Inhalation therapy for pulmonary fibrosis: chemical medicines and herbal medicines

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The authors declare no conflicts of interest.

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Abbreviations
BLM, bleomycin; CO, carbon monoxide; COPD, chronic obstructive pulmonary disease; CSP7, a 7-mer fragment of caveolin scaffolding domain peptide; DPI, dry powder inhalers; EMT, epithelial-to-mesenchymal transition; FDA, food and drug administration; FVC, forced vital capacity; GA, glycyrhrhetic acid; HMGB1, high mobility group protein 1; HYP, hydroxyproline; IFN-γ, interferon-γ; IL-1β, interleukin-1 beta; IPF, idiopathic pulmonary fibrosis; LPS, lipopolysaccharide; MDI, metered dosage inhalers; MMP-13, matrix metalloproteinase-13; NAC, N-acetylcysteine; NPHM, natural products derived from herbal medicines; PDSF, platelet-derived growth factor; PF, pulmonary fibrosis; TGF-β1, transforming growth factor-beta 1; TIMP, tissue inhibitors of metalloproteinase; TNF-α, tumor necrosis factor-alpha; TNFS, total saponins of panax notoginseng; α-SMA, α-smooth muscle actin.

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Abstract
Pulmonary fibrosis (PF) is a chronic, progressive, and irreversible pulmonary interstitial disease with unclear pathogenesis. Currently, there are few treatment options for managing PF. Inhalation therapy, as a routine treatment for respiratory diseases, is being used to study the treatment of PF. Some herbal medicines and their active ingredients have been reported to have anti-PF effects. This review aims to provide an overview of the latest developments in inhalation therapy, focusing on the utilization of chemical medicines and herbal medicines for the treatment of PF in both clinical practice and basic research. The inhalation of chemical drugs such as pirfenidone, nintedanib, N-acetylcysteine, and interferon-γ has been shown to demonstrate anti-PF effects. Additionally, the inhalation of various natural products derived from herbal medicines, encompassing polyphenols, alkaloids, flavonoids, saponins, terpenoids, and herbal extracts, contributes to the therapeutic management of PF through diverse mechanisms. The inhalation of both chemical and herbal medicines presents promising advantages in the treatment of PF. Further clinical trials are required to investigate the effectiveness, safety, and mechanism of action of inhalation therapy utilizing natural products derived from herbal medicines.

Keywords: herbal medicine; nebulizer; pulmonary fibrosis; natural product; inhalation
**Introduction**

Pulmonary fibrosis (PF) is a multifactorial lung-destructive disease and a pathological change in end-stage lung disease [1]. It is characterized by alveolar injury, fibroblast proliferation, and excessive extracellular matrix deposition, eventually leading to severe damage to lung function, respiratory failure, and death [2]. Furthermore, it is a severe sequela of coronavirus disease 2019 (COVID-19) [3]. Idiopathic pulmonary fibrosis (IPF) is the most common interstitial lung disease. Approximately 90% of patients with IPF have pulmonary interstitial changes and scarring of the lung parenchyma [4]. If adequate treatment measures are not applied, the pulmonary function of patients with IPF deteriorates irreversibly, resulting in an average survival time of only 3–5 years [5]. The disease seriously threatens the lives of patients and results in a substantial economic burden to the medical system, patients, and society [6]. Numerous drugs are now under clinical trials for drugs are underway to test their safety and efficacy against IPF. Only pirfenidone and nintedanib are the two drugs approved for treating IPF by the US Food and Drug Administration (FDA) [7]. These drugs are effective against PF as they delay lung function decline and disease progression [8]. However, these drugs have severe adverse effects and are very expensive. Hence, patients are often forced to reduce the dosage or interrupt treatment due to adverse reactions such as those affecting the gastrointestinal system [9]. Only lung transplantation can improve the life span of the patients [10].

Inhalation is a conventional therapeutic modality for respiratory diseases, which facilitates precise drug delivery to the lungs and elicits a localized or systemic therapeutic response. Furthermore, inhalation therapy is emerging as a promising strategy for reducing the side effects of certain medications. This route can avoid hepatic and intestinal drug absorption and metabolism [11]. Inhalation therapy has an obvious advantage over oral and intravenous administration because inhalation allows for direct drug absorption into the lungs and avoids unwanted adverse effects as lower doses are required [12]. Some studies have reported promising data on treating PF through inhalation therapy.

Some reviews have summarized that herbal medicines and their active ingredients have anti-PF effects [13–15]. Recently, natural products have emerged as a promising avenue for the research and development of pharmacological interventions targeting PF, owing to their demonstrated efficacy in mitigating fibrosis and the abundance of potential candidate compounds [16]. Furthermore, drugs derived from natural sources are considered to be relatively safe and exhibit minimal adverse effects. The oral route is the most common way of administering herbal medicines. However, some studies have stated to research inhalation therapy with natural products derived from herbal medicines (NPHM) for treating PF. Studies on their mechanisms of action have focused on signaling pathways such as TGF-β and NF-κB, inhibiting the inflammatory response and deposition of extracellular matrix elements such as collagen I, thus effectively reducing the extent of PF. In this review, we summarized the characteristics of three kinds of atomizing inhalation devices. We reviewed the application and prospect of inhalation therapy using herbal and chemical medicine for treating PF, especially NPHM.

