans manifests as severe inflammatory bowel disease and encephalopathic syndromes.[20] As a pivotal orchestrator of hepatic immunity, TGF-β fine-tunes immune cell responses to sustain equilibrium between tolerance and effector activation. It is crucial for immune homeostasis through its dual regulation of immunosuppressive regulatory T cells and pro-inflammatory Th17 cell differentiation.[17] Accordingly, pan-ALK5 inhibitors such as LY2157299 produced dose-limiting aortic-valve thickening and anemia in first-in-human studies.[21] Therefore, systemic blockade therapy may trigger autoimmunity, colitis, and impaired tumor surveillance.

TGF-β is a central regulator in chronic liver disease, involved in all stages of progression from initial liver injury through inflammation and fibrosis to cirrhosis and HCC. Upon liver injury, active TGF-β ligands appear in the liver and induce downstream signaling across all cell types. During hepatocarcinogenesis, TGF-β acts as a tumor suppressor in the early stages but later promotes tumor progression.[22]

Due to the key role of TGF-β in liver fibrosis, it has become a potential therapeutic target. Researchers are working to develop strategies targeting the TGF-β signaling pathway, including TGF-β receptor antagonists and TGF-β neutralizing antibodies. These strategies aim to slow or reverse the fibrotic process, thereby improving the prognosis for patients with liver disease.[23] This review describes the current literature on the use of TGF-β inhibitors for treating liver fibrosis.

TGF-β signaling pathways

TGF-β itself (TGF-β1, -β2, and -β3) signals through specific receptor complexes composed of two different proteins, TGFβRII and TGFβRI, which are expressed in all cell types.[8,24] These receptors are transmembrane glycoproteins with kinase activity and can transmit signals across the cell membrane.[25] TGF-β exists initially in an inactive precursor form and binds to TGFβRII after enzymatic activation. TGF-βRII acts as a tyrosine kinase receptor; upon binding to TGF-β, it recruits and promotes the phosphorylation of TGF-βRI.[8] Once activated, TGFβ-RI phosphorylates its substrates, namely the SMAD family proteins. Specifically, TGF-βRI phosphorylates SMAD2 and SMAD3 in the case of TGF-β, or SMAD1, SMAD5, and SMAD8 in the case of BMPs.[26] Phosphorylation of TGFβRI further activates downstream signaling pathways, including both SMAD-dependent and non-SMAD pathways. The SMAD family comprises signal transduction molecules activated by ligands of the TGF-β superfamily (e.g., TGF-β, BMPs), mainly divided into three categories: receptor-regulated SMADs (R-SMADs), common-mediator SMADs, and inhibitory SMADs.[27]

The SMAD-dependent TGF-β signaling pathway in hepatic fibrosis

The SMAD signaling pathway is a classic TGF-β signaling pathway. TGF-β binds to the TGFβRII on the cell membrane in its precursor form, causing a conformational change in TGFβRII and recruitment of TGFβRI (ALK5), which is then phosphorylated. This leads to the phosphorylation of intracellular SMAD2 and SMAD3.[28] These R-SMADs form a heteromeric complex with common-mediator SMAD (SMAD4), which accumulates in the nucleus.[27] In the nucleus, the SMAD complex associates with other transcription factors and regulatory proteins to regulate the transcription of target genes. Additionally, phosphorylation of SMAD2/3 enhances production of MMP1, α-SMA, and type I collagen, promoting liver fibrosis (Fig. 1).[14]

SMAD2/3 signaling plays a vital role in liver fibrosis. Deletion of SMAD3 was reported to prevent liver fibrosis induced by dimethylnitrosamine. SMAD3 acts as a potent stimulator of ECM accumulation and may be a novel target for treating chronic hepatitis complicated by fibrosis.[29] Hepatocyte-specific deletion of SMAD4 inhibited hepatocarcinogenesis in mice by attenuating fibrosis and reducing myeloid-derived suppressor cell infiltration.[30] Moreover, inhibitory SMADs, including SMAD6 and SMAD7, are important antagonists of TGF-β signaling. Studies show that SMAD6 competes with SMAD4 to bind activated SMAD1, thereby inhibiting SMAD1 signaling and SMAD complex formation.[31]

Therefore, SMAD6 and SMAD7 act as negative regulators of TGF-β-mediated liver fibrosis.[32] SMAD6 primarily inhibits BMP signaling, whereas SMAD7 is involved in both BMP and TGF-β signaling (Fig. 1).[31] SMAD7 binds directly to activated type I TGF-β receptors, occupying the same kinase surface that would normally dock SMAD2/3. This competitive binding prevents further phosphorylation and activation of R-SMADs. SMAD7 also competes with SMAD4, preventing the formation of a functional transcriptional complex.[33]

