Natural Products against Pulmonary Fibrosis

Subjects: Medicine, Research & Experimental

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Pulmonary fibrosis (PF) is defined as a diverse set of lung illnesses manifested by the gradual and permanent deterioration of the lung architecture, induced by scar formation, which eventually results in organ dysfunction, interruption of gas exchange, and mortality from respiratory failure. PF is a disease-refractive lung condition with an increased rate of mortality. The potential factors causing PF include viral infections, radiation exposure, and toxic airborne chemicals. Idiopathic PF (IPF) is related to pneumonia affecting the elderly and is characterized by recurring scar formation in the lungs. An impaired wound healing process, defined by the dysregulated aggregation of extracellular matrix components, triggers fibrotic scar formation in the lungs. The potential pathogenesis includes oxidative stress, altered cell signaling, inflammation, etc. Nintedanib and pirfenidone have been approved with a conditional endorsement for the management of IPF. In addition, natural product-based treatment strategies have shown promising results in treating PF.

pulmonary fibrosis | natural products | therapeutic targets | plant active compounds | plant extracts | herbal medicine

1. Introduction

Idiopathic Pulmonary fibrosis (IPF) is a chronic, recurrent form of fibrosing interstitial pneumonia that primarily affects elderly persons and is restricted to the lungs. Considering the growing attention to the pathophysiology of IPF, the disease continues to have a poor prognosis [3][4]. Moreover, IPF is a very aggressive type of pulmonary fibrosis with an unclear etiology and a 2–6-year survival rate following diagnosis [3][5]. After viral infection or exposure to chemotherapeutic medications, radiotherapy, or environmental toxins, Pulmonary fibrosis (PF) can also progress [6][7]. Additionally, PF develops in multiple bone marrow transplant patients who have continuous grafts against host disease and in a group of people who have long-term inflammatory disorders such as rheumatoid arthritis or scleroderma [8]. Reportedly, lung transplantation is an efficient treatment for developing lung fibrosis.

Even though PF can progress with the deficiency of a specific initiating factor and can reach a clinically apparent acute inflammatory stage, it is more frequently linked with significant lung damage triggered by respiratory infections, persistent granulomatous illnesses, drug side effects, or connective tissue abnormalities [9][10]. In addition, PF is a vital component of the pathogenesis of MERS and SARS, as demonstrated by clinical, autopsy, and radiographic evidence [11][12][13]. Given the lack of a documented, effective, and specific treatment for

pulmonary fibrosis, risk mitigation efforts are implemented to reduce the intensity of the infection and to shield the lung from additional accidental damage.

2. Natural Products against Pulmonary Fibrosis with Specific Mechanisms of Action

Natural product-based treatment strategies were found to be very promising in treating PF in preclinical and clinical studies. The recently published literature have been reviewed. The natural products are classified into active compounds, most of which are plant secondary metabolites, crude extract of plants, and traditional herbal medicine, consisting of mixtures of different plant products (root, stem, fruits, seeds, etc.).

Secondary metabolites are chemical compounds produced by plants through the metabolic process and are not directly involved in the plants' growth and reproduction. Secondary metabolites that play essential roles in treating pulmonary fibrosis include alkaloids, aristolactams, oxoaporphines, amides, indoles, ionones, flavonoids, benzenoids, and steroids, as well as different volatile oils, lipophilic diterpene, tannins, essential oils, triterpenoid, phenolic compound, xanthone, etc.

2.1. Inhibition of the EMT Pathway

Specific active components have been studied and confirmed to alleviate PF through the inhibition of the transition of epithelial to mesenchymal cells. β-carbolines are alkaloids derived from *Arenaria kansuensis*, used for treatment in BLM-induced PF mice [14]. β-carbolines significantly decrease pulmonary index and inflammatory cell infiltration. Further in vitro studies with TGF-β-induced A549 cells confirmed the inhibition of the nuclear factor-kappa B (NF-κB) and EMT pathways. Celastrol is a triterpenoid collected from the root of *Trpterygium wilfordii*, which was found to be effective in treating BLM-induced rats [15]. Celastrol also regulates the HSP90-mediated inhibition of EMT. Another xanthonoid compound, gambogic acid, derived from *Garcinia hanburyi* reverse EMT, was revealed in association with reduced vimentin and increased cadherin in TGF-β1-stimulated A549 and HPME cells.

