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Review

An Overview of Herbal Medicines for Idiopathic Pulmonary Fibrosis

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Abstract: Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung scarring condition with the histological characteristic of typical interstitial pneumonia. Injury to alveolar epithelial cells is a critical precursor in the pathogenesis of this disease. The prevalence of IPF is growing exponentially, with substantial morbidity and mortality rates increasing the burden on economic healthcare costs. A multidisciplinary approach for diagnosis is used to rule out the alternative causes of interstitial lung disease. Pirfenidone and nintedanib, two innovative antifibrotic medicines introduced in recent years, have provided therapeutic benefits to many IPF patients, and several IPF medications are in the early phases of clinical trials. However, available medications can cause unpleasant symptoms such as nausea and diarrhoea. More efforts have been made to uncover alternative treatments towards a more personalised patient-centred care and hence improve the outcomes in the IPF patients. Through a multi-level and multi-target treatment approach, herbal medicines, such as Traditional Chinese Medicine (TCM), have been identified as revolutionary medical treatment for IPF. Due to their natural properties, herbal medicines have shown to possess low adverse effects, stable therapeutic impact, and no obvious drug dependencies. Herbal medicines have also shown anti-inflammatory and anti-fibrotic effects, which make them a promising therapeutic target for IPF. A growing number of formulas, herbal components, and various forms of Chinese herbal medicine extracts are available for IPF patients in China. This review summarises the role of herbal medicines in the prevention and treatment of IPF.

Keywords: idiopathic pulmonary fibrosis; herbal medicine; Traditional Chinese Medicine

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1. Introduction

Interstitial lung diseases (ILDs) are a broad group of diseases defined by interstitial inflammation, cell growth, fibrosis, or a combination of symptoms associated with the alveolar wall. They are classified as chronic fibrotic lung diseases with a median survival duration of 3 to 5 years after diagnosis [1]. ILDs are progressive and influenced by genetic and environmental variables. Researchers have identified many factors that are associated with ILDs, such as exposure to toxins and infectious agents, medications, the hepatitis C virus, chronic obstructive lung disease, neoplastic disease, immunologic conditions, and a history of pneumonia or tuberculosis [2,3]. There are many varieties of interstitial pneumonia, but idiopathic pulmonary fibrosis (IPF) is one of the most common [4].

IPF is characterised by progressive and persistent lung fibrosis. When alveolar epithelial cells die, they are replaced by fibroblasts, and this is the hallmark of IPF. Alveolar cells are responsible for the regeneration of alveolar epithelial cells [5,6]. IPF often affects people over 50 years old and is accompanied with a radiological and/or histological pattern of typical interstitial pneumonia.

The true incidence and prevalence of IPF is not well documented. The results of epidemiological studies vary greatly depending on the criteria used to describe the disease,

the research population, the technique, and the study design [7]. Nevertheless, the incidence is predicted to be 4.6–7.4 occurrences per 100,000 population, with a frequency of 13 cases per 100,000 in women and 20 cases per 100,000 in men. The number of IPF patients in Spain is estimated to be between 8000 and 12,000 people. It is unclear whether ethnic, racial, or geographical factors influence the statistics [8].

IPF is a life-threatening condition with a dismal prognosis. Despite administered treatment, lung function continues to deteriorate as the disease advances, eventually leading to respiratory failure and death. From the time of diagnosis, the median survival time is only 2 to 3 years [8]. Glucocorticoids, immunosuppressive or cytotoxic medicines, tyrosine kinase inhibitors, and antifibrotic drugs are now used to treat IPF. Nonetheless, clinical studies have revealed that several medicines are possibly inefficient or hazardous [5,6], with only pirfenidone and nintedanib proving to be effective disease-modifying therapy for IPF [9,10]. Lung transplantation, in addition to pharmaceutical therapy, can extend survival and enhance quality of life in IPF patients, with a 5-year survival rate of over 50% [10]. However, due to the high cost and scarcity of donor organs, only a few patients are eligible for transplantation. In short, a novel therapy for IPF with a demonstrable impact and fewer side effects is urgently needed.

Traditional Chinese Medicine (TCM) has shown promising effects against IPF in animal models and humans in recent years. TCM was indicated as an experimental treatment for IPF, and many different techniques of TCM were widely employed in the clinical settings of China [11]. The treatment efficacy of TCM on IPF is still debated due to a lack of large-scale, multi-centre, randomised controlled trials. Apart from TCM, Ayurvedic medicine as well as contemporary systems such as anthroposophical medicine, naturopathic medicine, chiropractic medicine, and homeopathy comprise the umbrella term "complementary and alternative medicine" (CAM). CAM is frequently associated with a distinct medical methodology that incorporates the diagnosis and therapy based on established healing systems and beliefs. This medical system takes a customised and non-reductionist approach, which is exemplified by a complex nonlinear intervention that functions in both independent and interdependent forms [12].

This article discusses several types of herbal medicines, mainly TCM, natural compounds, phytochemicals, Korean medicine, and Ayurverdic medicine, which can be used to treat or alleviate the symptoms of IPF, in comparison with conventional treatments such as medications and surgical options. This review discusses in vitro, in vivo, and clinical studies within the last 5 to 10 years that were obtained by searching the keywords (such as herbs, traditional Chinese medicine, natural product, idiopathic pulmonary fibrosis) on search engines such as PubMed, Google Scholar, and other resources. This review also aims to provide more information on different categories of herbal medicine albeit similar review articles being published before, that mostly focused on reviewing with or without meta-analysis on a single type of herbal medicine, such as TCM only [13–15]. Hence, this review article aims to cover the broader topic of herbal medicine for IPF. Furthermore, the future directions and role of herbal medicine as a viable treatment option are highlighted.

