Herbal Remedies Effective on Treating Idiopathic Pulmonary Fibrosis

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Abstract

Idiopathic Pulmonary Fibrosis (IPF) poses a significant challenge in the realm of respiratory diseases, characterized by progressive lung scarring and compromised breathing function. While conventional medical interventions provide some relief, the exploration of complementary therapies has gained traction, and herbal remedies stand out as a promising avenue. This abstract delves into the efficacy of numerous herbal remedies in the treatment of IPF, shedding light on their potential impact on disease progression and symptom management. Turmeric, derived from Curcuma longa, emerges as a golden healer due to its anti-inflammatory and antioxidant properties, with curcumin exhibiting promise in mitigating lung inflammation and fibrosis. Boswellia serrata, or Indian frankincense, demonstrates anti-inflammatory effects through boswellic acids, suggesting its potential role in suppressing pathways leading to fibrosis. Gingko biloba, renowned for enhancing blood circulation, may contribute to improved oxygenation in individuals with IPF, offering support for compromised lung function. Licorice root, with its anti-inflammatory and expectorant qualities, presents a potential ally in soothing inflammation associated with IPF. Green tea, rich in antioxidants like catechins, shows promise in protecting lung tissues from oxidative stress and inflammation. This abstract emphasizes the importance of caution in integrating herbal remedies, particularly licorice root, and encourages consultation with healthcare professionals to ensure safety, especially in individuals with pre-existing conditions like high blood pressure. In conclusion, the integration of herbal remedies into the treatment paradigm for IPF presents a holistic approach to addressing the complexities of this debilitating condition. As ongoing research explores the mechanisms and efficacy of these herbal interventions, the potential for natural remedies to play a crucial role in managing idiopathic pulmonary fibrosis continues to offer hope for improved patient outcomes.
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Introduction

Lung scarring due to an underlying illness is known as idiopathic pulmonary fibrosis (IPF). Prognosis is usually poor because the condition worsens with time. Progressive dyspnea and a dry, hacking cough are hallmarks of the condition. Restrictive impairment and decreased carbon monoxide diffusing capacity are common findings in pulmonary function tests. If the imaging tests, clinical history, and elimination of other illnesses are all consistent with the diagnosis, then a biopsy is not necessary. Computed tomography (CT) scans often display a characteristic pattern in which bilateral fibrosis is peripherally distributed and most evident at the bases (1). Lung biopsies can be used to confirm a diagnosis of IPF when other tests come out negative. Respiratory assistance, supplemental oxygen, anti-fibrotic medication, and, in severe cases, lung transplantation is all part of the treatment regimen.

Etiology: Tobacco smoke, metal, wood, dust, and gastroesophageal reflux have all been linked to an increased chance of developing IPF, while the disease's actual cause remains unknown. Current theories on the origin of IPF suggest that repeated damage to the alveolar epithelium sets off an immune system signaling cascade that ultimately results in fibrosis. Tissue remodeling might result from an improper immune response to damage (2). There are probably a number of factors at play here. It is unclear if inflammation is a result of fibrosis or its underlying cause

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(3). Most cases occur for unknown reasons, although researchers have pinpointed a few genes that seem to play a role in familial occurrences. Pulmonary fibrosis has been linked to mutations in several different genes, including telomerase (e.g., TERT), surfactant (e.g., SFTPA2), and mucin (e.g., MUC5B). Albinism, platelet abnormalities, and pulmonary fibrosis are all symptoms of Hermansky Pudlak syndrome, another rare autosomal recessive disorder caused by deficiencies in lysosome-related organelles (4).

Epidemiology: Idiopathic pulmonary fibrosis is more prevalent in the elderly and typically does not manifest until the sixth or seventh decade of life. The spread is worldwide, and the frequency seems to be rising. This may be due to the fact that the population is becoming older, or it may be due to the fact that this phenomenon is becoming more widely known (5). The estimated prevalence in the US is between 10 and 60 per 100,000 (6).

Pathophysiology: Environmental variables, such as smoking, chronic aspiration, or viral infections, and ageing, are likely driving factors in the etiology of idiopathic pulmonary fibrosis. Fibroblast activation and dysregulated healing of the alveolar epithelium follow epithelial damage. Pulmonary fibrosis develops when this process causes excessive scarring and matrix deposition in the lung interstitium (7). Destroying the structure of the lungs reduces their capacity to exchanges gases, which leads to hypoxic respiratory failure and ultimately death in advanced disease.