Moreover, in vivo treatment with gambogic acid causes reductions in the pathological score, collagen deposition, and the expression of α-SMA, PDGF, and FGF-2 [16]. Plant sterol β-sitosterol effectively suppressed EMT through the inhibition of the TGF-β1/Snail pathway. β-sitosterol decreased ECM accumulation in human alveolar epithelial cells by inhibiting EMT. Moreover, β-sitosterol downregulated Snail, a transcription factor of EMT, and blocked cell migration [17].

Andrographolide is a diterpenoid lactone that effectively reduces the expression of N-cadherin, α-SMA, vimentin, and collagen deposition in silica-induced pulmonary fibrosis mice [18]. A neolignin compound, Honokiol, derived from *Magnolia officinalis,* inhibits the fundamental pathways of EMT and TGF-β/Smad signaling. Honokiol also significantly mitigated the IL-6/CD44/STAT3 axis both in vitro and in vivo [19]. Nimbolide is a terpenoid compound from *Azadirachta indica*, used for treatment against BLM-induced PF mice and TGF-β-stimulated cells to regulate autophagy through attenuation of the EMT pathway. Nimbolide treatment results in the reduced expression of

fibrotic and mesenchymal markers and the increased expression of epithelial markers. Nimbolide also regulates autophagy by reducing microtubule-associated protein 1A/1B-light chain 3 and p-62 expression and increasing Beclin-1 expression [20].

Sulforaphane is an isothiocyanate compound derived from cruciferous vegetables. It restores epithelial morphology in vitro (confirmed by the increased expression of the epithelial marker E-cadherin) and inhibits the expression of EMT-related transcription factors (Slug, Snail, and Twist) and decreases BLM-induced fibronectin expression [21]. Emodin (anthraquinone compound) significantly reduces lung distortion, collagen overproduction, cell infiltration, and proinflammatory cytokine expansion. It induces Nrf2 signaling and dampens p-IIκBα, NF-κB, EMT transition, TGF-β1, and the p-Smad2/3 pathway [22]. Galanin is a flavonoid compound that attenuates inflammatory damage and prevents EMT in BLM-induced PF mice [23].

The effective treatment strategies using plant extracts targeting the EMT pathway include β-peltoboykinolic acid. β-peltoboykinolic acid, from the extract of *Astilbe rubra*, inhibits the COL1 and fibronectin. In addition, ethanol extract of the *A. Rubra* whole plant inhibits TGF-β1-induced EMT in A549 Cells. Furthermore, dichloromethane fractions show the most substantial inhibitory effect on TGF-β1-induced EMT. β-peltoboykinolic acid interrupts the activation of the Smad pathway by TGF-β1 [24].

2.2. Inhibition of TGF-β Signaling

Among the soluble immune mediators, TGF-β-mediated signaling is most commonly involved in the pathogenesis of PF. Therefore, an array of approaches targeting the inhibition of TGF-β signaling is inevitable. Salvianolic acid B (SAB) is a polyphenol compound derived from *Salviae miltiorrhza.* It downregulates collagen expression and changes the expression of other fibrotic genes in NIH/3T3 fibroblasts. Treatment with SAB (50μg/mL) inhibited this proliferation with no apparent toxicity. TGF-β-sensitized MRC-5 fibroblasts increased the expression of collagen type 1 alpha 1 (COL1A1) and COL1A2 by 240% and 170%, respectively. SAB significantly downregulated the TGF-β-induced expression of COL1A1, COL1A2, and COL3A1. SAB also attenuated the TGF-β- and TNF-α-induced inhibition of E-cadherin expression [25].