**Nebulizer inhalation device**

Metered dosage inhalers (MDI), nebulizers, and dry powder inhalers (DPI) are the three primary types of pulmonary inhalation devices [17]. Compared with MDI and DPI, nebulizers can deliver drugs with large dose and compatible use [18]. Using it to deliver traditional Chinese medicine (TCM) is one of the widely used drug delivery strategies in clinical practice. Aerosol inhalation is a direct drug delivery method targeting the respiratory tract and lungs [19]. A nebulizer inhalation device is a drug delivery device that converts a drug into an aerosol form that is inhaled through the oral cavity or nasal cavity. It has the advantages of fast onset of action, high local drug concentration, low dosage, convenient application, and few systemic adverse reactions [20]. Small-volume nebulizers are the most used nebulizer inhalation devices in clinical practice, and their liquid storage capacity is generally less than 10 ml. The personal selection of inhalation devices will be based on factors such as clinical status, age, doctor’s experience, patient preference, drug availability, and proper use of equipment [21]. Presently, a wide range of commercially available nebulizers is available. Nebulizer devices are divided into three basic types according to their functional principles: ultrasonic nebulizer, jet nebulizer, and mesh nebulizer. Jet nebulizers are further divided into air-driven and oxygen-driven nebulizers. These atomizing devices can nebulize most drug solutions and are suitable and convenient for most patients with lung disease. Each device type has distinct advantages and disadvantages (Table 1) [22–24].

<table>
<thead>
<tr>
<th>Type</th>
<th>Operating principle</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound nebulizer</td>
<td>Aerosols are generated by high frequency (&gt;1 MHz) vibrations of piezoelectric crystals through the drug solution.</td>
<td>High fog volume and uniform droplets.</td>
<td>Large average particle size and residuals of the drug. It causes drug degradation and cannot nebulize suspensions and proteins.</td>
</tr>
<tr>
<td>Jet nebulizer</td>
<td>Based on the Venturi principle, compressed gas is used to achieve a high-speed airflow that causes the liquid to be sprayed onto the baffle to form mist particles.</td>
<td>It is easy and convenient to operate and inexpensive. It enables therapeutic dose modification and dose compounding and can effectively nebulize suspensions.</td>
<td>Relatively large particle size and noisy in operation.</td>
</tr>
<tr>
<td>Mesh nebulizer</td>
<td>Aerosols are produced using micro-pump technology to pass the drug through multiple holes in a mesh or pore plate.</td>
<td>It does not denature the drug and can nebulize suspensions, liposomes, and nucleic acids. The nebulizer is lightweight, small, portable, and operates almost silently with minimum treatment time. Low drug residue, higher output efficiency, and a high percentage of fine particles discharged.</td>
<td>Conveying viscous and suspended liquids can clog voids. Cleaning is difficult, and it is expensive.</td>
</tr>
</tbody>
</table>

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The jet nebulizer is suitable for patients with lower respiratory tract lesions or infections, more airway secretions, especially minor airway spasms, and severe shortness of breath with hypoxemia. Compared with jet nebulizers, ultrasonic nebulizers have limitations such as large residuals and drug degradation. Furthermore, ultrasonic nebulizer affects the release ratio of suspensions (such as glucocorticoid aerosol inhalation preparations). It can increase the temperature of the liquid in the container, affecting the stability of protein or peptide compounds [25]. Moreover, it releases a large amount of mist. However, due to the extensive drug capacity and low output efficiency of drug mist particles, it is unsuitable for treating asthma and other wheezing diseases. The aerosol output and drug deposition rates of jet and mesh nebulizers differ significantly. The drug deposition in the lungs afforded by mesh nebulizers is three-fold higher than that achieved with jet nebulizers [26]. Mesh nebulizers offer enhanced delivery, convenience, and energy efficiency [27]. However, they are more expensive and therefore are not widely used.

The form and location of the drug's deposition in the lungs are influenced by the particle size of the lung-inhaled particles [17]. Aerosol inhalation therapy uses an aerosol inhalation device to convert the drug in a liquid form to aerosol particles with a particle size of approximately 0.01~10 μm, which are inhaled and deposited in the airways and lungs for therapeutic effect. The location has a direct impact, and the diameter of the effective atomized particles should be 0.5~10 μm [28] Among them, the majority of particles > 5 μm in diameter are retained in the oropharynx and eventually enter the body through swallowing; although particles < 0.5 μm in diameter can reach the lower respiratory tract, during tidal breathing, 90% of the particles can be expelled with exhalation [29]. The aerosol particles with a particle size of approximately 3~5 μm are primarily deposited in the lungs [30]. About 50% to 60% of the mist particles with a particle size of < 3 μm are deposited in the alveoli [31]. The most clinically used aerosol drugs are glucocorticoids, bronchodilators, inhaled steroids, antibiotics, antifungals, and prostaglandins.

