Chinese Medicine

REVIEW

Open Access

A systematic review of the research progress of traditional Chinese medicine against pulmonary fibrosis: from a pharmacological perspective

Shanbo Qin[1], Peng Tan[1*], Junjie Xie[1], Yongfeng Zhou[2] and Junning Zhao[1*]

Abstract

Pulmonary fibrosis is a chronic progressive interstitial lung disease caused by a variety of etiologies. The disease can eventually lead to irreversible damage to the lung tissue structure, severely affecting respiratory function and posing a serious threat to human health. Currently, glucocorticoids and immunosuppressants are the main drugs used in the clinical treatment of pulmonary fibrosis, but their efficacy is limited and they can cause serious adverse effects. Traditional Chinese medicines have important research value and potential for clinical application in anti-pulmonary fibrosis. In recent years, more and more scientific researches have been conducted on the use of traditional Chinese medicine to improve or reduce pulmonary fibrosis, and some important breakthroughs have been made. This review paper systematically summarized the research progress of pharmacological mechanism of traditional Chinese medicines and their active compounds in improving or reducing pulmonary fibrosis. We conducted a systematic search in several main scientific databases, including PubMed, Web of Science, and Google Scholar, using keywords such as idiopathic pulmonary fibrosis, pulmonary fibrosis, interstitial pneumonia, natural products, herbal medicine, and therapeutic methods. Ultimately, 252 articles were included and systematically evaluated in this analysis. The anti-fibrotic mechanisms of these traditional Chinese medicine studies can be roughly categorized into 5 main aspects, including inhibition of epithelial-mesenchymal transition, anti-inflammatory and antioxidant effects, improvement of extracellular matrix deposition, mediation of apoptosis and autophagy, and inhibition of endoplasmic reticulum stress. The purpose of this article is to provide pharmaceutical researchers with information on the progress of scientific research on improving or reducing Pulmonary fibrosis with traditional Chinese medicine, and to provide reference for further pharmacological research.

Keywords Pulmonary fibrosis, Traditional Chinese medicine, Anti-inflammation, Anti-oxidation, Endoplasmic reticulum stress

*Correspondence:
Peng Tan
2013tanpeng@sina.com
Junning Zhao
zarmy@189.cn
Full list of author information is available at the end of the article

Introduction

Pulmonary fibrosis (abbreviated as PF) is a chronic, progressive, irreversible interstitial lung disease commonly caused by multiple etiologies and characterized by the accumulation of inflammatory cells such as macrophages, neutrophils and lymphocytes in the alveoli, the proliferation and differentiation of fibroblasts, and the development of fibrous connective tissue. Ultimately, it leads to structural changes in the patient's normal lung tissue [1, 2]. In the late stages of many pulmonary diseases, PF is a common pathological manifestation. In modern medicine, interstitial lung disease is divided into two types: secondary interstitial lung disease and idiopathic interstitial lung disease. The former has a relatively clear etiology, including silicosis, pneumoconiosis, asbestosis, radiation-induced PF, and drug-induced interstitial lung disease. In contrast, the etiology of the latter is unknown, including idiopathic pulmonary fibrosis (abbreviated as IPF), cystic fibrosis, and interstitial pneumonia with autoimmune features, among which IPF is the most important [1, 3]. Due to IPF's wide involvement, long course, high mortality rate, and other characteristics, it is also known as a tumor-like disease [2]. Unfortunately, the prognosis for patients with IPF is often unfavorable, as they typically suffer from significant lung function impairment and a reduced quality of life during recovery [4, 5]. Epidemiological surveys have shown that the prevalence and incidence of IPF is increasing year by year and is more prevalent in the elderly. The mortality rate of IPF is high, and more than half of patients with IPF who were hospitalized for acute exacerbations will die during their hospitalization, and their average survival period after diagnosis is 2 to 4 years [6–8]. Notably, following the outbreak of COVID-19 in 2019, clinical observations have identified fibrosis in the lungs of patients with COVID-19 [9–11]. If PF is not controlled promptly and effectively, it will lead to a decline in lung function and seriously affect the quality of life and life expectancy of patients [12]. At present, glucocorticoids and Immunosuppressive drug, such as pirfenidone and nifanyl, are the main clinical treatments for PF, but their clinical efficacy is not satisfactory, and these drugs are also expensive and have many side effects [13–15]. In recent years, traditional Chinese medicines (abbreviated as TCM) has made great progress in improving or reducing of PF, and has become one of the alternative therapies for clinical treatment of IPF due to its significant efficacy and few side effects [16–18]. Of particular interest is that in the battle against COVID-19, TCM has shown the advantages of high efficiency and low toxicity in lung injury caused by the novel coronavirus and in the prognosis of rehabilitation, playing an important role in blocking the progression of PF and promoting the recovery of patients [19–21]. In this review article, we focus on the research progress of TCM in improving PF from a pharmacological perspective. Firstly, we summarized the research progress on the pharmacological mechanisms related to PF. Secondly, we systematically summarized the potential active compounds in TCM that can be used to improve PF, and classified the targets of these compounds. Finally, future research directions were envisioned. The following search terms were used: IPF, PF, interstitial pneumonia, natural product, herbs. The time limit is from June 2017 to June 2023. We did a systematic search of several major scientific databases, including PubMed, Web of Science, and Google Scholar. A total of 252 articles were retrieved. At that time, the focus was on screening original experimental articles that matched the theme, totaling 184 articles. We evaluated these literature and systematically reviewed the research progress of TCM in improving PF in the past five years.

Pathogenesis of pulmonary fibrosis

The pathogenesis of PF is not yet fully elucidated, but it is known to be caused by a variety of factors: for example, PF due to silica inhalation [22], PF induced by chemicals, such as bleomycin, paraquat [23, 24], and induced by different primary diseases [25].

Modern medicine generally agrees that fibrosis can be described as an irrational form of injury repair [26, 27]. Repeated microdamage to the alveolar epithelium is the first driving factor that induces an abnormal repair process in which persistent alveolar epithelial cell damage and repair abnormalities, proliferation of fibroblasts, and accumulation of extracellular matrix (abbreviated as ECM) lead to structural disorders in the lung and the formation of fibrosis [28–30]. In the early stages of PF, there are different influencing factors, but in the later stages of fibrosis, there are the same mechanisms of action [31, 32]. The pathogenesis of PF can be roughly divided into three stages: injury, inflammation, repair. The first stage: the lung is damaged or otherwise noxiously stimulated and fibroblasts are activated and begin to secrete ECM. This phase is disease-specific and it consists mainly of lymphocyte activation and differentiation, autoimmune and immune-mediated conditions of excessive immune response, and chronic granulomatous inflammation. This is due to the persistence of identified or unidentified antigens, or other exposures. These multiple environmental risk factors, such as smoking, occupational exposure, air pollution, toxic compounds, viral infections, can repeatedly damage alveolar cells [2, 33, 34]. The second stage: mitogen-activated protein kinase (abbreviated as MAPK) and nuclear factor kappa B (abbreviated as NF-κB) pathways are activated to promote the production of a large number of cytokines [35]. Activated fibroblasts undergo

structural and phenotypic changes and produce a large amount of ECM [36]. Through paracrine, inflammatory cells, including macrophages, move to the stimulated site. T cells are activated to secrete fibrogenic growth factors, such as interleukin and tumor necrosis factor alpha (abbreviated as TNF-α) [37]. Macrophages promote the proliferation and differentiation of fibroblasts and secrete a variety of cytokines, including transforming growth factor beta (abbreviated as TGF-β) and Interleukins-1 (abbreviated as IL-1) [38]. The third phase: the injury factors persisted, resulting in repeating damage of alveolar epithelial cells. Fibroblasts continue to be activated to produce more ECM [39–41]. Cytokines continue to cause tissue inflammation and collagen overexpression, ECM deposition, the beginning of a vicious circle, and finally lead to the gradual formation of PF, the loss of lung function at the idiopathic site [42–44].

Pulmonary fibrosis-related signaling pathways

TGF-β/Smad

Transforming growth factor-β/Smad (TGF-β/Smad) is a pleiotropic signaling pathway that plays a key role in inflammation, wound healing, fibrosis processes such as epithelial injury, myofibroblast fibroblast proliferation and differentiation and ECM production [45, 46]. TGF-β exerts its biological activity through activation of Smad-dependent and non-dependent pathways. The Smad protein family can be divided into three categories: receptor-activated (R-Smads, including Smads 1, 2, 3, 5, and 8), general-purpose (Co-Smad, including Smad 4), and inhibitory (I-Smads, including Smad 6 and 7) [47]. The TGF-β receptor is a receptor that belongs to the group with endogenous Ser/Thr kinase activity and binds to its type I and type II receptors to form a complex that leads to phosphorylation of Smad2 and Smad3 [48]. The phosphorylated Smad2 and Smad3 then further form a complex with Smad4, which undergoes nuclear translocation, activating the expression of transcription factors downstream of Epithelial-mesenchymal transition (EMT) and promoting EMT [49]. TGF-β1 also activates MAPK, phosphoinositide 3-kinase/protein kinase B pathway, and Rho pathways, induces EMT, increases the expression of collagen, fibronectin, and tissue inhibitor of matrix metalloproteinases (TIMPs), and promotes PF. Recent studies have shown that numerous active substances of natural products can improve PF through the TGF-β/Smad signaling pathway [50].

Nrf2/ARE

When the organism is damaged by external oxidative and chemical stimuli and other stresses, it generates corresponding self-defense responses and induces a series of protective proteins. The Nuclear Factor erythroid 2-Related Factor 2/antioxidant response element (Nrf2/ARE) pathway is a classical defensive transduction pathway that can reduce the oxidative stress damage occurring in cells [51]. Nrf2 is a key factor in the cellular oxidative stress response, with antioxidant, anti-inflammatory response and cytoprotective effects [52]. Nrf2 is a key transcription factor that is essentially expressed in oxidative stress and is present in multiple organs throughout the body, and its deletion or impaired activation directly causes changes in cellular sensitivity to stressors changes in the sensitivity of cells to stressors [53, 54]. The Nrf2/ARE pathway in the lung mainly regulates the expression of antioxidant genes, thus providing protection to lung tissue [55]. When cells are attacked by reactive oxygen species or other electrophile reagents in a state of oxidative stress, Nrf2 is uncoupled from keap1 and translocated across the membrane into the nucleus. By regulating ARE activity, it further initiates the transcription of downstream regulatory antioxidant proteins and phase II detoxification enzymes, and regulates the expression of various antioxidant genes, thereby increasing the production of antioxidant substances, reducing cellular oxidative damage and maintaining intracellular redox homeostasis, thus playing an antioxidant and anti-fibrotic role [55]. By activating the Nrf2/ARE signaling pathway, the synthesis of antioxidant proteins can be increased, and thus the body's enhanced antioxidant capacity can be achieved to delay the progression of PF [56]. The Nrf2/ARE pathway can also mediate a variety of antioxidant enzymes and phase II detoxification enzymes to protect tissues.

PI3K/AKT

The phosphoinositide 3-kinase/protein kinase B pathway (PI3K/AKT) is one of the central intracellular signaling pathways regulating cell growth, proliferation, motility, metabolism and survival [57, 58]. PI3K is a signal transduction enzyme that phosphorylates PI (4,5) P2 to form PI (3,4,5) P3, which is activated by tyrosine kinase receptors, G protein-coupled receptors/cytokine receptors and Ras protein-associated GD Pase receptors to promote cell proliferation, survival, adhesion, differentiation, cytoskeleton organization, etc. [59, 60]. Protein kinase B (AKT) is a serine/threonine kinase downstream of PI3k, and AKT binds to PI(3,4,5) P3 near the cell membrane to form a complex. The binding of the complex to 3-phosphoinositide-dependent protein kinase 1 promotes the phosphorylation of the PH domain at the amino acid terminus of AKT, which activates downstream factors such as hypoxia-inducible factor-1 and mammalian target of rapamycin (mTOR) to participate in cell proliferation and differentiation [59, 60]. AKT is a direct target protein downstream of PI3K, which can participate in regulating cell proliferation and metabolism, promoting

fibrosis-related gene transcription and protein synthesis, and activated AKT can participate in PF by activating mTOR [61]. AKT2-deficient mice can counteract bleomycin (BLM)-induced PF and inflammation, suggesting that PI3K/AKT signaling plays an important role in IPF development [62]. In addition, activation of PI3K/AKT can be involved in the development of PF by regulating its downstream genes such as mTOR, hypoxia-inducible factor-1 and Fox family [63]. It is due to the important role of PI3K/AKT in regulating receptor-mediated signaling that targeting PI3K/AKT has become a promising strategy for the treatment of IPF.

Wnt/β-catenin

Wnt signaling pathway can be divided into classical Wnt signaling pathway (i.e. Wnt/β-catenin signaling pathway) and non-classical Wnt signaling pathway. Among them, β-catenin is the key molecule that mediates classical Wnt signaling. Wnt proteins are a group of secreted glycoproteins expressed in a variety of tissue cells, involved in a variety of signaling pathways, and play a key role in cell differentiation, cell migration, organogenesis, stem cell self-renewal and maintenance of tissue homeostasis. β-catenin is a cytoskeletal protein that, together with E-cadherin and α-catenin, is involved in the construction of cell junctions and intercellular adhesion mechanisms, and plays an important role in maintaining the stability of the intracellular environment and signaling into the nucleus [64, 65].

The Wnt/β-catenin signaling pathway plays an important role in many pathological processes in the lung and is one of the major regulatory pathways in PF [66]. In pulmonary endothelial cells Wnt/β-catenin signaling causes a shift from perivascular fibroblasts to myofibroblast-like cells, leading to ECM accumulation and increased tissue stiffness, further promoting PF [67]. Downregulation of the Wnt signaling pathway also inhibited myofibroblast differentiation, thereby ameliorating PF lesions [68]. The Wnt/β-catenin signaling pathway was significantly activated in the IPF animal model [69], and blockade of the Wnt/β-catenin pathway was also effective in attenuating lung fibrosis in mice [70].

It has been shown that Wnt/β-catenin signaling is involved in the induction of EMT during the development of fibrosis [71]. Wnt1, Wnt3A, Wnt7B, Wnt10B, Fzd2, Fzd3 and β-catenin expression were significantly increased in lung tissues of IPF patients [72]. Wnt5A and Wnt5B ligands have been reported to exert effects on pulmonary fibroblast differentiation via TGF-β [73]. The Wnt/β-catenin pathway also interacts with the TGF-β/Smad, PI3K/AKT signaling pathway and plays an important role in the pathogenesis of IPF, and inhibition of this pathway can reduce or reverse PF [74].

NF-κB

NF-κB is one of the major nuclear transcription factors that regulate inflammatory and immune responses, as well as a signaling pathway that is present in many cell types and closely associated with intracellular biological functions and inflammatory responses [75, 76]. In addition, NF-κB binds to fixed nucleotide sequences in the promoter regions of many genes to initiate gene transcription, which plays a crucial role in the inflammatory response, the regulation of the immune system, and cell growth [77, 78]. Five transcription factors comprise the NF-κB family: NF-κB1 (p50), NF-κB2 (p52), Rel A (p65), Rel B, and c-Rel [79]. NF-κB proteins function as dimers that bind to the κB site and affect the transcription of target genes [80]. The phosphorylation of NF-κB is responsible for activating the NF-κB signaling pathway [81]. Inflammation is now believed to be one of the factors contributing to fibrosis [82–84], and during PF, NF-κB is activated, which promotes the release of large amounts of inflammatory factors such as TNF-α, IL-1β, IL-8 and TGF-β1 [85], stimulating the proliferation of fibroblasts and the deposition of collagen fibers, thereby promoting the development of organ fibrosis [86]. Several studies [87, 88] have elucidated the crucial role of the NF-κB signaling pathway in regulating acute lung injury-induced PF. NF-κB also plays a key role in the secretion of pro-fibrotic cytokines during the progression of PF [89]. In addition to inflammation, cellular senescence is an important factor leading to fibrosis that can promote the development of IPF through a variety of mechanisms, such as senescence associated secretory phenotype (SASP), telomere dysfunction, etc. [90, 91]. The NF-κB signaling pathway is a key regulator of SASP, according to [92]. SASP has been shown to be inhibited by the inhibition or knockdown of multiple components that regulate NF-κB signaling [93].

Cytokines related to pulmonary fibrosis

Transforming growth factor β

Transforming Growth Factor β (TGF-β) has been implicated as a central factor in the development of PF [94–96]. TGF-β has several biological roles, such as promoting wound repair by increasing ECM deposition, inflammatory cell recruitment and fibroblast differentiation [97, 98]. TGF-β1 is currently recognized as the most critical fibrogenic factor and the most potent promoter of ECM deposition ever identified. It has been shown in the literatures that the TGF-β1/Smad signaling pathway is activated during PF [99, 100], prompting the conversion of fibroblasts to myofibroblasts and alveolar epithelial and endothelial cells to mesenchymal cells. In addition, activation of the TGF-β1/Smad signaling pathway reduces the secretion and inhibits the activity of

matrix protein metallases, while increasing the synthesis and secretion of matrix metalloproteinase tissue inhibitory factor, which inhibits myofibroblast apoptosis and leads to the production of large amounts of ECM and its failure to degrade properly, allowing it to accumulate in the lung and cause PF [36, 101].

Platelet-derived growth factor

Platelet-derived growth factor (PDGF) is a peptide-like regulatory factor stored mainly in platelets, and when PF occurs, epithelial cells, alveolar macrophages and activated platelets will secrete large amounts of PDGF [102]. PDGF is closely related to the proliferation and differentiation of lung fibroblasts [103]. PDGF promotes the formation and development of PF by promoting the proliferation, migration and aggregation of lung fibroblasts, as well as regulating the synthesis and deposition of ECM. Therefore, PDGF is known as an energizing factor for fibroblast proliferation [104, 105]. In the process of PF, PDGF is mainly produced at the site of lung tissue injury, and TGF-β1 and TNF can regulate the expression of PDGF. On the one hand, PDGF can cross the cell membrane barrier through the damaged lung epithelial cells into the alveolar mesenchyme and chemotactic mesenchymal cells; On the other hand, similar to the function of TGF-β1, it can also induce fibroblast proliferation and differentiation and stimulate fibroblasts to secrete collagen, but the mechanism of action may be different from that of TGF-β1 [106]. It has been found that increased release of PDGF is observed in the lungs of IPF patients and that blocking PDGF receptor signaling in animal models of IPF attenuates the extent of PF [107].

Interleukins

Interleukins (IL) are a class of cytokines produced mainly by lymphocytes, monocytes or macrophages and act on a variety of cells. They are complex in structure and function and play an important role in a range of processes including immune regulation and inflammation in lung tissue [108, 109]. Thirty-eight species have been named, of which approximately one third are involved in the development of PF. During PF, IL-1, IL-4, IL-6, IL-11, and IL-13 play important roles in promoting proliferation and aggregation of pulmonary fibroblasts, ECM deposition, collagen synthesis, and lung tissue remodeling [110, 111]. Among them, IL-13 has a significant effect on tissue fibrosis. It has been shown that IL-4 and IL-13 can synergistically exert activation effects on M2 type macrophages, and the activated M2 type macrophages secrete pro-fibroblastic cytokines thereby promoting the development of fibrosis [112]. IL-7, IL-10, IL-12, and IL-18 reduce PF by inhibiting inflammatory factors and modulating immunity [113–117]. Among them, IL-10 may activate macrophages through the CCL2/CCR2 axis, causing fibroblast accumulation and eventually causing fibrous degeneration [118].

Tumor necrosis factor-α

Tumor necrosis factor-α (TNF-α) is a multi-temporal, cellular immune defense factor produced by mononuclear macrophages. TNF-α is highly expressed in the pathological process of lung injury and can participate in the local injury and inflammatory response, leading to the aggregation of inflammatory cells, which in turn stimulates massive proliferation of lung fibroblasts and secretion of collagen. Therefore, TNF-α is one of the important indicators for clinical testing of PF. On the one hand, TNF-α is involved in the process of acute inflammatory response and inhibits the repair of lung injury by promoting apoptosis of type II alveolar cells [119]. On the other hand, TNF-α promotes the differentiation of lung resident mesenchymal stem cells into myofibroblasts [120]. In the early stages of PF, macrophages aggregate, synthesize and release large amounts of TNF-α. TNF-α stimulates a massive increase in chemotactic and adhesion molecules, creating an inflammatory cell infiltrate. Therefore, TNF-α is also known as an early response factor [121]. In addition, TNF-α can act synergistically with IL-1 to promote neutrophil activation and aggregation and regulate the inflammatory response in the early stages of PF [122]. TNF-α acts mainly through the NF-κB pathway, and its mechanism may be related to the Wnt/β-catenin signaling pathway. There are NF-κB binding sites on the transcriptional promoter region or enhancer of the TNF-α gene, and the two promote each other and jointly regulate the development of PF [123].

Pharmacological mechanism of TCM in improving pulmonary fibrosis

TCM has demonstrated significant clinical efficacy and unique advantages in improving IPF. PF is closely related with TCM terminologies such as 'lung obstruction', 'lung atrophy', and 'lung abscess'. TCM mainly employs a dialectical treatment approach from the perspectives of tonifying the lung and kidney, invigorating the spleen and lung, and promoting blood circulation and removing blood stasis. In recent years, research on TCM therapy for PF has been increasing, and significant progress has been made in some aspects. In this section, we reviewed recent literatures and summarized that the mechanisms by which TCM improving PF can be roughly divided into five categories: inhibiting EMT, anti-inflammatory and anti-oxidative stress, improving ECM deposition, mediating cell apoptosis and autophagy, and inhibiting endoplasmic reticulum stress (ERS), a simple classification information was shown in Fig. 1.

Inhibition of epithelial cell-mesenchymal transformation

EMT is the process by which epithelial cells lose cellular activity through a specific procedure and are then transformed into mesenchymal cells. EMT is the main source of fibroblasts and myofibroblasts in IPF [124, 125]. It has been shown that approximately 33% of myofibroblasts in the lung can be traced to cells undergoing EMT in a bleomycin-induced lung fibrosis model [126]. EMT is mainly divided into 3 types: type I EMT is mainly related to normal physiological activities of cells; type II EMT is mainly related to injury repair, tissue regeneration and organ fibrosis; type III EMT is related to tumor metastasis [127, 128]. Among them, type II EMT is mainly caused by persistent inflammation and injury, regulated by a variety of signaling factors and signaling pathways, and is an important mechanism for the occurrence and development of PF, which can be treated by inhibiting EMT progression. There is growing evidence that EMT is closely associated with fibroblast activation and PF, characterized by increased expression of α-SMA and vimentin and decreased expression of the intercellular adhesion molecule E-cadherin. Therefore, inhibition of EMT is an important way to treat PF. At present, the signaling pathways involved in EMT inhibition by TCM mainly include TGF-β/Smad, NF-κB, PI3K-Akt, and so on.

Andrographolide, a diterpenoid compound isolated from andrographis paniculata, it has pharmacological effects such as anti-inflammatory, antioxidant, and participation in regulating EMT [129, 130]. Sachin Karkale's research team found that Andrographolide can effectively reduce the expression of mesenchymal markers in PF mice and increase the expression of epithelial markers [131]. This study revealed for the first time that andrographolide could shown good anti-fibrosis activity by inhibiting inflammation and targeting EMT, which provided a new idea for the study of TCM to improve silicon induced PF. In addition to silicon induced occupational PF, andrographolide also has a certain inhibitory effect on bleomycin induced IPF. The research results of Li Jingpei's team shown that andrographolide could improve BLM induced PF in rats, and explore its mechanism from different perspectives. First, andrographolide

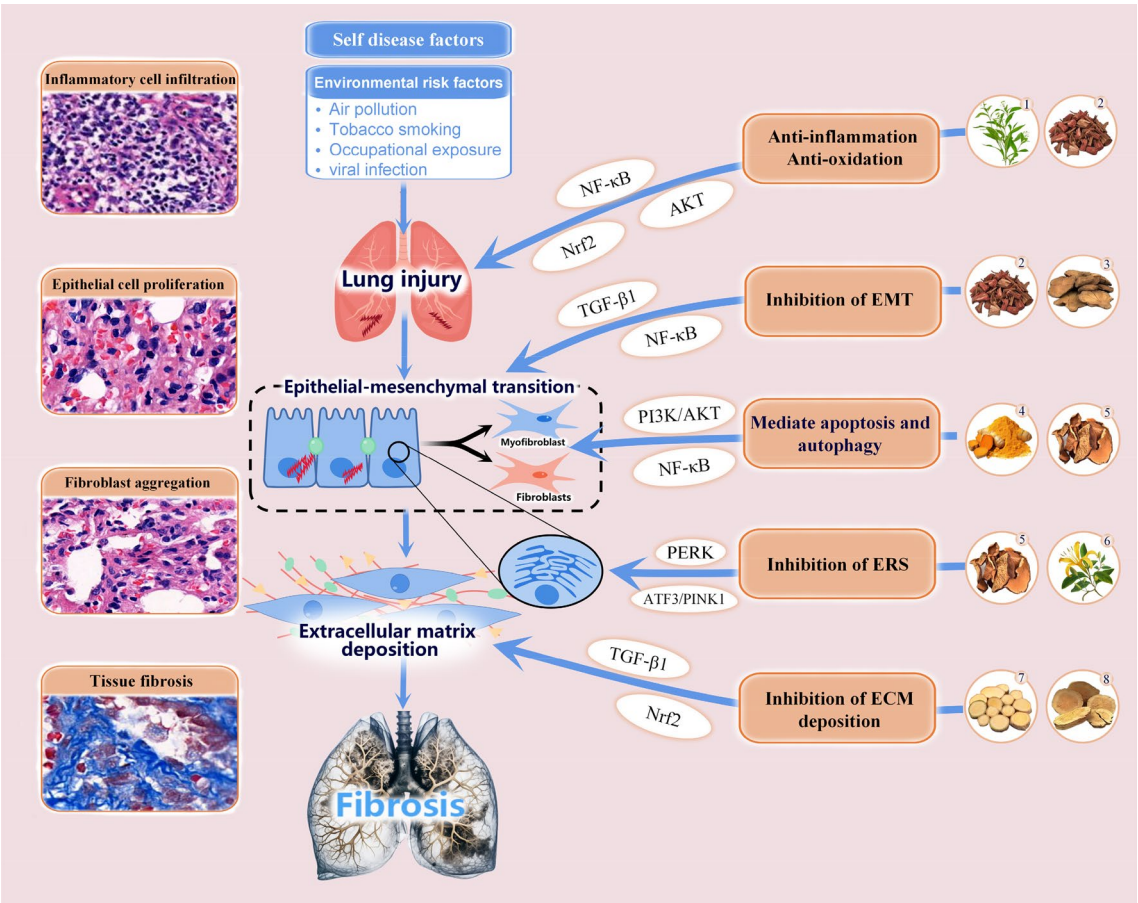

Fig. 1 Schematic diagram of the main intervention targets of traditional Chinese medicine against pulmonary fibrosis

could improve PF by inhibiting the proliferation of fibroblasts and the differentiation of myofibroblasts. This process is affected by TGF-β1 mediated regulation of Smad dependent and non dependent pathways [132]. Secondly, andrographide could inhibit TGF β1 in alveolar epithelial cells (AEC) by regulating the Smad2/3 and Erk1/2 signaling pathways [132]. Then, andrographolide could inhibit EMT in lung epithelial cells through AKT/mTOR signaling pathway, thereby reducing BLM induced PF [134]. These results shown that andrographis paniculata could improve PF through multiple ways and targets, which has great development potential and is worth our in-depth study.