In liver fibrosis, increased expression of SMAD2 and SMAD3 positively regulates fibrogenesis, whereas decreased expression of SMAD7 negatively regulates it.[34] Overexpression of SMAD7 inhibits SMAD3 and significantly reduces the fibrotic response in animal liver fibrosis models, demonstrating SMAD7's anti-fibrotic effects by antagonizing the TGF-β/SMAD3 signaling pathway.[35] Lemonine reduces hepatocyte EMT and HSC activation by upregulating SMAD7, reducing C-terminal phosphorylation (p-SMAD2/3c) and nuclear translocation of SMAD2/3, and inhibiting the TGF-β/SMAD signaling pathway, thereby inhibiting carbon tetrachloride (CCl4)-induced liver fibrosis in mice.[36]

The SMAD signaling pathway has been extensively studied in liver fibrosis. In human keratinocytes, TGF-β induces phosphorylation of SMAD2 and SMAD3, as well as SMAD1 and SMAD5, both dependent on type I and type II kinase activity of the TGF-β receptor.[37] Beyond the canonical SMAD pathway, TGF-β also promotes HSC activation via the ALK1/SMAD1/5 pathway and non-SMAD pathways, including MAPK and PI3K/AKT.[18,38] These pathways can act directly or synergistically with SMAD proteins to regulate gene expression, leading to increased ECM, decreased MMP expression, and promotion of fibrosis.[23,28,39] For example, activated TGF-β1 increases kindlin-2 expression through p38 and MAPK signaling, while kindlin-2 overexpression enhances TGF-β signaling by upregulating SMAD2/3 phosphorylation (Fig. 1).[40]

In HSCs, TGF-β promotes expression of differentiation-inducing factor-1 through the ALK1/SMAD1/5 pathway. Differentiation-inducing factor-1 is a key mediator of liver fibrosis, promoting transdifferentiation of HSCs into myofibroblasts and leading to fibrosis.[41] ALK1 is a transmembrane serine/threonine receptor kinase belonging to the TGF-β receptor family, mainly expressed in endothelial cells.[42] One study showed that ALK1 regulates SMAD1/5 phosphorylation via TGF-β.[43] Recently, Anassuya Ramachandran and colleagues

