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Review Article

Signaling Pathways in Pancreatic Stellate Cell Activation: A Review of Therapeutic Mechanisms by Traditional Chinese Medicine for Pancreatic Fibrosis

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Abstract

Pancreatic fibrosis, a major pathological feature of chronic pancreatitis, is primarily driven by the abnormal activation of pancreatic stellate cells (PSCs) and excessive deposition of extracellular matrix. Traditional Chinese medicine (TCM) offers a holistic and synergistic approach to preventing and treating pancreatic fibrosis through multi-target regulation of PSC activation. This review systematically elucidates the mechanisms by which TCM—encompassing both bioactive monomers and compound formulations—modulates key signaling pathways involved in PSC activation, including the mitogen-activated protein kinase, transforming growth factor-β/Smad, platelet-derived growth factor, nuclear factor kappa B, and Wingless/β-catenin pathways. By simultaneously targeting these interconnected signaling networks, TCM strategies effectively inhibit PSC activation, attenuate inflammatory responses, and reduce extracellular matrix deposition. In contrast to single-target pharmacological inhibitors, TCM embodies a "multi-component, multi-pathway" therapeutic paradigm that aligns with the complex pathophysiology of pancreatic fibrosis. This review also draws comparative insights from liver fibrosis, highlighting conserved pathways and organ-specific regulatory contexts. Ultimately, TCM represents a promising integrative avenue for the prevention and treatment of pancreatic fibrosis, supported by growing preclinical evidence and aligned with the principles of holistic intervention.

Introduction

Chronic pancreatitis (CP) is a chronic pancreatic disease resulting from persistent inflammation and chronic injury to pancreatic tissue.[1] CP typically presents as localized or diffuse progressive inflammation in the pancreas, easily leading to irreversible damage to the pancreatic parenchyma and ductal structures. Pancreatic fibrosis is a common histopathological feature of CP, characterized by excessive proliferation of fibrous tissue, causing abnormal tissue architecture and loss of function.[2] Quiescent pancreatic stellate cells (PSCs) play a key role in maintaining the normal physiological structure and function of the pancreas. However, the progression of CP leads to the continuous activation of PSCs by pro-inflammatory cytokines and chemokines. Activated PSCs secrete large amounts of extracellular matrix (ECM). The abundant fibrous tissue within the ECM replaces normal pancreatic tissue, leading to pancreatic fibrosis.[3,4] This process involves multiple signaling pathways, such as transforming growth factor-β (TGF-β), mitogen-activated protein kinase (MAPK), and nuclear factor kappa B (NF-κB). Exploring advances in the treatment of pancreatic fibrosis by modulating these signaling pathways is of great significance.[5] Currently, Western medicine treatment for CP focuses primarily on preventing acute attacks, with no specific drugs available. Traditional Chinese medicine (TCM) posits that CP treatment should be tailored based on different clinical manifestations. Preliminary clinical data suggest that Chinese herbal medicine has significant therapeutic effects, warranting further in-depth research.[6,7] Therefore, this study summarizes recent research on treatments targeting key signaling pathways in pancreatic fibrosis and related experiments, and compares them with the regulatory treatments of related signaling pathways in liver fibrosis, aiming to find new ideas for intervening in and treating pancreatic fibrosis.

Although TCM does not have the disease names "chronic pancreatitis" or "pancreatic fibrosis," based on its clinical manifestations such as abdominal pain, emaciation, and diarrhea, it is often categorized under "abdominal pain," "zhēng jiǎ" (masses and accumulations), "jī jù" (accumulation and gathering), or "splenic heart pain" (a TCM syndrome description for epigastric or ab-

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dominal pain). The core pathogenesis in TCM is often attributed to liver qi stagnation (which may correlate with dysregulated stress responses and the neuroendocrine-immune network) and spleen dysfunction (often associated with impaired digestion and metabolism), leading to internal dampness-heat (a TCM syndrome reflecting inflammatory and oxidative stress states), qi stagnation, and blood stasis (reflecting microcirculatory disturbances and pro-fibrotic signaling). Over time, this results in the formation of "micro zhēng jiǎ" (i.e., fibrotic lesions).[8] This pathological process of "deficiency of healthy qi and excess of pathogenic factors" (reflecting impaired immune/repair capacity with persistent inflammatory stimuli) highly aligns with the modern medical understanding of inflammation-driven stellate cell activation and collagen deposition in fibrosis.[9] Therefore, the advantage of TCM in treating CP and its fibrosis lies in "holistic regulation and multi-target intervention." It not only focuses on eliminating the cause, such as clearing dampness-heat (exerting anti-inflammatory and antioxidant effects), but also emphasizes restoring the functions of the zang-fu organs (TCM functional organ systems, often corresponding to, but not identical with, anatomical organs), including soothing the liver and regulating qi, strengthening the spleen and harmonizing the stomach (improving metabolic function and nutritional status), and removing pathological products, including activating blood circulation and resolving stasis (ameliorating microcirculation and inhibiting pro-fibrotic pathways), softening hard masses, and dissipating nodules (promoting resolution of fibrotic lesions). Thereby, it exerts therapeutic effects at multiple stages, including regulating immune inflammation and inhibiting PSC activation.[10] Therefore, the aim of this review is to systematically summarize and analyze the mechanisms by which TCM modulates key signaling pathways involved in PSC activation, to compare these with analogous pathways in liver fibrosis, and to provide new insights and potential therapeutic strategies for the prevention and treatment of pancreatic fibrosis.