Histopathology: Typically, the histology is inconclusive and shows a mixture of normal and diseased lung tissue. Changes such as interstitial inflammation, honeycomb change, and fibrosis are frequently observed, albeit they are also seen in other forms of severe lung illness. The histological hallmarks of a diagnosis are as follows:

1. Localization of fibroblasts is present.

2. Modifications to the normal structure of the lungs, such as honeycombing

3. Localized fibrosis in the lungs.

4. Negative evidence for a different diagnosis (8).

Presentation and diagnosis: Initial symptoms of IPF, which are most typically dyspnea and cough, are moderate and nonspecific, and they overlap with a wide variety of other common illnesses, making early identification challenging. Symptoms typically worsen before a diagnosis can be obtained and anti-fibrotic therapeutic alternatives explored. Physical examination findings may include the detection of Velcro crackles on respiratory auscultation and the observation of clubbing of the fingers (9).

Restrictive pulmonary function testing (PFT) is evidenced by decreased forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and lung gas transfer efficiency (as determined by measuring carbon monoxide diffusion capacity) (DLCO). A useful indicator and staging method for estimating the likelihood of death due to IPF is the Gender, Age, and Physiology (GAP) Index Score, which incorporates FVC and DLCO in addition to age and gender (10).

The 6-minute walk test is a simple and quick approach to measure exercise capacity, with prognostic relevance due to the correlation between a faster drop in distance travelled and an increased risk of death. IPF mimics the microscopic appearance of ordinary interstitial pneumonia (UIP), which is characterized by alternating patches of normal or nearly normal lung tissue and focal areas of fibrosis with hyperplastic alveolar epithelial cells next to these fibroblastic foci. Gas exchange is hampered because of the impairment in lung architecture.

CT scans are the standard for imaging IPF, but MRI is starting to play a significant role as well. UIP is the most common radiological presentation. CT fibrosis severity can be evaluated both visually and quantitatively with the help of computer techniques (11).

Honeycomb alterations, traction bronchiectasis, and a reticular pattern, most prominent in the periphery of the lower lobes, are common findings on high-resolution CT in patients with chronic obstructive pulmonary disease (12). In addition to the dismal prognosis, IPF patients often shave many comorbidities including hypertension, of chronic obstructive pulmonary disease (COPD) emphysema, diabetes mellitus, and gastroesophageal reflux disease (GERD), These can diminish quality of life, complicate therapy, increase hospitalization, and lead to deterioration of the patient's health.

Herbal medicine for treatment of Idiopathic Pulmonary Fibrosis

Treatment protocols that have been employed traditionally include anti-inflammatories, anti-fibrotics, cytokines, antioxidants, lung transplants, and oxygen therapy. Lung transplantation is the only proven treatment for IPF, according to the 2015 Guidelines for the Diagnosis and Treatment of Idiopathic Interstitial Pneumonia. Even though pirfenidone and nintedanib are recommended by the Guidelines, they are not frequently used in China because of the severe side effects and expensive costs associated with them. There is, therefore, an immediate need to investigate the use of natural medications for IPF treatment. Scientists from the fields of

immunology, biology, and chemistry have been studying the efficacy and worth of traditional medicine as an alternative therapy for quite some time now. There has been a lot of research into the potential of alternative medicine to replace pharmaceuticals (14).

Several researchers have proposed that traditional medicine should be utilized in conjunction with Western medicine as part of a "integrative approach," or individualized method that takes into account each patient's unique health situation. The goal of integrative medicine is to restore health using the best available evidence-based treatments from across the medical and scientific disciplines. Therefore, many specialists are of the opinion that traditional medicine will replace contemporary medicine as the standard approach. In traditional Chinese medicine (TCM), IPF is categorized as "pulmonary flaccidity," "pulmonary arthralgia," and "asthma syndrome," with a lack of vital energy and blood stasis being the root cause. The symptoms of phlegm and blood stasis can be traced back to an underlying lung and renal insufficiency. Low side effects, steady therapeutic action, prolonged duration, general modulation, and the absence of evident medication dependence are just a few of TCM's many advantages. A rising variety of formulations, herbal components, and various forms of Chinese herbal medicine extracts have showed beneficial outcomes in experimental IPF patients in China (15).

