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Review

Protective role of natural products in pulmonary fibrosis through immune regulation

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ABSTRACT

Pulmonary fibrosis (PF) is a progressive, fatal fibrotic disease caused by respiratory conditions. The condition can ultimately lead to severe organ failure and mortality, and is associated with multiple risk factors. Growing evidence highlights the immune system's role in PF, with various immune components participating in inflammatory and fibrotic processes. Different immune cells, including neutrophils, lymphocytes, and macrophages, demonstrate distinct effects on PF progression and development. Furthermore, key immune system cytokines, including the interleukin (IL) family, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, transforming growth factor (TGF)-β, and connective tissue growth factor (CTGF), contribute to PF initiation and progression through independent mechanisms and mutual regulation. Currently, limited effective treatments exist for PF, with several treatments causing severe adverse reactions. Natural products, characterized by multi-target effects, holistic regulation, and low toxicity, have emerged as a research focus. This review compiles the mechanisms, therapeutic potential, and active components of various natural products. These compounds can ameliorate pulmonary inflammation, epithelial-mesenchymal transition, and collagen deposition through diverse immune mechanisms, acting at specific stages or throughout the fibrotic process, thereby supporting PF management. This review examines current scientific understanding of natural products' immunological effects in PF, which is crucial for developing future anti-PF therapeutics.

1. Introduction

Pulmonary fibrosis (PF) represents a chronic, fatal, and progressive fibrotic condition resulting from respiratory disorders [1]. The development of PF correlates with various risk factors, including smoking [2], environmental pollutants [3], obesity [4], drug toxicity, viral infection, and genetic susceptibility. The condition is characterized by alveolar interstitial inflammation, excessive extracellular matrix (ECM) deposition, abnormal fibroblast proliferation and differentiation, and intracellular redox imbalance, ultimately leading to severe organ failure and mortality.

PF exhibits complex mechanisms, with research demonstrating the immune system's integral role in its onset and progression. Inflammation serves as a crucial defense mechanism and a repair phase. Persistent inflammatory responses recruit immune cells and promote PF development by mediating interconnected immune responses and epithelial damage. Studies indicate significant increases in macrophages, neutrophils, T cells, and other immune cells in the alveolar lavage fluid of PF patients [5]. In the early phase of alveolar injury, neutrophils are rapidly recruited to sites of epithelial damage, where they accumulate and release neutrophil elastase (NE), a proteolytic enzyme that activates downstream immune responses. NE not only contributes to sustained inflammation but also disrupts normal tissue repair processes, thereby promoting aberrant remodeling characteristic of PF. Macrophages primarily regulate PF occurrence through inflammation, lung injury, and repair *via* two polarization pathways. Initially, M0 macrophages polarize toward M1 and activate inflammation. Later-stage M2 polarization induces immune cytokine secretion, accelerating fibroblast transformation into myofibroblasts and collagen secretion, thereby promoting PF [6]. PF lesions contain numerous T lymphocytes, where helper T cells type 1 (Th1) resist PF by secreting interferon (IFN)-γ and interleukin (IL)-12, while Th2 promote fibrosis through IL-4 and IL-13 secretion. Th1/Th2 imbalance can enhance pro-fibrotic factor and immune cytokine expression, advancing PF development [7].

Normal alveoli comprise thin type I alveolar epithelial cells (AT1) and type II epithelial cells (AT2) that produce phospholipid-rich surfactants. AT1 forms gas exchange surfaces near endothelial cells, while AT2 subpopulations maintain stem cell characteristics and differentiate into AT1 daughter cells for gradual alveolar epithelium renewal [8]. However, PF patients exhibit reduced AT2 to AT1 transdifferentiation capacity. Recent evidence indicates that accelerated aging of AT2 epithelial cells contributes to the progression of PF. Key signaling pathways implicated in AT2 cell senescence, including Wnt, mechanistic target of rapamycin (mTOR), and nuclear factor-κB (NF-κB), have been shown to play

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critical roles in this process and are closely associated with the pathogenesis of PF [9]. During initial injury, activated alveolar epithelial cells and recruited inflammatory cells release potent pro-fibrotic growth factors [10], particularly transforming growth factor (TGF)-β, which contributes to alveolar epithelial cell injury and apoptosis, induces epithelial-mesenchymal transformation (EMT), activates and promotes fibroblast invasion, and facilitates ECM deposition (Fig. 1). Additionally, lungs contain abundant progenitor cells, including Clara cells in bronchiolar epithelium, which maintain normal airway epithelium. However, excessive bronchiolar epithelial cell proliferation can exacerbate PF [11].

PF can be induced through exosome-mediated intercellular communication, oxidative stress, and various cell death modes, including pyroptosis, apoptosis, ferroptosis and autophagy. Furthermore, the natural aging process contributes to age-related persistent PF through cellular aging, telomere deterioration, mitochondrial dysfunction, and related processes.

Recent comprehensive investigations of PF have demonstrated the therapeutic potential of numerous natural products and their active components. Immune function plays a crucial role in both disease prevention and treatment. Natural products exert their biological effects through immune cells and factors, including the regulation of inflammation, oxidative stress, EMT, ECM, and various fibrosis-related signaling pathways, thereby impeding PF progression. This review examines recent advances in natural compounds that ameliorate PF through immune regulatory mechanisms.

2. Natural products improve PF through immune cells

2.1. Macrophages

Recent research has established that macrophage polarization significantly influences the development and progression of PF. Macrophages, as innate immune cells, function to consume and eliminate infections upon stimulation [12]. The lung contains a high concentration of macrophages, primarily categorized as alveolar macrophages (AMs) and interstitial macrophages (IMs). AMs can either directly consume collagen or secrete matrix metalloproteinases (MMPs) to degrade ECM, depending on their polarization state. However, AMs also release various chemokines and pro-fibrotic cytokines that promote PF. AMs can differentiate into M1 and M2 phenotypic macrophages, with M1 macrophages generally promoting inflammation while M2 macrophages suppress it [13]. Research indicates that in PF, the M2 phenotype predominates while the M1 phenotype is diminished [14]. M2 macrophages secrete TGF-β, promoting lung fibrosis, though fibrosis may improve with reduced M2 macrophage presence.