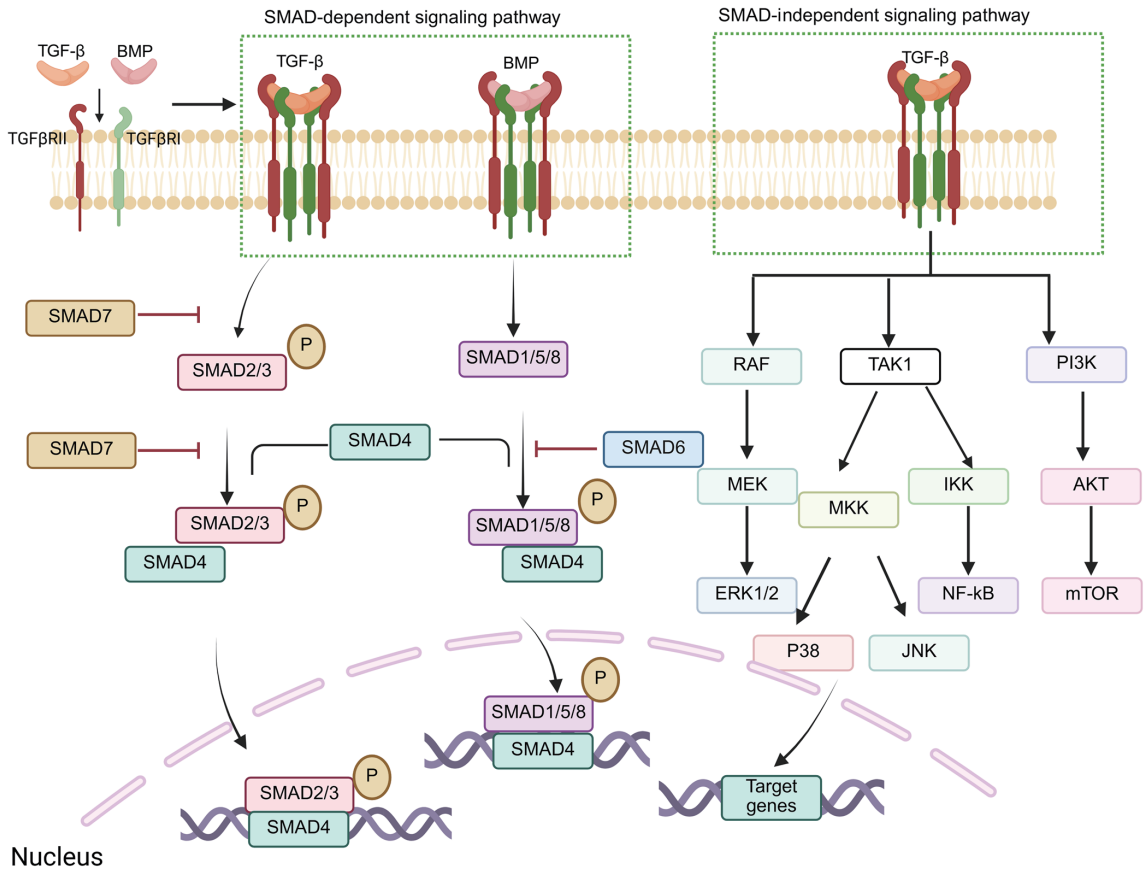

Fig. 1. TGF-β signaling pathway in hepatic fibrosis. TGF-β binds to TGF-β receptors and activates both SMAD-dependent and SMAD-independent pathways. SMAD-independent pathways include p38 MAPK, JNK, NF-κB, PI3K/Akt, and ERK1/2 signaling pathways. Created with BioRender.

found that TGF-β-induced SMAD1/5 phosphorylation requires two type I receptors: the typical TGF-β receptor TGF-βRI and the classic BMP type I receptor ACVR1. The kinase activity of TGF-βRI is necessary to activate ACVR1, and ACVR1 kinase activity is essential for SMAD1/5 phosphorylation (Fig. 1).[44]

The SMAD-independent TGF-β signaling pathway in liver fibrosis

PI3K/Akt pathway: The PI3K/AKT pathway plays an important regulatory role in liver fibrosis progression by modulating cell proliferation, differentiation, autophagy, apoptosis, and other functions, including promoting and inhibiting fibrosis.[45] TGF-β induces PI3K activation, possibly via interaction of the p85 subunit of PI3K with the TGF-β receptor. Activated AKT controls translational responses through mTOR1.[46] EMT is a crucial step in tumor progression and fibrosis, with TGF-β signaling playing a key role. Activation of the PI3K/AKT pathway contributes to TGF-β-induced EMT as well as fibroblast proliferation.[47,48] In an *in vitro* study, Mi *et al*. investigated the involvement of the PI3K/AKT pathway in HSC activation, a driver of liver fibrosis progression. Their study revealed that maltol attenuated liver fibrosis by inducing apoptosis in activated HSCs via regulation of the TGF-β1-mediated PI3K/Akt pathway.[49] Similarly, salvianolic acid A was reported to prevent HSC stimulation by inhibiting the PI3K/AKT/mTOR signaling pathway (Fig. 1).[50]

MAPK pathway: MAPKs are a family of serine/threonine kinases that regulate cellular processes by transmitting extracellular signals into intracellular responses. These include extracellular signal-regulated kinase (ERK), p38 MAPK, and c-Jun N-terminal kinase (JNK), which regulate apoptosis and proliferation.[51–54] MAPK signaling plays a critical role in regulating liver inflammation.[55] TGF-β1 activates HSCs by inducing autophagy through ERK and JNK activation in the MAPK pathway (Fig. 1).[55]

ERK is the most widely studied MAPK signaling pathway, consisting mainly of ERK1 (p44 MAPK) and ERK2 (p42 MAPK). The activation of ERK1/2 is closely associated with HSC activation. Studies have found that incubation of HSCs with cytokines induces interleukin (IL)-11 production, leading to the activation (phosphorylation) of ERK and increases fibrosis markers. Mice injected with IL-11 developed liver damage and fibrosis, whereas blocking IL-11 signaling reduced liver fibrosis in mice. Lee *et al*. found that TGF-β directly phosphorylates ShcA to activate ERK MAPK signaling.[56] ShcA is essential for TGF-β-induced ERK activation (Fig. 1).[57]

TGF-β ligand binding also activates JNK and p38 MAPK signaling pathways via TGF-β receptors.[58] TGF-β-activated kinase 1 (TAK1), a MAPK family member with anti-inflammatory effects,[51] can be activated by multiple stimuli, including TGF-β, tumor necrosis factor-α, IL-1, and lipopolysaccharide.[55] TGF-β1-induced TAK1 activation triggers downstream signaling through MKK4-JNK, MKK3/6-p38 cascades, and the NF-κB-inducing IκB kinase pathway, regulating apoptosis, proliferation, collagen synthesis, and inflammatory cytokines.[55] Hepatocyte-specific TAK1 deletion causes liver injury, fibrosis, and even HCC.[59] The critical role of this path-