Emodin is an anthraquinone compound with multiple biological activities isolated and purified from rhubarb. Zhou's team research shown that emodin could inhibit NE induced EMT in RLE-6TN and A549 cells, and its mechanism of action was related to NE induced Notch1 lysis [135]. This study preliminarily revealed the mechanism of emodin inhibiting EMT at the cellular level, which has certain reference value for further understanding the pharmacological effect of emodin in improving PF. Emodin can also regulated NF-κB and TGF- β1/Smad3 signaling pathway inhibits EMT and improves silica induced PF [136]. Rhapontin is another important compound in rhubarb, and Tao's team found in vitro experiments that rhapontin could activate AMPK and inhibit TGF- β/Smad pathway reversal of ECM [137]. This experiment confirmed the anti-PF activity of rhapontin for the first time. On the whole, rhubarb has important medicinal value in improving PF, but its pharmacology and toxicology still need further experimental and clinical research.

Salvia miltiorrhiza is a commonly used herbal medicine to treat cardiovascular and pulmonary diseases. Salvianolic acid B is a bioactive component extracted from Salvia miltiorrhiza, which has strong anti-inflammatory and antioxidant effects. Liu's team first confirmed the anti fibrotic activity of salvianolic acid B through a cell model, and further found in animal models that salvianolic acid B inhibits the transdifferentiation of lung fibroblasts by activating Nrf2 signaling [138]. Cryptotanshinone is a diterpenoid compound with antioxidant, anti-inflammatory, and antibacterial activities. Research has shown that CPT exhibits good anti-fibrotic effects in both in vitro and in vivo, inhibiting various cell proliferation and TGF-β induced EMT [139]. Although these research results suggest that Salvia miltiorrhiza may be a potential drug for improving IPF, these studies have only been conducted on animal or cell models and further clinical research is still needed.

In addition to the above-mentioned TCM that can improve PF, the detailed information of other TCM studies in the past five years that can improve PF by inhibiting EMT were summarized and presented in Table 1. It should be noted that the traditional efficacy of most Chinese medicines in the table is related to clearing away heat and detoxification, promoting blood circulation to remove blood stasis, relieving cough and resolving phlegm, which may suggest that the traditional efficacy is a reference factor that cannot be ignored when we are looking for natural drugs with anti PF activity.

Anti-inflammation and anti-oxidation

Oxidative stress is a pathological state in which the body undergoes some kind of stimulation resulting in excessive production of reactive nitrogen radicals and reactive oxygen radicals, leading to an oxidative/antioxidative imbalance. Oxidative stress is a major cellular stressor that can act directly or indirectly on cells, leading to structural necrosis, apoptosis and tissue inflammation [212]. The imbalance between oxidants and antioxidants plays a role in the pathophysiology of IPF, and NADPH oxidase (NOX), which generates reactive oxygen species (ROS), is the primary cause of IPF [213]. Excessive ROS and free radical production can cause lung damage [214]. The level of systemic oxidative stress and disease severity in IPF patients are significantly correlated with dyspnea, as shown by numerous studies [215]. Therefore, anti-oxidative stress is essential for the successful treatment of PF [216]. The inflammatory response is a defense mechanism of the body, and the inflammatory response of the body to different degrees of injury is one of the important factors against lung injury [217, 218]. The pathogenesis of PF may be due to damage to lung epithelial cells by fibrotic stimuli. Therefore, lung inflammation plays an important role in the development of PF. And inflammation is controlled by a variety of cells and cytokines [212, 219] Pro-inflammatory cytokines control tissue differentiation and morphogenesis through adhesion molecules and promote fibrotic responses in lung tissue [220]. Currently, many anti-inflammatory and antioxidant agents have shown effective antifibrotic effects in BLM-induced PF models. Therefore, the imbalance between oxidative stress, oxidants and antioxidants, and inflammation in the development of PF deserve further attention [221, 222].

Emodin is an anthraquinone compound extracted from rhubarb, which has antiviral, anti-cancer, anti-inflammatory and other pharmacological effects [223, 224]. Tian's team found that emodin can significantly reduce the increase of proinflammatory cytokines and oxidative damage caused by BLM [225]. Further experiments found that the anti-inflammatory and antioxidant activities of emodin may be through regulating NF-κB and

Table 1 Details about some traditional Chinese medicines improving pulmonary fibrosis by inhibiting epithelial cell-mesenchymal transformation

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	Cytokine	Refs.
1	*Scutellariae radix*	Scutellaria	Clearing away heat and dampness, purging fire and detoxifying	Astragalus polysaccharides	BLM-induced PF mice and A549 cells	Mice (200 mg/kg)	Inhibit NF-κB signaling	TGF-β1, NF-κB, α-SMA, Collagen I, CHOP	[140]
2				Baicalin	BLM-induced PF rats and RPF	Rats (50 mg/kg) Cell (20, 40, 60, 80 μg/mL)	Regulation of CaMKII and PI3K/AKT signaling	PI3K, AKT, Bax, Bcl-2	[141]
3					Radiation-induced EMT model	Cell (2, 10, 50 μmol/L)	Suppress EMT	Smad2/3, ERK, GSK3β	[142]
4				Baicalein	MRC-5 cells	Cell (1–80 μmol/L)	Inhibit miR-21	STAT3, TGF-β1, COL1 A1, α-SMA,	[143]
5				Calycosin, CA	BLM-induced PF mice and MLE-12 cells	Mice (7, 14 mg/kg) Cell (0–80 μmol/L)	Inhibit AKT/GSK3β/β-catenin signaling	AKT, GSK3β, β-catenin, E-cadherin	[144]
6	Curcumae longae rhizoma	Zingiberaceae	Promoting blood circulation and removing blood stasis, Regulating menstruation and relieving pain	Curcumin	HUVEC cells	Cell (5, 10 μmol/L)	Regulation of NRF2-DDAH-ADMA-NO signaling	TGF-β1, Nrf2, DDAH, PRMT, ERK1/2	[145]
7					BLM-induced PF mice and A549 cells	Mice (75 mg/kg) Cell (20 μmol/L)	Suppress EMT	EGFR, Ki67	[146]
8					A549 cells	Cell (20 μmol/L)	Inhibit TGF-β1/Smad/non Smad signaling	TGF-β1, Smad	[147]
9					A549 cells	Cell (0–1000 μmol/L)	Suppress EMT	ROS, α-SMA, TGF-β1	[148]
10					NHLF cells	Cell (10 μmol/L)	Down-regulation of hsa-miR-6724-5p expression	KLF10	[149]
11					CCD-19Lu cells	Cell (0–50 μmol/L)	activate PPARγ	TGF-β1, α-SMA, PPARγ	[150]
12					BLM-induced PF mice	Mice (75, 150 mg/kg)	Activates PPARγ and CREB signaling	PPARγ, CREB	[151]
13	*Andrographis herba*	Acanthaceae	Clearing heat and detoxification, cooling blood	Andrographolide	NIH 3T3, PLF cells	Rats (10 mg/kg) Cell (2, 5, 10 μmol/L)	Inhibits TGF-β1/Smad2/3 and Erk1/2 signaling	TGF-β1, Smad2/3	[132]
14					BLM-induced PF rats and A549 cells	Rats (10 mg/kg)	Regulation of AKT/mTOR signaling	AKT, mTOR	[134]
15					Silica-induced PF mice	Mice (3, 10 mg/kg)	Inhibition of ECM precipitate formation	GSH, NF-κB, CTGF	[131]
16					A549 cells	Cell (0–20 μmol/L)	Inhibits A and B signaling	TGF-β1, Smad2/3, MMP-9	[133]

Table 1 (continued)

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	Cytokine	Refs.
17	*Salviae miltiorrhizae*	Lamiaceae	Promoting blood circulation and removing blood stasis, reducing swelling and relieving pain	Tanshinone IIA	BLM-induced PF mice and PLFs, NIH-3T3 cells	Mice (5, 10, 20 mg/kg) Cell (0.01–500 μmol/L)	Inhibition of TGF-β1-Smad3 signaling	Nrf2, TGF-β1	[152]
18				Salvianolic acid B	BLM-induced PF rats and MRC-5 cells	Rats (20 mg/kg) Cell (40 μmol/L)	Regulates Nrf2 signaling	Nrf2, α-SMA, TGF-β1	[138]
19				Salvianolic acid B/sodium tanshinone IIA sulfonate	THP-1 cells	Cell (0–600 μg/mL)	Inhibit TGF-β1 signaling	TGF-β1, α-SMA	[153]
20				Cryptotanshinone	BLM-induced PF mice and A549, NIH/3T3, HPF cells	Mice (30, 60 mg/kg) Cell (0–20 μmol/L)	Suppress EMT		[139]
21	Rhei radix et rhizoma	Polygonaceae	Purging and defecating, clearing heat and detoxification	Emodin	Silica-induced PF mice and A549 cells	Mice (25, 50, 100 mg/kg)	Regulation of NF-κB and TGF-β1/Smad3 signaling	NF-κB, TGF-β1	[136]
22					RLE-6TN, A549 cells	Cell (50, 100, 200 nmol/L)	Suppress EMT	Notch1, C-MYC	[135]
23				rhapontin	BLM-induced PF rats and THP-1 cells	Rats (25, 50, 100 mg/kg) Cell (50 μmol/L)	Regulation of TGF-β/Smad signaling	TGF-β, Smad	[137]
24	Various plant sources			quercetin	RLE/Abca3 cells	Cell (20 μmol/L)	Regulation of Smad and b-catenin signaling	Smad, b-catenin	[154]
25					BLM-induced PF mice and HELF cells	Mice (25, 50, 100 mg/kg) Cell (10, 20, 40 μmol/L)	Inhibits SphK1/S1P signaling	TGF-β, SphK1, S1P	[155]
26	Polygoni cuspidati rhizoma et radix	Polygonaceae	Clearing heat and detoxification, promoting blood circulation and removing blood stasis	Polydatin	BLM-induced PF rats and A549 cells	Rats (10, 40, 160 mg/kg) Cell (0–120 μmol/L)	Inhibit TGF-β1/Smad signaling	TGF-β1, Smad2/3, Erk1/2	[156]
27					BLM-induced PF rats and HFL-1 cells	Rats (100 mg/kg) Cell (50, 150 mmol/L)	Regulation of TGF-β/Smad signaling	TGF-β, Smad2/3, TNF-α, IL-1β	[157]
28	*Astragali radix*	Fabaceae	Replenishing qi and solidifying the surface, strengthening the upright and dispelling evil	astragaloside IV	A549 cells	Cell (20 mg/mL)	Inhibit the expression of NLRP3	NLRP3, TGF-β1, Smad2/3, α-SMA	[158]
29					BLM-induced PF rats and A549 cells	Rats (20 mg/kg) Cell (100 μg/mL)	Inhibit TGF-β1/PI3K/Akt signaling	TGF-β1, PI3K, Akt	[159]

Table 1 (continued)

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	Cytokine	Refs.
30	*Tripterygium wilfordii* Hook. f	Ranunculaceae	Clearing heat and detoxification, promoting blood circulation and removing blood stasis	Triptolide	HFL-1 cells	Cell (5, 10, 15, 20 nmol/L)	Regulation of FAK/calin signaling	FAK, calain	[160]
31					paraquat-induced PF mice and BEAS-2B cells	Mice (0.25 mg/kg)	Suppress EMT	TGF-β1, α-SMA, Smad3, E-cadherin	[161]
32	*Schisandrae chinensis* fructus	Magnoliaceae	Astringent and astringent, replenishing qi and invigorating fluid	schisantherin A	BLM-induced PF mice and A549 cells	Mice (1, 2, 4 mg/kg) Cell (0.625, 10 μmol/L)	Inhibition of ERK signaling	ERK, α-SMA, IL-1β, IL-6, TNF-α	[162]
33				schisandrin B	BLM-induced PF mice	Mice (5, 10, 20 mg/kg)	Inhibits Wnt signaling	MMP7, SOD, TGF-β1	[163]
34	Inulae flos	Asteraceae	Clearing heat and detoxification, eliminating phlegm and relieving cough	Inula japonica Thunb.extract	Mlg, CAGA-NIH3T3 cells	Cell (0–80 μmol/L)	Inhibit TGF-β1/Smad3 signaling	TGF-β1, Smad3	[164]
35					BLM-induced PF mice	Mice (100, 200, 400 mg/kg)	Regulates GSK3β signaling	GSK3β, COX-2, GSK3β, p65	[165]
36	Ferulae resina	Apiaceae	Activating qi to relieve pain, warming menstruation and dispelling cold	ferulic acid	Silica-induced PF mice	Mice (100, 300 mg/kg)	Inhibit TGF-β1 signaling	TGF-β1, Smad2/3, CTGF, Slug	[166]
37	*Psoraleae fructus*	Fabaceae	Warm the kidney and consolidate the essence, strengthen the muscles and bones	Psoralen	BLM-induced PF mice and NIH3T3 cells	Mice (5 mg/kg) Cell (5, 10, 20, 40 μmol/L)	Inhibition of ECM precipitate formation	TNF-α, IL-1β	[167]
38	*Atractylodis rhizoma*	Asteraceae	Invigorating spleen and stomach, tonifying qi and blood	atractylon	OVA-induced asthma mice and TC-1 cells	Mice (25 mg/kg)	Regulate the mmu_circ_0000981/miR-211-5p/TGFBR2 axis	TFGBR2, Vimentin, α-SMA, collagen	[168]
39	*Angelicae sinensis* radix	Apiaceae	Tonifying blood and activating blood, regulating menstruation and relieving pain	Angelica Sinensis Polysaccharide	BLM-induced PF rats and RLE-6TN cells	Rats (20 mg/kg) Cell (μmol/L)	Suppress EMT	DANCR, AUF1	[169]
40	*Pyrethrum parthenium* (L.) Sm	Asteraceae	Dispelling wind and relieving pain and headache	Parthenolide	BLM-induced PF mice and A549 cells	Mice (12.5, 25, 50 mg/kg) Cell (5, 10 μmol/L)	Inhibits NF-κB/Snail signaling	NF-κB, Snail	[170]

Table 1 (continued)

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	Cytokine	Refs.
41	Erigeron breviscapus	Asteraceae	Promoting blood circulation and removing blood stasis, clearing heat and detoxification	Scutellarin	BLM-induced PF mice and A549 cells	Mice (30, 60, 90 mg/kg) Cell (0.1, 0.2, 0.4 mmol/L)	Regulation of NF-κB/NLRP3 signaling	NF-κB, NLRP3	[171]
42				Scutellarein	BLM-induced PF mice	Mice (10 mg/kg)	Inhibits PI3K/Akt signaling	PI3K, Akt, Smad2/3, α-SMA	[172]
43	Spirulina platensis			phycocyanin	BLM-induced PF mice	Mice (50 mg/kg)	Regulation of TLR2-MyD88-NF-κB signaling	TLR2, NF-κB	[173]
44	Curcuma aromatica Salisb	Zingiberaceae	Promoting blood circulation and removing blood stasis, reducing swelling and relieving pain	Curdione	BLM-induced PF mice and HPFS cells	Mice (100 mg/kg) Cell (100–500 μmol/L)	Inhibition of TGF-β/Smad3 signaling	TGF-β1, α-SMA, Collagen 1, Erk1/2	[174]
45	Citrus aurantium L	Rutaceae	Soothing the liver and regulating qi, resolving phlegm and relieving cough	Hesperidin	A549 cells	Cell (40–200 μmol/L)	Inhibit TGF-β/Smad2/3 signaling	TGF-β1, Smad2/3, Smad4, Smad7	[175]
46	Alpiniae officinarum rhizoma	Zingiberaceae	Regulating qi and relieving pain, removing dampness and resolving phlegm	Galangin	BLM-induced PF mice and A549 cells	Mice (25, 50 mg/kg) Cell (0–100 μmol/L)	Suppress EMT	TGF-β1, E-cadherin	[176]
47	Aronia melanocarpa	Rosaceae		Cyanidin-3-galactoside	Silica-induced PF mice	Mice (100, 200, 400 mg/kg)	Inhibition of TGF-β/mTOR signaling through the NRF2/HO-1 pathway	TGF-β1, p-mTOR, NRF2	[177]
48	Carthami flos	Asteraceae	Promoting blood circulation and removing blood stasis, regulating menstruation and relieving pain	safflower yellow	paraquat-induced PF rats	Rats (50 mg/kg)	Regulate Hippo signaling	Hippo, Smad2/3, TGF-β1	[178]
49	Juglans mandshurica	Juglandaceae	Moistening the intestines and relieving defecation, tonifying the kidney and strengthening yang	Juglanin	BLM-induced PF mice and MRC-5, MLE-12 cells	mice (80 mg/kg) Cell (0–160 μmol/L)	Suppress Sting	Sting, MMP-9, α-SMA, TGF-β1	[179]
50	Trigonellae semen	Fabaceae	Warming the middle and dispelling cold, regulating qi and relieving pain	Diosgenin	BLM-induced PF rats	Rats (100 mg/kg) Cell (10–30 μmol/L)	Regulation of TGF-β/Smad signaling	TGF-β1, snail, NF-κB, COX-2, IL-1β	[180]

Table 1 (continued)

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	Cytokine	Refs.
51	Gynostemma pentaphyllum (Thunb.) Makino	Cucurbitaceae	Clearing heat and detoxification, lowering blood pressure	Gypenoside, Gyps	BLM-induced PF mice	Mice (200 mg/kg)	Inhibits AKT/mTOR/c-Myc signaling	AKT, mTOR	[181]
52	Sophorae fla vescentis radix	Fabaceae	Clearing heat and detoxification, diuresis and purging gonorrhea	Matrine	MRC-5 cells	Cell (10 μmol/L)	Inhibit TGF-β/Smad2/3 signaling	TGF-β, Smad2/3	[182]
53	*Vaccinium* spp.	Ericaceae		Pterostilbene	A549 cells	Cell (0–100 μmol/L)	Inhibit TGF-β1 signaling	TGF-β1, Bcl-2, BAX, P62, P-21	[183]
54	Cyanobacteria			C-Phycocyanin	Oleic acid-induced PF mice and A549, HFL-1 cells	Mice (1, 3, 9 mg/kg) Cell (10, 30 μmol/L)	Regulation of TGF-β/Smad and MAPK signaling	TGF-β1, MAPK	[184]
55	*Eclipta prostrata* (L.) L	Saururaceae	Clearing heat and detoxification, stopping bleeding and generating hair	wedelolactone	BLM-induced PF mice and PLFs cells	Mice (2, 10 mg/kg) Cell (10 μmol/L)	Inhibition of RAF1-MAPKs signaling	Col I, α-SAM, AMPK	[185]
56	Nelumbinis semen	Nelumbonaceae	Clear the heart and calm the mind, moisturize the lungs and relieve cough	Lotus Plumule Extract	BLM-induced PF mice	Mice (80, 160, 240 mg/kg)	Inhibit TGF-β1/Smad3 signaling	TGF-β, α-SMA	[186]
57	Gentianae radix et rhizoma	Gentianaceae	Clearing heat, dryness and dampness, purging liver and gallbladder fire	Gentiopicroside	BLM-induced PF mice	Mice (2.5, 10 mg/kg)	Anti-inflammatory	TNF-α, IL-1β, TGF-β1, CTGF	[187]
58	*Siratia grosvenorii*	Cucurbitaceae	Clear heat and moisturize the lungs and open pharynx	Mogrol	BLM-induced PF mice and NIH3T3 cells	Mice (1, 5, 10 mg/kg) Cell (1, 5, 10 μmol/L)	Regulation of TGF-β1 and AMPK signaling	TGF-β1, AMPK	[188]
59	*Mangifera indica* L.	Anacardiaceae	Clearing heat and detoxification, invigorating the stomach and eliminating food	Mangiferin	BLM-induced PF rats and A549 cells	Rats (40 mg/kg) Cell (10 μg/mL)	Inhibit TGF-β1/Smad2/3 signaling	TLR4, TGF-β1	[189]
60	*Atractylodis rhizoma*	Asteraceae	Invigorate the spleen and appetizer, remove dampness and dissipate phlegm	Atractylodin	BLM-induced PF mice and A549 cells	Mice (50, 100 mg/kg) Cell (0–100 μmol/L)	Inhibit TGF-β1/Smad signaling	TGF-β1, Snail	[190]
61	Indigo naturalis	Brassicaceae	Clearing heat and detoxification, reducing swelling and relieving pain	Indirubin	BLM-induced PF mice and PMLFs HPFs cells	Mice (12.5, 25 mg/kg) Cell (2.5–60 μmol/L)	Inhibit TGF-β1/Smad signaling	TGF-β1, Collagen I, α-SMA, Smad2/3	[191]

Table 1 (continued)

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	Cytokine	Refs.
62	Ginseng radix et rhizoma	Araliaceae	Replenish qi and nourish blood, invigorate body and quench thirst	ginsenoside Rg3	BLM-induced PF mice and LL 29 cells	Mice (5 mg/kg)	Inhibits nuclear localization of HIF-1α	HIF-1α, TGF-β1	[192]
63	*Inonotus sanghuang*		Clearing heat and detoxification, promoting blood circulation and removing blood stasis	Inonotus sanghuang extract (ISE)	BLM-induced PF mice and A549 cells	Mice (0.6% w/w) Cell (2, 4 μg/mL)	Inhibit TGF-β1/Smad signaling	TGF-β1, Smad2/3	[193]
64	Hippophae fructus	Elaeagnaceae	Invigorate the stomach and eliminate food, relieve cough and expectoration	Isorhamnetin	BLM-induced PF mice	Mice (10, 30 mg/kg) Cell (25, 50, 100 μmol/L)	Suppress EMT	PERK, α-SMA, Collagen I, TGF-β1	[194]
65	Zingiberis rhizoma recens	Zingiberaceae	Warm the middle to dissipate the cold, solve the surface and dissipate the cold	6 gingerol	BLM-induced PF mice and human embryonic lung fibroblasts MRC-5	Mice (100, 250 mg/kg) Cell (10, 20 μmol/L)	Activates SIRT1 signaling signaling	SIRT1, α-SMA, TNF-α, IL-6, IL-1β	[195]
66	Silybi fructus	Asteraceae	Clearing heat and detoxification, soothing the liver and promoting gallbladder	Silibinin	Silica-induced PF mice	Mice (100, 300 mg/kg)	Anti-inflammatory Inhibits EMT	IL-1β, smad 2/3, α-SMA, TGF-β1	[196]
67	Ampelopsis grossedentata (Hand.-Mazz.) W. T. Wang (Vitaceae)	Lamiaceae	Promoting blood circulation and regulating menstruation, diuresis and detumescence	Dihydromyricetin	BLM-induced PF mice and MLG cells	Mice (50, 100, 200 mg/kg)	Inhibit TGF-β1/Smad signaling	TGF-β1, α-SMA	[197]
68					PMLFs, PHLFs cells	Cell (100, 200, 300 μmol/L)	Regulation of STAT3/p-STAT3/GLUT1 signaling	STAT3,p-STAT3,GLUT1	[198]
69	Dendrobii officinalis caulis	Orchidaceae	Lung heat coughing, deficiency heat dispelling thirst	Polysaccharides from Dendrobium officinale	BLM-induced PF rats	Rats (200 mg/kg)	Inhibition of TGF-β1-Smad2/3 signaling	TGF-β, Smad2/3, α-SMA, Collagen II	[199]
70	Galla chinensis	Anacardiaceae	Restrain the lungs and reduce the fire, astringent intestines and stop diarrhea	Tannic acid	BLM-induced PF mice	Mice (10 mg/kg) Cell (1, 3 μmol/L)	Inhibit TGF-β receptor signaling	TGF-β, Smad2/3	[200]
71	Camptotheca acuminata Decne	Nyssaceae	Relieve cough and resolve phlegm	Hyperoside	BLM-induced PF mice	Mice (50 mg/kg)	Regulation of AKT/GSK3b signaling	AKT, GSK3b	[201]
72	armeniacae semen amarum	Rosaceae	Moistening the bowels, relieving cough and resolving phlegm	amygdalin	smoking combined with LPS-induced COPD mice and BEAS-2B cells	mice (5, 10, 20 mg/kg) Cell (0–2000 μg/mL)	Inhibit TGF-β/Smad2/3 signaling	TGF-β, Smad2/3	[202]

Table 1 (continued)

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	Cytokine	Refs.
73	Arenaria kansuensis Maxim	Caryophyllaceae	Clearing heat and detoxification, diuresis and purging gonorrhea	A. kansuensis ethanol extract	paraquat-induced PF rats	Rats (170, 350, 700 mg/kg)	Inhibit NF-κB/TGF-β1/Smad2/3 signal transduction	TGF-β1, Smad2/3	[203]
74	Myrica rubra Sieb	Myricaceae	Moistening the lung and relieving cough, invigorating body and relieving thirst	Myricetin	BLM-induced PF mice and A549, HFL1 cells	Mice (25, 50, 100 mg/kg) cell (μmol/L)	Regulation of TGF-β/Smad and non-Smad signaling	TGF-β, Smad	[204]
75	Epimedii folium	Berberidaceae	Kidney deficiency and impotence, sore waist and knees	Icariin	BLM-induced PF mice and NIH3T3, HLF-1 cells	Mice (0.04, 0.02, 1 mg/kg) Cell (3 μmol/L)	Inhibit TGF-β1 signaling	TGF-β1, α-SMA	[205]
76	Houttuyniae herba	Saururaceae	Heat-clearing and detoxification, sore waist and knees	Sodium Houttuyfonate	BLM-induced PF mice	Mice (45, 90 mg/kg)	Anti-inflammatory	IL-1β, TNF-α	[206]
77	Hypericum longistylum	Hypericaceae	Promoting blood circulation and removing blood stasis, reducing swelling and relieving pain	Hypericum longistylum	MLFC cells	Cell (0–80 μmol/L)	Inhibition of TGF-β/Smad3 signaling	TGF-β	[207]
78	Aurantii fructus immaturus	Rutaceae	Regulating qi stagnation, resolving phlegm and relieving cough	Neohesperidin	BLM-induced PF mice and NIH3T3, MLg, A549 cells	Mice (20 mg/kg) cell (0–200 μmol/L)	Inhibition of TGF-β/Smad3 signaling	TGF-β1, Smad2/3, Erk, p-38, JNK	[208]
79	Multiple plant sources			Hederagenin	BLM-induced PF rats	Rats (10, 20, 50 mg/kg)	Adjust Ras/JNK/NFAT4 axis	JNK, NFAT4	[209]
80	Polyporus	Polyporaceae	Diuresis, detumescence and phlegm	Polyporus Polysaccharide	BLM-induced PF mice and HLF cells	Mice (50, 100 mg/kg) Cell (1 mg/mL)	Inhibit TGF-β1/Smad2/3 signaling	TGF-β1, Smad2/3	[210]
81	Podocarpus nagi	Podocarpaceae	Clearing heat and detoxification, dispelling wind and promoting dampness	Nagilactone D	BLM-induced PF mice and WI-38, VA-13, HFL-1 cells	Mice (1, 3 mg/kg) Cell (1, 2 μmol/L)	Inhibition of TGF-β/Smad3 signaling	TGF-β1, Collagen I, α-SMA	[211]

Nrf2 signal pathways. This study preliminarily revealed the anti-inflammatory and antioxidant activities of emodin in improving PF, and preliminarily explored the possible signal pathways involved. However, the mechanism by which emodin exerts its biological activity still needs to be further explored in order to better play its potential in the treatment of PF. Qi's team found the protective effect and potential mechanism of chrysophanol in IPF through research [226]. The research results shown that chrysophanol can effectively reduce ECM deposition and inflammatory cytokine levels in PF model mice, and chrysophanol can also inhibit Wnt/β-catenin signaling pathway and inhibition of lung fibroblast proliferation to alleviate BLM induced mouse PF. This study demonstrates that chrysophanol has anti-inflammatory biological activity, but further experimental verification is needed. In addition to emodin and chrysophanol, rhubarb also contains many active ingredients with anti-inflammatory and antioxidant effects. The improvement of PF by these active ingredients deserves further research.