Molecular mechanisms of PSC activation

Biological characteristics of PSCs

PSCs are interstitial cells located around pancreatic acini, accounting for approximately 4–7% of total pancreatic cells.[9] In their quiescent state, PSCs contain abundant vitamin A lipid droplets in their cytoplasm and express marker molecules such as desmin. Their primary functions include vitamin A metabolism and participation in pancreatic tissue repair and homeostasis maintenance.[11] When influenced by pathological signals such as inflammatory stimulation, oxidative stress, or tissue damage, PSCs undergo phenotypic transformation: intracellular vitamin A lipid droplets decrease, while markers of myofibroblasts such as α-smooth muscle actin (α-SMA) and vimentin are significantly upregulated.[12,13] Concurrently, they secrete large amounts of ECM components, like type I collagen, type III collagen, and fibronectin, as well as pro-fibrotic factors like TGF-β1 and platelet-derived growth factor (PDGF).[14,15]

Activated PSCs exhibit significant capabilities in proliferation, migration, and contraction. Their functional state is finely regulated by extracellular signals and intracellular signaling pathways. Research indicates that PSC activation is a multi-stage process, primarily including initial activation, sustained activation, and potential resolution phases.[16] In the initial activation stage, inflammatory factors and tissue damage-related signals trigger intracellular responses, accompanied by key events such as calcium homeostasis imbalance and reactive oxygen species (ROS) generation. Subsequently, PSCs maintain a sustained activated state through autocrine or paracrine mechanisms, where factors like TGF-β1 and connective tissue growth factor further amplify fibrotic signals through positive feedback loops.[15] The dynamic plasticity of this process provides potential intervention targets for anti-fibrotic therapy.

Molecular mechanisms of PSC activation

The activation of PSCs is a process driven by multiple pathological factors, primarily involving mechanisms such as inflammatory factors, oxidative stress, metabolic disorders, and intercellular communication. TGF-β1 is the most important pro-activation factor,[14] inducing α-SMA expression and ECM synthesis through both Smad-dependent and -independent pathways. Inflammatory factors like tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1β enhance the proliferation and migration abilities of PSCs via the NF-κB pathway.[17] Oxidative stress induced by alcohol, tobacco, etc., can generate ROS, activating signaling pathways like MAPK and PI3K-Akt, thereby promoting PSC activation, while ROS scavengers can effectively inhibit this activation.[18,19] Hyperglycemia acts through the p38 MAPK pathway, and fatty acid ethyl esters produced by lipid metabolism disorders can also stimulate PSCs to secrete ECM, exacerbating fibrosis.[20] Additionally, damaged acinar cells release exosomes carrying miR-130a-3p, which induce PSC activation by targeting peroxisome proliferator-activated receptor gamma (PPAR-γ). Macrophage-secreted IL-33 can bind to PSC receptors, forming a positive feedback loop of inflammation-fibrosis.[21] The combined action of these multiple signals keeps PSCs in a persistently activated state, driving the process of pancreatic fibrosis.

Key signaling pathways regulating PSC activation

MAPK signaling pathway

The MAPK pathway consists of a group of cascade-activated serine/threonine protein kinases. When activated by cytokines, growth factors, or physical stress, it can influence collagen synthesis and the occurrence of fibrosis. MAPK includes three signal transduction pathways: extracellular signal-regulated kinase 1/2 (ERK1/2), c-Jun N-terminal kinase (JNK), and p38 MAPK. These three pathways interact and participate in the development of pancreatic fibrosis.

The Ras-Raf-MEK-ERK cascade is an important signaling pathway through which ERK regulates gene expression and secretion involved in collagen synthesis, representing the classical ERK pathway.[22] The TGF-β1 factor can promote PSC proliferation via the ERK pathway, and PSC activation is associated with ERK cascade activity. Wang *et al*.[23] found that the anti-pancreatic fibrosis mechanism of Chaihu Guizhi Ganjiang Decoction is related to effectively inhibiting ERK1/2 expression and activity and upregulating the expression of dual-specificity phosphatases. Activated JNK binds to the N-terminal region of transcription activators like activating transcription factor and c-Jun, causing phosphorylation of the active regions of these transcription activators, thereby regulating gene expression and protein synthesis.[24] An *et al*.[25] analyzed the role of fibromodulin in regulating the pro-fibrotic phenotype of PSCs. In rat model experiments, they found that upregulated fibromodulin increased type I collagen and α-SMA expression, promoting PSC proliferation and migration, while ERK and JNK inhibitors attenuated fibromodulin expression.[25] The p38 MAPK regulatory pathway is primarily stimulated by TGF-β factors, af-

fecting apoptosis, proliferation, and inflammatory responses.

