Pulmonary fibrosis: therapeutic and mechanistic insights into the role of phytochemicals

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Abstract

Pulmonary fibrosis (PF) is the devastating consequence of various inflammatory diseases of the lung. PF leads to a reduction of lung function, respiratory failure and death. Several molecular pathways are involved in PF, such as inflammatory cytokines including TNFα, TNFβ1, IL-6 and IL-4, reactive oxygen species, matrix metalloproteases and transforming growth factor-beta (TGF-β). Targeting these processes involved in the progression of PF is essential for the treatment of this disease. Natural products, including plant extracts and active compound that directly target the processes involved in PF, could be suitable therapeutic options with less adverse effects. In the present study, we reviewed the protective effects and the therapeutic role of various bioactive compounds from plants in PF management.

Keywords: Pulmonary fibrosis; Curcumin; Herbal medicine; Lung

1. Introduction

Various inflammatory pulmonary diseases result in the development of pulmonary fibrosis (PF). PF is defined as an increase in collagen, accumulation of extracellular matrix (ECM), and infiltration of inflammatory cells. PF progressively reduces gas exchange and lung function leading to respiratory failure (1). Any injuries to the lungs, such as infections or inhalation of toxic particles, result in the damage of epithelial and endothelial cells. Injured cells release various inflammatory mediators and cytokines as well as activate the cascade of anti-fibrinolytic coagulation (2). PF also contributes to vasodilation, an increase in permeability of vasculature and production of matrix metalloproteases (MMP) that can destroy the basement membrane. This process results in the infiltration of inflammatory cells to lung parenchyma (3). Damaged cells, including endothelial, epithelial and inflammatory cells, produce reactive oxygen species (ROS) and inflammatory cytokines, resulting in oxidative stress. TGF-β is the crucial cytokine involved that helps in the activation of fibroblasts and inflammatory cells, thereby sustaining ECM production and inflammation, as well as fibroblast differentiation (4). IL-4 is another cytokine involved in the development of PF (5). It is a profibrotic cytokine that causes the macrophages activation and Th2 cells differentiation resulting in the production of TGF-α, IL-13, and MMPs. Another cytokine is IL-13 that stimulates the production of TGF-α and contributes to the differentiation of myofibroblasts from fibroblasts (6).

There are many types of fibrotic pulmonary diseases in humans, such as idiopathic pulmonary fibrosis (IPF), diffuse parenchymal lung disorders (DPLDs) and idiopathic interstitial pneumonia (IIPs) (7). There are three major processes involved in the PF physiopathology: (i) genetically and environmental induced alveolar epithelial lesions, (ii) vascular diseases with neo-vascularization of the non-fibrotic tissues and (iii) ROS induced oxidative stress.

Chronic inflammation is currently considered to be the fundamental contributing factor to induce PF (8). Many PF therapies that target growth factors and cytokines for fibroblast proliferation, activation, and differentiation are currently in the testing phase. Approved PF therapeutic drugs by the US Food and Drug Administration (FDA) are pirfenidone and nintedanib. These drugs reduce PF-related deaths via targeting molecular processes involved in PF progression, but their cost remains expensive (9, 10).

The use of phytochemicals for the management of PF was started in China for several years (11). Various studies with phytochemicals are being carried out to find their exact molecular mechanisms and better treatment for PF. In this review, we have summarized some of the plant extracts that may have beneficial effects in PF management (12).

2. Molecular mechanisms and signaling pathways of pulmonary fibrosis

The pathological processes in pulmonary fibrosis (uncontrolled extracellular matrix (ECM) accumulation and pulmonary architecture remodeling) result from disruptions in two physiologically balanced ways that include apoptosis and proliferation of fibroblasts, as well as ECM aggregation and dissociation. When the natural balance between ECM turnover and deposition is tilted towards deposition, the ECM accumulates. While the balance between

apoptosis and fibroblast proliferation is tilted towards slowed apoptosis or accelerated proliferation of fibroblasts, the ECM accumulates, thereby resulting in fibrosis (13, 14).
There are two routes for progression of diffuse pulmonary fibrosis: a) the inflammatory pathway that is represented by non-IPF interstitial lung diseases, where there is a primary, clearly distinguishable alveolitis stage, and a late fibrotic stage, and b) the epithelial pathway represented by idiopathic pulmonary fibrosis (15, 16).
Various mechanistic studies have centered on the crosstalk, between damaged lung mesenchymal cells and epithelial cells. This mesenchymal-epithelial interaction supports the development of PF in which altered mesenchymal cells combined with alveolar epithelial cell injury result in the aggregation ECM and pulmonary architecture remodeling (17).
Furthermore, evidence suggests that activated myofibroblasts by synthesizing ECM proteins play a fundamental part in the pulmonary fibrosis pathogenesis. Myofibroblasts are derived from different cells, including 1) alveolar type II epithelial cells, 2) bone marrow-derived "fibrocytes," and 3) resident stromal fibroblasts, which undergoes epithelial-mesenchymal transition (EMT). During EMT, epithelial cells lose apical-basal polarity, cell to cell contact and attachment to the basement membrane. They acquire mesenchymal properties such as increased migratory conduct, cytoskeletal rearrangements, and migrating to the pulmonary interstitium to produce more ECM. (18). TGF-β1 is the crucial intermediator in pulmonary fibrosis which stimulates both the fibroblast proliferation and differentiation into myofibroblasts (19). During the healing process, inflammation is resolved, and alveolar-capillary permeability is restored.
Inflammation is an important event which precedes the development of PF. It has been shown that inflammation has a vital role in the pro-fibrotic process (20). Based on the observations of chemokines, cytokines, inflammatory cells, and cell surface molecules, the inflammation pathway hypothesis has dominated the field of PF. Most authorities tend to classify IPF as a chronic inflammatory disorder in the pulmonary parenchyma (21-23). Furthermore, macrophage inflammatory protein (MIP)-1 alpha and monocyte chemoattractant protein-1 (MCP-1) are upregulated in animal models of PF which are chemotactic for eosinophils, basophils, macrophages, and subsets of T-lymphocytes. Neutralization of these proteins significantly reduce inflammatory cell aggregation. Levels of these chemokines have also been found to be raised considerably in patients with systemic sclerosis in addition to patients with PF (24, 25). Moreover, other studies have shown that spatiotemporally restricted but closely orchestrated interference with aberrantly activated developmental signaling pathways (e.g., Wnt, Notch, and SHH) may affect differentiation and repair of lung architecture (26).