While balanced M1 and M2 macrophage polarization benefits the body, dysregulation leading to excessive M1 or M2 macrophages can exacerbate inflammation or fibrosis [15]. Acute injury stimuli polarize lung macrophages toward the M1 phenotype, activating Th1 immune responses involving INF-γ and toll-like receptors in inflammation. M1 macrophages produce high levels of chemokines and pro-inflammatory substances, including IL-6, IL-1β, tumor necrosis factor (TNF)-α, IL-12, and chemokine ligand (CCL) [16], mediating inflammatory responses and tissue damage. These pro-inflammatory factors may enhance M1 polarization, with persistent inflammation potentially leading to PF [17]. M2 macrophages play a crucial role in the post-inflammatory fibrotic phase. Th2 cytokines, including IL-14, TNF-α, and IL-13, induce polarization toward pro-fibrotic M2 macrophages [18]. Additionally, the production of pro-fibrotic mediators like TGF-β, vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) activates fibroblast transformation to myofibroblasts, generating substantial collagen [19] and promoting ECM deposition. M2 macrophages also secrete cytokines, including IL-10 [20], CCL16, and CCL18. These factors collectively impair gas exchange, promote lung tissue remodeling, and advance PF development.

In PF, Th2 cytokines IL-4 and IL-13 activate and polarize M2 macrophages, with IL-13 demonstrating more pronounced pro-fibrotic effects. Eucalyptol inhibits IL-13-induced M2 macrophage polarization. Through this inhibition, eucalyptol reduces pro-fibrotic TGF-β release and collagen production, thereby limiting pulmonary ECM deposition. Eucalyptol also suppresses M2

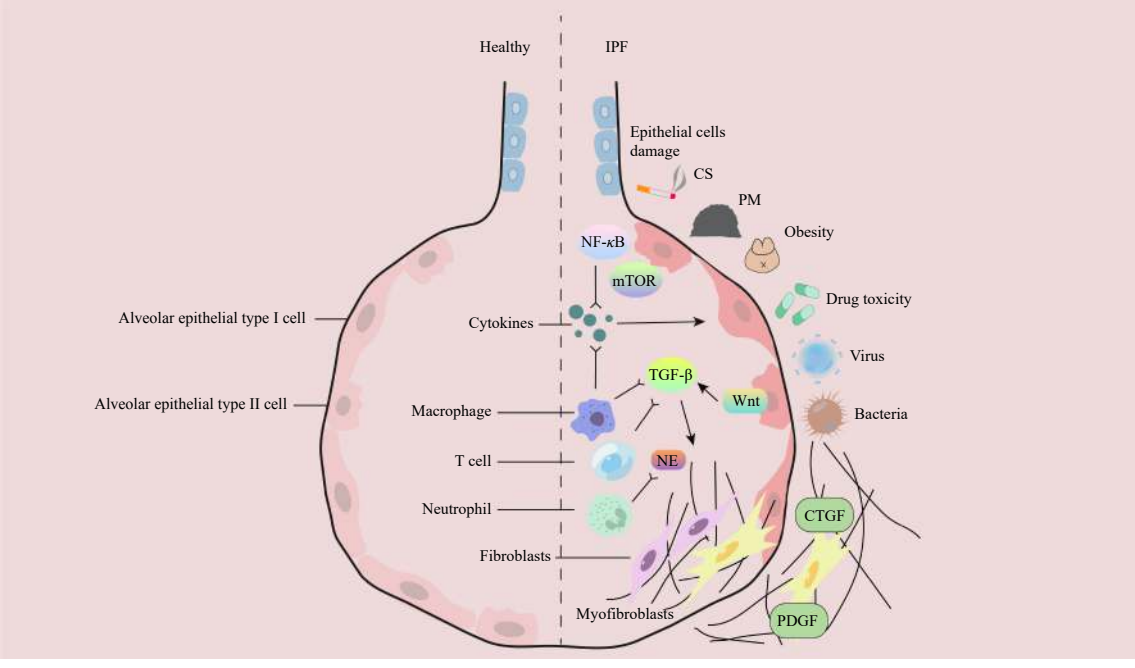

Fig. 1 Elements that induce the development of PF.

macrophage polarization by downregulating signal transducer and activator of transcription (STAT) 6 expression [21]. However, research on eucalyptol in PF remains limited. Current evidence only confirms eucalyptol's inhibition of PF through M2 macrophage polarization *in vitro*, without detection in lung tissue or BALF of model mice, limiting its clinical relevance.

STAT6 signaling within the STAT family represents a primary signaling pathway regulating M2 macrophage polarization when stimulated by Th2 cytokines such as IL-4 or IL-13. Thymoquinone reduces STAT6 protein phosphorylation levels and inactivates the IL-4/STAT6-mediated signaling pathway responsible for M2 phenotypic polarization. Furthermore, inducible nitric oxide synthase (iNOS), a marker of M1 macrophages, exhibits high expression when stimulated by lipopolysaccharide and IFN-γ, producing substantial nitric oxide. Arginase-1 (Arg1), an M2-type macrophage marker, shows elevated expression induced by IL-4 and IL-13. In M2-type macrophage polarization intervention, thymoquinone inhibits Arg1 expression while enhancing iNOS expression, indicating its ability to reverse the M2 phenotype and direct macrophage polarization toward the M1-type, thereby ameliorating PF [22]. As a natural molecule present in numerous plant species, thymoquinone's low toxicity presents significant potential for PF drug development. Recent developments include thymoquinone nanopreparations studied for various lung injury-related diseases. However, clinical trials remain necessary to translate *in vitro* findings into therapeutic benefits.

Similarly, neotuberostemonin (NTS) reduces macrophage recruitment in mouse lung tissue and inhibits M2 polarization. *In vitro* experiments demonstrate that NTS significantly decreases Arg1 expression in a dose-dependent manner, while only downregulating iNOS expression at 100 μmol·L^{-1} [23]. Although NTS inhibits M2 macrophage polarization in RAW264.7 cells, its effect on AMs and IMs in lung tissue requires further investigation. NTS, derived from the potato root and known as *Stemona japonica*, demonstrates high concentrations in the lung and liver but cannot traverse the blood-brain barrier following oral administration of *Stemona japonica* as a crude drug. Consequently, NTS purification and dosage form development remain significant challenges for its therapeutic application.