Table 1. Targeted therapies against liver fibrosis

Mechanistic class	Generic name	Gov number	Ref
FXR agonist	Obeticholic Acid	NCT02548351	66
CCR2/CCR5 dual antagonist	Cenicriviroc	NCT02217475	67
Pan-PPAR agonist	Lanifibranor	NCT03008070	68
THR-β selective agonist	Resmetirom	NCT03900429	69
LOXL2 monoclonal antibody	Simtuzumab	NCT01672866, NCT01672879	70
ALK5 inhibitor	Galunisertib	NCT01246986	65

way was further demonstrated as mice deficient in both TAK1 and Tgfbr2 exhibited fewer activated HSCs and reduced fibrogenic gene expression.[60] TGF-β1-induced TAK1 activation regulates collagen and inflammatory cytokine expression via the MKK4-JNK and MKK3-p38 cascades.[55] Within cells, JNK activates fibrotic genes and stimulates collagen production. Proinflammatory cytokines activate JNK, which in turn promotes TGF-β expression, amplifying fibrosis. Fabre *et al*. found that IL-17A enhances the response of HSCs to TGF-β by activating the JNK pathway, resulting in increased profibrotic gene expression and collagen production (Fig. 1).[61]

p38 MAPK plays a significant role in promoting liver inflammation progression. Both JNK and p38 MAPK participate in HSC activation, which leads to ECM production and liver fibrosis.[62] A previous study showed that the RING finger protein PNF2, aberrantly expressed in tumors, is highly upregulated in human fibrotic liver tissue. Knockdown of PNF2 inhibited ERK/p38 signaling, thereby reducing liver fibrosis.[63] Additionally, HSCs treated with IL-6 differentiate into myofibroblast-like cells; inhibition of the MAPK pathway suppresses HSC activation (Fig. 1).[64]

Targeting TGF-β to treat liver fibrosis

Current therapeutic strategies for hepatic fibrosis still focus primarily on etiological control. However, etiological treatment alone cannot meet the needs of all patients, making the development of specific anti-fibrotic agents urgently necessary. Table 1 summarizes drugs currently in use for treating hepatic fibrosis that are undergoing clinical trials.[65–70]

Given the vital role of TGF-β in liver fibrosis, inhibition of the TGF-β signaling pathway is considered a promising therapeutic strategy.[14,71] Most anti-TGF-β treatments target various steps of the canonical TGF-β/SMAD signaling pathway to inhibit TGF-β signaling. These approaches can be broadly divided into three categories: (1) monoclonal antibodies that prevent TGF-β receptor binding to ligands, (2) TGF-β receptor kinase small-molecule inhibitors, and (3) small molecules or antibodies that selectively interfere with TGF-β1 activation.[72] These inhibitors include both natural and synthetic compounds. Several TGF-β signaling inhibitors, such as neutralizing antibodies and receptor kinase inhibitors, have been tested in clinical trials.[73] The latest TGF-β inhibitors and related pathway blockers as potential therapies for liver fibrosis are summarized in Table 2.[74–86] Additionally, we screened TGF-β inhibitors for fibrosis treatment, and clinical trial results are presented in Table 3.[87–89]

The effects of TGF-β and its targeted interventions may produce either beneficial or detrimental outcomes for the organ, largely depending on the disease stage. Therefore, it is critical to strategically select the precise therapeutic window, target the correct cell types, and interfere with detrimental signaling branches downstream of the pathway while preserving its protective functions.[71]

Direct blockade of TGF-β

TGF-β antibodies are monoclonal antibodies that specifically target TGF-β. By directly binding to the TGF-β protein, they prevent it from binding to its receptor, thereby inhibiting its biological effects.[90] Monoclonal antibodies targeting TGF-β include CAT-152, CAT-192, and GC1008, which have been tested for systemic inhibition in fibrotic diseases and cancer.[91]

Fresolimumab (GC1008) is a fully human monoclonal antibody targeting all three TGF-β isoforms (TGF-β1, -β2, and -β3). It is currently used in clinical trials for idiopathic pulmonary fibrosis, focal segmental glomerulosclerosis, and cancer.

Table 2. The latest TGF-β inhibitors and related pathway blockers as potential therapies for liver fibrosis

Drug	Targets	Disease	Ref
GC1008 (Fresolimumab)	Pan-TGF-β	Advanced malignant melanoma and renal cell carcinoma	74,75
CAT-152 (Genzyme)	TGF-β2/3	Reduction of scar after glaucoma surgery	76
CAT192 (Metilimumab)	TGF-β1	Diffuse Systemic Sclerosis	77
AP-12009 (Trabedersen)	TGF-β2 mRNA	Oncology	83
LY2157299 (Galunisertib)	TGFβRI kinase	Liver fibrosis	79
TP-0427736	ALK5 inhibitor	Liver fibrosis	80
LY2109761	TGFβRI & RII Kinase	Liver fibrosis	81,82
P11 P12 P144, P54 P106	TGF-β1	Liver fibrosis	78
Pirfenidone	TGF-β/SMAD signaling	Liver fibrosis	84
Hydronidone	TGF-β/SMAD signaling	Liver fibrosis	85
Pentoxifylline	TGF-β/SMAD signaling	Liver fibrosis	86

