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A review on importance of bioactive compounds of medicinal plants in treating idiopathic pulmonary fibrosis (special emphasis on isoquinoline alkaloids)

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Abstract

Background: Idiopathic pulmonary fibrosis (IPF) is a fatal lung disease of unknown cause which disrupts the normal lung architecture and functions by deregulating immune responses and ultimately leads to the death of the individual. A number of factors can lead to its development and currently there is no cure for this disease.

Main text: There are synthetic drugs available to relieve the symptoms and decelerate its development by targeting pathways involved in the development of IPF, but there had also been various side effects detected by their usage. It is known since decades that medicinal plants and their compounds have been used all over the world in natural medicines to cure various diseases. This review article is focused on the effects of various natural bioactive compounds of 26 plant extracts that show prophylactic and therapeutic properties against the disease and so can be used in treating IPF replacing synthetic drugs and reducing the side effects.

Short conclusion: This review includes different mechanisms that cause pulmonary fibrosis along with compounds that can induce fibrosis, drugs used for the treatment of pulmonary fibrosis, diagnosis, the biochemical tests used for the experimental study to determine the pathogenesis of disease with a special note on Isoquinoline alkaloids and their role in reducing various factors leading to IPF thus providing promising therapeutic approach.

Keywords: Pulmonary Fibrosis, Idiopathic, Isoquinoline, Berberine

Background

Fibrosis is the surplus development of fibrous connective tissue in an organ that interferes or inhibits the normal function and architecture of the underlying organ or tissue. Fibrosis arises from a single cell line called fibromas which are benign tumours and are composed of fibrous or connective tissue. Rising from mesenchymal tissue, they can grow at any organ or tissue [1]. The formation of fibromas in the lungs is termed pulmonary fibrosis, which is also known as idiopathic pulmonary fibrosis (IPF). IPF is a disease or condition which arises spontaneously for which the cause is unknown. IPF is a progressive, age-related, devitalizing lung disorder that is fatal with a high mortality rate. Different disorders can arise during the wound healing process of the damaged or scarred lung tissue which can be characterized as fibroblasts differentiation, infiltration of inflammatory cells, extracellular matrix remodelling and collagen deposition [2]. In general, the extracellular matrix (ECM) is mainly constituted by collagens and it gives strength to the tissues. Amino acids such as glycine, proline and lysine

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enable its formation. Non-elastin and proteoglycans like glycosamino glycans are essential to matrix resiliency. Enzymes and glycoproteins are useful to create tissue cohesiveness [3]. Epithelial mesenchymal transition (EMT) is one of the factors that thicken the lung tissue making it difficult to work properly and as fibrosis worsens, it will ultimately lead to shortness of breathing. Various additional conditions co-occurring with IPF are pulmonary hypertension, gastro-oesophageal reflux, coronary artery disease, malignancy, telomeropathy, pleuroparenchymal fibroelastosis and hypoxaemia [4]. There is a higher chance of getting affected with lung cancer in IPF because of mutation in the p53 tumour suppressor gene, which is involved in DNA repair, apoptosis and cell proliferation and differentiation [5].

IPF treatment remains unsatisfactory due to few treatment options and therapeutic measures, whereas in critical cases, lung transplantation is the only cure. There is no specific drug to cure IPF, but the drugs currently available are used only to reduce the symptoms by targeting specific pathways that led to IPF. Hence, there is a substantial need to discover various novel means to treat chronic lung diseases and at the same time reduce the side effects caused by the use of available drugs.

Medicinal plants and their compounds have been used all over the world in natural medicines to cure various diseases. Moreover, their usage is increasing in modern society as an alternative remedy for synthetic chemicals. These are also being commercialized on a large scale in various forms as medicines, cosmetics, ointments, essential oils in therapy etc., due to their useful properties. In addition, treating diseases with medicinal plant extracts is cost effective and has fewer side effects. Apart from this, the biological activity of any plant, its compounds and their effect on health can be known through research. Many plants are used across the globe in traditional medicine to cure various diseases and are also used in various therapies related to lung diseases. Examples of some plants used in treating lung diseases are *Papaver somniferum* for cough, cramps; *Lobella* spp for asthma; *Ephedra* spp. in respiratory alignments; *Coffea arabica* as a stimulant etc. Likewise, various plants and their extracted oils and compounds are used in treating various lung diseases [6]. Hence, this review focuses on pulmonary fibrosis and its mechanisms, chemicals that induce fibrosis, diagnosis, the synthetic treatment and details of natural plants and its compounds used to treat IPF with a special note on isoquinoline alkaloids.

Pulmonary fibrosis and mechanisms involved in its development

Pulmonary diseases are caused due to an imbalance and dysregulation of various immune response mechanisms in the body, and if these disturbances persist for a long time, these lead to pulmonary fibrosis. The mechanisms leading to IPF include the following

Disturbances in the regular wound healing process

Wound healing is an essential process for the repair of the skin and the tissues underlying it after injury. The healing process undergoes four different stages: coagulation/clotting phase, migratory phase of inflammatory cells, proliferation/activation/migration phase of fibroblast, remodelling and resolution phase of tissue. Each process is regulated by different growth factors and cytokines. As the focus of the review is on pulmonary fibrosis, the wound healing mechanism with respect to lung fibrosis is shown in Fig. 1 [7]. Injury to lung epithelial cells enables the release of various inflammatory mediators which recruit an antifibrinolytic coagulation cascade. Pro-fibrotic cytokines such as tumour necrosis factor alpha (TNF-α), interleukins (IL) IL-1β, transforming growth factor beta (TGF-β), IL-6, IL-8, IL-10, IL-13, chemokines, MCP-1(monocyte chemo attractant protein) and IP-10 (interferon-gamma-inducible protein) are secreted by leukocytes. The activated neutrophils and macrophages remove dead cells thereby eliminating invading organisms. In the consequent phase, ECM, a three-dimensional network of extracellular macromolecules such as collagen, glycoproteins and enzymes, is released by the fibrocytes which proliferate by differentiating into myofibroblasts. Fibroblasts and myofibroblasts resulting from epithelial cells can undergo epithelial mesenchymal transition (EMT). The activated myofibroblasts may promote wound repair in the remodelling and resolution phase; it leads to the restoration of blood vessels and wound contraction which is the regular process occurring in wound healing, but if the same process is dysregulated at any stage in the tissue repair programming process, it leads to the occurrence of fibrosis and lung damage stimulus persists as shown in Fig. 1 [8–13].