Similar signaling pathway changes have also been reported in liver fibrosis. Studies showed that inhibiting the proliferation and activation of hepatic stellate cells (HSCs) and combating severe hepatitis can be achieved by regulating the three MAPK signal transduction pathways, namely reducing the phosphorylation levels of p38 MAPK, JNK, and ERK.[26] Wang *et al*.[27] found that ferulic acid, an extract from *Angelica sinensis* and *Ligusticum chuanxiong*, can effectively inhibit HSC activation, the MAPK signaling pathway, and reduce p38 MAPK phosphorylation levels, thereby resisting liver fibrosis. Yu *et al*.[28] investigated the anti-fibrotic mechanism of gambogic acid in liver fibrosis. The results indicated that gambogic acid improves liver fibrosis and serum markers, reduces ECM accumulation, and initiates mitochondrial-mediated apoptosis pathways to induce HSC autophagy. The anti-fibrotic mechanism is associated with the inhibition of the PI3K/Akt and MAPK signaling pathways.[28]

TGF-β/Smad signaling pathway

TGF-β plays a crucial role in regulating cell generation, differentiation, and development in many biological systems, including three isoforms: TGF-β1, TGF-β2, and TGF-β3. Smad proteins are signal transduction molecules downstream of TGF-β receptors. Based on their functional differences in TGF-β signal transduction, Smads can be classified into receptor-regulated, common-mediator, and inhibitory types. TGF-β1 is mainly secreted by lymphocytes, macrophages, platelets, etc. It binds to receptors on the cell membrane, and the signal is transmitted into the nucleus via Smad molecules in the cytoplasm. Research shows that TGF-β1 is a pro-fibrotic factor. After binding to downstream Smad proteins, TGF-β1 induces HSC activation and promotes ECM deposition, leading to liver fibrosis.[29] In contrast, Smad3 may play a distinct role in regulating PSC proliferation,[30] TGF-β1 can also promote the activating effects of IL-1β and IL-6 on PSCs through an autocrine loop involving Smad2/3 and ERK-mediated pathways.[31] Fan *et al*.[32] found that in the process of baicalin preventing and treating pancreatic fibrosis, the expression levels of the TGF-β1, TGF-β-activated kinase (TAK1), and NF-κB signaling pathways were all reduced, indicating a close association between the activation of these three pathways and pancreatic fibrosis. Dou *et al*.[33] discovered that the modified Chinese herbal formula Chaihu Shugan San exerts its clinical effect against pancreatitis by reducing the expression of TGF-β1 and TNF-α, thereby slowing the fibrosis process.

A similar activation process is also confirmed in the progression of liver fibrosis. Chen *et al*.[34] found that saikosaponin d can achieve anti-liver fibrosis effects by regulating the TGF-β/Smad signaling pathway, inhibiting TGF-β1 and Smad3 mRNA expression levels in rat HSC-T6 cells, and upregulating Smad7 mRNA expression levels.

Pathways related to PDGF activation of PSCs

PDGF can increase the migratory ability of PSCs. As one of the most potent mitogenic stimuli, PDGF promotes the activation, proliferation, collagen synthesis, and ECM production of PSCs. The PDGF protein family consists of four ligands: A, B, C, and D, and functions in regulating cell proliferation, migration, and ECM synthesis. PDGF has a significant chemotactic effect on PSCs, causing activated PSCs to migrate towards damaged sites, exacerbating fibrosis in those areas. The main pathways involved in PDGF-mediated PSC activation are ERK1/2 (MAPK), PI3K/Akt, and the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway.[35] PDGF promotes PSC proliferation primarily by activating the ERK1/2 pathway. ERK1/2 plays an important role in the early stage of PSC activation. Existing research has found that blocking the Ras-Raf-ERK signaling pathway can inhibit PSC proliferation. Activated PSCs express IL-33 in their nuclei, a process promoted by IL-1β through pathways including NF-κB, ERK, p38 MAPK, and PDGF-BB via the ERK pathway. IL-33 may regulate PDGF-induced PSC proliferation.[15] This mechanism is particularly relevant in ethanol- and acetaldehyde-induced PSC activation models.

Simultaneously, studies have shown that the PI3K/Akt pathway also plays a prominent role in fibrosis of other organs, directly participating in the synthesis of inflammatory cells and promoting the fibrotic process.[36] Ye *et al*.[37] found that increased PDGF secretion promotes HSC activation and activates the PI3K/Akt pathway. Seo *et al*.,[38] in mouse model experiments, found that honokiol reduced the expression of TGF-β1 and α-SMA in liver tissue during the inhibition of liver degeneration and necrosis, providing evidence that honokiol resists liver fibrosis by activating JNK and inhibiting the PKB/ERK signaling. Sun *et al*.,[39] in cell experiments, discovered that Jiawei Chaihu Danggui Decoction could inhibit HSC activation and reverse the process of liver fibrosis by regulating the PI3K/Akt signaling pathway. Yang *et al*.[40] discussed that TCM monomers targeting the PI3K/Akt pathway can inhibit HSC activation and promote HSC apoptosis, suggesting that TCM shows potential clinical benefits against hepatic fibrosis.

The PI3K/Akt signaling pathway is primarily related to cell proliferation, protein synthesis, and metabolism. Akt is a downstream molecule of the PI3K pathway. Once activated, Akt can mediate a series of regulations concerning cell growth and metabolism. The JAK/STAT pathway is primarily activated by the binding of cytokines, hormones, and growth factors to their respective receptors, subsequently regulating PSC proliferation. Nintedanib has been approved for the treatment of pulmonary fibrosis. To investigate its mechanism in CP, Han *et al*.[41] used cerulein to induce a rat CP model and found that nintedanib alleviated pancreatic injury and inhibited PSC activation and proliferation through the JAK/STAT3 and ERK1/2 pathways.

