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Searching for Novel Candidate Small Molecules for Ameliorating Idiopathic Pulmonary Fibrosis: a Narrative Review

Kyung-il Kim[1,2,†], Rajib Hossain[1,2,†], Xin Li[1,2], Hyun Jae Lee[3,*] and Choong Jae Lee[1,2,*]

[1]*Department of Pharmacology, School of Medicine, Chungnam National University, Daejeon 35015,*
[2]*Brain Korea 21 FOUR Project for Medical Science, Chungnam National University, Daejeon 35015,*
[3]*Smith Liberal Arts College and Department of Addiction Science,Graduate School, Sahmyook University, Seoul 01795, Republic of Korea*

Abstract

Idiopathic pulmonary fibrosis (IPF) can be defined as a progressive chronic pulmonary disease showing scarring in the lung parenchyma, thereby resulting in increase in mortality and decrease in the quality of life. The pathophysiologic mechanism of fibrosis in IPF is still unclear. Repetitive microinjuries to alveolar epithelium with genetical predisposition and an abnormal restorative reaction accompanied by excessive deposition of collagens are involved in the pathogenesis. Although the two FDA-approved drugs, pirfenidone and nintedanib, are under use for retarding the decline in lung function of patients suffered from IPF, they are not able to improve the survival rate or quality of life. Therefore, a novel therapeutic agent acting on the major steps of the pathogenesis of disease and/or, at least, managing the clinical symptoms of IPF should be developed for the effective regulation of this incurable disease. In the present review, we tried to find a potential of managing the clinical symptoms of IPF by natural products derived from medicinal plants used for controlling the pulmonary inflammatory diseases in traditional Asian medicine. A multitude of natural products have been reported to exert an antifibrotic effect *in vitro* and *in vivo* through acting on the epithelial-mesenchymal transition pathway, transforming growth factor (TGF)-β-induced intracellular signaling, and the deposition of extracellular matrix. However, clinical antifibrotic efficacy of these natural products on IPF have not been elucidated yet. Thus, those effects should be proven by further examinations including the randomized clinical trials, in order to develop the ideal and optimal candidate for the therapeutics of IPF.

Key Words: Idiopathic pulmonary fibrosis, Therapeutic agents, Natural products

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) can be defined as a progressive chronic pulmonary disease showing scarring in the lung parenchyma associated with the stiffness and thickening of perialveolar tissues in the lung and an irreversible and progressive exacerbation of lung function, thereby resulting in increase in mortality and decrease in the quality of life.

In one year, twelve out of every 100,000 people develop IPF, and a total of five million people worldwide suffer from this disease. It was reported that life expectancy is four to five years on average after the diagnosis. Usually, dry cough and dyspnea occur gradually as symptoms and fatigue, pneumonia, heart failure, pulmonary embolism, and pulmonary hypertension occur as complications. The cause of IPF is unclear, although genetic predisposition, cigarette smoking, inhalation of diverse particles and dust, and gastroesophageal reflux disease are the risk factors (Meltzer and Noble, 2008; Raghu *et al*., 2011).

Although oxygen supplementation, pulmonary rehabilitation, and lung transplantation are options for patients, the two FDA-approved drugs, pirfenidone and nintedanib, are used to slow down the decline in lung function in patients suffering from IPF. However, they are unable to improve the survival rate or quality of life (King *et al*., 2014; Richeldi *et al*., 2014). Therefore, a novel therapeutic agent acting on the major steps of the pathogenesis of disease and/or, at least, managing the clinical symptoms of IPF should be developed for the effective

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***Corresponding Authors**
E-mail: hjy1213@syu.ac.kr (Lee HJ), LCJ123@cnu.ac.kr (Lee CJ)
Tel: +82-2-3399-1909 (Lee HJ), +82-42-580-8255 (Lee CJ)
Fax: +82-2-3399-1909 (Lee HJ), +82-42-585-6627 (Lee CJ)
[†]The first two authors contributed equally to this work.

regulation of this incurable disease.

On the other hand, it has been reported that natural products showed a multitude of pharmacological activities and have a possibility of being developed as novel agents to control the diverse diseases. Some natural products showed an antifibrotic effect and can be utilized as a prototype agent during the development of novel antifibrotic drugs.

In this context, in the present review, we tried to find a potential of managing the clinical symptoms of IPF by natural products derived from medicinal plants used for regulating the pulmonary inflammatory diseases in traditional Asian medicine, based on a multitude of original research articles. A multitude of natural products have been reported to exert an antifibrotic effect *in vitro* and *in vivo* through acting on the epithelial-mesenchymal transition pathway, transforming growth factor (TGF)-β-induced intracellular signaling, and the deposition of extracellular matrix. However, clinical antifibrotic efficacy of these natural products on IPF have not been elucidated yet. Thus, the effects on humans should be proven through further examinations, including randomized clinical trials, in order to develop the ideal and optimal candidate for the treatment of IPF.

PATHOPHYSIOLOGY OF PULMONARY FIBROSIS

IPF is a member of hundreds of pulmonary diseases known as interstitial lung diseases. IPF is a specific type of idiopathic interstitial pneumonia, the same disease as diffuse parenchymal lung disease (Travis *et al*., 2013). The etiology of IPF has not been well established, although extensive examinations were done. To date, cigarette smoking is recognized as the strongest risk factor for IPF. The inhalational exposure to the environmental gas and particles derived from coal dust, wood dust, metal dust, stone dust, and various dust from agricultural works has been known to increase the risk for IPF. Also, respiratory viral infection, gastroesophageal reflux disease, and genetic predisposition might be associated with IPF (García-Sancho *et al*., 2011; Raghu *et al*., 2011; Olson and Swigris, 2012; Williams, 2014).