Table 3. Clinical trial landscape of TGF-β inhibitors

Drug	Target	Disease	Gov number	Safety	Effectiveness	Completion rate	Ref
Galunisertib	TGFβRI kinase	Liver fibrosis	NCT01246986	well tolerated	Improved overall survival	93%	87
Vactosertib	ALK5 inhibitor	Desmoid Tumors	NCT03802084	well tolerated	Prolonged survival	100%	88
Pirfenidone	TGF-β/SMAD signaling	Pulmonary fibrosis	NCT01366209	well tolerated	delayed disease progression	/	89

To date, no clinical trial data on liver fibrosis have been reported.[74,75] A clinical trial in chemotherapy-refractory metastatic breast cancer patients found that high-dose fresolimumab improved overall survival compared with low-dose.[75]

The human monoclonal antibody CAT-152 (Cambridge Antibody Technology, Genzyme) primarily inhibits TGF-β2 activation. Two Phase III clinical studies have suggested that CAT-152 may treat fibrosis after trabeculectomy and prevent postoperative scar formation.[76,92] Another study showed that CAT-152 significantly inhibited streptozotocin-induced renal fibrosis in diabetic rats compared to controls.[93]

Metelimumab (CAT-192) is a human IgG4 monoclonal antibody developed as a TGF-β1-specific antagonist. It was tested in clinical trials for early diffuse cutaneous systemic sclerosis. However, Phase I/II trials showed no evidence of therapeutic effect, and the study was terminated due to lack of efficacy.[77]

Polypeptides derived from TGF-β1 (P11 and P12) and from its type III receptor (P54, P144, and P106) have shown potential in reducing liver fibrosis in chronic liver injury. Studies demonstrated that these peptides block TGF-β1 binding to its cellular receptors and antagonize its activity *in vitro*. In a rat CCl4-induced liver fibrosis model, low-dose intraperitoneal injection of P144 improved fibrosis (Fig. 2).[78]

As noted, the effects of TGF-β and its targeted interventions may yield either beneficial or detrimental outcomes for the organ, largely contingent on the disease stage. It is therefore essential to select the optimal therapeutic window, target appropriate cell types, and inhibit harmful downstream signaling branches while preserving protective functions.[71]

TGF-β1 is the predominant profibrotic and immunosuppressive isoform in liver disease, while TGF-β2/3 maintain