2. Idiopathic Pulmonary Fibrosis (IPF)

2.1. Pathogenesis of IPF

The pathogenesis of IPF remains ambiguous, and proposed theories are constantly evolving. To the author's knowledge, there is no single mechanism which can explain all forms of lung fibrogenesis, as a multitude of factors are likely to be involved in the process [16].

IPF was once thought to be the outcome of an inflammatory process. More current perspectives imply that repetitive subclinical lung injury causes epithelial damage, which leads to the breakdown of the alveolar capillary basement membrane [17]. This allows fibrogenic cells to infiltrate the alveolar interstitium, where they activate fibroblasts and produce highly contractile alpha-smooth muscle actin (α-SMA)-positive myofibroblasts, which are thought to be the primary effector cells in pulmonary fibrosis [16]. It is unclear at

which point the epithelial repair failure leads to excessive deposition of disordered collagen and eventually, lung fibrosis.

Nevertheless, factors that promote epithelial injury, such as persistent inflammation, or factors that hinder epithelial repair, such as decreased epithelial proliferation and increased apoptosis, may induce fibrosis. Processes that promote matrix deposition through improved myofibroblast transformation and proliferation together with slowed apoptosis are fibrogenic. These processes, in addition to disrupted epithelial-mesenchymal interaction, are hypothesised to be the cause of IPF [17]. Notably, epithelial transforming growth factor (TGF)-beta activation is a critical step in epithelial injury and repair. TGF-beta has a big impact on epithelial cells and fibroblasts, the key players in pulmonary fibrosis development. Epithelial cell death, epithelial-to-mesenchymal transition (EMT), epithelial cell migration, collagen synthesis, fibroblast proliferation, and myofibroblast transformation are all aided by TGF-beta stimulation [16].

2.2. Aetiology of IPF

Although the cause of IPF is uncertain, it is thought to be caused by a combination of circumstances in people who are genetically susceptible to the disease. Interstitial lung diseases, such as non-specific interstitial pneumonia and cryptogenic organising pneumonia, can affect members of the same family. This condition is caused by mutations in telomerase genes such as telomerase reverse transcriptase (TERT), telomerase RNA component (TERC), or dyskerin (DKC), as well as surfactant protein C and mucin 5B promoters (MUC5B) [18].

Risk factors for the disease are smoking, silica, brass, and steel dust exposure, working with livestock or in agriculture, and building wooden houses. Furthermore, gastroesophageal reflux (GER) that can lead to aspiration or microaspiration of gastroesophageal content may play a role in the aetiology of IPF [19]. Damage to the alveolar epithelial cells, a feature of IPF, may be triggered by GER. Despite much research interest, there is little evidence to imply that viral infections (hepatitis C virus, herpes virus, adenovirus) cause IPF [20].

Interstitial pneumonia is associated with connective tissue disorders, including rheumatoid arthritis, which suggests that autoimmunity may play a role in IPF pathogenesis [21]. A recent study suggested that the primary pulmonary condition is classical interstitial pneumonia in undifferentiated connective tissue disease [22]. On the other hand, inflammatory pulmonary disease is thought to be a result of lung senescence, in which specific pathogenic mechanisms arise in people with advancing age. Human interstitial disease has been detected incidentally in persons over 75 without respiratory symptoms, through high-resolution computed tomography (HRCT). However, it is not apparent if these alterations are the result of lung ageing or an actual interstitial disease [23,24].

2.3. Signs and Symptoms of IPF

During the initial clinic visit, dyspnoea is the most common complaint by IPF patients [25]. Persons with IPF are more likely to develop cough if they have never smoked or if their disease is more advanced. Cough is regarded as an independent predictor of disease development and the presence of MUC5B promoter polymorphism is significantly linked with the severity of cough, which is a prevalent, debilitating component of IPF [26].

Symptoms such as arthralgia or sicca may also be present in IPF. Hence, clinicians, including rheumatologists, should look for these symptoms when diagnosing IPF [27]. Thirty to 50 percent of IPF patients have been documented to have fine crackles, primarily in the lower posterior lung zones, and clubbed fingers. The occurrence of clubbing is linked with the degree of smooth muscle proliferation in areas of fibrotic alteration [25].

A chest X-ray in IPF patients shows basilar peripheral and bilateral reticular opacities, which may or may not be linked with a honeycomb pattern. In addition, HRCT reveals typical interstitial pneumonia features, involving basilar and subpleural regions of lungs, as well as reticular and honeycomb features with or without traction bronchiecta-

sis/bronchiectasis [28]. Neutrophilia with or without eosinophilia is found in 85 percent of instances with bronchoalveolar lavage. Occasionally, these cells appear normal. In the case of lymphocytosis (more than 20%), other underlying conditions, such as chronic hypersensitivity pneumonitis, should be further explored [28].

An anomaly in ventilatory activity with reduced lung volumes and carbon monoxide diffusing capacity is revealed by respiratory function tests using diffusing capacity for carbon monoxide (DLCO), a simple stress test used to determine exercise tolerance. Hypoxaemia and hypercapnia often develop in the later stages of IPF [28].

2.4. Treatment and Management of IPF

Since 2014, immunosuppressive medicine (despite a lack of data to support its efficacy or safety in this patient population), oxygen saturation, and palliative therapy were the mainstays of IPF treatment. However, the prednisone, azathioprine, and N-acetylcysteine triple treatment was associated with an increased risk of hospitalisation and death in the PANTHER-IPF study [29]. Steroid treatment may be employed in cases of severe, progressive respiratory distress when immunosuppressants are no longer suggested [29]. Antifibrotic medicines which include pirfenidone and nintedanib have been incorporated in the treatment for IPF in recent years to impede disease progression [10]. Patients with mild-moderate IPF with forced vital capacity (FVC) > 50% and DLCO > 30% are generally treated with these drugs. The duration of treatment depends on the progression of the condition [10].