Finally, over several years of studies into the mechanism of PF, various studies have described considerable alterations in inflammatory and oxidative stress pathway. A diversity of inflammatory factors, growth factors, and oxidative factors to foster and develop fibrotic process, and in some instances, inhibition of these factors were associated with improvement of lung fibrosis (17). Therefore, the natural components with anti-fibrotic potential such as phytochemicals that can affect different pathologic mechanisms involved in PF could be potentially useful in managing PF.

3. The potential effect of phytochemicals in the management of pulmonary fibrosis

3.1. Polyphenols and flavonoids

Natural phenolic compounds have received a growing interest in the management of various conditions. Studies revealed that polyphenols possess anti-fibrotic and anti-inflammatory effects. Several studies have shown some beneficial effects of these compounds in PF. For example, a Chinese herb*, hedysari radix,* contains flavonoids that inhibit some of the processes of PF. Polyphenols have antioxidant activities by reducing various processes, including NF-kBp65 translocation, down-regulating cyclo-oxygenase-2 (cox-2), and TGF-β1 (27, 28). Such investigations suggest that polyphenolic phytochemicals could have a potential role in the prevention and management of PF.

3.1.1. Curcumin

Curcumin is a turmeric component from the plant, *Curcuma longa,* and is used as a food flavoring agent. For many years curcumin has been used in traditional Indian medicine and traditional Chinese medicine as a therapeutic agent for many diseases including arthritis, anorexia, hepatic disorders (29).

Curcumin is a bioactive phytochemical with acceptable safety and multitude of salutary effects (30-38). The potential role of curcumin in several conditions, including inflammatory bowel disease, psoriasis and rheumatoid arthritis has been determined in the last decades (39). Curcumin also has an effect in respiratory diseases including chronic obstructive pulmonary disease (COPD) (40), asthma (41), PF (1), and acute lung injury (ALI) (42, 43), that are mainly identified by abnormal chronic inflammatory responses.

Currently, there are no clinical studies to determine the efficacy of curcumin in patients with PF. Nevertheless, research studies utilise animal models, in which fibrosis has been induced by chemotherapeutic agents and radiations (44-46) or viruses (47). The effect of curcumin on PF is due to several mechanisms. For example, in asthma, curcumin inhibits NF-κB and, thus, impacts PF by causing a reduction of TNF-α, COX-2 (46) and TGF-β1 levels (47). A reduction in TGF-β1 has anti-fibrotic effects. Besides, curcumin inhibits AP-1, contributing to blocking the TGF-β1 production and myofibroblast differentiation (4). Curcumin contributes to caspase-independent apoptosis pathways by downregulation of TGF-β1and upregulation of cathepsins K and L, collagenases, and elastases (48), with consequent antifibrotic effect. Curcumin inhibits TGF-β receptor phosphorylation and leads to a reduction of TGF-β levels in fibroblast (49). Moreover, it reduces oxidative stress in pulmonary fibrosis models by decreasing the ROS NOS, iNOS levels, and increasing the levels of heme oxygenase-1 (HO-1) (50, 51).

Hu et al. revealed that the inhalable form of curcumin-loaded poly(lactic-co-glycolic) acid (PLGA) large porous microparticles (LPMPs) had higher antifibrotic activity in comparison with powders of curcumin powders. Hence, curcumin LPMPs could be a promising inhalable option for managing idiopathic pulmonary fibrosis (52).

3.1.2. Resveratrol

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a polyphenolic substance present plant species such as peanuts and grapes. Takaoka first defined this compound in roots of plant *Veratrum grandiflorum* (53). Resveratrol has demonstrated antifibrotic activities in several tissues and organs such as the liver, kidney, and blood vessels in animal studies (54-56). Therefore, it can manage various conditions of the respiratory system resulting from oxidation, apoptosis and inflammation. Resveratrol has shown to have a protective effect on lung fibrosis in BLM-induced animals. Anti-fibrotic effects of resveratrol in lungs are mostly associated with inhibition of EMT- associated molecular pathways, activation of SIRT1 and Nrf2 pathway, and decreased differentiation of myofibroblast and expression of extracellular matrix (57).

3.1.3. Quercetin

Quercetin is member of a plant flavonoids. The plant, *Camellia sinensis* is rich in quercetin (58). Many fruits and vegetables, including red onions and kale, are other quercetin sources (59). Quercetin exerts many biological effects, including anti-inflammatory (60), antioxidant (61) and immune-regulatory actions (62). Quercetin also has been demonstrated to decrease fibrosis in injured organs. Quercetin has been demonstrated to have beneficial effects in cell culture and animal studies for several lung diseases, including lung cancer (63), COPD (64) and asthma (65). Quercetin ameliorated PF in bleomycin-treated mice through inhibiting pro-fibrotic factors such as COL-1, COL-3, LC3, IL-8, VEGF, TNF-α, TGF-β1, NF-κB and SphK1/S1P signaling (66). Several studies use animal models of PF to investigate the anti-fibrotic mechanisms of polyphenols in lung fibrosis (Table 1).