Studies have shown that ethyl acetate extract of Salvia miltiorrhiza can reduce the degree of active oxygen-related PF by targeting Nrf2-NOX4 REDOX equilibrium [227, 238]. Tanshinone IIA is a bioactive ingredient extracted from Salvia miltiorrhiza with anti-inflammatory, antioxidant and anti-fibrotic properties. Feng's research team studied the protective effect of Tanshinone IIA on silica-induced PF and its potential mechanism [229], and the results showed that tanshinone IIA could down-regulate the level of oxidative stress markers in silicosis rats and attenuate pulmonary inflammatory response. In addition, Tanshinone IIA may protect the lung from silica damage by inhibiting TGF-β1/Smad signaling, inhibiting NOX4 expression, and activating the Nrf2/ARE pathway. An's team found a similar phenomenon in mice with bleomycin-induced PF treated with tanshinone IIA [152]. The study found that tanshinone IIA can inhibit PF by activating Nrf2, regulating REDOX homeostasis and glutamine breakdown. Liu's study showed that salvianolic acid B can reduce experimental lung inflammation by protecting endothelial cells from oxidative stress [230], further demonstrating that the anti-inflammatory effects of Salvianolic acid B may be mediated through MAPK and NF-κB signaling pathways. Notably, Salvianolic acid B and Tanshinone IIA sulfonates reduce PF by affecting the inflammatory system and controlling the TGF-β1 pathway, which may be the result of a synergistic effect between the two drugs [153]. In summary, many active compounds in salvia miltiorrhiza have pharmacological effects on improving PF, and the synergistic effect between these compounds is worthy of further study. In addition to the above-mentioned TCM that can improve PF, the detailed information of other TCM studies in the past five years that can improve PF through anti-inflammation and anti-oxidation were summarized and presented in Table 2.

Improve extracellular matrix deposition

ECM is a three-dimensional network of non-cellular macromolecules, made primarily of collagen, non-collagenous proteins, and glycoproteins, among others [297]. A pathological characteristic of PF is the massive buildup of ECM in the interstitium. Excessive ECM deposition promotes alveolar structural loss, which generates or aggravates PF. Initial damage to alveolar epithelial cells stimulates the production of multiple pro-fibrotic cytokines that induce fibroblast proliferation, aggregation, and transdifferentiation, generating myofibroblasts that secrete stronger ECM, releasing high levels of ECM, and promoting the development of PF [298]. Under pathological situations, excessive deposition of ECM in the interstitial lung can stimulate ECM synthesis and alter the regulatory function of matrix metalloproteinases (MMPs)/TIMPs [299, 300]. Under pathological situations, excessive deposition of ECM in the interstitial lung can stimulate ECM synthesis and alter the regulatory function of matrix metalloproteinases (MMPs)/TIMPs [301]. The majority of animal investigations have concentrated on the independent detection of TGF-β1, Smads, and MMPs/TIMPs, and the precise mechanism of action is still unknown. Furthermore, Smads, MMPs, and TIMPs comprise several family members whose activities and mutual effects have yet to be thoroughly investigated [45].

In addition to its anti-inflammatory and antioxidant properties, Salvia miltiorrhiza can also play an anti PF role by inhibiting ECM deposition. Feng's research suggests that tanshinone IIA inhibits TGF-β1/Smad signaling pathway to reduce silica induced PF [302]. Further research found that tanshinone IIA may improve silicosis fibrosis by inhibiting the EMT phase. Cryptotanshinone is a lipophilicity compound derived from salvia miltiorrhiza, which has antioxidant, anti-inflammatory and anti-angiogenesis properties [303]. Zhang research team found that cryptotanshinone improved the lung function of the rat model of bleomycin induced PF, alleviated pathological changes and inhibited ECM precipitation [304]. This experiment found that cryptotanshinone may prevent PF by inhibiting Smad and STAT3 signaling pathways through cell experiments. In conclusion, many active compounds in Salvia miltiorrhiza have good anti PF effects in terms of anti inflammation, anti-oxidation, inhibition of EMT and inhibition of ECM precipitation.

Astragalus membranaceus is a TCM with various pharmacological effects such as enhancing immune function,

protecting lung function, and reducing oxidative stress. Astragaloside IV is one of the most important active ingredients in astragalus membranaceus. Some studies have shown that astragaloside IV not only improves the secretion of collagen induced by bleomycin, but also reduces the level of type III collagen, serum laminin and hyaluronic acid in lung homogenate [305]. These findings indicated that astragaloside IV can effectively inhibit ECM deposition in PF mice, providing experimental data support for its use as a candidate compound for the treatment of PF. Li's team also studied the anti PF effect of astragaloside IV [306]. The difference is that this experiment uses the silicon induced PF model. The experiment shown that astragaloside IV can effectively inhibit the formation of silicosis fibrosis. Further cell experiments have found that astragaloside IV can inhibit ECM precipitation in fibroblasts, and its mechanism of action may be related to TGF-β1/Smad signaling pathway is involved. These results suggest that astragalus may have the potential to improve PF by inhibiting ECM precipitation in a variety of disease induced PF. In addition to the abovementioned TCM that can improve PF, the detailed information of other TCM studies in the past five years that can improve PF through inhibition of ECM deposition were summarized and presented in Table 3.

Mediate apoptosis and autophagy

Autophagy is the degradation of intracytoplasmic foreign bodies, damaged, and senescent cells by the cell's own structures via lysosomes, which helps maintain a homeostatic equilibrium between degradation and recirculation [319]. Cellular autophagy can promote PF by promoting fibroblast activation, myofibroblast differentiation, and ECM deposition, indicating that autophagy may be one of the key mechanisms in the pathogenesis of PF [320, 321]. The expression of cellular autophagy is typically deficient in all IPF lung tissues, which appears to be one of the risk factors for IPF, as suggested by the current study [322]. When autophagy is inhibited, lung fibroblast epithelial senescence and myofibroblast differentiation can be accelerated. Numerous studies have demonstrated that herbal medicine regulates cellular autophagy primarily via mTOR-dependent and -independent pathways. Apoptosis is a form of programmed cell death characterized primarily by cell shrinkage and the formation of apoptotic vesicles [323]. Excessive apoptosis of alveolar epithelial cells induces aberrant secretion of numerous cytokines, including TGF-β1, and accelerates the progression of PF [324]. Inadequate apoptosis of lung fibroblasts results in their massive transformation into myofibroblasts, which promotes ECM deposition and lung fibrosis [325]. There are multiple signaling pathways involved in the role of apoptosis in lung fibrosis. It has been hypothesized that the MAPK/NF-κB signaling pathway plays a crucial role in this.Autophagy and apoptosis are complex mechanisms that control cell growth and death under physiological and pathological conditions. It has been suggested that the two processes, reduced autophagic activity and apoptotic resistance, may be interrelated in IPF fibroblasts [326]. When mTOR activity is inhibited, autophagy increases, apoptosis increases, and resistance to apoptosis decreases. Enhanced autophagy is accompanied by increased apoptosis. Consequently, insufficient autophagy can result in insufficient apoptosis in fibroblastic cells and excessive apoptosis in alveolar epithelial cells, which, through a cascade of biological responses, leads to IPF.

Various components in the peel of citrus reticulata blanco have anti-inflammatory and antioxidant activities [327]. Wu's experimental team extracted primary lung fibroblasts from normal mice and bleomycin induced PF mice for experiments. The results indicate that citrus alkaloid extract can effectively induce apoptosis in mouse lung fibroblasts, and its mechanism of action may be related to the p38/COX-2/Fas signaling pathway regulated by oxidative stress [328]. In addition, the experimental team explored the intervention effect of citrus alkaline extract on bleomycin induced PF in mice and its mechanism [329]. The experiment shows that citrine extract can effectively delay the degree of PF mice, and its mechanism may be through inhibiting NF-κB/p38-mediated signaling pathway inhibits cell apoptosis. In addition, studies have shown that citrus alkaloid extracts can activate COX-2 and β-Catenin/P53 pathway inhibits cellular senescence and reduces PF [330, 331]. To sum up, citrus extract can mediate cell apoptosis through multiple signaling pathways, but the specific pharmacodynamic substances in the extract that play a role in improving PF are still unclear, and further experimental research is needed.

Quercetin is a flavonol compound in TCM [332], which has anti-inflammatory, antioxidant, immunomodulatory and anti-tumor activities [333]. Literature studies have shown that quercetin alone cannot promote apoptosis, but quercetin can eliminate fibroblast resistance to apoptosis [334]. Further studies suggest that quercetin may enhance the susceptibility of aging fibroblasts to apoptosis by regulating the expression of caveolin-1 and Fas and activating AKT. In addition, Xiao found that quercetin not only promotes autophagy activity, but also improves fibrosis by inhibiting pro-fibrotic factors and AKT/mTOR signaling pathway [335]. These studies demonstrate quercetin's potential to combat PF by mediating apoptosis, adding to therapeutic strategies for IPF and other fibrotic diseases. However, these studies have only been conducted in vitro or in animals, and

Table 2 Details about some traditional Chinese medicines improving pulmonary fibrosis by anti-inflammation and anti-oxidation effects

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	Cytokine	Refs.
1	Salviae miltiorrhizae radix et rhizoma	Lamiaceae	Promoting blood circulation and removing blood stasis, reducing swelling and relieving pain	Salvia miltiorrhiza	BLM-induced PF mice and NIH3T3 cells	Mice (21, 40, 80 mg/kg) Cell (0.1, 1, 3 μmol/L)	Anti-oxidation	Nrf2, NOX4	[228]
2				Tanshinone IIA	Silica-induced PF rats	Rats (25 mg/kg)	Regulation of TGF-β1/Smad and Nrf2/ARE signaling	TGF-β1, Nrf2	[229]
3					BLM-induced PF mice and PLFs, NIH-3T3 cells	Mice (5, 10, 20 mg/kg) Cell (0.01–500 μmol/L)	Inhibition of TGF-β1-Smad3 signaling	Nrf2, TGF-β1	[152]
4				Sodium Tanshinone IIA sulfonate	Silica-induced PF rats and A549, RLE-6TN, MRC-5, NIH-3T3 cells	Rats (25 mg/kg) Cell (μmol/L)	Up-regulation of Nrf2 nuclear expression	Nrf2, Trx, TrxR	[231]
5				Salvianolic acid B	BLM-induced PF mice and hy926 cells	Mice (10 mg/kg) Cell (50 μg/mL)	Anti-inflammatory and antioxidant	IL-1β, TNF-α, NF-κB	[230]
6					BLM-induced PF rats and MRC-5 cells	Rats (20 mg/kg) Cell (40 μmol/L)	Regulates Nrf2 signaling	Nrf2, α-SMA, TGF-β1	[138]
7				Salvianolic acid B/sodium tanshinone IIA sulfonate	THP-1 cells	Cell (0–600 μg/mL)	Inhibit TGF-β1 signaling	TGF-β1, α-SMA	[153]
8	Curcumae longae rhizoma	Zingiberaceae	Promoting blood circulation and removing blood stasis, Regulating menstruation and relieving pain	Curcumin	BLM-induced PF mice	Mice (75 mg/kg)	Inhibit NF-κB signaling	AMPK, COX-2	[232]
9					paraquat-induced PF rats	Rats (200 mg/kg)	Improve pulmonary fibrosis	Smad 4, Smurf 2	[233]
10					LMSCs cells	Cell (2.5, 5, 10, 20 μmol/L)	Regulation of Akt/Nrf2/HO-1 signaling	Akt, Nrf2, HO-1	[234]
11					BLM-induced PF rats	Rats (300 mg/kg)	Inhibition of ECM precipitate formation	/	[235]
12					A549 cells	Cell (20 μmol/L)	Inhibit TGF-β1/Smad/non Smad signaling	TGF-β1, Smad	[147]
13	Rhei radix et rhizoma	Polygonaceae	Purging and defecating, clearing heat and detoxification	Chrysophanol	BLM-induced PF mice	Mice (10 mg/kg)	Inhibits Wnt/β-catenin signaling	β-catenin, Bax, TNF-α, IL-1β	[226]
14				Emodin	BLM-induced PF rats and A549 cells	Rats (20 mg/kg) Cell (60 μmol/L)	Anti-inflammatory and antioxidant	IL-1β, IL-6, TNF-α, NF-κB	[225]
15				Rhapontin	BLM-induced PF rats and THP-1 cells	Rats (25, 50, 100 mg/kg) Cell (50 μmol/L)	Regulation of TGF-β/Smad signaling	TGF-β1, Smad	[137]

Table 2 (continued)

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	Cytokine	Refs.
16	Polygoni cuspidati rhizoma et radix	Polygonaceae	Clearing heat and detoxification, promoting blood circulation and removing blood stasis	Polydatin	MTX-induced PF rats	Rats (25, 50, 100 mg/kg)	Inhibit TGF-β1 signaling	TGF-β1, HYP, α-SMA, TNF-α	[236]
17					BLM-induced PF rats and A549 cells	Rats (10, 40, 160 mg/kg) Cell (0–120 μmol/L)	Inhibit TGF-β1/Smad signaling	TGF-β1, Smad2/3, Erk1/2	[156]
18					BLM-induced PF rats and HFL-1 cells	Rats (100 mg/kg) Cell (50, 150 mmol/L)	Regulation of TGF-β/Smad signaling	TGF-β, Smad2/3, TNF-α, IL-1β	[157]
19	Astragali radix	Fabaceae	Replenishing qi and solidifying the surface, strengthening the upright and dispelling evil	Baicalin	BLM-induced PF rats	Rats (25, 100 mg/kg)	Activate SOD	/	[237]
20				Astragaloside IV	Silica-induced PF rats	Rats (20 mg/kg)	Inhibit TGF-β1/Smad signaling	TGF-β1, α-SMA	[238]
21					A549 cells	Cell (20 mg/mL)	Inhibit the expression of NLRP3	NLRP3, TGF-β1, Smad2/3, α-SMA	[158]
22	Tripterygium wilfordii Hook. f	Ranunculaceae	Clearing heat and detoxification, promoting blood circulation and removing blood stasis	Triptolide	radiation-induced PF mice and NIH3T3 cells	Mice (0.25 mg/kg) cell (5 ng/mL)	Inhibit NF-κB signaling	NF-κB, LOX, IκBα	[239]
23					HFL-1 cells	Cell (5, 10, 15, 20 nmol/L)	Regulation of FAK/calin signaling	FAK, calain	[160]
24				Isorhynchophylline	Silica-induced PF mice	Mice (20 mg/kg)	Anti-inflammatory	/	[240]
25	Andrographis herba	Acanthaceae	Clearing heat and detoxification, cooling blood	Andrographolide	BLM-induced PF rats and A549 cells	Rats (10 mg/kg)	Regulation of AKT/mTOR signaling	AKT, mTOR	[134]
26					A549 cells	Cell (0–20 μmol/L)	Inhibits A and B signaling	TGF-β1, Smad2/3, MMP-9	[133]
27	Schisandrae chinensis fructus	Magnoliaceae	Astringent and astringent, replenishing qi and invigorating fluid	Schisantherin A	BLM-induced PF mice and A549 cells	Mice (1, 2, 4 mg/kg) Cell (0.625, 10 μmol/L)	Inhibition of ERK signaling	ERK, α-SMA, IL-1β, IL-6, TNF-α	[162]
28				Schisandrin B	BLM-induced PF mice	Mice (5, 10, 20 mg/kg)	Inhibits Wnt signaling	MMP7, SOD, TGF-β1	[163]
29	glycyrrhizae radix et rhizoma	Fabaceae	Nourishes qi and nourishes yin, clears away heat and detoxifies	Licorice extract	paraquat-induced PF mice and A549, HepG2 cells	Mice (20, 40, 60 mg/kg) Cell (0–100 μmol/L)	Regulates Nrf2 signaling	Nrf2, TGF-β1, CYP3A4, MDA	[241]
30				Deglycyrrhizinated licorice	BLM-induced PF rats	Rats (75, 150, 300 mg/kg)	Anti-inflammatory and antioxidant	/	[242]
31	Ferulae resina	Apiaceae	Activating qi to relieve pain, warming menstruation and dispelling cold	Ferulic acid	Silica-induced PF mice	Mice (100, 300 mg/kg)	Inhibit TGF-β1 signaling	TGF-β1, Smad2/3, CTGF, Slug	[166]

Table 2 (continued)

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	Cytokine	Refs.
32	Birch bark	Betulaceae	Clear away heat and dampness, detoxify	Betulinic acid	BLM-induced PF mice and MLG, PPF cells	Mice (20, 40, 80 mg/kg) Cell (5, 10, 20 μmol/L)	Inhibit Wnt/β-catenin signaling	β-catenin, Col 1, α-SMA	[69]
33	Bletillae rhizoma	Orchidaceae	Convergence to stop bleeding, reduce swelling and promote muscle growth	Bletilla striata	RAW264.7 cells	Cell (2.5 μg/mL)	Anti-inflammatory	/	[243]
34	Chelidonii herba	Papaveraceae	Clearing heat and detoxification, reducing swelling and relieving pain	Chelerythrine	BLM-induced PF mice	Mice (0.375, 0.75 mg/kg)	activate Nrf2/ARE signal transduction	Nrf2, ARE	[244]
35	Stemonae radix	Stemonaceae	Expelling phlegm and relieving cough, killing insects and expelling Ascaris	Stemona alkaloids	BLM-induced PF mice and PFB cells	Mice (30, 60 mg/kg) Cell (1, 10, 100 μg/mL)	Inhibits JAK2/STAT3 and CXCR4/PI3K/AKT1 signaling	STAT3, PI3K, AKT1	[245]
36	Atractylodis rhizoma	Asteraceae	Invigorate the spleen and appetizer, remove dampness and dissipate phlegm	Atractylenolide III	BLM-induced PF rats	Rats (0.6, 1.2, 2.4 mg/kg)	activate Nrf2/NQO1/HO-1 signal transduction	Nrf2, NQO1, HO-1	[246]
37	Rehmanniae radix	Oleaceae	Nourishing yin and tonifying blood, clearing heat and cooling blood	catalpol	BLM-induced PF rats	Rats (10, 20, 40 mg/kg)	Antioxidant inhibits EMT	TGF-β, Smad3	[247]
38	Erigeron breviscapus	Asteraceae	Promoting blood circulation and removing blood stasis, clearing heat and detoxification	Scutellarin	BLM-induced PF mice and A549 cells	Mice (30, 60, 90 mg/kg) cell (0.1, 0.2, 0.4 mmol/L)	Regulation of NF-κB/NLRP3 signaling	NF-κB, NLRP3	[171]
39	Spirulina			Phycocyanin	BLM-induced PF mice	Mice (50 mg/kg)	Anti-inflammatory	IL-6, TNF-α	[248]
40	Various plant sources			Epicatechin	BLM-induced PF mice	Mice (20, 50, 100 mg/kg)	Anti-inflammatory and antioxidant	/	[249]
41				Sinapic acid	BLM-induced PF rats	Rats (10, 20 mg/kg)	Inhibit NF-κB/NRF2/HO-1 signaling	NF-κB, NRF2, HO-1	[250]
42				Pinocembrin	BLM-induced PF mice	Mice (5, 25, 50 mg/kg) cell (100, 200, 300 μmol/L)	Inhibit TLR4/NF-κB/NLRP3 signaling	NF-κB, NLRP3	[251]

Table 2 (continued)

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	Cytokine	Refs.
43	Cymbopogon winterianus	Cymbopogon		Essential oil of Cymbopogon winterianus	BLM-induced PF rats	Rats (50, 100, 200 mg/kg)	Inhibit TGF-β1 signaling	TGF-β1, SOD. MDA	[252]
44	Citrus fruits	Rutaceae	Invigorate the spleen and replenish qi, moisturize the lungs and relieve cough	Hesperidin	BLM-induced PF rats	Rats (25, 50, 100 mg/kg)	Inhibits TGF-β1/Smad3/AMPK and I-κBα/NF-κB signaling	TGF-β1, NF-κB	[253]
45	Alpiniae officinarum rhizoma	Zingiberaceae	Regulating qi and relieving pain, removing dampness and resolving phlegm	Galangin	BLM-induced PF mice and A549 cells	Mice (25, 50 mg/kg) Cell (0–100 μmol/L)	Suppress EMT	E-cadherin, vimentin, α-SMA, MMP-9	[176]
46	Puerariae lobatae radix	Fabaceae	Relieving cold, sweating and detoxification	Puerarin	HLF1 cells	Cell (200, 400, 600 μg/mL)	Inhibition of TGF-β/Smad3 signaling	TGF-β1, Caspase3, Bcl-2, Smad3	[254]
47	Glycyrrhizae radix et rhizoma	Fabaceae	Clearing heat and detoxification, moistening the lungs and relieving cough	Glycyrrhiza glabra	BLM-induced PF rats	Rats (500 mg/kg)	Anti-inflammatory and antioxidant	HYP, LPO	[255]
48	Laminaria japonica	Phaeophyta	Clearing heat and detoxification, softening and dispersing knots	Low molecular weight fucoidan	BLM-induced PF mice and A549 cells	Mice (25, 50, 100 mg/kg) Cell (50, 100, 200 μg/mL)	Antioxidant inhibits fibrosis	NRF-2, HO-1, NQO1	[256]
49	Carthami flos	Asteraceae	Promoting blood circulation and removing blood stasis, regulating menstruation and relieving pain	Hydroxysafflor Yellow A	MRC-5 cells	Cell (5, 15, 45 μmol/L)	Inhibit NF-κB/AP-1 signaling	NF-κB, AP-1	[257]
50					BLM-induced PF rats	Rats (35.6, 53.3, 80 mg/kg)	Anti-inflammatory	α-SMA, IL-1β, IL-6, TNF-α, TGF-β	[258]
51	Rhodiolae crenulatae radix et rhizoma	Crassulaceae	Replenishing qi and activating blood circulation, dredging pulse and relieving asthma	Rutin	BLM-induced PF rats	Rats (50, 100 mg/kg)	Regulation of TGF-β1/α-SMA/Col I/III signaling	TGF-β1, α-SMA	[259]
52	Juglans	Juglandaceae	Moistening the bowels, relieving cough and resolving phlegm	Juglanin	BLM-induced PF mice and MRC-5, MLE-12 cells	Mice (80 mg/kg) Cell (0–160 μmol/L)	Suppress sting	Sting, MMP-9, α-SMA, TGF-β1	[179]

Table 2 (continued)