Gastrointestinal problems are the most common side effects of IPF treatments. There were 61.5% more cases of diarrhoea recorded with nintedanib than with a placebo, and 5.3% of patients who received nintedanib discontinued treatment due to the condition. Treatment interruption, dose decrease (to 100 mg twice daily), and strategies to minimise symptoms (e.g., use of loperamide) are usually effective in managing the gastrointestinal side effects associated with nintedanib [30]. Thirty-five percent of IPF patients treated with pirfenidone 2403 mg/d (the recommended dose) experienced nausea compared to 15.1% of patients in the placebo group. Consistent with nintedanib, ways to control the gastrointestinal toxicity associated with pirfenidone include reducing the dose or stopping the medication. Furthermore, this medication can also be used after meals [31].

As for non-pharmacological treatment, lung transplantation is an option to patients who are in the severe stages of the disease. Eighty one percent of people survived the first year, 64% survived the third year, and 51% survived the fifth year post-transplant. Unilateral and bilateral transplants have equal survival rates [32]. More recent advancements in research explored cell treatment and gene therapy to treat IPF in vivo. The success of this treatment as an alternative treatment or in conjunction with pharmaceuticals will have to be determined over time [32].

A Cochrane Collaboration's 2008 review, which was revised in 2010, found that pulmonary rehabilitation improved the distance travelled in the 6-min walk test and overall health-related quality of life in patients with diffuse interstitial lung disorders, including IPF [33]. Mild-moderate illness, according to recent research, has the longest-lasting impacts. As such, before the disease advances, IPF patients are recommended to participate in a pulmonary rehabilitation programme [34].

3. Herbal Medicines for IPF

Anti-inflammatories, antifibrotics, cytokines, antioxidants, lung transplantation, and oxygen therapy have been the commonly used regimes in conventional treatment. As noted in the 2015 Guidelines for the Diagnosis and Treatment of Idiopathic Interstitial Pneumonia, the only effective treatment for IPF is lung transplantation. Pirfenidone and nintedanib are recommended in the Guidelines, but they are not widely used in China due to their severe side effects and high costs [29]. Therein lies an urgent need to explore herbal medicines for IPF management.

For years, researchers in the fields of immunology, biology, and chemistry have studied the effectiveness and value of traditional medicine as an alternative therapy. The use of traditional medicine as a substitute for pharmaceuticals has been studied extensively [35]. Several investigators argued that modern and traditional medicines should not be separated, and traditional medicine should be used in an "integrative approach", which is a personalised strategy that considers the patient's specific conditions [36]. Integrative medicine aims to use all appropriate interventions from a wide range of science fields to restore health [37]. Hence, many experts believe that traditional medicine will eventually become the mainstream of modern medicine. In TCM, IPF is classified as "pulmonary flaccidity", "pulmonary arthralgia", and "asthma syndrome", with deficiency of vital energy and blood stasis as the essence. The root cause of the disease is noted to be a deficiency in the lung and kidney, with phlegm and blood stasis emerging as the symptoms [38]. Benefits of TCM include low adverse effects, stable therapeutic impact, long duration, overall regulation, and no obvious drug dependencies. Preclinical experimental IPF patients in China have shown positive outcomes with a growing number of formulas, herbal components, and various forms of Chinese herbal medicine extracts [11,39].

3.1. Traditional Chinese Medicine (TCM)

A derived form of TCM includes the Danlou prescription (DLP) that consists of ten different herbs, which are *Trichosanthes kirilowii* Maxim (Gualoupi), *Allium macrostemon* Bunge, *Puerariae Lobatae* Radix, *Salvia miltiorrhiza* Bunge, *Astragalus mongholicus* Bunge, *Davallia trichomanoides* Blume, *Paeonia lactiflora* Pall, *Alisma plantago-aquatica* L., *Ligusticum chuanxiong* Hort, and *Curcuma aromatica* Salisb [14]. Bleomycin (BLM)-induced IPF was reduced after prescribing DLP as it inhibited the TGF-activated myofibroblast differentiation and α-SMA expression. DLP also contributed to regulation of genes that are related to endocytosis and collagen secretion. In addition, it also promoted alveolar macrophage and regulated myofibroblast differentiation. Hence, these contributing factors and the ability of DLP to suppress both pro-inflammatory and pro-fibrotic pathways at the same time makes it a promising treatment option for IPF [40].

Another TCM regime that has been tested to be a promising therapeutic agent for IPF is the BuqiHuoxueTongluo formula (BHTF). BHTF consists of Astragali Radix (Huangqi, 30 g), Lonicerae Japonicae Flos (Jinyinhua, 30 g), Angelicae Sinensis Radix (Danggui, 30 g), Glycyrrhizae Radix et Rhizoma (Gancao, 10 g), Dioscoreae Nipponicae Rhizoma (Chuanshanlong, 15 g), Pyrrosiae Folium (Shiwei, 15 g), Fritillariae Thunbergii Bulbus (Zhebeimu, 10 g), Trichosanthis Fructus (Gualou, 15 g), Platycodonis Radix (Jiegeng, 10 g), Aurantii Fructus (Zhiqiao, 10 g), and Rhodiolae Crenulatae Radix et Rhizoma (Hongjingtian, 10 g). Evidence reported that the BHTF can promote anti-inflammatory effects in BLM-induced IPF which in turns alleviates fibrosis progression [41]. It was found that in the pulmonary mesenchyme, the BHTF reduced inflammatory cells infiltration, collagen deposits, and fibrosis while also suppressing the TGF-β1 and α-SMA expression, which are the key starting points for IPF [41,42]. Furthermore, it was presented that BHTF also helped to preserve the function of type II alveolar epithelial cell during IPF as it exhibited the potential to affect pulmonary surfactant secretion [41].