NF-κB pathway

NF-κB is a nuclear factor in B lymphocytes. When stimulated, NF-κB dissociates from its inhibitory protein and becomes an active p50/p65 heterodimer. This dimer then enters the nucleus to regulate gene expression. When this dimer regulates the expression of factors like TNF-α, IL-1, and adhesion molecules (ICAM-1), it can activate PSCs.[42] Stimuli involved in the activation process mainly include inflammatory cytokines (e.g., IL-1, IL-6, IL-8), TNF-α, immune receptors, growth factors, viruses, and bacteria.[17] During this process, inhibitor of kappa B (IκB) proteins inhibit NF-κB activation, and IκB kinase promotes the phosphorylation of IκB. Upon stimulation, IκB is phosphorylated by IKK and subsequently degraded, which releases NF-κB to enter the nucleus and regulate gene expression.[43]

Zhao *et al*.[44] summarized the mechanism of curcumin in preventing and treating acute pancreatitis, suggesting that curcumin improves PSC autophagy and inhibits activation to resist fibrosis by inhibiting NF-κB pathway activity, regulating the MAPK pathway, inhibiting JAK/STAT3, and activating PI3K/Akt, among other pathways. In research on the mechanism of action in acute pancreatitis, it was found that reducing the expression levels of TNF-α, IL-1β, IL-6, and alleviating oxidative stress could mitigate the progression of pancreatitis. The mechanism of action manifested as inhibition of the NF-κB/MAPK signaling pathway.[44,45]

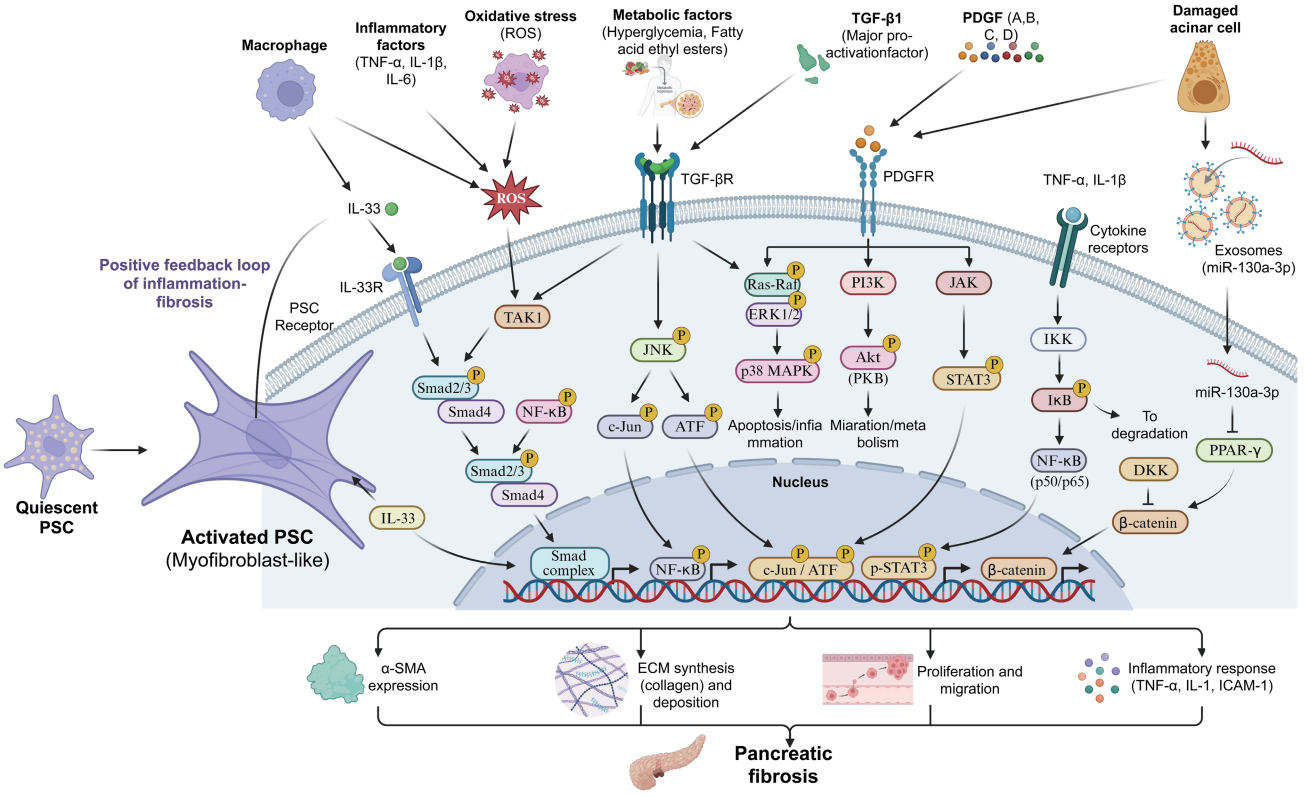

Fig. 1. Signaling pathways and regulatory networks underlying pancreatic stellate cells (PSC) activation and pancreatic fibrosis. Akt, protein kinase B; ATF, activating transcription factor; ECM, extracellular matrix; IL, interleukin; NF-κB, nuclear factor kappa B; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; PPAR-γ, peroxisome proliferator-activated receptor gamma; PSC, pancreatic stellate cell; ROS, reactive oxygen species; Smad, small mothers against decapentaplegic; TGF, transforming growth factor; TNF-α, tumor necrosis factor alpha; α-SMA, alpha-smooth muscle actin.

Tan *et al*.[46] found that the anti-fibrotic mechanism of triptolide in a cerulein-induced CP mouse model was manifested by the inhibition of NF-κB P65 and IL-6 protein expression.