Traditional Chinese Medicine (TCM): The Danlou prescription (DLP) is a derivation of traditional Chinese medicine that calls for the use of ten different herbs: Trichosanthes kirilowii Maxim (Gualoupi), Allium macrostemon Bunge, Puerariae Lobatae Radix, Salvia miltiorrhiza Bunge, Astragalus mongholicus Bunge, and Eleutherococcussenticosus Root. Alisma plantago-aquatica L., Ligusticum officinale Mill. Paeonia lactiflora Pall., Davallia trichomanoides Blume Curcuma aromatica Salisb and chuanxiong Hort. Idiopathic pulmonary fibrosis (IPF) caused by bleomycin (BLM) was TGF-activated myofibroblast differentiation and -SMA expression were both suppressed by DLP treatment, leading to a decrease in inflammation. In addition, DLP played a role in the regulation of genes involved in secretion of collagen and endocytosis. Alveolar macrophage and neutrophil recruitment was also enhanced. Controlled myofibroblast differentiation because of these considerations and the potential of due to the ability of DLP to simultaneously inhibit pro-inflammatory and pro-fibrotic pathways, In the case of IPF, it is a potentially effective therapy option (16).

The BuqiHuoxueTongluo formula is another traditional Chinese medicine regime that shows promise as a treatment agent for idiopathic pulmonary fibrosis (BHTF). Ingredients for BHTF include: Astragalus root Japanese honeysuckle flowers, Chinese angelica root, glycyrrhiza root and rhizome, Japanese dandelion root, Korean prickly ash, chinese there is some evidence that the BHTF can reduce the advancement of fibrosis in BLM-induced IPF by promoting anti-inflammatory actions. The BHTF was discovered to suppress the expression of TGF-1 and -SMA in the pulmonary mesenchyme, hence reducing inflammatory cell infiltration, collagen deposition, and fibrosis, all of which are critical initiators of IPF. Also, it was shown that BHTF has the capacity to impact pulmonary surfactant secretion, which assisted to preserve the function of type II alveolar epithelial cells during IPF (17). Qizhukangxian granules (QG) are another TCM that has been studied for their potential to aid individuals with idiopathic pulmonary fibrosis (IPF). Ingredients include: Huangqi (Astragalus mongolicus) and Ezhu (Curcuma longa) rhizomes, Danggui (Angelica sinensis) roots, Shanzhuyu (Macrocarpon fruit), Ziwan (Asteristatarica) roots, Scutellariabaicalensis roots, Zhebeimu (Fritillariathunbergii) bulbs, and Glycyrr QG administration has been linked to a slower decline in pulmonary function, suggesting that it may be a useful therapy option for IPF. Quality of life was also improved due to a reduction in IPF symptoms as compared to the control group. Over the course of 48 weeks of treatment, QG reduced the rate of acute exacerbations without causing any serious side effects. Therefore, the results of this study provide preliminary support for the use of QG as a therapy for IPF. Schisandraechinensis fructus is another commonly used TCM for lung-related conditions such pulmonary fibrosis and bronchitis (Wuweizi, Schisandra). A study done on the BLM-induced model found that Schisandra displayed protective effects in two phases: by improving inflammatory cell infiltration and significant damage to \slung structures, as well as by reducing the biomarkers for the M2 macrophage subtype (18).

Previous studies have demonstrated that M2 macrophages induce fibrosis, so an M2-targeted approach could be a possible treatment option for IPF. Schisandra's ability to suppress M2 polarization was verified by in vitro studies, which also showed that the M2 ratio was reduced. In addition, Schisandraechinensisfructus is another often used traditional Chinese medicine for lung-related conditions such pulmonary fibrosis and bronchitis (Wuweizi, Schisandra). A study done on the BLM-induced model found that Schisandra displayed protective effects in two phases: by improving inflammatory cell infiltration and significant damage to lung structures, as well as by reducing the biomarkers for the M2 macrophage subtype (19).