2.2. Lymphocytes

Lymphocytes serve as key mediators in specific immune responses. Current research indicates that T lymphocyte aggregation constitutes a common pathological basis for various PF diseases. T lymphocytes exhibit different roles in fibrosis development based on their phenotype and lung tissue environment, potentially promoting or inhibiting the process [24]. T helper (Th) cell subsets, classified according to lymphocyte functions, play crucial roles in the immune system, primarily comprising Th1 and Th2 [25]. Under normal conditions, these subsets contribute to the maintenance of tissue homeostasis through reciprocal regulation mediated by their distinct cytokine secretion profiles. Th1 cells primarily mediate cellular immune responses, with Th1-type immune responses typically associated with inflammation, where overreaction may cause tissue damage. Th2 cells primarily mediate humoral immune responses. Under certain stimuli, dominant Th2 cytokine effects lead to fibroblast activation and proliferation, increased collagen synthesis, reduced degradation, and subsequent ECM deposition [26]. INF-γ and IL-4 serve as signature factors for Th1 and Th2, respectively [27]. IL-4 induces fibrosis through various mechanisms, including promoting TGF-β overexpression, related collagen production, and fibroblast activity, while restricting T lymphocyte aggregation in early alveolitis. Conversely, INF-γ demonstrates anti-fibrotic effects.

Polygonum prevents or delays fibrosis onset by downregulating IL-4 in early fibrosis stages and counteracts fibrosis primarily through INF-γ upregulation in later stages, effectively modulating the Th1/Th2 balance to influence PF progression. Studies examining polygonum treatment at different PF stages demonstrate inhibitory effects during late-stage fibrosis, though complete PF prevention remains unachieved. Given that PF treatment requires long-term intervention, extended animal experiments highlight polygonum's advantages of low toxicity and high safety, establishing groundwork for future long-term clinical therapeutic applications [28].

In examining the therapeutic effects of Astragalus water extract and Astragalus polysaccharide on PF rats, comparative analysis with the model group and dexamethasone group revealed significant changes in cytokine levels. The model group showed notably decreased serum INF-γ and INF-γ/IL-4 ratios while IL-4 levels increased substantially, indicating type I/II cytokine imbalance. Astragalus water extract and its polysaccharide fractions significantly increased IFN-γ levels and the IFN-γ/IL-4 ratio, while reducing IL-4 expression, suggesting that Astragalus may exert antifibrotic effects by modulating the Th1/Th2 cytokine balance, an effect comparable to that of dexamethasone [29]. According to *The Truth of Materia Medica*, Astragalus is described as "entering the lung Qi and the surface of the body's defensive Qi, among the most potent Qi-tonifying herbs". Due to its low toxicity and favorable therapeutic profile, Astragalus is widely used in traditional Chinese medicine. However, long-term use is not recommended for individuals with Qi stagnation or Yin deficiency. Recent studies on Astragalus in the context of PF often involve its combination with other herbal medicines, underscoring the need for further research into its pharmacologically active constituents and mechanisms of action.

Regulatory T cells (Tregs), crucial human immune cells, serve an essential function in inflammatory response suppression and lung tissue repair promotion. Through secretion of PDGF, TGF-β, and related factors, Tregs facilitate EMT and Th1 to Th2 conversion, contributing to PF development [30]. Tregs inhibit the progression of pulmonary fibrosis (PF) by promoting epithelial tissue repair, limiting fibroblast accumulation, and suppressing pro-inflammatory cytokines and immune cell activation. The $CD4^+CD25^+Foxp3^+$ Treg subset represents a population of thymus-derived $CD4^+$ T cells that play a central role in maintaining immune homeostasis. Studies using silica-induced PF mouse models have shown that depletion of $CD4^+CD25^+Foxp3^+$ Tregs enhances the Th1 immune response and shifts the Th1/Th2 balance toward a Th2-dominant phenotype, which is commonly associated with fibrotic progression. $CD8^+$ T cells, which express the CD8 glycoprotein, typically differentiate into cytotoxic T lymphocytes (CTLs) and are essential for the elimination of infected or malignant cells. In models of renal fibrosis, $CD8^+$ T cells, along with IFN-γ, have been shown to suppress $CD4^+$ T cell-mediated transdifferentiation of monocytes into fibroblast-like cells, thereby attenuating fibrotic remodeling [31]. Additionally, they secrete IL-13, mediating bleomycin (BLM)-induced PF through IL-21-dependent mechanisms [32].

Research indicates that naringenin significantly ameliorates PF by modulating the immunosuppressive microenvironment. Specifically, it downregulates TGF-β1 expression, resulting in a reduced proportion of $CD4^+CD25^+Foxp3^+$ and an increased abundance of activated T cells [33]. However, comprehensive mechanistic studies remain insufficient. Additional data is required to identify naringenin's cellular targets in various environments. Furthermore, human studies have not fully established naringenin's safety and efficacy, necessitating large-scale clinical trials to

evaluate its dosage, toxicity, and effectiveness. Galangin has been shown to reduce the populations of $CD4^+CD69^+$ and $CD8^+CD69^+$ T cells, as well as dendritic cells, in BLM-induced PF models. It also decreases inflammatory cell infiltration in lung tissue. *In vitro*, galangin suppresses TGF-β1-induced EMT and fibroblast differentiation, supporting its potential antifibrotic activity [34]. Current galangin research in PF remains limited, with more studies focusing on lung cancer cells. Additional research is necessary to confirm galangin's safety and efficacy, with considerable development required from monomer to marketable drugs. In amiodarone-induced mouse PF models, neferine has been shown to restore $CD4^+CD25^+$ Treg levels, rebalance Th1/Th2 cytokine responses, and alleviate fibrosis, potentially through inhibition of surfactant protein D expression [35]. Pharmacokinetic studies revealed that 50 $mg{\cdot}kg^{-1}$ oral neferine administration in rats resulted in maximal lung distribution, with lower doses showing stronger anti-fibrotic effects. However, the limited scope of neferine research, primarily confined to amiodarone-induced models, and the absence of data across other PF models restrict its broader applicability and therapeutic development.