A pilot clinical trial was also done to test the effects of another TCM, which is the Qizhukangxian granules (QG) on IPF patients [43]. The granules are composed of Huangqi (*Radix Astragali Mongolici*), Ezhu (*Rhizoma Curcumae Phaeocaulis*), Danggui (*Radix Angelicae Sinensis*), Shanzhuyu (*Fructus Macrocarpii*), Ziwan (*Radix Asteris Tatarici*), Huangqin (*Radix Scutellariae Baicalensis*), Zhebeimu (*Bulbus Fritillariae Thunbergii*), and Gancao (*Radix Glycyrrhizae*). Evidence showed that administration of QG could be an effective treatment option for IPF as it contributed to the delay in pulmonary function deterioration. It was also shown to relieve IPF symptoms as compared to the control group, which in turn improves the quality of life. Administration of QG also demonstrated a lower incidence rate of acute exacerbations throughout a 48-week therapy term with no noticeable negative effects [43]. Hence, this study suggests that QG could be a potential treatment option for IPF.

Besides that, another Chinese herbal medicine that has been used for lung-associated diseases is the citrus alkaline extract (CAE), which originates from the peel of *Citrus reticulata*. The therapeutic effect of CAE against IPF is demonstrated through a study on BLM-induced pulmonary fibrosis mice. Evidence showed that CAE decreased the synthesis of collagen, crosslinking, and deposition, hence alleviating the BLM-induced pulmonary fibrosis. This bioactivity was exerted through downregulation of the TGF-β1/Smad-3 pathway. Thus, this study suggests that CAE could be a potential therapeutic agent for IPF [44].

Moreover, another widely used TCM specifically for lung-associated diseases such as pulmonary fibrosis and bronchitis is *Schisandrae chinensis fructus* (Wuweizi, Schisandra). A study done on the BLM-induced model demonstrated that Schisandra showed protective effects in two phases: by improving inflammatory cell infiltration and extensive damage to lung structures, as well as by reducing the biomarkers for the M2 macrophage subtype [45]. Previous studies have shown that M2 macrophages promote fibrosis, hence an M2-targeted approach could be a potential therapeutic strategy for IPF [46–48]. In vitro tests also revealed that Schisandra decreased the M2 ratio, confirming that M2 polarisation was suppressed [45].

Another study was done to test the effect of cryptotanshinone (CPT) on a BLM-induced rat model [49]. CPT is a diterpenoid quinone compound isolated from Danshen, which is a widely used TCM herb [50]. CPT has antioxidant, anti-inflammatory, and antibacterial effects. Downregulation of fibrotic markers was observed after administration of CPT, which reduces inflammation and Stat3 phosphorylation levels. Inhibition of NIH/3T3 (mouse embryonic fibroblasts) cells, human primary fibroblasts cells, and primary rat pulmonary fibroblasts was also found upon administering CPT in a time and dose-dependent manner. A rise in epithelial markers and a drop in mesenchymal markers were also seen after CPT administration. This indicates that there was an inhibition of the EMT process [49]. Hence, these anti-fibrotic effects of CPT make it a promising treatment option for IPF.

Another promising anti-IPF compound is triptolide (TPL). Extracted from a Chinese herbal plant, *Tripterygium wilfordii* Hook F has been widely used in TCM. It is also known to be anti-inflammatory and immunosuppressive [51]. A recent study reported that TPL inhibited EMT of lung epithelial cells through direct binding to TGF-β, an EMT-inducing factor which in turn affected Smad-3, E-cadherin and vimentin, the markers of EMT initiation. An in vivo study also demonstrated an inhibition of lung fibrosis by TPL in mice. As EMT is closely associated with IPF, TPL could be a potential therapeutic agent for IPF [51].

Gancao Ganjiang decoction (GGD) is another Chinese herb composite commonly used for atrophic lung disease treatment. This decoction consists of the extract of dried rhizomes and roots of *Glycyrrhiza uralensis* Fisch. and *Zingiber officinale* Roscoe (2:1) [52]. Wang et al. (2021) discovered that 14 days treatment with GGD in IPF mice had shown an inhibition of early fibrosis and slowed disease progression. Furthermore, at 28 days of the treatment, it was shown that GGD effectively reduced the deposition of extracellular matrix in pulmonary fibrotic mice and alleviated the degradation of lung tissue structure at the end stage of the disease. Similar to TPL, administration of GGD decreased the expression of TGF-β, vimentin, and α-SMA. Taken together, these in vivo findings suggest the potential use of GGD as an anti-IPF treatment [52].

Similarly, in a study done by Tian et al. (2019), the Yiqi Huayu Hutan 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 presented in the treatment group, particularly in the "moderate concentration" decoction [53]. Hence, this decoction could also be a promising therapeutic agent for IPF.

3.2. Bioactive Compounds and Phytochemicals

Besides TCM, natural compounds isolated from plants or roots may also confer a potential therapeutic effect on IPF. A natural compound and the most prevalent flavonoid in plants, quercetin (QE), may be isolated and separated from vegetables, fruits, and Chinese herbs. QE is derived from a wide range of sources, inexpensive, and has a high level of safety and few side effects [54]. Antitumour, antiviral, anti-inflammatory, antioxidant, and anti-thrombotic are a few of its pharmacological actions. Zhang et al. (2018) discovered that QE may alleviate BLM-induced lung fibrosis and TGF-induced fibrosis in human embryonic lung fibroblasts (HELFs) through decreasing sphingosine kinase 1 (SphK1)/ sphingosine 1-phosphate (S1P) signalling [54]. According to Veith et al. (2017), a disruption of pulmonary redox balance linked with inflammation is a defining feature of IPF. By boosting the expression of nuclear factor erythroid 2-related factor (Nrf-2) and Nrf-2-regulated genes, QE, as an exogenous antioxidant, may alleviate redox-associated diseases [55].