In a separate experiment, the effects of cryptotanshinone

(CPT) were examined in a rat model that had been induced with BLM. Danshen, a popular TCM plant, is the source of CPT, a diterpenoidquinone molecule. CPT possesses anti-inflammatory, antibacterial, and antioxidant properties. Fibrotic markers were shown to be downregulated after CPT administration, which is consistent with its ability to decrease inflammation and Stat3 phosphorylation. Cell proliferation was inhibited by CPT in a time- and dose-dependent way when tested in NIH/3T3 (mouse embryonic fibroblasts), human primary fibroblasts, and primary rat pulmonary fibroblasts. After CPT treatment, epithelial markers increased while mesenchymal markers decreased. This suggests that the EMT process was stifled. Consequently, CPT's anti-fibrotic actions make it a potentially effective treatment for IPF (20).

Triptolide is another promising anti-IPF chemical (TPL). Tripterygium wilfordii Hook F, derived from a plant native to China, has had extensive usage in traditional Chinese medicine. It has anti-inflammatory and immunosuppressive properties as well. Smad-3, E-cadherin, and vimentin are hallmarks of EMT beginning and a recent study found that TPL suppressed EMT of lung epithelial cells by directly binding to TGF-. TPL was shown to reduce lung fibrosis in mice in an in vivo investigation. TPL has therapeutic promise for IPF because of the strong correlation between EMT and IPF. Gancao Ganjiang decoction (GGD) is another Chinese herb compound commonly used for atrophic lung disease treatment. Extract from dried rhizomes and roots of Glycyrrhizauralensis Fisch. And Zingiber officinale Roscoe (2:1) is used to make this decoction (21).

Wang et al., (2021) discovered that 14 days' therapy with GGD in IPF mice had exhibited an inhibition of early fibrosis and reduced disease development. Furthermore, during 28 days of the treatment, it was found that GGD substantially reduced the deposition of extracellular matrix \sin pulmonary fibrotic mice and alleviated the degradation of lung tissue structure at the \send stage of the disease. Similar to TPL, treatment of GGD inhibited the expression of TGF-β, vimentin, and α-SMA. Taken together, our in vivo findings support the potential use of GGD as an anti-IPF medication (22).

Similarly, in a study done by Tian et al., (2019), the YiqiHuayuHutan decoction alleviated expression of the TGF-β/Snail pathway in the BLM-induced pulmonary fibrosis mice. A

decrease in the TGF-β, Snail-1, and fibronectin protein levels appeared in the treatment group, particularly in the "moderate concentration" decoction. As a result, this concoction shows promise as a potential IPF treatment (23).

Bioactive Compounds and Phytochemicals: Natural chemicals derived from plants or roots may also have a therapeutic effect on IPF, in addition to TCM. Among plant foods, quercetin (QE) is the most abundant flavonoid and can be extracted from a variety of sources, including fruits, vegetables, and even some Chinese herbs. QE is cheap, safe, and has few adverse effects; it can be made from a variety of sources. It has pharmacological effects against tumors, viruses, inflammation, free radicals, and blood clots. Researchers Zhang et al., (2018) found that knocking down sphingosine kinase 1 (SphK1)/ sphingosine 1-phosphate (S1P) signaling in human embryonic lung fibroblasts (HELFs) may reduce BLM-induced lung fibrosis and TGF-induced lung fibrosis. According to Veith et al., (2017), a disruption of pulmonary redox balance coupled with inflammation is a defining feature of IPF. QE, as an exogenous antioxidant, may ameliorate

redox-associated disorders by increasing the expression of nuclear factor erythroid 2-related factor (Nrf-2) and Nrf-2-regulated genes (24).

The development of the illness in the BLM-induced mouse model was also inhibited by a bioactive component derived from Sorbusaucuparia. Treatment with aucuparin was associated with a reduction in inflammatory gene expression and indicators of macrophage activation. Following aucuparin administration, profibrotic marker gene expression was reduced while antifibrotic marker gene expression was elevated. In addition, aucoparin administration was shown in this study to reduce TGF—induced activation of inflammatory cytokines and collagen formation in macrophages and fibroblasts (25). These findings point to aucaparin as a potential treatment for IPF. Isolated from green walnut husks of Juglansmandshurica, juglanin (Jug) is another natural chemical that showed promise therapeutic impact towards IPF. These chemicals have been shown to have beneficial effects against oxidation, inflammation, and scarring. The survival rate of mice treated with Jug was dramatically higher than those of mice challenged with BLM (26).