2.3. Neutrophils

The bone marrow produces neutrophils, which are essential components of the innate immune system. These cells participate in pulmonary tissue remodeling [36]. Beyond their anti-microbial functions, neutrophils release oxidases, proteases, cytokines, and chemokines that alter the tissue environment [37]. NE represents one of the most destructive compounds secreted by neutrophils. NE damages alveolar epithelial cells and capillary endothelial cells, disrupts alveolar architecture, hydrolyzes bronchial tissue, and degrades various ECM components, including type I collagen, laminin, fibronectin, and elastin, ultimately contributing to PF [38]. MMPs are enzymes responsible for ECM degradation and tissue remodeling, initially believed to possess anti-fibrotic properties [39]. Neutrophils primarily secrete MMP-8 and MMP-9 [40]. *In vivo*, the absence of MMP-8 significantly improves PF through upregulation of the anti-fibrotic cytokine IL-10. During PF, neutrophils exhibit elevated MMP-9 levels compared to other cell types.

MMPs are regulated by tissues that inhibit metalloproteinases [tissue inhibitor of metalloproteinases (TIMPs)], with both showing minimal expression in normal lung tissue. During early injury phases, an elevated MMPs/TIMPs ratio favors MMPs, leading to predominant degradation, basement membrane disruption, and lung tissue injury. Subsequently, fibroblast infiltration causes lung structure remodeling, with aberrant repair mechanisms initiating PF [41]. In the fibrotic phase, the balance shifts toward TIMPs, reducing degradation and promoting excessive ECM accumulation, thereby intensifying fibrosis. When administered to BLM-PF rats, *Reynoutria japonica* reduced both MMP-2 protein expression and its corresponding inhibitor protein in lung tissue across prevention and treatment groups, with sustained TIMP-2 suppression compared to the model group. This indicates that resveratrol modulates abnormally elevated TIMP-2 expression in lung tissue, maintaining the MMPs/TIMPs equilibrium and preventing excessive ECM deposition and subsequent PF [42]. In silicon-induced PF rats exhibiting MMP-9/TIMP-1 imbalance, schisandrin B treatment induced a gradual increase in *TIMP-1* mRNA expression while reducing *MMP-9* mRNA expression. This resulted in decreased early MMP-9 expression and restored MMP-9/TIMP-1 balance throughout all stages [43]. Schisandra B demonstrates relevant applications in animal experiments and clinical studies of hepatic and renal fibrosis. Investigation of its therapeutic effects in PF may inform related clinical drug development.

In addition to the natural remedies already stated, Table S1 summarizes other natural products that prevent and treat PF by regulating immune cells.

3. Natural products improve PF through immune cytokines

Cytokines are low molecular weight soluble proteins produced in various cells in response to immunogens, mitogens, or other stimulants. Research has demonstrated that cytokines, as immune regulators, participate in autocrine, paracrine, and endocrine signaling. The cytokine family encompasses ILs, IFNs, TNFs, and growth factors. The following sections examine their immunoregulatory mechanisms in PF and outline corresponding natural products.

3.1. IL

ILs represent a specific category of cytokines essential for maintaining homeostasis and regulating the immune system. They are primarily produced by macrophages, monocytes, or lymphocytes, and exhibit complex structures and functions. These molecules play vital roles in immune system regulation within lung tissues [44, 45]. During PF, ILs significantly influence lung tissue remodeling, ECM deposition, collagen synthesis, and lung fibroblast proliferation and aggregation [46-48]. Notably, IL-1β, IL-10, IL-7, and IL-18 mitigate PF through inflammation suppression and immune response modulation [49-52].

3.1.1. IL-1β

The principal cytokine product of inflammasomes, predominantly produced by activated macrophages, dendritic cells, neutrophils, and epithelial cells, demonstrates involvement in PF development [53]. IL-1β induces PF and inflammation by attracting lymphocytes and neutrophils to damage sites [54]. Furthermore, IL-1β stimulates fibroblasts to produce collagen and promote fibrosis [55-56]. *IL-1β* mRNA expression increases in a BLM-induced PF model [57], and IL-1β overexpression promotes PF in rats, characterized by ECM accumulation, fibrotic lesions, and myofibroblast formation.

Psoralen reduces IL-1β in BLM-stimulated mouse lungs, inhibiting fibroblast proliferation and collagen synthesis, while partially reversing *α*-smooth muscle actin (*α*-SMA) expression at tissue and cellular levels [58]. Despite psoralen's effectiveness in reversing PF, mortality occurred in the experimental group, with some mice succumbing to an inflammatory cascade or respiratory dysfunction before or after treatment initiation, indicating that early psoralen administration yields optimal results. Research indicates that psoralen exhibits hepatotoxicity [59], nephrotoxicity [60], and embryonic toxicity [61]. When administering therapeutic doses, hepatotoxicity indicators require monitoring, and potential risks to pregnant women and embryos warrant evaluation to ensure safe use during pregnancy.

BLM-induced rats demonstrated elevated IL-1β expression, while diosgenin-treated rats showed significantly reduced IL-1β levels [62]. Research indicates that diosgenin doses exceeding 1125 $mg{\cdot}kg^{-1}$ produced adverse effects and mortality in a dose-dependent manner. However, the traditional dose of 510 $mg{\cdot}kg^{-1}{\cdot}d^{-1}$ demonstrates minimal toxicity [63]. Additional studies confirm diosgenin's safety in drug combinations [64]. The primary therapeutic limitation of diosgenin concerns its low bioavailability. Nanopreparations may enhance the compound's bioavailability and pharmacokinetic properties, facilitating its development as a potential therapeutic agent.

3.1.2. IL-4/IL-13

Research has established that Th2 cells secrete IL-13 and IL-4 cytokines. IL-4 exhibits dual functionality in PF: initially inhibiting T lymphocyte recruitment while subsequently promoting fibroblast differentiation into myofibroblasts, thus advancing fibrosis. IL-13 shares biological characteristics with IL-4 and specifically activates TGF-β to induce tissue fibrosis. Evidence confirms IL-13's role as a critical Th2 cytokine in fibrosis development. Studies utilizing a BLM-induced PF model have investigated the therapeutic potential of targeting resident lung cells responsive to IL-13 and IL-4. Findings indicate the essential role of IL-13 and IL-4 in BLM-induced lung fibrosis, suggesting that targeting these cytokines may represent an effective strategy for future PF treatments.