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	Cytokine	Refs.
53	Trigonellae semen	Fabaceae	Warming the middle and dispelling cold, regulating qi and relieving pain	Diosgenin	BLM-induced PF rats	Rats (100 mg/kg) Cell (10–30 μmol/L)	Regulation of TGF-β/Smad signaling	TGF-β1, snail, NF-κB, COX-2, IL-1β	[180]
54	Coptidis rhizoma	Ranunculaceae	Clearing heat and dryness, purging fire and detoxification	Berberine	BLM-induced PF mice	Mice (50, 100, 200 mg/kg)	Activate PPAR-γ	HGF, PPAR-γ	[260]
55	Astragali radix/ferulae resina	Fabaceae/Apiaceae	Replenishing qi and solidifying the surface, strengthening the upright and dispelling evil	Astragaloside IV/ferulic acid	BLM-induced PF mice	Mice (24 + 40.8 mg/kg)	Inhibit TGF-β1/Smad3 signaling	TGF-β1, Nrf2	[261]
56	Scutellariae radix	Scutellaria	Clearing away heat and dampness, purging fire and detoxifying	Baicalin	BLM-induced PF rats and RPF	Rats (50 mg/kg) Cell (20, 40, 60, 80 μg/mL)	Regulation of CaMKII and PI3K/AKT signaling	PI3K, AKT	[141]
57				Calycosin, CA	BLM-induced PF mice and MLE-12 cells	Mice (7, 14 mg/kg) cell (0–80 μmol/L)	Inhibit AKT/GSK3β/β-catenin signaling	AKT, GSK3β	[144]
58	Centellae herba	Apiaceae	Clearing heat and detoxification, promoting diuresis and detumescence	Asiaticoside	BLM-induced PF mice	Mice (50 mg/kg)	Activates cAMP and RAP1 signaling	A2AR, RAP1	[262]
59					BLM-induced PF mice	Mice (50 mg/kg)	Up-regulation of BMP7/Smad1/5 signaling	BMP7, Smad1/5	[263]
60	Tribuli fructus	Cucurbitaceae	Soothing the liver and relieving depression, promoting diuresis and reducing swelling	Terrestrosin D	BLM-induced PF mice	Mice (10 mg/kg)	Anti-inflammatory	HYP, IL-6, IL-8, TGF-β, PDGF-AB	[264]
61	Zingiberis rhizoma recens	Zingiberaceae	Warm the middle to dissipate the cold, solve the surface and dissipate the cold	Zingerone	BLM-induced PF rats	Rats (50, 100 mg/kg)	Affects TGF-β1 and iNOS signaling	TGF-β1, MDA, SOD, TNF-α, IL-1β	[265]
62	Lonicerae japonicae caulis	Caprifoliaceae	Clearing heat and detoxification, relieving surface and dissipating heat	Blue honeysuckle extract	Silica-induced PF mice and HLN cells	Mice (100, 200, 400 mg/kg)	Regulation of NRF2/HO-1 MAPK signaling	NRF2, HO-1, MAPK	[266]
63				Cyanidin-3-glucoside	Silica-induced PF mice	Mice (100, 200, 400 mg/kg)	Inhibits STAT1/3 signaling	STAT1, STAT3	[267]

Table 2 (continued)

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	Cytokine	Refs.
64	Blueberry	Ericaceae		Pterostilbene	LPS-induced PF mice	Mice (12.5, 25, 50 mg/kg)	Activation of Keap-1/Nrf2 inhibits A20/NF-κB and NLRP3 signaling	NF-κB, NLRP3	[268]
65	Cyanobacteria			C-Phycocyanin	Oleic acid-induced PF mice and A549, HFL-1 cells	Mice (1, 3, 9 mg/kg) Cell (10, 30 μmol/L)	Regulation of TGF-β/Smad and MAPK signaling	TGF-β1, MAPK	[184]
66	Eclipta prostrata L	Asteraceae	Heat-clearing and detoxification, black hair	Wedelolactone	BLM-induced PF mice and PLFs cells	Mice (2, 10 mg/kg) cell (10 μmol/L)	Inhibition of RAF1-MAPKs signaling	Col I, α-SAM, AMPK	[185]
67	Nelumbinis semen	Nelumbonaceae	Clear the heart and calm the mind, moisturize the lungs and relieve cough	Lotus plumule extract	BLM-induced PF mice	mice (80, 160, 240 mg/kg)	Inhibit TGF-β1/Smad3 signaling	TGF-β1, α-SMA	[186]
68	Oxytropis falcata Bunge	Fabaceae	Clearing heat and detoxification, dispelling wind and dispersing blood stasis	Flavonoids of Oxytropis falcata	BLM-induced PF rats	Rats (100, 200, 400 mg/kg)	Regulates JAK/STAT1 signaling	SOCS, p-JAK1	[269]
69	gentianae radix et rhizoma	Gentianaceae	Clearing heat, dryness and dampness, purging liver and gallbladder fire	Gentiopicroside	BLM-induced PF mice	Mice (2.5, 10 mg/kg)	Anti-inflammatory	TNF-α, IL-1β, TGF-β1, CTGF	[187]
70	Cervi cornu pantotrichum		Tonifying the kidney and tonifying essence, strengthening muscles and bones	Pilose antler peptide	BLM-induced PF mice and A549 cells	Mice (50, 100 mg/kg)	Regulation of ROCK/NF-κB signaling	NF-κB, MPO, SOD, IL-1β, IL-6, TNF-α, IκBα	[270]
71	Siratia grosvenorii	Cucurbitaceae	Clear heat and moisturize the lungs, invigorate body and quench thirst	Mogrol	BLM-induced PF mice and NIH3T3 cells	Mice (1, 5, 10 mg/kg) Cell (1, 5, 10 μmol/L)	Regulation of TGF-β1 and AMPK signaling	TGF-β1, AMPK	[188]
72	Gallnut	Anacardiaceae	Stop diarrhea, converge, astringent intestines	Gallic acid derivative	BLM-induced PF mice	Mice (75, 150, 300 mg/kg)	Anti-inflammatory and antioxidant	NOX4, Nrf2	[271]
73	Ophiopogonis radix	Liliaceae	Nourish yin and moisturize dryness, clear the heart and calm the mind	Ophiopogonin C	radiation-induced PF mice	Mice (3 mg/kg)	Inhibit TGF-β1 signaling	TGF-β1, IL-6, HYP, SOD, MDA, MMP-2	[272]

Table 2 (continued)

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	Cytokine	Refs.
74	Mangifera indica	Anacardiaceae	Clearing heat and detoxification, invigorating the stomach and eliminating food	Mangiferin	BLM-induced PF rats and A549 cells	Rats (40 mg/kg) Cell (10 μg/mL)	Inhibit TGF-β1/Smad2/3 signaling	TLR4, TGF-β1	[189]
75	Rosmarinus officinalis	Lamiaceae		Rosmarinic Acid	radiation-induced lung damage rats	Rats (30, 60, 120 mg/kg)	Inhibits RhoA/Rock signaling	RhoA, Rock	[273]
76				Carnosol	BLM-induced PF rats	Rats (10, 20, 40 mg/kg)	Anti-inflammatory and antioxidant	HYP, MDA, PC, NO, GSH, SOD, TNF-α, IL-6	[274]
77	Oroxyli semen	Palmaceae	Detoxify and remove phlegm, relieve cough and asthma	Chrysin	BLM-induced PF rats	Rats (50 mg/kg)	Inhibit TGF-β1 signaling	TGF-β1, TXNIP	[275]
78	Aucklandiae radix	Asteraceae	Regulate spleen and stomach, remove dampness and eliminate phlegm	Costunolide	BLM-induced PF mice and HELF cells	Mice (10, 20 mg/kg) Cell (10, 20 μmol/L)	Regulation of NF-kB and TGF-β1/Smad2/Nrf2-NOX4 signaling	NF-kB, TGF-β1	[276]
79	Grape			Resveratrol	BLM-induced PF rats and BEAS-2B cells	Rats (25, 50, 100 mg/kg) Cell (2.5, 5, 10 mg/mL)	Inhibits HIF-1α and NF-κB signaling	HIF-1α, NF-κB	[277]
80					PM-induced PF mice and BEAS-2B cells	Mice (100 mg/kg) Cell (1, 5 μmol/L)	Inhibit the expression of NLRP3	NLRP3, TGF-β1, IL-1β, IL-6, TNF-α, α-SMA	[278]
81					FCA-induced arthritis rats	Rats (10 mg/kg)	Regulation of JAK/STAT/RANKL signaling	JAK, STAT	[279]
82				Grape seed proanthocyanidin extract (GSPE),	BLM-induced PF mice and A549 cells	Mice (30, 60, 90; 50, 100, 150 mg/kg) Cell (1 μg/mL)	Inhibition of oxidative stress inhibits epithelial cell apoptosis	HYP, TNF-α, IL-1β, IL-6, PARP, Bak	[280]
83	Indigo naturalis	Brassicaceae	Clearing heat and detoxification, reducing swelling and relieving pain	Indirubin	BLM-induced PF mice and PMLFs HPFs cells	Mice (12.5, 25 mg/kg) Cell (2.5–60 μmol/L)	Inhibit TGF-β1/Smad signaling	TGF-β1, ALT, CR, HYP, Collagen I, α-SMA	[191]
84	*Artemisia annua* L.	Asteraceae	Clear deficiency heat and remove bone steaming	Dihydroartemisinin	BLM-induced PF mice	Mice (25, 50, 100 mg/kg)	Reduced expression of TNF-α, IL-6 and TGF-β1 via TGF-β/JAK2/STAT3 signaling	TGF-β1, JAK2, STAT3	[281]
85					BLM-induced PF rats	Rats (50 mg/kg)	anti-oxidation	SOD, GSH, MDA, HO-1, Nrf2	[282]

Table 2 (continued)

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	Cytokine	Refs.
86	Nervilia fordii	Orchidaceae	Clearing heat and moistening the lungs, relieving cough and resolving phlegm	The extract of Nervilia fordii	BLM-induced PF rats and CT6 cells	Rats (100, 200, 400 mg/kg) Cell (100, 200, 500 μg/mL)	Inhibit TGF-β1/Smad signaling	TGF-β1, HYP, MPO, T-AOC, GSH, SOD, TNF-α	[283]
87	Cinnamomi cortex	Lauraceae	Warming the meridians and dispelling cold, dredging yang and reaching the camp	Trans-cinnamaldehyde	V79-4 cells	Cell (0–50 μmol/L)	Activates Nrf2/HO-1 signaling	Nrf2, HO-1, ROS, MMP	[284]
88	Notoginseng radix et rhizoma	Araliaceae	Promoting blood circulation and removing blood stasis, clearing heat and detoxification	Panax notoginseng saponin	ferric trichloride-induced PF Japanese rabbits	Rabbit(50 mg/kg)	Alleviate lung damage	IL-6, NF-κB	[285]
89	Inonotus sanghuang		Clearing heat and detoxification, promoting blood circulation and removing blood stasis	Inonotus sanghuang extract (ISE)	BLM-induced PF mice and A549 cells	Mice (0.6% w/w) Cell (2, 4 μg/mL)	Inhibit TGF-β1/Smad signaling	TGF-β1, Smad2/3	[193]
90	Kaempferiae rhizoma	Zingiberaceae	Promoting qi to relieve pain and regulating qi in a broad way	Alpha-Mangostin	BLM-induced PF mice	Mice (10 mg/kg)	Regulates AMPK signaling	AMPK, α-SMA, Smad2/3, Col I, MMP-9	[286]
91	Cnidii fructus	Loranthaceae	Warming the kidney to help yang, tonifying essence and astringent	Osthole	BLM-induced PF mice	Mice (40 mg/kg)	Downregulation of TGF-β1/nox4 signaling	TGF-β1, nox4	[287]
92	Zingiberis rhizoma recens	Zingiberaceae	Warm the middle to dissipate the cold, solve the surface and dissipate the cold	6 gingerol	BLM-induced PF mice and human embryonic lung fibroblasts MRC-5	Mice (100, 250 mg/kg) Cell (10, 20 μmol/L)	Activates SIRT1 signaling signaling	SIRT1, α-SMA, TNF-α, IL-6, IL-1β	[195]
93	Amaryllidaceae	Amaryllidaceae	Dispel wind and detoxification, kill insects and stop itching	Lycorine	BLM-induced PF mice and BMDMs cells	Mice (5, 10, 20 mg/kg) Cell (0–40 mmol/L)	Inhibit the expression of NLRP3	NLRP3, MPO, IL-6, IL-1β, α-SMA	[288]
94	Salvia officinalis	Lamiaceae	Clearing heat and detoxification, dispelling wind and relieving pain	Salvia officinalis	BLM-induced PF rats	Rats (50, 100, 150 mg/kg)	Anti-oxidation	CAT, MDA, SOD	[289]

Table 2 (continued)

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	Cytokine	Refs.
95	Silybi fructus	Asteraceae	Clearing heat and detoxification, soothing the liver and promoting gallbladder	Silibinin	Silica-induced PF mice	Mice (100, 300 mg/kg)	Anti-inflammatory Inhibits EMT	MDA, GSH, HYP, IL-6, IL-1β, IL-17, TGF-β1	[196]
96	Ampelopsis grossedentata (Hand.-Mazz.) W. T. Wang (Vitaceae)	Lamiaceae	Promoting blood circulation and regulating menstruation, diuresis and detumescence	Dihydromyricetin	BLM-induced PF mice and MLG cells	Mice (50, 100, 200 mg/kg)	Inhibit TGF-β1/Smad signaling	TGF-β1, α-SMA	[197]
97	Schisandrae chinensis fructus/glycyrrhizae radix et rhizoma	Magnoliaceae/Fabaceae	Astringent and astringent, replenishing qi and invigorating fluid	Schizandrin B + Glycyrrhizic acid	BLM-induced PF mice	Mice (100, 75, 100 + 75 mg/kg)	Regulation of TGF-β/Smad2 signaling	NOX1, Smad2	[290]
98	Croci stigma	Iridaceae	Promoting blood circulation and removing blood stasis, regulating menstruation and relieving pain	Crocin	BLM-induced PF rats	Rats (25 mg/kg)	Anti-inflammatory and antioxidant	HYP, GSH, CAT, SOD, TNF-α, MDA	[291]
99					BLM-induced PF rats	Rats (20 mg/kg)	Regulation of NRF2 and HO-1 signaling	NRF2, HO-1	[292]
100	Rhododendron brachycarpum G. Don	Ericaceae	Clearing heat and detoxification, reducing swelling and relieving pain	Hyperoside	BLM-induced PF mice	Mice (50 mg/kg)	Regulation of AKT/GSK3b signaling	AKT, GSK3b	[203]
101	Arenaria kansuensis	Caryophyllaceae	Clearing heat and detoxification, diuresis and purging gonorrhea	A. kansuensis ethanol extract	paraquat-induced PF rats	Rats (170, 350, 700 mg/kg)	Inhibit NF-κB/TGF-β1/Smad2/3 signal transduction	NF-κB, TGF-β1, Smad2/3	[203]
102	Morchella esculenta	Morchellaceae	Tonifying the kidney, tonifying qi, nourishing blood and calming the mind	FMP-1	A549 cells	Cell (50–300 μg/mL)	Regulation of PI3K/AKT-Nrf2/HO-1 signaling	ROS, PI3K	[293]
103	Leonuri herba	Lamiaceae	Promoting blood circulation and regulating menstruation, reducing swelling and relieving pain	Leonurine	BLM-induced PF mice	Mice (50, 100 mg/kg)	Up-regulation of AKT signaling	AKT, ECAD, TGF-β, BAX, ACTA2	[294]
104	Epimedii folium	Berberidaceae	Kidney deficiency and impotence, sore waist and knees	Icariin	BLM-induced PF rats	Rats (60 mg/kg)	Inhibit hippo signaling	YAP, IL-1β, IL-6, TGF-β1, TNF-α	[295]

Table 2 (continued)

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	Cytokine	Refs.
105	Houttuyniae herba	Saururaceae	Heat-clearing and detoxification, sore waist and knees	Sodium Houttuyfonate	BLM-induced PF mice	Mice (45, 90 mg/kg)	Anti-inflammatory	IL-1β, TNF-α	[206]
106	Anemarrhenae rhizoma	Liliaceae	Clearing heat and moistening dryness, promoting fluid to quench thirst	total extract of Anemarrhenae Rhizoma (TEAR)	BLM-induced PF rats	Rats (1.33, 4, 12 g/kg)	Inhibit TGF-β1/Smad signaling	TGF-β1, HYP, COII, ColIII, MPO, NO	[296]
107	Hedara nepalensis var.sinensis	Araliaceae	Clearing heat and detoxification, dispelling wind and promoting dampness	Hederagenin	BLM-induced PF rats	Rats (10, 20, 50 mg/kg)	Adjust Ras/JNK/NFAT4 axis	JNK, NFAT4	[209]

further clinical studies are still needed. In addition to the above-mentioned TCM that can improve PF, the detailed information of other TCM studies in the past five years that can improve PF through mediate apoptosis and autophagy were summarized and presented in Table 4.

Inhibition of endoplasmic reticulum stress

The endoplasmic reticulum (ER) is an organelle responsible for maintaining protein homeostasis in cells. The accumulation of misfolded proteins in the ER is referred to as ERS. Existing literature suggests that ERS is a key mechanism mediating PF in AEC [345, 346]. For example, ER stress promotes inflammation, induces EMT, and activates pro-apoptotic pathways, leading to the generation of PF [345]. In order to maintain homeostasis, cells rely on protective mechanisms to help them cope with ER stress, collectively known as the unfolded protein response (UPR). When the UPR mechanism fails or is over-activated, it can lead to cell apoptosis [347].

ERS can be triggered by various factors, including genetics, environmental exposure, viral infections, and cellular aging. Studies have demonstrated that ERS induced by genetic mutations, such as those found in surfactant protein C (SFTPC), plays a significant role in the development of PF [348, 349]. Additionally, environmental factors can also induce ERS, which is a critical factor in the pathogenesis of PF. For example, research has shown that environmental factors like silica and cigarette smoke can trigger ERS, and airborne particulate matter can activate signaling pathways like PERK and ATF, inducing ERS in cells [350]. Cigarette smoke can cause ERS in bronchial epithelial cells, leading to cell apoptosis in both in vitro and in vivo settings [351, 352]. Viral infections may contribute to fibrosis development by inducing ERS and activating UPR. Research has demonstrated that aging mice infected with herpes virus may develop PF through mechanisms related to ERS [353]. Additionally, aging can impair normal ER function in organisms [354, 355], which is in line with clinical observations indicating that PF is more prevalent in older individuals. In conclusion, enhancing protein processing and mitigating downstream effects of ERS may be an effective strategy to treat fibrosis resulting from ERS.

Citrus reticulata Blanco peel is used to treat lung diseases in Chinese Traditional medicine. Recently, Wang's team carried out a study on citrus extract to improve PF [336]. The results shown that citrus extract could reduce collagen deposition in PF mice and inhibit the increase of endoplasmic reticulum stress biomarkers. Further cell experiments shown that citrus extract regulated ERS through PERK and ATF3/PINK1 pathways. However, it is unclear whether citrus alkaline extract can improve PF by regulating ERS, which still needs further experiments. This study provides an important reference for the mechanism of citrus extract in improving PF.

Chlorogenic acid is the main active ingredient of many TCMs, which has antibacterial, antiviral, and free radical scavenging pharmacological effects. Wang's team evaluated the effect of chlorogenic acid on improving PF related markers through mice and cell models [356]. The results shown that chlorogenic acid can effectively regulate the expression of PF related pathological markers, and reduce the degree of PF by inhibiting the ERS pathway. At the same time, chlorogenic acid plays a certain role in regulating apoptosis involved in PF. Although this study did not deeply explore the signal pathway involved in chlorogenic acid inhibiting ERS, it provided a new experimental reference for chlorogenic acid to improve PF.

Isorhamnetin is a flavonoid active compound in hippophae fructus, which has pharmacological effects such as antioxidant, anti-inflammatory, and anti-tumor. Recent research literature suggests that isorhamnetin can effectively inhibit bleomycin induced collagen deposition and reduce type I collagen and α-SMA [194]. In addition, they further demonstrated that isorhamnetin can improve the degree of PF by inhibiting EMT and ERS. Although more studies are needed to clarify the mechanism of Isorhamnetin in improving PF, this study shown for the first time the potential important value of isorhamnetin in improving PF.

In recent years, the research of citrus alkaline extracts, isorhamnetin and chlorogenic acid to improve PF has made great progress. These studies have explored the activity and pharmacological mechanism of these compounds to improve PF in animal or cell experiments, making these compounds possible candidates for new drugs to treat PF. However, it should be pointed out that these studies have failed to delve into the association between ERS and inflammatory response, EMT, and cell apoptosis, and also lack in-depth research on signaling pathways and molecular mechanisms. Therefore, future research should pay more attention to exploring the molecular mechanism and signal pathway of TCM in improving PF, so as to better understand the pharmacology and toxicology of these candidate compounds. In addition to the above-mentioned TCM that can improve PF, the detailed information of other TCM studies in the past five years that can improve PF through inhibition of endoplasmic reticulum stress were summarized and presented in Table 5.

Conclusion

PF is a prevalent lung disease, the prevalence and incidence of IPF increasing annually [6, 7]. If PF is not promptly and effectively treated, it will lead to a decline

Table 3 Details about some traditional Chinese medicines improving pulmonary fibrosis by inhibiting extracellular matrix deposition

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	Cytokine	Refs.
1	Andrographis herba	Acanthaceae	Clearing heat and detoxification, cooling blood	Andrographolide	NIH 3T3, PLF cells	Rats (10 mg/kg) cell (2, 5, 10 μmol/L)	Inhibits TGF-β1/Smad2/3 and Erk1/2 signaling	TGF-β1, Smad2/3	[132]
2					Silica-induced PF mice	Mice (3, 10 mg/kg)	Inhibition of ECM precipitate formation	GSH, HYP, MDA, IL-1β, IL-6, TNF-α, TGF-β1	[131]
3	Rhei radix et rhizoma	Polygonaceae	Purging and defecating, clearing heat and detoxification	Chrysophanol	BLM-induced PF mice	Mice (10 mg/kg)	Inhibits Wnt/β-catenin signaling	β-catenin, HYP, TNF-α, IL-1β, IL-6, IFN-γ	[226]
4				Rhapontin	BLM-induced PF rats and THP-1 cells	Rats (25, 50, 100 mg/kg) cell (50 μmol/L)	Regulation of TGF-β/Smad signaling	TGF-β, Smad	[137]
5	Salviae miltiorrhizae radix et rhizoma	Lamiaceae	Promoting blood circulation and removing blood stasis, reducing swelling and relieving pain	Salvia miltiorrhiza	BLM-induced PF mice and NIH3T3 cells	Mice (21, 40, 80 mg/kg) Cell (0.1, 1, 3 μmol/L)	anti-oxidation	Nrf2, NOX4	[228]
6				Tanshinone IIA	Silica-induced PF mice	Mice (25 mg/kg)	Inhibit TGF-β1/Smad signaling	TGF-β1, α-SMA, Smad2/3/4/7	[307]
7				Cryptotanshinone	BLM-induced PF rats and HLFs cells	Rats (7.5, 15, 30, 60 mg/kg) Cell (0.75–18 mg/mL)	Inhibition of TGF-β/Smad signaling	TGF-β1, HYP, TNF-α, IL-6, ColI, ColIII, α-SMA	[304]
8	Astragalus membranaceus	Fabaceae	Replenishing qi and solidifying the surface, strengthening the upright and dispelling evil	Astragaloside IV	Silica-induced PF rats	Rats (20 mg/kg) Cell (7, 20, 60 μg/mL)	Inhibition of TGF-β/Smad3 signaling	TGF-β1, α-SMA, Collagen III, Smad2/3	[306]
9					BLM-induced PF rats	Rats (10 mg/kg)	Inhibition of ECM precipitate formation	HMGB1, HYP, Col-III, LN, HA	[305]
10	Scutellaria baicalensis Georgi	Scutellaria	Clearing away heat and dampness, purging fire and detoxifying	Baicalein	MRC-5 cells	Cell (1, 10 μmol/L)	Downregulation of CTGF expression	CTGF, TGF-β1, Smad2/3	[308]
11	Curcumae longae rhizoma	Zingiberaceae	Promoting blood circulation and removing blood stasis, Regulating menstruation and relieving pain	Curcumin	BLM-induced PF rats	Rats (300 mg/kg)	Inhibit TGF-β1 signaling	TGF-β1, HYP, Collagen III	[309]
12					BLM-induced PF rats	Rats (300 mg/kg)	Inhibition of ECM precipitate formation	fibronectin, lung glycoproteins	[235]
13	Tripterygium wilfordii Hook. f	Ranunculaceae	Clearing heat and detoxification, promoting blood circulation and removing blood stasis	Triptolide	radiation-induced PF mice and NIH3T3 cells	Mice (0.25 mg/kg) Cell (5 ng/mL)	Inhibit NF-κB signaling	NF-κB, LOX, IκBα	[239]
14				Isorhynchophylline	Silica-induced PF mice	Mice (20 mg/kg)	Anti-inflammatory	/	[240]

Table 3 (continued)

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	Cytokine	Refs.
15	Rhodiolae crenulatae radix et rhizoma	Crassulaceae	Replenishing qi and activating blood circulation, dredging pulse and relieving asthma	Rutin	BLM-induced PF rats	Rats (50, 100 mg/kg)	Regulation of TGF-β1/α-SMA/Col I/III signaling	TGF-β1, α-SMA	[259]
16	Ginseng radix et rhizoma	Araliaceae	Replenish qi and nourish blood, invigorate body and quench thirst	Total ginsenoside	BLM-induced PF mice	Mice (40, 80, 160 mg/kg)	Regulation of TGF-β1/Smad signaling	TGF-β1, α-SMA, Smad2/3/7, MMP-2, MMP-9	[310]
17	Dioscorea polystachya Turczaninow	Dioscoreaceae	Tonifying spleen and lung, nourishing yin and moistening dryness	Dioscin	Silica-induced PF mice and AM MH-S cells	Mice (mg/kg) Cell (200, 400, 800 nmol/L)	Promotes autophagy in alveolar macrophages	LC3, p62, AKT, mTOR, BECN1	[311]
18	Artemisia annua L	Asteraceae	Clear deficiency heat and remove bone steaming	Dihydromyricetin	BLM-induced PF mice and MLG cells	Mice (50, 100, 200 mg/kg)	Inhibit TGF-β1/Smad signaling	TGF-β1, α-SMA	[197]
19	Epimedii folium	Berberidaceae	Kidney deficiency and impotence, sore waist and knees	Icariin	BLM-induced PF rats	Rats (60 mg/kg)	Inhibit Hippo signaling	YAP, IL-1β, IL-6, TGF-β1, TNF-α	[295]
20	Chelidonii herba	Papaveraceae	Clearing heat and detoxification, reducing swelling and relieving pain	Chelerythrine	BLM-induced PF mice	Mice (0.375, 0.75 mg/kg)	activate Nrf2/ARE signal transduction	Nrf2, ARE	[244]
21	Psoraleae fructus	Fabaceae	Warm the kidney and consolidate the essence, strengthen the muscles and bones	Psoralen	BLM-induced PF mice and NIH3T3 cells	Mice (5 mg/kg) Cell (5, 10, 20, 40 μmol/L)	Inhibition of ECM precipitate formation	TNF-α, IL-1β	[167]
22	Citri reticulatae pericarpium	Rutaceae	Regulating qi and eliminating food, resolving phlegm and relieving cough	citrus alkaline extracts (CAEs)	BLM-induced PF mice	Mice (16, 32, 64 mg/kg)	Inhibit TGF-β1/Smad3 signaling	TGF-β1, LOX, HYP	[312]
23	Salviae miltiorrhizae radix et rhizoma/chuanxiong rhizoma	Lamiaceae/Apiaceae	Promoting blood circulation and removing blood stasis, Clearing heat and detoxification	Salvia miltiorrhiza and ligustrazine	BLM-induced PF rats	Rats (125 + 43.75, 250 + 87.5, 500 + 175 mg/kg)	Regulation of TGF-β/Smad signaling	TNF-α, TGF-β1	[313]
24	Rabdosiae rubescentis herba	Lamiaceae	Clearing heat and detoxification, reducing swelling and relieving pain	Oridonin	BLM-induced PF mice and MRC-5 cells	Mice (10, 20 mg/kg) Cell (5, 10 μmol/L)	Regulation of TGF-β/Smad signaling	TGF-β, Smad	[314]