Effect of pro-inflammatory and pro-fibrotic mediators

Various pro-inflammatory and pro-fibrotic mediators play a major role in immune responses. Irritants like asbestos, silica, carbon tetrachloride, bleomycin and uric acid can induce fibrosis in pulmonary epithelial cells which can be sensed in macrophages by the NALP3 inflammasome. The mediators like reactive oxygen species (ROS), chemokines and cytokines produced during this process, which are responsible for inflammation, increase the accumulation and initiation of leukocytes at the sites of wound or injury as shown in Fig. 2 [14]. Cytokine IL-1β allows the initiation of neutrophil-expressing ROS and stimulates the production of pro-fibrotic cytokine TGF-β, which may additionally lead to epithelial cell damage. The TGF-β initiates fibroblast

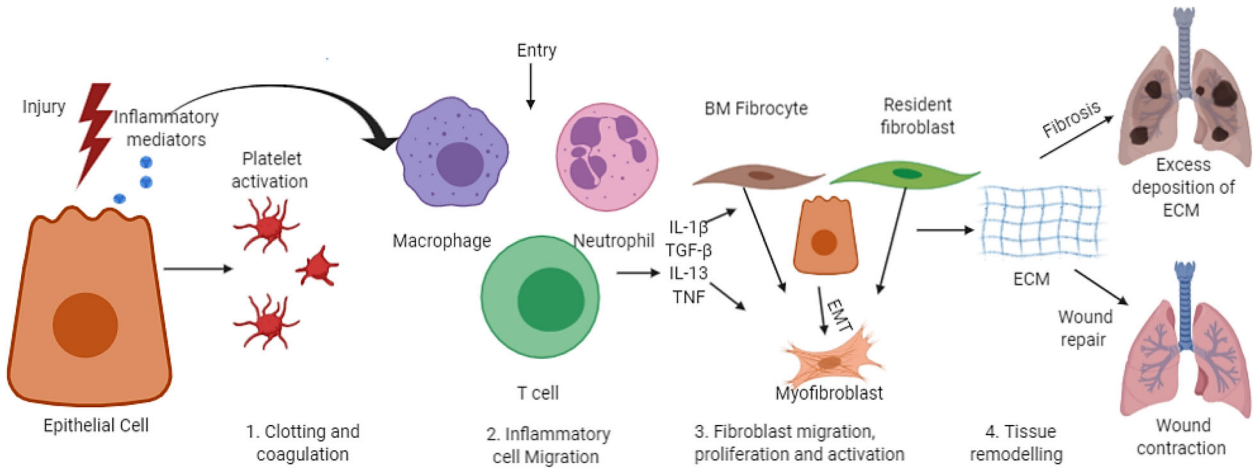

Fig. 1 Mechanism of wound healing [7]

proliferation and activation. This aims epithelial cells towards the formation of ECM by myofibroblasts as shown in Fig. 2 [15]. Hence, TGF-β worsens the inflammatory reaction by allowing a subset of pro-inflammatory T helper cell differentiation to Th17 cells which leads to the production of IL-17 which upon overactivation can also lead to an inappropriate extent of inflammation [16].

Specific subsets of macrophages and T helper cells

Macrophages are involved in all stages of the fibrotic process, and hence, these are key regulators in the recruitment, proliferation and activation of fibroblasts. Macrophages are classified as M1 and M2 based on differences in their activation, stimuli and amount of pro-inflammatory cytokines. The compounds produced and their function are listed in Table 1 [17]. Macrophages promote fibrosis by producing chemokines and matrix metalloproteinases (MMP) which degrade ECM and facilitating the enrolment of inflammatory cells at the site of injury [18]. The macrophages release TGF-β1 and platelet-derived growth factor (PDGF) which are pro-fibrotic mediators and also involves in the proliferation

