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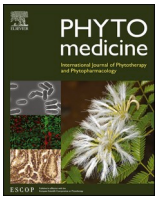

A three-year review (2023–2025) on the effectiveness of natural products from plants in treating major types of fibrosis

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ABSTRACT

Background: Fibrosis, or fibrotic scarring, is the body's response to injury that leads to the formation of fibrous connective tissue. It impacts various illnesses and can contribute to mortality. Currently, there are no effective treatments targeting the release of extracellular matrix (ECM) from fibroblasts, highlighting the urgent need for new therapies. Medicinal plants and their derivatives may offer a promising alternative for treating fibrosis.
Purpose: This review aims to summarize the findings from reports published between 2023 and 2025 on the role of natural substances derived from plants in the treatment of four major types of fibrosis: myocardial fibrosis (MF), liver fibrosis (LF), pulmonary fibrosis (PF), and renal fibrosis (RF).
Methods: Data were sourced from PubMed, Google Scholar, ScienceDirect, and Scopus using terms related to fibrosis, such as "diagnosis," "treatment," "plant extracts," and "phytochemicals." Information on antifibrotic plant extracts and formulations from 2023 to 2025 was compiled.
Results: This review presents essential information on four main types of fibrosis and documents 72 botanicals. These consist of 28 individual plants studied separately and 44 combined herbal formulations. The botanicals are categorized according to the different types of fibrosis: 21 for LF, 8 for MF, 23 for PF, and 20 for RF. The review provides detailed information on 10 polyherbal formulations, which include: *Guizhi Fuling Wan* (GFW), *Jiawei Taohe Chengqi* decoction (JTCD), *Longdan Xiegan Tang* (LXT), and *Tao-Hong-Si-Wu-Tang* (THSWT) for LF; *Linggui Zhugan* decoction (LGZGD) and *Qili Qiangxin* (QLQX) for MF; *Sha-Shen Mai-Dong* (SMT) and *Xuanfei Baidu* decoction (XFBD) for PF; and *Huangqi-Danshen* (HDD) and *Jian-Pi-Yi-Shen* (JPYS) for RF. Additionally, the document lists 35 phytochemicals, which include 19 terpenoids and 16 phenolic compounds.
Conclusion: This work highlights that, over the past three years, numerous scientific publications have underscored the importance of medicinal plants in treating various types of fibrosis globally. To improve the management of fibrosis, it is essential to conduct both preclinical and clinical studies on these promising samples to identify potential drug candidates.

Abbreviations: **1**, (20*S*,22*R*)-15α-acetoxy-5α-chloro-6β,14β-dihydroxy-1-oxowitha- 2,24-dienolide; **2**, 12-*O*-acetylphorbol-13-isobutyrate; **3**, 25-OH-PPT; **4**, 8-*O*-acetyl shanzhiside methyl ester; **5**, loganate; **6**, loganin; **7**, physagulide I; **8**, physagulin A; **9**, physagulin B; **10**, physagulin C; **11**, physalin B; **12**, physalin F; **13**, physapubescin; **14**, scabrol B; **15**, scabrol C; **16**, shanzhiside methyl ester; **17**, tagitinin C; **18**, withagulide F; **19**, withgulatin A; **20**, acteoside.

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Introduction

Fibrosis, commonly referred to as fibrotic scarring, is a critical response of the body in which fibrous connective tissue forms following an injury. This process can either be a normal part of healing or, in some cases, an excessive response driven by disease (Wynn, 2004). The consequences of fibrosis often occur after repeated injuries, chronic inflammation, or ongoing repair, resulting in the overwhelming production of extracellular matrix (ECM) components, particularly collagen, by fibroblasts (Birbrair et al., 2014; Wynn, 2004). This can culminate in the development of a permanent fibrotic scar. Understanding fibrosis is essential, as it highlights the body's complex healing mechanisms and the potential for tissue damage that can lead to lasting health challenges. Understanding the need to prevent and manage fibrosis is crucial for recovery and overall well-being. Injuries frequently lead to scarring, a complex process with serious health implications. If fibrosis arises from a single cell line, it becomes a fibroma. This condition, while part of the body's healing response through connective tissue deposition, can disrupt the normal structure and function of vital organs. Fibrosis is characterized by excessive accumulation of fibrous tissue and the buildup of ECM proteins, which can lead to scarring and thickening that impairs organ function (Neary et al., 2015). Although it is a natural healing process, it can have serious consequences, making awareness and proactive management essential. Fibrosis, like scarring, is an essential biological response where activated fibroblasts produce connective tissue, including collagen and glycosaminoglycans. This process begins when immune cells, particularly macrophages, release factors like transforming growth factor beta (TGF-β), the most prominent pro-fibrotic mediator, along with connective tissue growth factor (CTGF), nowadays known as cellular communication network factor 2 (CCN2), platelet-derived growth factor (PDGF), and interleukin 10 (IL-10) (Mitra et al., 2015). These mediators activate crucial signaling pathways such as AKT/mTOR and SMAD, leading to fibroblast proliferation and activation (Leask and Abraham, 2004; Mitra et al., 2015). As fibroblasts function, they deposit ECM in the surrounding tissue, driving repair. However, while tissue repair is necessary, it must be carefully regulated. Disruption of this balance, often due to severe tissue injury or a misguided healing response, can result in a progressive and irreversible fibrotic response. Common areas affected by fibrosis include the lungs, liver, kidneys, brain, and heart. Many fibrotic disorders are caused by infections, with bacteria, viruses, fungi, and multicellular parasites causing chronic inflammation and fibrosis. Pathogen-associated molecular patterns (PAMPs) found in these organisms are thought to keep myofibroblasts in an activated state (Meneghin and Hogaboam, 2007). Additionally, gut bacteria can also activate these cells. PAMPs, which include lipoproteins, bacterial DNA, and double-stranded RNA, are recognized by pattern recognition receptors on various cells, including fibroblasts (Otte et al., 2003). This interaction serves as a defense mechanism during infections and triggers pro-inflammatory responses. Fibroblasts, expressing toll-like receptors (TLRs), can be stimulated by Toll ligands to differentiate into collagen-producing myofibroblasts (Coelho et al., 2005; Meneghin and Hogaboam, 2007; Otte et al., 2003). However, not all fibrotic disorders are caused by pathogens. In systemic sclerosis (SSc), fibroblasts from affected tissues show a constantly activated myofibroblast-like phenotype, driven by an autocrine signal from TGF-β (Abraham and Varga, 2005; Kaviratne et al., 2004). Other mechanisms, such as viruses like cytomegalovirus (CMV), can also stimulate myofibroblast activation by producing autoantibodies and CTGF/CCN2 (Markiewicz et al., 2004). Additionally, epigenetic changes and cytokine production by B cells and Th2-type cells may play a significant role. Hence, both paracrine signals from activated lymphocytes and autocrine factors from fibroblasts, along with inputs from pathogens, can work together to initiate and maintain myofibroblast activation.

Fibrosis was historically considered an irreversible process, but now, reversal in liver and lung tissue, as well as cases of renal, myocardial, and oral-submucosal fibrosis, have been demonstrated (Chang et al., 2018; Eddy, 2005; Frangogiannis, 2019; Ismail and Pinzani, 2009; Shetty et al., 2021). Fibrosis is a major contributor to morbidity and mortality in modern society, with very few treatment options effectively targeting the release of ECM from fibroblasts. This gap underscores the urgent need for innovative therapies that can address the root causes of fibrosis and improve patient outcomes. The role of medicinal plants and their constituent as an undeniable source of medicine for treating various human and animal ailments has been widely established (Efferth et al., 2021; Kuete, 2025). Medicinal plants and their derivatives are a promising alternative for treating fibrosis (Bahri et al., 2017; Hassan et al., 2019; Weiskirchen et al., 2015). In this review, we will provide fundamental information about fibrosis and summarize data from the years 2023 to 2025 of data demonstrating the significance of natural substances from the plant kingdom as potential alternatives in the treatment of four major types of fibrosis: myocardial fibrosis (MF), liver fibrosis (LF), pulmonary fibrosis (PF), and renal fibrosis (RF). The rationale for conducting a review every three years is based on the significant amount of work published in the past three years.

Material and methods

Data was collected from the PubMed, Google Scholar, ScienceDirect, and Scopus databases using relevant terms related to fibrosis, including "diagnosis," "treatment," "plant extracts," and "phytochemicals." Information on antifibrotic plant extracts, phytochemicals, and plant-based formulations from 2023 to 2025 was gathered and compiled.

Results

Anatomical location of fibrosis and possible contributing factors

Fibrosis is the process of excessive scarring that exceeds normal healing, disrupting the architecture of tissues and impairing the function of organs. This complex process involves specific molecular signals and cellular responses triggered by ongoing injury and cell death. These events lead to inflammation, activation of macrophages, and the infiltration of immune cells (Weiskirchen et al., 2019). Biologically active mediators, such as alarmins and cytokines, stimulate collagen-producing mesenchymal cells, promote the transformation of various cells into myofibroblasts, and recruit fibroblast precursors (Weiskirchen et al., 2019). Fibrosis can develop in various tissues throughout the body, often because of inflammation or injury. Common areas affected by fibrosis include the lungs (such as fibrothorax, PF including cystic fibrosis and idiopathic PF (IPF), and radiation-induced lung injury from cancer treatments), liver (including bridging fibrosis and cirrhosis), kidneys, brain (leading to glial scars), and heart (Chang et al., 2018; Eddy, 2005; Frangogiannis, 2019; Ismail and Pinzani, 2009). The possible contributing factors for LF include viral hepatitis, schistosomiasis, and alcoholism, which are among the leading causes of cirrhosis worldwide (Wynn, 2004). Lung fibrosis is often associated with interstitial lung diseases (ILDs), a diverse group of disorders characterized by pulmonary inflammation and fibrosis as the final common pathological manifestations. There are over 150 different causes of ILDs, including sarcoidosis, silicosis, drug reactions, infections, and collagen vascular diseases such as rheumatoid arthritis and systemic sclerosis (scleroderma). IPF, the most common type of ILD, has no known cause. In the case of heart and vascular disease following a heart attack, scar tissue can impede the heart's ability to pump blood effectively. Additionally, factors such as hypertension, atherosclerosis, and restenosis can also contribute to complications. Alzheimer's disease significantly contributes to brain fibrosis.

Fibrosis can have a significant impact on various parts of the body, leading to serious health issues. These include arterial stiffness, which increases the risk of cardiovascular problems, arthrofibrosis, which restricts motion in joints such as the knee and shoulder, chronic kidney

disease (CKD), which can threaten kidney function, Crohn's disease, causing digestive complications, and Dupuytren's contracture, limiting hand and finger mobility. Other consequences of fibrosis may include keloids (resulting in raised scars on the skin), lipedema (causing abnormal fat accumulation in the lower limbs), mediastinal fibrosis (obstructing vital soft tissue), myelofibrosis (affecting blood health due to compromised bone marrow), and myofibrosis (impacting muscle strength and movement). Additionally, conditions such as Peyronie's disease (leading to penile curvature and affecting sexual health), nephrogenic systemic fibrosis (causing skin discomfort), progressive massive fibrosis (resulting in severe lung issues due to pneumoconiosis), retroperitoneal fibrosis (potentially affecting vital organs), scleroderma/systemic sclerosis (compromising skin and lung function), and certain forms of adhesive capsulitis (limiting shoulder mobility) can also arise due to fibrosis (Duffield, 2014; Wynn, 2004).

Wound healing versus fibrosis

Wound healing and fibrosis are two distinct responses to tissue injury, each with important health implications. Wound healing is a complex process that restores tissue integrity through stages like hemostasis, inflammation, proliferation, and remodeling, ultimately aiming to regenerate healthy tissue. In contrast, fibrosis involves excessive scar tissue formation following injury or chronic inflammation, leading to compromised organ function and often associated with chronic diseases. While wound healing seeks to restore normal function, fibrosis results in stiff, dysfunctional tissue. In effect, when epithelial and endothelial cells are damaged, they release inflammatory mediators that trigger a coagulation cascade, leading to blood clot formation and the creation of a provisional ECM (Kumar et al., 2005). Platelets aggregate and form clots, while degranulation promotes vasodilation and increases blood vessel permeability. Myofibroblasts and endothelial cells produce matrix metalloproteinases (MMPs) that disrupt the basement membrane, allowing inflammatory cells to reach the injury site. Growth factors, cytokines, and chemokines are released to recruit leukocytes, including macrophages and neutrophils, which eliminate debris and produce additional cytokines that stimulate endothelial cell activity. As these cells migrate toward the wound, they help form new blood vessels. Concurrently, lymphocytes activate and secrete profibrotic cytokines like TGF-β, IL-13, and PDGF, which further stimulate macrophages and fibroblasts (Li et al., 2006; Parsons et al., 2007; Wynn, 2003). Activated fibroblasts convert into myofibroblasts, which aid in wound contraction by bringing the wound edges closer together. Subsequently, epithelial and endothelial cells proliferate and migrate to restore the tissue. Nevertheless, prolonged inflammation may cause an excessive accumulation of ECM, resulting in fibrotic scarring. The balance between collagen synthesis and degradation, controlled by matrix metalloproteinases (MMPs) and their inhibitors, determines the overall amount of collagen. Fibrosis arises when collagen synthesis exceeds its degradation (Parsons et al., 2007).

Cellular and molecular mechanisms in fibrosis

The activation of fibroblasts plays a crucial role in normal tissue remodeling, particularly during wound healing. However, when regulatory mechanisms fail and fibroblasts remain abnormally activated, it triggers an excessive buildup of ECM(Dees et al., 2021; Wynn, 2004). This unchecked process leads to tissue fibrosis, which can severely impair the function of the affected organ or even result in its complete loss of function. This highlights the importance of maintaining proper fibroblast regulation to ensure healthy tissue repair and prevent debilitating outcomes. The key mediator of fibrosis is the myofibroblast, a critical cell that takes charge of collagen production upon activation. Myofibroblasts emerge from various origins, including resident mesenchymal cells, as well as epithelial and endothelial cells through processes known as epithelial-mesenchymal transition (EMT) and endothelial-mesenchymal transition (EndMT). Additionally, myofibroblasts can arise from circulating fibroblast-like cells, known as fibrocytes, which are sourced from bone marrow stem cells. The activation of myofibroblasts is triggered by a complex interplay of mechanisms. They respond to paracrine signals from lymphocytes and macrophages, autocrine factors that they produce, and PAMPs from harmful organisms that engage pattern recognition receptors, such as TLRs, on fibroblasts (Wynn, 2004). The regulation of fibrosis is heavily influenced by a suite of key players, including chemokines (like MCP-1 and MIP-1β), cytokines (notably IL-13, IL-21, and TGF-β1), angiogenic factors (such as vascular endothelial growth factor (VEGF)), and growth factors (including PDGF). Furthermore, peroxisome proliferator-activated receptors, acute phase proteins (*e.g.*, SAP), caspases, and components of the renin-angiotensin-aldosterone system (notably angiotensin II, ANGII) also play crucial roles in this dynamic process. Given the vital role these factors play in fibrosis, they represent a promising frontier for the development of innovative antifibrotic drugs, making them a focal point of ongoing research and exploration (Wynn, 2004).

Chemokines play a crucial role in fibrogenesis by regulating the recruitment of myofibroblasts. Chemokines are molecules that attract leukocytes and work with profibrotic cytokines to promote fibrosis by recruiting myofibroblasts, macrophages, and other key effector cells to tissue injury sites. The CC- and CXC-chemokine receptor families play crucial regulatory roles in this process. Key profibrotic mediators include CCL3 (macrophage inflammatory protein 1α) and CCL2 (monocyte chemoattractant protein-1), which attract mononuclear phagocytes. Macrophages and epithelial cells are major sources of CCL3. Studies using the bleomycin (Bleomycin) (BLM) model of PF show that anti-CCL3 and anti-CCL2 antibodies significantly reduce fibrosis, indicating the involvement of multiple CC-chemokines (Lloyd et al., 1997; Smith et al., 1994, 1995). Studies with CCR1- and CCR2-deficient mice confirm the significance of CCL3/CCL2 signaling in fibrogenesis (Tokuda et al., 2000; Wynn, 2004). Blease and collaborators, as well as Gao and his team, have demonstrated that the absence of fibrosis correlates with lower IL-4 and IL-13 expression, suggesting a link between CC-chemokines and profibrotic cytokines (Blease et al., 2000; Gao et al., 1997). IL-13 promotes several CC-chemokines, including CCL3, CCL4 (MIP-1β), CCL20 (MIP-3α), CCL2, CCL11, CCL22 (macrophage-derived chemokine), and CCL6 (C10), among others, indicating a potential feedback mechanism between IL-13 and the CC-chemokine family (Belperio et al., 2002; Ma et al., 2004). Additionally, antibodies against CCL3 and CCL2 reduce lung remodeling in both IL-13-transgenic mice and BLM-challenged mice, highlighting the distinct roles of various CC-chemokines in fibrosis (Belperio et al., 2002; Ma et al., 2004). It was also shown that chemokine receptors such as CXCR4, CCR7, and CCR2 also regulate fibrocyte recruitment to the lungs in mice (Moore et al., 2005; Phillips et al., 2004). Interrupting specific chemokine signaling pathways could greatly benefit the treatment of fibroproliferative diseases.