Table 1 . Polyphenols and flavonoids potential effects in the treatment of pulmonary fibrosis

Polyphenols	Source	Mechanism	IC50/dose	Model	Ref
Curcumin	*Curcuma longa*	TGF-β1 and collagen content ⍰	200 mg/kg	Paraquat (PQ)-treated rats	(67)
Curcumin	*Curcuma longa*	IL-1β, LT-C4, histamine, total protein levels ⍰ NAG activity, MDA, hydroxyproline and elastin ⍰ GSH levels ⍰	200 mg/kg	Cyclophosphamide (CP) -induced lung fibrosis Wistar rats	(45)
Curcumin	*Curcuma longa*	NF-κB and COX-2, TNFR1, TNF-α, TGF-β1 ⍰ CTGF expression, and collagen accumulation ⍰	200 mg/kg	Radiation-induced inflammation and fibrosis rats	(46)
Curcumin	*Curcuma longa*	HO-1 ⍰ ROS, TNF-α and hydroxyproline content ⍰	5% curcumin by weight/weight in dietary and 5, 10, 25 50 or 100 μM in cell culture	Radiation-induced lung fibrosis C57BL/6 mice	(44)
Curcumin	*Curcuma longa*	IFN-γ, IL-6, IL-10, MCP-1, levels ⍰ Phosphorylated form of NF-κB p65 and TGF-ß Receptor II ⍰ Expression of α-SMA and Tenascin-C ⍰	50 mg/kg	Viral-induced ARDS mice	(47)
Curcumin	*Curcuma longa*	hydroxyproline contents, collagen I ⍰ MMP9, NF-κB, TNF-α, p65, TGF-β1, ⍰	6 mg with inhalable curcumin-LPMPs and 1 mg with curcumin powders	BLM-treated Sprague-Dawley rats	(68)
Curcumin	*Curcuma longa*	Artery blood PaCO2, serum Smad4, Smurf2 and IL-4 ⍰	200 mg/kg	PQ-treated Wistar rats	(69)
Curcumin	*Curcuma longa*	Myofibroblast activation and proliferation-associated genes such as COL1A1 ⍰ and PCNA, oxidative stress and activating an apoptotic cascade ⍰	20 μM to 40 μM	Primary epithelial cells and fibroblasts isolated from IPF patients	(70)

Curcumin	*Curcuma longa*	MMP-9 activities α-SMA, TIMP-1, eotaxin, and collagen deposition	5 mg/kg (intranasal)	Ovalbumin-treated BALB/c mice	(71)
Curcumin	*Curcuma longa*	expression levels of Ki67 and EGFR		BLM-treated mice	(72)
Curcumin	*Curcuma longa*	α-SMA, CCN2, Col IV, and vimentin, phosphorylated MAPK and PERK	30 mg/kg	BLM-treated mice	(73)
Curcumin	*Curcuma longa*	TGF-β1-dependent differentiation of lung fibroblasts via PPARγ-driven Cathepsins B and L	0–50 μM	CCD-19Lu human lung cell line	(74)
Curcumin	*Curcuma longa*	IL-17A mediated p53-PAI-1 expression	20 μM	BLM-treated A549 cells	(75)
Curcumin	*Curcuma longa*	α-SMA, MMP-9, TGF-β and EMT	30 μM	PQ-treated A549 cells	(76)
Resveratrol	*Vitis vinifera*	SirT 1 and EMT transition	50 mg/kg	BLM-treated mice	(77)
Resveratrol	*Vitis vinifera*	PARP activation, COX-2, ERK activation, IκB-α degradation NF-κB and NF-κBp65 nuclear translocation and neutrophil migration	50 mg/kg	BLM-treated mice	(28)
Resveratrol	*Vitis vinifera*	MDA levels Lung tissue plasma total antioxidant capacity Number of neutrophils in BAL fluids	10 mg/kg	BLM-treated Wistar rat	(78)
Resveratrol	*Vitis vinifera*	TNFα, TNFβ1, IL-6 and Nrf2	10 μM	PQ-Induced fibrosis in BEAS-2B cells	(79)
Resveratrol	*Vitis vinifera*	SIRT3 and TGFβ1		BLM-treated mice	(80)
Resveratrol	*Vitis vinifera*	mir-21, TGFβ1 and p-Smad2/3, c-Jun, and c-Fos levels phosphorylation levels of p38, JNK, ERK	60 mg/kg	BLM-treated Sprague Dawley rats	(81)
Resveratrol	*Vitis vinifera*	Autophagic process, NLRP3 inflammasome activation and IL-1β	50 and 100 mg/kg.bw	PM2.5- treated mice	(82)
Resveratrol	*Vitis vinifera*	TAK1 IL-1β, MMPs, TGF-β and TNF-α p-p38, p-JNKp-TAK1, p-Smad3 and n-p65 Collagen subtypes	10 and 20 mg/kg for in vivo 10, 25 and 50 μm for in vitro	silica-exposed rats and silica-exposed cultured alveolar macrophage NR8383 cells	(83)
Resveratrol	*Vitis amurensis Rupr*	Autophagy markers and TGF-IL-17, TNF-α, IL-6, β	50 mg/kg	Cigarette Smoke-treated mice	(84)
Resveratrol	*Vitis vinifera*	NF-κB mediated inflammatory response (TNF-α, IL-1β, IL-6, iNOS, MMP-9 and COX-2)	2 and 4 mg/kg	Cigarette Smoke-treated mice	(85)