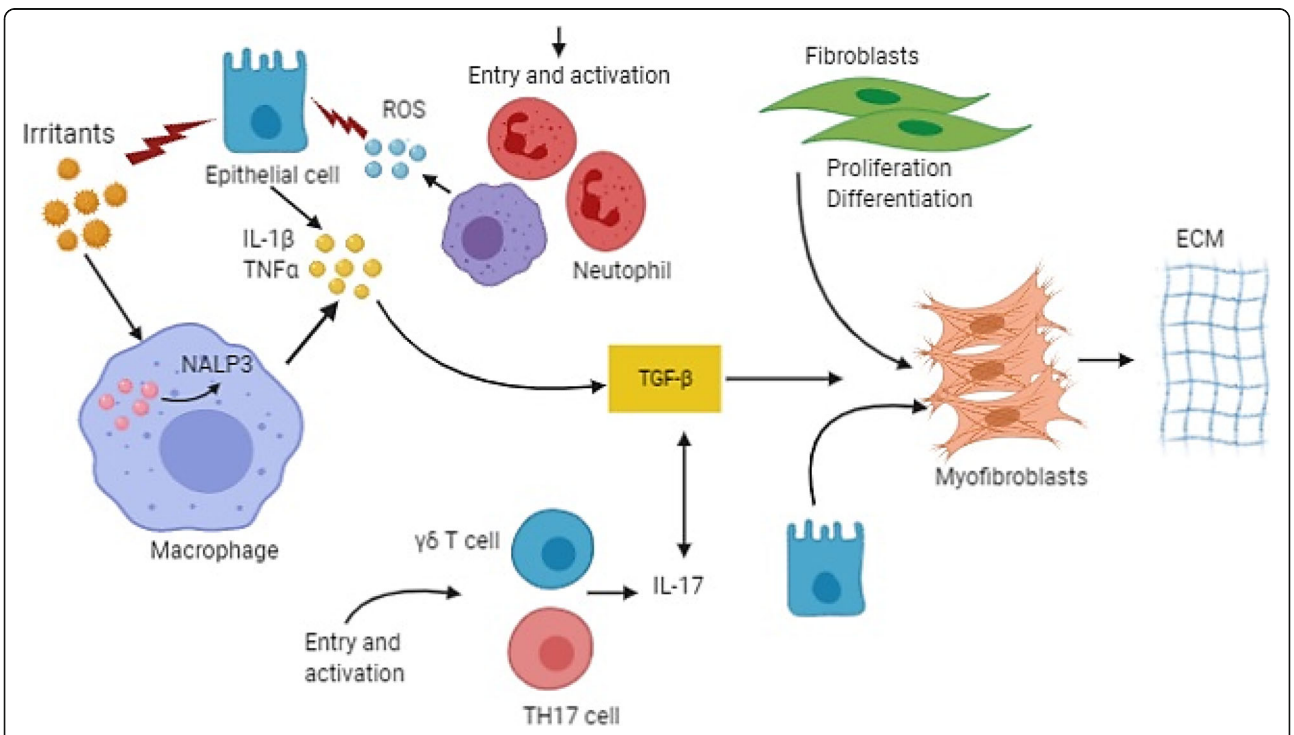

Fig. 2 Effect of proinflammatory and pro-fibrotic mediators [7]

Table 1 Difference between M1 and M2 macrophages

	M1 macrophages	M2 macrophages
Activation	Classically activated	Alternatively activated
Th cell involved	Th1 cells	Th2 Cells
Subtypes	–	M2a, M2b and M2c
Stimuli	IFN-γ or lipopolysaccharide (LPS)	IL-4, IL-10 or IL-13
Antigen presentation	Yes	No
Proinflammatory cytokines	High levels	Low Levels
Autophagy	Induced	Decreased
Nitric oxide production	Yes	No
Phagocytosis	Increases	Decreases
Function	Protect against bacteria and viruses	Wound healing and tissue repair build extracellular matrix

and activation of myofibroblasts to secrete collagen [19–21]. Macrophages can also inhibit fibrosis by releasing mediators that allow apoptosis of myofibroblast and take away cell debris and drive inflammation by digesting, engulfing ECM components and collagen by degrading matrix metallopeptidases in cells which includes neutrophils and myofibroblasts [22]. Epithelial cells when injured release thymic stromal lymphopoietin, IL-25 and IL-33 which enable the progress of pro-fibrotic T helper type 2 (Th2) responses. Th2 differentiation is promoted by T cells which release IL-25 and IL-21 [23]. Th2 cytokines also amplify fibrotic responses by initiating chemokines that enable the release of fibrocytes from the bone marrow for collagen secretion [24]. The subsequent myofibroblasts in this mechanism release ECM components as shown in Fig. 3 obtained from Wynn [7]. M2 macrophages which constitute Th2 cytokines further inhibit IL-13 production and myofibroblast differentiation by activating arginase-1 which also activates antifibrotic feedback mechanisms, whereas Th1 cells produce interferon gamma (IFN-γ), show strong antifibrotic activity by reducing the synthesis of collagen in fibroblasts and stimulate inflammatory M1 macrophages promoting ECM degradation [25]. The entire mechanism of action of macrophages and T helper cells in fibrosis is shown in Fig. 3.

Intrinsic activation changes in fibroblasts and epithelial cells

Fibroblasts and epithelial cells promote growth factor independent pulmonary fibrosis, EMT and synthesis of ECM components. In this mechanism, Wnt-β-catenin