The NF-κB signaling pathway is also a key factor in activating HSCs, influencing hepatic fibrosis by regulating inflammatory signals and fibrotic responses triggered by macrophages and inflammatory cells in the liver. Cai *et al*.,[47] in experiments inducing activation with ginsenoside Rh2, found that ginsenoside Rh2 could inhibit the protein expression of NF-κB P65, p-P65, and p-IκBα, and reduce the levels of α-SMA and inflammatory factors TNF-α, IL-6, and IL-1β, thereby achieving anti-inflammatory and anti-liver fibrosis effects. The process of inhibiting fibrosis was related to the regulation of the TNF/MAPK and NF-κB signaling pathways.[47]

Wingless/β-catenin (Wnt/β-catenin) pathway

The Wnt/β-catenin signaling pathway includes canonical and non-canonical pathways, with the canonical pathway involving β-catenin accumulation and nuclear translocation. Dickkopf-related protein (DKK) is an antagonist of this pathway, specifically inhibiting it. Administration of DKK-1 can inhibit β-catenin nuclear translocation and reduce PSC proliferation and ECM deposition.[48] Cai *et al*.,[49] through rat pancreatic fibrosis model experiments, found that the mechanism by which Dachengqi Decoction improves pancreatic fibrosis is related to the Wnt/β-catenin pathway. The mRNA and protein levels of Wnt/β-catenin in the model group were significantly elevated during the anti-fibrotic process.[49]

Similarly, in research on anti-liver fibrosis, scholars have found that the Wnt/β-catenin signaling pathway primarily plays a role in cell proliferation, differentiation, and apoptosis, activating HSCs and thereby contributing to liver fibrosis.[50] In the Wnt/β-catenin signaling pathway, β-catenin is a multifunctional protein with dual activities in mediating cell adhesion and signal transduction. In activated HSCs, the expression level of β-catenin is five to seven times that in quiescent HSCs.[51] Xiao *et al*.[52] used Fuhu Huayan Decoction in experimental research on inhibiting HSC proliferation in rats. The experimental results showed that the inhibitory mechanism was associated with reduced expression of Wnt1, β-catenin, and Cyclin D1. Activation of the Wnt/β-catenin signaling pathway can exert inhibitory effects on liver fibrosis.[52] The key signaling pathways and molecular regulatory networks involved in PSC activation and pancreatic fibrosis progression are schematically illustrated in Figure 1.

Therapeutic mechanisms and strategies for pancreatic fibrosis

Multidimensional therapeutic approaches

Current research on pancreatic fibrosis encompasses a range of therapeutic strategies aimed at inhibiting PSC activation and halting fibrotic progression. These approaches can be broadly categorized into pharmacological interventions targeting key signaling pathways and cellular-level strategies designed to modulate the fibrotic microenvironment. While small-molecule inhibitors and bi-

ologic agents represent a direct, target-driven modern therapeutic direction, TCM offers a systemic, multi-target intervention model rooted in holistic regulation. These diverse strategies collectively enrich the toolkit for combating pancreatic fibrosis, each with its distinct mechanistic basis and translational potential.

Targeted pharmacological interventions

Small-molecule inhibitors targeting signaling pathways related to PSC activation are an important research direction in current pancreatic fibrosis treatment. SPHK1 inhibitors can reduce S1P production, inhibit S1PR2-mediated PSC autophagy and activation, thereby decreasing the deposition of α-SMA and collagen in the pancreas and improving its function.[53,54] The PI3K/Akt pathway inhibitor LY294002 blocks Akt phosphorylation, suppressing PSC proliferation, migration, and ECM secretion, and significantly alleviates fibrosis.[55] Furthermore, COMP protein is found to induce PSC activation via the CD36-ERK/Akt pathway. Interfering with COMP expression or blocking its interaction with CD36 on PSCs represents a potential therapeutic direction.[22] Additionally, multi-target natural products like curcumin exhibit anti-inflammatory and anti-fibrotic effects by simultaneously modulating pathways such as NF-κB and MAPK.[43] Although these targeted inhibitors show promise in preclinical studies, challenges remain in clinical translation, including potential off-target effects and toxicity, underscoring the need for optimized drug delivery systems and treatment regimens.

Cellular-level intervention strategies

Beyond molecular pharmacology, interventions at the cellular and microenvironmental levels offer complementary avenues. Cell ablation techniques, such as those utilizing the Lrat-Cre system to establish PSC-specific ablation models, demonstrate that targeted elimination of PSCs can effectively reduce fibrosis-related proteins like Col I and Fn, thereby alleviating pancreatic tissue damage.[56] Mesenchymal stem cell therapy represents another advanced strategy, where mesenchymal stem cell-secreted cytokines and exosomes can inhibit PSC activation and promote ECM degradation, leading to improved pancreatic fibrosis and function in animal models. Moreover, since exosomes released by acinar cells carrying miR-130a-3p can induce PSC activation by targeting PPAR-γ,[21] inhibiting exosome production or blocking their delivery emerges as a novel potential anti-fibrotic strategy. These approaches highlight the importance of disrupting the cellular communication networks that sustain fibrogenesis.

The role of TCM in treating pancreatic fibrosis

In contrast to the single-target paradigm of many modern inhibitors, TCM embodies a holistic therapeutic philosophy characterized by "multi-component, multi-target, multi-pathway" synergistic regulation. This approach aligns with the complex, networked pathology of pancreatic fibrosis, where crosstalk among signaling pathways such as TGF-β/Smad, MAPK, and NF-κB sustains PSC activation.