A bioactive compound isolated from *Sorbus aucuparia* also showed an inhibitory effect on the disease progression in the BLM-induced mouse model. Inflammatory gene expression and macrophage activation-related markers were shown to decrease after treatment with aucuparin [56]. Profibrotic marker gene expression decreased, whereas the levels of antifibrotic marker genes increased after aucuparin treatment. This study also demonstrated a suppression of TGF-β-induced activation of inflammatory cytokines as well as the collagen synthesis from macrophage and fibroblasts after treatment with aucoparin [56]. Hence, these results suggest that aucaparin is a promising therapeutic agent for IPF.

Another natural compound that shows a promising therapeutic effect towards IPF is juglanin (Jug), isolated from green walnut husks of *Juglans mandshurica*. This chemical was proven to have anti-oxidative, anti-inflammatory, and anti-fibrotic properties [57]. Jug-treated mice had a significantly higher survival rate compared to the BLM-challenged mice. Treatment with Jug had caused a reduction in neutrophil alveolar infiltration and lung vascular permeability, as well as anti-inflammatory responses in BLM-induced mice [57]. It was also shown that there was a reduction in the expression of fibrotic markers such as TGF-β1, fibronectin, matrix metalloproteinase (MMP)-9, α-SMA, and collagen I. The stimulator of interferon genes (Sting), which is known for mediating fibrosis, was also found to be significantly reduced in Jug-treated mice as compared to BLM mice [57]. Therefore, Jug could be a potential therapeutic agent for IPF as it may increase tissue regeneration and slow down the progression of IPF.

Gambogic acid (GA) is the principal active component in Gamboge, which is a dry resin exuded by *Garcinia hanburyi* Hook.f., a native plant of Southeast Asia. GA demonstrated anti-tumour cell proliferation and anti-inflammatory, anti-bacterial, and neuroprotective properties. Additionally, it has the benefits of low toxicity and low residue as a pure natural Chinese herbal medication [58]. Qu et al. (2016) discovered that GA could regulate the rate of vasohibin-1 and -2, block TGF-β1, and reduce platelet-derived growth factor (PDGF) as well as fibroblast growth factor (FGF)-2 [58]. As a result, GA can be employed as a new medication for the treatment of IPF in its early and fibrotic stages.

The principal active element in the dried roots of Mongolian Astragalus, also known as *Astragalus membranaceus*, is astragaloside IV (ASV). ASV was shown to have anti-inflammatory and anti-fibrotic properties [59]. As the pathogenesis of IPF involves EMT, ASV that could cause a significant reversal of EMT in the BLM-induced model could be protective against pulmonary fibrosis, hence making it a promising therapeutic agent for IPF [60]. ASV could also inhibit TGF-β1/ phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt)-induced forkhead box class O (FOXO)3a hyperphosphorylation and down-regulate EMT in fibrosis [60]. The degenerative alterations of alveolar epithelial cells had been substantially reduced after administration of ASV, which is a natural saponin with anti-fibrotic properties [60]. This is in line with a previous study that discovered the ability of ASV to reduce the levels of collagen III, laminin, hyaluronic acid, and hydroxyproline in lung tissue homogenate [61].

The roots and rhizomes of *S. miltiorrhiza* Bunge, another herb with potential anti-IPF properties, are rich in salvianolic acid B (SAB). Liu et al. (2016) showed that SAB had a therapeutic effect on IPF by inhibiting cell infiltration, alveolar structure destruction, and collagen deposition [62]. In addition, SAB inhibited TGF-induced myofibroblast differentiation in MRC-5 normal human foetal lung fibroblasts and TGF-mediated EMT in A549 lung carcinoma epithelial cells via Smad-dependent and -independent mitogen-activated protein kinases (MAPK) signalling pathways. Another study found that SAB protected cells against oxidative stress in vitro by inducing Nrf-2 nuclear translocation. Immunohistochemistry findings revealed that SAB treatment increased Nrf-2 expression in fibrotic lung tissues [63].

Gallic acid is a polyphenol isolated from plants such as *Rheum palmatum* L. and *Eucalyptus robusta* Smith, with the purported title of the "finest organic polyphenol compound". Chen et al. (2013) demonstrated that gallic acid-mediated hydrogen peroxide production is a promoter of the c-Jun N-terminal kinase (JNK) signalling pathway, which triggered the human tumour suppressor gene p53 and apoptosis of mouse pulmonary fibroblasts in the treatment of IPF [64]. Rong et al. (2018) concluded that gallic acid derivatives possibly suppressed inflammation via the TGF-β1/Smad-2 signalling pathway and balanced the NADPH oxidase-4 (NOX4)/Nrf-2 ratio, which underpins the potential therapeutic efficacy on IPF [65].

Another derivative of *S. miltiorrhiza* Bunge, tanshinone IIA (TSIIA), is a fat-soluble diterpenoid active compound. He et al. (2015) discovered that TSIIA treatment reduced BLM-induced inflammation, pro-inflammatory cytokine levels, and collagen expression in rat lung tissues [50]. Furthermore, TSIIA inhibited BLM-induced aberrant oxidation and nitric oxide generation in the rodent model. Furthermore, Wu et al. (2014) discovered that TSIIA could diminish TGF overexpression and restore the loss of angiotensin-converting enzyme 2 (ACE-2) and angiotensin-(1-7) in lung tissues [66]. In other words, TSIIA confers a likely protection against IPF.