Th1 and Th2 cells differentially regulate organ fibrosis. Chronic inflammatory reactions are defined by a significant infiltration of mononuclear cells, including macrophages, lymphocytes, eosinophils, and plasma cells. Upon encountering antigens at injury sites, lymphocytes activate and produce lymphokines that enhance the activity of macrophages and local inflammatory cells, fueling the adaptive immune response critical to many chronic inflammatory diseases. Interestingly, while inflammation often precedes fibrosis, it was shown that the mechanisms behind fibrosis can differ. The studies of Wynn on schistosomiasis-induced LF demonstrate that progressive fibrosis is linked to schistosome eggs, triggering a chronic granulomatous response with $CD4^+$ *T* cells playing a key role (Wynn, 2004). Furthermore, experiments with cytokine-deficient mice reveal a strong connection between LF and a $CD4^+$ Th2 cell response, involving IL-4, IL-5, IL-13, and IL-21 (Cheever et al., 1994; Chiaramonte et al., 1999; Pesce et al., 2006; Reiman et al., 2006; Wynn et al., 1995). Several experimental models of fibrosis have documented potent antifibrotic activities for the

Th1-associated cytokines gamma-interferon (IFN-γ) and IL-12 (Wynn, 2004; Wynn et al., 1995). Th2 cytokines IL-4, IL-5, IL-13, and IL-21 are significant in tissue remodeling and fibrosis (Emura et al., 1990). IL-4 levels are higher in the bronchoalveolar lavage fluids of IPF patients, in the interstitial tissue of cryptogenic fibrosing alveolitis, and in peripheral blood mononuclear cells (PBMCs) of individuals with periportal fibrosis (Emura et al., 1990; Wynn, 2004). It is a potent profibrotic mediator, potentially almost twice as effective as TGF-β, and its inhibitors can reduce dermal fibrosis in chronic skin graft rejection and mouse models of scleroderma (Fertin et al., 1991). IL-5 regulates the differentiation, activation, and recruitment of eosinophils, which produce fibrogenic cytokines such as TGF-β1 and IL-13. These eosinophils and IL-5 have been linked to diseases such as skin allograft rejection and PF (Ochkur et al., 2007; Wynn, 2004). Their key role may be to promote profibrotic cytokines, essential mediators of fibrosis. IL-13 and IL-4 perform similar functions by utilizing the IL-4Rα/STAT6 signaling pathways. In mice, the overexpression of IL-13 in the lungs has been linked to significant subepithelial airway fibrosis, even in the absence of additional inflammation (Zhu et al., 1999). Also, treatment with an anti-IL-13 antibody has been shown to reduce collagen deposition in the lungs of mice exposed to *Aspergillus fumigatus* conidia or BLM (Belperio et al., 2002; Blease et al., 2001). Pesce and his collaborators demonstrated that IL-21/IL-21R signaling promotes fibrosis by enhancing the CD4+ Th2 response and is essential for the survival and migration of Th2 cells (Pesce et al., 2006). Additionally, IL-21 increases IL-4 and IL-13 receptor expression on macrophages, which supports the development of alternatively activated macrophages that regulate fibrosis (Duffield et al., 2005; Hesse et al., 2001; Pesce et al., 2006). TGF-β is a key regulator of the ECM and is linked to fibrosis in various diseases. There are three isotypes in mammals (TGF-β1, −2, and −3), all with similar biological activity. TGF-β1, primarily sourced from circulating monocytes and tissue macrophages, plays a central role in tissue fibrosis. In macrophages, control occurs mainly through the regulation of TGF-β1 secretion and activation rather than mRNA expression (Wynn, 2004). TGF-β activates transmembrane receptors, which in turn trigger SMAD proteins that regulate the transcription of key genes, such as procollagen I and III. In mice lacking SMAD3, both dermal fibrosis caused by irradiation and renal interstitial fibrosis resulting from unilateral ureteral obstruction are significantly reduced (Flanders et al., 2002; Sato et al., 2003), underscoring the critical role of the TGF-β pathway. Macrophage-derived TGF-β1 likely promotes fibrosis by activating resident mesenchymal cells, which leads to the differentiation of myofibroblasts through EMT.

The development of fibrotic diseases such as IPF, SSc, and LF involves significant changes in blood vessels, often occurring before the onset of fibrosis. In systemic sclerosis, early vascular changes include impaired angiogenesis and reduced blood vessels, possibly linked to lower circulating $CD34^{+}$ endothelial progenitor cells (Abraham and Varga, 2005). Targeting the CXC-chemokine family may help regulate angiogenesis and fibrosis due to their angiogenic and angiostatic activities (Strieter et al., 2007).

Endogenous mechanisms that can slow fibrosis progression include IL-10 and the IL-13 decoy receptor (IL-13Rα2). IL-10 acts as an immunosuppressive cytokine that down-regulates chronic inflammation and inhibits fibrosis in various models (Moore et al., 2001). It was shown that mice treated with IL-10 show significantly less fibrosis in the liver, lung, and pancreas when exposed to fibrosis-inducing agents (Thompson et al., 1998). Conversely, IL-10-deficient mice are more susceptible to these compounds. IL-10 was also found to suppress type I collagen synthesis in human fibroblasts and reduce LF severity in patients with chronic hepatitis C (Wangoo et al., 1997). In a schistosomiasis model, IL-10 deficiency alone has shown little impact on hepatic fibrosis, but crossing $IL\text{-}10^{-/-}$ mice with other deficient strains such as $IFN\text{-}\gamma^{-/-}$, $IL\text{-}12^{-/-}$ or $IL\text{-}13R\alpha2^{-/-}$ leads to accelerated fibrosis, indicating its cooperation with Th1 cytokines and the IL-13 decoy receptor to reduce collagen deposition (Hoffmann et al., 2000; Vaillant et al., 2001; Wilson et al., 2007). Low levels of IL-10 and IFN-γ have been associated with severe fibrosis in human *Schistosoma mansoni* infections (Booth et al., 2004). Soluble IL-13Rα2-Fc effectively inhibits the actions of IL-13, which helps slow the progression of fibrotic disease (Wynn, 2004). It does this by blocking the interaction between IL-13 and the type II IL-4R complex. Mice that lack IL-13Rα2 show increased activity of IL-13 and significantly greater LF after infection with *S. mansoni*, even though their inflammatory responses remain unchanged (Wood et al., 2003). It was shown that IL-13Rα2 directly inhibits the ECM-remodeling effects of IL-13 (Wood et al., 2003). Additionally, IL-13Rα2-deficient mice exhibited more severe granulomatous inflammation and LF, resulting in rapid death (Mentink-Kane et al., 2004). This highlights the critical role of IL-13Rα2 in regulating Th2-driven inflammation and fibrosis.

In PF, TGF-β1 plays a central role, with emerging reports on the involvement of TGF-β2 and TGF-β3 (Kruit et al., 2006). Additionally, there are experimental anti-fibrotic therapies in development targeting hepatic stellate cells, collagen synthesis, and TGF-β (Breitkopf et al., 2005; Puche et al., 2013; Zois et al., 2008). TGF-β is crucial in renal fibrosis (RF) related to CKD. It is produced by kidney cells and infiltrating leukocytes and can also be filtered from plasma during proteinuria. The three isoforms-TGF-β1, TGF-β2, and TGF-β3-signal through Smad proteins. In the unilateral ureteral obstruction (UUO) model, TGF-β1 interacts with fibrogenic SMADs (SMAD2 and SMAD3) as well as fibrosis-inhibiting Smad7 (Fukasawa et al., 2004). TGF-β activates myofibroblasts in various kidney cells, contributing to both glomerular and interstitial fibrosis through processes such as apoptosis and epithelial-to-mesenchymal transition (EMT). While trials targeting TGF-β have been conducted, their results have been inconclusive, partly due to complications such as TGF-β deficiency leading to inflammation (Cheng and Wong, 2017). ANGII plays a crucial role in inflammation and fibrosis in kidney diseases through its type 1 receptors (AT1) (Ruiz-Ortega et al., 2006; Yayama and Okamoto, 2008). The type 2 receptor (AT2), more common in fetal tissue, may help mitigate the harmful effects of ANGII (Wenzel et al., 2010). ANGII contributes to ECM accumulation *via* profibrotic factors like TGF-β; blocking ANGII in chronic kidney conditions can reduce plasma TGF-β levels. Moreover, ANGII causes oxidative stress, negatively impacting nitric oxide levels and kidney blood flow. While angiotensin-converting enzyme (ACE) inhibitors are critical for kidney development, they may worsen inflammation and fibrosis in conditions such as partial UUO in neonatal rats (Cheng and Wong, 2017). CTGF/CCN2 is a key profibrotic factor in RF and plays a role in tubuloepithelial transdifferentiation by mediating TGF-β activity. In humans, CTGF/CCN2 levels increase with chronic renal injury but can be reduced by ACE inhibitors and AT1 receptor antagonists (Cheng and Wong, 2017). Lin et al. found that pentoxifylline suppresses CTGF/CCN2 activity in rats with unilateral ureteral obstruction by targeting Smad3 and Smad4-dependent transcription (Lin et al., 2002). In RF, the UUO model, which simulates human obstructive nephropathy, involves ligating one ureter while leaving the other as a control. Signs of interstitial fibrosis and tubular apoptosis can appear as early as three days after the surgical procedure (Cho, 2010). In chronic UUO models, tubular atrophy and interstitial fibrosis occur before significant renal pelvic dilation and reduced renal growth. Research involving Wilms' tumor 1 gene (WT-1) knockout and transgenic mice indicates they may develop either crescentic glomerulonephritis or mesangial sclerosis based on WT-1 levels in the Denys-Drash syndrome murine model. Additionally, transgenic mice possessing the Thy-1.1 antigen on podocytes can develop focal glomerulosclerosis (Cho, 2010). PDGF is crucial in RF, similar to CTGF/CCN2 (Ostendorf et al., 2001). In a rat model of mesangioproliferative glomerulonephritis, a PDGF-B antagonist reduced mesangioproliferative changes, glomerular hypertrophy, and podocyte damage, while also preventing long-term glomerulosclerosis and tubulointerstitial damage (Ostendorf et al., 2001). Increased levels of PDGF-C and PDGF-D in fibrotic lesions indicate their potential role in RF. Other key factors involved in RF include endothelin-1 (ET-1), tumor necrosis factor-alpha (TNF-α),

interleukin-1 (IL-1), hepatocyte growth factor, bone morphogenetic protein-7, IFN-γ, and insulin-like growth factor-1 (IGF-1), all of which are known to have antifibrotic effects (Cho, 2010).

Overview of the major types of fibrosis

In this section, we will discuss the major types of fibrosis: pulmonary, liver, cardiac, and renal fibrosis.

Pulmonary fibrosis. PF occurs in about 25 % of chronic sarcoidosis patients (Kruit et al., 2006). The most prevalent form of PF is IPF. Other common types of PF are often associated with systemic diseases, primarily systemic sclerosis and rheumatoid arthritis, or they can develop as fibrosing forms of hypersensitivity pneumonitis (HP) (Kreuter et al., 2021). They are diagnosed based on clinical, radiological, and, when necessary, histological findings. The treatment of PF varies based on its subtype and clinical behavior. For IPF, antifibrotic therapy is recommended (Kreuter et al., 2021). In contrast, for fibrotic hypersensitivity pneumonitis, the main approach is to avoid the triggering antigen and to modulate the immune system; in cases of PF associated with systemic diseases, the primary mode of treatment is immune suppression (Kreuter et al., 2021). Additionally, antifibrotic agents can be beneficial for other types of progressive PF beyond IPF. The treatment of PF includes non-pharmacological and pharmacological options. Non-pharmacological treatments aim to improve symptoms and physical condition, with long-term oxygen therapy being one example. Pharmacological treatment targets the specific type of PF; for IPF, antifibrotic therapies like nintedanib or pirfenidone are recommended as soon as the diagnosis is made (Kreuter et al., 2021). Fibrosing HP has less established treatment evidence, but avoiding the culprit antigen is crucial for a better prognosis. Immune suppressants may be used, though data on their effectiveness is limited. In PF related to systemic inflammatory diseases, controlling the underlying disease can reduce progression, and immune modulation is preferred. Methotrexate, abatacept, and rituximab have been discussed, but evidence largely comes from retrospective studies (Kreuter et al., 2021). For treating systemic sclerosis-associated PF, the primary drugs include immunomodulators such as mycophenolate and cyclophosphamide, often with low-dose prednisone. Cyclophosphamide is recommended despite its relatively weak effects, as shown in a Cochrane analysis, while mycophenolate offers similar efficacy with lower discontinuation rates and side effects (Kreuter et al., 2021). The SENSCIS trial investigated nintedanib as antifibrotic therapy, showing a beneficial effect on pulmonary function and well-tolerated side effects (Kreuter et al., 2021). Its relative effect size was about 45 %, like that for IPF, with less decline in systemic sclerosis patients. Nintedanib is used alongside mycophenolate in about half of the trial participants, but its combination with other drugs needs clarification (Kreuter et al., 2021). The American Thoracic Society (ATS) 2023/24 strongly recommends the use of mycophenolate mofetil (CellCept®) as the primary treatment. They conditionally suggest the use of cyclophosphamide, rituximab, tocilizumab, nintedanib, and a combination of nintedanib with MMF (Raghu et al., 2024). The ATS also calls for further research on pirfenidone and its combination with MMF. The European Respiratory Society (ERS) 2024 aligns with the ATS by ranking MMF as the primary treatment option. They support exploring additional therapies depending on the severity of the condition and emphasize the importance of tailored therapy and ongoing monitoring (Ciplamed, 2024).

Liver fibrosis. LF or hepatic fibrosis is the excessive buildup of ECM proteins in the liver due to chronic injury and inflammation, often seen in individuals with chronic alcoholism or obesity (Hassan et al., 2019; Tacke and Weiskirchen, 2021). LF plays a crucial role in the diagnosis and management of chronic liver diseases. Although liver biopsy is still relevant, non-invasive assessments are now preferred in most cases. Techniques such as transient elastography, acoustic radiation force impulse imaging, shear wave elastography, and magnetic resonance elastography are effective for diagnosing advanced fibrosis and cirrhosis. Additionally, serum test formulas like FibroTest®, FibroMeter®, and Enhanced LF are available, and combining different methods can improve diagnostic accuracy (Cheng and Wong, 2017). These assessments also have prognostic capabilities, such as predicting the risk of hepatocellular carcinoma (HCC) using the LSM-HCC score. Treatment primarily focuses on managing underlying conditions, especially chronic viral hepatitis, and there are ongoing trials aimed at addressing non-alcoholic fatty liver disease (Cheng and Wong, 2017; George et al., 2009).

Cardiac fibrosis. Cardiac fibrosis also refers to an abnormal thickening of the heart valves, involving the excessive deposition of ECM in the heart muscle or thickening of heart valves due to increased activity of cardiac fibroblasts. This fibrotic tissue results in stiffer cardiac muscle and is associated with the progression of heart failure. MF can manifest in different forms, including interstitial fibrosis, which occurs in conditions such as congestive heart failure and hypertension; subepicardial fibrosis that can arise from non-infarction diagnoses; and replacement fibrosis, which indicates old heart attacks (Bhaskaran et al., 2019; Chute et al., 2019). Traditionally, MF has been evaluated through endocardial biopsy or autopsy, with collagen volume fraction used to measure the extent of fibrosis (Sun et al., 2019; Zhu et al., 2022). However, these methods are invasive and may not accurately reflect the condition of the myocardium, which has led to the development of non-invasive techniques. Cardiovascular magnetic resonance has emerged as the non-invasive gold standard for assessing MF, offering valuable insights into myocardial anatomy, function, and tissue characteristics (Zhu et al., 2022). Treatment options for cardiac fibrosis include discontinuing stimulatory medications, utilizing somatostatin analogs for functional neuroendocrine tumors, performing surgical valve replacements, and exploring potential interventions such as resveratrol and microRNA inhibition (Nguyen et al., 2019; Olson et al., 2005).