It was reported that repetitive microinjuries to alveolar epithelial cells (pneumocytes) lining the alveolar surface with genetical predisposition and an abnormal restorative reaction accompanied by excessive deposition of collagens are involved in the pathogenesis. When type I pneumocytes (alveolar epithelial cells, AECs) are injured, type II pneumocytes proliferate in order to conceal the exposed basement membrane. Under the condition of physiological repair, the hyperplastic type II pneumocytes are perished and the remnant cells disperse and differentiate to become type I pneumocytes. However, in the presence of TGF-β and in the pathologic conditions, fibroblasts accumulate in the damaged lesion and differentiate into myofibroblasts secreting some proteins including collagen (Harari and Caminati, 2010; Loomis-King *et al*., 2013).

Although the fibroblastic foci development antedates the inflammatory cells accumulation and the deposition of collagen, IPF has been known to be a disease of plural mechanisms that the abnormalities in wound healing pathways including the inflammation might function as the trigger of disease. The oxidative stress might contribute to alveolar epithelial cell injury and inflammation. Also, angiogenesis is a pivotal process for tissue regeneration and repair. In IPF, dysregulated angiogenesis was involved, thereby leading to abnormal formation of blood vessel and impaired oxygen exchange in the lungs. (Selman *et al*., 2001; Pardo and Selman, 2002; Maher *et al*., 2007). Genetically, the mutations in airway MUC5B mucin, human telomerase genes, and pulmonary surfactant proteins C, A2, and A1are known to be associated with IPF. Increased cellular senescence and impaired tissue repair might occur, since telomeres may become dysfunctional or shortened (Kropski *et al*., 2014; Mathai *et al*., 2014).

For the development of therapeutic options for IPF, several approaches are being pursued. Gene therapy means that the delivery of genetic material to cells for correcting or replacing abnormal genes. Several gene therapy approaches are being studied for IPF, including the delivery of genes that inhibit fibrosis or promote tissue repair. Immunomodulatory therapies target the immune system and aim to reduce inflammation in the lungs. One approach being studied is the use of monoclonal antibodies that target specific immune cells or cytokines involved in IPF pathogenesis. Stem cells have the potential to regenerate damaged lung tissue and may have a role in the treatment of IPF. Studies are ongoing to determine the safety and efficacy of stem cell therapies for IPF. Pulmonary rehabilitation involves a combination of exercise, education, and breathing techniques to enhance lung function and quality of life in patients with pulmonary disease. Studies have shown that pulmonary rehabilitation can be beneficial for patients with IPF. Pharmacologically, the two antifibrotic agents, nintedanib and pirfenidone, have been approved for the treatment of IPF. These drugs work by inhibiting fibrosis and reducing inflammation in the lungs. Due to the complex pathophysiology of IPF, combination therapies targeting multiple pathways may be more effective than single-method therapies. Studies are ongoing to determine the efficacy and safety of combination therapies for IPF (Kreuter *et al*., 2015; Canestaro *et al*., 2016; Somogyi *et al*., 2019).

MOLECULAR AND CELLULAR TARGETS UTILIZED FOR THE DEVELOPMENT OF THERAPEUTIC OPTIONS

The epithelial-mesenchymal transition (EMT) pathway might be defined as a biological phenomenon that the differentiated phenotype of epithelial cells is lost and a mesenchymal phenotype characterized by increased migratory and invasive properties is acquired. In IPF, the EMT pathway is believed to play an important role during the development of fibrosis. In normal tissue of lung, epithelial cells form a barrier that separates the alveoli from the adjacent tissues. In IPF, however, epithelial cells undergo EMT, leading to the formation of fibroblasts and myofibroblasts, the primary producers of extracellular matrix (ECM) proteins contributing to fibrosis. Several studies have examined the use of inhibitors of EMT pathway for the treatment of IPF. One potential target is the TGF-β pathway, which is a key regulator of the EMT pathway. In animal models of IPF, inhibition of the TGF-β pathway decreased EMT and fibrosis. Another potential target is the transcription factor Snail, which is a key regulator of the EMT pathway. Inhibition of Snail expression decreased fibrosis and improved function of lung, in animal models of IPF. Other potential targets include inhibitors of specific signaling pathways that are involved in EMT, including the phosphatidylinositol

3-kinase (PI_3K)/Akt pathway and the mitogen-activated protein kinase (MAPK) pathway.

For the treatment of IPF, it is encouraging to regulate TGF-β signaling pathway. The synthesis of ECM and growth and differentiation of the cells are the cellular processes exerted by TGF-β. Dysregulation of TGF-β signaling is in volved in the pathogenesis of IPF, where it leads to the activation of fibroblasts and myofibroblasts and the deposition of excessive ECM. Several approaches to inhibit TGF-β signaling are being studied for the treatment of IPF. One approach is the use of small molecule inhibitors of TGF-β receptors and downstream signaling. These inhibitors might decrease fibrosis and improve pulmonary function in animal models of IPF. Another approach is the use of monoclonal antibodies that specifically target TGF-β isoforms. For example, fresolimumab is a monoclonal antibody targeting TGF-β1 and decrease fibrosis and improve pulmonary function in preclinical studies. Other approaches include the use of inhibitors of downstream signaling pathways that are activated by TGF-β including Smad inhibitors or inhibitors of MAPK pathway.

A dysequilibrium exists between the cells' ability to neutralize reactive oxygen species (ROS) and the production of ROS. This provokes oxidative stress. In IPF, oxidative stress contributes to the development of fibrosis by promoting the activation of fibroblasts and myofibroblasts and the deposition of ECM. Anti-oxidative therapies may include the use of antioxidants, such as N-acetylcysteine, which has been shown to reduce oxidative stress and improve lung function in patients with IPF. Inflammation is a contributor to the pathogenesis of IPF. Anti-inflammatory therapies may be effective in controlling fibrosis. Glucocorticosteroids are commonly utilized as anti-inflammatory agents in IPF, but their efficacy is limited, and they showed various adverse effects. Other potential anti-inflammatory therapies include the use of immunosuppressive agents, such as azathioprine, cyclosporine, or mycophenolate mofetil, which have been shown to reduce inflammation and improve lung function in some patients with IPF. Other potential therapies for IPF may include the use of agents that target both oxidative stress and inflammation, such as pirfenidone and nintedanib. Pirfenidone is an anti-fibrotic agent suppressing the production of inflammatory cytokines and ROS. Nintedanib is a tyrosine kinase inhibitor targeting the multiple signaling pathways regulating the development of fibrosis and inflammation.