Treatment with Jug had generated a decrease in neutrophil alveolar infiltration and lung vascular permeability, as well as anti-inflammatory effects in BLM-induced animals. Fibrotic markers like transforming growth factor 1, fibronectin, matrix metalloproteinase (MMP)-9, -smooth muscle actin (-SMA), and collagen I were reported to be downregulated. The stimulator of interferon genes (Sting), which is known for causing fibrosis, was also observed to be significantly reduced in Jug-treated mice as compared to BLM mice. As a result, Jug has promise as a treatment agent for IPF due to its propensity to stimulate tissue regeneration and mitigate the

disease's development (27).

Gamboge, also known as garciniahanburyi Hook. f, is a Southeast Asian plant that produces a dry resin called gambogic acid (GA). GA displayed anti-tumor cell proliferation and anti-inflammatory, anti-bacterial, and neuroprotective effects. As a 100% natural Chinese herbal remedy, it also has a reduced potential for side effects and minimal chance of contamination. GA was found to inhibit transforming growth factor beta 1, inhibit platelet-derived growth factor (PDGF), and decrease fibroblast growth factor (FGF)-2 expressions by Qu et al. (2016). This means that GA can be used as a novel medicine for the treatment of IPF, both in its incipient and fibrotic forms (28).

Astragaloside IV is the active component found in the dried roots of Mongolian Astragalus, also known as Astragalus membranaceus (ASV). Research has revealed that ASV can reduce inflammation and prevent tissue scarring. Because EMT is involved in the development of IPF, an ASV that significantly reverses EMT in the BLM-induced model may protect against the development of pulmonary fibrosis and thus be a useful therapeutic treatment for IPF. It has been found that ASV can downregulate EMT in fibrosis by inhibiting TGF-1- and PI3K/Akt-induced forkhead box class O (FOXO)3ahyperphosphorylation. Administration of ASV, a natural saponin with anti-fibrotic characteristics, significantly mitigated degenerative changes to alveolar

epithelial cells. Consistent with a prior study finding that ASV may decrease collagen III, laminin, hyaluronic acid, and hydroxyproline in lung tissue homogenate, the present results show that ASV can really accomplish this (29).

Salvianolic acid B is abundant in the roots and rhizomes of S. miltiorrhiza Bunge, another herb with possible anti-IPF effects (SAB). To treat IPF, Liu et al. (2016) found that SAB reduced cell infiltration, prevented alveolar structural degradation, and reduced collagen deposition. SAB also blocked Smad-dependent and -independent MAPK signaling to suppress TGF-induced myofibroblast development in MRC-5 normal human foetal lung fibroblasts and TGF-mediated EMT in A549 lung cancer epithelial cells. According to another study, SAB induced nuclear translocation of the antioxidant protein Nrf-2, which protected cells from oxidative stress in vitro (30).

Treatment with SAB upregulated Nrf-2 expression in fibrotic lung tissues, as evidenced by immunohistochemistry (31). Rheum palmatum L. and Eucalyptus robusta Smith are two examples of plants from which gallic acid was extracted, and its reputed role as the "finest organic polyphenol molecule" has garnered it much attention. In order to treat IPF, Chen et al. (2013) found that gallic acid induced hydrogen peroxide production stimulated the c-Jun N-terminal kinase (JNK) signaling pathway, leading to activation of the human tumor suppressor gene p53 and apoptosis of mice pulmonary fibroblasts. Gallic acid derivatives may have therapeutic promise for idiopathic pulmonary fibrosis (IPF) since they have been shown to reduce inflammation through the TGF-1/Smad-2 signaling pathway and to maintain a healthy NADPH oxidase-4 (NOX4)/Nrf-2 ratio (32).

Tanshinone IIA (TSIIA) is a fat-soluble diterpenoid active chemical that is also derived from S. miltiorrhiza Bunge. Treatment with TSIIA decreased BLM-induced inflammation, pro-inflammatory cytokine levels, and collagen expression in rat lung tissues, as reported by He et al., (2015). In addition, TSIIA prevented the production of nitric oxide and abnormal oxidation that BLM produced in the mouse model. Additionally, it was found by Wu et al. (2014) that TSIIA may reduce TGF overexpression and recover the loss of ACE-2 and ACE-1-7 in lung tissues. That is to say, TSIIA is associated with a higher likelihood of protection from IPF (33).