Table 3 (continued)

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	Cytokine	Refs.
25	Curcumae longae rhizoma	Zingiberaceae	Promoting blood circulation and removing blood stasis, Regulating menstruation and relieving pain	curcumin/Curcumol	HFL cells	Cell (8, 16, 32 μg/mL)	Inhibition of ECM precipitate formation	Col-I, Col-III, TGF-β1, α-SMA	[315]
26	Citrus fruits	Rutaceae	Invigorate the spleen and replenish qi, moisturize the lungs and relieve cough	Hesperidin	BLM-induced PF rats	Rats (25, 50, 100 mg/kg)	Inhibits TGF-β1/Smad3/AMPK and I-κBα/NF-κB signaling	TGF-β1, NF-κB	[253]
27	Polygoni cuspidati rhizoma et radix	Polygonaceae	Clearing heat and detoxification, promoting blood circulation and removing blood stasis	Polydatin	BLM-induced PF rats and A549 cells	Rats (10, 40, 160 mg/kg) Cell (0–120 μmol/L)	Inhibit TGF-β1/Smad signaling	TGF-β1, Col-1, α-SMA, TNF-α, IL-6, IL-13	[156]
28	Coptidis rhizoma	Ranunculaceae	Clearing heat and dryness, purging fire and detoxification	berberine	BLM-induced PF mice	Mice (50, 100, 200 mg/kg)	activate PPAR-γ	HGF, PPAR-γ	[260]
29	Astragali radix/ferulae resina	Fabaceae/Apiaceae	Replenishing qi and solidifying the surface, strengthening the upright and dispelling evil	astragaloside IV/ferulic acid	BLM-induced PF mice	Mice (24 + 40.8 mg/kg)	Inhibit TGF-β1/Smad3 signaling	TGF-β1, Nrf2	[261]
30	Centellae herba	Apiaceae	Clearing heat and detoxification, promoting diuresis and detumescence	Asiaticoside	BLM-induced PF mice	Mice (50 mg/kg)	Up-regulation of BMP7/Smad1/5 signaling	BMP7, Smad1/5	[263]
31	sophorae fla vescentis radix	Fabaceae	Clearing heat and detoxification, diuresis and purging gonorrhea	Matrine	MRC-5 cells	Cell (10 μmol/L)	Inhibit TGF-β/Smad2/3 signaling	TGF-β, Smad2/3	[182]
32	Blueberry	Ericaceae		Pterostilbene	A549 cells	Cell (0–100 μmol/L)	Inhibit TGF-β1 signaling	TGF-β1, Bcl-2, Bax, LC3, p62, p21	[183]
33	Siratia grosvenorii	Cucurbitaceae	Clear heat and moisturize the lungs and open pharynx	Mogrol	BLM-induced PF mice and NIH3T3 cells	Mice (1, 5, 10 mg/kg) Cell (1, 5, 10 μmol/L)	Regulation of TGF-β1 and AMPK signaling	TGF-β1, AMPK	[188]
34	Rosmarinus officinalis	Lamiaceae		Rosmarinic Acid	radiation-induced lung damage rats	Rats (30, 60, 120 mg/kg)	Inhibits RhoA/Rock signaling	RhoA, Rock	[273]
35	Grape			Resveratrol	BLM-induced PF rats and MRC-5 cells	Rats (60 mg/kg) Cell (10 μmol/L)	Regulates MAPK/AP-1 signaling	MAPK/AP-1	[316]

Table 3 (continued)

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	Cytokine	Refs.
36	Kaempferiae rhizoma	Zingiberaceae	Promoting qi to relieve pain and regulating qi in a broad way	Alpha-Mangostin	BLM-induced PF mice	Mice (10 mg/kg)	Regulates AMPK signaling	AMPK, α-SMA, Smad2/3, Col I, MMP-9	[286]
37	Silybi fructus	Asteraceae	Clearing heat and detoxification, soothing the liver and promoting gallbladder	Silibinin	Silica-induced PF mice	Mice (100, 300 mg/kg)	Anti-inflammatory Inhibits EMT	MDA, GSH, HYP, IL-6, IL-1β, IL-17, TGF-β1	[196]
38	Pseudostellariae radix	Caryophyllaceae	Yiqi Jianpi, Shengjin fluid	Heterophyllin B	BLM-induced PF mice and MLE-12 cells	Mice (5, 20 mg/kg) Cell (1–100 μmol/L)	Activates AMPK, inhibits TGF-β1-Smad2/3 signaling, and down-regulates STING	TGF-β1, CoL-1, α-SMA	[317]
39	Arenaria kansuensis	Caryophyllaceae	Clearing heat and detoxification, diuresis and purging gonorrhea	A. kansuensis ethanol extract	paraquat-induced PF rats	Rats (170, 350, 700 mg/kg)	Inhibit NF-κB/TGF-β1/Smad2/3 signal transduction	NF-κB, TGF-β1, Smad2/3	[203]
40	Aurantii fructus immaturus	Rutaceae	Regulating qi stagnation, resolving phlegm and relieving cough	Neohesperidin	BLM-induced PF mice and NIH3T3, MLg, A549 cells	Mice (20 mg/kg) Cell (0–200 μmol/L)	Inhibition of TGF-β/Smad3 signaling	TGF-β1, Smad2/3, Erk, p-38, JNK	[208]
41	Polyporus	Polyporaceae	Diuresis, detumescence and phlegm	Polyporus Polysaccharide	BLM-induced PF mice and HLF cells	Mice (50, 100 mg/kg) Cell (1 mg/mL)	Inhibit TGF-β1/Smad2/3 signaling	TGF-β1, Smad2/3	[210]
42	Arnebiae radix	Boraginaceae	Clearing heat and detoxification, moistening dryness and invigorating muscle	Shikonin	MLFC cells	Cell (0.1, 0.3, 1, 3, 10 μmol/L)	Inhibit Akt signaling	MAPK, akt	[318]

Table 4 Details about some traditional Chinese medicine improving pulmonary fibrosis by mediating apoptosis and autophagy

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	cytokine	Refs.
1	Citri reticulatae pericarpium	Rutaceae	Regulating qi and eliminating food, resolving phlegm and relieving cough	citrus alkaline extracts (CAEs)	A549 cells	Cell (0.01 μmol/L)	Inhibit b-catenin/p53 signaling	PDGF, TNF-α, p21, p53, MMP-7, CTGF	[331]
2					BLM-induced PF mice and PMLF, MRC-5 cells	Mice (32, 64, 96 mg/kg) Cell (50, 100, 200 μmol/L)	prevent cellular senescence	COX-2, α-SMA, Fibronectin, p21, p16	[330]
3					BLM-induced PF mice	Mice (16, 32, 64 mg/kg)	Inhibit p38/NF-κB signaling	p38, NF-κB	[329]
4					HPFS cells	Cell (50, 250, 500 μmol/L)	Induces apoptosis of lung fibroblasts	COX-2, Fas	[328]
5					BLM-induced PF mice and A549 cells	Mice (32, 64, 96 mg/kg) Cell (50, 100, 200 μg/mL)	Regulates PERK and ATF3/PINK1 signaling	PERK, ATF3, PINK1	[336]
6	Curcumae longae rhizoma	Zingiberaceae	Promoting blood circulation and removing blood stasis, Regulating menstruation and relieving pain	Curcumin	LMSCs cells	Cell (2.5, 5, 10, 20 μmol/L)	Regulation of Akt/Nrf2/HO-1 signaling	Akt, Nrf2, HO-1	[234]
7					BLM-induced PF rats	Rats (300 mg/kg)	Inhibit TGF-β1 signaling	TGF-β1, HYP, Collagen III	[309]
8	Erigeron breviscapus	Asteraceae	Promoting blood circulation and removing blood stasis, clearing heat and detoxification	Scutellarein	BLM-induced PF mice	Mice (10 mg/kg)	Inhibits PI3K/Akt signaling	PI3K, Akt, Smad2/3, α-SMA	[172]
9	Amaryllidaceae	Amaryllidaceae	Dispel wind and detoxification, kill insects and stop itching	Lycorine	BLM-induced PF mice and BMDMs cells	Mice (5, 10, 20 mg/kg) Cell (0–40 mmol/L)	Inhibit the expression of NLRP3	NLRP3, MPO, IL-6, IL-1β, α-SMA	[288]
10	Dioscorea polystachya Turczaninow	Dioscoreaceae	Tonifying spleen and lung, nourishing yin and moistening dryness	Dioscin	Silica-induced PF mice and AM MH-S cells	Mice (mg/kg) Cell (200, 400, 800 nmol/L)	Promotes autophagy in alveolar macrophages	MMP9,mtROS	[311]
11	Blueberry	Ericaceae		Pterostilbene	LPS-induced PF mice	Mice (12.5, 25, 50 mg/kg)	Activation of Keap-1/Nrf2 inhibits A20/NF-κB and NLRP3 signaling	NF-κB, NLRP3	[268]
12	Various plant sources			Quercetin	Tracheal Trauma Rabbit and WI-38 cells	Cell (5–200 μmol/L)	Inhibits AKT/mTOR signaling	AKT, mTOR	[335]
13					BLM-induced PF mice	Mice (30 mg/kg)	Enhance fibroblast apoptosis	Fas, DR4/5, CAveolin-1, AKT	[334]
14				Sinapic acid	BLM-induced PF rats	Rats (10, 20 mg/kg)	Inhibit NF-κB/NRF2/HO-1 signaling	NF-κB, NRF2, HO-1	[250]

Table 4 (continued)

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	cytokine	Refs.
15	Bletillae rhizoma	Orchidaceae	Convergence to stop bleeding, reduce swelling and promote muscle growth	Bletilla striata	Silica-induced PF mice and A549 cells	Mice (20, 40 mg/kg) Cell (10, 25, 50 μmol/L)	Inhibit Bax/Bcl-2 signaling	HO-1, Nrf2, γGCSc, Bax, Bcl-2	[337]
16	Atractylodis rhizoma	Asteraceae	Invigorating spleen and stomach, tonifying qi and blood	Atractylenolide III	BLM-induced PF rats	Rats (0.6, 1.2, 2.4 mg/kg)	activate Nrf2/NQO1/HO-1 signal transduction	Nrf2, NQO1, HO-1	[246]
17	Chuanxiong rhizoma	Apiaceae	Activating blood circulation and promoting qi, expelling wind and relieving pain	Ligustrazin	paraquat-induced PF mice and A549 cells	Mice (30 mg/kg)	Inhibit mTOR/Akt signaling	mTOR, Akt	[338]
18	Rhei radix et rhizoma	Polygonaceae	Purging and defecating, clearing heat and detoxification	Emodin	Silica-induced PF mice and A549 cells	Mice (25, 50, 100 mg/kg)	Regulation of NF-κB and TGF-β1/Smad3 signaling	NF-κB, TGF-β1	[136]
19	Salviae miltiorrhizae radix et rhizoma/ puerariae lobatae radix	Lamiaceae/Fabaceae	Promoting blood circulation and removing blood stasis, reducing swelling and relieving pain	Tanshinone IIA/ puerarin	BLM-induced PF mice and MRC-5 cells	Mice (5 + 14 mg/kg)	Inhibition of IL 6-JAK2-STAT3/STAT1 signaling	IL6, STAT1	[339]
20	Glycyrrhizae radix et rhizoma	Fabaceae	Nourishes qi and nourishes yin, clears away heat and detoxifies	Isoliquiritigenin	MRC-5 cells	Cell (0–40 mg/L)	Inhibit PI3K/AKT/mTOR signaling	PI3K, AKT, mTOR	[340]
21	Scutellariae radix	Scutellaria	Clearing away heat and dampness, purging fire and detoxifying	Baicalin	BLM-induced PF rats and RPF	Rats (50 mg/kg) Cell (20, 40, 60, 80 μg/mL)	Regulation of CaMKII and PI3K/AKT signaling	PI3K, AKT	[141]
22	Rosmarinus officinalis	Lamiaceae/Fabaceae		Rosmarinic Acid + carnosic acid	BLM-induced PF rats and HLFs cells	Rats (5 + 3 mg/kg) Cell (50 + 10, 100 + 20 μmol/L)	Induces apoptosis of lung fibroblasts	p21, AKT, p38	[341]
23	Cinnamomi cortex	Lauraceae	Warming the meridians and dispelling cold, dredging yang and reaching the camp	Trans-cinnamaldehyde	V79-4 cells	Cell (0–50 μmol/L)	Activates Nrf2/HO-1 signaling	Nrf2, HO-1	[284]
24	Rhizoma Kaempferiae	Zingiberaceae	Relieving pain by activating qi and dispelling cold in the middle of warming	Kaempferol	Silica-induced PF mice	Mice (150 mg/kg)	Anti-inflammatory	Beclin-1, p62, LC3, MMP-9, MMP-2	[342]

Table 4 (continued)

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	cytokine	Refs.
25	Schisandrae chinensis fructus	Magnoliaceae	Astringent and astringent, replenishing qi and invigorating fluid	Schisandra	BLM-induced PF rats	Rats (5 mg/kg)	Inhibit TGF-β1/Smad signaling	TGF-β1, Smad3/4/7	[343]
26	Leonuri herba	Lamiaceae	Promoting blood circulation and regulating menstruation, reducing swelling and relieving pain	Leonurine	BLM-induced PF mice	Mice (50, 100 mg/kg)	Up-regulation of AKT signaling	AKT, ECAD, TGF-β1, ACTA2, BAX	[294]
27	Ginkgo folium	Ginkgoaceae	Calming the liver and eyesight, moistening the lungs and relieving cough	Ginkgo biloba Extract EGb761	BLM-induced PF mice	Mice (25, 50, 100 mg/kg)	Regulation of NF-κB signaling	NF-κB, TNF-β, IL-1β, IL-6, α-SMA, TGF-β1	[344]

Table 5 Details about some traditional Chinese medicines improving pulmonary fibrosis by inhibiting endoplasmic reticulum stress

No	Source	Genus information	Traditional efficacy	Active compound	Experiment model	Administration dose	Therapeutic target	cytokine	Refs.
1	Citri reticulatae pericarpium	Rutaceae	Regulating qi and eliminating food, resolving phlegm and relieving cough	citrus alkaline extracts (CAEs)	BLM-induced PF mice and A549 cells	Mice (32, 64, 96 mg/kg) cell (50, 100, 200 μg/mL)	Regulates PERK and ATF3/PINK1 signaling	PERK, ATF3, PINK1	[336]
2	Hippophae fructus	Elaeagnaceae	Invigorate the stomach and eliminate food, relieve cough and expectoration	Isorhamnetin	BLM-induced PF mice	Mice (10, 30 mg/kg) Cell (25, 50, 100 μmol/L)	Suppress EMT	PERK, α-SMA, Col III, CHOP, GRP78, TGF-β1	[194]
3	Lonicerae japonicae flos	Caprifoliaceae	Clearing heat and detoxification, dispelling wind and detoxification	Chlorogenic acid	BLM-induced PF mice	Mice (15, 30, 60 mg/kg)	Inhibits endoplasmic reticulum stress	α-SMA, Col I, CHOP, PERK, IRE-1, GRP78	[356]

in lung function, which will have a negative impact on patients' quality of life and life expectancy [12]. In the last decade, glucocorticoids and immunosuppressants are commonly used in the treatment of PF, such as pirfenidone and nintedanib, but their efficacy is not ideal, they have many side effects, and they are expensive [14, 15]. Finding some reliable drugs from natural plants is becoming a research hotspot. TCM has been widely concerned because of its remarkable efficacy in treating or improving PF, mild side effects and low price. In the last five years, the scientific research on the improvement of PF by TCMs are increasing and has made great progress. Systematic and comprehensive summary of these research advances will help pharmaceutical researchers to understand the current research progress more quickly [16–18].

This article systematically reviews the progress in improving or reversing PF using traditional Chinese medicine in the last 5 years, and analyzes the major signaling pathways involved from a pharmacological perspective. Overall, the mechanism of improving PF mainly includes inhibiting EMT, anti-inflammatory and antioxidant, improving ECM deposition, mediating apoptosis and inhibiting ERS. The involved signaling pathways include TGF-β1/Smad, Nrf2/ARE, PI3K/AKT, NF-κB, etc. It is worth noting that the same Chinese medicine often involves multiple signaling pathways to improve pulmonary fibrosis, suggesting that these Chinese medicines have multi-target effects.

Although the experimental research of improving or treating PF with TCM has made some important progress, there are still some shortcomings. First, these experiments are mostly based on animal or cellular models and lack clinical trial validation. Secondly, most experiments often study only one or a few signaling pathways, lacking overall and comprehensive research. Third, because the pathogenesis of PF has not been fully elucidated, it also limits the depth of corresponding research in TCM, especially the toxicology research needs to be strengthened. What is most worth thinking about is how current pharmacological research can support the transformation of these TCM into new drugs.

On the basis of the existing known mechanisms of drug action, research methods based on artificial intelligence and big data computing are becoming the mainstream of drug development. The combination of computer aided drug design, drug molecular-target interaction, signaling pathway and pharmacological network, these new technologies will provide more than traditional research approaches to decrypt TCM treatment of PF, which will become a research hotspot in the near future.

Abbreviations

PF	Pulmonary fibrosis
IPF	Idiopathic pulmonary fibrosis
ECM	Extracellular matrix
MAPK	Mitogen-activated protein kinase
IL	Interleukin
TNF-α	Tumor necrosis factor alpha
TGF-β	Transforming growth factor Beta
TIMPs	Tissue inhibitor of matrix metalloproteinases
ARE	Antioxidant response element
PI3K	Phosphoinositide 3-kinase
AKT	Protein kinase B
mTOR	Mammalian target of rapamycin
SASP	Senescence associated secretory phenotype
PDGF	Platelet-derived growth factor
TCM	Traditional Chinese medicine
EMT	Epithelial-mesenchymal transition
SAB	Salvianolic acid B
Tan-IIA	Tanshinone IIA
CPT	Cryptotanshinone
ROS	Reactive oxygen species
AG	Andrographolide
NOX	NADPH oxidase
TanIIA	Tanshinone IIA
ASV	Astragalus methyloside
Pts	Pterostilbene
ERS	Endoplasmic reticulum stress
AEC	Alveolar epithelial cells
ER	Endoplasmic reticulum

Author contributions

TP and ZJN conceived and designed the review; QSB and ZYY drafted the manuscript and designed the table; QSB designed the fgure and edited the graphic abstract; ZYY modifed the language and checked the text; QSB and ZYY checked the fgure and table, confrmed information. All authors read and approved the fnal manuscript.

Funding

This work was supported by Sichuan Science and Technology Program (Grant numbers 2022YFS0429, 2022ZYD0102, 2022JDKY0036).

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Key Laboratory of Biological Evaluation of TCM Quality of State Administration of Traditional Chinese Medicine, Sichuan Academy of Chinese Medicine Sciences, Chengdu 610041, China. [2]State Key Laboratory of Southwestern Chinese Medicine Resources, Chengdu University of Traditional Chinese Medicine, Chengdu 611137, China.

Received: 27 April 2023 Accepted: 6 July 2023
Published online: 03 August 2023

References

1. Richeldi L, Collard HR, Jones MG. Idiopathic pulmonary fibrosis. Lancet. 2017;389(10082):1941–52.

2. Wijsenbeek M, Cottin V. Spectrum of fibrotic lung diseases. N Engl J Med. 2020;383(10):958–68.
3. Martinez FJ, Collard HR, Pardo A, Raghu G, Richeldi L, Selman M, et al. Idiopathic pulmonary fibrosis. Nat Rev Dis Primers. 2017;3:17074.
4. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis an official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med. 2018;198(5):E44-68.
5. Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis an international working group report. Am J Respir Crit Care Med. 2016;194(3):265–75.
6. Hutchinson J, Fogarty A, Hubbard R, McKeever T. Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. Eur Respir J. 2015;46(3):795–806.
7. Hopkins RB, Burke N, Fell C, Dion G, Kolb M. Epidemiology and survival of idiopathic pulmonary fibrosis from national data in Canada. Eur Respir J. 2016;48(1):187–95.
8. Lee HE, Myong JP, Kim HR, Rhee CK, Yoon HK, Koo JW. Incidence and prevalence of idiopathic interstitial pneumonia and idiopathic pulmonary fibrosis in Korea. Int J Tuberc Lung Dis. 2016;20(7):978–84.
9. George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and covid-19: the potential role for antifibrotic therapy. Lancet Respir Med. 2020;8(8):807–15.
10. Xu YH, Dong JH, An WM, Lv XY, Yin XP, Zhang JZ, et al. Clinical and computed tomographic imaging features of novel coronavirus pneumonia caused by SARS-cov-2. J Infect. 2020;80(4):394–400.
11. Spagnolo P, Balestro E, Aliberti S, Cocconcelli E, Biondini D, Della Casa G, et al. Pulmonary fibrosis secondary to COVID-19: a call to arms? Lancet Respir Med. 2020;8(8):750–2.
12. Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. N Engl J Med. 2018;378(19):1811–23.
13. Somogyi V, Chaudhuri N, Torrisi SE, Kahn N, Muller V, Kreuter M. The therapy of idiopathic pulmonary fibrosis: what is next? Eur Respir Rev. 2019;28(153):190021.
14. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071–82.
15. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh S, Inoue Y, et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med. 2019;381(18):1718–27.
16. Wang J, Zhao XT, Feng WW, Li YX, Peng C. Inhibiting TGF-beta 1-mediated cellular processes as an effective strategy for the treatment of pulmonary fibrosis with chinese herbal medicines. Am J Chin Med. 2021;49(08):1965–99.
17. Chen DQ, Feng YL, Cao G, Zhao YY. Natural products as a source for antifibrosis therapy. Trends Pharmacol Sci. 2018;39(11):937–52.
18. Hosseini S, Imenshahidi M, Hosseinzadeh H, Karimi G. Effects of plant extracts and bioactive compounds on attenuation of bleomycin-induced pulmonary fibrosis. Biomed Pharmacother. 2018;107:1454–65.
19. Yang Y, Islam MS, Wang J, Li Y, Chen X. Traditional chinese medicine in the treatment of patients infected with 2019-new coronavirus (SARS-cov-2): a review and perspective. Int J Biol Sci. 2020;16(10):1708–17.
20. Huang K, Zhang P, Zhang ZH, Youn JY, Wang C, Zhang HC, et al. Traditional chinese medicine (TCM) in the treatment of COVID-19 and other viral infections: efficacies and mechanisms. Pharmacol Ther. 2021;225:107843.
21. Huang FF, Li Y, Leung E, Liu XH, Liu KF, Wang Q, et al. A review of therapeutic agents and chinese herbal medicines against SARS-cov-2 (covid-19). Pharmacol Res. 2020;158:104929.
22. Hoy RF, Baird T, Hammerschlag G, Hart D, Johnson AR, King P, et al. Artificial stone-associated silicosis: a rapidly emerging occupational lung disease. Occup Environ Med. 2018;75(1):3–5.
23. Della Latta V, Cecchettini A, Del Ry S, Morales MA. Bleomycin in the setting of lung fibrosis induction: from biological mechanisms to counteractions. Pharmacol Res. 2015;97:122–30.
24. Xu LJ, Xu J, Wang Z. Molecular mechanisms of paraquat-induced acute lung injury: a current review. Drug Chem Toxicol. 2014;37(2):130–4.
25. Crouser ED, Maier LA, Wilson KC, Bonham CA, Morgenthau AS, Patterson KC, et al. Diagnosis and detection of sarcoidosis an official american thoracic society clinical practice guideline. Am J Respir Crit Care Med. 2020;201(8):E26-51.
26. Pardo A, Selman M. Lung fibroblasts, aging, and idiopathic pulmonary fibrosis. Ann Am Thorac Soc. 2016;13:S417–21.
27. Wolters PJ, Collard HR, Jones KD. Pathogenesis of idiopathic pulmonary fibrosis. Annu Rev Pathol. 2014;9:157–79.
28. Mack M. Inflammation and fibrosis. Matrix Biol. 2018;68–69:106–21.
29. Heukels P, Moor CC, von der Thusen JH, Wijsenbeek MS, Kool M. Inflammation and immunity in IPF pathogenesis and treatment. Respir Med. 2019;147:79–91.
30. Spagnolo P, Distler O, Ryerson CJ, Tzouvelekis A, Lee JS, Bonella F, et al. Mechanisms of progressive fibrosis in connective tissue disease (CTD)-associated interstitial lung diseases (ILDs). Ann Rheum Dis. 2021;80(2):143–50.
31. Weiskirchen R, Weiskirchen S, Tacke F. Organ and tissue fibrosis: molecular signals, cellular mechanisms and translational implications. Mol Aspects Med. 2019;65:2–15.
32. Distler J, Gyorfi AH, Ramanujam M, Whitfield ML, Konigshoff M, Lafyatis R. Shared and distinct mechanisms of fibrosis. Nat Rev Rheumatol. 2019;15(12):705–30.
33. Sgalla G, Iovene B, Calvello M, Ori M, Varone F, Richeldi L. Idiopathic pulmonary fibrosis: pathogenesis and management. Respir Res. 2018;19(1):32.
34. Cottin V, Hirani NA, Hotchkin DL, Nambiar AM, Ogura T, Otaola M, et al. Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. Eur Respir Rev. 2018;27(150):180076.
35. Phan T, Paliogiannis P, Nasrallah GK, Giordo R, Eid AH, Fois AG, et al. Emerging cellular and molecular determinants of idiopathic pulmonary fibrosis. Cell Mol Life Sci. 2021;78(5):2031–57.
36. Herrera J, Henke CA, Bitterman PB. Extracellular matrix as a driver of progressive fibrosis. J Clin Invest. 2018;128(1):45–53.
37. Gieseck RL, Wilson MS, Wynn TA. Type 2 immunity in tissue repair and fibrosis. Nat Rev Immunol. 2018;18(1):62–76.
38. Morse C, Tabib T, Sembrat J, Buschur KL, Bittar HT, Valenzi E, et al. Proliferating SPP1/MERTK-expressing macrophages in idiopathic pulmonary fibrosis. Eur Respir J. 2019;54(2):1802441.
39. Adams TS, Schupp JC, Poli S, Ayaub EA, Neumark N, Ahangari F, et al. Single-cell rna-seq reveals ectopic and aberrant lung-resident cell populations in idiopathic pulmonary fibrosis. Sci Adv. 2020;6(28):eaba1983.
40. Hinz B, Lagares D. Evasion of apoptosis by myofibroblasts: a hallmark of fibrotic diseases. Nat Rev Rheumatol. 2020;16(1):11–31.
41. Chanda D, Otoupalova E, Smith SR, Volckaert T, De Langhe SP, Thannickal VJ. Developmental pathways in the pathogenesis of lung fibrosis. Mol Aspects Med. 2019;65:56–69.
42. Upagupta C, Shimbori C, Alsilmi R, Kolb M. Matrix abnormalities in pulmonary fibrosis. Eur Respir Rev. 2018;27(148):180033.
43. Noble PW, Barkauskas CE, Jiang DH. Pulmonary fibrosis: patterns and perpetrators. J Clin Invest. 2012;122(8):2756–62.
44. Luppi F, Kalluri M, Faverio P, Kreuter M, Ferrara G. Idiopathic pulmonary fibrosis beyond the lung: understanding disease mechanisms to improve diagnosis and management. Respir Res. 2021;22(1):109.
45. Yan Z, Kui Z, Ping Z. Reviews and prospectives of signaling pathway analysis in idiopathic pulmonary fibrosis. Autoimmun Rev. 2014;13(10):1020–5.
46. Li XH, Ma L, Huang K, Wei YL, Long SD, Liu QY, et al. Regorafenib-attenuated, bleomycin-induced pulmonary fibrosis by inhibiting the TGF-beta 1 signaling pathway. Int J Mol Sci. 2021;22(4):1985.
47. Macias MJ, Martin-Malpartida P, Massague J. Structural determinants of smad function in TGF-beta signaling. Trends Biochem Sci. 2015;40(6):296–308.
48. Wrighton KH, Lin X, Feng XH. Phospho-control of TGF-beta superfamily signaling. Cell Res. 2009;19(1):8–20.
49. Miyazono K. Transforming growth factor-beta signaling in epithelial-mesenchymal transition and progression of cancer. Proc Jpn Acad Ser B Phys Biol Sci. 2009;85(8):314–23.
50. Shi KY, Jiang JZ, Ma TL, Xie J, Duan LR, Chen RH, et al. Pathogenesis pathways of idiopathic pulmonary fibrosis in bleomycin-induced lung injury model in mice. Respir Physiol Neurobiol. 2014;190(1):113–7.