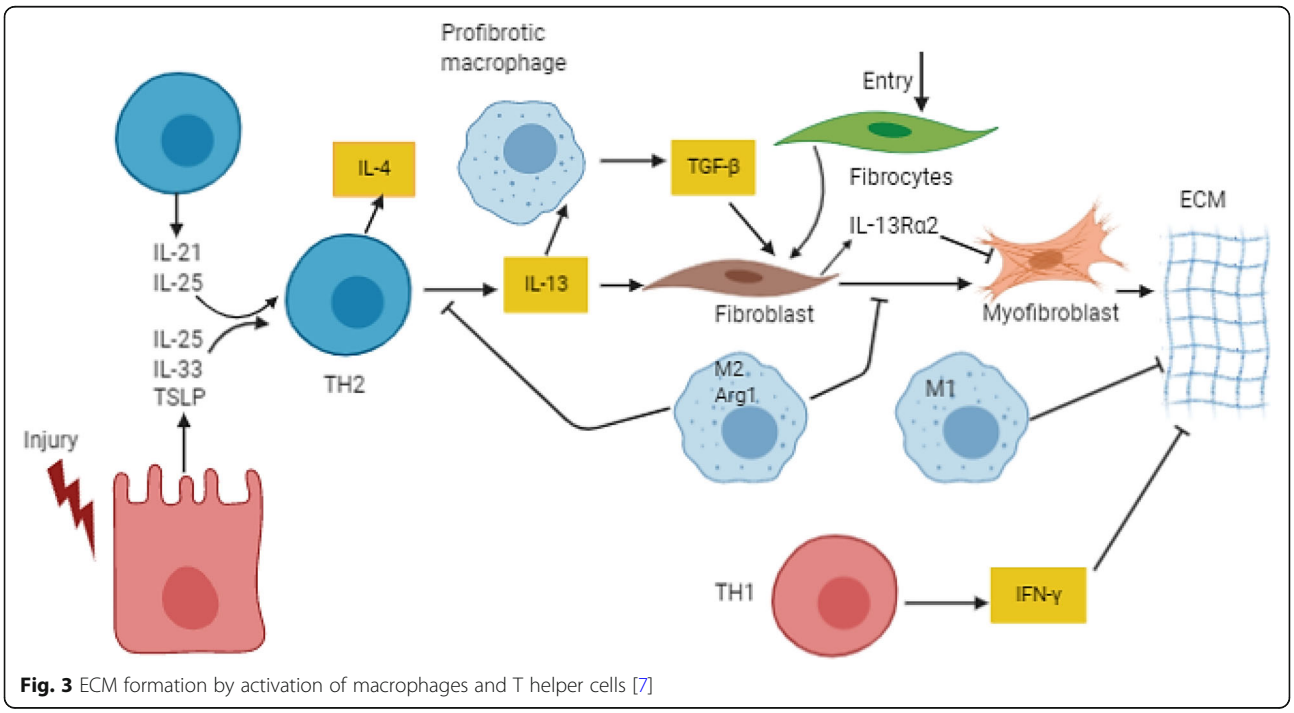

Fig. 3 ECM formation by activation of macrophages and T helper cells [7]

signalling triggered by WNT1-inducible signalling pathway protein 1 (WISP-1) is significantly active in some alveolar type II epithelial cells which are responsible for the regeneration of the alveolar epithelium [26, 27]. In cardiac fibroblasts, collagen-mediated stimulation of β1 integrin upregulates phosphatase and tensin homologue (PTEN) activity and prevents its proliferation. The pathological pattern of β1 integrin expression and signalling displayed by fibroblasts can lead to declined PTEN expression and abnormal phosphoinositide 3-kinase (PI3K) activation and extreme proliferation [28]. Pro-fibrotic mediators are also responsible for epigenetic changes in fibroblasts leading to fibrosis development where the promoter regions of various genes encoding differentiation factors and autocrine growth factors can be demethylated for controlling heritable and sustained activation. Moreover, methylation and further inactivation of tumour suppressor genes can lead to activation of oncogenes and promotes proliferation of fibroblasts which are independent of growth factors. In this, miRNA may operate alike by obstructing translation or promoting the degradation of tumour suppressor genes [29]. Dysfunction of any of these mechanisms mentioned above can lead to the formation of fibrosis. Some plant extracts and their bioactive compounds have the capability to overcome the fibrotic process in any stage of the mechanism and help to prevent the formation of fibrosis.

Particles and chemical compounds which are fibrinogenic to lungs

Various compounds which upon interaction induce pulmonary fibrosis are listed below. These are also used in particular to induce pulmonary fibrosis during experimental studies. The most commonly used compounds are bleomycin and carbon tetrachloride.

Bleomycin (BLM) is a glycopeptide antibiotic commonly used to induce pulmonary fibrosis in rats for experimental studies [30]. It was first isolated from *Streptomyces verticillatus* [31, 32]. Crystalline silica dusts upon pulmonary exposure in humans cause silicosis which is characterized by the occurrence of inflammation and fibrosis in lungs, weakening of lung functions and premature death [33]. Paraquat (N, N-dimethyl-4, 4′-bipyridinium dichloride) is a herbicide and is a potent toxin to the lungs which will cause intra-alveolar fibrosis in epithelial cells and damage lung architecture [34]. Amioahrone, a cardiac anti arrhythmic agent, is linked with the development of interstitial pulmonary fibrosis upon prolonged therapy [35]. Cyclophosphamide is an alkylating agent used as a drug which when administrated causes interstitial lung disease, which leads to pulmonary fibrosis and lung abrasion [36]. Periostin is a matrix cellular protein that shows a distinctive role like chemokine inducer in the recruitment of macrophages and neutrophils which play a key role in causing pulmonary fibrosis in bleomycin-administered mice [37]. Carbon tetrachloride (CCl_4) had been used to induce pulmonary fibrosis in rats with increased volume densities of type III and type IV collagen, and laminin [38, 39]. Carbon tetrachloride is commonly used to induce liver fibrosis [40]. Aerosol particle polyhexamethylene guanidine phosphate induces pulmonary inflammatory and fibrotic response although its mechanism to induce fibrosis was unclear [41]. Irradiation can also induce pulmonary fibrosis [42].

Diagnosis of pulmonary fibrosis

Pulmonary fibrosis is commonly diagnosed by chest X-ray [43], computerized tomography (CT) scan [44], echocardiogram [45, 46], pulmonary function testing [47, 48], pulse oximetry [49], exercise stress test [50], arterial blood gas test [51], bronchoscopy [52] and surgical biopsy [53].

Treatment for pulmonary fibrosis with synthetic drugs

Pulmonary fibrosis was currently treated with corticosteroids, endothelin receptor antagonists, tyrosine kinase inhibitors glucocorticoids, colchicine, γ-interferon, antioxidants, cyclophosphamides and cyclosporin A which are listed in Table 2. These drugs, even though are therapeutic, have high side effects. The long-term effect and safety of the new drugs like pirfenidone and nintedanib remain ambiguous. Therefore, it is essential to screen drugs with progressive therapeutic effects to treat pulmonary fibrosis [69, 70]. IPF in patients is frequently identified late in the course of the disease and many die before receiving a transplant. Therefore, initial diagnosis is necessary for evaluation and transplantation.