**Treatment of PF with inhalation of chemical drugs**

**Small molecule drugs**

**Pirfenidone.** Pirfenidone and nintedanib are the only two drugs recommended for treating PF. Pirfenidone is a synthetic small-molecule pyridone derivative that is taken orally. The non-peptide synthetic chemical pirfenidone prevents or reduces the buildup of excessive scar tissue in many organs by inhibiting the production of the growth factors transforming growth factor-beta 1 (TGF-β1) [32] and tumor necrosis factor-alpha (TNF-α), platelet-derived growth factor (PDGF), collagen 1 [33], interleukin-1 beta (IL-1β), IL-6 and IL-17 [34]. Oral medications require specific doses to achieve good therapeutic results. However, patients often have to reduce the oral dose of the drug or even stop treatment because of serious adverse effects such as gastrointestinal upset and photosensitivity [35]. These adverse events may limit pirfenidone use in IPF [36].

Some studies have explored inhalation therapy of pirfenidone to treat PF. A Japanese pharmaceutical laboratory developed an inhalable powder preparation of pirfenidone and explored the risk of digestive symptoms after inhalation in rats [37]. The study showed that orally taken pirfenidone at doses above 30 mg/kg significantly inhibited intestinal motility, but inhaled 0.3 mg pirfenidone led to comparable intestinal motility. The gastrointestinal exposure levels of the respirable powder formulation of the pirfenidone group were significantly lower than that of the oral pirfenidone group. One clinical trial was performed to evaluate the pharmacokinetics and safety/tolerability of inhaled pirfenidone in normal volunteers, smokers, and IPF patients [38]. The study’s findings indicate that pirfenidone aerosol inhalation was well-tolerated among the subjects. Additionally, the systemic exposure following inhaled powder formulation at its pharmacologically effective dose (0.3 mg) was observed to be 600-fold lower than that of oral administration at its phototoxic dose (160 mg/kg) [39]. The effectiveness of both oral and inhalation routes was evaluated through a paraquat-induced PF model in rats [40]. The outcomes demonstrated equal therapeutic benefits and efficacy for both oral and inhalation modes, but the dose for oral administration was substantially higher than that for inhalation.

**Nintedanib.** Nintedanib is a triple receptor tyrosine kinase inhibitor approved for treating IPF. It is used to treat non-small cell lung cancer and other solid tumors such as prostate, kidney, and colorectal cancers [41-43]. The critical molecular pathways that nintedanib affects include MAPK, PI3K/AKT, JAK/STAT, TGF-β, VEGF, and WNT/β-catenin signaling [44]. A majority of nintedanib’s side effects are gastrointestinal reactions, especially diarrhea [45]. Moreover, liver enzyme levels are at least three times higher than the upper limit of the normal range. Symptomatic treatment and dose adjustment are the most important ways to minimize these adverse reactions. It shows poor oral bioavailability of about 4.7% due to low solubility and intestinal absorption [42, 46]. Typically, malabsorption and low bioavailability can significantly affect the pharmacodynamic effects of nintedanib in vivo. A study developed a self-microemulsion formulation of nintedanib for its oral absorption [47]. One study confirmed that nintedanib inhalation therapy is well-tolerated and reduces bleomycin (BLM)-induced PF, and contributes to weight gain [48]. Another study prepared niosomes using the thin-film hydration method as a delivery vehicle for inhalation therapy of nintedanib [49]. The results showed that it could enhance the therapeutic activity against non-small cell lung cancer. Therefore, designing appropriate delivery vehicles for nintedanib inhalation treatment could be a promising strategy to address the delivery challenges and improve its therapeutic efficacy.

**N-acetylcysteine (NAC).** NAC is a sulfur-based compound containing cysteine. Clinical studies have confirmed that NAC, as an expectorant, can act as an anti-oxidant and anti-fibrotic agent when taken orally at high doses. Patients with mild-to-moderate IPF responded well to inhaled NAC therapy, and those patients who had experienced higher forced vital capacity (FVC) reductions before starting treatment benefited the most [50, 51]. Although the combination of inhaled NAC and pirfenidone reduces the annual rate of decline in FVC and improves progression-free survival in patients with advanced IPF, this may lead to worse outcomes [52, 53]. According to a meta-analysis, NAC was not effective in reducing FVC decline and might bring some adverse events in IPF patients [54]. Therefore, the efficacy of NAC on IPF is more studied IPF patients are needed to demonstrate the effectiveness of inhaled NAC.

**Interferon-γ (IFN-γ).** IFN-γ is an immunomodulatory cytokine of therapeutic relevance that has shown promise in the treatment of PF. Sweeney et al. used a vibrating mesh nebulizer to effectively atomize IFN-γ while maintaining the integrity and biological activity of IFN-γ [55]. Inhaled IFN-γ is safe and may improve pulmonary function in volunteers with IPF [56]. Coughing during inhalation was the only side effect of inhaled therapy with IFN-γ in a 2-year safety study in IPF patients [57]. Inhaled IFN-γ was linked to minor alterations in the lower airway microbial composition [58].