		TGF-β1, Nrf2 ubiquitylation, and ROS ↓ Nrf2 and GSH levels ↑			
Resveratrol	*Vitis vinifera*	TGF-β-induced phosphorylation of both ERK1/2 and the serine/threonine kinase, Akt, TGF-β-induced decrease in PTEN expression levels, TGF-β–induced α-SMA expression and collagen deposition ↓	1–20 μM	Primary cell lines of human lung fibroblasts	(86)
Quercetin	*Fruits and vegetables*	PARP activation, COX-2, ERK activation, IκB-α degradation ↓ NF-κB and NF-κBp65 nuclear translocation and neutrophil migration ↓	10 mg/kg	BLM-treated mice	(28)
Quercetin	*Fruits and vegetables*	TGF-β and SphK1/S1P signaling ↓	25, 50, 100 mg/kg	BLM-treated mice	(66)
Quercetin	*Fruits and vegetables*	Regulates caveolin-1 and Fas expression and modulates AKT activation ↓ Apoptosis and expression of senescent cell markers such as p2, p19-ARF, MCP1, MMP12, and IL6 ↓	50 μM in cell culture and 30 mg/kg in mice	Human primary pulmonary fibroblasts and BLM-treated mice	(87)
Quercetin	*Fruits and vegetables*	Hydroxyproline content and increased catalase and GSH-Px activity ↓	50 mg/kg	Silicon dust-treated mice	(88)
liposomal Quercetin	*Fruits and vegetables*	TNF-α, IL-1beta, and IL-6 in bronchoalveolar lavage fluid ↓ Collagen deposition, and TGF-β1 ↓	5 mg/kg	BLM-treated mice	(89)
Quercetin	*Fruits and vegetables*	COL-1, COL-3, IL-6, IL-8, LC3, VEGF, TGF-β ↓ mTOR and AKT, and ATG5 ↓	5 μM, 10 μM, 20 μM, 40 μM, 100 μM, and 200 μM in cell culture and 120 mg/kg/day in rabbits	LPS-induced WI-38 and trauma-induced rabbit tracheal stenosis model	(90)
Mangiferin	*Mangifera indica*	PARP activation, COX-2, ERK activation, IκB-α degradation ↓ NF-κB and NF-κBp65 nuclear translocation and neutrophil migration ↓	10 mg/kg	BLM-treated mice	(28)
Mangiferin	*Mangifera indica*	Hydroxyproline content, TGF-b1, SMA levels, inflammatory cytokine ↓ TLR4 and phosphorylation of p65, phosphorylation of Smad2/3 ↓ MMP-9 expression, EMT and ROS ↓	40 mg/kg	BLM-treated mice	(91)
Dihydroquercetin	*Fruits and vegetables*	PARP activation, COX-2, ERK activation, IκB-α degradation ↓ NF-κB and NF-κBp65 nuclear translocation and neutrophil migration ↓	10 mg/kg	BLM-treated mice	(28)

Isorhamnetin	*Hippophae rhamnoides L*	Collagen deposition, type I collagen and α-SMA expression ↓ EMT, ERS, and PERK signaling ↓	10 and 30 mg/kg	BLM-treated mice	(92)
Epicatechin	*Spondias mombin*	GSH, catalase, SOD and GPX activity ↑ Tissue levels of MDA, HP, TGF-β ↓	25, 50 and 100 mg/kg	BLM-treated mice	(93)
Kaempferol	*many fruits and vegetables*	Silica induced inflammation, collagen deposition, autophagy activity, mTOR ↓ MMP-2 and MMP-9 ↓ Restores silica-induced LC3 lipidation without increasing the p62 levels	150 mg/kg	silicosis mouse models	(94)
Astilbin	*astilbe thunbergill*	pathological score and collagen deposition ↓ α -SMA, hedgehog signaling pathway and Snail, E-cadherin TGF-β1 and SP-C ↓	20 and 40 mg/kg	Mouse type II alveolar epithelial cell and mouse lung fibroblast cell lines and BLM-treated mice	(95)
Juglanin	*Polygonum aviculare*	α- α-SMA, collagen type I, collagen type III ↓ TGF-β1, inflammatory cytokine secretion ↓ Phosphorylated NF-κB expression, IKKα/IκBα signaling pathway ↓	10 and 20 mg/kg	LPS-treated mice	(96)
Neohesperidin	*Citrus aurantium*	TGF-β1/Smad3 signaling, ECM production, and fibroblast migration ↓	20 μM in cell culture and 20 mg/kg in mice	The mouse embryonic fibroblast NIH-3T3, mouse lung fibroblast MLg, human alveolar epithelial cell (AEC) A549 lines and BLM-treated mice	(97)
Puerarin	*Radix puerariae*	CD31 expressions and VE-cadherin ↑ Inhibits vimentin, α-SMA, and fibronectin ↓	20 mg·kg	Rat model of hypoxia	(98)
Hydroxysafflor yellow A (HSYA)	*Carthamus tinctorius L.*	Fibrosis and collagen deposition, PaCO2, TGF-β1, α-SMA ↓ Increases PaO2 ↑	35.6, 53.3, and 80.0 mg/kg/day	BLM-treated rats	(99)
Hydroxysafflor yellow A (HSYA)	*Carthamus tinctorius L.*	The lung consolidation area and collagen deposition ↓ α-SMA expression, Smad3 phosphorylation ↓ the morphological changes in lung tissue, Smad3 phosphorylation ↓ collagen I, and EMT induced by TGF-β1 ↓	60 mg/kg/day	BLM-treated mice	(100)
Naringenin	*Lycopersicum esculentum*	TGF-β, MP-induced autophagy relative protein LC3 ↑ MP-induced P62, Beclin-1 expression, IL-6, IL-1β,, TNF-α, ↓	25, 50, 100, and 250 μM in	Peripheral blood samples of 60 patients with	(101)

		collagen I, collagen III, α-SMA, □	cell culture and 100 mg/kg in mice	*Mycoplasma pneumoniae* pneumonia (MPP), human lung epithelial BEAS-2B cell line and MPP-infected mice	
Gossypol	*Gossypium spp.*	Collagen accumulation and TGF-β1 □ Lactate dehydrogenase-A □	5, 10, or 20 mg/kg	BLM-treated mice	(102)

3.2. Alkaloids

Alkaloids are a subclass of phytochemicals found in many plants. The term alkaloid generally refers to basic substances, usually a cyclic system that include one or more nitrogens. They are water-soluble in the protonated form due to their primary character at low pH, but at high pH, they found in the lipophilic neutral form. This feature makes them ideal agents because of their solubility in the water they can pass through membranes. The therapeutic effect of alkaloids in PF was first explored by Xiao et al. showing that seed embryo of *Nelumbo nucifera Gaertn* contains bisbenzylisoquinoline alkaloid named Isoliensinine, that can reduce the elevated levels of hydroxyproline, MDA, TNFa and TGFb and increase SOD level in BLM induced mouse models of lung fibrosis (103). (Table 2)