Techniques and procedures used in experimental studies to determine the extent and cure for fibrosis

Before concluding on the activities of any drug which is synthetic or natural in origin, experimental studies are necessary and a must. The various techniques used in experimental studies on pulmonary fibrosis are:

Microscopy techniques are used to count differential alveolar cells by using the May-Grunwald-Giemsa stain. Differential cell count from broncho alveolar lavage fluid provides information regarding the total cell count and percentage of lymphocytes, neutrophils, eosinophils and macrophages. Biochemical analyses of proteins, hydroxyproline are needed to be assessed in order to measure the amount of collagen deposited in the lung tissue. Myeloperoxidase and malondialdehyde levels need to be measured. Transcription of fibrotic genes is done by

Table 2 Drug designed to treat idiopathic pulmonary fibrosis

S. no.	Type/effect	Drug used	Reference
1	Corticosteroids	Cochrane	[54]
2	Immunomodulator agent	Azathioprine	[55]
3	Cytokine inhibitor	Etanercept	[56]
4	Cytokine	Interferon-γ	[57]
5	Phosphodiesterase inhibitor	Sildenafil	[58]
6	Endothelin receptor antagonist	Bosentan, macitentan and ambrisentan	[59–61]
7	Anti-oxidant	N-Acetylcysteine	[62]
8	Anticoagulant	Warfarin or heparin	[63]
9	Tyrosine kinase inhibitor	Imatinib	[64]
10	Tyrosine kinase inhibitor	Nintedanib	[65]
11	anti-inflammatory, anti-oxidant and anti-fibrotic	Pirfenidone	[66]
12	Immunosuppressant	Cyclosporine A	[67]
13	Immunosuppressant	Tacrolimus	[68]

isolating RNA and reverse transcribed using RT PCR with primers against TGF-β1 which is responsible for inducing extreme production and deposition of collagen, procollagen Iα, tissue inhibitor of metalloproteinase (TIMP-1) and matrix metallopeptidase 9 (MMP-9). These are gelatinases, matrix metalloproteinases and tissue inhibitors of metalloproteinases. Antioxidant assays are carried out to determine the levels of catalase, superoxide dismutase, peroxidase, nitric oxide, glutathione reductase, glutathione peroxidase, glutathione-S-transferase, γ-glutamyl transpeptidase and quinone reductase. Along with cell viability, IL-6, TNF-α, MCP-1 and endothelin-1 levels need to be determined.

Role of plants and their bioactive compounds that can be used to treat pulmonary fibrosis

The name of the plant, its active compound and the experimental model that is used in treating pulmonary fibrosis are listed in Table 3. The mode of activity of plants and their bioactive compounds are illustrated in Fig. 4.

Nelumbo nucifera

Neferine, which is a bisbenzylisoquinline alkaloid, is extracted from the embryo seed of the plant *Nelumbo nucifera gaertn* and it attenuates bleomycin-induced pulmonary fibrosis. Neferine was found to be more effective in reversing the bleomycin-triggered activities such as reduction of superoxide dismutase (SOD) in the lungs, rise in myeloperoxidase (MPO) and malondialdehyde (MDA) levels. Neferine additionally relieved the bleomycin-induced rise of pro-inflammatory cytokines like endothelin-1, TNF-α and IL-6 in tissue or plasma. Neferine also obstructed the bleomycin-induced rise of TGF-β1 and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) in total protein extracts and nuclear extracts respectively [71].

Arenaria kansuensis

The β-carboline alkaloids present in ethylacetate extract of *Arenaria kansuensis* showed an antifibrogenic effect by suppressing inflammatory cytokines TNF-α, IL-1β, MCP-1 and IL-6. The β-carboline alkaloids of this plant inhibited the initial inflammation by inhibiting NF-κB/p65 pathway and backing the process of EMT. The expression of indicators vimentin, alpha-smooth muscle actin (α-SMA) and E-cadherin of EMT was considerably amended after the administration of different β-carboline alkaloids [72, 73]. The expression of TGF-β1, α-SMA, E-cadherin and collagen deposition was significantly raised after the administration of this plant extract. All the twelve alkaloids isolated from this plant, monoacetylarenarine B, 3-hydroxymethyl-β-carboline, arenarine A, glusodichotomine AK, cordysinin C, arenarine D, 7-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline, 3-hydroxy-β-carboline, β-carboline1-carboxylic acid, cordysinin E, 1,2,3,4-tetrahydro-1,3,4-trioxo-β-carbo1ine and arenarine B, are together used to treat IPF and found to reduce fibrotic activities [73].

Mahonia aquifolium

The bark of *Mahonia aquifolium* contains a lot of isoquinoline alkaloids like berberine, berbamine, palmatine, magnoflorine and jatrorrhizine [74, 75]. The action of isoquinoline alkaloids and their action on various factors leading to pulmonary fibrosis are dealt with later in this article.