**Others.** A new sodium cromoglicate inhalation formulation (PA101) reduced daytime cough frequency in IPF patients by 31.1% after 14 days of nebulized inhalation [59]. Low-dose carbon monoxide (CO) reversed experimental lung fibrosis in preclinical tests. However, in clinical trials, CO inhalation did not result in significant changes in study endpoints [60]. There was no difference in the anti-PF effect between paclitaxel liposome nebulized inhalation and intravenous injection, but the safety of inhalation delivery was higher [61]. The pulmonary delivery of prostaglandin E2 with liposome as the carrier can prevent the disorder of expression of many genes related to IPF development, significantly limit the inflammation and fibrosis damage in lung tissue, and almost eliminate the mortality of animals after intratracheal instillation of BLM. The study also found that liposomes mainly accumulated in the lungs after inhalation [62]. Conversely, the main locations where liposomes accumulated after intravenous delivery were the kidney, liver, and spleen.
Large molecule drugs
Large molecule drugs including proteins and peptides are less studied to treat PF. The inhalation of B7, a recombinant human relaxin B chain, was found to be effective in reducing the quantity of inflammatory leukocytes and neutrophils present in the bronchoalveolar lavage fluid of mice with BLM-induced PF. Additionally, this treatment led to improvements in the structural integrity of damaged alveoli, decreased collagen deposition, and mitigated the primary pathological characteristics of PF [63]. Some researchers have used jet milling technology to reduce the particle size of peptide powder, which can effectively create stable, excipient-free CSP7 (a 7-mer fragment of cavelin scaffolding domain peptide) inhalation powder that can reduce collagen deposition in PF [64, 65].

Supramolecular nanodrugs
In addition, new pulmonary agents such as mRNA nano-agents and inhaled nanobions have been studied in recent years. In a BLM-induced mouse model, an inhaled ribosomal protein-based mRNA nanopreparation improved lung function by promoting intra-lesional expression of matrix metalloproteinase-13 (MMP-13) and keratinocyte growth factor-mediated alveolar epithelialization. When inhaled using nebulizer, the microdrop-carried nanoformulations deposit in the alveoli and penetrate into fibrotic lesions, followed by intracellular mRNA delivery [66]. Lung spheroocyte secretory and exosome inhalation treatment reduced collagen accumulation; and myofibroblast proliferation and reconstructed normal alveolar structure [67].

Table 2 summarizes the studies of chemical drug inhalation therapy for PF. Chemical drug inhalation therapy offers evident therapeutic advantages, but the efficacy, safety, and compliance still need further study.

Table 2 Inhalation of chemical drugs for treatment of pulmonary fibrosis.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Research subjects</th>
<th>Results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salbutamol</td>
<td>Patients with IPF</td>
<td>Higher lung utilization in inhalation therapy for PF; 1.5-μm drug particles have better lung penetration than 6-μm particles.</td>
<td>[132]</td>
</tr>
<tr>
<td>Pirfenidone</td>
<td>Rat model of BLM-induced PF</td>
<td>The results showed that both the inhalation and oral methods had equal therapeutic benefits and efficacy; however, the dose for the inhalation route was substantially lower than that for oral administration.</td>
<td>[40]</td>
</tr>
<tr>
<td>Sodium cromoglicate (PA101)</td>
<td>Patients with IPF and chronic cough</td>
<td>Inhaled PA101 reduces cough symptoms in patients with IPF.</td>
<td>[59]</td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td>Patients with IPF</td>
<td>Patients with mild-to-moderate IPF responded well to inhaled N-acetylcysteine therapy, and those patients who had experienced higher FVC reductions prior to starting treatment benefited the most.</td>
<td>[50]</td>
</tr>
<tr>
<td>Inhaled mRNA nanof ormulation</td>
<td>Mouse model of BLM-induced PF</td>
<td>It promotes MMP-13 expression and keratinocyte growth factor-mediated alveolar re-epithelializing to accelerate local collagen clearance, thereby improving lung function.</td>
<td>[66]</td>
</tr>
<tr>
<td>RVT-1601 (cromolyn sodium)</td>
<td>Patients with IPF and chronic cough</td>
<td>RVT-1601 inhalation failed to provide benefit over placebo in the treatment of chronic cough in patients with IPF.</td>
<td>[133]</td>
</tr>
<tr>
<td>Nintedanib</td>
<td>Rat model of BLM-induced PF</td>
<td>Inhaled nintedanib treatment increased body weight by approximately 44%, significantly reduced PF, and was well tolerated.</td>
<td>[48]</td>
</tr>
<tr>
<td>Lung spheroid cell secretome and exosomes</td>
<td>Mouse and rat models of BLM-and silica-induced PF</td>
<td>The secretome and exosomes of lung spheroid cells have been found to effectively prevent and reverse fibrosis through the restoration of normal alveolar structure, as well as the reduction of collagen accumulation and myofibroblast proliferation.</td>
<td>[67]</td>
</tr>
<tr>
<td>A 7-mer fragment of cavelin scaffolding domain peptide</td>
<td>Mouse model of BLM-induced PF</td>
<td>Reduced collagen in lungs of mice.</td>
<td>[64]</td>
</tr>
<tr>
<td>Hydrogen (H2)</td>
<td>Rat model of BLM-induced PF</td>
<td>Reduced PF by inhibiting TGF-β1 and related oxidative stress and EMT</td>
<td>[134]</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Patients with IPF</td>
<td>Inhaled IFN-γ is safe and may improve pulmonary function in volunteers with IPF.</td>
<td>[56]</td>
</tr>
<tr>
<td>INS1009, a treprostinil prodrug formulation</td>
<td>Rat model of BLM-induced PF</td>
<td>Reduced lung HYP content and the severity of subepithelial fibrosis.</td>
<td>[135]</td>
</tr>
<tr>
<td>Paclitaxel liposome</td>
<td>Rat model of BLM-induced PF</td>
<td>Improved survival index and PF Ashcroft score, decreased the thickness of the alveolar interval, and reduced the collagen and TGF-β1 expression.</td>
<td>[61]</td>
</tr>
<tr>
<td>Chitosan</td>
<td>Rat model of LPS-induced PF</td>
<td>The administration of chitosan via aerosol inhalation resulted in the suppression of MMP-3 and TIMP-1 expression, thereby mitigating pulmonary remodeling and fibrosis induced by LPS in rats.</td>
<td>[136]</td>
</tr>
<tr>
<td>Prostaglandin E2</td>
<td>Mouse model of BLM-induced PF</td>
<td>It reduced inflammation and fibrotic injury in lung tissues, avoided body weight loss, controlled HYP accumulation in the lungs, and practically eliminated mouse death.</td>
<td>[62]</td>
</tr>
</tbody>
</table>
**Inhalation therapy for PF: natural products derived from herbal medicines**