The prevention and treatment of pancreatic fibrosis with TCM follows the principles of "treatment based on syndrome differentiation" (TCM diagnostic and therapeutic tailoring based on holistic symptom patterns) and "treating the root cause of disease" (addressing underlying pathogenesis rather than only symptoms). In the preventive stage, TCM emphasizes early intervention to regulate the internal environment, such as clearing dampness-heat (exerting anti-inflammatory and antioxidant effects), soothing liver qi (modulating stress or inflammatory responses), and strengthening spleen function (improving metabolic function and nutritional status), thereby mitigating inflammatory triggers, oxidative stress, and metabolic disturbances that initiate PSC activation. This proactive approach aligns with the TCM concept of "treating disease before it arises," aiming to delay or halt fibrosis at its origin.

In the therapeutic stage, TCM demonstrates unique advantages of multi-component, multi-target actions. The therapeutic goals are to ameliorate microcirculation, inhibit pro-fibrotic pathways, and promote resolution of fibrotic lesions. These are achieved through TCM methods such as activating blood circulation and resolving stasis (ameliorating microcirculation and inhibiting pro-fibrotic pathways), and softening hard masses and dissipating nodules (promoting resolution of fibrotic lesions), forming a complete system ranging from single herbs or active monomers to compound formulations. Its action does not rely on the blockade of a single target, but rather on the synergistic effects of multiple components that regulate the complex network underlying PSC activation. For instance, TCM monomers such as resveratrol can inhibit ROS-induced PSC activation and glycolysis by downregulating miR-21 and upregulating PTEN expression, alleviating fibrosis.[57] Rhein synergistically inhibits inflammation and PSC activation by regulating the Hedgehog and PI3K/Akt signaling pathways. Epigallocatechin gallate exerts antioxidant effects and intervenes in the PI3K/Akt/Smad pathway, reducing the proliferation and migration capabilities of PSCs.[58]

Among TCM compound formulations, Jianpi Shuyi Decoction reduces the expression of α-SMA and COL-1 by regulating the PI3K/Akt pathway, improving inflammation and collagen deposition.[59] In Dahuang Mudan Decoction combined with Sijunzi Decoction for DBTC-induced pancreatic fibrosis in rats, the expression of α-SMA and COL-1 decreased significantly.[16] Dachaihu Decoction (Da Chaihu Tang) alleviates fibrotic responses by intervening in macrophage-PSC interactions and downregulating inflammatory factors like IL-6 and MCP-1.[60] Modified Xiaochaihu Decoction regulates the TGF-β/Smad pathway, inhibiting the overexpression of type I and III collagen and delaying disease progression.[61]

The core value of TCM in the prevention and treatment of pancreatic fibrosis lies in its ability to synergistically regulate multiple targets within the complex signaling network of disease progression, based on the theories of "holistic view" and "treatment based on syndrome differentiation." This strategy effectively addresses the intricate crosstalk among key pathways such as TGF-β/Smad, MAPK, and NF-κB during the activation of PSCs. Consequently, inhibiting a single pathway may not fully halt fibrosis progression. The "multi-target" nature of TCM compounds and active ingredients enables simultaneous intervention at multiple key nodes within this network, achieving synergistic effects, a core advantage distinguishing TCM from single-target Western drugs and the central theme of this discussion.[62]

Take the classic compound Dachaihu Decoction as an example: its anti-fibrotic effects have been proven to result from coordinated modulation of multiple signaling pathways. Network pharmacology and experimental studies show that active ingredients in Dachaihu Decoction (e.g., saikosaponins, baicalin) significantly downregulate phosphorylated p38 MAPK and ERK1/2 expression in CP models, thereby inhibiting MAPK pathway activation.[63] Additionally, the formula reportedly modulates pathways such as PI3K-Akt.[64] Such synchronous intervention across MAPK, NF-κB, and other pathways synergistically alleviates fibrosis by curbing inflammation and reducing PSC activation/proliferation, exemplifying TCM's "multi-component, multi-target, multi-

pathway" mode of action. Another example is the TCM monomer resveratrol. Research indicates that resveratrol downregulates microRNA-21 expression while upregulating phosphatase and tensin homolog, thereby inhibiting ROS-induced PSC activation, invasion, and glycolysis.[65] This mechanism involves not only oxidative stress regulation but also pathways like PI3K/Akt, closely tied to cell metabolism and survival, again showcasing TCM monomers' capacity to intervene in complex networks.

To systematically summarize the multi-target mechanisms by which TCM intervenes in pancreatic fibrosis through the regulation of signaling pathways, this article compiles the main TCM compounds, active monomers, and their modes of action discussed in the text into Table 1.[16,24,28,29,33–35,45,48,49,51,60–64,66,67] The table details the key signaling pathways affected by each intervention, the experimental models used, and the core effects on PSC activation/fibrosis.