Another natural active ingredient that could be a useful therapy agent for IPF is black tea extract (BTE) (BTE). Reports indicate that BTE, at a dose of 50 mg BTE/ kg, inhibits fibrosis in a BLM-induced mouse model (Chakraborty et al., 2019). Collagen deposition was lower in BTE-treated mice compared to untreated mice (34). Reducing -SMA expression, which plays a critical role in contributing to pulmonary fibrosis, eased experimental lung fibrosis in the BTE-treated mouse. TGF- was greatly reduced and interferon gamma (IFN-), an anti-fibrotic molecule, was increased after treatment with a 50 mg/kg dosage of BTE (35).

Furthermore, a study by Li et al., (2022) found that the flavonoids of Oxytropisfalcata Bunge (FOFB) have demonstrated potential therapeutic actions towards IPF by targeting the TGF-

madsignalling pathway. TGF-β is known to promote fibrosis as EMT \sis triggered through the TGF-β/Smadsignalling pathway. This study has found that with an increasing dose of FOFB, the pulmonary fibrosis was gradually attenuated with clear suppression of the TGF-β/Smad pathway. At a dose of 400 mg kg1 day1, FOFB significantly attenuated the development of lung fibrosis in rats (36).

Myrtle (Myrtuscommunis L.), a member of the family Myrtaceae native to Iran's tropical regions, is the source of another naturally occurring chemical. Because of its antioxidant and anti-inflammatory characteristics, it has found widespread application in the treatment of respiratory-related disorders. Myrtle may contribute to

the therapy of IPF by inhibiting inflammation, reducing lung parenchymal fibrosis, and lowering hydroxyproline levels. Histopathological investigations demonstrated that myrtle slowed fibrotic abnormalities such as bronchioles and alveolar wall thickening in both the early and late stages of BLM-induced fibrosis, with little side effects. Extract of grape seed proanthocyanidin (GSPE) has been shown to reduce inflammation and prevent lung damage caused by amiodarone. Sul et al., (2022) investigated the effectiveness of GSPE in a mouse model of BLM-induced lung fibrosis. Reducing oxidative stress and subsequent epithelial apoptosis slowed the development of pulmonary fibrosis. Since oxidative stress is linked to alveolar damage, inflammation, and fibrosis, treating this factor might be useful in the treatment of IPF. GSPE dramatically decreased histological alterations and collagen deposition in BLM-induced lungs. Lung inflammation was reduced, and bronchoalveolar lavage volume was reduced, in response to GSPE therapy. Oxidative stress in the lungs was brought on by the increased production of hydrogen peroxide that was triggered by BLM. We found that GSPE significantly mitigated the oxidative stress after treatment (37).

Rosemary leaf extract, which is rich in carnosic acid (CA) and rosmarinic acid, is another natural chemical with anti-IPF properties (RA). Rats with BLM-induced lung fibrosis were subjected to tests of CA rich extract, RA rich extract, and their synergistic impact. Both extracts (separately and together) were found to diminish lung fibrosis and oxidative stress, even when administered at the lowest effective level (10 mg/kg). When administered, the synergistic treatment proved to be more curative than the individual components. However, the extracts lost their efficacy when given in greater quantities (38).

Emodin and andrographolide are two more phytochemicals that showed promise in combating IPF. Reynoutria japonica Houtt and Rheum palmatum L., both of the family Polygonaceae, are the main sources of emodin. IPF patients who take this drug have less pulmonary edoema and fibrosis, less collagen deposition, and less myofibroblast and inflammatory cell invasion. Emodin also reduced levels of inflammatory markers in the lungs, including tumour necrosis factor alpha, interleukin-6, transforming growth factor beta 1, and heat shock protein 47. Conversely, Andrographispaniculata's primary active component, andrographolide (AND), has been shown to increase glutathione levels while decreasing malondialdehyde levels and oxidised glutathione.

This may help reduce the changes in the MMP-1/tissue inhibitors of MMP-1 ratio that result from BLM. Therefore, it might have a curative effect on IPF (39).