Many studies have confirmed that oral administration of herbal medicines can reduce PF and improve pulmonary function. The bioavailability of some natural products is suboptimal when administered orally. Inhalation therapy transports the drug directly to the core organ, providing a new choice for treating PF. The existing research on inhalation of NPHM mainly focuses on the therapeutic effect of chronic obstructive pulmonary disease (COPD), asthma, pneumonia, and other respiratory diseases. The types of inhalated herbal medicines include herbal preparations, water decoctions, and herbal injections [68]. Although studies on treating PF by natural product nebulization started late and are few, they show sound curative effects. Therefore, we searched PubMed, Web of Science, CNKI, and other databases, sorted and summarized the relevant studies on the anti-PF activity of natural medicine inhalation (Table 3).

Most current studies involve animal experiments, and a few involve clinical trials. Most of the studied drugs are components of natural medications, including polyphenols, flavonoids, alkaloids, saponins, and terpenoids, which are the herb's active ingredients (Figure 1).

![Image](image-url)

**Table 3 Inhalation of herbal medicines for treatment of pulmonary fibrosis.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Source</th>
<th>Subjects</th>
<th>Inhalation Method</th>
<th>Dose and Duration</th>
<th>Results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astragalus poly saccharides and salvianolic acid B</td>
<td>Astragalus membranaceus (Fisch.), Salvia miltiorrhiza Bge.</td>
<td>Rat model of BLM-induced PF</td>
<td>Nebulizer</td>
<td>10 mg/ml, 30 min/day, 28 days</td>
<td>Decreased the expression of fibrosis markers in lung tissue.</td>
<td>[137]</td>
</tr>
<tr>
<td>Baicalin</td>
<td>Scutellaria baicalensis Georgi</td>
<td>Rat model of BLM-induced PF</td>
<td>DPI</td>
<td>9 mg/kg, 3mg/day, 28 days</td>
<td>Improved lung function and reduced the levels of IL-4, IL-6, IL-1β, HYP, SOD, MDA, LDH</td>
<td>[106]</td>
</tr>
<tr>
<td>Tetrandrine</td>
<td>Stephania tetrandra S. Moore</td>
<td>Rat model of BLM-induced PF</td>
<td>Nebulizer</td>
<td>8 mg/kg/day, 28 days</td>
<td>Reduced inflammation and fibrosis, restricted HYP accumulation, controlled protein expression in the development of PF, and enhanced postoperative survival.</td>
<td>[92]</td>
</tr>
<tr>
<td>Glycyrrhizic acid</td>
<td>Glycyrrhiza uralensis Fisch.</td>
<td>Mouse model of BLM-induced PF</td>
<td>Nebulizer</td>
<td>12/24 mg/ml, 4 ml/day, 21 days</td>
<td>Alleviates BLM-induced PF and decreased the levels of IL-17, TGF-β1 and p-Smad2 in lungs of mice.</td>
<td>[117]</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Curcuma Longa L.</td>
<td>Rat model of BLM-induced PF</td>
<td>Nebulizer</td>
<td>10 mg/time, 2/7/14 days after modeling</td>
<td>Attenuated lung injuries, decreased HYP and collagen I, and inhibited the expressions of TNF-α, TGF-β1, NF-κB p65 and MMP-9.</td>
<td>[91]</td>
</tr>
<tr>
<td>Salvianolic acids and tanshinones</td>
<td>Salvia miltiorrhiza Bge. Ginkgo biloba L., Ardisia japonica (Thunb. b.) Blume, Astragalus membranaceus, etc. (ten herbs)</td>
<td>Rat model of silica-induced PF</td>
<td>DPI</td>
<td>10 mg/kg, 1 time/3 days, 27 days</td>
<td>Reduced the content of HYP and the level of TGF-β 1 in lung tissue.</td>
<td>[138]</td>
</tr>
<tr>
<td>Miao medicine formula</td>
<td>Ligusticum chuanxiong Hort.</td>
<td>Patients with PF</td>
<td>Nebulizer</td>
<td>2.5 mg/ml, 15–30 min/time, 2 times/day, 8 months</td>
<td>Reduced fibrosis, increased the inhibition rate of serum SOD and reduced serum NO and the expression of the FasL gene.</td>
<td>[139]</td>
</tr>
<tr>
<td>Tetramethylpyrazine (combined with ambroxol and erythrocin)</td>
<td>Salvia miltiorrhiza Bge.</td>
<td>Rat model of BLM-induced PF</td>
<td>DPI/Nebulizer</td>
<td>DPF: 10 mg/kg/day, 28 days; Nebulizer: 0.15, 0.30, 0.45 mg/kg, 28 days</td>
<td>Improved the clinical symptoms, signs, pulmonary function, blood oxygen partial pressure, chest X-ray, and CT results.</td>
<td>[97]</td>
</tr>
<tr>
<td>Total saponins of Panax notoginseng</td>
<td>Panax notoginseng (Burk.) F. H. Chen</td>
<td>Rat model of BLM-induced PF</td>
<td>Nebulizer</td>
<td>1.04 mg/kg for 10 min, 2.09 mg/kg for 20 min, 3.13 mg/kg for 30 min, 14 or 28 days</td>
<td>Improved pulmonary function indexes, inhibited collagen deposition and coagulation activation, and decreased inflammatory factors.</td>
<td>[74, 75]</td>
</tr>
</tbody>
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Inhalation of natural products derived from herbal medicines for the treatment of pulmonary fibrosis.