Another natural active compound that could be a promising therapeutic agent for IPF is black tea extract (BTE). Chakraborty et al. (2019) have reported that BTE at 50 mg BTE/kg exerted anti-fibrotic effects in the BLM-induced mice model. Evidence exhibited a decrease in collagen deposition in the BTE-treated group as compared to untreated mice [67]. The expression of α-SMA, which is crucial in the contribution of pulmonary fibrosis [68], reduced in the BTE-treated model which in turn alleviated experimental lung fibrosis [67]. After treatment with 50 mg/kg dose of BTE, TGF-β was significantly decreased whereas the anti-fibrotic molecule interferon gamma (IFN-γ) was elevated [67].

Furthermore, according to a study done by Li et al. (2022), the flavonoids of *Oxytropis falcata* Bunge (FOFB) has also shown potential therapeutic effects towards IPF by targeting the TGF-β/Smad signalling pathway [69]. TGF-β is known to promote fibrosis as EMT is induced through the TGF-β/Smad signalling pathway [70,71]. This study has found that with an increasing dose of FOFB, the pulmonary fibrosis was gradually attenuated with evident suppression of the TGF-β/Smad signalling. In rats treated with FOFB at a dose of 400 mg kg^{-1}·day^{-1}, there was a significant reduction in the severity of pulmonary fibrosis [69].

Another natural compound is a flavonoid derived from myrtle (*Myrtus communis* L.), which is a plant from the Myrtaceae family found in the tropical regions of Iran. It has been widely used for respiratory-associated diseases due to its antioxidant and anti-inflammatory properties [72,73]. Myrtle may contribute to the treatment of IPF by inhibiting inflammation, reducing lung parenchymal fibrosis, and lowering hydroxyproline levels. In both early and late stages of BLM-induced fibrosis, histopathological studies indicated that myrtle delayed fibrotic alterations including bronchioles and alveolar wall thickening, with minimal side effects [72].

Grape seed proanthocyanidin extract (GSPE) is also found to be anti-inflammatory and has been proven to inhibit amiodarone-induced lung toxicity [74,75]. A study done by Sul et al. (2022) tested the efficacy of GSPE on the BLM-induced lung fibrosis mice

model. The progression of pulmonary fibrosis was inhibited through inhibition of oxidative stress and thereby reducing epithelial apoptosis. Alveolar damage, inflammation, and fibrosis are influenced by oxidative stress, hence a targeted therapy towards oxidative stress could be a potential approach for IPF treatment [76]. Histological changes and collagen deposition were significantly reduced in the GSPE-treated BLM-induced lungs. The amount of bronchoalveolar lavage was also seen to be reduced and thereby reduced lung inflammation after GSPE treatment. BLM induced higher levels of hydrogen peroxide which caused oxidative stress in the lungs. Upon treatment with GSPE, a significant reduction in the oxidative stress was observed [76].

Another natural compound that has shown inhibitory effects towards IPF is rosemary leaf extract, which contains high levels of carnosic acid (CA) and rosmarinic acid (RA). A study was done to test the effect of CA rich extract, RA rich extract, and their synergistic effect in BLM-induced lung fibrosis rats. Evidence showed that at the lowest dose given (10 mg/kg), both extracts (individually and combined) reduced pulmonary fibrosis and oxidative stress. The synergistic treatment exhibited a better curative effect upon administration. However, if administered at higher doses, the extracts became ineffective [77].

Two other phytochemicals, emodin and andrographolide, exerted similar protective effects against IPF. Emodin is the primary component of *Reynoutria japonica* Houtt and *Rheum palmatum* L., derived primarily from Polygonaceae. The compound can alleviate pulmonary oedema and fibrosis, diminish collagen deposition, and prevent invasion of myofibroblasts and inflammatory cells in IPF patients. Emodin also lowered tumour necrosis factor (TNF)-α, interleukin (IL)-6, TGF-β1, and heat shock protein (HSP)-47 levels in lung tissues [78]. Andrographolide (AND), on the other hand, is the principal active compound of *Andrographis paniculata* with the ability to reduce oxidative stress, lower malondialdehyde levels, and raise the glutathione/oxidised glutathione ratio. This can help to ameliorate MMP-1/ tissue inhibitors of MMP-1 ratio alterations caused by BLM. As a result, it may have a therapeutic impact on IPF [79].

3.3. Korean Herbal Medicine

A form of herbal medication that has been widely used, specifically in Korea for pulmonary diseases, is the PM014, which consists of seven components of Chung-Sang-Bo-Ha-Tang (root of *Rehmannia glutinosa*, cortex of *Paeonia suffruticosa*, fruit of *Schizandra chinensis*, root of *Asparagus cochinchinensis*, seed of *Prunus armeniaca*, root of *Scutellaria baicalensis*, and root of *Stemona sessilifolia*) [80,81]. An anti-inflammatory effect was observed upon administering PM014 in radiation-induced pulmonary inflammation via inhibition of inflammasome activation, which in turn improved the overall lung function [81]. In a recent study, it was found that the PM014 compound had improved pulmonary fibrosis through the TGF-β1 pathway inhibition. An in vitro study of IPF reported that PM014 suppressed the TGF-1-induced EMT and fibroblast activation in alveolar epithelial cells by targeting the Smad-dependent and p38 MAPK pathways. PM014 that suppressed the initiation and progression of inflammatory responses in lung fibrosis might be a promising therapeutic agent for IPF [80].