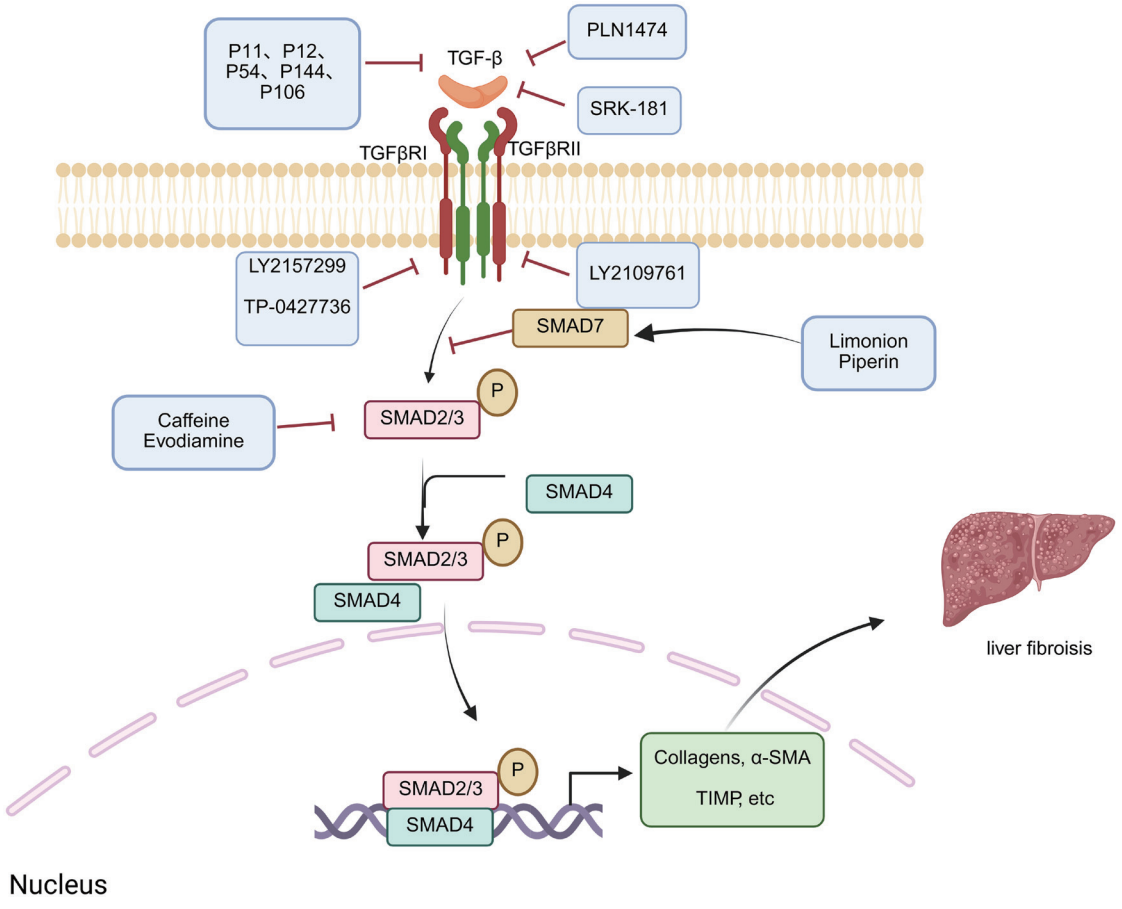

Fig. 2. Therapeutic approaches to inhibit TGF-β/SMAD-induced liver fibrosis. Schematic representation of different strategies targeting TGF-β signaling for liver fibrosis therapy. Created with BioRender.

regenerative capacity and immune homeostasis. SRK-181, a selective TGF-β1 inhibitor, prevented valvulopathy in rats and exhibited no measurable effect on human platelet aggregation, activation, or binding. This agent is currently in a Phase 1 clinical trial.[33] SRK-181, combined with anti-PD-(L)1 antibodies, is also under evaluation in a Phase I trial for solid tumors.[33]

The critical role of integrin-mediated TGF-β activation in hepatic fibrosis is well established. Conditional knockout of αv integrins in HSCs profoundly suppresses fibrogenesis in experimental models.[94,95]

PLN-1474, a selective αvβ1 integrin inhibitor, targets TGF-β1 activation in the liver to reduce fibrosis. It has completed a Phase I clinical trial for NASH-associated liver fibrosis, demonstrating favorable safety and pharmacokinetic profiles.[96]

TGF-β receptor inhibitor

LY2157299 (Galunisertib) is an oral small-molecule inhibitor of TGF-β receptor I kinase with antitumor activity and potential use in treating glioblastoma, pancreatic cancer, and HCC.[65,79] Galunisertib blocks activation of the ALK5 pathway and inhibits SMAD2 phosphorylation, while SMAD1 phosphorylation remains unchanged. Studies have shown that galunisertib inhibits TGF-β-induced collagen production by blocking TGF-β receptors. The treatment has a manageable safety profile.[87] A clinical study involving patients with advanced liver cancer showed that LY2157299 exhibits favorable pharmacokinetics and antitumor efficacy, with no cardiovascular toxicity detected.[79] Luangmonkong *et al*. used precise liver sections from healthy adults and cirrhotic patients to evaluate galunisertib's anti-fibrotic properties, finding significant anti-fibrotic effects likely mediated by inhibition of SMAD2 phosphorylation.[97] Galunisertib was administered on an intermittent dosing regimen (14 days on/14 days off). In HCC patients exhibiting a TGF-β1 response, treatment significantly prolonged median overall survival (22.8 months vs. 12.0 months) while maintaining an acceptable safety profile.[65]

TP-0427736, a novel ALK5 inhibitor first reported in 2013, inhibits TGF-β1-induced SMAD2/3 phosphorylation in A549 cells in a concentration-dependent manner and shows potential as a therapy for Androgenic alopecia.[80] Employing delivery vehicles to selectively transport ALK5 inhibitors to HSCs significantly enhances therapeutic efficacy while reducing systemic exposure risks.[98]

Another TGF-β receptor I kinase inhibitor, LY2109761, has been evaluated in HCC models and found to block HCC cell migration and invasion (Fig. 2).[81,82]

The αvβ8 integrin binds latent TGF-β1 and induces ligand activation *in situ* without releasing the complex, providing a structural basis for compartment-specific blockade of pathogenic TGF-β signaling.[99] Bexotegrast exerts dual-target inhibition of αvβ6/αvβ1-mediated latent TGF-β activation, simultaneously blocking disease-driving TGF-β signaling from epithelial and fibroblast sources while avoiding systemic TGF-β-related toxicities. Phase I-II data indicate favorable safety and dose-dependent anti-fibrotic signaling responses, demonstrating promising therapeutic potential in pulmonary fibrosis.[100]

Antisense oligonucleotides (ASOs)

The key step in activating the TGF-β signaling pathway is ligand binding to its receptor. Classical TGF-β signal transduction involves ligand binding to the TGF-β type II receptor, phosphorylation of SMAD2/3, and activation of SMAD2/3/4 complexes that regulate TGF-β target gene transcription.[27] Therefore, targeting the transcriptional effects of TGF-β is critical.[91] ASOs are single-stranded, modified oligonucleotides that regulate gene expression by binding specifically to target mRNAs. One study showed that using ASOs to antagonize TGF-β1 and SMAD3 inhibited TGF-β signaling, thereby reducing postoperative scar formation.[101]