Renal fibrosis. RF, marked by tubulointerstitial fibrosis and glomerulosclerosis, is the final stage of CKD (Liu, 2006). This progression can lead to end-stage renal disease, requiring treatments like dialysis or transplantation. Conditions such as glomerulonephritis, diabetes, and obstructive nephropathy contribute to CKD, with RF as the common endpoint characterized by ECM accumulation (Cho, 2010). Evaluating kidney fibrosis is essential for assessing prognosis and guiding therapy in both native and transplanted kidneys. Currently, biopsy remains the gold standard for evaluating fibrosis using histological techniques (Klinkhammer and Boor, 2023). Nephrotoxic serum nephritis is a model for anti-glomerular basement membrane (anti-GBM) disease and immune-complex glomerulonephritis, characterized by linear deposition of anti-GBM antibodies and an autologous immune response (Cho, 2010). It is effective for studying fibrosis in mice, showing collagen deposition and EMT within 1–2 weeks, and severe tubulointerstitial fibrosis by weeks 3–6. Despite identifying potential targets for treating RF, effective treatments are still lacking. Boor et al. highlighted several challenges, including discrepancies between rodent models and clinical situations, inadequate modeling, inconsistent evaluation methods, and poorly timed treatments in experimental fibrosis (Boor et al., 2007).

The use of botanicals and phytochemicals as a therapeutic approach to treating fibrosis

Fibrotic diseases are associated with significant morbidity and mortality, yet few drugs have been approved by the U.S. Food and Drug Administration for their treatment. Developing effective anti-fibrotic therapies faces several challenges, including the complexity of fibrotic signaling, undesirable side effects on healthy tissues, the slow progression of fibrosis requiring lengthy clinical trials, and variable patient responses (Azeredo et al., 2024). There is a crucial need for better treatments, and research is increasingly exploring plant-derived compounds for their potential to stop or reverse fibrosis. Botanicals have long been recognized as a source of medicine for various human and animal ailments (Efferth et al., 2021; Kuete, 2025). Numerous studies

explore the mechanisms of fibrosis, examining pharmacological agents and plant extracts as potential therapeutic alternatives due to their bioactive compounds. In China, plant extracts have been used for over thirty years to treat PF (Bahri et al., 2017; Imadaya et al., 1983). For example, Chen (1987) demonstrated that red sage (*Salvia miltiorrhiza* Bunge, Lamiaceae) and IH764–3 protect against BLM-induced PF in mice by inhibiting fibroblast proliferation *in vitro* (Chen, 1992, 1987). Similarly, *Angelica sinensis* (Oliv.) Diels (Apiaceae) has shown protective benefits in rat models of lung fibrosis (Dai et al., 1996). Some reported plant constituents that modulate fibrosis include α-lipoic acid (organosulfur dithiol), curcumin (diferuloylmethane), capsaicin (alkaloid), emodin (anthraquinone), ellagic acid, spigallocatechin-3-gallate (polyphenol), genistein, naringin, naringenin (flavonoids), quercetin (biflavonoid), resveratrol (stilbene), and sulforaphane (isothiocyanate) (Azeredo et al., 2024).

A systematic review published in 2017 by Bahri and his team examined the efficacy of plant extracts and bioactive compounds in treating PF (Bahri et al., 2017). The authors compiled data on both *in vivo* and *in vitro* effects of various botanicals and phytochemicals, using BLM to induce lung inflammation, oxidative stress, and PF in rats. They identified some promising plants, including *Camellia sinensis* (L.) Kuntze (Theaceae), *Vitis vinifera* L. (Vitaceae), and *Rosmarinus officinalis* L. (Lamiaceae). Additionally, they highlighted phytochemicals such as terpenoids (*e.g.*, triptolide and madecassoside), phenolics (*e.g.*, resveratrol, quercetin, mangiferin, and dihydroquercetin), and alkaloids (*e.g.*, isolinensinine). In an interesting review of promising treatments for cardiac fibrosis using herbal plants and their extracts, Yu in 2023 has cataloged several botanicals, such as *Corydalis hendersonii* Hemsl. (Papaveraceae), *Sophora alopecuroides* L. (Fabaceae), *Nigella sativa* L. (Ranunculaceae), *Hibiscus sabdariffa* L. (Malvaceae), *R. officinalis L., Ulmus wallichiana* Planchon (Ulmaceae) (Yu, 2023); He has also cataloged phytochemicals such as andrographolide (diterpene), arctiin (lignan glycoside), arjunolic acid (triterpenoid), astragaloside IV (triterpenoid saponin), baicalin (flavonoid), kaempferol (flavonoid), myricitrin (flavonoid glycoside), scutellarin (flavonoid glycoside), and zingerone (phenylpropanoid). In a compelling review of edible plant-derived natural compounds for the treatment of LF, Xu et al. in 2023 examined the current advancements in the use of dietary plant natural compounds for this condition. The review highlights several categories of compounds, including phenolic compounds (capsaicin, chlorogenic acid, curcumin, ellagic acid, epigallocatechin-3-gallate, resveratrol, sinapic acid, syringic acid, vanillic acid, and vitamin E), flavonoid compounds (genistein, hesperidin, hesperetin, naringenin, naringin, and quercetin), sulfur-containing compounds (S-allyl cysteine, ergothioneine, lipoic acid, and sulforaphane) and other compounds (betaine, caffeine, cucurbitacin B, lycopene, α-mangostin, γ-mangostin, ursolic acid, vitamin C and yangonin) (Chen et al., 2022). In a 2022 review, Chen and collaborators systematically summarized the latest research on treating RF with natural products derived from Chinese herbal medicines (Chen et al., 2022). They identified various secondary plant metabolites including the flavonoids such as quercetin, puerarin, isoliquiritigenin, and barleriside A, polyphenols such as curcumin, resveratrol, epigallocatechin gallate, salvianolic acid A, schisandrin B, quinones such as tanshinone IIA, emodin, and chrysophanol, terpenoids such as poricoic acid A, poricoic acid ZC, ZD, ZE, ZG, ZH, ZI, ZM, and Z, alisol B23-acetate, and triptolide, as well as alkaloids such as ligustrazine, leonurine, berberine, and glycosides such as astragaloside IV, salidroside, dioscin. In a compelling review of the therapeutic potential of natural products for schistosomiasis-associated LF, Liu and his collaborators have compiled a list of several effective botanicals and phytochemicals (Liu et al., 2024). The identified samples included silymarin (a standardized dried extract of the fruit and seeds of *Silybum marianum* (l.) Gaertn.: silybin, isosilybin, silydianin, and silychristin), extracts from *Citrus sinensis*, and *Boswellia serrata* Roxb. (Burseraceae) resin, *Ampelopsis grossedentata* (Hand.-Mazz.) W.T. Wang (Vitaceae), *Zingiber officinale* Roscoe (Zinziberaceae), and *Ziziphus spina-christi* L.. (Rhamnaceae); hey identified various plant constituents, including artemisinin and its derivatives (sesquiterpene lactone), chlorogenic acid (a polyphenol), corilagin (an ellagitannin), resveratrol (a stilbene), curcumin (a polyphenol), genistein (an isoflavone), and paeoniflorin (a monoterpene glycoside).

This discussion will examine key plant-derived products that influence fibrosis and their underlying mechanisms, as summarized in Tables 1 and 2. It will also provide updated information on effective antifibrotic agents sourced from plants for the major types of fibrosis, including liver, myocardial, and PF, covering the period from 2023 to 2025.

Potential of botanicals against fibrosis

A variety of botanicals have been assessed for their antifibrotic potential, either individually or in combinations of plants, as outlined in Table 1. This document reports on 72 botanicals, which include 28 individual plants studied separately and 44 combined herbal formulations. These are categorized by different fibrotic types: 21 botanicals for LF, 8 botanicals for MF, 23 botanicals for PF, and 20 botanicals for RF.

Botanicals against LF. The LF models examined in the screening of the reported botanicals included several *in vitro* and *in vivo* models. These are: the *in vitro* cell culture model using hepatic stellate cells (HSCs), the bile duct ligation (BDL)-induced LF model in mice and rats, the methionine and choline-deficient (MCD) diet-induced LF model in mice, the chronic diet-induced high-fat diet-induced LF model in mice, the dimethylnitrosamine (DMN)-induced LF model in rats, the silibinin (SILT)-induced LF model in mice, and the thioacetamide (TAA)-induced LF models in both rats and mice (Table 1). As a result, the plants with established effects on LF or hepatic fibrosis included the crude extracts from *Artemisia argyi* Levl. et Vaniot -Argyi Wormwood. (Asteraceae), *Baccharis anomala* DC. (Asteraceae), *Carthamus tinctorius* L. (Asteraceae), *Corydalis saxicola* Bunting (Papaveraceae), *Crocus sativus* L. (Iridaceae), *Ficus hirta* Vahl. (Moraceae), *Lonicera japonica* Thunberg (Caprifoliaceae), *Portulaca oleracea* L. (Portulacaceae), and *Tithonia diversifolia* A. Gray (Asteraceae), and the polyherbal preparations *Da Huang Zhe Chong* pill (DHZCP), *Er Tao* decoction (ETD), *Fu Zheng Hua Yu* tablets, *Gan Shuang* granule (GSG), *Gui Zhi Fuling Wan* (GFW), *Jiawei Qi Gong Wan* (JQGW), *Jiawei Taohe Chengqi* decoction (JTCD), *Longdan Xiegan Tang* (LXT), *Shu Gan Jian Pi* formula (SGJPF), *Si Wu Tang* (SWT), *Tao Hong Si Wu Tang* (THSWT), and *Wu Ling* capsule (WL) (Table 1). GFW, JTCD, LXT, and THSWT are discussed in more detail below. These botanicals influence genes related to fibrosis, lower levels of NF-κB, and affect liver metabolism; they block the PI3K/AKT/mTOR pathway, inhibit the upregulation of HIF-1α and VEGFα, and regulate the gut microbiota; additionally, these they prevent STING-mediated macrophage activation and inhibit the NLRP3 inflammasome; they also down-regulate TIMP-1, PDGF-B, and TGF-β1; key pathways affected include PTEN/AKT/mTOR and TLR-4/NF-κB; overall, these botanicals contribute to decreased LF scores, reduced collagen and alpha-smooth muscle actin (α-SMA) deposition, and alleviation of liver inflammation (Table 1).

Botanicals against MF. The MF models evaluated in the screening of the reported botanicals included both *in vitro* and *in vivo* models. These models consisted of surgically ligating the left anterior descending (LAD)-induced MF in mice and rats, bilateral thyroidectomy (BTE)-induced MF in rats, transverse aortic constriction (TAC)-induced MF in mice, an *in vitro* cell culture model of MF using myocardial cells, and isoproterenol (ISO)-induced MF in mice (Table 1). Several plants have demonstrated significant effects on MF, including crude extracts from various sources. Notable examples include the crude extract from *Malus toringoides* (Rehd.) Hughes (Rosaceae) and several polyherbal formulations, such as *Dan Shen Yin* (DSY), *Er Shen Zhen Wu* decoction (ESZWD), *Guan Xin Ning* injection (GXN), *Ling Gui Zhu Gan* decoction (LGZGD), *Qi Li Qiang Xin* (QLQX), *Tong Xin Luo* (TXL), and *Zhen-Wu-Tang* (ZWT). Detailed information about LGZGD and QLQX is discussed below. The mechanisms of action of these botanicals, as summarized in Table 1,

Table 1
Anti-fibrotic botanicals and other plant-based preparations recorded in various experimental models from 2023 to 2025.

Botanicals	Composition	Experimental models	Anti-fibrotic effects
Alpinia officinarum Hance (Zingiberaceae)	Rhizome extract	BLM-induced PF in rats	Rhizome extract decreases histopathological injuries, inducible nitric oxide synthase, α-smooth muscle actin, and TGF-β immune-expression (Al-Gholam et al., 2025)
Angelica sinensis (Oliv.) Diels (Apiaceae)	Angelicae Sinensis Radix	Radiation-induced PF in rats	The dried root referred to as Angelicae Sinensis Radix improves PF by regulating NRF2/xCT/GPX4 signaling pathway (Wang et al., 2024a).
Antrodia cinnamomea AC (Fomitopsidaceae)	Crude extract	BLM-induced PF in mice; *in vitro* cell culture model	The crude extract decreases collagen expression in TGF-β1-induced MRC-5 cells, increases body weight, improves pulmonary function, and decreases the levels of inflammatory factors and fibrosis markers in BLM-induced PF mice (Lan et al., 2024).
Artemisia argyi Levl. et Vaniot, Argyi Wormwood. (Asteraceae)	Crude EtOH extract	CDAHFD-induced LF in mice	The crude extract improves plasma and liver lipid profiles, modulates hepatic mRNA expression levels of antioxidant, lipolytic, and fibrosis-related genes (Erdenebileg et al., 2024).
Astragalus membranaceus (Fisch.) Bge., (Fabaceae)	Astragali Radix	Radiation-induced PF in rats	The dried root referred to as Astragali Radix extract improves PF by regulating NRF/xCT/GPX4 signaling pathway (Wang et al., 2024a).
Baccharis anomala DC. (Asteraceae)	Crude extract	CCl_4-induced LF in mice	The crude extract reduces inflammation and alleviates hepatic fibrosis in mice by decreasing NF-κB levels and ECM components (de Souza Basso et al., 2024).
Dang Gui Bu Xue decoction (DBD)	*A. membranaceus* and *A. sinensis*	*In vitro* cell culture model of RF	DBD regulates autophagy in renal podocytes to improve FF in diabetic mice through the miR-27a/PI3K/AKT pathway (Cai et al., 2025).
Bu Shen Huo Xue (BSHX)	*Astragalus mongholicus* Bunge and *Trigonella foenum-graecum* L.l. (Fabaceae), *Rheum palmatum* L., *Vaccaria segetalis* (Neck.) Garcke. (Caryophyllaceae), and *Curcuma phaeocaulis* Val. (Zingiberaceae)	5/6 Nephrectomy-induced RF in rats	BSHX decreases RF and pyroptosis through the inhibition of ROS and NLRP3-mediated inflammasome activation (Liao et al., 2024).
Bu Yang Huan Wu decoction (BYHWD)	*A. membranaceus, A. sinensis, Prunus persica* (L.) Batsch (Rosaceae), *Pheretima aspergillum* (Megascolecidae), *Ligusticum striatum* DC. (Apiaceae), *Carthamus tinctorius* L. (Asteraceae), and Radix Paeoniae Rubra (the dried root of *Paeonia lactiflora* Pallas and *Paeonia veitchii* Lynch (Paeoniaceae))	BLM-induced PF in mice	BYHWD down-regulated the mRNA expression levels of TNF, IL-6, IL-1β, and NOS2 and inhibited NF-κB and p38 phosphorylation (Dai et al., 2024).
Cannabis sp. (Cannabaceae)	cannabis oil	FA-induced RF in rats	Protective effect of Lebanese cannabis oil extract from flower as it increases serum creatinine, decreases serum creatinine, and reduces serum sodium in FA-induced RF in rats; showed restores the migratory capacity of podocytes, increases of phospho-(S473)-AKT along with a decrease in phospho (T180 + Y182) p38 levels *in vitro* in podocyte cells (Bylan et al., 2024).
Carthamus tinctorius L. (Asteraceae)	Crude extract	CCl_4-induced LF in rats	Crude extract Inhibits hepatic fibrosis and HSCs activation by blocking the PI3K/AKT/mTOR signaling pathway (Dong et al., 2024).
Centella asiatica (L.) Urban (Apiaceae)	Crude extract	BLM-induced PF in rats	Crude extract succeeds in treating fibrosis in rats exposed to BLM as evidenced by histopathological analyses (Soeroso et al., 2024).
Chai Huang Yi Shen granules (CHYS)	*Bupleurum scorzonerifolium* Willd. (Apiaceae), *A. membranaceus, A. sinensis, Pyrrosia lingua* (Thunb.) Farw. (Polypodiaceae), *Dioscorea nipponica* Makino (Dioscoreaceae), *Polyporus umbellatus*, and *Hirudo*	UUO-induced RF in mice	CHYS protects against Tert-butyl hydroperoxide (t-BHP)-induced mtDNA leakage in renal tubular cells, maintaining mitochondrial function and stability. This effect is weakened by the knockdown of PRDX5 (Xu et al., 2025).
Clerodendrum phlomidis L. (Lamiaceae)	Ethyl acetate extract	BLM-induced PF in rats	Ethyl acetate extract from the whole plant material induces marked restoration of antioxidant enzyme levels (GSH, GST, and GPX) in lung tissue and serum in BLM-induced PF in rats, activates the NRF2/HO-1 pathway with enhanced IL-10 expression, reduced TNF-α levels in lung tissue *in vivo*, improves lung function by inhibiting interalveolar fibrotic tissue formation and reducing the levels of chemokines, pro-inflammatory cytokines, and collagen (Sangaraju et al., 2025).
Cornus officinalis var. *koreana* Kitam (Cornaceae)	Crude extract	Cadmium-induced RF in mice	The crude extract reduces RF in mice induced by cadmium chloride by targeting MMP9 (Cai et al., 2025).
Corydalis saxicola Bunting (Papaveraceae)	Total alkaloids of *C. saxicola* (TACS)	CCl_4-induced LF in rats	TACS demonstrates anti-fibrotic effects by modulating liver metabolic pathways, including bile acid, glutathione, tryptophan, and purine metabolism (Wang et al., 2022).
Crocus sativus L. (Iridaceae)	Dried stigmas (Safron)	CCl_4-induced LF in mice	Saffron treatment inhibits the upregulation of HIF-1α, VEGFα, AKT, and PI3K induced by CCl_4, indicating that saffron may regulate the AKT/HIF-1α/VEGF pathway and alleviate LF (Cai et al., 2023).