Gentiopicroside (GPS) is a secoiridoid glycoside. GPS significantly decreased the levels of inflammatory cytokines, including TNF-α and IL-1β, in BAL fluid and reduced the content of hydroxyproline in the lungs of PF mice. GPS significantly downregulated the expression of TGF-β1 and CTGF in the lungs of PF mice. Moreover, in an in vitro study in TGF-β1-stimulated A549 cells, GPS dose-dependently inhibited the EMT pathway [26]. The phenolic compound zingerone is derived from ginger. It decreases collagen accumulation and TNF-α, IL-1β, and malondialdehyde (MDA) levels. Ginger inhibits TGF-β1 and iNOS expression and increases superoxide dismutase (SOD) and glutathione peroxidase activity in PF-induced rats [27]. The TGF-β/Smad pathway is inhibited by oridonin, a diterpenoid from *Rabdosia rubesecens*. Oridonin inhibits the mRNA and protein expression of α-SMA and COL1A1 in TGFβ-induced MRC-5 cells and in vivo in BLM-induced PF mice [28]. Myricetin dose-dependently inhibits TGF-β1/Smad2,3 signaling and attenuates fibroblast activation and EMT transition [29]. Rutin is a flavonoid compound from the citrus plant that significantly reduces lactate dehydrogenase activity, as well as the total cell,

macrophage, and lymphocyte counts in BAL fluid. Rutin-treated PF-mice showed decreased lung MDA, and nitric oxide increased glutathione and SOD. Moreover, the reduced expression of TGF-β1, Col 1, Col III, and α-SMA is associated with reduced collagen deposition and lung hydroxyproline content [30]. An ex vivo study with a precision-cut lung slice model revealed the role of caffeine in inhibiting TGF-β activation in epithelial cells but not in fibroblasts. Caffeine inhibited α-SMA gene expression and reduced fibrosis after a 5-day treatment in the lung slice model [31]. Rhapontin is effective in lowering ECM deposition and reduced the expression of LOX2 and p-Smad2/3 in vitro. Moreover, rhapontin ameliorates BLM-induced PF with low LOX2 and a high level of AMPK. It also reduces collagen deposition and the expression of TGF-β1, α-SMA, and hypoxia-inducing factor (HIF)-α in the lung [32]. Alantolactone and isoalatolactone are sesquiterpene lactones derived from *Inula helenium L*, which also inhibited the TGF-β1/Smad3 signaling pathway and ultimately reduced the myofibroblast activation and ECM deposition [33]. Paeonol was also found to inhibit TGF-β-induced cellular processes in vitro [34].

Arenaria kansuensis ethanol extract (AE) reduced collagen deposition and α-SMA through inhibition of the TGF-β/Smads pathway. AE is also effective in reducing inflammatory infiltration and inflammatory cytokines in the lungs through the NF-κB/p65 pathway. Moreover, AE reduced oxidative stress by inhibiting ROS levels and induced GSH and SOD activities [35]. Ethyl acetate extract of *Salvia miltiorrhiza* (EASM) alleviates oxidative stress by upregulating Nrf2 and concomitantly downregulating Nox4 in the lungs of BLM-treated mice. EASM reduced ROS generation in fibroblasts by stabilizing Nrf2 protein by promoting kelch-like ECH-associated protein 1 (Keap1) degradation. Nrf2 knockdown in the lungs of BLM-treated mice diminished the inhibitory effects of EASM on fibrosis. EASM suppressed myofibroblast activation with reduced ECM deposition [36].

Black tea extract (BTE) from *Camellia sinensis* reduces α-SMA and TGF-β expression and increases IFN-γ expression in BLM-induced PF mice [37]. Grape seed extracts (GSE) are well known for their inhibitory role in ECM deposition. Moreover, GSE reduces pulmonary inflammation, cytokine, and lactate dehydrogenase activity. GSE alleviates MMP-9 and TGF-β1 protein expression in the lungs [38] and *Rhodiola rosea* L. (RRL) increased SOD and GSH and reduced the hydroxyproline levels in BLM-induced PF rats. The upregulated MMP-9 and α-SMA were decreased significantly in a dose-dependent manner in response to RRL. The levels of TGF-β1 and TIMP-1 in lung tissues were also reduced. In addition, RRL treatment lowered TGF-β1, TNF-α, and IL-6 proteins, indicating that RRL has anti-inflammatory properties in rats with BLM-induced lung fibrosis [39].