Trabedersen (AP-12009) is an 18-mer phosphorothioate ASO designed to bind specifically to TGF-β2 mRNA, preventing its translation.[83] It inhibits TGF-β2 production in advanced glioma, melanoma, and colorectal cancer cells. AP15012 and AP11014 have been tested in preclinical trials for prostate, non-small-cell lung, and colorectal cancers. Currently, no clinical trials for HCC have been reported.[102] A clinical study of trabedersen (AP-12009) in glioma treatment showed significantly improved survival rates compared with controls, with 10 μM identified as the optimal dose (Fig. 2).[83]

Inhibition of TGF-β/SMAD signaling

Seniutkin found that pirfenidone exhibited a strong anti-fibrotic effect in early liver fibrosis, but was less effective in late-stage fibrosis and showed no protective effect against liver cancer.[84] Hydronidone, a derivative of pirfenidone, demonstrated in a Phase II clinical trial that when combined with entecavir, it significantly improved liver fibrosis in patients with chronic hepatitis B compared with entecavir alone after 52 weeks.[85] Another study showed that hydroxynidone inhibited phosphorylation of proteins in the TGF-β signaling pathway and alleviated CCl4-induced liver fibrosis in rats (Fig. 2).[103]

As a pirfenidone derivative, hydroxynidone can inhibit phosphorylation within the TGF-β signaling pathway. Additionally, a clinical study showed that fenofibrate combined with pentoxifylline significantly reduced liver fibrosis markers and liver stiffness in patients with non-alcoholic fatty liver disease compared to fenofibrate alone (Fig. 2).[104]

Pentoxifylline is considered an effective antifibrotic agent that inhibits HSC activation *in vitro*. Pentoxifylline exhibits anti-hepatic fibrosis effects both *in vitro* and *in vivo*.[105] In addition, it has protective effects on the lungs and kidneys. Evidence shows that pentoxifylline treatment benefits patients with chronic hepatitis C, improving inflammation and fibrosis, with effects becoming more pronounced after two years of treatment (Fig. 2).[86,106]

Traditional Chinese medicine (TCM)

Natural products contribute to drug discovery, especially for cancer and infectious diseases.[107] TCM, characterized by multi-component, multi-target, and multi-pathway actions, offers unique advantages in treating liver fibrosis.[108,109] Many natural products derived from TCM, including flavonoids, alkaloids, and terpenoids, have demonstrated significant anti-fibrotic activity.[109] TCM-derived compounds with anti-fibrotic potential are summarized in Table 4.[14,36,110–130]

Alkaloids are highly bioactive nitrogen-containing organic compounds widely found in TCM. Numerous studies have shown that alkaloids possess anti-hepatic fibrosis effects.[131] For example, piperine inhibits TGF-β/SMAD signaling by restoring SMAD7, thereby further inhibiting HSC activation (Fig. 2).[110] Chen *et al*. reported that sinomenine suppressed activation of the TGF-β/SMAD pathway both *in vitro* and *in vivo*, alleviating acute liver injury.[111] In addition, caffeine, capsaicin, evodiamine, and matrine can inhibit liver fibrosis by modulating the TGF-β/SMAD pathway (Fig. 2).[112–114,132]

Flavonoids, abundant in plants and berries, exhibit various biological effects. They reduce or reverse liver fibrosis via multiple pathways and targets.[133] Chrysin inhibits HSC activation through the TGF-β/SMAD.[115] Ligustroflavone alleviates CCl4-induced liver fibrosis by downregulating the

Table 4. TCM-derived compounds with anti-fibrotic potential

Compounds	Source	Molecular formula	Mechanisms	Ref	Additional targets	Ref
Piperine	Piper nigrum	C17H19NO3	Inhibiting TGF-β expression	110	NF-κB	120
Sinomenine	Sinomenium acutum	C19H23NO4	Inhibiting TGF-β/ SMAD path-way	111	Nrf2-HO-1	121
Caffeine	Coffea arabica L	C8H10N4O2	Inhibiting SMAD2/3 phosphorylation	112	Adenosine A_2A receptors	122
Capsaicin	Capsicum annuum L.	C18H27NO3	Inhibiting TGF-β1/ SMAD pathway	113	TRPV1	123
Evodiamine	Euodia rutaecarpa (Juss.) Benth	C19H17N3O	Inhibiting TGF-β1/ SMAD pathway	14	Gut microbiota	124
Matrine	Sophora flavescens Alt.	C15H24N2O	Inhibiting TGF-β1 expression	114	PI3K-Akt	125
Chrysin	Oroxylum indicum (Linn.) Kurz	C15H10O4	Inhyibiting TGF-β1/ SMAD path-way	115	AMPK	126
Ligustroflavone	Ligustrum lucidum Ait	C33H40O	Inhibiting TGF-β/ SMAD path-way	116	/	/
Quercetin	Sophora flavescens Ait.	C15H10O7	Regulating p38 MAPK and TGF-β1/SMADs pathway	117,127	PI3K/Akt	127
Limonin	Citrus aurantium L	C26H30O8	Upregulating SMAD7	36	AMPK	128
Andrographolide	Andrographis paniculate	C20H30O5	Inhibiting the TGF-β1/ SMAD2 pathway	119	NF-κB	129
Paeoniflorin	Paeonia lactiflora Pall.	C23H28O1	Inhibiting TGF-β1/ SMADs signaling	118	PPAR-γ	130