**Polyphenols**
Polyphenolic herbs are the most common inhaled drugs used for treating PF, such as herbal active substances like curcumin and salvianolic acid. In TCM theory, *Salvia miltiorrhiza* Bge. (Danshen in Chinese) is a herb with the function of promoting blood circulation and resolving blood stasis. Animal experiment proved that it alleviated BLM-induced PF via targeting Nrf2-Nox4 Redox Balance [69]. A meta analysis showed that compound Danshen injection is effective in improve symptons and arterial partial pressure of oxygen of PF patients [70]. Salvianolic acid B is a valuable natural substance obtained from *Salvia miltiorrhiza* Bge [71]. Salvianolic acid B reduces BLM-induced peroxide-stress injury and control fibrosis-related cytokines like tumor necrosis factor to prevent or treat PF [72, 73]. A DPI is a new drug delivery form widely used as a substitute for traditional drug delivery methods. The salvianolic acid B DPI has been successfully prepared by spray drying. It overcomes the disadvantages of poor oral absorption and low bioavailability of salvianolic acid B through pulmonary drug delivery technique, improves the drug concentration at the focal site, and enhances the therapeutic effect for IPF [74]. Salvianolic acid B nebulized inhalation solution demonstrated its significant anti-fibrotic and anti-inflammatory effects, possibly by blocking protease-activated receptor-1 expression and protein kinase C phosphorylation [75].

A natural polyphenol called curcumin, which is produced from rhizome of *Curcuma Longa* L. (Jianghuang in Chinese), has a long history of use as medicine in Asian countries for a number of pathological conditions and diseases [76]. Modern pharmacological studies have found that curcumin has anti-inflammatory [77], antioxidant [78], anti-fibrotic [79], anti-tumor [80], oxygen radical scavenging [81], and other pharmacological effects. In rat lungs exposed to BLM, curcumin regulates collagen turnover, assembly, and deposition to prevent fibrotic deposits [82]. Curcumin inhibits the expression of inflammatory cytokines associated with PF such as TNF-α, IL-6, IL-4, MMP, and TGF-β1 [83]. Intranasal curcumin inhibited airway inflammation and PF by decreasing MMP-9 activities in ovalbumin-induced chronic asthma [84]. Curcumin, however, has a low bioavailability due to its poor solubility in water [85]. Several other studies have used poly(lactic-co-glycolic)acid large porous microparticles, liposomes, mannnitol, mesoporous materials, and novel nano as carriers to develop inhaled formulations of curcumin for treating pulmonary diseases such as COPD and lung cancer [86–91].

**Alkaloids**
For alkaloid inhalation therapy, tetrandrine and tetramethylpyrazine (chuanxiongzine) have been investigated. A tetrandrine-hydroxypropyl-β-cyclodextrin inclusion compound (TET-HP-β-CD) was developed for treating PF through inhalation administration. The inhalation of TET-HP-β-CD resulted in a reduction of fibrosis and inflammation, a restriction of hydroxyproline (HYP) accumulation in the lungs, a regulation of protein expression involved in PF formation, and an increase in the survival rate of a rat model with PF induced by BLM [92].