Inhibition of ECM deposition is a potential therapeutic option for the treatment of IPF, since excessive deposition of ECM is a hallmark of the disease. In IPF, fibroblasts and myofibroblasts produce and deposit huge amount of ECM provoking the formation of fibrotic tissue and impaired lung function. Several approaches to inhibit ECM deposition are being investigated for the treatment of IPF. For example, potential inhibitors are being developed for an enzyme that enhances the cross-linking of collagen and other ECM proteins. Inhibition of this enzyme called as lysyl oxidase-like 2 showed a possibility of deceasing fibrosis and improving lung function in preclinical studies of IPF. Another approach is the use of agents that inhibit the activation of fibroblasts and myofibroblasts, which are responsible for ECM deposition. It was reported that angiotensin receptor blockers and angiotensin-converting enzyme inhibitors decreased pulmonary fibrosis through inhibiting the activation of fibroblasts and myofibroblasts. The use of agents enhancing the degradation of ECM such as matrix metalloproteinase (MMP) inhibitors or tissue plasminogen activator decreased fibrosis to improve lung function, preclinically.

There are several intracellular signaling pathways playing a significant role in the pathogenesis of IPF. Some of the key pathways that have been studied are as follows: (1) The Wnt/β-catenin pathway is involved in cellular differentiation, proliferation, and survival. (2) The Nuclear factor-kappa B (NF-κB) pathway plays a pivotal role in inflammation and immune response. (3) The Hedgehog pathway is involved in repair of tissue and regeneration. (4) The MAPK pathway is involved in cell proliferation, differentiation, and survival. (5) The PI_3K/Akt pathway is involved in cell growth and survival. (6) The TGF-β pathway was aforementioned. The dysregulation of these intracellular signaling pathways might play an important role in the development and progression of idiopathic pulmonary fibrosis. It is desirable to target these pathways in order to develop novel therapeutic options for this disease (Raghu *et al*., 2011; Richeldi *et al*., 2017; Ma *et al*., 2022).

PHARMACOLOGICAL AGENTS TRIED FOR THE REGULATION OF IDIOPATHIC PULMONARY FIBROSIS TO DATE

Pharmacological approaches in IPF aim to slow down or stop the progression of fibrosis and improve the quality of life of patients suffering from IPF. Clinically, azathioprine, cyclophosphamide, and mycophenolate mofetil, have been used off-label to treat IPF. These immunosuppressants work by suppressing the immune system and reducing inflammation. N-acetylcysteine is an antioxidant that has been shown to improve lung function and reduce oxidative stress in patients with IPF. It is believed to work by reducing the production of reactive oxygen species, which contribute to lung injury and fibrosis. Corticosteroids, such as prednisone and methylprednisolone, are commonly used as anti-inflammatory agents in IPF. However, their efficacy is limited, and they showed various adverse effects. Other potential anti-inflammatory agents include macrolide antibiotics, such as azithromycin, which have been shown to reduce inflammation and improve lung function in some patients with IPF. Antifibrotic gene therapy is an emerging approach for the treatment of IPF. One potential strategy is to deliver genes that produce proteins that can inhibit fibrosis, such as decorin, to the lung tissue (Canestaro *et al*., 2016). Although there is no definitive clinical therapeutic agent for IPF up to date, the two antifibrotic agents, nintedanib and pirfenidone are clinically used for the regulation of the disease. These two agents might retard the progression of IPF. However, they are not able to enhance the quality of life, improve or stabilize the function of lung (Kreuter *et al*., 2015). In addition to these two agents, several compounds are under being investigated, based on the drug repositioning strategy (Table 1).

Nintedanib

It has been reported that nintedanib shows an inhibitory effect on the function of platelet-derived growth factor receptor, fibroblast growth factor receptor, and vascular endothelial growth factor receptor, thereby inhibiting the differentiation of fibroblasts to myofibroblasts and migration and proliferation of lung fibroblasts, the important processes involved into the pathogenesis of IPF. In clinical trials, nintedanib exerted an

Table 1. Pharmacological agents tried to use for the regulation of idiopathic pulmonary fibrosis to date

Classification	Agents
Antifibrotic agents	Nintedanib (Wollin *et al*., 2015) Pirfenidone (Noble *et al*., 2011)
Antidiabetic agent	Metformin (Tzouvelekis *et al*., 2018)
Antihelminthic agent	Niclosamide (Boyapally *et al*., 2019)
Antidiarrheal agent	Nifuroxazide (Gan *et al*., 2022).
HDAC (histone deacetylase) inhibitors	Vorinostat, Panobinostat, Romidepsin, Trichostatin A, Spiruchostatin A, Pracinostat, Tubastatin (P *et al*., 2021)

ameliorating action on IPF including decreased mortality rate and risk of progression of the disease (Wollin *et al*., 2015; Canestaro *et al*., 2016; Richeldi *et al*., 2017).

Pirfenidone

Pirfenidone was reported to retard the progression of disease and the rate of reduction of pulmonary function and decrease the risk of mortality, in patients with IPF. Pirfenidone decreased lipid peroxidation and oxidative stress, down-regulated TGF-β, which is one of the key profibrotic growth factors, and suppressed the production and release of inflammatory cytokines. As a result, it exerted antioxidative, anti-inflammatory, and anti-fibrotic effects (Iyer *et al*., 1999; Taniguchi *et al*., 2010; Noble *et al*., 2011; Nathan *et al*., 2017).

Metformin

In experimental models of pulmonary fibrosis, metformin, an antidiabetic agent, shows a possibility of exerting antifibrotic activity via affecting the autophagy and cellular bioenergetics through activation of adenosine monophosphate-activated protein kinase. However, metformin failed to show a remarkable impact on major disease outcomes, in clinical trials (Tzouvelekis *et al*., 2018).