Xin Jia Xuan Bai Cheng Qi Decoction (XJXBCQ) treatment in vivo significantly improved lung function, inhibited hydroxyproline levels, and increased the levels of Smad7. XJXBCQ induced a dramatic decrease in the expression of lung TGF-β1 protein. XJXBCQ treatment decreased the expression of α-SMA and fibronectin, IL-17A, and IL-25 in TGFβ1-treated MRC-5 cells. XJXBCQ could downregulate the levels of p-Smad2 in TGF-β1-stimulated MRC-5 cells in a dose-dependent manner. XJXBCQ also regulates the Smad signaling pathway, decreasing Smad2 expression and increasing Smad7 expression in terms of mRNA and protein levels [40]. Qing-Xuan Granule (QX) is a children's cough medicine patented in China. QX decreased Col I and α-SMA in lung tissues via the inhibition of TGF-β1-Smad2/3 signaling, suppressed EMT, and effectively reversed abnormal mRNA expression of MMP-1, TIMP-1, and LOXL-2 in the lung tissues of BLM-induced PF mice [41]. A Chinese medicine extract triptolide (TPL) inhibits the EMT of lung epithelial cells by directly binding with TGF-β. PQ-induced PF resulted in increased

vimentin expression but inhibited E-cadherin expression. TPL reversed EMT progression, increased E-cadherin expression, and decreased vimentin expression. TPL bound to TGF-β and inhibited the TGB1/Smad3 pathway [42].

Renshen pingfei decoction (RPFS) reduces lung injury and the fibrosis degree and improves lung function by decreasing hydroxyproline content. RPFS lowers the gene and protein expression of TGF-β1 and Smad3 in lung tissue. It reduces NFκ-B levels in the BAL fluid of rats. It regulates the level of SOD and MDA in the serum of rats by downregulating the TGF-β1/Smad3-mediated intracellular signal transduction pathway [43]. Astragalus injection (AI) significantly prevented BLM-induced α-SMA, TGF-β1, Jagged1, and Notch1 expression, accompanied by alleviation of the collagen deposition and fibrosis [44]. A combination of salvia miltiorrhiza and ligustrazine (SML) dose-dependently ameliorated BLM-induced PF rats through downregulating TNF-α, TGF-β1, and Smad4. It was also proven to be safer than treating subjects with dexamethasone [45]. Yangyin Yiqi, ixture (YYYQ) treatment at medium and high doses significantly reduced TGF-β1, CTGF, and hydroxyproline levels and the mRNA expression of TGF-β1, TβRI, TβRII, Smad3, α-SMA, laminin, and collagen I. In comparison, YYYQ induced the expression of Smad7 and E-cadherin in the BLM group and the prednisolone-treated BLM group. Therefore, it was supposed to be related to suppressing the EMT and TGF-β1/Smad signaling pathways [46]. Total alkaloids from Alstonia Scholaris (L.) R. Br. decreased Krebs von den Lungen-6, lactate dehydrogenase, TGF-β, hydroxyproline, type I collagen, and malonaldehyde levels. This also enhanced the activity of SOD in the serum and lung tissues. Moreover, the alkaloid treatment resulted in decreased TGF-β and MMP-1 expressions [46]. Ophiocordyceps lanpingensis polysaccharides (OLP) alleviated collagen deposition and oxidative stress and decreased macrophage accumulation. The attenuation of macrophage accumulation inhibited the activation of TGF-β1. OLP also suppressed the expression levels of the TNF-α, IL-1β, IL-6, Oncostatin M (OSM), IL-10, and IL-13 genes [47].