Besides that, another perennial herbaceous plant that can be found in the mountainous areas of Korea is *Astilbe rubra* Hook. F. et Thomas. (family Saxifragaceae) [82]. A study done by Bang et al. (2019) tested the inhibitory effect of β-peltoboykinolic acid isolated from *A. rubra* on EMT [83]. As EMT is responsible for gaining mesenchymal characteristics, which give rise to fibroblasts contributing to the progression of fibrosis, a targeted inhibitory agent against EMT could be beneficial for the treatment of IPF. Inhibition of TGF-β1-induced EMT and overproduction of extracellular matrix components such as type I collagen and fibronectin were noted after treatment with β-peltoboykinolic acid. Moreover, inhibition of TGF-β1-induced Smad/Snail signalling reduced EMT after the β-peltoboykinolic acid treatment [83]. As the Smad pathway is crucial for regulating fibrotic EMT [84], an inhibitory agent such as β-peltoboykinolic acid would be a promising therapeutic agent for IPF.

3.4. Ayurvedic Medicine

Aside from TCM, Ayurvedic medicine also plays an important role in the treatment of IPF. Curcumin (CUR) is a widely known diketone isolated from turmeric and is insoluble in water due to its unsaturated esters and aromatic groups [85]. Numerous pharmacological activities have been identified in CUR, including anti-inflammatory, anti-bacterial, antioxidant, hypolipidemic, and cancer-fighting properties. Even hepatitis C viral infections can be treated with this active compound [14], and there are very few side effects reported because of its low toxicity. Myofibroblasts are formed when lung fibroblasts are stimulated by TGF-b in IPF, and CUR was found to inhibit this process [85]. MMP-9 inhibition is another way in which CUR can help to prevent the development of IPF in a mouse model, when used in conjunction with MMP-9 inhibitors [86]. Table 1 summarises the herbal medicines used for the management of IPF as discussed in this article.

Table 1. Herbal medicines for the management of idiopathic pulmonary fibrosis.

Category	Name	Findings	Reference
Traditional Chinese Medicine	(1) Danlou prescription - *Trichosanthes kirilowii* Maxim (Gualoupi) - *Allium macrostemon* Bunge - *Puerariae Lobatae* Radix - *Salvia miltiorrhiza* Bunge - *Astragalus mongholicus* Bunge - *Davallia trichomanoides* Blume - *Paeonia lactiflora* Pall - *Alisma plantago-aquatica* L. - *Ligusticum chuanxiong* Hort - *Curcuma aromatica* Salisb	- Inhibited transforming growth factor (TGF)-activated myofibroblast differentiation and α-smooth muscle actin (SMA) expression - Regulated genes that are related to endocytosis and collagen secretion - Suppressed pro-inflammatory and pro-fibrotic pathways	[14]
	(2) BuqiHuoxueTongluo formula - *Astragali Radix* (Huangqi) - *Lonicerae Japonicae* Flos (Jinyinhua) - *Angelicae Sinensis* Radix (Danggui) - *Glycyrrhizae Radix* et Rhizoma (Gancao) - *Dioscoreae Nipponicae* Rhizoma (Chuanshanlong) - *Pyrrosiae Folium* (Shiwei) - - *Fritillariae Thunbergii* Bulbus (Zhebeimu) - *Trichosanthis Fructus* (Gualou) - *Platycodonis Radix* (Jiegeng) - *Aurantii Fructus* (Zhiqiao) - *Rhodiolae Crenulatae* Radix et Rhizoma (Hongjingtian)	- Exhibited anti-inflammatory effects - Reduced collagen deposits - Suppressed TGF-β1 and α-SMA expressions	[41]
	(3) Qizhukangxian granules - Huangqi (*Radix Astragali* Mongolici) - Ezhu (*Rhizoma Curcumae* Phaeocaulis) - Danggui (*Radix Angelicae* Sinensis) - Shanzhuyu (*Fructus Macrocarpii*) 1. Ziwan (*Radix Asteris* Ta-tarici) - Huangqin (*Radix Scutellariae* Baicalensis) - Zhebeimu (*Bulbus Fritillariae* Thun-bergii) - Gancao (*Radix Glycyrrhizae*)	- Delayed pulmonary function deterioration - Lower incidence rate of acute exacerbations	[43]

Table 1. *Cont.*

Category	Name	Findings	Reference
Traditional Chinese Medicine	(4) Citrus alkaline extract - Peel of Citrus reticulata.	- Decreased synthesis of collagen, crosslinking, and deposition - Downregulated the TGF-β1/Smad-3 pathway	[44]
	(5) Wuweizi, Schisandra - *Schisandrae chinensis fructus*	- Protected against inflammatory cell infiltration and lung damages - Reduced and suppressed M2 macrophages	[45]
	(6) Cryptotanshinone - Danshen	- Reduced inflammation and Stat3 phosphorylation - Inhibited epithelial-to-mesenchymal transition (EMT)	[49]
	(7) Triptolide - *Tripterygium wilfordii* Hook F	- Inhibited EMT of lung epithelial cells through direct binding to TGF-β - Regulated Smad-3, E-cadherin, and vimentin expressions	[51]
	(8) Gancao Ganjiang decoction - Extraction of dried rhizomes and roots of *Glycyrrhiza uralensis* Fisch. and *Zingiber officinale* Roscoe (2:1).	- Inhibited early fibrosis and slowed disease progression - Reduced deposition of extracellular matrix in pulmonary fibrotic mice - Alleviated degradation of lung tissue structure - Decreased the expression of TGF-β, vimentin and α-SMA	[52]
	(9) Yiqi Huayu Hutan decoction	- Alleviated TGF-β/Snail pathway	[53]
Bioactive compounds and phyto-chemicals	(1) Quercetin	- Decreased sphingosine kinase 1 (SphK1)/ sphingosine 1-phosphate (S1P) signalling - Exhibited antioxidative effects	[54]
	(2) Aucuparin - *Sorbus aucuparia*	- Decreased inflammatory gene expression, macrophage activation-related markers, and profibrotic marker gene expression - Increased antifibrotic marker genes - Suppressed inflammatory cytokines and collagen synthesis	[56]
	(3) Juglanin - Green walnut husks of *Juglans mandshurica*	- Reduced neutrophil infiltration and 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 interferon genes (Sting)	[57]
	(4) Gambogic acid - A dry resin exuded by *Garcinia hanburyi* Hook F.	- Regulated vasohibin-1 and -2 - Blocked TGF-β1 - Reduced platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF)-2	[58]