Tetramethylpyrazine is an alkaloid compound extracted from the herbal medicine *Ligusticum chuanxiong* Hort (Chuanxiong in Chinese) [93]. *Ligusticum chuanxiong* Hort is an herbal medicine for promoting blood circulation and resolving blood stasis. Data mining shows that it is one of the most commonly used herbal medicines for PF in clinical practice [94]. It reduces monocrotaline-induced pulmonary hypertension by interacting with the ROS/INOS/PKG-1 axis [95]. Furthermore, it inhibits the NF-κB-p65/TNF-α signaling pathway, thereby attenuating IL-17-induced bronchial mucosal epithelial cell damage [96]. The combination of tetramethylpyrazine with aminoglutethimide and erythromycin by nebulized inhalation offers the benefits of low dose, high local drug concentration, mild side effects, and simple operation [97]. After more than one year of clinical application, it can improve the quality of life and prolong the survival time of patients with PF, and has good economic and social benefits.
Flavonoids

A significant flavonoid called baicalin, obtained from the plant Scutellaria baicalensis Georgi (Huangqin in Chinese), has demonstrated a range of pharmacological actions in the liver and lungs [98], including anti-inflammatory [99], anti-oxidant, anti-cancer [100], and anti-fibrotic [99] properties. Baicalin alleviates the progression of PF in a mouse model by inhibiting the expression of TGF-β1, MMP-2, and tissue inhibitor of metalloproteinases (TIMP2) [101]. Baicalin inhibits lung fibroblast proliferation and histopathological damage in BLM-induced PF, and this effect may be mediated by PI3K/AKT and CaMKII signaling pathways [102]. Through the TGF-1-induced ERK1/2 signaling pathway linked to the adenosine A2A receptor, baicalin reduces BLM-induced PF [103]. Baicalin inhibits inflammatory factor secretion by inhibiting the TLR4-MyD88- NF-κB/NLRP3 pathway as well as the MAPK signaling pathway [104]. However, baicalin has a very low solubility resulting in low oral absorption and utilization [105]. A DPI for pulmonary delivery is a new drug delivery technology consisting of insoluble and unstable drugs and moisture-proof, liquid, and non-irritating excipients. The formulation has a large surface area with a small particle size, which also improves the solubility of the drug. In a study, baicalin/ambrroxol hydrochloride-DPI particles were developed by spray drying for pulmonary delivery [106]. The results showed that the intrapulmonary bioavailability of baicalin and ambroxol hydrochloride could be significantly improved. Future research could focus on nano-emulsions, solid-liquid nanoparticles, nano-crystallization, and baicalin-loaded liposomes to improve the bioavailability of baicalin [107].

Saponins

The extraction of total saponins of Panax notoginseng (PfNS) is derived from the taproots or rhizomes of Panax notoginseng (Burk) F. H. Chen (Sanqi in Chinese). They mainly includes notoginsenoside R1, ginsenosides Rg1, ginsenosides Re, and ginsenosides Rh1 [108]. PfNS have significant anti-inflammatory, anti-ischemic, and anti-fibrotic effects [109]. Ginsenoside Rg1 a effectively mitigates PF induced by BLM in rats through the caveolin-1 and TGF-β1 signaling pathways [110]. However, due to its hydrophilic nature, tPNS is subject to significant first-pass effects of the liver and enterohepatic circulation, which limits its oral bioavailability [111]. The researchers formulated an inhalation solution containing tPNS for the purpose of administering it to a rat model of BLM-induced PF via the lungs. The administration of tPNS for a duration of 14 days yielded a noteworthy decrease in lung coefficients and alveolitis scores. It was clear that aerosol inhalation delayed the development of PF and that the dose was low. There were no significant adverse effects.

Terpenoids

The natural compound Glycyrrhizic acid (GA), extracted from the herbal medicine Glycyrrhiza uralensis Fisch. (Gancao in Chinese), has demonstrated potential therapeutic effects on lung injury and liver fibrosis in animal models [112]. It is a high mobility group protein 1 (HMGB1) inhibitor approved by the FDA for treating hepatitis [113]. By preventing the expression of HMGB1, GA can influence the PI3K/Akt/mTOR pathway and prolong the development of silicosis in mice [114]. HMGB1 rises in the late stages of PF and the early stages of pulmonary inflammation. GA reduces the expression of HMGB1, which slows the progression of pulmonary toxicity [115]. One study indicated that GA could reduce BLM-induced lung fibrosis in vivo and prevent the epithelial-to-mesenchymal transition (EMT) process [116]. In another study, GA nebulized inhalation was used and compared with GA gavage [117]. The results showed that GA nebulized inhalation with a lower dose could inhibit BLM-induced PF in mice by suppressing the TGF-β1/Smads pathway in PF. Nebulized inhalation of GA has value for clinically treating PF.

Discussion

IPF is a fatal interstitial lung disease [118]. There are presently very few medications that are clinically accessible. More effective anti-PF drugs are required. Many studies have demonstrated herbal medicine’s effectiveness and advantages in treating PF. Natural active ingredients have the biological ability to simultaneously modulate multiple factors (e.g., oxidative stress, inflammation, autophagy, apoptosis, pyroptosis) to minimize PF damage [119]. Therefore, herbal medicines are an important source for researching drugs for PF. However, the absorption and bioavailability of many NPHM, such as salvinolic acid B [74], curcumin [85], baicalin [105], and tPNS [81] are generally low. To address these issues, researchers have used a variety of strategies in new drug development and delivery system design. Inhalation therapy can improve efficacy and reduce drug side effects by lowering drug dosage and acting directly on the lungs. Herbal medicine inhalation therapy has been used to treat various lung diseases in countries like China. Therapeutic medications are no longer limited by their solubility and stability in biological fluids, leading to successful absorption and distribution in the lung [120]. Moreover, the lung has direct access to the outside world. It has the advantage of unique physiological characteristics, such as its large surface area and thin alveolar blood barrier, as well as first-pass metabolism [121]. The convenient conversion of herbal liquid into an aqueous aerosol ensures that inhalation is a feasible route of administration [122].