Table 3 Plants and their bioactive component for pulmonary fibrosis

S no.	Plant name	Active ingredient type	Name of compound	Extracted from	Model organism used	Insertion through (plant/ compound)	Compound used to induce IPF for study	Levels in effected group	Application of plant extract/bioactive compound	Effective dose	Reference
1	*Nelumbo mucifera*	Bisbenzylisoquinline	Neferine	Seed embryo	Kunming mice	Intratracheal	Bleomycin (20 mg/ kg)	**Hydroxyproline content: –** 255.77 ± 97.17 μg/lung; 269.74 ± 40.92 μg/ lung **Endothelin-1**: **–** 187.97 ± 49.90 pg/ 100 mg protein **SOD**: – 75.18 ± 13.89 and 85.28 ± 20.80 U/mg protein); MPO,MDA,TGFβ1,NF-κB, TNF-α are increased	**Hydroxyproline content: –** 193.07 ± 39.55 μg/lung and 201.08 ± 71.74 μg/ lung **Endothelin-1**: **–** 123.98 ± 18.91 pg/ 100 mg protein **SOD**: **–** 102.62 ± 27.44 U/mg protein; MPO, MDA, TGFβ1, NF-κB, TNF-α are decreased	98% pure 20 mg/kg	[71]
2	*Arenaria kansuensis*	β-Carboline alkaloids	Monoacetylarenarine B, 3-hydroxymethyl-β-carboline, glu-sodichotomine, arenarine A, cordysinin C, 7-methoxy-1-oxo-1,2,3,4-tetrahydro-β-carboline, 3-hydroxy-β-carboline, arenar-ine D, β-carboline-1-carboxylic acid, 1,2,3,4-tetrahydro-1,3,4-trioxo-β-carbo1ine, arenarine B, cordysinin E	Crude extract	Adult male and female Kunming mice	Gastric gavage	Bleomycin (2.5 U/ kg)	Increase in macrophages, TNF-α, TGF-β1and IL-1β	TNF-α, TGF-β1 and IL-1β decreased; survival rate increased; macro-phages decreased	100–150 mg/ kg dose	[72, 73]
3	*Mahonia aquifolium*	Isoquinoline alkaloids	Berberine, berbamine, palmatine, magnoflorine and jatrorrhizine	Stem bark	Male Wistar rats	Intraperitoneal	Bleomycin	MPO, MDA, TGFβ1, NF-κB, TNF α are in-creased; SOD, CAT, GPx, GSH, vitamins A, C, E are decreased	MPO, MDA, TGFβ1, NF-κB, TNFα are de-creased; SOD, CAT, GPx, GSH, vitamins A, C, E are increased	200 mg/kg/day	[74–76]
4	*Camellia sinensis*	Tea catechin	Epigallocatechin-3-gallate (EGCG)	Black tea extract	Swiss albino mice	Oral gavage	Bleomycin (50 μL of 5 mg/kg body weight)	IL-10, TNF-α increases INF-γ decreases	IL-10, TNF-α decreases INF-γ increases	25 mg /kg body weight/ day and 50 mg/kg body weight/day	[77]
5	*Punica granatum*	Dilactone	Ellagic acid	Seed extract	Male Spraque-Dawley rats	Gastric Gavage	Bleomycin 7.5 IU/ kg	Assessed by lung histology that showed increased inflammatory cell infiltration	Reduced inflammatory cell infiltration and reduced collagen deposition	400 mg/kg dose of pomegranate extract;	[78]
					Wistar rats		Bleomycin and cyclophosphamide 10 U/kg/body weight 150 mg/kg body weight respectively	Hydroxy proline MPO,GSH, NO production increased	Hydroxy proline MPO,GSH, NO production are attenuated	15 mg/kg body weight of ellagic acid	[79]
6	*Acnistus arborescens*, *Withania obtusifolia*	Steroidal lactone	Withaferin A	Leaves	Mice	Intraperitoneally	Bleomycin (0.025 U)	Invasiveness of fibroblasts with increased vimentin expression	Decreased vimentin expression, collagen increased beclin 1 and LC3B expression	2 mg per kg body weight	[80–82]

Table 3 Plants and their bioactive component for pulmonary fibrosis *(Continued)*

S no.	Plant name	Active ingredient type	Name of compound	Extracted from	Model organism used	Insertion through (plant/ compound)	Compound used to induce IPF for study	Levels in effected group	Application of plant extract/bioactive compound	Effective dose	Reference
7	*Pistacia chinensis*	Phenolic, flavonoid compound	Gallic acid, rutin	Bark	Male Sprague-Dawley	Orally	CCl_4 (30%)	Rise in hydrogen peroxide, NO, eosinophils, lymphocytes, monocytes; Decrease in CAT, POD, GSH, GPx, GST, leukocytes, neutrophils, Haemoglobin	Showed protective effect by bringing all these levels to normal by ameliorating toxicity.	400 mg/kg body weight	[83]
8	*Rosmarinus officinalis*	Phenolic diterpene	Rosmarinic acid and carnosic acid	Leaves	Male Wistar rats	Intraperitoneal injection	Bleomycin (4 mg/ kg)	Lower CAT, GST and increased MDA	Normalized levels and showed lower fibrotic score	75 mg/kg	[84]
9	*Nigella sativa*	Enzymes, vitamins, aromatic oils	Thymoquinone	Seeds	Male Wistar rats	Oral gavage	Bleomycin (2 mg/ kg)	Inflammatory score 3.8 ± 0.89; fibrosis 4.88 ± 0.21	TGF-β reduction; inflammatory score 1.2 ± 0.45; fibrosis 1.83 ± 0.68	1 mL/kg/day	[85, 117]
10	*Pistacia lentiscus*	Essential fatty acids	Linoleic and palmitic acid	Seeds	Male Wistar Rat	Orally	Bleomycin (50μL of 4 mg/kg body weight)	Decreased CAT, POD, SOD and increase in MDA, hydrogen peroxide, TGF-β1; Fibrosis score (mg g^{-1}) 7.91 ± 0.23	Normalize the levels of CAT, POD, SOD, MDA, TGF-β1; Fibrosis score (mg g^{-1}) 4.62 ± 0.09	3g/kg, body weight	[86]
11	*Linum usitatissimum*	Fatty acids	Omega 3 and omega 6	Seeds	Male Wistar rats	Gavage	Bleomycin 4.8 mg/ kg body weight	Fibrosis score 3.7 ± 0.94; inflammatory score 3.3 ± 0.48; and decrease in CAT, SOD	Fibrosis 3.0 ± 1.05; Inflammatory score 1.9 ± 0.87; SOD, CAT levels are raised. Here the fatty acid content is increased in cells	2 mL/kg body weight	[87]
12	*Passiflora edulis*	Flavonoids	Cyanidin-3-O-glucoside, quercetin-3-O-glucoside and edulilic acid	Peel	C57BL/6J mice	Oral	Bleomycin (50 μL of 0.05 U)	SOD is decreased and MPO, hydroxyproline is increased	Hydroxyproline deposition is supressed, MPO levels are reduced and SOD levels are increased	100 mg/kg body weight	[88]
13	*Tanacetum parthenium*	Sesquiterpene lactone	Parthenolide	Crude extract	Mice; A549 cell lines	Intragastric	Bleomycin (5 mg/ kg body weight)	Increases TGF-β1, NF-κB, Snail, IL-4, TNF-α, collagen deposition, α SMA, vimentin	Inhibit TGF-β1, NF-κB, Snail, IL-4, TNF-α, collagen deposition, vimentin, α SMA and rise in MMP, E-cadherin	50 mg/kg	[89]
14	*Curcuma longa*	Polyphenol	Curcumin	Crude extract	Male Wistar rats	Oral	Bleomycin (0.75 U/100 g)	increases TNF-α release, and superoxide and NO	Reduced hydroxyproline	300 mg/kg	[90]