Table 2 Alkaloids potential effects in the treatment of pulmonary fibrosis

Alkaloid	Source	Mechanism	IC50/dose	Model	Ref
Isoliensinine	*Nelumbo nucifera Gaertn*	Hydroxyproline, MDA, TNF-α and TGF-β SOD level	40 mg/kg BW	BLM-treated murine models	(103)
Matrine	*Sophora plant*	JAK-STAT pathway	25 mg/kg BW	BLM-treated rats	(104)
Aloperine	*Sophora alopecuroides*	Fibroblast proliferation and differentiation TGF-β/Smad and PI3K/AKT/mTOR signaling	40 mg/kg	BLM-treated mice	(105)
β-Carboline	*Arenaria kansuensis*	NF-kb/p65 pathway EMT, vimentin, α-SMA, E-cadherin	50, 100 and 150 mg/kg	BLM-treated mice	(106)
Berberine	*European barberry, goldenseal, goldthread, Oregon grape, phellodendron, and tree turmeric*	PPAR-γ, HGF secretion in colonic fibroblasts and HGF	200 mg/kg	BLM-treated mice	(107)
Berberine	*European barberry, goldenseal, goldthread, Oregon grape, phellodendron, and tree turmeric*	Smad 2/3 and FAK-dependent PI3K/Akt-mTOR signaling cascades fibronectin, α-SMA, collagens I and III Beclin-1, LC3-II levels with enhanced autophagosome	200 mg/kg/i.p./day	BLM-treated rats	(108)
Neotuberostemonine	*Stemona tuberosa Lour*	Collagen, α-SMA, MMP-2, TGF-β1, TIMP1 and iNOS MMP-9	40 mg/kg	BLM-treated mice	(109)

Neotuberostemonine	*Stemona tuberosa Lour*	HIF-1α, TGF-β, FGF2 and α-SMA ⍰	30 mg/kg/d	BLM-treated mice	(110)
Rutaecarpine	*Euodia ruticarpa*	Notch1/eukaryotic initiation factor 3a (eIF3a) signaling pathway ⍰ EMT process, collagen I, vimentin and α-SMA ⍰	100, 300 mg/kg	BLM-treated rats	(111)
β-Carboline	*Arenaria kansuensis*	MCP-1IL-1β, IL-6, TNF-α deposition of collagen, TGF-β1, α-SMA, NF-kb/p65 ⍰ Phosphorylation, and EMT process. E-cadherin ⍰	50, 100 and 150 mg/kg	BLM-treated mice	(106)

3.3. Terpenoids

Terpenoids are a very diverse category of natural products with broad applications. Terpenoids serve a part of the plant's defense system. They can be divided into monoterpenes, sesquiterpenes, diterpenes, and triterpenes (112). Krishna et al. studied the effect of plant triterpene in the treatment of PF for the first time. They showed that PG-490-88, a water-soluble triptolide derivative, can represent the antifibrotic effect in a mouse model of BML induced mouse model of PF (113). Recently various studies have been conducted to illustrate more anti-fibrotic effects of terpenoids (Table 3) such as reduced inflammatory cytokines and TGF-β1, deposition of collagen and other substitutes of the ECM and inhibition of Smad2/3/TGF-β1 signaling pathway.

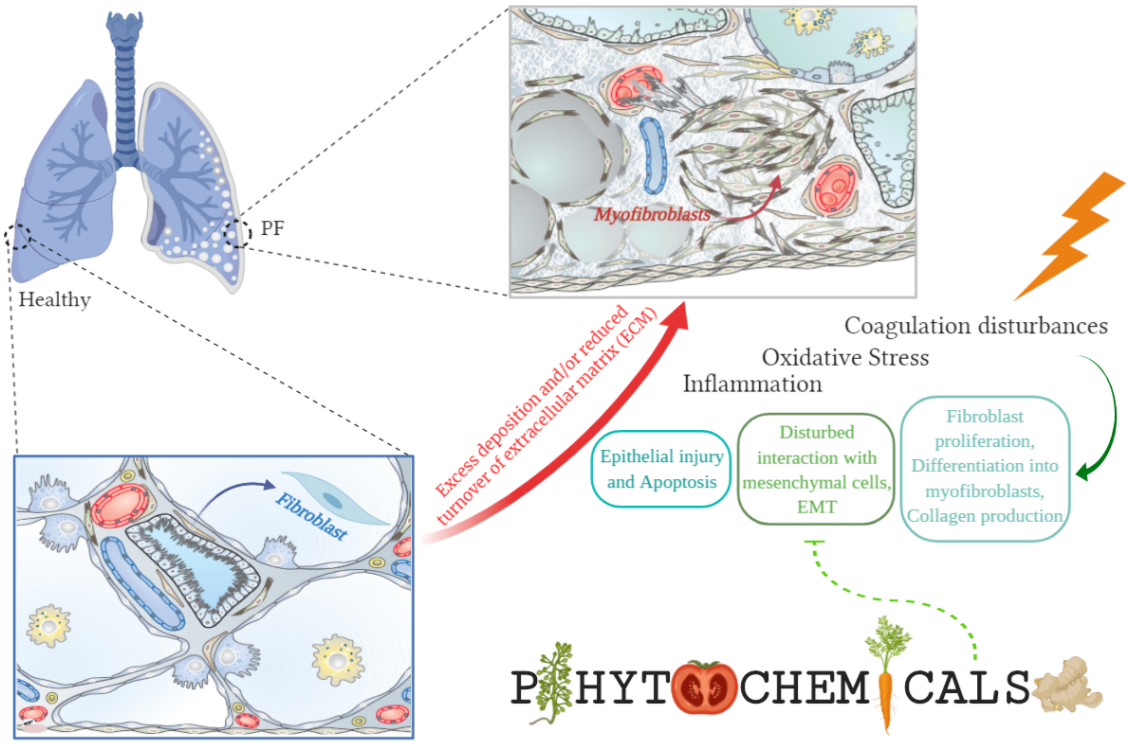

Figure 1 Therapeutic potential effects of phytochemicals in the inhibition of pulmonary fibrosis pathogenesis