Korean Herbal Medicine: Root of Rehmanniaglutinosa, cortex of Paeonia suffruticosa, fruit of Schizandrachinensis, root of Asparagus cochinchinensis, seed of Prunusarmeniaca, root of Scutellariabaicalensis, and root of Stemonasessilifolia make up the PM014, an herbal medication used extensively in Korea for pulmonary diseases. PM014 increased lung function by reducing inflammation caused by radiation exposure. This effect was achieved by blocking inflammasome activation. A recent study demonstrated that blocking the TGF-1 pathway with the chemical PM014 reduced lung fibrosis. PM014 inhibited TGF-1-induced EMT and fibroblast activation in alveolar epithelial cells via the Smad-dependent and p38 MAPK pathways, according to an in vitro investigation of idiopathic pulmonary fibrosis. Inhibiting the onset and development of inflammatory responses in lung fibrosis, PM014 shows promise as a treatment for IPF. Astilberubra Hook. F. et Thomas. (familySaxifragaceae) is another perennial herbaceous plant that grows in the mountains of Korea. Inhibitory effects of A. rubra-isolated -peltoboykinolic acid on EMT were investigated by Bang et al. (2019). Because epithelial-mesenchymal transition (EMT) results in the development of fibroblasts that promote fibrosis progression, blocking EMT with a specific inhibitory drug may be beneficial. Treatment of IPF may benefit from taking action against EMT. To reduce TGF-1-induced extreme morphological change (EMT) and excessive production of extracellular matrix components (such as type I collagen and the effects of -peltoboykinolic acid on fibronectin were observed. Furthermore, the inhibition of after treatment with -peltoboykinolic acid, TGF-1-induced Smad/Snail signaling suppressed EMT. For proper control of fibrotic EMT, the Smad pathway must be inhibited. To treat IPF, a compound like -peltoboykinolic acid could prove quite useful (40).

Ayurvedic Medicine: Idiopathic pulmonary fibrosis (IPF) is effectively treated with both traditional Chinese medicine and Ayurvedic medication. A well-known diketone, curcumin (CUR) is extracted from turmeric but is insoluble in water due to its unsaturated esters and aromatic groups. CUR has been found to have many beneficial pharmacological effects, including anti-inflammatory, antibacterial, antioxidant, hypolipidemic, and cancer-fighting characteristics. This active chemical is so low in toxicity that it can even be used to treat hepatitis C virus infections, with minimal risk of adverse consequences. The formation of myofibroblasts, which occur when lung fibroblasts are activated by TGF-b in IPF, was found to be suppressed by CUR. By inhibiting matrix metalloproteinase-9 (MMP-9), CUR also protects against IPF in a mouse model (41). The herbal medications used to treat IPF are summarized in Table 1 below.

Category	Name	Findings	Reference
	1. Danlou prescription ■ Trichosanthes kirilowii Maxim (Gualoupi) ■ AlliummacrostemonBunge ■ PuerariaeLobataeRadix ■ SalviamiltiorrhizaBunge ■ Astragalus mongholicus Bunge ■ Davallia trichomanoides Blume ■ PaeonialactifloraPall ■ Alismaplantago-aquatica L. ■ LigusticumchuanxiongHort Curcuma aromatica Salisb	■ Inhibited transforminggrowth factor (TGF)-activated myofibroblast differentiationand α-smooth muscle actin ■ (SMA) expression – ■ Regulated genes thatarerelatedto endocytosis and collagensecretion- Suppressed pro- inflammatory wand pro-fibrotic pathways ● Exhibitedanti- inflammatory effects ● Reducedcollagen deposits ● SuppressedTGF- β1 and α-SMA expressions	(42,43)
	2. BuqiHuoxueTongluoformula ● AstragaliRadix (Huangqi) ● LoniceraeJaponicaeFlos (Jinyinhua) ● Angelicae Sinensis Radix (Danggui) - Glycyrrhizae Radix etRhizoma (Gancao) ● Dioscoreae Nipponicae Rhizoma(Chuanshanlong) ● PyrrosiaeFolium (Shiwei) ● FritillariaeThunbergiiBulbus (Zhebeimu) ● TrichosanthisFructus (Gualou) ● PlatycodonisRadix (Jiegeng) ● AurantiiFructus (Zhiqiao) ● RhodiolaeCrenulataeRadix et Rhizoma (Hongjingtian)	Delayed pulmonary function deterioration ● Lowerincidence rate of acute	(44) (45)
	3. Qizhukangxiangranules ● Huangqi(RadixAstragali Mongolici) ● Ezhu(RhizomaCurcumae Phaeocaulis)		