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Table 1 (*continued*)

Botanicals	Composition	Experimental models	Anti-fibrotic effects
Da Huang Zhe Chong pill (DHZCP)	*Rheum officinale* Baill. (Polygonaceae), *Eupolyphaga sinensis* Walker (Corydiidae), *Prunus mandshurica* (Maxim.) Koehne) (Rosaceae), *Prunus davidiana, Scutellaria baicalensis* Georgi (Lamiaceae), *Rehmannia glutinosa* (Gaetn.) Libosch. ex-Fisch. et Mey. (Orobanchaceae), *P. lactiflora, Glycyrrhiza uralensis* Fisch. (Fabaceae), *Tabanus mandarinus* Schiner (Tabanidae), *Hirudo nipponica* Whitman (Hirudinidae), *Holotrichia diomphalia* Bates (Scarabaeidae), and *Toxicodendron vernicifluum* (Stokes) F. A. Barkl. (Anacardiaceae)	CCL_4-induced LF in rat	HZCP inhibits LF by regulating gut microbiota and metabolites, enhancing the intestinal barrier's integrity (WHO), 2024).
Dan Sshen Yin (DSY)	*Salvia miltiorrhiza* Bunge (Lamiaceae), *Santalum album* L. (Santalaceae), *Amomum villosum Lour. (Zingiberaceae)*	LAD-induced MF in rats	DSY prevents MF by reducing ECM organization, focal adhesion ECM-receptor interaction, and inflammation through the regulation of TGF-β-mediated PI3K/AKT, MAPK, and Smad signaling pathways (Ngassoum et al., 2003).
Elephantopus scaber L. (Asteraceae)	Leaf extract	BLM-induced PF in mice	Leaf extract reduces TNF-α, increases IFN-γ, and maintains stable IL-10 levels in macrophages of PF mice, showing more effective reduction of pro-fibrotic cytokines compared to dexamethasone (Alghoull et al., 2025).
Er Shen Zhen Wu decoction (ESZWD)	*Aconitum carmichaelii* Debeaux (Ranunculaceae), Panax ginseng C. A. Mey (Araliaceae), *S. miltiorrhiza, Poria cocos* (Schw.) Wolf (Polyporaceae), *P. lactiflora, Atractylodes macrocephala* Koidz. (Asteraceae), *Zingiber officinale* Roscoe (Zingiberaceae)	BTE-induced MF in rats	ESZWD reduces MF in chronic heart failure with heart-kidney *Yang* deficiency by inhibiting the RAS homolog gene family member A/RHO-associated coiled-coil kinases signaling pathway (Jiang et al., 2025).
Er Tao decoction (ETD)	*Pinellia ternata* (Thunb.) Ten. ex Breitenb (Araceae), *Citrus tangerina* (Rutaceae) (Schw.) Wolf (Polyporaceae), *G. uralensis, Vitex doniana* Sweet (Lamiaceae), Zingiberis rhizoma Recens (Zingiberaceae), *R. glutinosa, A. sinensis, P. lactiflora, Ligusticum sinense* Oliv. cv. (Umbelliferae)	CCl_4-and MCD-induced LF in mice	ETD reduces LF by inhibiting the activation of STING-mediated macrophages and the NLRP3 inflammasome (Cai et al., 2025).
Eucommia ulmoides Oliver (Eucommiaceae)	Crude cortex extract	High-purine diet-RF in rats and mice	Anti-RF effects of crude cortex extract through attenuation of TGF-β signaling pathway with regulation of the expression levels of TGF-β1, p-SMAD3, p-p38, and BMP-7 in rats (Cai et al., 2025); Anti-RF effects in mice by decreasing the levels of creatinine and urea nitrogen, down-regulated the TGF-β1/SMAD signaling pathway's expression levels of TGF-β1, α-SMA, SMAD3, and phospho-SMAD3 (Jiang et al., 2025).
Ficus hirta Vahl. (Moraceae)	Roots extract reduces	CCl_4-and MCD diet-induced LF in mice; *in vitro* cell culture model	Roots extract reduces LF in mice by inducing ferroptosis in HSCs and modulating the GSH/GPX4 pathway (Yang et al., 2024b).
Fu Fang Shen Hua tablet (SHT)	*Astragalus mongholicus, Ligustrum lucidum* W. T. Aiton (Oleaceae), *Curcuma longa* L. (Zingiberaceae), *P. lactiflora, Lonicera japonica* Thunberg (Caprifoliaceae), *Sparganium stoloniferum* (Buch. Ham. ex Graebn.) (Sparganiaceae), and *A. Macrocephala*	5/6 Nephrectomy-induced RF in rats; *in vitro* cell culture model	SHT exhibits anti-RF properties by inhibiting the PI3K/AKT signaling pathway (Abdel Ghani et al., 2023).
Fu Zheng Hua Yu Tablets	Radix Salviae Miltiorrhizae, Fermented Mycelium Powder (Clavicipitaceae), *Schisandra chinensis* (Schisandraceae), Semen Persicae (Rosaceae), Pollen Pini (Pinaceae), *Gynostemma pentaphyllammak* (Cucurbitaceae)	CCl_4-induced LF in rats	Down-regulation of mRNA expression of TIMP-1, PDGF-B and PDGF-Rβ, and suppression of protein expression of PDGF-Rβ and TGF-β1 (Cheung et al., 2009).
Gan Shuang granule (GSG)	*Odonopsis pilosula* (Franch.) Nannf. (Campanulaceae), *Nasturtium officinale* R. Br. (Brassicaceae), *P. lactiflora* Pallas (Paeoniaceae), *A. sinensis, Wolfiporia extensa* (Peck) Ginns (Polyporaceae), *A. macrocephala*, Hedgehog, Dandelion, Giant knotweed, Selfheal, *S. miltiorrhiza*, peach kernel, and turtle shell.	DMN-induced LF in rats	GSG reduces DMN-induced fibrosis in rats by regulating inflammatory and fibrosis factors, lowering hepatic TGF-β1, PDGF, and TNF-α levels, increasing mRNA of IFN-γ, IL-2, and IL-4, and decreasing α-SMA expression (Wang et al., 2024b).
Guan Xin Ning injection (GXN)	*S. miltiorrhiza* and *Ligusticum chuanxiong* Hort. (Umbelliferae)	TAC-induced MF in mice	GXN preserves cardiac function and slows the progression of kidney fibrosis in heart failure mice by regulating the redox metabolism of aspartate, glycine, serine, and cystine, as well as the SLC7A11/GPX4 axis in the kidney (Wang et al., 2023a).
Ginkgo biloba L. (Ginkgoaceae)	Standardized *Ginkgo biloba* extract (GBE50)	BLM-induced PF in mice	GBE50 exerts antifibrotic effects on PF in mice by regulating the NRF2 and TGF-β1/SMAD pathways (Ding et al., 2024).
Guizhi Fuling Wan (GFW)	*Cinnamomum cassia* Presl (Lauraceae), *P. cocos, Paeonia suffruticosa* Andr (Paeoniaceae), *P. lactiflora*, and *P. persica*	CCl_4-induced LF in rats and *in vitro* cell culture model	GFW reduces CCl_4-induced hepatic fibrosis in rats by regulating the PTEN/AKT/mTOR signaling pathway (Yao et al., 2024).
Huang Qi-Dan Shen (HQDS)	*A. membranaceus*. and *S. miltiorrhiza*	UUO-induced RF in mice	HDD decreases the expressions of PI3K, STAT3, SRC, EGFR, and MMP2 in the kidneys of UUO mice and in TGF-β1-induced HK-2 cells, while enhancing the expression of MMP9 (Huang et al., 2024b).
Hua Xian formula (HXF)	L. *japonica, S. baicalensis, Morus alba* L. (Moraceae), *Bamboo shavings, Eriobotrya japonica* (Thunb.) Lindl. (Rosaceae), *A. membranaceus*, Lily (*Lilium* sp.), *Ophiopogon japonicas* (Thunb.) Farw. (Asparagaceae), *Pinellia ternata, Citrus reticulata* Blanco (Rutaceae), *P. cocos, G. uralensis, S.*	Radiation-induced PF in mice	HXF inhibits the pro-fibrotic effects of macrophages, preventing the progression of radiation-induced PF.

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Table 1 (*continued*)

Botanicals	Composition	Experimental models	Anti-fibrotic effects
	miltiorrhiza, C. tinctorius, Panax notoginseng Burkill (Araliaceae)		
Huoxue Jiedu Huayu recipe (HJHR)	*A. membranaceus,* Lumbricus, *Carapax Trionycis, P. lactiflora,* and *S. baicalensis*	UUO-induced RF in rats	HJHR reduces contralateral RF by inhibiting angiogenesis induced by VEGFα (Xiaomeng et al., 2024).
Jian Pi Yi Shen (JPYS)	*A. membranaceus* and *G. uralensis, A. macrocephala, Dioscorea opposita* Thunb. (Dioscoreaceae), *Cistanche deserticola* Y.C. Ma (Orobanchaceae), *Amomum kravanh* Pierre ex Gagnep. (Zingiberaceae), *S. miltiorrhiza*, and *R. palmatum* l. (Polygonaceae)	Adenine-induced RF in rats	JPYS can enhance RA by reducing RF through the inhibition of the NF-κB and TGF-β/Smad pathways (Huang et al., 2024a).
Jiawei Qi Gong Wan (JQGW)	*Pinellia ternata, C. reticulata, P. cocos, A. macrocephala, Atractylodes lancea* (Thunb.) DC. (Asteraceae), *Cyperus rotundus* L. (Cyperaceae), *Conioselinum anthriscoides* Fisch. ex Hoffm. (Apiaceae), Massa Medicata Fermentata, *G. uralensis*	SILT-induced LF in mice	JQGW alleviates LF and inflammation through the AKT2-FOXO1 and YAP/TAZ signaling pathways (Al-Gholam et al., 2025).
Jiawei Taohe Chengqi decoction (JTCD)	*R. palmatum, P. persica, C. cassia, Glycyrrhiza acanthocarpa* (Lindl.) J.M.Black (Fabaceae), and Natrii Sulfas (sodium sulfate)	CCl_4-induced LF in mice	JTCD effectively treats LF by inhibiting HSC activation, reversing LF through the TGF-β1/CUGBP1 signaling pathway, and upregulating the IFN-γ/SMAD7 pathway (Ye et al., 2024).
Kang Xian Ling formula (KXL)	*Achyranthes bidentata* Blume (Amaranthaceae), *Rheum officinale, S. miltiorrhiza, P. persica*, and *A. membranaceus*	UUO-induced RF in rats	The *Kangxianling* formula reduces RF by regulating the gut microbiota (Tao et al., 2024).
Ling Gui Zhu Gan decoction (LGZGD)	*C. cassia, A. macrocephala*, and *Glycyrrhiza glabra* L. (Fabaceae)]	*In vitro* cell culture model of MF	LGZGD improves MF through the regulation of the WNT/β-catenin pathway, a reduction in collagen deposition, and the protection of myocardial cells (Ding et al., 2024).
Longdan Xiegan Tang (LXT)	*Gentiana scabra* Bunge (Gentianaceae), *S. baicalensis, Gardenia jasminoides* Ellis (Rubiaceae), *Alisma plantago-aquatica* L. (Alismataceae), *Akebia quinata* (Houtt.) Decne. (Lardizabalaceae), *Plantago asiatica* L. (Plantaginaceae), *A. sinensis, R. glutinosa, Bupleurum chinense* DC. and *B. scorzonerifolium* (Apiaceae), *G. uralensis*	CCl_4-induced LF in mice; *in vitro* cell culture model	LXT treatment suppresses HSCs activation by upregulating the expression of Parkin, thereby inhibiting LF through the activation of the Parkin signaling pathway (Deng et al., 2024).
Lonicera japonica Thunberg (Caprifoliaceae)	Crude water extract	TAA-induce LF in rats; *in vitro* cell culture model	The crude extract improves antioxidant capacity, reduces inflammation in rats through decrease in LF scores, collagen deposition, and α-SMA deposition in TAA-treated liver, and decreases apoptosis in FL83B hepatocytes (Afshar et al., 2018).
Macaranga denticulata (Blume) Müll.Arg. (Euphorbiaceae)	Bark extract	STZ-induced RF in rats	Bark extract lowers various biomarkers associated with kidney functions, RF biomarker levels, and reverses dysregulation of sirtuins and claudin-1 in the kidneys of rats with STZ-induced diabetes (Gali et al., 2024).
Maimendong decoction (MMDD)	*Ophiopogon japonicus* (Thunb.) Ker Gawl. (Asparagaceae), *Pinellia ternata, G. uralensis, P. ginseng, Oryza sativa* L.. (Poaceae), *Ziziphus jujuba* Mill. (Rhamnaceae)	BLM-induced PF in mice	MMDD alleviates idiopathic PF by regulating the PINK1/PARKIN signaling pathway, reducing AEC2 senescence, and enhancing mitochondrial autophagy (Zhou et al., 2025).
Malus toringoides (Rehd.) Hughes (Rosaceae)	Decoction	ISO-induced MF in mice	Decoction protects against ISO-induced MF by inhibiting inflammation and pyroptosis, as mediated by the HK1/NLRP3 signaling pathway (Du et al., 2024).
Man Shen Kang granules (MSKG)	*Rheum tanguticum* Maxim. ex Balf. (Polygonaceae)), *S. miltiorrhiza, Citrus aurantium* L.. (Rutaceae), *Codonopsis pilosula* (Franch.) Nannf. (Campanulaceae), *Polygonatum cyrtonema* Hua (Asparagaceae), *Smilax glabra* Roxb. (Liliaceae), *Ostrea rivularis* Gould. (Ostreidae), and *G. uralensis*	Adenine-induced RF in rats	MSKG reduces renal failure in rats with adenine-induced chronic kidney disease by regulating the PDE4b/cAMP/Epac1 pathway (Yang et al., 2025).
Mimosa pudica L. (Fabaceae)	Crude EtOH extract	BLM-induced PF in mice; *in vitro* cell culture model	The crude extract inhibits TNF-α-induced cytokine expression and inactivates MAPK and NF-κB pathways in A549 lung cancer cells and lung fibroblasts; reverses TGF-β-induced EMT; lowers fibrosis-related genes/ proteins like collagen I, fibronectin, and αSMA, suppresses collagen secretion, and hindered myofibroblast differentiation in mice (Nguyen et al., 2024).
Morus alba L. (Moraceae)	Fraction of the bark (*Sang-Bai-Pi*)	UUO-induced RF in rats	Fraction of the bark (*Sang-Bai-Pi*) extract alleviated RF by suppressing the EMT, accumulation of extracellular matrix, and activation of the TGF-β/SMAD and WNT/ β-catenin signaling pathways (Wei et al., 2025)
Olea europaea L. (Oleaceae)	Crude leaf extract	BLM-induced PF in mice	Leaf extract offers protection against PF by regulating oxidative parameters and reducing collagen deposition (Bahri et al., 2023).
Physalis alkekengi L. var. *franchetii* (Mast.) Makino (Solanaceae)	Physalis Calyx seu Fructus	BLM-induced PF in mice	EtOH extract of Physalis Calyx seu Fructus refers to as calyxes and fruits of *P. alkekengi* improved PF by reducing inflammation and ECM deposition, inhibiting the WNT/β-catenin pathway by decreasing β-catenin nuclear accumulation and increasing phosphorylation (Wang et al., 2024d).