Nifuroxazide

In bleomycin-induced pulmonary fibrosis, nifuroxazide, an antidiarrheal agent, has shown potential in alleviating the symptoms of the disease by suppressing the expression of various immune cells and inflammatory factors. It inhibited TGF-β-stimulated epithelial-mesenchymal transition of epithelial cells and fibroblasts activation. However, the clinical usefulness of nifuroxazide has not yet been proven and should be examined through clinical trials (Gan *et al*., 2022).

Niclosamide

Niclosamide, an anti-helminthic agent, has been reported to have the potential to exhibit anti-fibrotic activity. It suppressed epithelial-mesenchymal transition and migration of fibroblasts, as well as the WNT/β-catenin signaling pathway, in an *in vitro* model of pulmonary fibrosis induced by TGF-β and an *in vivo* model induced by bleomycin (Boyapally *et al*., 2019).

HDAC (histone deacetylase) inhibitors

Vorinostat, Panobinostat, Romidepsin, Trichostatin A, Spiruchostatin A, Pracinostat, and Tubastatin are HDAC inhibitors. These agents showed a possibility of attenuating fibrotic diseases observed in hepatic, pulmonary, and renal system, through regulating TGF-β-mediated intracellular signaling pathways. They inhibited the expression of connective tissue growth factor, type 1 collagen, α-smooth muscle actin (α-SMA), and fibronectin, the profibrotic proteins induced by TGF-β, via epigenetic mechanism (P *et al*., 2021).

NATURAL PRODUCTS POTENTIAL FOR REGULATING THE PATHOGENESIS OF PULMONARY FIBROSIS AS SMALL MOLECULE DRUG CANDIDATES

In this section of the review, we tried to find the possibility of regulating the pathogenesis of pulmonary fibrosis by natural products, derived from medicinal plants used for controlling the pulmonary inflammatory diseases, in folk medicine (Table 2). As can be seen in the following texts, a multitude of natural products have been reported to exert a potential antifibrotic activity through affecting the epithelial-mesenchymal transition pathway, TGF-β-induced intracellular signaling, and the deposition of extracellular matrix.

Alantolactone

Alantolactone isolated from Inula helenium is a sesquiterpene lactone compound suppressing the TGF-β1/Smad3 signaling pathway, thereby inhibiting the deposition of extracellular matrix and the activation of myofibroblast (Li *et al*., 2018a).

Andrographolide

Using mouse model for pulmonary fibrosis induced by silica, andrographolide, another lactone compound, was reported to inhibit the deposition of collagen and the expression of α-SMA, vimentin, and N-cadherin (Karkale *et al*., 2018).

Apigenin

Apigenin, a well-known flavonoid compound with anti-inflammatory and anti-oxidative activities, was reported to decrease the content of hydroxyproline and the infiltration of inflammatory cells. In the lungs, apigenin potentiated the expressions of superoxide dismutase and PPAR-γ, and increased the levels of E-cadherin and Smad-7, although it suppressed the expression of TGF-β, vimentin, MMP-9, and NF-κB (Chen and Zhao, 2016).

Asiatic acid

Asiatic acid, a triterpenoid compound isolated from Centella asiatica, showed a potential of the attenuation of progression of pulmonary fibrosis. Asiatic acid mitigated the infiltration of inflammatory cells and the expression of TGF-β and proinflammatory cytokines (Dong *et al*., 2017).

Table 2. Natural products potential for regulating the pathogenesis of pulmonary fibrosis as small molecule drug candidates

Compound	Mechanism of action
Alantolactone	Suppression of the TGF-β1/Smad3 signaling pathway Inhibition of the deposition of extracellular matrix and the activation of myofibroblast (Li *et al*., 2018a)
Andrographolide	Inhibition of the deposition of collagen and the expression of α-SMA, vimentin, and N-cadherin (Karkale *et al*., 2018)
Apigenin	Potentiation of the expressions of superoxide dismutase and PPAR-γ Increase in the levels of E-cadherin and Smad-7 Suppression of the expression of TGF-β, vimentin, MMP-9, and NF-κB (Chen and Zhao, 2016)
Asiatic acid	Mitigation of the infiltration of inflammatory cells and the expression of TGF-β and proinflammatory cytokines (Dong *et al*., 2017)
Astragaloside IV	Suppression of the deposition of collagen and TGF-β-induced epithelial-mesenchymal transition through the PI3K/Akt signaling pathway (Qian *et al*., 2018)
Berberine	Stimulation of the expression of mRNA and proteins of hepatocyte growth factor and phosphatase and tensin homolog on chromosome ten through PPAR-γ (Guan *et al*., 2018)
β-carbolines	Suppression of the epithelial-mesenchymal transition and nuclear factor-kappa B signaling pathways (Cui *et al*., 2019)
Celastrol	Regualtion of the heat shock protein 90-mediated suppression of epithelial-mesenchymal transition (Divya *et al*., 2018)
Coelonin	Suppression of lipopolysaccharide-induced expression of proinflammatory cytokines including TNF-α, IL-6, and IL-1β (Jiang *et al*., 2019)
Curcumin	Inhibition of the deposition of α-smooth muscle actin, hydroxyproline, collagen III, and collagen I (Chun-Bin *et al*., 2020)
Dioscin	Mitigation of the deposition of type 1 collagen and the gene expression levels of TNF-α, IL-1β, and IL-6 (Li *et al*., 2017a)
Emodin	Mitigation of the overproduction of collagen, infiltration of inflammatory cells, structural distortion of lung, and expansion of proinflammatory cytokines Decrease in epithelial-mesenchymal transition and the expression of TGF-β1, pSmad-2, and pSmad-3 Stimulation of the Nrf2-antioxidant signaling, while inhibiting the NF-κB signaling pathway (Tian *et al*., 2018)
Galangin	Increase in the expression of E-cadherin and decrease in the expression of α-smooth muscle actin and vimentin Suppression of epithelial-mesenchymal transition and fibroblast differentiation induced by TGF-β1 (Wang *et al*., 2020a)
Gambogic acid	Decrease in the deposition of collagen and the expression of platelet-derived growth factor, α-smooth muscle actin, and fibroblast growth factor-2 (Qu *et al*., 2016)
Gentiopicroside	Suppression of the lung hydroxyproline content, the levels of IL-1β and TNF-α, and the expression of connective tissue growth factor and TGF-β1 Suppression of epithelial-mesenchymal transition stimulated by TGF-β1 (Chen *et al*., 2018)
Glaucocalyxin A	Suppression of the levels of proinflammatory cytokine, the infiltration of neutrophils and macrophages, the deposition of collagen, and the content of hydroxyproline (Yang *et al*., 2017)
Honokiol	Suppression of the TGF-β/Smad signaling and fundamental pathways of epithelial-mesenchymal transition Reduction in the inflammation and the deposition of collagen Inhibition of IL-6/CD44/STAT3 signaling pathway (Pulivendala *et al*., 2020)
Juglanin	Suppression of the expression of collagen I, α-smooth muscle actin, transforming growth factor-β1, matrix metallo-proteinase-9, and fibronectin Suppression of the stimulator of interferon genes which plays a pivotal role in the progress of fibrosis (Sun *et al*., 2020)
Madecassoside	Potentiation of the action of PPAR-γ, which provokes the expression of hepatocyte growth factor (HGF). HGF might enter into the systemic circulation and reach to the lung to manifest an antifibrotic effect (Xia *et al*., 2016)
α-Mangostin	Suppression of the extracellular matrix deposition, the gene expression of collagen I and α-smooth muscle actin, and transforming growth factor-β1/Smad2/3 signaling pathway Regulation of the protein expression of matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 (Li *et al*., 2019)
Morin	Mitigation of the transformation of fibroblasts towards myofibroblasts via affecting peroxisome proliferator activated receptor-γ - glutaminolysis - DEP domain-containing mTOR-interacting protein signaling pathway (Miao *et al*., 2022)
Myricetin	Regulation of the TGF-β1 - Smad2/3 signaling pathway and mitigation of the activation of fibroblasts and epithelial-mesenchymal transition (Li *et al*., 2020)