Following magnesium lithospermate B (MLB) treatment, the relative mRNA expressions of pro-fibrotic cytokines *IL-4* and *IL-13* were suppressed, confirming MLB's anti-fibrotic properties [65]. Animal experimental results demonstrate that 7-d MLB treatment can mitigate BLM-induced PF in mice. However, research specifically examining MLB treatment for PF remains limited. While converting therapeutic MLB doses from animal studies to human medicine appears safe, comprehensive toxicological studies and large-scale clinical trials are still lacking.

3.1.3. IL-6

In BLM-induced PF, IL-6 functions as a pleiotropic cytokine capable of stimulating both inflammation and fibrosis [66]. Research has identified anti-fibrotic properties in the IL-6/IL-12 cytokine family that benefit type II alveolar epithelial cells [67]. However, during later BLM-PF phases, IL-6, in conjunction with IL-4 and IL-13, activates pro-fibrotic M2 macrophages, leading to ECM deposition and PF exacerbation [68]. In a BLM-induced PF mouse model, phycocyanin significantly altered intestinal microbiota composition toward that of the blank group by reducing IL-6, TNF-α, and LPS levels in lung, serum, and intestinal tissues. These changes indicate substantial gut-lung crosstalk. While phycocyanin reduces pro-inflammatory cytokines and modulates gut microbiota in BLM-induced PF mice, the precise mechanism linking phycocyanin's anti-fibrotic effects to gut microbiota requires further investigation [69].

3.1.4. Others

IL-17 is primarily produced by Th17 cells, with additional sources including γδ T cells [70], NKT cells [71], and type 3 innate lymphoid cells (ILC3) [72]. IL-17 inhibits PF through reduced collagen autophagic degradation. Decreased IL-17 expression can worsen silica-induced lung fibrosis, correlating with delayed neutrophil recruitment. Furthermore, it may cause alveolar basement membrane and epithelial cell damage, promoting PF progression and inflammatory responses. In humans, IL-8 is released by fibroblasts, monocytes, pulmonary macrophages, epithelial cells, and other inflammatory and structural cells [73–74]. Elevated IL-8 expression in lung biopsies and bronchoalveolar lavage fluid from PF patients correlates with inflammatory components [75-78], indicating its fibrotic role. Additionally, IL-18 expression significantly influences pulmonary inflammation processes [79] and human PF [80]. PF patients exhibit substantial IL-18 expression in most lung cells, while interstitial cells, particularly fibroblast foci, show strong IL-18Ra expression [81]. This suggests the importance of IL-18 and its receptor in fibroblast and myofibroblast recruitment and phenotypic modification [82].

Research demonstrates that glycyrrhizic acid (GA) exhibits significant anti-PF effects. GA suppresses elevated expression of p-Smad2, IL-17, TGF-β1, and IL-17 in PF-developing mice, suggesting that its anti-PF mechanism operates through the IL-17/TGF-β1/Smad2 pathway [83]. While previous studies confirm GA's anti-PF effects at higher doses, aerosol inhalation delivery shows advantages over gavage administration. GA aerosol inhalation reduces initial IL-6 levels to decrease inflammatory response, subsequently diminishing fibrosis by inhibiting IL-17, p-Smad2, and TGF-β1 expression, thereby improving BLM-induced PF more effectively than gavage. Scutellarin therapy offers rapid onset, effective treatment, and minimal systemic adverse reactions, making it ideal for respiratory disease treatment. This flavonoid downregulates IL-18 and IL-1β expression by inhibiting NF-κB/NLRP3 mediated EMT. Scutellarin reverses BLM-induced caspase-1 upregulation. The NLRP3 inflammasome activates caspase-1, which promotes the maturation of pro-inflammatory cytokines IL-1β and IL-18 and induces pyroptosis. Scutellarin has been shown to significantly attenuate inflammation and inhibit EMT processes by modulating this pathway [84].

3.2. TNF-α

TNF-α is secreted by multiple immune cell types, including activated macrophages, dendritic cells, monocytes, NK cells, as well as $CD4^+$ and $CD8^+$ T lymphocytes. During lung injury, elevated TNF-α expression leads to inflammatory cell recruitment, stimulation of lung fibroblast proliferation, enhanced collagen secretion, and inhibition of type II alveolar epithelial cell apoptosis, thereby impeding lung injury repair. In the initial inflammatory phase, extensive TNF-α secretion works synergistically with IL-1 to accumulate neutrophils, subsequently intensifying inflammation [85].

Sodium houttuyfonate (SH), a compound synthesized from the reaction between fisetin and sodium bisulfite, is widely utilized in China for treating respiratory conditions. SH demonstrates TNF-α inhibitory properties and exhibits preventive effects comparable to prednisone acetate against BLM-induced lung fibrosis in mice [86]. This indicates SH's potential as an anti-inflammatory agent for pulmonary infections. Furthermore, mice administered high-dose SH *via* gavage for 60 d showed no toxic reactions or visceral pathological changes during 30-d observation, suggesting SH's low toxicity and potential safety in medical applications. SH effectively activates histamine H1 receptors, which can initiate various histamine-related allergic responses. While oral SH-containing formulations remain approved, additional safety evaluations are necessary before expanding its clinical applications.

3.3. IFN-γ

IFNs comprise a group of cytokines essential for viral defense, tumor suppression, and disease treatment through various immune cells, including DC cells [87], NK cells [88], and cytotoxic T cells [89]. Among all IFNs, IFN-γ represents the sole type II variant [90]. Activated lymphocytes generate IFN-γ in response to specific antigens or mitogens [91]. Beyond its anti-viral properties, it possesses significant immunoregulatory functions [92]. It serves as a potent macrophage activator [93] and exhibits anti-proliferative effects on altered cells. IFN-γ functions as a crucial mediator of immune responses and inflammation, activating the STAT1 transcription factor *via* the Janus kinase (JAK)-STAT signaling pathway [94]. Type II IFN demonstrates substantial immunoregulatory functions, acting as an effective activator of macrophages and Th1 cells, while exhibiting anti-viral, anti-proliferative, and anti-tumor properties [95].