TGF-β/SMAD pathway.[116] Quercetin prevents liver fibrosis by reducing TGF-β levels and inhibiting the p38 MAPK signaling pathway.[117]

Terpenoids exhibit antioxidant, metabolic, immunomodulatory, and anti-inflammatory activities. Recognized as anticancer agents, they show good prospects for treating chronic liver diseases.[133] For example, Euphorbesulin A (10), extracted from Euphorbia sieboldiana, inhibits the TGF-β/SMAD signaling pathway and represents a novel anti-liver fibrosis drug; its target may be the TGF-β type I receptor.[134] Limonin alleviates CCl4-induced liver fibrosis by upregulating SMAD7, which suppresses the TGF-β/SMAD cascade.[36] Furthermore, andrographolide and paeoniflorin can treat liver fibrosis by regulating the TGF-β1/SMAD pathway (Fig. 2).[118,119]

Discussion

Hepatic fibrosis is a complex pathological process involving multiple factors, targets, and pathways that can seriously harm human health. Numerous studies have demonstrated that TGF-β plays a critical role in liver fibrosis through multiple signaling pathways, and TGF-β inhibitors hold significant promise for its treatment. Notably, the TGF-βRI kinase inhibitor galunisertib has been clinically used to improve overall survival in patients with HCC. However, in recent years, few clinical trials have targeted TGF-β for treating HCC and liver fibrosis. This may be because dysregulation of the TGF-β cascade is not the primary driver of HCC development, and currently, no TGF-β inhibitors for liver fibrosis have reached the market.

Although the TGF-β signaling pathway is a core driver of fibrosis, current inhibitors face challenges related to efficacy and safety. Therefore, developing next-generation TGF-β inhibitors with improved selectivity, tissue-targeting capabilities, or mechanisms to overcome existing limitations, such as isoform-specific inhibitors, prodrugs, or targeted delivery systems, should be prioritized in the anti-fibrotic drug development pipeline.

Due to the diverse structures, wide availability, multiple targets, and pathways of natural products, exploration of these compounds for liver fibrosis treatment is expanding rapidly. In recent years, many TCMs and their active ingredients have been found to effectively treat hepatic fibrosis through multiple mechanisms with significant effects. However, most of these studies remain at the *in vitro* and *in vivo* experimental stages and lack detailed preclinical and clinical evaluation. Furthermore, research on targets and mechanisms is not yet comprehensive, and pharmacokinetic and pharmacological profiles require further investigation. Therefore, thorough mechanistic studies are essential to define precise targets, pathway modulation, and metabolic behavior *in vivo*, facilitating the rapid translation of these agents into clinical-grade therapeutics.

Given the complex pathological mechanisms underlying fibrosis, combination therapies targeting distinct pathways or cell types, such as combining anti-inflammatory and anti-fibrotic agents or co-administering drugs against different fibrogenic drivers, demonstrate significant potential to overcome drug resistance and enhance therapeutic efficacy, warranting active progression to clinical evaluation.

The TGF-β pathway regulates multiorgan homeostasis, and systemic inhibition may cause immunosuppression, impaired wound healing, and increased tumorigenic risk. Traditional small-molecule inhibitors exhibit off-target effects, and monotherapy struggles to modulate multiple pathological processes simultaneously, including fibrogenesis, inflammation, and metabolic dysregulation. Future research should focus on enhancing localized targeting through organ-re-

stricted inhibitors or novel drug delivery systems (e.g., nanoparticles) to improve selectivity, as well as developing synergistic combination therapies for multi-pathway intervention in hepatic fibrosis.

Conclusions

TGF-β signaling inhibitors hold important therapeutic potential for hepatic fibrosis. Although many challenges remain, detailed exploration of these inhibitors, including certain natural products, is necessary to clarify their anti-fibrotic effects. In the future, effective anti-fibrotic drugs may be developed to alleviate or even reverse the progression of liver fibrosis, ushering in a new era in its pharmacological treatment.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conceptualization (WZ, YC), writing - original draft preparation (WZ, JQ), writing - review and editing (XZ, YG), and supervision (ZS, LH). All authors have read and agreed to the published version of the manuscript.

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