Table 2. Continued

Compound	Mechanism of action
Nimbolide	Inhibition of the expression of mesenchymal and fibrotic markers Potentiation of the expression of epithelial markers Suppression of the expression of p62 and microtubule-associated protein 1A/1B-light chain 3 Increase in the expression of Beclin-1, thereby affecting autophagy (Prashanth Goud *et al*., 2019)
Oridonin	Mitigation of the inflammatory cell infiltration, collapse of alveolar space, and emphysema Suppression of both the gene expression of α-smooth muscle actin and collagen type I alpha 1 chain and the phosphorylation of Smad2/3 (Fu *et al*., 2018)
Parthenolide	Amelioration of the pathological changes provoked by fibrosis progression via suppressing the NF-κB/Snail signaling (Li *et al*., 2018b)
Phycocyanin	Inhibition of the production of myeloperoxidase, tumor necrosis factor-α, interleukin-6, α-smooth muscle actin, hydroxyproline, surfactant-associated protein C, fibroblast specific protein-1, and vimentin and stimulation of the production of podoplanin and E-cadherin, through toll-like receptor 2 - MyD88 - NF-κB signaling pathway (Li *et al*., 2017b)
Pterostilbene	Decrease in both the levels of hydroxyproline, transforming growth factor-β, and collagen I and the release of interleukin-6, interleukin-1β, and tumor necrosis factor-α Activation of Keap-1/Nrf2 and inhibition of caspase-dependent A20/NF-κB and NLRP3 signaling pathways (Yang *et al*., 2020)
Rhapontin	Decrease in the deposition of collagen, lung pathological score and the expressions of lipoxygenase 2, transforming growth factor-β1, hypoxia-inducible factor-1α, and α-smooth muscle actin (Tao *et al*., 2017)
Rutin	Decrease in the levels of nitric oxide and malondialdehyde in lung Increase in the total antioxidant capacity in serum, the level of glutathione, and the activity of superoxide dismutase (Bai *et al*., 2020)
Salvianolic acid B	Inhibition of the production of reactive oxygen species and malondialdehyde Increase in the levels of glutathione, the expression of nuclear factor erythroid-derived 2-like 2 at the transcriptional and translational steps (Liu *et al*., 2018)
Scutellarein	Suppression of the expression levels of fibrotic markers and mitigation of the differentiation of fibroblasts to myofibroblasts (Miao *et al*., 2020)
Schisandrin B	Decrease in the content of hydroxyproline and the level of transforming growth factor-β1 Increase in the levels of total antioxidant capacity, hydroxyproline, and superoxide dismutase (Wang *et al*., 2020b)
Sulforaphane	Mitigation of collagen I level, the expression of transforming growth factor-β1, and the expression of fibronectin (Kyung *et al*., 2018)
Wedelolactone	Suppression of the infiltration of inflammatory cells, the expression of proinflammatory factors, and the deposition of collagen Increase in the expression of fibrotic markers and decrease in an antifibrotic marker (Yang *et al*., 2019)
Zingerone	Inhibition of the accumulation of collagen and the expression of inducible nitric oxide synthase and transforming growth factor-β1 Increase in the activity of glutathione peroxidase and superoxide dismutase (Gungor *et al*., 2020)

Astragaloside IV

In pulmonary fibrosis animal model, Astragaloside IV, a triterpene glycoside compound isolated from Astragalus membranaceus, inhibited the deposition of collagen and the epithelial-mesenchymal transition. Astragaloside IV suppressed TGF-β-induced epithelial-mesenchymal transition through the PI_3K/Akt signaling pathway (Qian *et al*., 2018).

Berberine

Berberine, an alkaloid compound isolated from Coptis chinensis, was reported to ameliorate the pathology of pulmonary fibrosis. Orally-administered berberine stimulated the expression of mRNA and proteins of hepatocyte growth factor and phosphatase and tensin homolog on chromosome ten (PTEN) through PPAR-γ in the colon of bleomycin-induced pulmonary fibrosis mouse model (Guan *et al*., 2018).