In an LPS-induced rat PF model, a volatile extract of *Houttuynia cordata* (HC) enhances IFN-γ expression without increasing STAT1 expression. Concurrently, it inhibits TGF-β1 and Smad2/3, while maintaining minimal Smad4 expression and significantly increasing Smad7 expression. The volatile HC extract ameliorates PF by increasing IFN-γ expression, suppressing the JAK/STAT1 signaling pathway, and reducing lung inflamm-

ation [96]. HC injection directly inhibits pseudorabies herpes virus *in vitro*, and HC functions as a selective COX-2 inhibitor. The volatile chemical components constitute HC's primary pharmacologically active elements, suggesting its potential as an alternative PF treatment. However, additional clinical trials are required to establish optimal dosage ranges and requirements for effective treatment.

Paeoniflorin, a terpenoid compound extracted from the roots of plants in the Ranunculaceae family, exhibits anti-fibrotic effects through similar mechanisms. It downregulates the expression of TGF-β1, Smad4, and phosphorylated Smad2/3, while upregulating Smad7 and IFN-γ levels. However, its minimal effect on *MMP-1* and *TIMP-1* mRNA expression in mouse lung tissue suggests limited influence on MMPS-mediated type I collagen degradation. Studies indicate that moderate doses of paeoniflorin significantly extend survival and reduce inflammatory cell infiltration, interstitial fibrosis, and ECM deposition in the lung tissue of BLM-treated mice [97].

3.4. Growth factors

3.4.1. TGF-β

The TGF-β superfamily comprises at least 40 structurally and functionally related cytokines involved in immunological modulation, inflammation, cancer, ECM formation, embryonic development, and inflammation. TGF-β represents a classical pro-fibrotic mediator and remains one of the most extensively studied cytokines in fibrosis [98]. Among its three isoforms, TGF-β1 demonstrates the strongest association with PF. From a mechanistic perspective, TGF-β1 enhances ECM accumulation, particularly fibronectin and collagen, while modifying fibroblast phenotype [99–100]. TGF-β1 induces the expression of α-SMA, facilitating fibroblast differentiation into myofibroblasts. Moreover, the TGF-β/Smad pathway represents a well-characterized pleiotropic signaling route essential for ECM synthesis, fibrosis, myofibroblast development, and inflammation. TGF-β mediates fibrosis through both Smad-dependent and Smad-independent mechanisms.

Sennoside A (SA), derived from the medicinal herb *Cassia angustifolia*, has demonstrated the capacity to reduce TGF-β, α-SMA, and FN expression in BLM-treated rats. This suggests SA may achieve its anti-fibrotic effects through inhibiting FN, α-SMA, and TGF-β overexpression, thereby limiting excessive ECM deposition. Furthermore, SA reduces IL-1β and iNOS levels while enhancing IL-10 and IL-4 expression, suggesting potential to mitigate inflammation and regulate immune dysregulation in BLM-induced PF [101]. However, prolonged administration of high-dose SA may induce adverse effects, including large intestine melanosis and potential carcinogenic effects in colon cancer, thus restricting its clinical application.

Saffloryellow suppresses TGF-β1 and α-SMA expression while reducing hydroxyproline content in lung tissues. Evidence suggests saffloryellow diminishes pro-fibrotic factor TGF-β1 release, thereby reducing myofibroblast numbers and inhibiting α-SMA, preventing lung myofibroblasts' transformation to fibroblasts, thus achieving anti-fibrotic effects [102]. *Gentiana cruciata*, an important medicinal plant from Yunnan, China, contains gentiopicroside as its primary component, which can improve lung injury and PF in rats [103]. *Gentiana cruciata* inhibits early-stage lung inflammation and later-stage collagen fiber deposition, with its anti-PF effect linked to inhibition of the TGF-β1/Smad signal transduction pathway and subsequent prevention of alveolar epithelial cell EMT [104]. Treatment reduces serum TGF-β1 content and tissue expression of TGF-β1 and Smad2/3 protein, indicating that *Gentiana cruciata* significantly downregulates TGF-β1 and Smad2/3 protein expression, thereby exhibiting anti-PF effects. Research indicates that the plant's natural products demonstrate no significant animal toxicity, cytotoxicity, or genotoxicity, making it suitable for long-term anti-fibrosis treatment.

3.4.2. Connective tissue growth factor (CTGF)

CTGF functions as a matrix protein that sustains fibrotic responses, enhances collagen deposition, and promotes tissue remodeling [105]. Moreover, substantial evidence indicates that increased CTGF expression leads to elevated α-SMA expression [106]. As a downstream mediator of TGF-β, which shows elevation in lung fibroblasts, CTGF plays a crucial role in tissue fibrosis through promoting myofibroblast growth, synthesizing collagen and ECM, thereby contributing to fibrosis [107]. Studies in murine skin fibrosis have confirmed that TGF-β and CTGF independently play essential roles in fibrosis development and maintenance [108].

Dihydroartemisinin demonstrates inhibitory effects on inflammatory factor aggregation, fibroblast proliferation, and collagen deposition in fibrotic rat pulmonary tissue. The extracellular signal-regulated kinase (ERK) pathway represents a crucial signaling pathway regulating CTGF expression. ERK pathway inhibition can suppress CTGF expression in angiotensin II-induced cells. The dihydroartemisinin treatment group showed reduced gene expressions of *ERK1* and *ERK2* and decreased protein expressions of CTGF, ERK1/2, and pERK1/2 in rat lung tissue compared to the model control group, indicating dihydroartemisinin's capacity to inhibit CTGF and ERK gene and protein expression [109]. Dihydroartemisinin exhibits advantages over artemisinin, including enhanced water solubility, reduced toxicity, fewer side effects, improved absorption, and higher biological activity. While recent years have seen increased research on dihydroartemisinin in PF treatment, its therapeutic application remains in early stages, with mechanisms requiring further elucidation.

In experimental studies of BLM-induced PF in rats, researchers discovered that total saponin of notogina decreased fibroblast proliferation, ECM production, granulation tissue formation, and fibrosis by inhibiting CTGF. Additionally, it reduced TGF-β1-induced collagen synthesis through CTGF inhibition. The total saponins of *Panax notoginseng* demonstrate fewer side effects compared to dexamethasone, with medium doses being suitable for long-term use. However, the side effects of total saponins of *Panax notoginseng* are dose-dependent, and prolonged use of high doses can significantly impact food intake and liver and kidney function [110].