Table 3 Terpenoids potential effects in the treatment of pulmonary fibrosis

Terpenoid	Source	Mechanism	IC50/dose	Model	Ref
PG-490-88	*Tripterygium wilfordii hook.f (Celastraceae)*	TGF-β and NF-κB-mediated cytokine production by immune cells	0.25 mg/kg	BLM treated murine models	(113)
Triterpene acid	*Eriobotrya japonica (Thunb.)*	TNF-a, TGF-β1 and macrophage	50, 150 and 450 mg/kg	BLM-treated rats	(114)
Baccatin III	*yew tree*	Inflammatory infiltration, TGF-β1, collagen deposition, ECM α-SMA, fibronectin and Smad2/3/TGF-β1 signaling pathway	5 and 10 mg/kg	BLM-treated mice	(115)
Madecassoside	*Centella asiatica*	ECM deposition, inflammation, oxidative stress and TGF-β1	10, 20 or 40 mg/kg	BLM-treated rats	(116)
Parthenolide	*Tanacetum parthenium*	NF-κB/Snail signaling pathway, migration of lung fibroblasts, Col1 α-SMA and EMT-related protein expression (Col-1 and MMP1)	2.5, 5, 10 and 20 μM in cell culture and 12.5, 25 and 50 mg/kg in mice	Serum-starved primary lung fibroblasts and HFL1 cell and BLM-treated mice	(117)
Costunolide	*Saussurea lappa Clarke*	TGF-β 1/Smad 2/Nrf 2-NOX 4 Signaling Pathways and NF-kB	10, 20 and mg/kg	BLM-treated mice	(118)
Dihydroartemisinin	*Artemisia annua*	Collagen, α-SMA, Nrf2, HO-1, and MDA SOD, GSH, E-cadherin	50 mg/kg/day	BLM-treated rats	(119)
Dihydroartemisinin	*Artemisia annua*	Hydroxyproline content of collagen TGF-β1, α-SMA, TNF-α, NF-κB expression	25 mg/kg, 50 mg/kg, 100 mg/kg	BLM-treated rats	(120)
Oridonin	*Rabdosia rubesecens*	Pathological changes, including alveolar space collapse, emphysema Infiltration of inflammatory cells, COL1A1 and α-SMA and the phosphorylation of Smad2/3	10 and 20 mg/kg	BLM-treated mice	(121)
Andrographolide	*Andrographis paniculata*	N-cadherin, α-SMA, vimentin, and EMT E-cadherin	3 and 10 mg/kg	Silica-Induced Pulmonary Fibrosis mice	(52)

Asiatic acid	*Centella asiatica*	TGF-β expression, Collagen I, Collagen III ↓ matrix metalloproteinase (TIMP)-1, α-SMA, Smads ↓ ERK1/2 inactivation, NOD-like receptor pyrin domain containing-3 (NLRP3) inflammasome ↓	10 and 20 mg/kg	BLM-treated mice	(122)
Triptolide	*Tripterygium wilfordii*	Hydroxyproline, IL-1β, TGF- β1, IL-13 ↓	0.25 mg/kg i.v	radiation-induced lung fibrosis C57BL/6 mice	(123)
Triptolide	*Tripterygium wilfordii*	The infiltrated alveolar macrophages in IR-lung tissues ↓ NOX2 and NOX4 in alveolar macrophages ↓ Alveolar macrophages-NOXes-ROS-myofibroblasts axis ↓	i.v. 0.25 mg/kg	Radiation-induced lung fibrosis C57BL/6 mice	(124)
Glaucocalyxin A	*Rabdosia japonica var*	Collagen deposition and hydroxyproline content ↓ Infiltration of macrophages and neutrophils in lungs ↓ Pro-inflammatory cytokines in lung tissue and bronchoalveolar lavage fluid, and NF-κB ↓	10 mg/kg	BLM-treated mice	(125)
ginkgolides meglumine	*Ginkgo biloba*	MDA level and Akt-Nrf-2 pathway ↓ SOD level, the lung to body weight ratio, IL-6, IL-1β, and TNF- α levels ↓	1.25, 2.5, 50 mg/kg, i.p	PQ-treated rats	(126)
Tanshinone IIA	*Salvia miltiorrhiza Bunge*	Collagen deposition, macrophage infiltration ↓ α-SMA, fibronectin, and vimentin ↓ TGF-β1, EMT, phosphorylated Smad-2/3 ↓	15 mg/kg	BLM-treated rats	(127)
Nimbolide	*Azadirachta indica*	TGF-β1, cell migration, EMT ↓ Infiltration of lymphocytes, monocytes, leukocytes and neutrophils ↓ Lactate dehydrogenase, NF-κB p65 IL-1β, GSH, TGF-β1/Smad Signaling, Beclin 1 and Bcl-2 ↓	100-300 µg/kg	BLM-treated rats	(128)
Aucubin	*Aucuba japonica, Plantago asiatica* and *Eucommia ulmoides*	Collagen disposition and inflammation ↓ TGF-β, α-SMA, Ki67 and prPCNA induced by TGF-β1 and cell proliferation ↓	1, 10, and 100 µmol/L	BLM-treated mice	(129)

3.4. Glycosides

Glycosides are natural compounds found in abundance in plants with various therapeutic applications. Glycosides maybe alcohol, phenol, or sulfur substances. They are defined by sugar parts connected by a special bond to one or more non-sugar parts. Glucose is the most commonly found sugar in glycosides. They exert several biological activities, including anti-inflammatory effects (130). Recently, they have shown to have an impact on PF (Table 4). *Fenugreek* seed extract that contains glycosides has been shown to has an anti-fibrotic effect through overexpression of Nrf2, which in turn downregulates IL-1b, IL-6, IL-8 and TNF-α and inhibit collagen-1, TGF-β, NF-kB, VEGF, Smad-3, for treatment of rats lung fibrosis induced by BLM (131).