51. Zhao YW, Tang HC, Zeng X, Ye DC, Liu JJ. Resveratrol inhibits proliferation, migration and invasion via Akt and ERK1/2 signaling pathways in renal cell carcinoma cells. Biomed Pharmacother. 2018;98:36–44.
52. Ramkumar KM, Sekar TV, Foygel K, Elango B, Paulmurugan R. Reporter protein complementation imaging assay to screen and study Nrf2 activators in cells and living animals. Anal Chem. 2013;85(15):7542–9.
53. Dodson M, de la Vega MR, Cholanians AB, Schmidlin CJ, Chapman E, Zhang DD. Modulating NRF2 in disease: timing is everything. Annu Rev Pharmacol Toxicol. 2019;59:555–75.
54. Iddir M, Brito A, Dingeo G, Del Campo S, Samouda H, La Frano MR, et al. Strengthening the immune system and reducing inflammation and oxidative stress through diet and nutrition: considerations during the covid-19 crisis. Nutrients. 2020;12(6):1562.
55. Hecker L, Logsdon NJ, Kurundkar D, Kurundkar A, Bernard K, Hock T, et al. Reversal of persistent fibrosis in aging by targeting NOX4-NRF2 redox imbalance. Sci Transl Med. 2014;6(231):231–47.
56. Buendia I, Michalska P, Navarro E, Gameiro I, Egea J, Leon R. Nrf2-ARE pathway: an emerging target against oxidative stress and neuroinflammation in neurodegenerative diseases. Pharmacol Ther. 2016;157:84–104.
57. Wang JC, Hu KL, Cai XY, Yang B, He QJ, Wang JJ, et al. Targeting PI3K/AKT signaling for treatment of idiopathic pulmonary fibrosis. Acta Pharm Sin B. 2022;12(1):18–32.
58. Barnes PJ, Baker J, Donnelly LE. Cellular senescence as a mechanism and target in chronic lung diseases. Am J Respir Crit Care Med. 2019;200(5):556–64.
59. Spangle JM, Roberts TM, Zhao JJ. The emerging role of PI3K/AKT-mediated epigenetic regulation in cancer. Biochim Biophys Acta Rev Cancer. 2017;1868(1):123–31.
60. Fruman DA, Chiu H, Hopkins BD, Bagrodia S, Cantley LC, Abraham RT. The PI3K pathway in human disease. Cell. 2017;170(4):605–35.
61. Wang Y, Zhang L, Wu GR, Zhou Q, Yue HH, Rao LZ, et al. MBD2 serves as a viable target against pulmonary fibrosis by inhibiting macrophage M2 program. Sci Adv. 2021;7(1):eabb6075.
62. Qiu T, Tian YQ, Gao YJ, Ma M, Li H, Liu XQ, et al. Pten loss regulates alveolar epithelial cell senescence in pulmonary fibrosis depending on akt activation. Aging. 2019;11(18):7492–509.
63. Lawrence J, Nho R. The role of the mammalian target of rapamycin (mTOR) in pulmonary fibrosis. Int J Mol Sci. 2018;19(3):778.
64. Bastakoty D, Young PP. Wnt/β-catenin pathway in tissue injury: roles in pathology and therapeutic opportunities for regeneration. FASEB J. 2016;30(10):3271–84.
65. Tzouvelekis A, Gomatou G, Bouros E, Trigidou R, Tzilas V, Bouros D. Common pathogenic mechanisms between idiopathic pulmonary fibrosis and lung cancer. Chest. 2019;156(2):383–91.
66. Okazaki H, Sato S, Koyama K, Morizumi S, Abe S, Azuma M, et al. The novel inhibitor PRI-724 for Wnt/β-catenin/CBP signaling ameliorates bleomycin-induced pulmonary fibrosis in mice. Exp Lung Res. 2019;45(7):188–99.
67. Andersson-Sjöland A, Karlsson JC, Rydell-Törmänen K. ROS-induced endothelial stress contributes to pulmonary fibrosis through pericytes and Wnt signaling. Lab Invest. 2016;96(2):206–17.
68. Cao H, Chen X, Hou J, Wang C, Xiang Z, Shen Y, et al. The Shh/Gli signaling cascade regulates myofibroblastic activation of lung-resident mesenchymal stem cells via the modulation of Wnt10a expression during pulmonary fibrogenesis. Lab Invest. 2020;100(3):363–77.
69. Li X, Liu X, Deng R, Gao S, Jiang Q, Liu R, et al. Betulinic acid attenuated bleomycin-induced pulmonary fibrosis by effectively intervening Wnt/β-catenin signaling. Phytomedicine. 2021;81:153428.
70. Ji J, Hou J, Xia Y, Xiang Z, Han X. NLRP3 inflammasome activation in alveolar epithelial cells promotes myofibroblast differentiation of lung-resident mesenchymal stem cells during pulmonary fibrogenesis. Biochim Biophys Acta Mol Basis Dis. 2021;1867(5):166077.
71. Froidure A, Marchal-Duval E, Homps-Legrand M, Ghanem M, Justet A, Crestani B, et al. Chaotic activation of developmental signalling pathways drives idiopathic pulmonary fibrosis. Eur Respir Rev. 2020;29(158):190140.
72. Vukmirovic M, Kaminski N. Impact of transcriptomics on our understanding of pulmonary fibrosis. Front Med. 2018;5:87.
73. Newman DR, Sills WS, Hanrahan K, Ziegler A, Tidd KM, Cook E, et al. Expression of WNT5A in idiopathic pulmonary fibrosis and its control by TGF-β and WNT7B in human lung fibroblasts. J Histochem Cytochem. 2016;64(2):99–111.
74. Li X, Liu X, Deng R, Gao S, Yu H, Huang K, et al. Nintedanib inhibits Wnt3a-induced myofibroblast activation by suppressing the Src/β-catenin pathway. Front Pharmacol. 2020;11:310.
75. Liu T, Zhang L, Joo D, Sun S. NF-kappa B signaling in inflammation. Signal Transduct Target Ther. 2017;2:17023.
76. Yu H, Lin L, Zhang Z, Zhang H, Hu H. Targeting NF-kappa B pathway for the therapy of diseases: mechanism and clinical study. Signal Transduct Target Ther. 2020;5(1):209.
77. Zhong Z, Umemura A, Sanchez-Lopez E, Liang S, Shalapour S, Wong J, et al. NF-kappa B restricts inflammasome activation via elimination of damaged mitochondria. Cell. 2016;164(5):896–910.
78. Sun X, Icli B, Wara AK, Belkin N, He S, Kobzik L, et al. MicroRNA-181B regulates NF-kappa B-mediated vascular inflammation. J Clin Invest. 2012;122(6):1973–90.
79. Ghosh S, May M, Kopp E. NF-kappa B and REL proteins: evolutionarily conserved mediators of immune responses. Annu Rev Immunol. 1998;16:225–60.
80. Hayden MS, Ghosh S. Nf-kappa b, the first quarter-century: remarkable progress and outstanding questions. Genes Dev. 2012;26(3):203–34.
81. Christian F, Smith EL, Carmody RJ. The regulation of NF-kappa B subunits by phosphorylation. Cells. 2016;5(1):12.
82. Jiang WG, Ablin RJ. Cancer metastasis, challenges, progress and the opportunities. Front Biosci. 2011;3(1):391–4.
83. Afonina IS, Zhong Z, Karin M, Beyaert R. Limiting inflammation-the negative regulation of NF-kappa B and the NLRP3 inflammasome. Nat Immunol. 2017;18(8):861–9.
84. Mitchell JP, Carmody RJ. NF-kappa B and the transcriptional control of inflammation. Int Rev Cell Mol Biol. 2018;335:41–84.
85. Li C, Xia W, Huo L, Lim S, Wu Y, Hsu JL, et al. Epithelial-mesenchymal transition induced by TNF-alpha requires NF-kappa B-mediated transcriptional upregulation of Twist1. Cancer Res. 2012;72(5):1290–300.
86. Sigal LH. Basic science for the clinician 39-NF-kappa B—function, activation, control, and consequences. J Clin Rheumatol. 2006;12(4):207–11.
87. Gross CM, Kellner M, Wang T, Lu Q, Sun X, Zemskov EA, et al. LPS-induced acute lung injury involves NF-kappa B-mediated downregulation of SOX18. Am J Respir Cell Mol Biol. 2018;58(5):614–24.
88. Ju M, Liu B, He H, Gu Z, Liu Y, Su Y, et al. MicroRNA-27A alleviates lps-induced acute lung injury in mice via inhibiting inflammation and apoptosis through modulating TLR4/MyD88/NF-kappa B pathway. Cell Cycle. 2018;17(16):2001–18.
89. Liu H, Dong F, Li G, Niu M, Zhang C, Han Y, et al. Liuweiwuling tablets attenuate BDL-induced hepatic fibrosis via modulation of TGF-beta/smad and NF-kappa B signaling pathways. J Ethnopharmacol. 2018;210:232–41.
90. Blokland KEC, Waters DW, Schuliga M, Read J, Pouwels SD, Grainge CL, et al. Senescence of IPF lung fibroblasts disrupt alveolar epithelial cell proliferation and promote migration in wound healing. Pharmaceutics. 2020;12(4):389.
91. Lee J, La J, Aziz S, Brownell R, Jones K, Green G, et al. Molecular markers of telomere dysfunction and senescence are common findings in the usual interstitial pneumonia pattern of lung fibrosis. Eur Respir J. 2018;52:67–76.
92. Lopes-Paciencia S, Saint-Germain E, Rowell M, Ruiz AF, Kalegari P, Ferbeyre G. The senescence-associated secretory phenotype and its regulation. Cytokine. 2019;117:15–22.
93. Fafian-Labora JA, O'Loghlen A. Classical and nonclassical intercellular communication in senescence and ageing. Trends Cell Biol. 2020;30(8):628–39.
94. Lodyga M, Hinz B. TGF-beta 1-a truly transforming growth factor in fibrosis and immunity. Semin Cell Dev Biol. 2020;101:123–39.
95. Liu G, Philp AM, Corte T, Travis MA, Schilter H, Hansbro NG, et al. Therapeutic targets in lung tissue remodelling and fibrosis. Pharmacol Ther. 2021;225:107839.
96. Caja L, Dituri F, Mancarella S, Caballero-Diaz D, Moustakas A, Giannelli G, et al. TGF-beta and the tissue microenvironment: relevance in fibrosis and cancer. Int J Mol Sci. 2018;19(5):1294.

97. Kim KK, Sheppard D, Chapman HA. TGF-beta 1 signaling and tissue fibrosis. Cold Spring Harb Perspect Biol. 2018;10(4):a022293.
98. Hinz B. The extracellular matrix and transforming growth factor-beta 1: tale of a strained relationship. Matrix Biol. 2015;47:54–65.
99. Saito A, Horie M, Nagase T. TGF-beta signaling in lung health and disease. Int J Mol Sci. 2018;19(8):2460.
100. Walton KL, Johnson KE, Harrison CA. Targeting TGF-beta mediated smad signaling for the prevention of fibrosis. Front Pharmacol. 2017;8:461.
101. Hu HH, Chen DQ, Wang YN, Feng YL, Cao G, Vaziri ND, et al. New insights into TGF-beta/Smad signaling in tissue fibrosis. Chem Biol Interact. 2018;292:76–83.
102. Nagaoka I, Trapnell BC, Crystal RG. Upregulation of platelet-derived growth factor-B and -B gene expression in alveolar macrophages of individuals with idiopathic pulmonary fibrosis. J Clin Invest. 1990;85(6):2023–7.
103. Sasaki M, Kashima M, Ito T, Watanabe A, Izumiyama N, Sano M, et al. Differential regulation of metalloproteinase production, proliferation and chemotaxis of human lung fibroblasts by PDGF, interleukin-1β and TNF-α. Mediators Inflamm. 2000;9(3–4):155–60.
104. Li Q, Niu YM, Diao HJ, Wang LT, Chen XP, Wang YT, et al. In situ sequestration of endogenous PDGF-BB with an ECM-mimetic sponge for accelerated wound healing. Biomaterials. 2017;148:54–68.
105. Sun QZ, Liu L, Mandal J, Molino A, Stolz D, Tamm M, et al. PDGF-BB induces PRMT1 expression through ERK1/2 dependent STAT1 activation and regulates remodeling in primary human lung fibroblasts. Cell Signal. 2016;28(4):307–15.
106. Sato S, Shinohara S, Hayashi S, Morizumi S, Abe S, Okazaki H, et al. Antifibrotic efficacy of nintedanib in pulmonary fibrosis via the inhibition of fibrocyte activity. Respir Res. 2017;18(1):172.
107. Grimminger F, Gunther A, Vancheri C. The role of tyrosine kinases in the pathogenesis of idiopathic pulmonary fibrosis. Eur Respir J. 2015;45(5):1426–33.
108. Ruaro B, Salton F, Braga L, Wade B, Confalonieri P, Volpe MC, et al. The history and mystery of alveolar epithelial type II cells: focus on their physiologic and pathologic role in lung. Int J Mol Sci. 2021;22(5):2566.
109. van Geffen C, Deissler A, Quante M, Renz H, Hartl D, Kolahian S. Regulatory immune cells in idiopathic pulmonary fibrosis: friends or foes? Front Immunol. 2021;12:663203.
110. Klee S, Lehmann M, Wagner DE, Baarsma HA, Konigshoff M. WISP1 mediates IL-6-dependent proliferation in primary human lung fibroblasts. Sci Rep. 2016;6:20547.
111. Passalacqua G, Mincarini M, Colombo D, Troisi G, Ferrari M, Bagnasco D, et al. IL-13 and idiopathic pulmonary fibrosis: possible links and new therapeutic strategies. Pulm Pharmacol Ther. 2017;45:95–100.
112. Su SC, Zhao QY, He CH, Huang D, Liu J, Chen F, et al. miR-142-5p and miR-130a-3p are regulated by IL-4 and IL-13 and control profibrogenic macrophage program. Nat Commun. 2015;6:8523.
113. Song C, He LJ, Zhang J, Ma H, Yuan XN, Hu GY, et al. Fluorofenidone attenuates pulmonary inflammation and fibrosis via inhibiting the activation of NALP3 inflammasome and IL-1/IL-1R1/MyD88/NF-B pathway. J Cell Mol Med. 2016;20(11):2064–77.
114. Sziksz E, Pap D, Lippai R, Beres NJ, Fekete A, Szabo AJ, et al. Fibrosis related inflammatory mediators: role of the IL-10 cytokine family. Mediators Inflamm. 2015;2015:764641.
115. Huang M, Sharma S, Zhu LX, Keane MP, Luo J, Zhang L, et al. IL-7 inhibits fibroblast TGF-beta production and signaling in pulmonary fibrosis. J Clin Invest. 2002;109(7):931–7.
116. Groves AM, Johnston CJ, Misra RS, Williams JP, Finkelstein JN. Effects of IL-4 on pulmonary fibrosis and the accumulation and phenotype of macrophage subpopulations following thoracic irradiation. Int J Radiat Biol. 2016;92(12):754–65.
117. Liu Y, Lu F, Kang LR, Wang ZH, Wang YF. Pirfenidone attenuates bleomycin-induced pulmonary fibrosis in mice by regulating Nrf2/Bach1 equilibrium. BMC Pulm Med. 2017;17(1):63.
118. Sun L, Louie MC, Vannella KM, Wilke CA, LeVine AM, Moore BB, et al. New concepts of IL-10-induced lung fibrosis: fibrocyte recruitment and M2 activation in a CCL2/CCR2 axis. Am J Physiol Lung Cell Mol Physiol. 2011;300(3):L341–53.
119. Kuroki M, Noguchi Y, Shimono M, Tomono K, Tashiro T, Obata Y, et al. Repression of bleomycin-induced pneumopathy by TNF. J Immunol. 2003;170(1):567–74.
120. Sinclair K, Yerkovich ST, Chambers DC. Mesenchymal stem cells and the lung. Respirology. 2013;18(3):397–411.
121. Huang XP, Wang X, Xie XL, Zeng SL, Li ZF, Xu XX, et al. Kallistatin protects against bleomycin-induced idiopathic pulmonary fibrosis by inhibiting angiogenesis and inflammation. Am J Transl Res. 2017;9(3):999–1011.
122. Dinarello CA. Role of pro- and anti-inflammatory cytokines during inflammation: experimental and clinical findings. J Biol Regul Homeost Agents. 1997;11(3):91–103.
123. Hou J, Ma T, Cao H, Chen Y, Wang C, Chen X, et al. Tnf-α-induced nf-κb activation promotes myofibroblast differentiation of lr-mscs and exacerbates bleomycin-induced pulmonary fibrosis. J Cell Physiol. 2018;233(3):2409–19.
124. King TEJ, Pardo A, Selman M. Idiopathic pulmonary fibrosis. Lancet. 2011;378(9807):1949–61.
125. Ikegami T, Zhang Y, Matsuzaki Y. Liver fibrosis: possible involvement of EMT. Cells Tissues Organs. 2007;185(1–3):213–21.
126. Tanjore H, Xu XC, Polosukhin VV, Degryse AL, Li B, Han W, et al. Contribution of epithelial-derived fibroblasts to bleomycin-induced lung fibrosis. Am J Respir Crit Care Med. 2009;180(7):657–65.
127. Kim KK, Sisson TH, Horowitz JC. Fibroblast growth factors and pulmonary fibrosis: it's more complex than it sounds. J Pathol. 2017;241(1):6–09.
128. Desai P, Yang J, Tian B, Sun H, Kalita M, Ju H, et al. Mixed-effects model of epithelial-mesenchymal transition reveals rewiring of signaling networks. Cell Signal. 2015;27(7):1413–25.
129. Ji X, Li C, Ou Y, Li N, Yuan K, Yang G, et al. Andrographolide ameliorates diabetic nephropathy by attenuating hyperglycemia-mediated renal oxidative stress and inflammation via Akt/NF-κB pathway. Mol Cell Endocrinol. 2016;437:268–79.
130. Kayastha F, Johar K, Gajjar D, Arora A, Madhu H, Ganatra D, et al. Andrographolide suppresses epithelial mesenchymal transition by inhibition of MAPK signalling pathway in lens epithelial cells. J Biosci. 2015;40(2):313–24.
131. Karkale S, Khurana A, Saifi MA, Godugu C, Talla V. Andrographolide ameliorates silica induced pulmonary fibrosis. Int Immunopharmacol. 2018;62:191–202.
132. Li J, Feng M, Sun R, Li Z, Hu L, Peng G, et al. Andrographolide ameliorates bleomycin-induced pulmonary fibrosis by suppressing cell proliferation and myofibroblast differentiation of fibroblasts via the TGF-β1-mediated smad-dependent and -independent pathways. Toxicol Lett. 2020;321:103–13.
133. Li J, Liu J, Yue W, Xu K, Cai W, Cui F, et al. Andrographolide attenuates epithelial-mesenchymal transition induced by TGF-β1 in alveolar epithelial cells. J Cell Mol Med. 2020;24(18):10501–11.
134. Li J, Yang X, Yang P, Xu K, Peng X, Cai W, et al. Andrographolide alleviates bleomycin-induced NLRP3 inflammasome activation and epithelial-mesenchymal transition in lung epithelial cells by suppressing AKT/mTOR signaling pathway. Ann Transl Med. 2021;9(9):764.
135. Zhou L, Gao R, Hong H, Li X, Yang J, Shen W, et al. Emodin inhibiting neutrophil elastase-induced epithelial-mesenchymal transition through Notch1 signalling in alveolar epithelial cells. J Cell Mol Med. 2020;24(20):11998–2007.
136. Pang X, Shao L, Nie X, Yan H, Li C, Yeo AJ, et al. Emodin attenuates silica-induced lung injury by inhibition of inflammation, apoptosis and epithelial-mesenchymal transition. Int Immunopharmacol. 2021;91:107277.
137. Tao L, Cao J, Wei W, Xie H, Zhang M, Zhang C. Protective role of rhapontin in experimental pulmonary fibrosis in vitro and in vivo. Int Immunopharmacol. 2017;47:38–46.
138. Liu M, Xu H, Zhang L, Zhang C, Yang L, Ma E, et al. Salvianolic acid B inhibits myofibroblast transdifferentiation in experimental pulmonary fibrosis via the up-regulation of Nrf2. Biochem Biophys Res Commun. 2018;495(1):325–31.
139. Zhang Q, Gan C, Liu H, Wang L, Li Y, Tan Z, et al. Cryptotanshinone reverses the epithelial-mesenchymal transformation process and attenuates bleomycin-induced pulmonary fibrosis. Phytother Res PTR. 2020;34(10):2685–96.
140. Zhang R, Xu L, An X, Sui X, Lin S. Astragalus polysaccharides attenuate pulmonary fibrosis by inhibiting the epithelial-mesenchymal transition and NF-κB pathway activation. Int J Mol Med. 2020;46(1):331–9.