3.4.3. PDGF

Platelets serve as the primary storage organ for PDGF, which is mainly produced at sites of lung tissue injury and functions as a crucial pro-fibrotic growth factor. During PF, activated platelets, AMs, and epithelial cells secrete substantial amounts of PDGF [111]. PDGF expression has been identified in AMs, endothelial cells, fibroblasts, vascular smooth muscle cells, and alveolar epithelial cells within the basal lamina of PF patients. PDGF stimulates lung fibroblast differentiation and proliferation, exhibits expression regulated by TGF-β1 and TNF, enhances ECM formation and deposition, and ultimately leads to pneumonia. Furthermore, PDGF promotes macrophage secretion of fibronectin, stimulating fibroblast proliferation and significantly expanding alveolar septa, which is crucial for chronic fibrosis development [112].

PPAR-γ agonists inhibit lung fibroblast migration, proliferation, and differentiation, while also suppressing IL-13-induced collagen expression in bronchial fibroblasts by inhibiting PDGF-B production following PPAR-γ activation. Curcumin treatment inhibits PDGFR-B and downstream signal transduction through PPAR-γ activation, reducing type I and III collagen expression and decreasing silicosis fibrosis severity [113]. However, curcumin exhibits low water solubility, unstable chemical properties, and poor bioavailability. Additional rigorous clinical trials are necessary to translate curcumin experimental research into clinical applications. Moreover, further research is needed to develop new preparations or derivatives that improve its bioavailability and enhance targeted therapy concentration for PF.

3.4.4. VEGF

VEGF functions as a critical cytokine in normalizing physiological or pathological angiogenesis. It triggers substantial inflammatory cell infiltration into the pulmonary interstitium, increases vascular permeability, and stimulates ECM production, promoting endothelial cell migration and proliferation for new blood vessel formation [114]. These newly formed capillaries nourish fibroblasts that produce collagen and ECM, thereby intensifying fibrosis. VEGF also enhances CTCF expression, promoting fibroblast proliferation. The VEGF/VEGFR2 signaling pathway serves as the primary pathway in the VEGF signaling cascade, promoting vascular endothelial cell propagation, migration, and differentiation.

Studies on astragaloside treatment for PF demonstrate significantly reduced expression of *VEGF* and *VEGFR2* genes in mice following treatment, suggesting that astragaloside may regulate local pulmonary angiogenesis by inhibiting VEGF expression, thereby reducing PF severity [115]. Astragaloside undergoes metabolization through intestinal flora hydrolysis *in vivo* and *in vitro*. Clinical practice rarely employs astragaloside as a single drug treatment for PF. Understanding its absorption, distribution, metabolism, and excretion patterns remains essential, as does further research into drug combinations, new dosage forms, and preparations to enhance pharmacological effects while minimizing side effects. Table S2 presents additional natural products that prevent and treat PF through immune cytokine regulation.

4. Conclusion

PF represents a complex disease characterized by rapid and irreversible progression, presenting a fatal threat. Current clinical medication therapies cannot fully cure the condition but only delay its progression. Lung transplantation remains the sole therapeutically viable option for PF, though it carries high risks and poor prognosis. While the exact etiology of PF remains unclear, immune responses are present throughout all stages of fibrosis (Fig. 2), including macrophage polarization toward an anti-fibrotic phenotype, PF improvement through Th1/Th2 balance regulation, and TGF-β1 expression downregulation to inhibit ECM accumulation. The immune system demonstrates a complex role in PF, suggesting potential future applications for targeted immunomodulators. Notably, immune cells and factors exhibit both anti-fibrotic and fibrotic properties, necessitating further investigation of underlying mechanisms. Although nintedanib and pirfenidone have received approval for PF therapy, they merely delay disease progression without providing a cure. Additionally, these treatments present multiple side effects, limited long-term safety, and high costs. Traditional Chinese medicine (TCM) research on PF prevention and treatment has revealed natural products as valuable resources for anti-PF drug development, offering advantages in affordability, multiple targeting capabilities, and diverse biological activities.