Category	Name	Findings	Reference
	Danggui(RadixAngelicae Sinensis) • Shanzhuyu(Fructus Macrocarpii) •	exacerbation	
	4. Citrusalkalineextract-Peelof Citrus reticulata.	• Decreased synthesis of collagen, crosslinking,and deposition • Downregulatedthe TGF-β1/Smad-3 pathway • Protected against inflammatorycell infiltration and lung damages Reducedandsuppressed M2 macrophages	(46)
	5. Wuweizi, Schisandra - Schisandrae-chinensisfructus	• Reduced inflammationand Stat3 phosphorylation • Inhibitedepithelial to mesenchymal transition (EMT)	(47)
	6. Cryptotanshinone- Danshen	• Inhibited EMT of lungepithelialcells through direct binding to TGF-β • RegulatedSmad-3, E-cadherin, and vimentin expressions	(48)
	7. Triptolide-Tripterygium wilfordii Hook F	• Inhibited early fibrosisandslowed	(49)
	8. GancaoGanjiangdecoction- Extraction of dried rhizomes and		

Category	Name	Findings	Reference
Bioactive compounds and chemicals	**1. Quercetin1. Danlou prescription**	• Decreased sphingosinekinase 1 (SphK1)/ sphingosine 1- phosphate(S1P) signalling - Exhibited antiox idative effects	(54)
	2.Aucuparin-Sorbusaucuparia	• Decreased inflammatorygene expression, macrophage activation-related markers, and profibrotic marker gene expression • Increased antifibroticmarker genes-Suppressed inflammatory cytokines and collagen synthesis • Reducedneutrophil	(55)

Category	Name	Findings	Reference
	3. Juglanin-Greenwalnuthusks of Juglans mandshurica	infiltrationand lung vascular permeability ● Reduced the expression of fibrotic markers such as TGF-β1, fibronectin,matrix metalloproteinase (MMP)-9,α-SMA, collagen I, and stimulator of interferongenes (Sting) ● Regulated vasohibin-1and-2 -BlockedTGF-β1 - Redudplatelet- derived growth factor(PDGF) and fibroblast growth factor (FGF)-2	(56)
	4.Gambogic acid - A dry resin exudedby Garciniahanburyi HookF.	● Reversed EMT process ● Inhibited TGF-β1/ phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt)- induced forkhead box class O (FOXO)3a hyperphosphorylati on ● Reduced degenerative alterations of alveolar epithelial	(57)
	5. Astragaloside IV - Dried roots of MongolianAstragalus,alsoknownas Astragalus membranaceus		(58)

Category	Name	Findings	Reference
	6. SalvianolicacidB-Rootsand rhizomes of Salvia miltiorrhiza Bunge	Cells	
	7. Gallicacid-RheumpalmatumL. and Eucalyptus robusta Smith	• Inhibited cell infiltration, alveolarstructure • destruction, collagen deposition,and myofibroblast differentiation	(59)
		• Regulatedc-JunN- terminal kinase (JNK) • signallingpathway, tumour suppressor • genep53,and apoptosis	(60)

Category	Name	Findings	Reference
Korean herbal medicine	**1. PM014-Chung-Sang-Bo-Ha- Tang (root of Rehmannia glutinosa - Cortex of Paeonia suffruticosa - Fruit of Schizandra chinensis - Root**	● Exerted anti- inflammatoryeffect ● Inhibited TGF-β1 pathway	(61,62)
	ofAsparaguscochinchinensis -Seed of Prunus armeniaca - RootofScutellariabaicalensis -Root of Stemonasessilifolia)	● Suppressed EMT and fibroblast activation by targeting Smad- dependent and p38 MAPK pathways ● Inhibited EMT and extracellularmatrix production - Inhibited Smad/Snail signalling pathway	
Ayurvedic 2medicine	Curcumin	Inhibited TGF-beta-inducedmyofibroblasts- Inhibited MMP-9	(62)

Conflict of interest

The authors declare that they have no conflict of interest in this work..

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