Research challenges and prospects

In recent years, although certain progress has been made in research on pancreatic fibrosis, many problems still need to be solved urgently. Multiple signaling pathways interact during PSC activation and the fibrotic process. Particularly, the synergistic mechanisms between different pathways and their hierarchical relationships at various pathological stages still require further clarification. In reality, the progression of fibrosis is a networked process driven by complex crosstalk among key pathways such as MAPK, TGF-β/Smad, NF-κB, PI3K/Akt, and Wnt/β-catenin. TGF-β1 not only activates the canonical Smad pathway but also stimulates ERK and JNK through non-Smad routes, collectively driving PSC activation, proliferation, and ECM synthesis to promote pancreatic fibrosis.[68] Meanwhile, the NF-κB pathway mediates inflammatory responses by upregulating chemokines like MCP-1 to recruit macrophages, and its activation in PSCs induced by TGF-β1 via p-TAK1 can further amplify the fibrotic microenvironment, forming an "inflammation-fibrosis" positive feedback loop.[44] This multilayered, interconnected pathway network implies that "precision" inhibition targeting a single node may have limited efficacy due to signal redundancy or compensatory activation, potentially failing to disrupt the core network of fibrosis progression.

The complex regulatory relationships among these pathways are not yet fully understood, especially the synergistic mechanisms between pathways and their primary/secondary order at different pathological stages, which still need further clarification. Secondly, PSCs themselves possess heterogeneity. The specific roles of different subpopulations in the fibrotic process remain unclear. How to accurately identify and target these subpopulations is a major difficulty in current research. Additionally, existing animal models have discrepancies with human disease in terms of pathological features and disease progression, limiting the clinical translation of experimental results. Furthermore, most treatment approaches are still in the laboratory research stage, lacking systematic clinical validation, and their long-term efficacy and safety have not yet been clearly established.

Notably, although current research has revealed the potential of TCM in multi-target interventions, this field remains in its early stages and faces several fundamental challenges. The active material basis and precise mechanisms of action are still not fully elucidated. For example, while potential bioactive markers such as saikosaponin B2 and baicalin have been identified in formulations like Dachaihu Decoction, there is still a lack of clear and direct pharmacokinetic and molecular interaction evidence regarding their *in vivo* metabolism, interplay, and collaborative regulation of specific pathway proteins. Most mechanistic studies rely on phenotypic observations and pathway protein expression in cell or animal models, which are essentially correlational and require stronger causal validation. In terms of therapeutic strategies, the "multi-component, multi-target, systemic regulation" model of TCM demonstrates unique advantages in addressing such complex disease networks. Compared to small-molecule inhibitors (such as the PI3K/Akt inhibitor LY294002 or the JAK/STAT inhibitor nintedanib) designed to highly selectively block specific kinases or receptors,[43,57] TCM compound formulas or their active monomers can simultaneously regulate multiple key nodes.[45,59,61] For example, the Da Chaihu Decoction can not only downregulate the phosphorylation levels of p38 MAPK and ERK1/2 but also modulate the PI3K/Akt and NF-κB pathways, thereby producing synergistic effects across multiple levels, including anti-inflammatory, antioxidant, and inhibition of PSC activation.[63] This "systems pharmacology" strategy aligns more closely with the pathological essence of fibrotic diseases. However, it must also be clearly recognized that this "multi-target" characteristic of TCM is a double-edged sword; while it brings holistic therapeutic benefits, it also leads to scientific challenges such as unclear material bases of action, complex pharmacokinetics, and difficulties in assessing potential off-target effects. These are precisely the core issues that modern translational medicine needs to address.

Furthermore, academic debates over the "dominant pathway" highlight the complexity of mechanistic research. Some scholars emphasize TGF-β/Smad as the core hub of fibrosis,[69] while others suggest that MAPK or NF-κB may play more critical roles at different disease stages.[66] This discrepancy reflects an insufficient understanding of the spatiotemporal dynamics of signaling pathways during PSC activation. This controversy further suggests that fibrosis in different organs may exhibit profound specificity. Although pancreatic and hepatic fibrosis share conserved pathways such as TGF-β and MAPK in stellate cell activation, the deep-seated organ-specific differences dictate that treatment strategies cannot be simply transposed. The cellular origins and microenvironments differ. PSCs are closely adjacent to pancreatic acinar cells, making them more susceptible to direct stimulation from pancreas-specific injuries like abnormal activation of pancreatic enzymes or acinar cell necrosis.[67] In contrast, HSCs interact with sinusoidal endothelial cells and hepatocytes, rendering them more vulnerable to influences from gut-derived toxins and lipid metabolites in portal venous blood.[70] The disease progression and clinical outcomes diverge significantly. Pancreatic fibrosis often leads to pancreatic duct distortion and impaired pancreatic juice drainage, resulting in intractable pain and exocrine insufficiency, whereas liver fibrosis primarily causes portal hypertension and liver failure.[71] There may be differences in cellular phenotypes and plasticity. Therefore, even when targeting the same pathway, PI3K/Akt, the efficacy and adverse effect profiles of inhibitors may vary between the two organs.[72] Future drug development must be optimized in the context of organ-specific pathophysiological backgrounds. Whether TCM interventions exhibit stage-specific effects remains an unexplored gap.