β-carbolines

In bleomycin-induced pulmonary fibrosis mouse model, β-carbolines, the alkaloid compounds isolated from Arenaria kansuensis, showed a potential of regulation of pulmonary fibrosis pathology, including mitigation of infiltration of inflammatory cells. In TGF-β-induced A549 cells, β-carbolines suppressed the epithelial-mesenchymal transition and nuclear factor-kappa B signaling pathways (Cui *et al*., 2019).

Celastrol

In bleomycin-induced pulmonary fibrosis rat model, Celastrol, a triterpenoid compound contained in Tripterygium wilfordii, showed a potential of improvement of pulmonary fibrosis pathology. It affected the heat shock protein 90-mediated suppression of epithelial-mesenchymal transition (Divya *et al*., 2018).

Coelonin

Ethanol extract of Bletilla striata has significant anti-pulmonary fibrotic and anti-inflammatory effects in the rat silicosis model of pulmonary fibrosis. To elucidate the active components and potential molecular mechanism of the Bletilla striata extract, the lipopolysaccharide-induced macrophage inflammation model and phospho antibody array were adopted. It was reported that Coelonin, a dihydrophenanthrene compound isolated from Coelogyne ochracea and Bletilla striata, suppressed lipopolysaccharide-induced expression of pro-inflammatory cytokines including TNF-α, IL-6, and IL-1β, in macrophage inflammation model. In phospho antibody array, Coelonin inhibited the phosphorylation of PTEN and NF-κB (Jiang *et al*., 2019).

Curcumin

In TGF-β1-induced hyperproliferation model of human lung fibroblast, curcumin inhibited the deposition of α-smooth muscle actin, hydroxyproline, collagen III, and collagen I. Curcumin degraded prolyl-hydroxylase, N-terminal pro-peptide for Type III collagen, and N-terminal pro-peptide for Type I collagen, all of which are the proteins related to the collagen synthesis (Chun-Bin *et al*., 2020).

Dioscin

Dioscin, a natural product isolated from diverse medicinal plants including Dioscorea villosa, has been reported to exert anti-inflammatory effect. Dioscin mitigated the deposition of type 1 collagen and the gene expression levels of TNF-α, IL-1β, and IL-6 in the lungs of pulmonary fibrosis model mouse, induced by silica. Dioscin decreased the infiltration of macrophages and lymphocytes into lung tissues, thereby ameliorating the pulmonary inflammation (Li *et al*., 2017a).

Emodin

Emodin derived from a medicinal plant Rheum palmatum has been reported to exert anti-inflammatory and antioxidative effects. In bleomycin-induced pulmonary fibrosis animal model, Emodin mitigated the overproduction of collagen, infiltration of inflammatory cells, structural distortion of lung, and expansion of proinflammatory cytokines. Emodin decreased epithelial-mesenchymal transition and the expression of TGF-β1, pSmad-2, and pSmad-3. It stimulated the Nrf2-antioxidant signaling, while inhibiting the NF-κB signaling pathway (Tian *et al*., 2018).

Galangin

In bleomycin-induced pulmonary fibrosis mouse model, Galangin, a flavonoid natural product isolated from Alpinia officinarum, increased the expression of E-cadherin and decreased the expression of α-smooth muscle actin and vimentin. Galangin suppressed epithelial-mesenchymal transition and fibroblast differentiation induced by TGF-β1, *in vitro*. These results showed a potential of ameliorating and preventing effect of Galangin on pulmonary fibrosis (Wang *et al*., 2020a).

Gambogic acid

In bleomycin-induced pulmonary fibrosis rat model, Gambogic acid, a natural product isolated from Garcinia hanburyi, provoked the decreases in the deposition of collagen and the expression of platelet-derived growth factor, α-smooth muscle actin, and fibroblast growth factor-2 (Qu *et al*., 2016).

Gentiopicroside

Gentiopicroside, a natural compound isolated from Gentiana scabra, improved the pathological changes including fibrotic and inflammatory responses in lungs of bleomycin-induced pulmonary fibrosis model mouse. It suppressed the lung hydroxyproline content, the levels of IL-1β and TNF-α, and the expression of connective tissue growth factor and TGF-β1. Gentiopicroside also suppressed epithelial-mesenchymal transition in A549 cells stimulated by TGF-β1 (Chen *et al*., 2018).

Glaucocalyxin A

Glaucocalyxin A, an anti-inflammatory natural product isolated from Rabdosia japonica, was reported to suppress the levels of proinflammatory cytokine, the infiltration of neutrophils and macrophages, the deposition of collagen, the content of hydroxyproline in the lung of bleomycin-induced pulmonary fibrosis model mouse (Yang *et al*., 2017).

Honokiol

Honokiol, a neolignan natural product isolated from Magnolia officinalis, suppressed the TGF-β/Smad signaling and fundamental pathways of epithelial-mesenchymal transition, *in vitro* and *in vivo*. Honokiol reduced the inflammation and the deposition of collagen and inhibited IL-6/CD44/STAT3 signaling pathway (Pulivendala *et al*., 2020).

Juglanin

Juglanin, a natural product derived from Juglans mandshurica, inhibited the pro-inflammatory response, vascular permeability of lung, and alveolar infiltration of neutrophil, in bleomycin-induced pulmonary fibrosis mouse model. Juglanin suppressed the expression of collagen I, α-smooth muscle actin, TGF-β1, matrix metallo-proteinase-9, and fibronectin, all of which are the hallmarks of fibrosis. Also, juglanin suppressed the stimulator of interferon genes which plays a pivotal role in the progress of fibrosis (Sun *et al*., 2020).

Madecassoside

Oral administration of Madecassoside derived from Centella asiatica exerted a significant antifibrotic effect, in bleomycin-induced pulmonary fibrosis mouse model. The mechanism of action of Madecassoside was suggested to be mediated by gut hormones. Effect of orally-administered madecassoside was not mediated by it or its metabolites, after absorption into blood. Madecassoside might potentiate the action of PPAR-γ, which provokes the expression of hepatocyte growth factor, in colonic epithelial cells. Eventually, hepatocyte growth factor might enter into the systemic circulation and reach to the lung to manifest an antifibrotic effect (Xia *et al*., 2016).