(*continued on next page*)

Table 1 (*continued*)

Botanicals	Composition	Experimental models	Anti-fibrotic effects
Portulaca oleracea L. (Portulacaceae)	Crude extract	CCl_4-induced LF in mice	the crude extract alleviates LF in mice by inhibiting the TLR-4/NF-κB, Bcl-2/Bax, and TGF-β1/SMAD2 signaling pathways (Cai et al., 2025).
Qi-Dan-Dihuang decoction (QDD)	*A. membranaceus, S. miltiorrhiza, R. glutinosa, D. opposita*, and *G. uralensis*	UUO-induced RF in rats	QDD inhibits EMT and the inflammatory response through the p38 MAPK and AKT/mTOR signaling pathways in RF in rats with diabetic kidney disease (Kuang et al., 2024).
Qi Li Qiang Xin (QLQX)	*A. membranaceus, P. ginseng, S. miltiorrhiza, Alisma orientale* (Sam.) Juzep (Alismataceae), *A. macrocephala, Lepidium apetalum* Willd (Brassicaceae), *A. carmichaelii, C. cassia, C. tinctorius, C. reticulata*, and *Polygonatum odoratum* (Mill.) (Asparagaceae)	LAD coronary artery ligation- induced MF in rats	QLQX treatment improved cardiac function and mitigated MF by regulating collagen homeostasis and enhancing angiogenesis (Sun et al., 2024b).
Qing Fei Tong Luo mixture (QFTL)	*Pseudostellaria heterophylla* (Miq.) Pax (Caryophyllaceae), *Adenophora stricta* Miq. or *Adenophora tetraphylla* (Thunb.) Fisch. (Campanulaceae), *M. alba, A. macrocephala*, Indigo Naturalis, *Phragmites communis* Trin (Poaceae), *Platycodon grandiflorum* (Jacq.) A. DC. (Campanulaceae), Pheretima, *S. miltiorrhiza, Coix lacryma-jobi*, Semen Benincasae, *Pinellia ternata* (Thunb.) (Araceae), *Amomum villosum* Lour. (Zingiberaceae), and *G. glabra*	BLM-induced PF in rats	QFTL reduces pulmonary inflammation and fibrosis induced by BLM in rats through mTOR-dependent autophagy.
Qing Fei Xie Ding prescription (QFXD)	*Ephedra sinica, M. alba* L., *Bombyx Batryticatus* (Bombycidae), Gypsum Fibrosum, *Prunus armeniaca* L. (Rosaceae), *Houttuynia cordata* Thunb. (Saururaceae), *Pueraria edulis* Pamp. (Fabaceae), *P. lactiflora, S. baicalensis, Anemarrhena asphodeloides* Bunge (Liliaceae)	BLM-induced PF in mice; *in vitro* cell culture model	QF restores cell viability affected by TGF-β, inhibits ferroptosis, and alleviates PF by activating the ACE2 signaling axis in MLE-12 lung epithelial cells; improves lung coefficients, body weight, and inflammatory factor expression in BLM-induce PF mice (Sun et al., 2024a).
Qing Kai Ling granule (QKL)	*Isatis tinctoria* L. (Brassicaceae), L. *japonica*, and *G. jasminoides*, along with two animal-derived ingredients, Concha Margaritifera Usta and Cornu Bubali, and three compounds, baicalin (flavone glycoside), cholic acid (sterol), and hydeoxycholic acid (sterol)	BLM-induced PF in mice	QKL reduces pulmonary inflammation and fibrosis through the downregulation of PI3K/AKT and SRC/STAT3 signaling pathways (H. Li et al., 2024).
ShaShen-MaiDong (SMT)	*Glehnia littoralis* F.Schmidt ex Miq (Apiaceae), *O. japonicus, P. odoratum, G. uralensis, M. alba* L. (Moraceae), *Dolichos lablab* l. (Fabaceae)], and *Trichosanthis kirilowii* Maxim. (Cucurbitaceae)	BLM-induced PF in mice	SMT was effective in PF mice and a TGF-β-induced cell model and restored the balance of $CD4^+$ and $CD8^+$ *T* cells in PF mice, increasing $CD4^+$ *T* cells and decreasing $CD8^+$ *T* cells (Huang et al., 2025).
Sheng Xian decoction (SXD)	*Astragalus mongholicus, Bupleurum chinense* DC. (Apiaceae), *Anemarrhena asphodeloides, Platycodon grandiflorus* (Jacq.) A. DC. (Campanulaceae), and *Actaea cimicifuga* l. (Ranunculaceae)	BLM-induced PF in rats	SXD alleviates or reverses early pathological changes in BLM-induced PF by inhibiting PANoptosis (Liang et al., 2024).
Shen Qi Chong Cao (SQCC)	*P. ginseng, Polygonum cuspidatum* Siebold & Zucc (Amaryllidaceae), *Panax notoginseng*, and *Cordyceps sinensis* (Ophiocordycipitaceae)	BLM-induced PF in rats	SQCC reduces PF in rats potentially by activating the ASS1/SRC/STAT3 signaling pathway within lung tissues (He et al., 2024).
Shen Qi pill (SQP)	*C. cassia*, Processed aconite, *R. glutinosa, C. officinalis, D. opposita* Thunb. (Dioscoreaceae), *P. cocos, A. orientale*, (Alsmataceae), and *P. suffruticosa*	UUO-induced RF in rats; *in vitro* cell culture model	SQP provides a reno-protective effect against RF both *in vivo* and *in vitro*, through the NF-κB pathway-related inflammatory response (Chen et al., 2024).
Shen Qi Wan (SQW)	*A. carmichaelii, C. cassia, R. glutinosa, Moutan officinalis* (L.) Lindl. & Paxton ((Paeoniaceae), *C. officinalis, P. cocos, D. opposita, Alisma acanthocarpum* F.Muell. (Alismataceae)	Adenine-induced RF and cell culture model	SQW promotes EMT through aquaporin 1 knockdown, eliminating the protective effect of SQW-containing serum on EMT in HK-2 cells, and thereby enhances the EMT process in RIF by upregulating aquaporin 1 expression (Abdel Ghani et al., 2023).
Shu Gan Jian Pi formula (SGJPF)	*Bupleurum chinense, Astragalus mongholicus, P. lactiflora, A. macrocephala, P. cocos, C. lacryma-jobi, Polyporus umbellatus, Lycopus lucidus* var. hirtus Regel (Lamiaceae), *Artemisia capillaris* Thunb. (Asteraceae), *Isatis indigotica* Fort. (Brassicaceae), *Citrus aurantium*	CCl_4-induced LF in mice; *in vitro* cell culture model	SGJPF improves CCl_4-induced LF by regulating miR-193a-3p and TGF-β2 in HSCs (Cai et al., 2025).
Si Wu Tang (SWT)	*R. glutinosa, A. sinensis, P. lactiflora*, and *Ligusticum chuanxiong*	BDL-induced LF in mice	SWT reduces ECM deposition and liver bile duct reactions; it alleviates LF by modulating the transcription of genes related to cytoskeleton remodeling, in HSCs, and affecting cytoskeleton-related angiogenesis and hepatocellular damage in mice (Afshar et al., 2018).
Suyin detoxification granule (SDG)	*Perilla frutescens* (l.) Britton (Lamiaceae), *Artemisia capillaris, Serissa japonica* (Thunb.) Thunb. (Rubiaceae), *Smilax glabra, C. tinctorius, Typha angustifolia* L. (Typhaceae), *Rheum officinale, P. cocos, A. membranaceus, C. officinalis, Ostrea gigas* Thunberg (Ostreidae), animals excrement (*Faeces Trogopterori*)	*In vitro* cell culture model of RF	SDG lowered circulating TMAO levels by regulating gut microbiota, inhibiting TMAO-induced renal tubular ferroptosis, secretion of profibrotic factors, and RF, thereby preventing CKD progression (2024).
Tao Hong Si Wu Tang (THSWT)	*R. glutinosa, P. lactiflora, A. sinensis, P. davidiana*, L. *striatum*, and *C. tinctorius*	TAA-induced LF in mice	THSWT is effective on LF by modulating lipid metabolism and promoting mitophagy in the liver (Wu et al., 2024).
Teucrium polium L. (Lamiaceae)	Crude extract	PQ-induced PF in rats	The crude extract alleviates and reverses PQ-induced PF by improving the biochemical and histological abnormalities induced in rats (Molavinia et al., 2023).
Tithonia diversifolia A. Gray (Asteraceae)	Stems ethanol extract	CCl_4-induced LF in mice	Stems ethanol extract ameliorates CCl_4-induced liver pathological injury, reducing liver inflammatory infiltration and fibrous deposition, reduces the protein

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Table 1 (*continued*)

Botanicals	Composition	Experimental models	Anti-fibrotic effects
			expression of α-SMA, E-cadherin, and vimentin and the mRNA levels of COL I/III in CCl_4-damaged liver tissue, thereby inhibiting the accumulation of ECM in liver tissues (Wang et al., 2025a)
Tong Xin Luo (TXL)	*P. ginseng*, Scorpio, Hirudo, *Eupolyphaga sinensis, Scolopendra* sp., *Periostracum cicadae, P. lactiflora*, and Borneolum syntheticum (a synthetic compound)	LAD coronary artery ligation-induced MF in mice	TXL activates the PI3K/AKT signaling pathway, inhibiting EndMT and reducing MF after MIRI in mice (Wei et al., 2024).
Wu Ling capsule (WL)	Bupleuri radix (dried root of the Apiaceae plants *Bupleurum chinense* L. and *Bupleurum scorzonerifolium, Ganoderma lucidum* (Curtis) P. Karst. (Polyporaceae), *S. miltiorrhiza,* and *Schisandra chinensis* (Turcz.) Baill. (Schisandraceae)	CCl_4-induced LF in rats	WL influences the polarization of macrophages by inhibiting the TLR4-NF-κB signaling pathway, which helps alleviate LF (Ren et al., 2024).
Xuan Fei Bai Du decoction (XFBD)	*C. reticulata, E. sinica, Gypsum fibrosum* ($CaSO_4{\cdot}2H_2O$), *P. armeniaca, C. lacryma-jobi* and L. *apetalum, A. lancea, Pogostemon cablin* (Blanco) Benth (Lamiaceae), *P. communis, G. uralensis*, and *Reynoutria japonica* Houtt (Polygonaceae), *Artemisia annua* L. (Asteraceae) and *Verbena officinalis* L. (Verbenaceae)	BLM-induced PF in mice	XFBD improved the condition of BLM-induced IPF mice by modulating the IFN-γ/STAT1/STAT3 signaling pathway (Jia et al., 2024).
Yi Qi Juan Shen decoction (YQJSD)	*A. membranaceus, A. macrocephala, Curcuma phaeocaulis* Valeton (Zingiberaceae), *Curcuma longa, Chosanthes kirilowii* Maxim (Cucurbitaceae), *Sargassum horneri* (Turner) C. Agardh (Sargassaceae)	UUO-induced RF in mice	YQJSD reduces renal interstitial fibrosis by targeting the LOXL2/PI3K/AKT pathway to inhibit epithelial-mesenchymal transition and inflammation (2025).
Zhen Wu decoction (ZWD)	*Aconitum carmichaeli, P. lactiflora, P. cocos, A. macrocephala*, and *Z. officinale*	UUO-induced RF in rats	ZWD decreases Selective catalytic reduction, BUN, NT-proBNP, and urine protein while increasing LVEF, FS, and CO, and decreasing LVIDS in rats. It reduces RF, up-regulates miR-451, and inhibits TLR4, NF-κB, and HIF-1α, leading to a decrease in inflammatory and fibrosis-related factors.
Zhen Wu Tang (ZWT)	*A. carmichaelii, P. cocos, A. macrocephala, P. lactiflora,* and *Z. officinale*	ISO-induced MF in mice	ZWT inhibits M1 macrophage polarization *via* the TLR4/NF-κB pathway (Fang et al., 2024).
Ziziphus spina-christi L. (Rhamnaceae)	Crude extract	BLM-induced PF in mice	Regulation of the TGF-β1/SMAD pathway (Elhady et al., 2024).

BLM: bleomycin (Bleomycin); BDL: bile duct ligation; BTE: bilateral thyroidectomy; CDAHFD: choline-deficient, l-amino acid-defined, high-fat diet; CKD: chronic kidney disease; DMN: dimethylnitrosamine; FA: folic acid; EMT: epithelial-mesenchymal transition; EtOH: ethanol; HSCs: hepatic stellate cells; ISO: isoproterenol; LAD: surgically ligating the left anterior descending; LF: liver fibrosis; MCD: methionine- and choline deficient; MF: myocardial fibrosis; MIRI: myocardial ischemia-reperfusion injury; MMP: matrix metalloproteinase; PF: pulmonary fibrosis; PQ: Paraquat; RF: renal fibrosis; ROS: reactive oxygen species; SILT: subcutaneously implanting letrozole (Femara) tubes; STZ: streptozotocin; TAA: thioacetamide; TAC: transverse aortic constriction; t-BHP: *tert*-butyl hydroperoxide; TGF-β: transforming growth factor β; TMAO : trimethylamine N-oxide; UUO: unilateral ureteral obstruction.

include the reduction of ECM organization and inflammation. This is accomplished by regulating TGF-β-mediated signaling pathways, such as PI3K/AKT, mitogen-activated protein kinase (MAPK), and SMAD. Additionally, these botanicals inhibit the Ras homolog gene family member A/Rho-associated coiled-coil kinases pathway and modulate redox metabolism in the kidneys. They also influence the WNT/β-catenin pathway, decrease collagen deposition, protect myocardial cells, and inhibit inflammation through the HK1/NLRP3 pathway. Furthermore, they regulate collagen homeostasis and angiogenesis and reduce MF after mild ischemia-reperfusion injury (MIRI) by modulating the PI3K/AKT pathway and inhibiting macrophage polarization *via* the TLR4/NF-κB pathway.

Botanicals against PF. The experimental models of PF evaluated in this review for screening the reported botanicals included both *in vitro* and *in vivo* approaches. These models consisted of bleomycin (Bleomycin)-induced PF in mice and rats, radiation-induced PF in rats, an *in vitro* cell culture model using MRC-5 fibroblasts, and paraquat (PQ)-induced PF in rats. Table 1 presents various botanicals that have shown effects on PF. This includes 13 single plant extracts and 10 polyherbal formulations derived from multiple sources. Among these botanicals are *Alpinia officinarum* Hance (Zingiberaceae), *Aquilaria sinensis (Lour.) Spreng, Antrodia cinnamomea* AC (Fomitopsidaceae), *Astragalus membranaceus* (Fisch.) Bge., (Fabaceae), *Centella asiatica* (L.) Urban (Apiaceae), *Clerodendrum phlomidis* L. (Lamiaceae), *Elephantopus scaber* L. (Asteraceae), *Ginkgo biloba* L. (Ginkgoaceae), *Mimosa pudica* L. (Fabaceae), *Olea europaea* L. (Oleaceae), *Physalis alkekengi* L. var. *franchetii* (Mast.) Makino (Solanaceae), *Teucrium polium* L. (Lamiaceae), *Z. spina-christi* L.. Additionally, several herbal formulations, such as *Bu Yang Huan Wu* decoction (BYHWD), *Hua Xian* formula (HXF), *Mai Men Dong* decoction (MMDD), *Qing Fei Tong Luo* mixture (QFTL), *Qing Fei Xie Ding* prescription (QFXD), *Qing Kai Ling* granule (QKL), *ShaShen-MaiDong* (SMT), *Sheng Dian* decoction (SXD), *Shen Qi Chong Cao* (SQCC), and *Xuan Fei Bai Du* decoction (XFBD) have been identified. The way these botanicals exert their effects involves several key mechanisms. They regulate the NRF2/xCT/GPX4, PI3K/AKT, and non-receptor tyrosine kinase (SRC)/STAT3 pathways, which leads to a decrease in collagen production and a downregulation of mRNA levels for TNF, IL-6, IL-1β, and NOS2. This regulation inhibits the phosphorylation of NF-κB and p38, enhances IL-10 expression, and reduces TNF-α levels in lung tissue. Consequently, lung function improves by limiting the formation of fibrotic tissue and decreasing the levels of pro-inflammatory cytokines and chemokines. Additionally, these pathways regulate TGF-β1/SMAD signaling, inhibit the pro-fibrotic effects of macrophages, and involve the PINK1/Parkin pathway to help reduce inflammation and ECM deposition. They also inhibit the WNT/β-catenin pathway, modulate mTOR-dependent autophagy, activate the ACE2 signaling axis, and regulate the ASS1/SRC/STAT3 pathway. Further details regarding SMT and XFBD are discussed below.

Botanicals against RF. The experimental models of RF used to test various botanicals include the following: 5/6 nephrectomy-induced RF in rats, *in vitro* cell culture models of RF using renal podocytes, UUO-induced RF in mice and rats, cadmium-induced RF in mice, high-purine diet-induced RF in rats and mice, adenine-induced RF in rats, streptozotocin (STZ)-induced RF in rats, and FA-induced RF in rats (Table 1). Table 1 presents a variety of botanicals that have demonstrated effects on RF. This includes five single plant extracts and fifteen polyherbal formulations derived from multiple sources. The single plant extracts are as follows: *Cannabis* spp. (Cannabaceae), *Cornus officinalis* var. *koreana* Kitam (Cornaceae), *Eucommia ulmoides* Oliver (Eucommiaceae), *Macaranga denticulata* (Blume) Müll.Arg. (Euphorbiaceae),

Table 2
Anti-fibrotic phytochemicals as recorded in various experimental models from 2023 to 2025.