Table 3 Plants and their bioactive component for pulmonary fibrosis *(Continued)*

S no.	Plant name	Active ingredient type	Name of compound	Extracted from	Model organism used	Insertion through (plant/ compound)	Compound used to induce IPF for study	Levels in effected group	Application of plant extract/bioactive compound	Effective dose	Reference
								production			
15	*Cordyceps sinensis*	Purine nucleoside antimetabolite and antibiotic	Cordycepin	Crude extract	Male Sprague-Dawley rats	Intragastric	Bleomycin (2.5 mg/kg)	Rise in TIMP-1, TGF-β1, collagen and ROS	TIMP-1, TGF-β1, collagen and ROS are reduced	1.35 g/kg	[91]
16	*Salvia officinalis*	Phenolic compounds	Vanillic, gallic, ellagic, rosmarinic and carnosic acids	Leaves	Male Wistar rats	Intraperitoneal	Bleomycin (4 mg/kg)	Rise in MDA, collagen with decrease in SOD, CAT	The levels were normalized by reduction of MDA and increase in SOD, CAT	150 mg/kg	[92]
17	*Silybum marianum*	Flavonolignan	Silymarin	Fruits	BALB/c mice	Intraperitoneally	Bleomycin (1.5 U/kg)	Rise in MPO, TNF-α, IL-6, MDA and reduction of GST, GSH.	Induced GST, GSH and reduced MPO, TNF-α, IL-6, MDA	100 mg/kg	[93, 94]
18	*Oxalis corniculata*	C-glycosyl flavonoids	Isoorientin, isovitexin and swertisin	Crude extract	Female Sprague-Dawley rats	Intragastrically	CCl_4 (20%)	Reduction of CAT, POD, GSH, GPx, GST. Visibility of pulmonary edema and fibrosis	Rise in CAT, POD, GSH, GPx, GST levels. No occurrence of edema and fibrosis	200 mg/kg body weight	[95, 117]
19	*Tinospora cordifolia*	Isoquinoline alkaloids	Berberine, palmatine, magnoflorine and jatrorrhizine	Leaf, stem root	Male Wistar albino rat	Intraperitoneally	Bleomycin (2.5 U/kg)	Rise in NF-κB, iNOS, TNF-α, TGF-β1	Inhibited NF-κB, iNOS and reduced TNF-α, TGF-β1	200 mg/kg	[76, 96]
20	*Phyllanthus emblica*	Polyphenolics, Flavanoids	Gallic acid, rutin, caffeic acid, kaempferol, pyrogallol	Leaf	Sprague-Dawley male rats	Orally	CCl_4 (30 %)	Reduction of CAT, POD, GSH, GPx, GST	Rise in CAT, POD, GSH, GPx, GST levels; disrupted alveoli, macrophages infiltration was reversed to normal	200, 400 mg/kg	[97, 98]
21	*Angelica sinensis*	Polysaccharides	Heteropolysaccharides	Root	Sprague-Dawley rats	Intragastrically	Bleomycin (5 mg/kg)	TGF-β1 increased DANCR mediates *Angelica Sinensis*-induced suppression by rise in FOXO3 protein levels	*Angelica Sinensis* reduce the DANCR expression which in turn suppresses AUF1-intervened FOXO3 translation to overwhelm the EMT and pulmonary fibrosis	20 mg/kg with adenovirus-associated packaging DANCR sequence	[99]
22	*Citrus reticulate*	Flavonoids	Hesperidin, narirutin, rutin	Pericarp	Sprague-Dawley rats	Orally	Bleomycin (5 mg/kg)	Low MMP-9 and rise in TIMP-1 and TNF-α	Rise in MMP-9 and reduced TIMP-1 and TNF-α	32 mg/kg/day	[100, 101]
23	*Houttuynia cordata*	Amino acids, flavonoids, polysaccharides, volatile acids	Quercetin, quercitrin, hyperoside and rutin	Whole plant	Male Wistar rats	Orally	Bleomycin (15 mg/kg)	IFN-γ, TNF-α, hydroxyproline, MDA, lung weight are increased whereas CAT, body weight is decreased	IFN-γ, TNF-α, hydroxyproline, MDA, lung weight is reduced with rise in CAT, body weight	1 g/kg	[102]

Table 3 Plants and their bioactive component for pulmonary fibrosis *(Continued)*

S no.	Plant name	Active ingredient type	Name of compound	Extracted from	Model organism used	Insertion through (plant/ compound)	Compound used to induce IPF for study	Levels in effected group	Application of plant extract/bioactive compound	Effective dose	Reference
24	*Carthamus tinctorius L*	Flavonoid	Hydroxysafflor yellow A	Whole plant	Male C57BL/6 mice	Intraperitoneally	Bleomycin (4.5 mg/kg)	Increased collagen deposition, TGF-β1, α-SMA, hydroxyproline, CTGF,	inhibited TGF-β induced collagen production	Hydroxysafflor yellow A 60 mg/kg/day	[103]
25	*Eriobotrya japonica*	Triterpene acids	Oleanolic acid, a-hydroxyoleanolic acid, arjunic acid, euscaphic acid, ursolic acid	Leaves	Male Sprague-Dawley rats	Intragastrically	Bleomycin (5 mg/kg)	Rise in TNF-α and TGF-β1	Reduction of TNF-α and TGF-β1	Triterpene acids (450 mg/kg)	[104]
26	*Centella asiatica*	Triterpenoid saponin	Madecassoside	Leaves	Mice	Orally	Bleomycin (5 mg/kg)	Rise in TGF-β1, oxidative damage, MPO.	Increased SOD and glutathione and reduced leucocyte in BALF, MPO and oxidative damage	Madecassoside (40 mg/kg)	[105]