Table 1. *Cont.*

Category	Name	Findings	Reference
Bioactive compounds and phyto-chemicals	(5) Astragaloside IV - Dried roots of Mongolian Astragalus, also known as *Astragalus membranaceus*	- Reversed EMT process - Inhibited TGF-β1/ phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt)-induced forkhead box class O (FOXO)3a hyperphosphorylation - Reduced degenerative alterations of alveolar epithelial cells - Reduced the levels of collagen III, laminin, hyaluronic acid, and hydroxyproline in lungs	[59–61]
	(6) Salvianolic acid B - Roots and rhizomes of *Salvia miltiorrhiza* Bunge	- Inhibited cell infiltration, alveolar structure destruction, collagen deposition, and myofibroblast differentiation - Regulated Smad-dependent and -independent mitogen-activated protein kinases (MAPK) signalling pathways - Protected cells against oxidative stress	[62,63]
	(7) Gallic acid - *Rheum palmatum* L. and *Eucalyptus robusta Smith*	- Regulated c-Jun N-terminal kinase (JNK) signalling pathway, tumour suppressor gene p53, and apoptosis - Suppressed inflammation via TGF-β1/Smad-2 signalling pathway - Balanced NADPH oxidase-4 (NOX4)/Nrf-2 ratio	[64,65]
	(8) Tanshinone IIA - Derivative of *S. miltiorrhiza* Bunge	- Reduced inflammation, pro-inflammatory cytokine levels, and collagen expression - Inhibited aberrant oxidation and nitric oxide generation - Diminished TGF overexpression - Restored the loss of angiotensin-converting enzyme 2 (ACE-2) and angiotensin-(1-7) in lung tissues	[50,66]
	(9) Black tea extract	- Decreased collagen deposition, α-SMA, and TGF-β - Elevated the anti-fibrotic molecule, interferon-γ	[67]
	(10) Flavonoids of *Oxytropis falcata* Bunge (FOFB)	- Suppressed TGF-β/Smad signalling pathway	[69]
	(11) Flavonoid from Myrtle - *Myrtus communis* L.	- Inhibited inflammation - Lowered hydroxyproline levels	[72]
	(12) Grape seed proanthocyanidin extract	- Inhibited oxidative stress and thereby reduced epithelial apoptosis - Reduced collagen deposition and lung inflammation	[76]

Table 1. *Cont.*

Category	Name	Findings	Reference
	(13) Rosemary leaf extract - Carnosic acid and rosmarinic acid	- Reduced oxidative stress	[77]
	(14) Emodin - Primary component of *Reynoutria japonica* Houtt. and *Rheum palmatum* L	- Alleviated pulmonary oedema - Diminished collagen deposition - Prevented invasion of myofibroblasts and inflammatory cells - Lowered tumour necrosis factor (TNF)-α, interleukin (IL)-6, TGF-β1, and heat shock protein (HSP)-47 levels in lung tissues	[78]
	(15) Andrographolide - Principal active compound of *Andrographis paniculata*	- Reduced oxidative stress and malondialdehyde levels - Increased glutathione/oxidised glutathione ratio - Ameliorated MMP-1/tissue inhibitors of MMP-1 ratio alterations	[79]
Korean herbal medicine	(1) PM014 - Chung-Sang-Bo-Ha-Tang (root of *Rehmannia glutinosa* - Cortex of *Paeonia suffruticosa* - Fruit of *Schizandra chinensis* - Root of *Asparagus cochinchinensis* - Seed of *Prunus armeniaca* - Root of *Scutellaria baicalensis* - Root of *Stemona sessilifolia*)	- Exerted anti-inflammatory effect - Inhibited TGF-β1 pathway - Suppressed EMT and fibroblast activation by targeting Smad-dependent and p38 MAPK pathways	[80,81]
	(2) β-Peltoboykinolic acid - *Astilbe rubra* Hook. f. et Thomas	- Inhibited EMT and extracellular matrix production - Inhibited Smad/Snail signalling pathway	[82,83]
Ayurvedic medicine	Curcumin	- Inhibited TGF-beta-induced myofibroblasts - Inhibited MMP-9	[85]

4. Conclusions

IPF is a progressive, interstitial inflammatory lung disorder with no known cause, and it primarily affects older adults. Currently, conventional treatment can only impede disease progression but not reverse it. The adverse effects that accompany allopathic treatments provide a dire prognosis, and while lung transplantation is the only effective method, the risk of mortality and morbidity are significant. Herbal medicine is an ideal strategy for a wide range of diseases, including IPF. Herbs and its combinations/decoctions as well as natural extracts or isolates can be very useful in treating IPF. This article provides an overview on herbal medicine, particularly TCM, natural active compounds, Korean medicine, and Ayurvedic medicine as alternative approaches for IPF treatment. Despite certain limitations, it is important to explore other treatment options besides herbal medicine that are much safer and more effective for treating IPF.

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