Table 4 Glycosides potential effects in the treatment of pulmonary fibrosis

Glycoside	Source	Mechanism	IC50/dose	Model	Ref
Total glucosides	*fenugreek*	Nrf2 induction ↑ IL-1b, IL-6 and IL-8, TNF-a, TGF-b ↓ Collagen-1, NF-kB, VEGF, and Smad-3 ↓	20 and 40 mg/kg	BLM-treated rats	(131)
Total glucosides	*Danggui Buxue Tang*	α-SMA, TGF-β, Type I collagen, hydroxyproline, and NOX4 ↓ MDA and SOD ↑	4,8,16 mg/kg	BLM-treated rats	(132)
Lettuce glycoside B	*Pterocypsela laciniata*	SOD and other antioxidant enzymes ↑ IL-6, TNF-a and TGF-b1 ↓	200 and 400 mg/kg	Radiation-induced lung fibrosis rats	(133)
Gentiopicroside	*Gentiana lutea L.*	IL-1β and TNF-α, TGF-β1, CTGF, hydroxyproline ↓	2.5 and 10 mg/kg	BLM-treated mice and A549 cells	(134)
Ginsenoside	*Panax ginseng*	MMP-2, MMP-9, Smad2, Smad3, TGF-β1↓ Smad7, tissue inhibitor of metalloproteinase-1 ↑	40, 80, and 160 mg/kg/d	BLM-treated mice	(135)
Ginsenoside	*Panax ginseng*	α-SMA, collagen I, and MMP 9 ↓ maintained the ratio of MMP to tissue inhibitor of metalloproteinase 1. phospho-Smad2, phospho-Smad3, TGF-β receptor I ↓	20 mg/kg/d	Cigarette Smoke-Induced Airway Fibrosis	(136)
Ginsenoside	*Panax ginseng*	α-SMA and hydroxyproline, and TGF-β1 ↓ Caveolin-1 ↑	18, 36 and 72 mg/kg	BLM-treated mice	(137)

3.5. Plant extracts

The utilization of plant extracts for the management of pulmonary fibrosis started in China several years ago. Numerous literature has been reported on plant extract's beneficial effects on PF therapy (Table 5) and related processes. Plant extracts have shown to modulate various fibrotic biomarkers (NF-kB, hydroxyproline, MMP-9, TIMPs, collagen-I, FGF-2, PDGF and VEGF) and inflammatory biomarkers (TNF-α, TGF-β, IFN-γ, interleukins and endothelin-1). They also modulate activities of antioxidant enzymes such as SOD, GPx and catalase. They stimulate the activation of various signaling pathways, including JAK-STAT, Smad, Keap1 and Nrf2, resulting in the suppression of pulmonary fibrosis (16).

Plant extracts can activate various signaling molecules. For example, numerous plant extracts can prevent only inflammatory lesions caused by an inflammatory agent. In contrast, others can prevent only oxidative stress caused by ROS formation, collagen deposition, and angiogenesis. Many researchers attribute the beneficial effect of plant extracts to the presence of the bioactive phenolic mixtures (17).

Table 5 plant extract potential effects in the treatment of pulmonary fibrosis

Plant extract	Active ingredients	Mechanism	IC50/dose	Model	Ref
Rosemary leaves		Fibrosis score □ Restored the activities of antioxidant enzymes and Thiol group content Malondialdehyde concentration □	75 mg / kg/day	Rat	(138)
Yupingfeng	*Polysaccharide*	Collagen-I synthesis and deposition □ TGF-β 1 level □	350 mg/kg	Rat	(139)
Cissampelos Owariensis	*Methanol Leaf*	Antioxidants □ Ameliorated total protein, LPO levels, ALP activity,	200 or 400 mg/kg	Rat	(140)
Ginkgo biloba	*Flavonoids* *Ginkgolide B Ginkgolide C*	Activities of catalase, glutathione peroxidase, superoxide dismutase □ Malondialdehyde and Nitrite level □	100 mg/kg	Rat	(141)
Grapeseed	*Proanthocyanidins*	IL-1 and IL-6 □ Activation of TGF-β1 and MMP-9 □ Collagen Type I alpha 1 and fibronectin 1 □ E-cadherin □	50 or 100 mg/kg	Mice	(142)
Curcuma longa	*Turmeric* *And Non-Cyclic Peptide*	Endogenous antioxidant activity □ Lipid Peroxidation and scavenging of nitric oxide □	40 mg/ml	Mice	(143)
Trigonellafoenum graceum	*Glycosides (Vicenin-1, Trigoneoside)*	IL-1β, IL-6, IL-8, HO-1, TNF-α □ Fibrogenic molecules □	200 mg/kg	Rat	(144)
Rosmarinus Officinalis	*Polyphenol*	Normalizing pro-oxidant parameters, Activities of antioxidant enzymes □	75 mg/kg	Rat	(145)
Green tea	*Epigallocatechin-3 Gallate (EGCG), Epicatechin-3 Gallate (ECG), Epigallocatechin (EGC), Epicatechin (EC), and Caffeine*	Oxidative stress, ET-1 expression □	10 mg/kg	Rat	(146)
Chrysanthemum indicum	*Glycosides* *Flavonoids*	TNF-α and IL-6 ? Activities of myeloperoxidase, and malondialdehyde □	240 and 360 and 480 mg/kg	Mice	(147)
Paenial lactiflora	*Paeoniflorin*	Type I collagen synthesis □ Activation of TGF-β/SMAD pathway □	50 mg/kg	Mice	(148)