Compound (Class)	Plant source	Experimental models	Anti-fibrotic effects
Terpenoids			
(20*S*,22*R*)-15α-acetoxy-5α-chloro-6β,14β-dihydroxy-1-oxowitha- 2,24-dienolide (Steroid) (**1**)	*Physalis angulata*	*In vitro* cell culture model of LF	Anti-LF effect through inhibition of COL1A1 expression (Wang et al., 2024c).
12-*O*-acetylphorbol-13-isobutyrate (Diterpenoid) (**2**)	*Croton tiglium*	*In vitro* cell culture model of LF	Downregulates the protein and mRNA expression of COLI, COLIII, α-SMA, and TGF-β1 in TGF-β1-induced LF in LX-2 cells and regulates the expression of proteins related to the TGF-β/SMAD pathway (Cai et al., 2025).
25-OH-PPT (Triterpenoid) (**3**)	*Panax ginseng*	ISO-induced MF	Regules fibrosis markers collagen I, collagen III, and α-SMA (Jin et al., 2024)
8-*O*-acetyl shanzhiside methyl ester (Iridoid glycoside) (**4**)	*Lamiophlomis rotata*	*In vitro* cell culture model of LF	Reduces LF by decreasing fibronectin, COL1A1, COL3A1, α-SMA, ColIV, LN, and PC-III levels (Cai et al., 2023).
Loganate (Iridoid glycoside) (**5**)	L. *rotata*	*In vitro* cell culture model of LF	Reduces LF by decreasing fibronectin, COL1A1, COL3A1, α-SMA, COL-IV, LN, and PC-III levels (Cai et al., 2023).
Loganin (Iridoid glycoside) (**6**)	L. *rotata*	*In vitro* cell culture model of LF	Reduces LF by decreasing fibronectin, COL1A1, COL3A1, α-SMA, ColIV, LN, and PC-III levels (Cai et al., 2023).
Physagulide I (Sterol) (**7**)	*P. angulata*	*In vitro* cell culture model of LF	Anti-LF effect through inhibition of COL1A1 expression (Wang et al., 2024c).
Physagulin A (Sterol) (**8**)	*P. angulata*	*In vitro* cell culture model of LF	Anti-LF effect through inhibition of COL1A1 expression (Wang et al., 2024c).
Physagulin B (Steroid) (**9**)	*P. angulata*	*In vitro* cell culture model of LF	Anti-LF effect through inhibition of COL1A1 expression (Wang et al., 2024c).
Physagulin C (Sterol) (**10**)	*P. angulata*	*In vitro* cell culture model of LF	Anti-LF effect through inhibition of COL1A1 expression (Wang et al., 2024c).
Physalin B (Sterol) (**11**)	*P. angulata*	*In vitro* cell culture model of LF	Anti-LF effect through inhibition of COL1A1 expression (Wang et al., 2024c).
Physalin F (Sterol) (**12**)	*P. angulata*	*In vitro* cell culture model of LF	Decreases the expression of collagen I and α-SMA stimulated by TGF-β1 in LX-2 cells (Wang et al., 2024c).
Physapubescin (Steroid) (**13**)	*Physalis alkekengi*	BLM-induced PF in rats	Reduces inflammation in RAW 264.7 cells and ECM deposition by inhibiting the WNT/β-catenin pathway in rats (Wang et al., 2024d).
Scabrol B (Iridoid) (**14**)	*Patrinia scabra*	*In vitro* cell culture model of RF	Protective effects against RF NRK-49f renal fibroblast by reducing the expression of fibronectin, collagen I, and α-SMA in NRK-49f cells mediated by TGF-β1 (H. Li et al., 2024).
Scabrol C (Iridoid) (**15**)	*P. scabra*	*In vitro* cell culture model of RF	Protective effects against RF NRK-49f renal fibroblast by reducing the expression of fibronectin, collagen I, and (α-SMA in NRK-49f cells mediated by TGF-β1(H. Li et al., 2024).
Shanzhiside methyl ester (Iridoid) (**16**)	L. *rotata*	*In vitro* cell culture model of LF	Reduces LF by decreasing fibronectin, COL1A1, COL3A1, α-SMA, COLIV, LN, and PC-III levels (Cai et al., 2023).
Tagitinin C (Sesquiterpene) (**17**)	*Tithonia diversifolia*	CCl_4-induced LF in mice	Inhibits fibrosis by inducing cell apoptosis and regulating the TGF-β1/Smad pathway in activated HSC-T6 cells, restores protein levels of E-cadherin and vimentin on the TGF-β1-stimulated HSC-T6 cells (Wang et al., 2025a)
Withagulide F (Sterol) (**18**)	*P. angulata*	*In vitro* cell culture model of LF	Anti-LF effect through inhibition of COL1A1 expression (Wang et al., 2024c).
Withgulatin A (Sterol) (**19**)	*P. angulata*	*In vitro* cell culture model of LF	Anti-LF effect through inhibition of COL1A1 expression (Wang et al., 2024c).
Phenolics			
Acteoside (Phenylethanoid glycoside) (**20**)	L. *rotata*	*In vitro* cell culture model of LF	Reduces LF by decreasing fibronectin, COL1A1, COL3A1, α-SMA, COLIV, LN,

(*continued on next page*)

Table 2 (*continued*)

Compound (Class)	Plant source	Experimental models	Anti-fibrotic effects
			and PC-III levels (Cai et al., 2023).
Apigenin (Flavonoid) (**21**)	*P. alkekengi*	BLM-induced PF in rats	Reduces inflammation in RAW 264.7 cells and ECM deposition by inhibiting the WNT/β-catenin pathway in rats (Wang et al., 2024d).
Calycosin (Isoflavone) (**22**)	*Astragalus membranaceus*	UUO-induced RF in mice	Reduces neutrophil extracellular traps production to alleviate RF *via* TLR4 and NF-κB pathway (Cao et al., 2025)
Gnetin C (Silbene) (**23**)	*Gnetum gnemon*	HFD-induced LF mice	Improves LF induced by a high-fat and carbohydrate diet through the downregulation of fibrosis markers in the TGF-β1 signaling (Kabir et al., 2023)
Hovenianin A (Biflavonoid) (**24**)	*Hovenia dulcis*	*In vitro* cell culture model of LF	Reduce LF by promoting the apoptosis of HSCs through the inhibition of the PI3K-AKT pathway in TGF-β1-induced HSCs (Kuang et al., 2023).
Lithospermic acid (Phenylpropanoid) (**25**)	*Salvia miltiorrhiza*	CCl_4-induced LF in mice	Limits the progression of LF by regulating Piezo1-mediated oxidative stress and inflammation (Luo et al., 2024).
Luteolin (Flavonoid) (**26**)	L. *rotata*	*In vitro* cell culture model of LF	Reduces LF by decreasing fibronectin, COL1A1, COL3A1, α-SMA, COLIV, LN, and PC-III levels (Cai et al., 2023).
Mulberroside A (Stilbenoid) (**27**)	*Morus* spp.	CCl_4-induced LF in mice	Reduces the expression of collagen I and α-SMA in the livers of CCl_4-treated mice, decreases the release of pro-inflammatory cytokines in liver tissues and HSCs, thus alleviating LF (Cai et al., 2023).
Naringin (Flavonoid glycoside) (**28**)	Ganshuang granule (GSG)	*In vitro* cell culture model of LF	Influences the TGF-β-SMAD signaling pathway by increasing MMP-1 expression and reducing TIMP-1 levels in TNF-α-stimulated HSCs.
Nobiletin (Flavonoid) (**29**)	*Astragalus mongholicus* Bunge and *Panax notoginseng* formula	UUO-induced RF in mice	ameliorates RF in CKD may be through the inhibition of Lgals1/PI3K/AKT signaling pathway (Yang et al., 2024a).
PSPA (Anthocyanin)	*Ipomoea batatas*	CCl_4-induced LF in mice	PSPA mitigates liver damage in mice, regulates key antioxidant enzymes; decreases the expression of inflammatory proteins, including CD3, CD4, CD45, IL-1β, TNF-α, and IL-17A, and reduces the accumulation of fibrotic markers like type I and III collagens and α-SMA; inhibits TGF-βR2, p-SMAD2, p-SMAD3, p-PDGFRβ, p-AKT, p-ERK1/2, p-JNK1/2, and p-p38; PSPA-1 (**30**) and PSPA-2 (**31**) directly target the PDGFRβ (Dai et al., 2024).
Regiafuran C (Furan) (**32**)	*Morus alba*	UUO-induced RF in rats	Inhibits TGF-β/SMAD and WNT/β-catenin signaling by blocking the interaction of SMAD3 with TGF-βRII and TGF-βRI (Wei et al., 2025)
Resveratrol (Silbenoid) (**33**)	*G. gnemon*	HFD-induced LF Mice	Improves LF induced by a high-fat and carbohydrate diet through the downregulation of fibrosis markers in the TGF-β1 signaling (Kabir et al., 2023)
Rhoifolin (Flavonoid glycoside) (**34**)	*Lonicerae Japonicae*	BLM-induced PF in rats	Reduces lung tissue damage and PF in rats by decreasing the expression of N-cadherin and α-SMA, while increasing the levels of SMAD7, HO-1, and SOD. *In vitro*, BLM-induced cell injury leads to lower mRNA levels of α-SMA, N-cadherin, and vimentin, while simultaneously increasing the protein expression of NRF2, HO-1, and Smad7 (Wang et al., 2025b).
Salidroside (Phenylpropanoid glycoside) (**35**)	*Rhodiola rosea*	*In vitro* cell culture model of MF	Mitigates ANGII-induced increases in

(*continued on next page*)

Table 2 (*continued*)

Compound (Class)	Plant source	Experimental models	Anti-fibrotic effects
			collagen I and α-SMA levels and oxidative stress markers in H9c2 cardiomyocytes (Zhang et al., 2024).

BLM: bleomycin (Bleomycin); Col1a1: alpha-1 chain of type I collagen; CKD: chronic kidney disease; ECM: extracellular matrix; HFD: High-Fat Diet; ISO: isoproterenol; LF: liver fibrosis; LN: laminin; PC-III: type III procollagen; PF: pulmonary fibrosis; RF: renal fibrosis; PPT: Protopanaxatriol-type saponins; PSPA: purple sweet potato anthocyanins (PSPA is a complex of 11 anthocyanins including PSPA-1 : peonidin 3-caffeoyl-p-hydroxybenzoyl sophoroside-5-glucoside, PSPA-2 : peonidin 3-caffeoyl sophoroside-5-glucoside, PSPA-3 : peonidin 3-p-hydroxybenzoyl sophoroside-5-glucoside, PSPA-4 : peonidin 3-sophoroside-5-glucoside, PSPA-5 : cyanidin 3-caffeoyl-p-hydroxybenzoyl sophoroside-5-glucoside, PSPA-6 : cyanidin 3-p-hydroxybenzoyl sophoroside-5-glucoside, PSPA-7 : cyanidin 3-dicaffeoyl sophoroside-5-glucoside, PSPA-8 : cyanidin 3-caffeoyl sophoroside-5-glucoside, PSPA-9 : cyanidin 3-feruloyl sophoroside-5-glucoside, PSPA-10 : cyanidin 3-sophoroside-5-glucoside, and PSPA-11 : pelargonidin 3-sophoroside-5-glucoside (Dai et al., 2024). α-SMA: alpha-smooth muscle actin; TGF-β: transforming growth factor β; TGF-βR: transforming growth factor β receptor; UUO: unilateral ureteral obstruction.

and *Morus alba* L. (Moraceae). The polyherbal formulations include *Dang Gui Bu Xue* decoction (DBD), *Bu Shen Huo Xue* (BSHX), *Chai Huang Yi Shen* granules (CHYS), *Fu Fang Shen Hua* tablet (SHT), *Huang Qi-Dan Shen* (HQDS), *Huoxue Jiedu Huayu* recipe (HJHR), *Jian Pi Yi Shen* (JPYS), *Kang Xian Ling* formula (KXL), *Man Shen Kang* granules (MSKG), *Qi Dan Dihuang* decoction (QDD), *Shen Qi* pill (SQP), *Shen Qi Wan* (SQW), *Suyin* detoxification granule (SDG), *Yi Qi Juan Shen* decoction (YQJSD), and *Zhen Wu* decoction (ZWD). The formulations HDD and JPYS will be discussed in more detail below. The *in vitro* and *in vivo* mechanisms involve the modulation of various signaling pathways, including the miR-27a/PI3K/AKT and the PI3K/AKT pathways, as well as the PDE4b/cAMP/EPAC1 pathway, the TGF-β/SMAD signaling pathway, the WNT/β-catenin signaling pathway, and NF-κB. Key actions include restoring the migratory capacity of podocytes, increasing levels of phospho-AKT while decreasing levels of phospho-P38, modulating matrix metalloproteinase 9 (MMP9), and attenuating TGF-β signaling. These mechanisms also downregulate TGF-β1, α-SMA, SMAD3, and phospho-SMAD3. They inhibit VEGFα-induced angiogenesis, regulate the gut microbiota, reverse the dysregulation of sirtuin and claudin-1 in rat kidneys, suppress EMT, and activate pathways related to ECM accumulation.

Below, we will examine in detail the effectiveness of ten selected established herbal formulations for treating various types of fibrosis.

Huang Qi Dan Shen. Huang Qi D*an Shen* decoction (HQDS) is a traditional Chinese medicine (TCM) used in the healing process of CKD in clinical settings for invigorating *Qi* and activating blood (Huang et al., 2024b). It comprises *A. membranaceus* and *S. miltiorrhiza* (Huang et al., 2024b). Huang et al. uncovered the mechanism by which *Huang Qi* decoction antagonizes RF through network pharmacology (NP) analysis and experimental validation (Huang et al., 2024b). They applied NP to identify the core common targets of HQDS components and RF. Subsequently, they induced RF in male C57BL/6 mice using UUO. The researchers further assessed renal function and histopathology and conducted Western blotting and immunohistochemistry analyses to evaluate the protective effects of HQDS on the UUO mice. They ultimately validated the effects of HDD on signaling pathways in both UUO mice and HK-2 cells induced by TGF-β1. Based on their scores in protein-protein interaction analysis and the degree values in the component-pathway-target triadic network, the researchers identified six core common targets related to the 25 components and RF. These targets are phosphoinositide 3-kinase (PI3K), signal transducer and activator of transcription 3 (STAT3), SRC, epidermal growth factor receptor (EGFR), MMP9, and MMP2. They also found that HDD improved renal tubular damage and reduced collagen deposition in UUO mice, while downregulating the expression of fibrosis-related proteins. Additionally, the study demonstrated that HDD decreases the expression of PI3K, STAT3, SRC, EGFR, and MMP2 in the kidneys of UUO mice and TGF-β1-induced HK-2 cells, while enhancing the expression of MMP9.

Guizhi Fuling Wan. GFW is used in TCM to treat conditions such as gynecological disorders, liver issues, and pelvic tumors, all classified under blood stasis syndrome (Yao et al., 2024). GFW comprises four TCM plants and a fungus: *Cinnamomum cassia* Presl (Lauraceae), *Poria cocos* (Schw.) Wolf (Polyporaceae), *Paeonia suffruticosa* Andr. and *Paeonia lactiflora* Pall. (Paeoniaceae), and *Prunus persica* (L.) Batsch (Rosaceae) (Yao et al., 2024). Yao et al. previously investigated the anti-fibrotic effects of GFW and its underlying mechanisms in both carbon tetrachloride (CCl_4)-induced LF (LF) rats and hepatic stellate cells and Lieming Xu-2 (LX-2) human HSCs (Yao et al., 2024). They applied NP to identify potential targets of GFW in LF and assessed the impact of GFW on the PTEN/AKT/mTOR pathway and PTEN ubiquitination in HSCs. They found that GFW reduced liver damage and scarring induced by CCl_4 and inhibited the activation of HSCs *in vivo*. They also evidenced that GFW suppressed the proliferation, migration, differentiation, and ECM production of activated HSCs, while promoting autophagy and apoptosis. NP and these *in vitro* studies indicated that GFW inhibits the AKT/mTOR pathway by preventing the degradation of PTEN through reduced ubiquitination. They concluded that GFW reduces CCl_4-induced hepatic fibrosis in rats by regulating the PTEN/AKT/mTOR signaling pathway, making it a potential candidate for hepatic fibrosis treatment.