PM014 is a herbal formula that is well known for its usage in the treatment of pulmonary disease. PM014 reduces tissue damage, including lesser degrees of intra-alveolar hyaline membrane formation, inflammatory cell infiltration, and thickness of the bronchiolar epithelium. PM014 treatment significantly inhibits immune cell recruitment and collagen deposition in lung tissue. Moreover, PM014 attenuates TGF-β signaling via the Smad and MAPKs pathways [48]. Yifei sanjie formula (YFSJF) treatment alleviated inflammatory injuries and collagen deposition in PF. The levels of hydroxyproline and the expression of TGF-β1, Col-I, and Col-III were significantly decreased. In addition, YFSJF activates autophagy via activating the PI3K/Akt-mTOR pathway to exert anti-PF effects [49].

2.3. Anti-Oxidative and Anti-Inflammatory Roles

Certain compounds are effective in treating PF through modulating inflammation and oxidative stress. Coelonin is a dihydrophenanthrene compound that significantly inhibited LPS-induced IL-1β, IL-6, and TNF-α expression. Moreover, NF-κB and the negative regulator phosphatase and tensin homolog on chromosome ten (PTEN) were significantly reduced [50]. Dioscin (Dio) is a steroidal saponin that significantly reduces type 1 collagen deposition in the lungs. Moreover, the mRNA levels of IL-6, Il-1β, and TNF-α in the lungs of silica-induced PF mice were decreased via Dio treatment. Dio also alleviates pulmonary inflammation by reducing macrophage and lymphocyte infiltration into lung tissues [51]. Asiatic acid is a triterpenoid compound from the medicinal plant *Centella asiatica*, with diverse therapeutic effects. Pretreatment with Asiatic acid inhibits PF progression. It also downregulates

inflammatory cell infiltration and pro-inflammatory cytokine and TGF-beta expression [52]. Morin is a very potent anti-inflammatory and anti-oxidative flavonoid compound from *Maclura pomifera.* Treatment with morin attenuates the infiltration of inflammatory cells and hydroxyproline content in the lungs [53]. Apigenin, derived from various vegetables, decreased inflammation and oxidative stress. Apigenin reduces hydroxyproline content and inflammatory cell infiltration. It also increases SOD and PPAR-γ expression in the lungs. Moreover, it causes increased E-cadherin and Smad-7 levels in the lungs and decreased NF-κB, MMP-9, vimentin, and TGF-β expression [54].

Salvianolic acid B (SAB) effectively inhibits myofibroblast trans-differentiation and the upregulation of Nrf2. In vitro treatment with SAB reduces ROS production, increases glutathione, and reduces MDA levels. The anti-fibrotic and anti-oxidative roles of SAB were confirmed in BLM-induced PF rats [55]. Moreover, the anti-inflammatory and anti-oxidative roles of SAB were also established in lipopolysaccharide (LPS)-treated fibroblast cells. SAB and sodium tanshinone IIA sulfonate (STS) downregulate the mRNA and protein expression of IL-1β and TNF-α. Moreover, SAB and STS inhibit α-SMA and COL1α mRNA and protein in TGF-β-induced MRC5 cells [56]. Pterostilbene is a polyphenol compound derived from blueberries that protects against oxidative stress, inflammation, and apoptosis by activating Keap-1/Nrf2. Pterostilbene also inhibited caspase-dependent A20/NF-κB and NLRP3 signaling [57].