Inhalation treatment has a long history in TCM. There are records of treating diseases by nasal inhalation in sources as early as the ancient Chinese medical book Huangdi’s Internal Classic. In the early stage of TCM, nasal inhalation was used mainly in the form of smoke, steam vapor, medicated pillows, and sachets. According to ancient medical records, most of these interventions were administered directly into the nasal cavity or inhaled with vapor for aid or treatment [68]. As recorded in Treatise on Febrile and Miscellaneous Diseases, medication nasal inhalation was used to treat syncope and sudden death, by “blowing the powder of Gleditsia into the nose” [123]. The Tang Dynasty’s Bei Ji Qian Jin Yao Fang recorded the treatment of apoplectic aphasia by fumigation and inhalation of TCM. The modes of inhalation and administration of TCM developed further during the Ming and Qing Dynasties. The Compendium of Materia Medica has many records on the treatment of hiccups, cough, malaria, and other diseases by inhaling Chinese medicine. In ancient India, inhalation therapy was also used to treat asthma and lung diseases [124]. With the emergence and developments of pharmaceutical technology and atomization instruments, modern inhalation equipment with better effectiveness and portability is emerging [125], which makes inhalation therapy with herbal medicine a good choice for treating PF. The safety of inhalation of herbal medicines is the focus of attention at present. Most of the TCM preparations are multi-component liquid preparations, with complex components and some macromolecular substances and some unknown components. One research has shown that 70% of herbal medicines can directly reach the respiratory mucosa and secretions after atomizing [126]. After being inhaled into the respiratory tract or lungs, these components, especially macromolecular substances, may accumulate in the lungs and cause chronic irritation to the respiratory tract or lung mucosa. A study on the irritation of aerosol inhalation of Reduning, a TCM injection, showed that the lungs of rats were slightly edema, the alveolar wall of pathological sections was significantly thickened, the tracheal epithelium was partially exfoliated, and some ciliary structures were exfoliated; slight bleeding and necrosis were also observed, which were positively correlated with the atomization concentration [127]. Another TCM injection Tanreqing also showed some irritation to the respiratory system of rats [128]. Therefore, it is necessary to establish a safety evaluation method for the irritation and injury of respiratory mucosa to eliminate the damage caused by herbal components, so as to ensure the safety of clinical medication. This is not only a toxicological problem, but also a higher requirement for the preparation process of inhalation preparations of TCM from the pharmaceutical point of view. In other words, its chemical composition should try to remove impurities and macromolecular substances that have no pharmacological effect. Hence, single or
combinational use of active herbal compounds to treat PF is more recommended. However, the development of drug inhalation formulations, inhalation concentrations, and doses is still in the exploratory stage.

Effective and safe inhalation therapy depends not only on the drug formulation but also on the design of the delivery system. Therefore, it is necessary to design delivery systems with high activity and utilization through ideal carriers for higher targeting efficiency. The drug-device combination must effectively atomize the drug, achieving a suitable particle size distribution and concentration, in order to ensure optimal deposition and dosage within the targeted pulmonary region [129]. A recent study suggested that lung preparations and drug-delivery devices based on nanoparticle technology are more effective in lung-delivery systems [130]. Modern multifunctional mesoporous silica nanoparticles, nanoparticles, and liposomes may help improve drug utilization. The advent of nanotechnology would help in developing inhalable drugs and advancing pulmonary drug delivery. That would enhance feasible physical conditions for drug delivery and utilization and may improve the bioavailability of inhaled drugs when delivered through the lungs [121]. Iterative updates of atomizers can yield a more advanced atomizer that can optimize lung sediment and reduce treatment time [28]. The easy operation of these new atomizers may also allow most patients to self-administer drugs, further promoting their widespread use in hospitals and family environments [131].

Although the inhalation of NPHM for PF has been effective in experiments, fewer clinical studies have been conducted. In the future, the following key issues affecting the research and development of inhaled preparations of NPHM need to be studied: 1) Screen effective inhaled NPHM in treating PF. 2) Carry out research on the absorption and metabolism of the effective ingredients in the lungs. Further comprehensive and validated pharmacokinetic assessment techniques are required to elucidate the rationality of inhalation of NPHM. 3) Study the mechanism of the action of the effective ingredients after inhalation of herbal medicines. 4) Strengthen the study on the safety of inhalation preparations of NPHM and establish evaluation methods.

**Conclusion**

At present, there is a shortage of clinical inhalation drugs for PF and it is urgent to develop. The inhalation drug for PF has a good market prospect and clinical demand. The clarification of the mechanism of action of natural active ingredients, coupled with the progress in inhalation therapy technology, has opened up promising prospects for the utilization of natural drug inhalation therapy in the treatment of PF.

**References**


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