		IFN-γ expression □			
Rhodiola rosea	*Flavonoids Polyphenols*	HYP □ , GSH and T-SOD contents □ α-smooth muscle actin, MMP-9 □ TGF-β1 and TIMP-1 □	125 and 250 and 500 mg/kg	Rat	(149)
Houttuynia cordata	*Aristolactam Indoles*	Superoxide dismutase, malondialdehyde, hydroxyproline, interferon-gamma, and TNF α □	1 g/kg	Rat	(150)
Eclipta prostrate	*Wedelolactone*	pro-inflammatory factors expression, Inflammatory cells infiltration, collagen deposition □ Collagen I, α-SMA □, E-cadherin □ Regulating RAF-MAPKS Signaling Pathway and Activating AMPK	2 or 10 mg/kg	Mice	(151)
Radix astragalus	*Astragaloside*	α-SMA, TGF-β1, Jagged1 and Notch1 □	8 mg/kg	Rat	(152)
Passiflora edulis	*Intraperitoneal*	Anti-inflammatory and antioxidant activities	100 mg/kg	Mice	(153)
Yupingfeng extract	*Glucosides*	Hydroxyproline and collagen-I □ Over-expression of TGF- β 1 and α -SMA □	12 mg/kg	Rat	(154)
Glycyrrhiza glabra	*Methyl-Prednisolone and Methanolic*	Pulmonary inflammatory and fibrotic indices □	500 mg/kg	Rat	(154)
Citrus reticulata	*Alkaloids, Flavonoids, Phenolic Acids, Anthocyanins, Carotenoids, Tannins (Amine Hydrochloride 1)*	Lung TGF-β1 protein expression □	5 and 10 and 20 mg/kg	Rat	(155)
Silybum marianum	*Thymoquinone Ellagic Acid Flavonoid*	Lung lipid peroxidation □ and glutathione □ TNF-α and IL-6 □	50 and 100 mg/kg	Mice	(156)
Feitai		The inflammatory response, lipid peroxidation □	3 g/kg	Rat	(157)
Rikkunshito		The amelioration of neutrophil alveolar infiltration, pulmonary vascular permeability, Induction of proinflammatory cytokines, apoptosis of alveolar epithelial cells, activation of the NF-κb	1000 mg/kg	mice	(158)
Juglans regia	*Ellagic Acid*	Glutathione reductase, catalase □	100 mg/kg	Rat	(159)

Nigella sativa	*Alkaloids*	Inflammatory index, fibrosis score and TGF-β1 distribution □	1mg/kg	Rat	(160)

4. Clinical research with phytochemicals for treatment of pulmonary fibrosis

There are several clinical studies using phytochemicals for the management of PF. IPF is identified by a disrupted pulmonary redox balance linked to inflammation. To restore this balance, antioxidants and anti-inflammatory components such as phytochemicals are frequently suggested as therapy for IPF (161) and many preclinical studies have shown promising results for PF therapy.

In the study by Rodriguez et al., primary epithelial cells and fibroblasts isolated from IPF patients were treated with a combination of N-acetylcysteine and curcumin. They demonstrated that curcumin alone does have anti-fibrotic potential, but that effect is accompanied by increasing the apoptosis in oxidative stress. Their results suggest a novel application for curcumin in IPF and encourage further research of this potential therapeutic strategy (162).

Veith et al. evaluated the protective effect of quercetin on inflammatory and oxidative markers in 11 patients with IPF. They showed that endogenous antioxidant defense in IPF patients was significantly decreased, demonstrated by a reduced total antioxidant capacity and reduced glutathione and uric acid levels compared to controls. Furthermore, they showed exvivo incubation with quercetin in the blood of both patients with IPF, and healthy controls diminish LPS-induced production of the pro-inflammatory cytokines. So, their results suggest that IPF patients may potentially benefit from the use of quercetin to return the disturbed redox balance and decrease inflammation (163).

Justice et al. in a pilot study on 14 participants with IPF (ClinicalTrials.gov identifier: NCT02874989) analyzed the effect of senolytics in idiopathic pulmonary fibrosis. Physical function was significantly improved. But pulmonary function, frailty index (FI-LAB), and reported health did not change significantly. The effect of dasatinib plus quercetin (DQ) on circulating senescence-associated secretory phenotype (SASP) factors were inconclusive; however, correlations were seen between alteration in function and change microRNAs, SASP-related matrix-remodeling proteins, and pro-inflammatory cytokines. Their first study in humans supports the feasibility of senolytics in the treatment of IPF (164).

5. Conclusion

Various histopathologic patterns of pulmonary fibrosis have been known in association with several patterns of risk factors. It remains unclear what mechanisms are shared across different forms of pulmonary fibrosis and their outcomes (165). PF is a chronic lung condition with characteristic clinical, pathologic, physiologic, and radiographic findings. Today, no proven effective therapies exist for the management of pulmonary fibrosis with minimal side effects. There are broad areas that may be responsible for PF development, including a combination of excessive accumulation of ECM, loss of alveolar epithelial cells, and altered lung fibroblasts (17).

Conventional therapy for PF has been steroids and immunosuppressive agents. But only a minority of patients respond to this type of treatment (166). So, considering the limitations and problems of current treatment for pulmonary fibrosis, we need novel therapeutic options such as the use of attractive therapeutic potentials of phytochemicals. Scientific studies over the last decade have demonstrated the ability of these compounds to modulate

multiple cellular targets. Thus, they have preventive and therapeutic value against a wide variety of conditions (167).

These phytochemicals have multiple effects to improve PF, such as inhibitory activity against serum elevation TGF-β, TNF-α, and interleukins. They also inhibit an increase in fibrotic markers such as NF-κB, MMP-9, and HYP. Furthermore, they can reduce the severity of alveolitis and prevent pulmonary fibrocyte growth by decreasing abnormal JAK-STAT expression and Jagged1/Notch1 signaling pathways. They can also restore the catalase and glutathione-S-transferase activities in the lung tissues (168).

The results of this review demonstrated that these components could attenuate PF by enhancing the activities of antioxidant enzymes, modulating inflammatory agent, and other mechanisms related to pulmonary fibrosis (Figure 1). Thus, the phytochemicals are a promising source of treatment agents for PF. Today, many preclinical studies show the positive anti-fibrotic effect of phytochemicals for the treatment of this disease. However, we need to conduct more clinical trials to confirm these compounds' therapeutic effect against lung fibrosis.

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