GHK (Gly-His-Lys) and GHK-Cu are tri-peptides that have been found to be effective in alleviating inflammatory responses in PF mice, confirmed by analyzing BAL fluid. GHK reduces TNF-α, IL-6, myeloperoxidase (MPO) activity, and collagen deposition. The BLM-induced imbalance of MMP-9/TIMP-1 was reversed after GHK treatment. GHK also prevents the EMT pathway via the TGF-β1/Smad 2/3 and insulin growth factor-1 pathways [58] [59]. Rosavin is an alcohol glycoside derived from *Rhodiola rosea* that reduces inflammatory cells' infiltration into BAL fluid and pro-inflammatory cytokines' expression in lung tissue. It has also been shown to reduce hydroxyproline and MDA contents. Furthermore, it was found to increase the activities of SOD and glutathione peroxidase in lung tissue. The upregulation of Nrf2 and the downregulation of NF-κB p65, TGF-β1, and α-SMA revealed the mechanism of the rosavin-mediated amelioration of fibrosis [60]. The plant flavonoid quercetin, which can be found in diverse plant sources, reduces inflammation via inhibiting the infiltration of inflammatory cells in the lungs [61]. Schisandrin B (SchB)-treated mice exhibited fewer inflammatory changes and fewer collagen fibers than lung tissues from the BLM group. Moreover, SchB decreased hydroxyproline content and TGF-β1 levels but increased SOD and total antioxidant capacity in the lungs [62]. Glaucocalyxin A (GlnA) is a terpenoid compound that significantly reduces collagen deposition and hydroxyproline content in the lungs. Moreover, GlnA inhibits the infiltration of macrophages and neutrophils and attenuates pro-inflammatory cytokine levels in BAL fluid [63]. Co-treatment with quercetin and gallic acid significantly decreases hydroxyproline, TNF-α, and GSH levels and increases catalase and SOD activity in the lungs compared with both single phytochemical-treated groups [64]. Coco et al. studied the ethanolic extract of Baru nuts, a native Brazilian species. The extract comprises phenolic compounds such as gallic acid, potentially exhibiting antioxidative and wound healing activity in human NCI-H441 and A549 lung epithelial cell lines [65].

Date palm sap (DPS) treatment reversed BLM-mediated increased MDA and SOD levels and decreased catalase activity. DPS further decreased hydroxyproline levels and morphological lesions induced by BLM [66]. In rats,

Nigella sativa oil (NSO) treatment reduces the inflammatory index and fibrosis score and increases the urinary secretion of histidine, fumarate, allantoin, and malate. Therefore, it is assumed that NSO attenuates PF through resistance from lung, kidney, and liver tissues [67]. The nutraceutical role of aged garlic extract (AGE) in alleviating pulmonary fibrosis was validated in a TiO_2-induced pulmonary and hepatic animal model. AGE diminishes TiO_2-induced toxicity by downregulating pulmonary MMP-9, TIMP-9, TGF-β1, collagen-1α, and fibronectin mRNA [68]. The methanolic extract of *Myrtus communis* (Myrtle) significantly reduces parenchymal inflammation, hydroxyproline content, and lipid peroxidation. It also increases catalase activity in PF mice [69]. The protective effects of *Berberis vulgaris* fruit extract (BVFE) against paraquat (PQ)-induced PF rats have also been validated. PQ significantly increases the lungs' MDA, hydroxyproline, TNF-α, IL-6, and TGF-β1 levels. BVFE ameliorated the biochemical and histological lung alterations induced by PQ [70]. *Pistacia lentiscus* oil (PLO) decreases the lipoperoxidation caused by BLM. PLO also protected against BLM-induced lung fibrosis and oxidative stress [71].

Citrus alkaline extracts (CAE) mitigated pulmonary fibrosis in a BLM-induced mouse model by preventing fibroblast senescence. CAE inhibited the expression of the senescent biomarkers $P16^{INK4a}$, P21, and the senescence-associated β-galactosidase (SA-β-Gal) positive cells, as well as the etoposide-induced senescence of lung fibroblasts in vitro. CAE regulates the senescence-associated secretory phenotype by inhibiting senescence in fibroblasts. Further mechanism studies confirmed that CAE inhibits lung fibroblast senescence via a P53-dependent mechanism, and cyclooxygenase-2 activation is required for CAE to inhibit P53-dependent fibroblast senescence [72].