141. Zhao H, Li C, Li L, Liu J, Gao Y, Mu K, et al. Baicalin alleviates bleomycin-induced pulmonary fibrosis and fibroblast proliferation in rats via the PI3K/AKT signaling pathway. Mol Med Rep. 2020;21(6):2321–34.
142. Lu J, Zhong Y, Lin Z, Lin X, Chen Z, Wu X, et al. Baicalin alleviates radiation-induced epithelial-mesenchymal transition of primary type II alveolar epithelial cells via TGF-β and ERK/GSK3**B** signaling pathways. Biomed Pharmacother. 2017;95:1219–24.
143. Cui X, Sun X, Lu F, Jiang X. Baicalein represses TGF-β1-induced fibroblast differentiation through the inhibition of miR-21. Toxicol Appl Pharmacol. 2018;358:35–42.
144. Liu X, Shao Y, Zhang X, Ji X, Xie M, Liu H. Calycosin attenuates pulmonary fibrosis by the epithelial-mesenchymal transition repression upon inhibiting the AKT/GSK3**B**/β-catenin signaling pathway. Acta Histochem. 2021;123(5):151746.
145. Chen X, Chen X, Shi X, Gao Z, Guo Z. Curcumin attenuates endothelial cell fibrosis through inhibiting endothelial-interstitial transformation. Clin Exp Pharmacol Physiol. 2020;47(7):1182–92.
146. Shaikh SB, Prabhu A, Bhandary YP. Curcumin suppresses epithelial growth factor receptor (EGFR) and proliferative protein (Ki 67) in acute lung injury and lung fibrosis in vitro and in vivo. Endocr Metab Immune Disord Drug Targets. 2020;20(4):558–63.
147. Shaikh SB, Prabhu A, Bhandary YP. Curcumin targets p53-fibrinolytic system in TGF-β1 mediated alveolar epithelial mesenchymal transition in alveolar epithelial cells. Endocr Metab Immune Disord Drug Targets. 2021;21(8):1441–52.
148. Tyagi N, Singh DK, Dash D, Singh R. Curcumin modulates paraquat-induced epithelial to mesenchymal transition by regulating transforming growth factor-β (TGF-β) in A549 cells. Inflammation. 2019;42(4):1441–55.
149. Chang W, Chen C, Sheu C, Liao S, Hsu Y, Tsai M, et al. The potential effects of curcumin on pulmonary fibroblasts of idiopathic pulmonary fibrosis (IPF)-approaching with next-generation sequencing and bioinformatics. Molecules. 2020;25(22):5458.
150. Saidi A, Kasabova M, Vanderlynden L, Wartenberg M, Kara-Ali GH, Marc D, et al. Curcumin inhibits the TGF-β1-dependent differentiation of lung fibroblasts via PPARγ-driven upregulation of cathepsins B and L. Sci Rep. 2019;9(1):491.
151. Miao Y, Zhang Y, Qiao S, Xia Y, Wei Z, Dai Y. Oral administration of curcumin ameliorates pulmonary fibrosis in mice through 15d-PGJ2-mediated induction of hepatocyte growth factor in the colon. Acta Pharmacol Sin. 2021;42(3):422–35.
152. An L, Peng L, Sun N, Yang Y, Zhang X, Li B, et al. Tanshinone iia activates nuclear factor-erythroid 2-related factor 2 to restrain pulmonary fibrosis via regulation of redox homeostasis and glutaminolysis. Antioxid Redox Signal. 2019;30(15):1831–48.
153. Jiang L, Wang J, Ju J, Dai J. Salvianolic acid b and sodium tanshinone II A sulfonate prevent pulmonary fibrosis through anti-inflammatory and anti-fibrotic process. Eur J Pharmacol. 2020;883:173352.
154. Takano M, Deguchi J, Senoo S, Izumi M, Kawami M, Yumoto R. Suppressive effect of quercetin against bleomycin-induced epithelial-mesenchymal transition in alveolar epithelial cells. Drug Metab Pharmacokinet. 2020;35(6):522–6.
155. Zhang X, Cai Y, Zhang W, Chen X. Quercetin ameliorates pulmonary fibrosis by inhibiting Sphk1/S1P signaling. Biochem Cell Biol. 2018;96(6):742–51.
156. Liu Y, Chen B, Nie J, Zhao G, Zhuo J, Yuan J, et al. Polydatin prevents bleomycin-induced pulmonary fibrosis by inhibiting the TGF-β/Smad/ERK signaling pathway. Exp Ther Med. 2020;20(5):62.
157. Qiu Y, Pan X, Hu Y. Polydatin ameliorates pulmonary fibrosis by suppressing inflammation and the epithelial mesenchymal transition via inhibiting the TGF-β/Smad signaling pathway. Rsc Adv. 2019;9(14):8104–12.
158. Hou Y, Zhen Y, Xue Q, Wang W. Astragaloside IV attenuates TGF-β-mediated epithelial-mesenchymal transition of pulmonary fibrosis via suppressing NLRP3 expression in vitro. Pharmazie. 2021;76(2):97–102.
159. Qian W, Cai X, Qian Q, Zhang W, Wang D. Astragaloside IV modulates TGF-β1-dependent epithelial-mesenchymal transition in bleomycin-induced pulmonary fibrosis. J Cell Mol Med. 2018;22(9):4354–65.
160. Zhang P, Liu J, Zong R. Triptolide protects against TGF-β1-induced pulmonary fibrosis by regulating FAK/calpain signaling. Exp Ther Med. 2019;18(6):4781–9.
161. Chen H, Chen Q, Jiang C, Shi G, Sui B, Zhang W, et al. Triptolide suppresses paraquat induced idiopathic pulmonary fibrosis by inhibiting TGFB1-dependent epithelial mesenchymal transition. Toxicol Lett. 2018;284:1–9.
162. Zhuang WY, Zhao N, Li D, Su XM, Wang YY, Chen JG, et al. Schisantherin a inhibits pulmonary fibrosis via regulating ERK signaling pathway. Nat Prod Commun. 2020;15(8):1934578X2094835.
163. Wang Y, Dong X, Zhao N, Su X, Wang Y, Li Y, et al. Schisandrin b attenuates bleomycin-induced pulmonary fibrosis in mice through the wingless/integrase-1 signaling pathway. Exp Lung Res. 2020;46(6):185–94.
164. Li XH, Huang MY, Liu F, Gao SY, Bai JK, Liu SS, et al. Analysis of chemical composition of inula japonica thumb. Extract and in vitro screening for anti-pulmonary fibrosis active components. Phytochem Lett. 2020;36:144–9.
165. Zhao W, Luan Z, Liu T, Ming W, Huo X, Huang H, et al. Inula japonica ameliorated bleomycin-induced pulmonary fibrosis via inhibiting soluble epoxide hydrolase. Bioorg Chem. 2020;102:104065.
166. Ali SA, Saifi MA, Pulivendala G, Godugu C, Talla V. Ferulic acid ameliorates the progression of pulmonary fibrosis via inhibition of TGF-β/Smad signalling. Food Chem Toxicol. 2021;149:111980.
167. Du M, Duan J, Zhang C, Yang H, Guan X, Zhong W, et al. Psoralen attenuates bleomycin-induced pulmonary fibrosis in mice through inhibiting myofibroblast activation and collagen deposition. Cell Biol Int. 2019;44(1):98–107.
168. Zeng H, Gao H, Zhang M, Wang J, Gu Y, Wang Y, et al. Atractylon treatment attenuates pulmonary fibrosis via regulation of the mmu_circ_0000981/miR-211-5p/TGFBR2 axis in an ovalbumin-induced asthma mouse model. Inflammation. 2021;44(5):1856–64.
169. Qian W, Cai X, Qian Q, Wang D, Zhang L. Angelica sinensis polysaccharide suppresses epithelial-mesenchymal transition and pulmonary fibrosis via a DANCR/AUF-1/FOXO3 regulatory axis. Aging Dis. 2020;11(1):17–30.
170. Li X, Xiao T, Yang J, Qin Y, Gao J, Liu H, et al. Parthenolide attenuated bleomycin-induced pulmonary fibrosis via the NF-κB/snail signaling pathway. Respir Res. 2018;19(1):111.
171. Peng L, Wen L, Shi Q, Gao F, Huang B, Meng J, et al. Scutellarin ameliorates pulmonary fibrosis through inhibiting NF-κB/NLRP3-mediated epithelial-mesenchymal transition and inflammation. Cell Death Dis. 2020;11(11):978.
172. Miao K, Pan T, Mou Y, Zhang L, Xiong W, Xu Y, et al. Scutellarein inhibits blm-mediated pulmonary fibrosis by affecting fibroblast differentiation, proliferation, and apoptosis. Ther Adv Chronic Dis. 2020;11:1754231961.
173. Li C, Yu Y, Li W, Liu B, Jiao X, Song X, et al. Phycocyanin attenuates pulmonary fibrosis via the TLR2-Myd88-NF-κB signaling pathway. Sci Rep. 2017;7(1):5843.
174. Liu P, Miao K, Zhang L, Mou Y, Xu Y, Xiong W, et al. Curdione ameliorates bleomycin-induced pulmonary fibrosis by repressing TGF-β-induced fibroblast to myofibroblast differentiation. Respir Res. 2020;21(1):58.
175. Ren ZX, Shen JL, Mei XF, Dong HR, Li JS, Yu HB. Hesperidin inhibits the epithelial to mesenchymal transition induced by transforming growth factor-beta 1 in A549 cells through smad signaling in the cytoplasm. Braz J Pharm Sci. 2019;55:e18172.
176. Wang L, Liu H, He Q, Gan C, Li Y, Zhang Q, et al. Galangin ameliorated pulmonary fibrosis in vivo and in vitro by regulating epithelial-mesenchymal transition. Bioorg Med Chem. 2020;28(19):115663.
177. Cui Y, Zhao J, Chen J, Kong Y, Wang M, Ma Y, et al. Cyanidin-3-galactoside from aronia melanocarpa ameliorates silica-induced pulmonary fibrosis by modulating the TGF-β/mTOR and NRF2/HO-1 pathways. Food Sci Nutr. 2022;10(8):2558–67.
178. Li H, Kan B, Song L, Liu Y, Jian X. Role of the hippo signaling pathway in safflower yellow pigment treatment of paraquat-induced pulmonary fibrosis. J Int Med Res. 2020;48(9):300060520905425.
179. Sun S, Han R, Hou S, Yi H, Chi S, Zhang A. Juglanin alleviates bleomycin-induced lung injury by suppressing inflammation and fibrosis via targeting sting signaling. Biomed Pharmacother. 2020;127:110119.

180. Dinesh Babu V, Suresh Kumar A, Sudhandiran G. Diosgenin inhibits TGF-β1/Smad signaling and regulates epithelial mesenchymal transition in experimental pulmonary fibrosis. Drug Chem Toxicol. 2022;45(3):1264–75.
181. Liu S, Yang Q, Dong B, Qi C, Yang T, Li M, et al. Gypenosides attenuate pulmonary fibrosis by inhibiting the AKT/mTOR/c-Myc pathway. Front Pharmacol. 2021;12:806312.
182. Li L, Ma L, Wang D, Jia H, Yu M, Gu Y, et al. Design and synthesis of matrine derivatives as novel anti-pulmonary fibrotic agents via repression of the TGF**B**/Smad pathway. Molecules. 2019;24(6):1108.
183. Peng Y, Zhang Y, Zhang Y, Wang X, Xia Y. Pterostilbene alleviates pulmonary fibrosis by regulating ASIC2. Chin Med. 2021;16(1):66.
184. Li Q, Peng W, Zhang Z, Pei X, Sun Z, Ou Y. A phycocyanin derived eicosapeptide attenuates lung fibrosis development. Eur J Pharmacol. 2021;908:174356.
185. Yang J, Tao L, Liu B, You X, Zhang C, Xie H, et al. Wedelolactone attenuates pulmonary fibrosis partly through activating AMPK and regulating Raf-MAPKs signaling pathway. Front Pharmacol. 2019;10:151.
186. Guo P, Li B, Liu M, Li Y, Weng G, Gao Y. Protective effects of lotus plumule ethanol extracts on bleomycin-induced pulmonary fibrosis in mice. Drug Chem Toxicol. 2022;45(3):1432–41.
187. Chen C, Wang Y, Wang Y, Cheng M, Yin J, Zhang X, et al. Gentiopicroside ameliorates bleomycin-induced pulmonary fibrosis in mice via inhibiting inflammatory and fibrotic process. Biochem Biophys Res Commun. 2018;495(4):2396–403.
188. Liu B, Yang JY, Hao JT, Xie HF, Shimizu K, Li RS, et al. Natural product mogrol attenuates bleomycin-induced pulmonary fibrosis development through promoting AMPK activation. J Funct Foods. 2021;77(8):104280.
189. Jia L, Sun P, Gao H, Shen J, Gao Y, Meng C, et al. Mangiferin attenuates bleomycin-induced pulmonary fibrosis in mice through inhibiting TLR4/p65 and TGF-β1/Smad2/3 pathway. J Pharm Pharmacol. 2019;71(6):1017–28.
190. Chang K, Zhang X, Lin S, Lin Y, Li C, Akhrymuk I, et al. Atractylodin suppresses TGF-β-mediated epithelial-mesenchymal transition in alveolar epithelial cells and attenuates bleomycin-induced pulmonary fibrosis in mice. Int J Mol Sci. 2021;22(20):11152.
191. Wang Q, Yu J, Hu Y, Chen X, Zhang L, Pan T, et al. Indirubin alleviates bleomycin-induced pulmonary fibrosis in mice by suppressing fibroblast to myofibroblast differentiation. Biomed Pharmacother. 2020;131:110715.
192. Fu Z, Xu Y, Cai C. Ginsenoside Rg3 inhibits pulmonary fibrosis by preventing HIF-1α nuclear localisation. Bmc Pulm Med. 2021;21(1):70.
193. Su X, Liu K, Xie Y, Zhang M, Wu X, Zhang Y, et al. Mushroom inonotus sanghuang alleviates experimental pulmonary fibrosis: implications for therapy of pulmonary fibrosis. Biomed Pharmacother. 2021;133:110919.
194. Zheng Q, Tong M, Ou B, Liu C, Hu C, Yang Y. Isorhamnetin protects against bleomycin-induced pulmonary fibrosis by inhibiting endoplasmic reticulum stress and epithelial-mesenchymal transition. Int J Mol Med. 2019;43(1):117–26.
195. Liu L, Yu N, Leng W, Lu Y, Xia X, Yuan H. 6-Gingerol, a functional polyphenol of ginger, reduces pulmonary fibrosis by activating Sirtuin1. Allergol Immunopathol. 2022;50(2):104–14.
196. Ali SA, Saifi MA, Godugu C, Talla V. Silibinin alleviates silica-induced pulmonary fibrosis: potential role in modulating inflammation and epithelial-mesenchymal transition. Phytother Res. 2021;35(9):5290–304.
197. Xiao T, Wei Y, Cui M, Li X, Ruan H, Zhang L, et al. Effect of dihydromyricetin on SARS-cov-2 viral replication and pulmonary inflammation and fibrosis. Phytomedicine. 2021;91:153704.
198. Li Z, Geng J, Xie B, He J, Wang J, Peng L, et al. Dihydromyricetin alleviates pulmonary fibrosis by regulating abnormal fibroblasts through the Stat3/p-Stat3/Glut1 signaling pathway. Front Pharmacol. 2022;13:834604.
199. Chen J, Lu J, Wang B, Zhang X, Huang Q, Yuan J, et al. Polysaccharides from dendrobium officinale inhibit bleomycin-induced pulmonary fibrosis via the TGF**B**1-Smad2/3 axis. Int J Biol Macromol. 2018;118(Pt B):2163–75.
200. Reed EB, Ard S, La J, Park CY, Culligan L, Fredberg JJ, et al. Anti-fibrotic effects of tannic acid through regulation of a sustained TGF-beta receptor signaling. Respir Res. 2019;20(1):168.
201. Huang J, Tong X, Zhang L, Zhang Y, Wang L, Wang D, et al. Hyperoside attenuates bleomycin-induced pulmonary fibrosis development in mice. Front Pharmacol. 2020;11:550955.
202. Wang Z, Fang K, Wang G, Guan X, Pang Z, Guo Y, et al. Protective effect of amygdalin on epithelial-mesenchymal transformation in experimental chronic obstructive pulmonary disease mice. Phytother Res PTR. 2019;33(3):808–17.
203. Cui Y, Xin H, Tao Y, Mei L, Wang Z. Arenaria kansuensis attenuates pulmonary fibrosis in mice via the activation of Nrf2 pathway and the inhibition of NF-kB/TGF-beta1/Smad2/3 pathway. Phytother Res. 2021;35(2):974–86.
204. Li X, Yu H, Liang L, Bi Z, Wang Y, Gao S, et al. Myricetin ameliorates bleomycin-induced pulmonary fibrosis in mice by inhibiting TGF-β signaling via targeting HSP90β. Biochem Pharmacol. 2020;178:114097.
205. Hua Q, Huang X, Xie W, Zhao F, Cheng H, Luo Z, et al. Pparγ mediates the anti-pulmonary fibrosis effect of icaritin. Toxicol Lett. 2021;350:81–90.
206. Shen Y, Cheng M, Liu X, Zhu D, Gao J. Sodium houttuyfonate inhibits bleomycin induced pulmonary fibrosis in mice. Front Pharmacol. 2021;12:596492.
207. Li X, Liu S, Zhai Y, Cao X, Gao S, Huang M, et al. In vitro screening for compounds from hypericum longistylum with anti-pulmonary fibrosis activity. Bioorg Med Chem Lett. 2019;29(22):126695.
208. Guo J, Fang Y, Jiang F, Li L, Zhou H, Xu X, et al. Neohesperidin inhibits TGF-β1/Smad3 signaling and alleviates bleomycin-induced pulmonary fibrosis in mice. Eur J Pharmacol. 2019;864:172712.
209. Ma W, Huang Q, Xiong G, Deng L, He Y. The protective effect of hederagenin on pulmonary fibrosis by regulating the Ras/JNK/NFAT4 axis in rats. Biosci Biotechnol Biochem. 2020;84(6):1131–8.
210. Jiang J, Wang F, Luo A, Lin S, Feng X, Yan W, et al. Polyporus polysaccharide ameliorates bleomycin-induced pulmonary fibrosis by suppressing myofibroblast differentiation via TGF-β/Smad2/3 pathway. Front Pharmacol. 2020;11:767.
211. Li A, Xiao X, Feng Z, Chen X, Liu L, Lin L, et al. Nagilactone d ameliorates experimental pulmonary fibrosis in vitro and in vivo via modulating TGF-β/Smad signaling pathway. Toxicol Appl Pharmacol. 2020;389:114882.
212. Cheresh P, Kim S, Tulasiram S, Kamp DW. Oxidative stress and pulmonary fibrosis. Biochim Biophys Acta. 2013;1832(7):1028–40.
213. Masamune A, Watanabe T, Kikuta K, Satoh K, Shimosegawa T. Nadph oxidase plays a crucial role in the activation of pancreatic stellate cells. Am J Physiol Gastrointest Liver Physiol. 2008;294(1):G99-108.
214. Birben E, Sahiner UM, Sackesen C, Erzurum S, Kalayci O. Oxidative stress and antioxidant defense. World Allergy Organ J. 2012;5(1):9–19.
215. Daniil ZD, Papageorgiou E, Koutsokera A, Kostikas K, Kiropoulos T, Papaioannou AI, et al. Serum levels of oxidative stress as a marker of disease severity in idiopathic pulmonary fibrosis. Pulm Pharmacol Ther. 2008;21(1):26–31.
216. Rodriguez LR, Bui SN, Beuschel RT, Ellis E, Liberti EM, Chhina MK, et al. Curcumin induced oxidative stress attenuation by N-acetylcysteine co-treatment: a fibroblast and epithelial cell in-vitro study in idiopathic pulmonary fibrosis. Mol Med. 2019;25(1):27.
217. Nathan C. Points of control in inflammation. Nature. 2002;420(6917):846–52.
218. Nathan C, Ding A. Nonresolving inflammation. Cell. 2010;140(6):871–82.
219. Wuyts WA, Agostini C, Antoniou KM, Bouros D, Chambers RC, Cottin V, et al. The pathogenesis of pulmonary fibrosis: a moving target. Eur Respir J. 2013;41(5):1207–18.
220. Gorowiec MR, Borthwick LA, Parker SM, Kirby JA, Saretzki GC, Fisher AJ. Free radical generation induces epithelial-to-mesenchymal transition in lung epithelium via a TGF-β1-dependent mechanism. Free Radic Biol Med. 2012;52(6):1024–32.
221. Cameli P, Carleo A, Bergantini L, Landi C, Prasse A, Bargagli E. Oxidant/antioxidant disequilibrium in idiopathic pulmonary fibrosis pathogenesis. Inflammation. 2020;43(1):1–7.
222. Otoupalova E, Smith S, Cheng G, Thannickal VJ. Oxidative stress in pulmonary fibrosis. Compr Physiol. 2020;10(2):509–47.
223. Rim H, Moon P, Choi I, Lee E, Kim H, Jeong H. Sososo or its active ingredient chrysophanol regulates production of inflammatory cytokines & adipokine in both macrophages & adipocytes. Indian J Med Res. 2013;137(1):142–50.

224. Chen J, Ma M, Lu Y, Wang L, Wu C, Duan H. Rhaponticin from rhubarb rhizomes alleviates liver steatosis and improves blood glucose and lipid profiles in KK/Ay diabetic mice. Planta Med. 2009;75(5):472–7.
225. Tian S, Yang Y, Liu X, Xu Q. Emodin attenuates bleomycin-induced pulmonary fibrosis via anti-inflammatory and anti-oxidative activities in rats. Med Sci Monit. 2018;24:1–10.
226. Qi XW, Ou YM, Xie Y, Cai KR, Gan HL, Wan QQ, et al. Chrysophanol administration alleviates bleomycin-induced pulmonary fibrosis by inhibiting lung fibroblast proliferation and wnt/beta-catenin signaling. Trop J Pharm Res. 2020;19(5):971–6.
227. Zhou L, Zuo Z, Chow MSS. Danshen: an overview of its chemistry, pharmacology, pharmacokinetics, and clinical use. J Clin Pharmacol. 2005;45(12):1345–59.
228. Peng L, An L, Sun N, Ma Y, Zhang X, Liu W, et al. *Salvia miltiorrhiza* restrains reactive oxygen species-associated pulmonary fibrosis via targeting Nrf2-Nox4 redox balance. Am J Chin Med. 2019;47(5):1113–31.
229. Feng F, Cheng P, Zhang H, Li N, Qi Y, Wang H, et al. The protective role of tanshinone iia in silicosis rat model via TGF-β1/Smad signaling suppression, NOX4 inhibition and Nrf2/ARE signaling activation. Drug Des Devel Ther. 2019;13:4275–90.
230. Liu Q, Shi X, Tang L, Xu W, Jiang S, Ding W, et al. Salvianolic acid b attenuates experimental pulmonary inflammation by protecting endothelial cells against oxidative stress injury. Eur J Pharmacol. 2018;840:9–19.
231. Zhu Z, Li Q, Xu C, Zhao J, Li S, Wang Y, et al. Sodium tanshinone iia sulfonate attenuates silica-induced pulmonary fibrosis in rats via activation of the Nrf2 and thioredoxin system. Environ Toxicol Pharmacol. 2020;80:103461.
232. Shaikh SB, Prabhakar BY. Effect of curcumin on il-17a mediated pulmonary AMPK kinase/cyclooxygenase-2 expressions via activation of NFkB in bleomycin-induced acute lung injury in vivo. Int Immunopharmacol. 2020;85:106676.
233. Chen H, Yang R, Tang Y, Fu X. Effects of curcumin on artery blood gas index of rats with pulmonary fibrosis caused by paraquat poisoning and the expression of Smad 4, Smurf 2, interleukin-4 and interferon-γ. Exp Ther Med. 2019;17(5):3664–70.
234. Ke S, Zhang Y, Lan Z, Li S, Zhu W, Liu L. Curcumin protects murine lung mesenchymal stem cells from H(2)O(2) by modulating the Akt/Nrf2/HO-1 pathway. J Int Med Res. 2020;48(4):300060520910665.
235. Durairaj P, Venkatesan S, Narayanan V, Babu M. Protective effects of curcumin on bleomycin-induced changes in lung glycoproteins. Mol Cell Biochem. 2020;469(1–2):159–67.
236. Ali YA, Ahmed AAE, Abd El-Raouf OM, Elkhoely A, Gad AM. Polydatin combats methotrexate-induced pulmonary fibrosis in rats: involvement of biochemical and histopathological assessment. J Biochem Mol Toxicol. 2022;36(5):e23019.
237. Chang H, Meng H, Bai W, Meng Q. A metabolomic approach to elucidate the inhibitory effects of baicalin in pulmonary fibrosis. Pharm Biol. 2021;59(1):1016–25.
238. Li N, Wu K, Feng F, Wang L, Zhou X, Wang W. Astragaloside iv alleviates silica-induced pulmonary fibrosis via inactivation of the TGF-β1/Smad2/3 signaling pathway. Int J Mol Med. 2021;47(3):16.
239. Guo K, Chen J, Chen Z, Luo G, Yang S, Zhang M, et al. Triptolide alleviates radiation-induced pulmonary fibrosis via inhibiting IKK**B** stimulated LOX production. Biochem Biophys Res Commun. 2020;527(1):283–8.
240. Qiu M, Yang Z, Bian M, Liu C, Zhao Y, Liu Q. Protective effects of isorhynchophylline against silicon-dioxide-induced lung injury in mice. Artif Cells Nanomed Biotechnol. 2020;48(1):1125–34.
241. Liu Z, Zhong J, Zhang M, Chen Z, Wang J, Chen H, et al. The alexipharmic mechanisms of five licorice ingredients involved in CYP450 and Nrf2 pathways in paraquat-induced mice acute lung injury. Oxid Med Cell Longev. 2019;2019:7283104.
242. Gad El-Hak HN, Mohamed OE, Nabil ZI. Evaluating the protective role of deglycyrrhizinated licorice root supplement on bleomycin induced pulmonary oxidative damage. Toxicol Mech Methods. 2022;32(3):180–93.
243. Jiang F, Li M, Wang H, Ding B, Zhang C, Ding Z, et al. Coelonin, an anti-inflammation active component of *Bletilla striata* and its potential mechanism. Int J Mol Sci. 2019;20(18):4422.
244. Peng L, Wen L, Shi Q, Gao F, Huang B, Wang C. Chelerythrine ameliorates pulmonary fibrosis via activating the Nrf2/ARE signaling pathway. Cell Biochem Biophys. 2021;79(2):337–47.
245. Ding Q, Sun J, Xie W, Zhang M, Zhang C, Xu X. Stemona alkaloids suppress the positive feedback loop between M2 polarization and fibroblast differentiation by inhibiting JAK2/Stat3 pathway in fibroblasts and CXCR4/PI(3)K/AKT1 pathway in macrophages. Int Immunopharmacol. 2019;72:385–94.
246. Huai B, Ding J. Atractylenolide III attenuates bleomycin-induced experimental pulmonary fibrosis and oxidative stress in rat model via Nrf2/NQO1/Ho-1 pathway activation. Immunopharmacol Immunotoxicol. 2020;42(5):436–44.
247. Yang F, Hou Z, Zhu H, Chen X, Li W, Cao R, et al. Catalpol protects against pulmonary fibrosis through inhibiting TGF-β1/Smad3 and Wnt/β-catenin signaling pathways. Front Pharmacol. 2020;11:594139.
248. Xie Y, Li W, Lu C, Zhu L, Qin S, Du Z. The effects of phycocyanin on bleomycin-induced pulmonary fibrosis and the intestinal microbiota in C57BL/6 mice. Appl Microbiol Biotechnol. 2019;103(20):8559–69.
249. Shariati S, Kalantar H, Pashmforoosh M, Mansouri E, Khodayar MJ. Epicatechin protective effects on bleomycin-induced pulmonary oxidative stress and fibrosis in mice. Biomed Pharmacother. 2019;114:108776.
250. Raish M, Ahmad A, Ahmad Ansari M, Ahad A, Al-Jenoobi FI, Al-Mohizea AM, et al. Sinapic acid ameliorates bleomycin-induced lung fibrosis in rats. Biomed Pharmacother. 2018;108:224–31.
251. Gan W, Li X, Cui Y, Xiao T, Liu R, Wang M, et al. Pinocembrin relieves lipopolysaccharide and bleomycin induced lung inflammation via inhibiting TLR4-NF-κB-NLRP3 inflammasome signaling pathway. Int Immunopharmacol. 2021;90:107230.
252. Tavares LA, Rezende AA, Santos JL, Estevam CS, Silva AMO, Schneider JK, et al. Cymbopogon winterianus essential oil attenuates bleomycin-induced pulmonary fibrosis in a murine model. Pharmaceutics. 2021;13(5):679.
253. Zhou Z, Kandhare AD, Kandhare AA, Bodhankar SL. Hesperidin ameliorates bleomycin-induced experimental pulmonary fibrosis via inhibition of TGF-b1/Smad3/AMPK and IkBa/NF-kB pathways. Excli J. 2019;2019(18):723–45.
254. Hu X, Huang X. Alleviation of inflammatory response of pulmonary fibrosis in acute respiratory distress syndrome by puerarin via transforming growth factor (TGF-β1). Med Sci Monit. 2019;25:6523–31.
255. Samareh Fekri M, Poursalehi HR, Sharififar F, Mandegary A, Rostamzadeh F, Mahmoodi R. The effects of methanolic extract of glycyrrhiza glabra on the prevention and treatment of bleomycin-induced pulmonary fibrosis in rat: experimental study. Comparative Study Drug Chem Toxicol. 2021;44(4):365–71.
256. Dong H, Xue T, Liu Y, He S, Yi Y, Zhang B, et al. Low molecular weight fucoidan inhibits pulmonary fibrosis in vivo and in vitro via antioxidant activity. Oxid Med Cell Longev. 2022;2022:7038834.
257. Liu S, Wang Y, Wen H, Sun X, Wang Y. Hydroxysafflor yellow a inhibits TNF-α-induced inflammation of human fetal lung fibroblasts via Nf-κB signaling pathway. Evid Based Complement Alternat Med. 2019;2019:4050327.
258. Jin M, Wang L, Wu Y, Zang B, Tan L. Protective effect of hydroxysafflor yellow a on bleomycin- induced pulmonary inflammation and fibrosis in rats. Chin J Integr Med. 2018;24(1):32–9.
259. Bai L, Li A, Gong C, Ning X, Wang Z. Protective effect of rutin against bleomycin induced lung fibrosis: involvement of TGF-β1/α-SMA/Col I and III pathway. BioFactors. 2020;46(4):637–44.
260. Guan C, Qiao S, Lv Q, Cao N, Wang K, Dai Y, et al. Orally administered berberine ameliorates bleomycin-induced pulmonary fibrosis in mice through promoting activation of PPAR-γ and subsequent expression of HGF in colons. Toxicol Appl Pharmacol. 2018;343:1–15.
261. Tong J, Wu Z, Wang Y, Hao Q, Liu H, Cao F, et al. Astragaloside IV synergizing with ferulic acid ameliorates pulmonary fibrosis by TGF-β1/Smad3 signaling. Evid Based Complement Alternat Med. 2021;2021:8845798.
262. Luo J, Zhang T, Zhu C, Sun J, Zhu W, Ai W, et al. Asiaticoside might attenuate bleomycin-induced pulmonary fibrosis by activating cAMP and Rap1 signalling pathway assisted by A2AR. J Cell Mol Med. 2020;24(14):8248–61.