α-Mangostin

In bleomycin-induced pulmonary fibrosis animal model, α-Mangostin derived from mangosteen, suppressed the extracellular matrix deposition, the gene expression of collagen I and α-smooth muscle actin, and TGF-β1/Smad2/3 signaling pathway. It affected the protein expression of matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 in pulmonary tissues (Li *et al*., 2019).

Morin

Morin, a flavonoid compound contained in diverse medicinal plants including Morus alba, mitigated the transformation of fibroblasts towards myofibroblasts via affecting peroxisome proliferator activated receptor-γ - glutaminolysis - DEP domain-containing mTOR-interacting protein signaling pathway, in bleomycin-induced pulmonary fibrosis mouse model (Miao *et al*., 2022).

Myricetin

Myricetin, a flavonoid compound isolated from various fruits and vegetables including Myrica rubra, was reported to regulate the TGF-β1 - Smad2/3 signaling pathway and mitigate the activation of fibroblasts and epithelial-mesenchymal transition, in pulmonary fibrosis model *in vitro* and *in vivo* (Li *et al*., 2020).

Nimbolide

Nimbolide, a terpenoid lactone compound isolated from neem tree, Azadirachta indica, inhibited the expression of mesenchymal and fibrotic markers. It also potentiated the expression of epithelial markers. Nimbolide suppressed the expression of p62 and microtubule-associated protein 1A/1B-light chain 3 and increased the expression of Beclin-1, thereby affecting autophagy (Prashanth Goud *et al*., 2019).

Oridonin

Oridonin, a natural product isolated from Rabdosia rubescens, was reported to mitigate the inflammatory cells infiltration, collapse of alveolar space, and emphysema, all of which are the pathological changes observed in bleomycin-induced pulmonary fibrosis mouse model. Also, it suppressed both the gene expression of α-smooth muscle actin and collagen type I alpha 1 chain and the phosphorylation of Smad2/3 (Fu *et al*., 2018).

Parthenolide

In bleomycin-induced pulmonary fibrosis animal model, parthenolide, a natural product isolated from Tanacetum parthenium, ameliorated the pathological changes provoked by fibrosis progression via suppressing the NF-κB/Snail signaling (Li *et al*., 2018b).

Phycocyanin

Phycocyanin, a phycobiliprotein derived from Spirulina, inhibited the production of myeloperoxidase, tumor necrosis factor-α, interleukin-6, α-smooth muscle actin, hydroxyproline, surfactant-associated protein C, fibroblast specific protein-1, and vimentin, in bleomycin-induced pulmonary fibrosis mouse model. It induced the production of podoplanin and E-cadherin. These antifibrotic action of Phycocyanin might be exerted through toll-like receptor 2 - MyD88 - NF-κB signaling pathway (Li *et al*., 2017b).

Pterostilbene

Pterostilbene, a polyphenol stilbenoid natural product found in blueberries, almonds, and vines and leaves of grape, was reported to alleviate the lung injury and fibrosis scores. It diminished both the levels of hydroxyproline, TGF-β, and collagen I and the release of interleukin-6, interleukin-1β, and tumor necrosis factor-α, in lipopolysaccharide-induced pulmonary fibrosis model. It activates Keap-1/Nrf2 and inhibits caspase-dependent A20/NF-κB and NLRP3 signaling pathways (Yang *et al*., 2020).

Rhapontin

Rhapontin, a stilbenoid natural product isolated from Rheum palmatum, decreased the deposition of collagen, lung pathological score and the expressions of lipoxygenase 2, TGF-β1, hypoxia-inducible factor-1α, and α-smooth muscle actin, in lung tissues of bleomycin-induced pulmonary fibrosis animal model (Tao *et al*., 2017).

Rutin

In bleomycin-induced pulmonary fibrosis animal model, Rutin, a well-known flavonoid compound found in a multitude of fruits, vegetables, and medicinal plants, reduced the numbers of lymphocytes, macrophages, and total cells in bronchoalveolar lavage fluid. It also reduced the levels of nitric oxide and malondialdehyde in lung, and increased the total antioxidant capacity in serum, the level of glutathione, and the activity of superoxide dismutase (Bai *et al*., 2020).

Salvianolic acid B

Salvianolic acid B, a natural product isolated from Salviae miltiorrhiza, was reported to show the antioxidative and antifibrotic potential, in bleomycin-induced pulmonary fibrosis animal model. The expression of nuclear factor erythroid-derived 2-like 2 was reduced in fibroblastic foci areas of the lung exposed to bleomycin, whereas Salvianolic acid B increased the expression. *In vitro* experiment using TGF-β1-stimulated MRC-5 cells showed that Salvianolic acid B inhibited the pro-

duction of reactive oxygen species and malondialdehyde, whereas it increased the levels of glutathione. It increased the expression of nuclear factor erythroid-derived 2-like 2 at the transcriptional and translational steps, *in vitro* (Liu *et al*., 2018).

Scutellarein

Scutellarein, a flavonoid compound isolated from several medicinal plants including Erigeron breviscapus and Scutellaria baicalensis, ameliorated bleomycin-induced pulmonary fibrosis by suppressing the expression levels of fibrotic markers and mitigating the differentiation of fibroblasts to myofibroblasts (Miao *et al*., 2020).

Schisandrin B

Schisandrin B, a natural product derived from Schisandra chinensis, mitigated inflammatory changes and production of collagen fibers in bleomycin-induced pulmonary fibrosis mouse model. It reduced the content of hydroxyproline and the level of TGF-β1, whereas it increased the levels of total antioxidant capacity, hydroxyproline, and superoxide dismutase in lung tissues (Wang *et al*., 2020b).

Sulforaphane

In bleomycin-induced pulmonary fibrosis mouse model, sulforaphane, a natural product derived from diverse vegetables including broccoli, mitigated collagen I level, the expression of TGF-β1, and the expression of fibronectin, in lung tissues (Kyung *et al*., 2018).