Chuanxiong Kangxian granules (CCKG) attenuate BLM-induced pulmonary fibrosis in rats. CCKG reduces BLM-induced collagen deposition, oxidative stress, and inflammatory responses, reducing the expression of MMP-2 and MMP-9, which are proteins involved in the construction of ECM [73]. Modified Kushen Gancao Formula (mKG) is a Chinese herbal medicine which shows anti-inflammatory activities. mKG treatment significantly decreased pulmonary alveolitis, fibrosis scores, hydroxyprolines, Col-1, Col-3 contents, IL-6, IL-17, and TGF-β in BLM-induced lung tissues [74]. Astragaloside IV (ASV) alleviated collagen deposition and the suppression of EMT in pulmonary fibrosis in vivo. In addition, ASV inhibited TGF-β and activated FOXO3a, which also inhibits TGF-β-induced EMT via the PI3K/Akt pathway [75].

Jinshu Huanxian formula (JHF) increased glutathione, glutathione peroxidase, catalase, and SOD and decreased the content of MPO. JHF also inhibits the expression of NOX4 and induces Nrf2 [76]. Polysaccharides from *Ganoderma luciderma* (PGL) ameliorate PF by increasing glutathione, glutathione peroxidase, catalase, and SOD and decreasing the contents of MDA and hydroxyproline [77]. In addition to the anti-TGF-β activity of PM014, it also acts via the inhibition of the expression of cytokines (IL-6, IL-13, IL-1b, and TGF-β), chemokines (MIP1a, MCP1, and CCL4), and fibrosis-related genes (Col3al and Fn1) in radiation-induced PF mice [78]. In the BLM-induced model, Pyunkanghwan (Pyunkang-tang) extract (PGT) alleviates the characteristic histopathological features of lung fibrosis and inhibits fibrotic lesions. PGT also inhibits BLM-induced MDA, demonstrating its protective effect against lipid peroxidation in lung cell membranes. In addition, PGT decreased TGF-β-stimulated type I collagen synthesis in vitro [79]. However, PGT inhibits TGF-β1-induced collagen accumulation and EMT by inhibiting the PI3K/Akt signaling pathway [80]. Feifukang (FFK) treatment significantly reduced the BLM-induced increase in

hydroxyproline content, collagen I, and a-SMA expression. Moreover, FEK regulates JAK-STAT signaling via the phosphorylation of Smad3, STAT3, and JAK1 [81].

2.4. Modulation of Cellular Signaling

Magnesium isoglycyrrhizinate (MgIG) treatment reduced collagen deposition, ROS production, and TGF-β1 elevation in vitro. Administration of MgIG achieved lower expression levels of Nox4 and p38/MAPK/Akt in vivo and in vitro [82]. Alpha-mangostin (α-MG) in vivo treatment dramatically reduced the expression of α-SMA and Col 1 at both the mRNA and the protein levels. α-MG treatments also reduced the abnormal expression of TGF-β1 and the phosphorylation of Smad 2/3 in the lungs. Moreover, α-MG alleviates the process of fibrogenesis by promoting AMPK-mediated inhibition of NOX4 expression and TGF-β1-induced trans-differentiation of lung fibroblast [83].

Polydatin (PD) treatment suppressed mycoplasma pneumonia-induced lung injury in mice by inhibiting the expression of inflammatory factors and the development of fibrotic scars. PD also inhibits the activation of the NLRP3 inflammasome and the NF-κB pathway [84]. Zingerone and Tetrandrine-hydroxypropyl-β-cyclodextrin inclusion compound (TET-HP-β-CD) are a ketone and an alkaloid natural compound which have effectively reduced MDA and hydroxyproline content in vivo. Moreover, zingerone inhibits the signaling pathways of NF-κB and MAPKs [85][86]. Juglanin (Jug) also reduced the expression of fibrotic hallmarks, including TGF-β1, fibronectin, MMP-9, α-SMA, and collagen I. The role of Jug in suppressing the stimulator of interferon genes (Sting) was confirmed in TGF-β-incubated cells [87]. Phycocyanin is a phycobilin compound from cyanobacteria that reduces MPO, IL-6, TNF-α, and type 1 alveolar epithelial cells. It also inhibits fibroblast proliferation and attenuates EMT [88]. Parthenolide, derived from *Tanacetum parthenium*, significantly reduced cell viability and migration and inhibited EMT markers in lung epithelial cells. The treatment of parthenolide in vivo results in attenuation of the pathological markers of fibrosis through inhibition of the NFκB/Snail signaling pathway [89].