263. Zhang T, Dai J, Ye W, Cai L, Wei J, Chen M, et al. Asiaticoside attenuates bleomycin-induced pulmonary fibrosis in A2aR(-/-) mice by promoting the BMP7/Smad1/5 signaling pathway. Biochem Biophys Res Commun. 2020;527(3):662–7.
264. Qiu M, An M, Bian M, Yu S, Liu C, Liu Q. Terrestrosin d from tribulus terrestris attenuates bleomycin-induced inflammation and suppresses fibrotic changes in the lungs of mice. Pharm Biol. 2019;57(1):694–700.
265. Gungor H, Ekici M, Onder Karayigit M, Turgut NH, Kara H, Arslanbas E. Zingerone ameliorates oxidative stress and inflammation in bleomycin-induced pulmonary fibrosis: modulation of the expression of TGF-β1 and iNOS. Naunyn Schmiedebergs Arch Pharmacol. 2020;393(9):1659–70.
266. Zhao J, Zang J, Lin Y, Wang YH, Li DN, Meng XJ. Polyphenol-rich blue honeysuckle extract alleviates silica-induced lung fibrosis by modulating th immune response and NRF2/Ho-1 mapk signaling. J Funct Foods. 2019;53:176–86.
267. Zhao J, Ma JX, Zhang Q, Tian JL, Wang YH, Meng XJ. Cyanidin-3-glucoside attenuates silica-induced pulmonary inflammatory responses by modulating t cell immune responses and STAT1/STAT3 signaling. J Funct Foods. 2020;68:103911.
268. Yang H, Hua C, Yang X, Fan X, Song H, Peng L, et al. Pterostilbene prevents lps-induced early pulmonary fibrosis by suppressing oxidative stress, inflammation and apoptosis in vivo. Food Funct. 2020;11(5):4471–84.
269. Wang Y, Li Y, Wang X, Li X, Chen Y, Yang L, et al. Effect of total flavonoids of oxytropis falcata bunge on the expression of p-JAK1-and p-STAT1-related proteins in idiopathic pulmonary fibrosis. Evid Based Complement Alternat Med. 2020;2020:2407239.
270. Zhao S, Zuo W, Chen H, Bao T, Liu X, Sun T, et al. Effects of pilose antler peptide on bleomycin-induced pulmonary fibrosis in mice. Biomed Pharmacother. 2019;109:2078–83.
271. Rong Y, Cao B, Liu B, Li W, Chen Y, Chen H, et al. A novel gallic acid derivative attenuates blm-induced pulmonary fibrosis in mice. Int Immunopharmacol. 2018;64:183–91.
272. Fu X, Li T, Yao Q. The effect of ophiopogonin c in ameliorating radiation-induced pulmonary fibrosis in C57BL/6 mice: an update study. Front Oncol. 2022;12:811183.
273. Zhang T, Ma S, Liu C, Hu K, Xu M, Wang R. Rosmarinic acid prevents radiation-induced pulmonary fibrosis through attenuation of ROS/MYPT1/TGF**B**1 signaling via miR-19b-3p. Dose Response. 2020;18(4):1559325820968413.
274. Kalantar H, Sadeghi E, Abolnezhadian F, Goudarzi M, Hemmati AA, Basir Z, et al. Carnosol attenuates bleomycin-induced lung damage via suppressing fibrosis, oxidative stress and inflammation in rats. Life Sci. 2021;287:120059.
275. Kseibati MO, Sharawy MH, Salem HA. Chrysin mitigates bleomycin-induced pulmonary fibrosis in rats through regulating inflammation, oxidative stress, and hypoxia. Int Immunopharmacol. 2020;89(Pt A):107011.
276. Liu B, Rong Y, Sun D, Li W, Chen H, Cao B, et al. Costunolide inhibits pulmonary fibrosis via regulating NF-kB and TGF-β(1)/Smad(2)/Nrf(2)-NOX(4) signaling pathways. Biochem Biophys Res Commun. 2019;510(2):329–33.
277. Wang Z, Li X, Chen H, Han L, Ji X, Wang Q, et al. Resveratrol alleviates bleomycin-induced pulmonary fibrosis via suppressing HIF-1α and Nf-κB expression. Aging. 2021;13(3):4605–16.
278. Ding S, Wang H, Wang M, Bai L, Yu P, Wu W. Resveratrol alleviates chronic "real-world" ambient particulate matter-induced lung inflammation and fibrosis by inhibiting nlrp3 inflammasome activation in mice. Ecotoxicol Environ Saf. 2019;182:109425.
279. Yang G, Lyu L, Wang X, Bao L, Lyu B, Lin Z. Systemic treatment with resveratrol alleviates adjuvant arthritis-interstitial lung disease in rats via modulation of JAK/STAT/RANKL signaling pathway. Pulm Pharmacol Ther. 2019;56:69–74.
280. Sul OJ, Kim JH, Lee T, Seo KW, Cha HJ, Kwon B, et al. Gspe protects against bleomycin-induced pulmonary fibrosis in mice via ameliorating epithelial apoptosis through inhibition of oxidative stress. Oxid Med Cell Longev. 2022;2022:8200189.
281. You X, Jiang X, Zhang C, Jiang K, Zhao X, Guo T, et al. Dihydroartemisinin attenuates pulmonary inflammation and fibrosis in rats by suppressing JAK2/STAT3 signaling. Aging. 2022;14(3):1110–27.
282. Yang D, Qiu J, Zhou H, Yu Y, Zhou D, Xu Y, et al. Dihydroartemisinin alleviates oxidative stress in bleomycin-induced pulmonary fibrosis. Life Sci. 2018;205:176–83.
283. Yao Y, Yuan Y, Lu Z, Ma Y, Xie Y, Wang M, et al. Effects of *Nervilia fordii* extract on pulmonary fibrosis through TGF-β/smad signaling pathway. Front Pharmacol. 2021;12:659627.
284. Choi YH. Trans-cinnamaldehyde prevents oxidative stress-induced apoptosis in V79-4 Chinese hamster lung fibroblasts through the Nrf2-mediated HO-1 activation. Biol Pharm Bull. 2020;43(11):1707–14.
285. Zhang J, Li Q, Shao Q, Song J, Zhou B, Shu P. Effects of panax notoginseng saponin on the pathological ultrastructure and serum il-6 and il-8 in pulmonary fibrosis in rabbits. J Cell Biochem. 2018;119(10):8410–8.
286. Li R, Xu G, Cao J, Liu B, Xie H, Ishii Y, et al. Alpha-mangostin ameliorates bleomycin-induced pulmonary fibrosis in mice partly through activating adenosine 5′-monophosphate-activated protein kinase. Front Pharmacol. 2019;10:1305.
287. Fang L, Wang W, Chen J, Zuo A, Gao H, Yan T, et al. Osthole attenuates bleomycin-induced pulmonary fibrosis by modulating nadph oxidase 4-derived oxidative stress in mice. Oxid Med Cell Longev. 2021;2021:3309944.
288. Liang Q, Cai W, Zhao Y, Xu H, Tang H, Chen D, et al. Lycorine ameliorates bleomycin-induced pulmonary fibrosis via inhibiting NLRP3 inflammasome activation and pyroptosis. Pharmacol Res. 2020;158:104884.
289. Bahri S, Ben Ali R, Nahdi A, Mlika M, Abdennabi R, Jameleddine S. Salvia officinalis attenuates bleomycin-induced oxidative stress and lung fibrosis in rats. Nutr Cancer. 2020;72(7):1135–45.
290. Zhang D, Liu B, Cao B, Wei F, Yu X, Li G, et al. Synergistic protection of schizandrin b and glycyrrhizic acid against bleomycin-induced pulmonary fibrosis by inhibiting TGF-β1/Smad2 pathways and overexpression of NOX4. Int Immunopharmacol. 2017;48:67–75.
291. Mehrabani M, Goudarzi M, Mehrzadi S, Siahpoosh A, Mohammadi M, Khalili H, et al. Crocin: a protective natural antioxidant against pulmonary fibrosis induced by bleomycin. Pharmacol Rep. 2020;72(4):992–1001.
292. Zaghloul MS, Said E, Suddek GM, Salem HA. Crocin attenuates lung inflammation and pulmonary vascular dysfunction in a rat model of bleomycin-induced pulmonary fibrosis. Life Sci. 2019;235:116794.
293. Li W, Cai Z, Mehmood S, Wang Y, Pan W, Zhang W, et al. Polysaccharide FMP-1 from Morchella esculenta attenuates cellular oxidative damage in human alveolar epithelial A549 cells through PI3K/AKT/Nrf2/HO-1 pathway. Int J Biol Macromol. 2018;120(Pt A):865–75.
294. Zhu YP, Lin BX, Ding FD, Ma FF, Zhou XH, Zong HY, et al. Leonurine negatively modulates T cells activity by suppressing recombination activation gene protein 2 in pulmonary fibrosis. Eur J Inflamm. 2021;19:205873922110359.
295. Du W, Tang Z, Yang F, Liu X, Dong J. Icariin attenuates bleomycin-induced pulmonary fibrosis by targeting hippo/yap pathway. Biomed Pharmacother. 2021;143:112152.
296. Shen X, Ding D, Yu L, Ni J, Liu Y, Wang W, et al. Total extract of anemarrhenae rhizoma attenuates bleomycin-induced pulmonary fibrosis in rats. Bioorg Chem. 2022;119:105546.
297. Theocharis AD, Skandalis SS, Gialeli C, Karamanos NK. Extracellular matrix structure. Adv Drug Deliv Rev. 2016;97:4–27.
298. Li J, Yao W, Zhang L, Bao L, Chen H, Wang D, et al. Genome-wide dna methylation analysis in lung fibroblasts co-cultured with silica-exposed alveolar macrophages. Respir Res. 2017;18(1):91.
299. Robert S, Gicquel T, Victoni T, Valença S, Barreto E, Bailly-Maître B, et al. Involvement of matrix metalloproteinases (MMPs) and inflammasome pathway in molecular mechanisms of fibrosis. Biosci Rep. 2016;36(4):e00360.
300. Giannandrea M, Parks WC. Diverse functions of matrix metalloproteinases during fibrosis. Dis Model Mech. 2014;7(2):193–203.
301. Cutroneo KR, White SL, Phan SH, Ehrlich HP. Therapies for bleomycin induced lung fibrosis through regulation of TGF-beta1 induced collagen gene expression. J Cell Physiol. 2007;211(3):585–9.
302. Feng F, Cheng P, Xu S, Li N, Wang H, Zhang Y, et al. Tanshinone iia attenuates silica-induced pulmonary fibrosis via nrf2-mediated inhibition of EMT and TGF-β1/Smad signaling. Chem Biol Interact. 2020;319:109024.
303. Tang Y, Chen Y, Chu Z, Yan B, Xu L. Protective effect of cryptotanshinone on lipopolysaccharide-induced acute lung injury in mice. Eur J Pharmacol. 2014;723:494–500.

304. Zhang Y, Lu W, Zhang X, Lu J, Xu S, Chen S, et al. Cryptotanshinone protects against pulmonary fibrosis through inhibiting Smad and STAT3 signaling pathways. Pharmacol Res. 2019;147:104307.
305. Li L, Xu L, Hu Y, Cui W, Cui W, Zhou W, et al. Astragaloside iv improves bleomycin-induced pulmonary fibrosis in rats by attenuating extracellular matrix deposition. Front Pharmacol. 2017;8:513.
306. Li N, Feng F, Wu K, Zhang H, Zhang W, Wang W. Inhibitory effects of astragaloside IV on silica-induced pulmonary fibrosis via inactivating TGF-β1/Smad3 signaling. Biomed Pharmacother. 2019;119:109387.
307. Feng F, Li N, Cheng P, Zhang H, Wang H, Wang Y, et al. Tanshinone IIA attenuates silica-induced pulmonary fibrosis via inhibition of TGF-β1-smad signaling pathway. Biomed Pharmacother. 2020;121:109586.
308. Sun X, Cui X, Chen X, Jiang X. Baicalein alleviated tgf β1-induced type I collagen production in lung fibroblasts via downregulation of connective tissue growth factor. Biomed Pharmacother. 2020;131:110744.
309. Durairaj P, Venkatesan S, Narayanan V, Babu M. Curcumin inhibition of bleomycin-induced changes in lung collagen synthesis, deposition and assembly. Mol Biol Rep. 2021;48(12):7775–85.
310. Yang L, Chen P, Luo M, Shi W, Hou D, Gao Y, et al. Inhibitory effects of total ginsenoside on bleomycin-induced pulmonary fibrosis in mice. Biomed Pharmacother. 2019;114:108851.
311. Du S, Li C, Lu Y, Lei X, Zhang Y, Li S, et al. Dioscin alleviates crystalline silica-induced pulmonary inflammation and fibrosis through promoting alveolar macrophage autophagy. Theranostics. 2019;9(7):1878–92.
312. Li R, Chen X, Xu Y, Feng F, He H, Zhou X. Inhibitory effects of alkaline extract from the pericarp of citrus reticulata blanco on collagen behavior in bleomycin-induced pulmonary fibrosis. J Ethnopharmacol. 2021;269:113761.
313. Huang C, Wu X, Wang S, Wang W, Guo F, Chen Y, et al. Combination of salvia miltiorrhiza and ligustrazine attenuates bleomycin-induced pulmonary fibrosis in rats via modulating tnf-α and tgf-β. Chin Med. 2018;13:36.
314. Fu Y, Zhao P, Xie Z, Wang L, Chen S. Oridonin inhibits myofibroblast differentiation and bleomycin-induced pulmonary fibrosis by regulating transforming growth factor β (TGFβ)/Smad pathway. Med Sci Monit. 2018;24:7548–55.
315. Chun-Bin S, Yi Y, Qin-Yi W, Yang L, Jing-Ze Y, Hai-Jing X, et al. The main active components of curcuma zedoaria reduces collagen deposition in human lung fibroblast via autophagy. Mol Immunol. 2020;124:109–16.
316. Wang J, He F, Chen L, Li Q, Jin S, Zheng H, et al. Resveratrol inhibits pulmonary fibrosis by regulating mIR-21 through MAPK/AP-1 pathways. Biomed Pharmacother. 2018;105:37–44.
317. Shi W, Hao J, Wu Y, Liu C, Shimizu K, Li R, et al. Protective effects of heterophyllin B against bleomycin-induced pulmonary fibrosis in mice via AMPK activation. Eur J Pharmacol. 2022;921:174825.
318. Nie Y, Yang Y, Zhang J, Cai G, Chang Y, Chai G, et al. Shikonin suppresses pulmonary fibroblasts proliferation and activation by regulating AKT and P38 MAPK signaling pathways. Biomed Pharmacother. 2017;95:1119–28.
319. Doherty J, Baehrecke EH. Life, death and autophagy. Nat Cell Biol. 2018;20(10):1110–7.
320. Araya J, Kojima J, Takasaka N, Ito S, Fujii S, Hara H, et al. Insufficient autophagy in idiopathic pulmonary fibrosis. Am J Physiol Lung Cell Mol Physiol. 2013;304(1):L56-69.
321. Mizumura K, Cloonan S, Choi ME, Hashimoto S, Nakahira K, Ryter SW, et al. Autophagy: friend or foe in lung disease? Ann Am Thorac Soc. 2016;13(Suppl 1):S40-47.
322. Haspel JA, Choi AMK. Autophagy: a core cellular process with emerging links to pulmonary disease. Am J Respir Crit Care Med. 2011;184(11):1237–46.
323. Wang RF. Progress in imaging agents of cell apoptosis. Anticancer Agents Med Chem. 2009;9(9):996–1002.
324. Jin Y, Peng L, Zhao A. Hyperoxia induces the apoptosis of alveolar epithelial cells and changes of pulmonary surfactant proteins. Eur Rev Med Pharmacol Sci. 2018;22(2):492–7.
325. Im J, Kim K, Hergert P, Nho RS. Idiopathic pulmonary fibrosis fibroblasts become resistant to FAS ligand-dependent apoptosis via the alteration of decoy receptor 3. J Pathol. 2016;240(1):25–37.
326. Romero Y, Bueno M, Ramirez R, Álvarez D, Sembrat JC, Goncharova EA, et al. Mtorc1 activation decreases autophagy in aging and idiopathic pulmonary fibrosis and contributes to apoptosis resistance in IPF fibroblasts. Aging Cell. 2016;15(6):1103–12.
327. Testai L, Calderone V. Nutraceutical value of citrus flavanones and their implications in cardiovascular disease. Nutrients. 2017;9(5):502.
328. Wu Q, Zhou Y, Feng F, Jin Y, Wang Z, Zhou X. Probing into the mechanism of alkaline citrus extract promoted apoptosis in pulmonary fibroblasts of bleomycin-induced pulmonary fibrosis mice. Evid Based Complement Alternat Med: eCAM. 2018;2018:9658950.
329. Wu Q, Zhou Y, Zhou X. Citrus alkaline extract delayed the progression of pulmonary fibrosis by inhibiting P38/Nf-κB signaling pathway-induced cell apoptosis. Evid Based Complement Alternat Med eCAM. 2019;2019:1528586.
330. Feng F, Wang Z, Li R, Wu Q, Gu C, Xu Y, et al. Citrus alkaline extracts prevent fibroblast senescence to ameliorate pulmonary fibrosis via activation of cox-2. Biomed Pharmacother. 2019;112:108669.
331. Han D, Xu Y, Peng W, Feng F, Wang Z, Gu C, et al. Citrus alkaline extracts inhibit senescence of A549 cells to alleviate pulmonary fibrosis via the β-catenin/P53 pathway. Med Sci Monit. 2021;27:e928547.
332. Häkkinen SH, Kärenlampi SO, Heinonen IM, Mykkänen HM, Törrönen AR. Content of the flavonols quercetin, myricetin, and kaempferol in 25 edible berries. J Agric Food Chem. 1999;47(6):2274–9.
333. Lee M, Yun S, Lee H, Yang J. Quercetin mitigates inflammatory responses induced by vascular endothelial growth factor in mouse retinal photoreceptor cells through suppression of nuclear factor kappa B. Int J Mol Sci. 2017;18(11):2497.
334. Hohmann MS, Habiel DM, Coelho AL, Verri WAJ, Hogaboam CM. Quercetin enhances ligand-induced apoptosis in senescent idiopathic pulmonary fibrosis fibroblasts and reduces lung fibrosis in vivo. Am J Respir Cell Mol Biol. 2019;60(1):28–40.
335. Xiao Y, Zhou L, Zhang T, Qin C, Wei P, Luo L, et al. Anti-fibrosis activity of quercetin attenuates rabbit tracheal stenosis via the TGF-β/AKT/mTOR signaling pathway. Life Sci. 2020;250:117552.
336. Wang Z, Feng F, He H, Wu Q, Gu C, Hrovat J, et al. Citrus alkaline extracts prevent endoplasmic reticulum stress in type II alveolar epithelial cells to ameliorate pulmonary fibrosis via the ATF3/PINK1 pathway. Phytomedicine. 2021;89:153599.
337. Chen G, Chang W, Li X, Han L, Zhou D, Feng Y, et al. N-buoh extract of *Bletilla striata* exerts chemopreventive effects on lung against SiO(2) nanoparticles through activation of Nrf2 pathway. Phytomedicine. 2021;82:153445.
338. Liu M, Su M, Tang D, Hao L, Xun X, Huang Y. Ligustrazin increases lung cell autophagy and ameliorates paraquat-induced pulmonary fibrosis by inhibiting PI3K/Akt/mTOR and hedgehog signalling via increasing mir-193a expression. BMC Pulm Med. 2019;19(1):35.
339. Xue Z, Zhao F, Sang X, Qiao Y, Shao R, Wang Y, et al. Combination therapy of tanshinone IIA and puerarin for pulmonary fibrosis via targeting IL6-JAK2-STAT3/STAT1 signaling pathways. Phytother Res PTR. 2021;35(10):5883–98.
340. He J, Peng H, Wang M, Liu Y, Guo X, Wang B, et al. Isoliquiritigenin inhibits TGF-β1-induced fibrogenesis through activating autophagy via PI3K/AKT/mTOR pathway in MRC-5 cells. Acta Biochim Biophys Sin. 2020;52(8):810–20.
341. Bahri S, Mies F, Ben Ali R, Mlika M, Jameleddine S, Mc Entee K, et al. Rosmarinic acid potentiates carnosic acid induced apoptosis in lung fibroblasts. PLoS ONE. 2017;12(9):e184368.
342. Liu H, Yu H, Cao Z, Gu J, Pei L, Jia M, et al. Kaempferol modulates autophagy and alleviates silica-induced pulmonary fibrosis. Dna Cell Biol. 2019;38(12):1418–26.
343. Guo Z, Li S, Zhang N, Kang Q, Zhai H. Schisandra inhibit bleomycin-induced idiopathic pulmonary fibrosis in rats via suppressing M2 macrophage polarization. Biomed Res Int. 2020;2020:5137349.
344. Pan L, Lu Y, Li Z, Tan Y, Yang H, Ruan P, et al. Ginkgo biloba extract EGb761 attenuates bleomycin-induced experimental pulmonary fibrosis in mice by regulating the balance of M1/M2 macrophages and nuclear factor kappa b (nf-κb)-mediated cellular apoptosis. Med Sci Monit. 2020;26:e922634.
345. Tanjore H, Lawson WE, Blackwell TS. Endoplasmic reticulum stress as a pro-fibrotic stimulus. Biochem Biophys Acta. 2013;1832(7):940–7.
346. Tanjore H, Blackwell TS, Lawson WE. Emerging evidence for endoplasmic reticulum stress in the pathogenesis of idiopathic pulmonary fibrosis. Am J Physiol Lung Cell Mol Physiol. 2012;302(8):L721–9.

347. Lin JH, Walter P, Yen TSB. Endoplasmic reticulum stress in disease pathogenesis. Annu Rev Pathol. 2008;3:399–425.
348. Nogee LM, Dunbar AER, Wert SE, Askin F, Hamvas A, Whitsett JA. A mutation in the surfactant protein c gene associated with familial interstitial lung disease. N Engl J Med. 2001;334(8):573–9.
349. Thomas AQ, Lane K, Phillips JR, Prince M, Markin C, Speer M, et al. Heterozygosity for a surfactant protein c gene mutation associated with usual interstitial pneumonitis and cellular nonspecific interstitial pneumonitis in one kindred. Am J Respir Crit Care Med. 2002;165(9):1322–8.
350. Jorgensen E, Stinson A, Shan L, Yang J, Gietl D, Albino AP. Cigarette smoke induces endoplasmic reticulum stress and the unfolded protein response in normal and malignant human lung cells. BMC Cancer. 2008;8:229.
351. Laing S, Wang G, Briazova T, Zhang C, Wang A, Zheng Z, et al. Airborne particulate matter selectively activates endoplasmic reticulum stress response in the lung and liver tissues. Am J Physiol Cell Physiol. 2010;299(4):C736–49.
352. Tagawa Y, Hiramatsu N, Kasai A, Hayakawa K, Okamura M, Yao J, et al. Induction of apoptosis by cigarette smoke via ROS-dependent endoplasmic reticulum stress and CCAAT/enhancer-binding protein-homologous protein (CHOP). Free Radic Biol Med. 2008;45(1):50–9.
353. Torres-González E, Bueno M, Tanaka A, Krug LT, Cheng D, Polosukhin VV, et al. Role of endoplasmic reticulum stress in age-related susceptibility to lung fibrosis. Am J Respir Cell Mol Biol. 2012;46(6):748–56.
354. Castriotta RJ, Eldadah BA, Foster WM, Halter JB, Hazzard WR, Kiley JP, et al. Workshop on idiopathic pulmonary fibrosis in older adults. Chest. 2010;138(3):693–703.
355. Selman M, Rojas M, Mora AL, Pardo A. Aging and interstitial lung diseases: unraveling an old forgotten player in the pathogenesis of lung fibrosis. Semin Respir Crit Care Med. 2010;31(5):607–17.
356. Wang Y, Dong J, Nie J, Zhu J, Wang H, Chen Q, et al. Amelioration of bleomycin-induced pulmonary fibrosis by chlorogenic acid through endoplasmic reticulum stress inhibition. Apoptosis. 2017;22(9):1147–56.

Publisher's Note