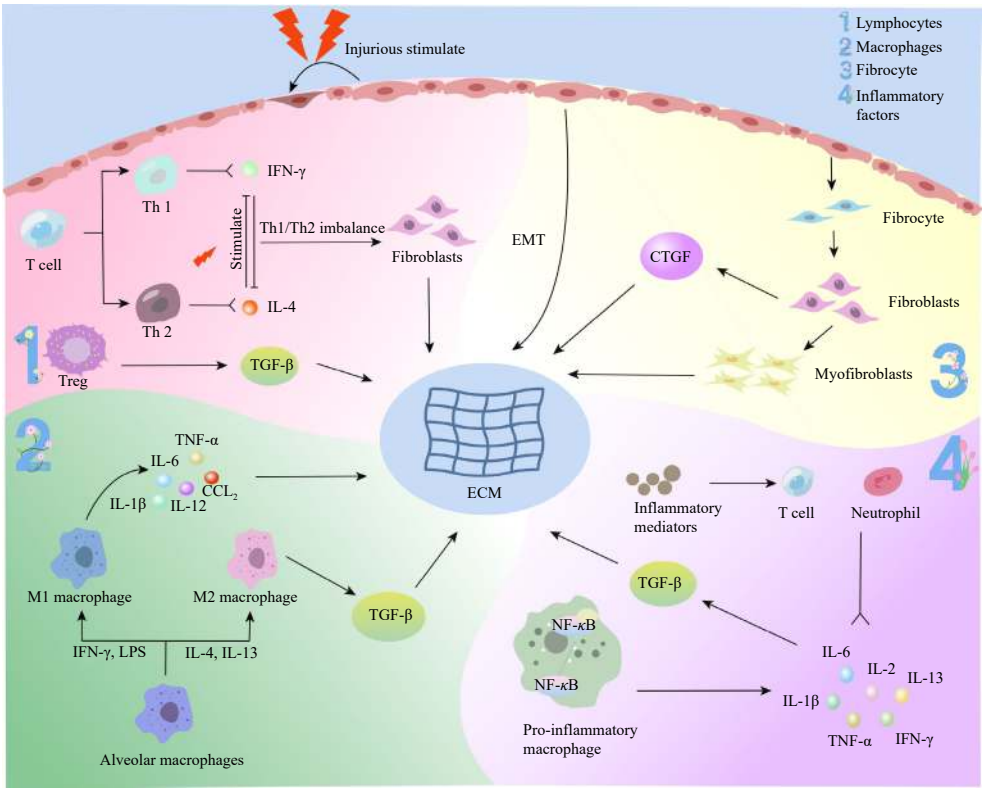

Fig. 2 Mechanisms of immune regulation in PF. 1) After alveolar epithelial cells are damaged, a large number of T lymphocytes will gather in the damaged part of the lung and activate Th1 and Th2. Th1 cells secrete IFN-γ, and Th2 cells secrete IL-4. When stimulated, the imbalance of Th1 and Th2 in the body promotes the proliferation, migration, and differentiation of fibroblasts, leading to the occurrence of ECM. 2) M0 macrophages can be polarized into M1 macrophages under LPS/IFN-γ induction and M2 macrophages under IL-4/IL-13 induction. M1 macrophages can release various cytokines and chemokines, which can promote collagen deposition and cause ECM; M2 macrophages can increase collagen deposition by secreting TGF-β. 3) After stimulation, alveolar epithelial cell injury triggers the activation of resident interstitial fibroblasts, which proliferate and differentiate into myofibroblasts. These myofibroblasts actively synthesize and secrete large amounts of collagen and other ECM components, leading to excessive ECM deposition and tissue remodeling. 4) When inflammation occurs, macrophages, neutrophils, T cells, and other immune cells gather in large numbers at the damaged site and secrete various inflammatory factors, activating TGF-β and other signaling pathways to promote ECM.

The pathophysiology of PF involves multiple pathways and targets, with natural products demonstrating significant advantages through their multi-mechanism and multi-target approach. This characteristic provides natural products with enhanced competitiveness compared to chemical drugs (Fig. 3). However, despite their considerable potential value, natural products present certain challenges that warrant attention. While natural products improve PF through multiple targets, some targets ex-

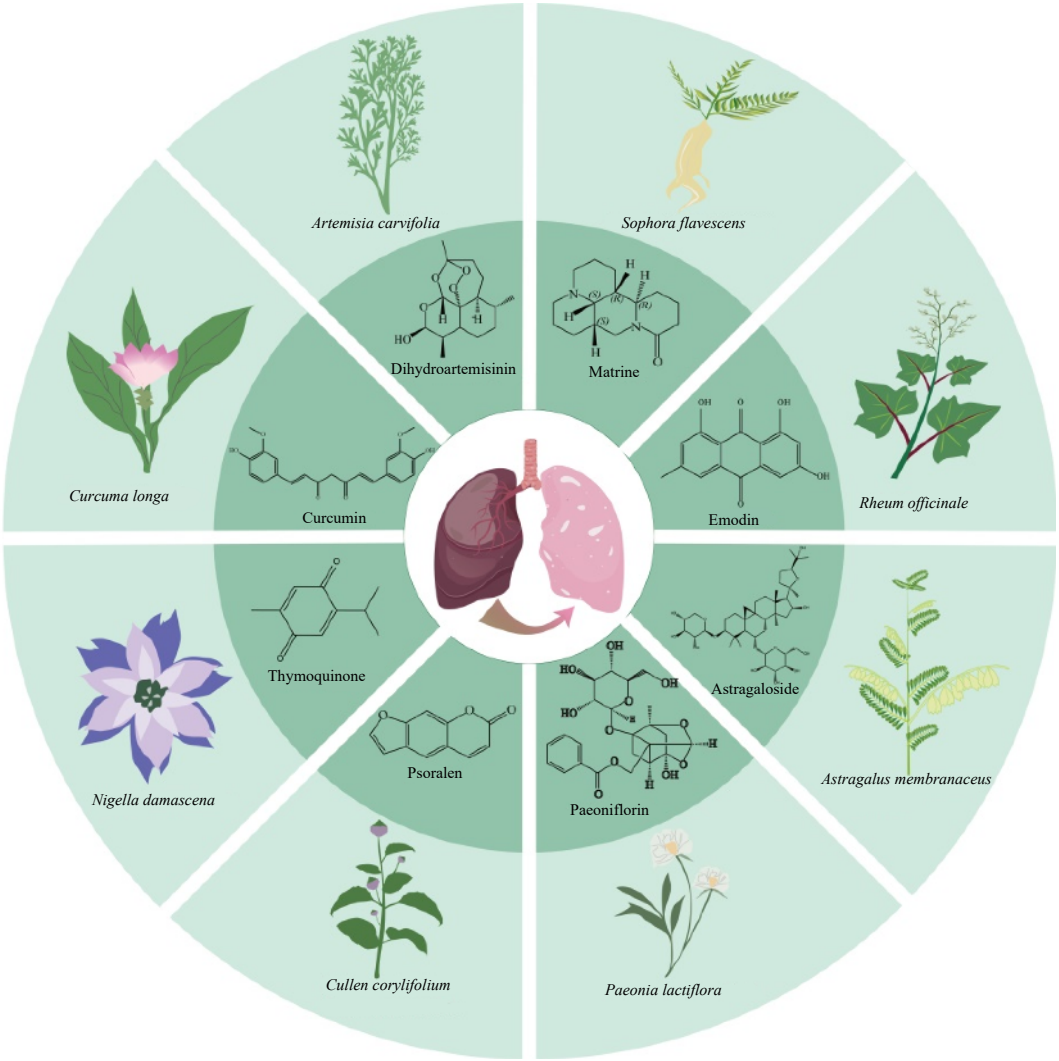

Fig. 3 Anti-PF natural products through immune regulation.

hibit dual effects on the human body, potentially causing treatment-related side effects. This necessitates increased focus on toxicological research. Furthermore, numerous studies investigating the anti-PF effects of natural products remain at the experimental stage, lacking clinical trial validation. Substantial work remains before initiating official clinical treatment. The transformation of TCM into new drugs faces multiple challenges. This review has elucidated the mechanism of immunological factors in PF regulation, contributing to future anti-PF medication development.

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Supporting information

Supporting information for this work can be obtained by contacting the corresponding authors *via* E-mail.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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