Coumarin compound wedelolactone (WEL), derived from *Eclipta Prostratacoumarin*, reduces inflammatory cell infiltration and collagen deposition in lung tissues. WEL also impairs the expression of fibrotic markers (α-SMA, Col I), the reduction in anti-fibrotic markers (E-cadherin), and the prevention of BLM-induced TGF-β1 and Smad2/3 phosphorylation [90]. Madecacassoside is a vital ingredient of *Centella asiatica* that significantly alters cellular signaling in the gut. Oral but not i.p. administration of madecacassoside has significant anti-fibrotic effects. Madecacassoside increases hepatocyte growth factor levels in colon tissue through the upregulation of PPAR-γ mRNA, nuclear translocation, and DNA binding activity in madecassoside-treated colonic epithelial cells [91]. Berberine is an alkaloid compound derived from various Chinese herbs that alleviates PF pathology when administered through either oral or rectal routes. Berberine also induces HGF and PTEN mRNA and protein expression via PPAR-γ in the colon of PF-mice [92]. Scutellarein alleviates the differentiation and proliferation of fibroblasts to myofibroblasts. Inhibiting fibroblast differentiation represses TGF-β/Smad signaling. Further in vitro studies have confirmed the inhibition of cell proliferation by repressing PI3K/Akt signaling and the inhibition of apoptosis by Bcl2 associated X protein/Bcl2 signaling [93].

2.5. Inhibition of ECM Deposition

The deposition of collagen, a vital ingredient of the ECM, facilitates the pathology of pulmonary fibrosis. Therefore, the targeted inhibition of ECM could be an essential strategy to treat pulmonary fibrosis. The curcuminoid ingredients from curcumin and curcumol reduce ECM deposition via autophagy. In vitro curcumin or curcumol treatment in human lung fibroblast cells significantly reduced hydroxyproline, α-SMA, Col-I, and Col-III deposition. Furthermore, N-terminal pro-peptide for type I collagen (PINP), N-terminal pro-peptide for type III collagen, and prolyl-hydroxylase related to ECM were deregulated in a dose-dependent manner [94].

Hydroxysafflor yellow A (HSYA) is a flavonoid from *Carthamus tinctorius* that reduces collagen deposition in the lung. HYSA also alleviates the BLM-induced increase in the mRNA of TGF-β, α-SMA, and collagen I and downregulates Smad3 phosphorylation [95]. 4-methoxy phenethylamine is a biological amine from the pericarp of *Citrus reticulate,* reducing hydroxyproline in serum and lung tissue. It also downregulates TGF-β expression [96]. Treatment with ascorbic acid in paraquat-induced PF mice significantly reduced immune cell infiltration, the secretion of IL-17 and TGF-β, and ECM deposition. Moreover, vitamin C increases the anti-oxidative enzymes, SOD, and catalase levels [97]. The antioxidant properties of *Radix puerariae* extracts (RPEs) ameliorate PQ-induced PF. RPE significantly suppressed lung fibrosis by downregulating Fstl 1 pathways through decreased miR-21 expression. Moreover, RPE suppressed the expression of CTGF, TGF-β1, p38MAPK, NF-kB65, pSmad2/3, and MMP-9 protein levels and attenuated pulmonary fibrosis [98]. The Chinese herbal medicine Hong Jing Tian contains small RNA (HJT-sRNA-m7) involved in reducing fibrotic markers in vitro and in vivo. The decoction formula contains the phosphocholines PC (18:0/18:2) and PC (16:0/18:2), which facilitate the uptake of small RNAs by living cells. HJT-sRNA-m7 effectively reduces the gene expressions of α-SMA, fibronectin, and collagen type I α 1 (COL1A1) [99].

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