Jian Pi Yi Shen. JPYS formula has been used for decades in clinical settings to protect against renal injury in CKD and rheumatoid arthritis; It enhances *Qi*, supports movement, replenishes blood, improves circulation, tonifies the spleen, nourishes kidney essence, and strengthens kidney yang (Huang et al., 2024a). JPYS contains eight different plants: *A. membranaceus* and *Glycyrrhiza uralensis* Fisch. (Fabaceae), *Atractylodes macrocephala* Koidz. (Asteraceae), *Dioscorea opposita* Thunb (Dioscoreaceae), *Cistanche deserticola* Y.C. Ma (Orobanchaceae), *Amomum kravanh* Pierre ex Gagnep. (Zingiberaceae), *S. miltiorrhiza*, and *Rheum palmatum* L. (Polygonaceae). Huang and his team earlier investigated the mechanisms of JPYS in protecting against renal anemia in rats using an adenine-induced anemia model (Huang et al., 2024a). The authors utilized Masson staining to assess RF in rats. Additionally, they employed WB and immunohistochemistry to evaluate the expression levels of fibrotic markers, erythropoietin (EPO), and hypoxia-inducible factor-2α (HIF-2α) in the kidneys of the animals. They then performed transcriptomic analysis to uncover the potential mechanisms through which JPYS may treat renal anemia. Finally, the expression levels of key targets were analyzed and validated using WB and enzyme-linked immunosorbent assay. They found that JPYS treatment improved kidney function and blood parameters in rats with CKD. It restored fibrotic markers and increased erythropoietin EPO expression over time. JPYS also promoted the translocation of HIF-2α into the nucleus, enhancing EPO levels. Additionally, it reduced the expression of proteins linked to the NF-κB and TGF-β/SMAD pathways associated with renal issues. They concluded that JPYS can enhance RA by reducing RF through the inhibition of the NF-κB and TGF-β/SMAD pathways.

Jiawei Taohe Chengqi decoction. JTCD is used in TCM to treat febrile diseases (Ye et al., 2024). It is composed of *R. palmatum, P. persica, C. cassia, Glycyrrhiza acanthocarpa* (Lindl.) J.M.Black (Fabaceae) and Natrii Sulfas (sodium sulfate) (Ye et al., 2024). Ye et al. evaluated the effect of JTCD on LF induced by CCl_4. The authors created an *in vivo* model of heart failure in mice using CCl_4 and activated LX-2 cells *in vitro* with TGF-β1. After this, the cells were treated with JTCD and specific inhibitors to investigate the mechanism of action (Ye et al., 2024). They evidenced that JTCD reduced liver injury and lowered serum ALT and AST levels in mice. Additionally, JTCD mitigated CCl_4-induced hepatic

fibrosis (HF) by decreasing the expression of markers associated with the activation of HSCs, such as α-SMA and α−1 chain of type I collagen (COL1A1), in liver tissue. JTCD effectively suppressed the levels of TGF-β1, phosphorylated SMAD3 (p-SMAD3), phosphorylated p38 MAPK (p-p38MAPK), phosphorylated ATF2 (p-ATF2), and CUGBP1, both *in vivo* and *in vitro*. Furthermore, it upregulated the levels of IFN-γ, phosphorylated STAT1 (p-STAT1), and SMAD7. The authors also observed that JTCD inhibited the activation of HSCs by restoring the balance between the TGF-β1/CUGBP1 and IFN-γ/SMAD7 signaling pathways. They concluded that JTCD effectively treats LF by inhibiting HSC activation, reversing LF through the TGF-β1/CUGBP1 signaling pathway, and upregulating the IFN-γ/SMAD7 pathway.

Ling Gui Zhu Gan. LGZGD is an ancient Chinese herbal formula from the TCM classic *Jin Gui Yao Lue*, used to treat phlegm-fluid retention; it warms yang and alleviates water retention, and has been applied to chronic congestive heart failure (CHF) and similar conditions (Liu et al., 2013). LGZGD is composed of the herbs of *C. cassia, A. macrocephala*, and *Glycyrrhiza glabra* L. (Fabaceae) (Dang et al., 2020). Ding et al. investigated the regulatory mechanism of LGZGD-medicated serum on cardiac fibroblasts (CFs) fibrosis and the protein expression within the WNT/β-catenin signaling pathway (Ding et al., 2024). They found that compared to the normal control group, the CFs in the model group exhibited an enhanced healing rate, increased levels of collagen types I and III (CILI and COLIII), an increased ratio of COLI/COLIII, upregulated protein expression of α-SMA, WNT1, p-GSK-3β, β-catenin, and nuclear β-catenin. Additionally, there was decreased expression of GSK-3β, elevated mRNA levels of β-catenin and MMP9, and enhanced fluorescence intensity and expression of β-catenin and α-SMA. Furthermore, when compared to the model group, various LGZGD-medicated serum samples significantly inhibited cell migration ability, reduced levels of COLI and COLIII, decreased the COLI/COLIII ratio, downregulated the protein expression of α-SMA, WNT1, p-GSK-3β, β-catenin, and nuclear β-catenin, while increasing GSK-3β expression. They also observed decreased mRNA levels of β-catenin and MMP9, along with reduced fluorescence intensity and expression of β-catenin and α-SMA. Compared to the empty plasmid plus LGZGD-medicated serum group, the effect of LGZGD-medicated serum was notably reversed after WNT1 was overexpressed. The authors concluded that LGZGD can reduce excessive collagen fiber deposition, inhibit excessive fibroblast proliferation, and improve the process of MF. They stated that the improvement of MF by LGZGD is associated with the regulation of the WNT/β-catenin pathway, a reduction in collagen deposition, and the protection of myocardial cells.

Longdan Xiegan Tang (LXT) or *Gentiana* decoction. This decoction is used to remove heat from organs and treats various diseases, including liver conditions, diabetes, and nervous system disorders (Deng et al., 2024). LXT consists of *Gentiana scabra* Bunge (Gentianaceae), *Scutellaria baicalensis* Georgi (Lamiaceae), *Gardenia jasminoides* Ellis (Rubiaceae), *Alisma plantago-aquatica* L. (Alismataceae), *Akebia quinata* (Houtt.) Decne. (Lardizabalaceae), *Plantago asiatica* L. (Plantaginaceae), *A. sinensis, Rehmannia glutinosa* (Gaetn.) Libosch. ex-Fisch. et Mey. (Orobanchaceae), *Bupleurum chinense* DC. and *Bupleurum scorzonerifolium* Willd. (Apiaceae), *G. uralensis* (Deng et al., 2024). Deng and his collaborators investigated the effects of LXT on CCl_4-induced LF in mice and HSCs (Deng et al., 2024). They noticed that LXT protects the liver from injuries caused by CCl_4-induced LF in mice and inhibits the activation of HSCs. Mice treated with LXT exhibited reduced levels of collagen I and lower expression of the HSC activation marker, α-SMA. Transcriptome sequencing of liver tissue from the mice indicated that levels of PARKIN, a marker for mitophagy, were decreased in CCl_4-induced LF. Furthermore, the injection of a PARKIN-overexpressing adeno-associated virus *via* the tail vein was shown to reduce CCl_4-induced liver fibrogenesis in mice. Ultimately, they concluded that LXT treatment suppresses HSC activation by upregulating the expression of PARKIN, thereby inhibiting LF through the activation of the PARKIN signaling pathway.

Qi Li Qiang Xin. QLQX is a TCM formula that has been proven to be safe and effective for treating chronic heart failure (Sun et al., 2024b). QLQX enhances myocardial contractility and diuresis, inhibits excessive activation of neuroendocrine systems such as the renin-angiotensin-aldosterone system (RAAS), and reduces inflammation, MF, apoptosis, and autophagy (Sun et al., 2024b). It also improves myocardial energy metabolism, promotes angiogenesis, and enhances endothelial function (Wang et al., 2023b). QLQX consists of eleven Chinese herbs: *A. membranaceus, Panax ginseng* C. A. Mey (Araliaceae), *S. miltiorrhiza, Alisma orientale* (Sam.) Juzep (Alismataceae), *A. macrocephala, Lepidium apetalum* Willd (Brassicaceae), *Aconitum carmichaelii* Debx (Ranunculaceae), *C. cassia, C. tinctorius, Citrus reticulata* Blanco (Rutaceae), and *Polygonatum odoratum* (Mill.) (Asparagaceae) (Sun et al., 2024b). Sun and his colleagues investigated the effects of QLQX on collagen fibers and its underlying mechanism by surgically ligating the left anterior descending (LAD) coronary artery in rats to create a model of myocardial infarction (MI) (Sun et al., 2024b). They observed that a 28-day treatment with QLQX significantly improved cardiac function. This improvement was reflected in several measurements, including reductions in heart mass index, cardiac volume, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, levels of N-terminal B-type natriuretic peptide, and high-sensitivity cardiac troponin I. Additionally, there were increases in left ventricular ejection fraction and left ventricular fraction shortening. Histological analyses using hematoxylin and eosin, Masson, and Picrosirius red staining revealed that QLQX treatment suppressed fibrosis and promoted angiogenesis. This was attributed to a decrease in the expression of proteins associated with cardiac remodeling, such as transforming growth factor-β1, metalloproteinase-9, and α-smooth muscle actin, alongside an increase in the concentration of tissue inhibitor of matrix metalloproteinase-1. Moreover, they found that MI led to increased levels of collagen types I and III while decreasing collagen types II and IV. In contrast, QLQX treatment not only improved cardiac function but also mitigated MF by regulating collagen homeostasis and enhancing angiogenesis.

ShaShen-MaiDong. SMT is a TCM used for treating lung diseases such as coughing and lung cancer (Huang et al., 2025). SMT is composed of seven plants, including *Glehnia littoralis* F. Schmidt ex Miq (Apiaceae), *Ophiopogon japonicus* (Thunb.) Ker Gawl. (Asparagaceae), *P. odoratum, G. uralensis, M. alba, Dolichos lablab* L. (Fabaceae), and *Trichosanthis kirilowii* Maxim. (Cucurbitaceae) (Huang et al., 2025). Huang and his collaborators investigated the antifibrotic efficacy of SMT and its primary active ingredients in BLM-induced PF in mice (Huang et al., 2025). They used NP to identify the mechanisms and active components of SMT in PF, finding that SMT increased hydroxyproline levels, lowered inflammatory cytokines, and reduced collagen deposition in BLM-induced PF mice. NP analysis predicted that SMT's active compounds, kaempferol, quercetin, and isorhamnetin-regulated several pathways, including MAPK, TGF-β/SMAD, and YAP/TAZ. These results were validated in PF mice and a TGF-β-induced cell model. SMT also restored the balance of $CD4^+$ and $CD8^+$ *T* cells in PF mice, increasing $CD4^+$ *T* cells and decreasing $CD8^+$ *T* cells.

Tao Hong Si Wu Tang. THSWT is a TCM formula used in clinics to treat gynecological conditions and chronic liver diseases (Wu et al., 2024). The formula is composed of *R. glutinosa, Paeonia lactiflora, Angelica sinensis, Prunus davidiana* (Carrišre) Franch. (Rosaceae), *Ligusticum striatum* DC. (Apiaceae), and *Carthamus tinctorius*. The effects of THSWT on TAA-induced LF in mice were evaluated by Wu and his collaborators (Wu et al., 2024). They administered THSWT orally to mice once daily for 6 weeks, along with a TAA challenge. They then assessed liver function through serum biomarkers and histopathological staining. Additionally, they applied RNA sequencing, non-targeted metabolomics, and molecular biology experiments to investigate the mechanisms of action of THSWT. They discovered that THSWT effectively repaired lipid metabolism dysfunction and inhibited collagen accumulation in mice and hepatocytes stimulated by TAA. RNA sequencing and

metabolomics studies confirmed its anti-fibrotic effects associated with improved lipid metabolism, leading to increased levels of acetyl-CoA and phosphatidylcholine and reduced levels of acyl-CoA and cholesterol. Additionally, they identified Long-chain acyl-CoA synthetases 4 (ACSL4) as a key profibrotic target, which disrupts lipid oxidation in liver mitochondria. Furthermore, they found that THSWT blocked ACSL4 and promoted mitophagy, a finding that was confirmed through mitophagy depletion experiments. They concluded that THSWT may be a promising therapeutic option for the treatment of LF and its complications by modulating lipid metabolism and promoting mitophagy in the liver.

Xuan Fei Bai Du. XFBD is a TCM prescription for the treatment of COVID-19. XFBD consists of 13 traditional Chinese medicines, including the fruit of *C. reticulata*, the stem of *Ephedra sinica* Stapf. (Ephedraceae), the inorganic substance *Gypsum fibrosum* ($CaSO_4{\cdot}2H_2O$), the seed of *Prunus armeniaca* L. (Rosaceae), *Coix lacryma-jobi* L. (Poaceae), and L. *apetalum*, the root of *Atractylodes lancea* (Thunb.) DC. (Asteraceae), *Pogostemon cablin* (Blanco) Benth. (Lamiaceae), *Phragmites communis* Trin (Poaceae), *G. uralensis*, and *Reynoutria japonica* Houtt (Polygonaceae), and the whole plant except the root of *Artemisia annua* L. (Asteraceae) and *Verbena officinalis* L. (Verbenaceae) (Jia et al., 2024). XFBD ameliorates BLM-induced PF in mice by regulating the lung-gut crosstalk *via* IFN-γ/STAT1/STAT3 pathway. In effect, Jia and his collaborators have evaluated how XFBD affects the lung-gut crosstalk for Idiopathic IPF amelioration. The authors first used micro-computed tomography and histopathology to examine pathological changes in the lungs and intestines of BLM-induced IPF mice (Jia et al., 2024). Then, they conducted reverse transcription and quantitative real-time polymerase chain reaction and WB assays to assess the integrity of the lung and intestinal barriers in these IPF mice. Following that, flow cytometry and 16S rRNA sequencing were employed to analyze the immune and microbial environments of the lungs and intestines. Finally, they investigated the crosstalk between lung and gut microbiota to explore the underlying mechanisms further. They discovered that XFBD helped maintain the integrity of the lung and intestinal barriers in the IPF mice. This was evidenced by the increased expression of zonula occludens-1, claudin-1, occludin, and VE-cadherin proteins. Additionally, they observed that XFBD significantly increased the production of IFN-γ and p-STAT1, while also decreasing the levels of p-STAT3. These changes had a positive impact on both the lung and gut barriers. In conclusion, they found that XFBD improved the condition of BLM-induced IPF mice by modulating the IFN-γ/STAT1/STAT3 signaling pathway.

Potential of phytochemicals against fibrosis

Numerous phytochemicals have been evaluated for their antifibrotic potential, as documented in Table 2, alongside similar fibrosis models reported for various botanicals above. This review identifies 35 phytochemicals with antifibrotic effects, comprising 19 terpenoids and 16 phenolic compounds, targeting four main types of fibrosis (MF, LF, PF, and RF).

Terpenoids, also known as isoprenoids, form the largest and most diverse group of naturally occurring terpenes. These organic compounds are primarily found in plants but are also present in animals and marine organisms. Terpenoids contribute to the smell, taste, and color of plants; they are categorized based on the number of isoprene units they contain, leading to a variety of structural forms, including linear hydrocarbons and chiral carbocyclic backbones. These structures can also undergo chemical modifications, such as the addition of hydroxyl groups and ketones. The main classes of terpenoids include: hemiterpenoids (C_5H_{10}), monoterpenoids ($C_{10}H_{16}$), sesquiterpenoids ($C_{15}H_{24}$), diterpenoids ($C_{20}H_{32}$), sesquiterpenoids ($C_{25}H_{40}$), triterpenoids ($C_{30}H_{48}$), tetraterpenoids ($C_{40}H_{64}$), and polyisoprenoids (Kuete et al., 2025). The antifibrotic terpenoids reported in Table 2 include the iridoid glycosides: 8-*O*-acetyl shanzhiside methyl ester (**4**), loganate (**5**), and loganin (**6**), the iridoids: scabrol B (**14**), scabrol C (**15**), and shanzhiside methyl ester (**16**), the sesquiterpenoid tagitinin C (**17**), the diterpenoid 12-*O*-acetylphorbol-13-isobutyrate (**2**), the triterpenoid 25-OH-protopanaxatriol-type saponins or OH-PPT (**3**), and the sterols: (20*S*, 22*R*)-15α-acetoxy-5α-chloro-6β,14β-dihydroxy-1-oxowitha- 2,24-dienolide (steroid) (**1**), physagulide I (**7**), physagulin A (**8**), physagulin B (steroid) (**9**), physagulin C (**10**), physalin B (**11**), physalin F (**12**), physapubescin (steroid) (**13**), withagulide F (**18**), and withgulatin A (**19**). Their chemical structures are shown in Fig. 1.

Phenolic compounds, commonly known as polyphenols, are natural molecules characterized by an aromatic ring that contains one or more hydroxyl groups. The main classes of pharmacologically relevant phenolics are simple phenols, phenolic acids, phenylpropanoids, coumarins, benzophenones, flavonoids, lignans, stilbenes, tannins, and quinones (Cowan, 1999; Kuete, 2017; Kuete et al., 2015; Mbaveng et al., 2017; Nchiozem-Ngnitedem et al., 2025; Poumale et al., 2013). The phenolic compounds reported in Table 2 to have antifibrotic effects include the phenylpropanoid lithospermic acid (**25**), the phenylethanoid glycosides acteoside (**20**) and salidroside (**35**), the flavonoids apigenin (**21**), luteolin (**26**), nobiletin (**29**), the biflavonoid hovenianin A (**24**), the flavonoid glycosides naringin (**28**) and rhoifolin (**34**), the isoflavone calycosin (**22**), the stilbene gnetin C (**23**), the stilbenoids mulberroside A (**27**) and resveratrol (Silbenoid) (**33**), the anthocyanins PSPA-1 (**30**) and PSPA-2 (**31**), and the furan regiafuran C (**32**). Their chemical structures are shown in Fig. 2. This review examines 35 phytochemicals: 25 targeting LF, 2 for MF, 3 for PF, and 5 for RF.