In terms of translational applications, significant challenges related to bioavailability and clinical validation persist. Polyphenolic compounds such as resveratrol and curcumin face well-known difficulties including low oral bioavailability, rapid metabolism, and poor targeting.[73] Although novel technologies like nano-formulations offer potential solutions, successful clinical translation remains distant.[74] More importantly, most evidence supporting TCM for anti-pancreatic fibrosis comes from preclinical studies, with a

Table 1. Summary of specific mechanisms of traditional Chinese medicine (TCM) in modulating signaling pathways for pancreatic fibrosis treatment

Category	TCM intervention	Key signaling pathways/ Molecular targets involved	Experimental model/context	Main effects on PSCs/Fibrosis	Ref.
Compound formulations	Chaihu Guizhi Ganjiang Decoction	Inhibits ERK1/2 pathway	Animal model	Anti-fibrosis	24
	Modified Chaihu Shugan San	Reduces expression of TGF-β1 and TNF-α	Clinical/experimental study	Slows fibrosis progression	34
	Dachaihu Decoction	Regulates MAPK (p38, ERK1/2); PI3K-Akt; modulates macrophage-PSC interaction	Animal models and network pharmacology	Inhibits PSC activation, reduces inflammation (IL-6, MCP-1)	63,66,67
	Dahuang Mudan Decoction + Sijunzi Decoction	Reduces α-SMA & COL-I expression	DBTC-induced rat model	Ameliorates fibrosis	16
	Dachengqi Decoction	Affects Wnt/β-catenin pathway	Rat pancreatic fibrosis model	Ameliorates fibrosis	51
	Modified Xiaochaihu Decoction	Regulates TGF-β/Smad pathway	Mechanistic summary	Inhibits collagen I & III overexpression	64
	Jianpi Shuyi Decoction	Regulates PI3K/Akt pathway	Animal experiments & network pharmacology	Reduces α-SMA & COL-I, improves inflammation	62
Active monomers	Baicalin	Inhibits TGF-β1/TAK1/NF-κB pathways	Mice with CP	Inhibits PSC activation	33
	Curcumin	Inhibits NF-κB; regulates MAPK, JAK/STAT3; activates PI3K/Akt	Mechanism review	Improves PSC autophagy, inhibits activation	45
	Triptolide	Inhibits NF-κB P65, reduces IL-6	Cerulein-induced CP mouse model	Anti-fibrotic	48
	Resveratrol	Downregulates miR-21, upregulates PTEN; inhibits ROS-induced activation	*In vitro* PSC studies	Inhibits activation, invasion, and glycolysis	60
	Rhein	Regulates Hedgehog and PI3K/Akt pathways	Mechanistic analysis	Inhibits inflammation and PSC activation	61
	Epigallocatechin gallate	Antioxidant; intervenes in PI3K/Akt/Smad pathway	Mechanistic analysis	Reduces PSC proliferation and migration	61
	Ferulic acid	Inhibits MAPK and NF-κB/IκBα pathways	Rat liver fibrosis model (mechanism analogy)	Anti-fibrotic (implied for pancreas)	28
	Gambogic acid	Inhibits PI3K/Akt and MAPK pathways	Liver fibrosis study (mechanism analogy)	Induces HSC autophagy/apoptosis	29
	Saikosaponin D	Regulates TGFβ-Smad pathway (inhibits TGF-β1/Smad3, upregulates Smad7)	Rat HSC-T6 cells (mechanism analogy)	Anti-fibrotic	35
	Ginsenoside Rh2	Regulates TNF/MAPK and NF-κB pathways	LX-2 cell activation model (mechanism analogy)	Anti-inflammatory, anti-fibrotic	49

Akt, protein kinase B; COL-I, collagen type I; CP, chronic pancreatitis; DBTC, dibutyltin dichloride; ERK1/2, extracellular signal-regulated kinase 1/2; HSCs, hepatic stellate cells; HSC-T6, rat hepatic stellate cell line T6; IL-6, interleukin-6; JAK, Janus kinase; LX-2, human hepatic stellate cell line LX-2; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; NF-κB, nuclear factor kappa B; PI3K, phosphoinositide 3-kinase; PSCs, pancreatic stellate cells; PTEN, phosphatase and tensin homolog; ROS, reactive oxygen species; Smad, small mothers against decapentaplegic; STAT3, signal transducer and activator of transcription 3; TAK1, transforming growth factor-β-activated kinase 1; TCM, traditional Chinese medicine; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; Wnt, Wingless/Integrated; α-SMA, alpha-smooth muscle actin.

notable lack of high-quality, large-scale randomized controlled trials to systematically evaluate its efficacy and safety.

Addressing the above issues, future research should develop in several directions. Integrating multi-omics technologies such as genomics, transcriptomics, and proteomics is expected to more comprehensively reveal the molecular mechanisms of pancreatic fibrosis and discover new intervention targets. Simultaneously, developing drug delivery systems with tissue specificity can improve

therapeutic efficacy while reducing adverse effects. The development of organoid technology provides the possibility to construct experimental models closer to the human physiological state, which is also expected to be used for more precise drug screening and mechanism research. Moreover, combining the advantages of TCM's multi-target and holistic regulation with modern pharmacological analysis methods will help promote innovation in integrated Chinese and Western medicine treatment strategies, providing new ideas for the clinical intervention of pancreatic fibrosis.

Conclusions

This review highlights that TCM intervenes in pancreatic fibrosis through a "multi-component, multi-pathway" paradigm, simultaneously modulating key signaling pathways such as TGF-β/Smad, MAPK, NF-κB, PI3K/Akt, and Wnt/β-catenin. Unlike single-target inhibitors, TCM's holistic approach, employing both compound formulations and bioactive monomers, synergistically inhibits PSC activation, attenuates inflammation, and reduces ECM deposition. Although challenges remain in elucidating precise material bases and clinical translation, TCM's ability to network-regulate the complex pathophysiology of fibrosis offers a promising integrative strategy for preventing and treating pancreatic fibrosis.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Conception of the study, literature collection, and manuscript preparation (ZG), and critical revision of the manuscript (HZ). Both authors have read and approved the final manuscript.

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