Wedelolactone

Wedelolactone, a natural compound isolated from Eclipta Prostrata and Sphagneticola calendulacea, suppressed the infiltration of inflammatory cells, the expression of proinflammatory factors, and the deposition of collagen, in lung tissues of bleomycin-induced pulmonary fibrosis mouse model. It provoked the increase in the expression of fibrotic markers and the decrease in an antifibrotic marker (Yang *et al*., 2019).

Zingerone

Zingerone, a natural phenolic compound derived from Zingiber officinale, was reported to decrease the levels of tumor necrosis factor-α, interleukin-1β, and malondialdehyde, in lung tissues of bleomycin-induced pulmonary fibrosis rat model. It inhibited the accumulation of collagen and the expressions of inducible nitric oxide synthase and TGF-β1. Zingerone increased the activity of glutathione peroxidase and superoxide dismutase. These results suggest that zingerone plays a significant role in amelioration of histopathological alterations, oxidative stress, and inflammation in pulmonary

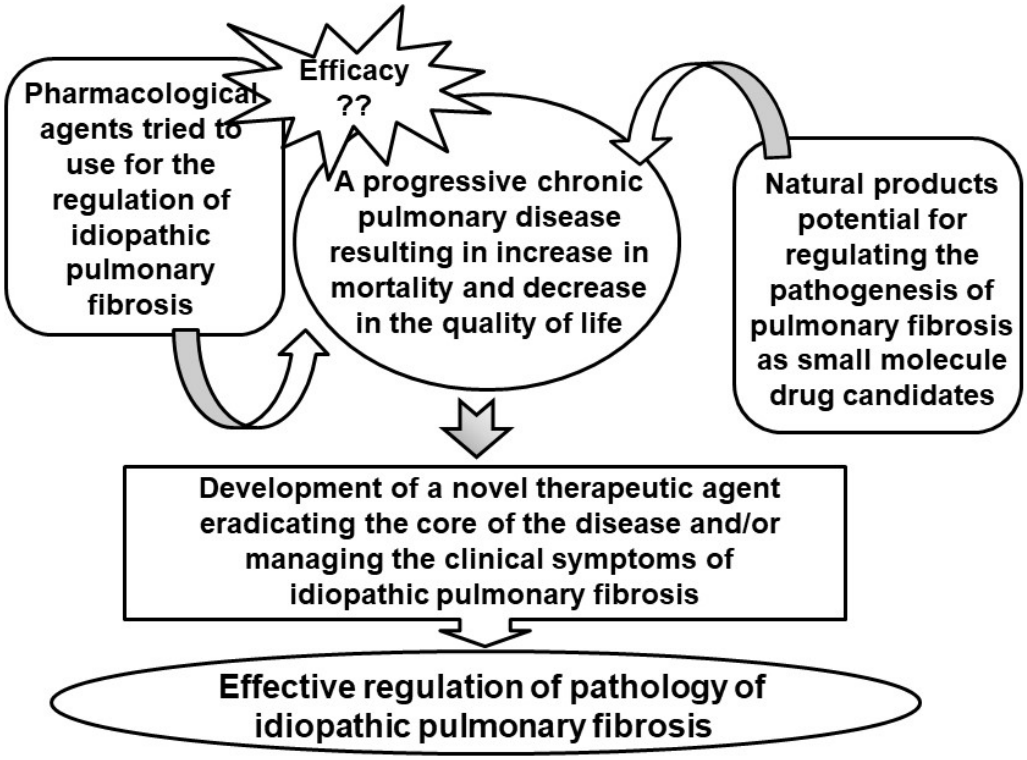

Fig. 1. The strategy for the development of a novel therapeutic agent eradicating the core of the disease and/or managing the clinical symptoms of pulmonary fibrosis. We tried to find a potential of managing the clinical symptoms of idiopathic pulmonary fibrosis (IPF) by natural products derived from medicinal plants used for regulating the pulmonary inflammatory diseases in traditional Asian medicine, based on a multitude of original research articles. A multitude of natural products have been reported to exert an antifibrotic effect in vitro and in vivo through acting on the epithelial-mesenchymal transition pathway, TGF-β-induced intracellular signaling, and the deposition of extracellular matrix. However, clinical antifibrotic efficacy of these natural products on IPF have not been elucidated, yet. Thus, effects on human should be proven by further examinations including the randomized clinical trials, to develop the ideal and optimal candidate for the therapeutics of IPF.

fibrosis (Gungor *et al*., 2020).

CONCLUSION AND FUTURE DIRECTION FOR SEARCHING THE NOVEL DRUGS FOR THE MANAGEMENT AND/OR TREATMENT OF PULMONARY FIBROSIS

A novel therapeutic agent acting on the major steps of the pathogenesis of disease and/or, at least, managing the clinical symptoms of IPF should be developed for the effective regulation of this incurable disease. A multitude of natural products have been reported to exert an antifibrotic effect *in vitro* and *in vivo* through acting on the EMT pathway, TGF-β-induced intracellular signaling, and the deposition of ECM. While the inhibition of the EMT pathway represents a promising approach for the treatment of IPF, it is important to determine the safety and efficacy of EMT pathway inhibitors, in human patients suffering from IPF. At the same time, complete inhibition of TGF-β signaling could have adverse effects, since TGF-β plays significant roles in tissue repair and regeneration. Future research is also needed to determine the safety and efficacy of TGF-β inhibitors. The safety and efficacy of anti-oxidative and anti-inflammatory therapies should be checked through clinical study. Also, complete inhibition of ECM deposition might produce adverse effects, since ECM proteins are reported to be pivotal for normal tissue repair and regeneration. As we review in the above section, the clinical antifibrotic efficacy of these natural products on IPF have not been elucidated, yet. Thus, taken together, those effects should be proven by further examinations including the randomized clinical trials, in order to develop the ideal, safe, and optimal candidate for the therapeutics of IPF (Fig. 1).

CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

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