Phytochemicals against LF. The experimental models of LF discussed in Table 2 for screening the reported phytochemicals included both *in vitro* and *in vivo* approaches. These models comprised an *in vitro* cell culture model of LF using HSCs, as well as CCl_4-induced LF and high-fat diet (HFD)-induced LF in mice. The plant constituents that have established effects on LF include the following: the sesquiterpene (**17**), the diterpenoid (**2**), iridoids (**4–6** and **16**), sterols (**1, 7–12, 18**, and **19**), the phenylpropanoid (**25**), flavonoids (**26, 24**, and **28**), anthocyanins (**30** and **31**), the phenylethanoid glycoside (**20**), and stilbenes (**23, 27**, and **33**), as summarized in Table 2. Their mechanisms of action involve several key processes, including decreasing the levels of fibronectin, COL1a1, COL3a1, α-SMA, ColIV, laminin (LN), and type III procollagen (PC-III). They also inhibit COL1A1 expression and downregulate COLI, COLIII, α-SMA, and TGF-β1 in LX-2 cells. Additionally, these mechanisms regulate the TGF-β/SMAD pathway, reduce collagen I and α-SMA expression induced by TGF-β1, inhibit the PI3K-AKT pathway, and manage oxidative stress and inflammation mediated by Piezo1.

Phytochemicals against MF. The experimental models of MF listed in Table 2 for screening the reported compounds include the ISO-induced MF model and the *in vitro* cell culture model using NRK-49F cells. Two compounds reported for their antifibrotic effects on MF include the triterpenoid (compound **3**) and the phenylpropanoid glycoside (compound **35**). The triterpenoid (**3**) regulates fibrosis markers such as collagen I, collagen III, and α-SMA. In contrast, the phenylpropanoid glycoside (**35**) reduces angiotensin II (ANGII)-induced increases in collagen I, α-SMA levels, and markers of oxidative stress in H9c2 cardiomyocytes.

Phytochemicals against PF. The experimental models for screening the compounds included BLM-induced PF in rats, identifying three compounds: steroid **13** and flavonoids **21** and **34**. Their modes of action involved reducing inflammation and ECM deposition by inhibiting the WNT/β-catenin pathway (compounds **3** and **21**), as well as decreasing lung tissue damage and PF through reduced expression of N-cadherin and α-SMA, while increasing NRF2, HO-1, and SMAD7 proteins (compound **34**).

Phytochemicals against RF. The models for screening compounds against RF included an *in vitro* cell culture model using neutrophils and renal fibroblasts, as well as a UUO-induced RF model in mice and rats. The identified compounds include flavonoid **29**, isoflavone **22**, iridoids **14** and **15**, and furan **32**. Their modes of action involve reducing the production of neutrophil extracellular traps to alleviate RF through the

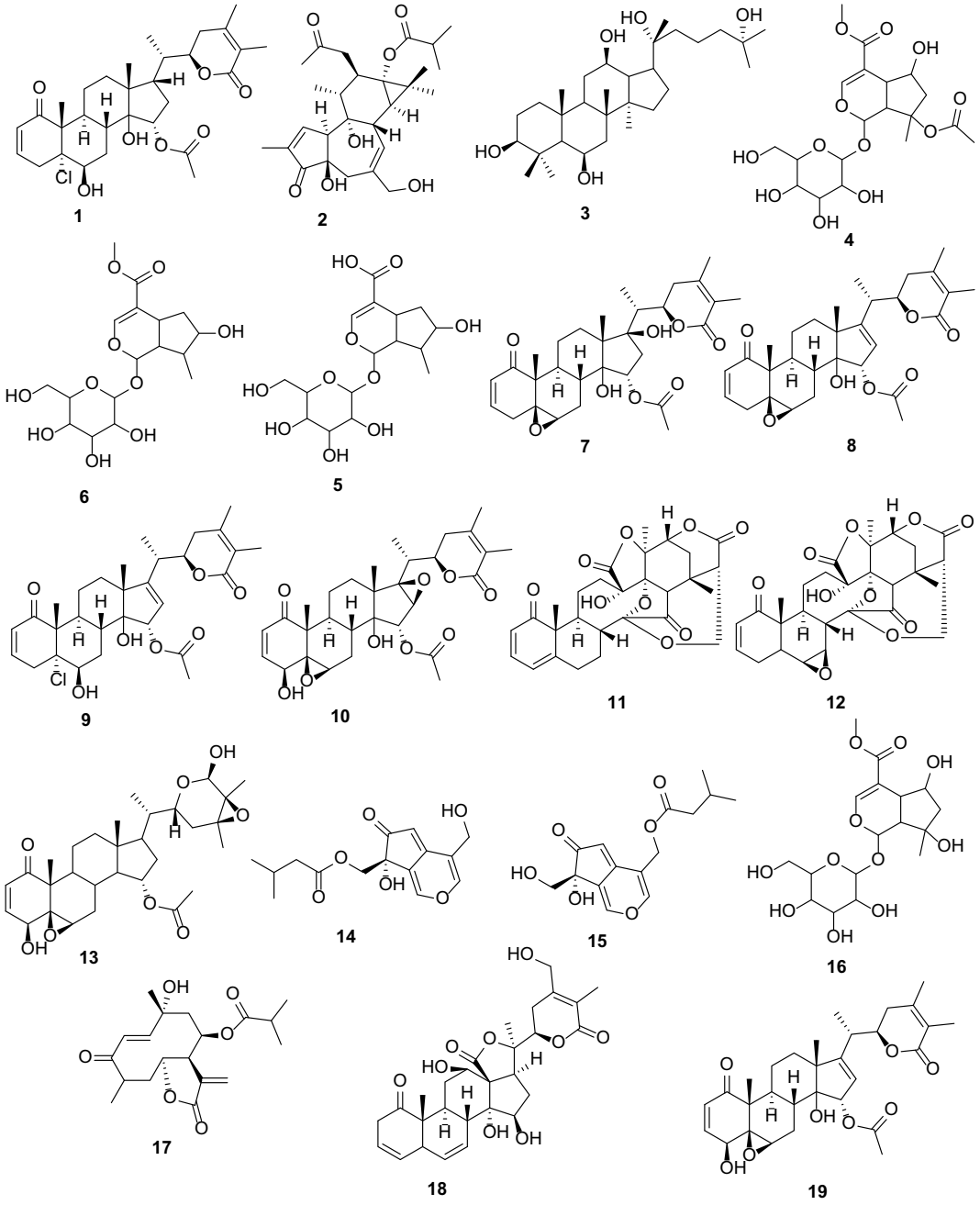

Fig. 1. Chemical structures of anti-fibrotic terpenoids reported in various research studies conducted between 2023 and 2025. **1**: (20*S*,22*R*)-15α-acetoxy-5α-chloro-6β,14β-dihydroxy-1-oxowitha- 2,24-dienolide; **2**: 12-*O*-acetylphorbol-13-isobutyrate; **3**: 25-OH-PPT; **4**: 8-*O*-acetyl shanzhiside methyl ester; **5**: loganate; **6**: loganin; **7**: physagulide I; **8**: physagulin A; **9**: physagulin B; **10**: physagulin C; **11**: physalin B; **12**: physalin F; **13**: physapubescin; **14**: scabrol B; **15**: scabrol C; **16**: shanzhiside methyl ester; **17**: tagitinin C; **18**: withagulide F; **19**: withgulatin A.

TLR4 and NF-κB pathways (compound **22**). Compounds **14** and **15** provide protective effects against RF in NRK-49f renal fibroblasts by decreasing the expression of fibronectin, collagen I, and α-SMA in NRK-49f cells, mediated by TGF-β1. Additionally, compound **29** inhibits the LGALS1/PI3K/AKT signaling pathway, while compound **32** inhibits the TGF-β/SMAD and WNT/β-catenin signaling pathways (Table 2).

Conclusion

This review begins by presenting the fundamental information on the four main types of fibrosis. It then summarizes three years of data on the antifibrotic effects of medicinal plants and their derivatives. The document reports on 72 botanicals, which include 28 individual plants studied separately and 44 combined herbal formulations. These botanicals are categorized according to different fibrotic types: 21 for liver fibrosis (LF), 8 for myocardial fibrosis (MF), 23 for pulmonary fibrosis (PF), and 20 for renal fibrosis (RF). The review provides detailed information on 10 polyherbal formulations: *Guizhi Fuling Wan* (GFW) and *Jiawei Taohe Chengqi* decoction (JTCD) for LF; *Ling Gui Zhu Gan* decoction (LGZGD) and *Qi Li Qiang Xin* (QLQX) for MF; *Sha-Shen Mai-Dong* (SMT) and *Xuan Fei Bai Du* decoction (XFBD) for PF; and *Huang Qi-Dan Shen* (HQDS) and *Jian-Pi-Yi-Shen* (JPYS) for RF. Additionally, the document lists 35 phytochemicals, including 19 terpenoids and 16 phenolic compounds. In summary, this review article discusses the antifibrosis activity of 72 botanicals and 35 phytochemicals. The key points are as follows: (a) No botanical or phytochemical has been

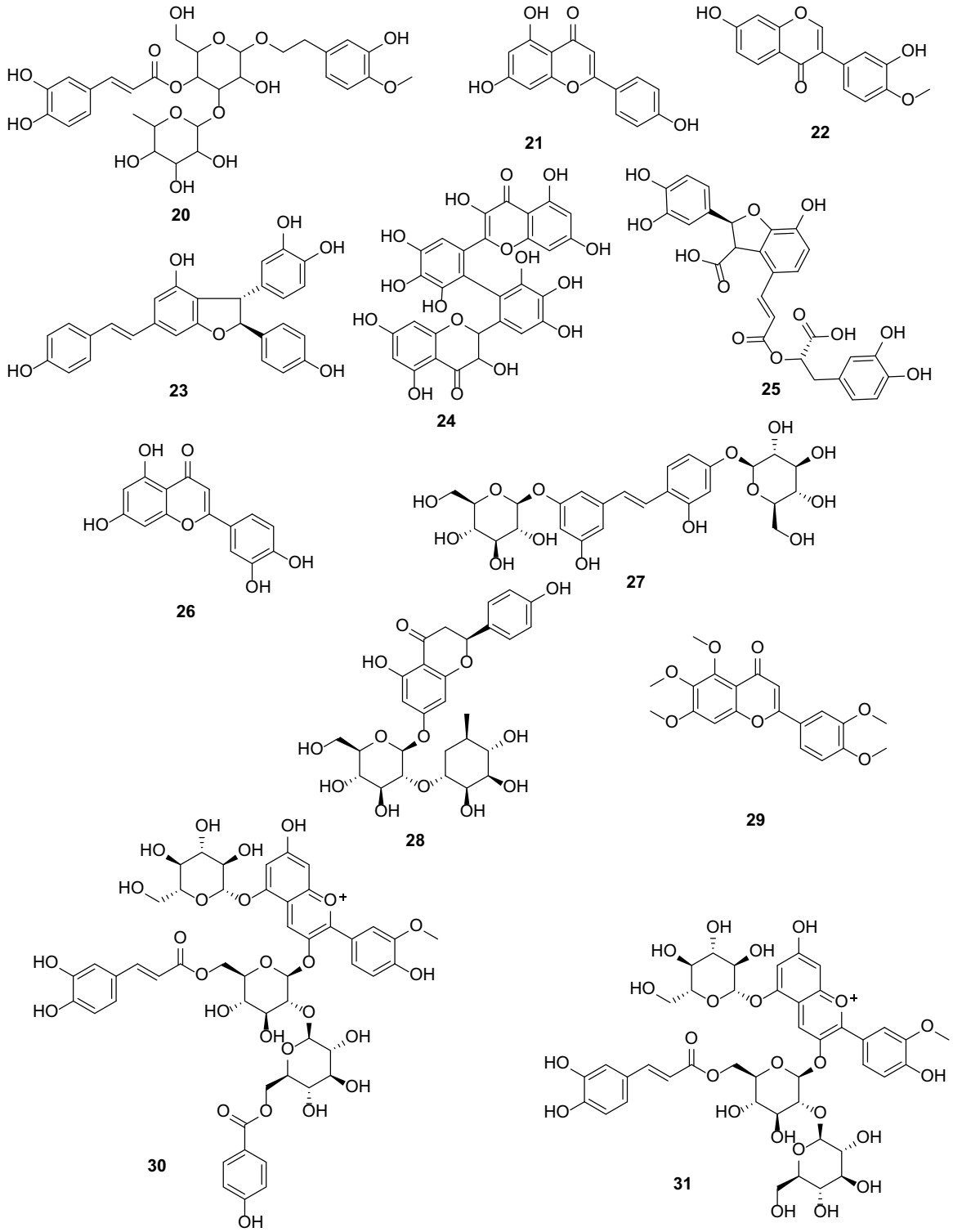

Fig. 2. Chemical structures of anti-fibrotic phenolics reported in various research studies conducted between 2023 and 2025.**20**: acteoside; **21**: apigenin; **22**: calycosin; **23**: gnetin C; **24**: hovenianin A; **25**: lithospermic acid; **26**: luteolin; **27**: mulberroside A; **28**: naringin; **29**: nobiletin; **30**: PSPA-1; **31**: PSPA-2. **32**: regiafuran C; **33**: resveratrol; **34**: rhoifolin; **35**: salidroside.

clinically tested for antifibrosis activity. (b) The active constituents of most botanicals have not been identified. (c) The chemical constituents responsible for the antifibrosis activity of only one out of the ten reported plant formulations have been documented. (d) The antifibrosis activity of most of the botanicals, from which 35 identified phytochemicals were isolated, has not been thoroughly studied. (e) While potential mechanisms of action have been described for all the discussed botanicals and phytochemicals, the overall identification of active ingredients in these botanicals remains incomplete.

It is essential to evaluate the antifibrosis activity of botanicals known to contain antifibrosis compounds. Furthermore, additional toxicological studies are necessary to assess the safety of these antifibrosis

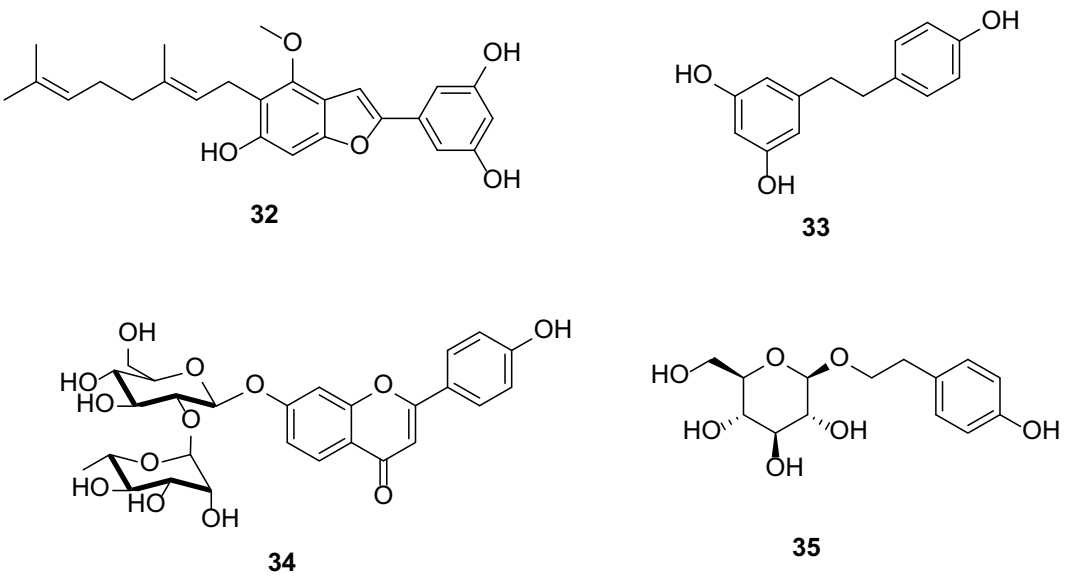

Fig. 2. (*continued*).

products.

CRediT authorship contribution statement

Jason B.T. Kuete: Writing – original draft, Methodology. **Jenifer R. N. Kuete:** Methodology, Investigation. **Armelle T. Mbaveng:** Writing – original draft, Validation, Formal analysis. **Victor Kuete:** Writing – original draft, Validation, Supervision, Formal analysis, Data curation. **Thomas Efferth:** Writing – review & editing, Supervision, Conceptualization. **Ralf Weiskirchen:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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