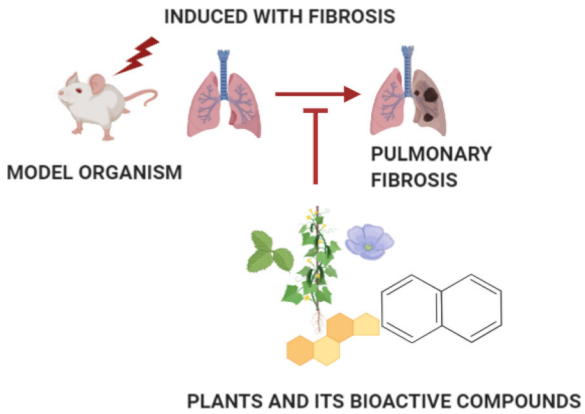

Fig. 4 Effect of plants and bioactive compounds in treating IPF

Camellia sinensis

The decreased α-SMA expression in bleomycin-induced mice and downregulated TGF-β expression and upregulated expression of IFN-γ in experimental pulmonary fibrosis showed that black tea extract (*Camellia sinensis*) can be effective for treating pulmonary fibrosis [77]. Epigallocatechin-3-gallate (EGCG), a bioactive compound isolated from green tea extract, prevents pulmonary fibrosis induced by irradiation and provides a strong, persistent antioxidant capacity by preventing the synthesis and emission of ROS/RNS free radicals which is responsible for oxidative damage in parenchymal cells; the anti-inflammatory capacity is enhanced by suppressing the expression of key inflammatory cytokines TNF-α, TGF-β1, IL-6 and IL-10, and the anti-proliferative activity is also enhanced to protect against irradiation-induced pulmonary fibrosis in rats. EGCG inhibits myofibroblast proliferation and (AE2) anion exchange protein 2-cell dysplasia by suppressing TGF-β1 [106]. Epigallocatechin-3-gallate is a tea catechin [107, 108]. EGCG binds directly to the proinflammatory chemokines CXCL9, CXCL10 and CXCL11 and intensely inhibits their chemotactic capabilities. EGCG also reduced Th1 cell and other inflammatory cell recruitment and inflammatory response in airways and lung tissues [109].

Nuts and fruits

Ellagic acid is the dilactone of hexahydroxydiphenic acid present in many nuts and fruits such as black raspberries, pomegranates, strawberries, raspberries, almonds and walnuts attenuates cyclophosphamide and bleomycin-induced pulmonary toxicity. Ellagic acid a polyphenolic compound when given orally showed a significant decrease in hydroxyproline, lipid peroxidation, nitric oxide production, protein carbonyl level, myeloperoxidase activity and increase in glutathione levels and antioxidant levels [78].

Punica granatum

The *Punica granatum* (pomegranate) seed extract has been shown to prevent pulmonary fibrosis induced by bleomycin in rats. Low inflammatory cell infiltration and reduced collagen deposition have been observed when compared with that of bleomycin-induced rats. Overall, the study showed the antioxidant effects of the pomegranate seed extract in a dose-dependent manner and was also found to have the best antioxidant effect when given in high dosages [79].

Pistacia chinensis

Pistacia chinensis bark (PCEB) is used as a potent ameliorator for carbon tetrachloride (CCl_4)-induced lung toxicity and found to possess antioxidant activity by free radical-quenching components. The major constituents of the plant are the phenolic compound gallic acid and the flavonoid compound rutin. The other compounds detected by thin-layer chromatography are ascorbic acid, catechin, kaempferol and tannin. Toxicity of CCl_4 was ameliorated with PCEB treatment which significantly inhibited the increase of hydrogen peroxide, thiobarbituric acid-reactive substances, nitrite and protein content. The activity levels of various antioxidant enzymes like superoxide dismutase, peroxidase, catalase, glutathione peroxidase, glutathione-S-transferase, γ-glutamyl transpeptidase, glutathione reductase and quinone reductase are restored in both thyroid and lung tissues in rats treated with CCl_4. It also increased the total leukocyte count and neutrophil and haemoglobin levels. In addition, it decreased the number of lymphocytes, monocytes and eosinophils. These actions are reliant on dosage. All the results presented show that this plant can be used in the treatment of pulmonary fibrosis [83].

Rosmarinus officinalis L.

Rosmarinus officinalis L. (Lamiaceae) leaves extract which contains a high amount of carnosic acid has a protective effect against bleomycin-induced oxidative stress and lung fibrosis. The effect of these leaf extracts includes restored catalytic activity of the lung treated with bleomycin. It has antioxidant activity. Lipid peroxidation was assessed by malondialdehyde which is produced due to oxidative breakdown of lipids. Polyunsaturated fatty acids were deduced when compared with that of the bleomycin group. Glutathione-S-transferase which is essential for stimulation of antioxidant enzymes, ROS detoxification and thiol group levels in the lungs were significantly increased by rosemary extract, whereas in the bleomycin group, they are decreased giving us hope for using this plant for treating pulmonary fibrosis [84].

Nigella sativa

Nigella sativa (black cumin), which is used as a traditional Tunisian herbal medicine, in which oil extracted from seeds denoted by NSO, attenuates bleomycin-induced pulmonary fibrosis. Immunohistochemical studies determined that this extract reduced the concentration of TGF-β in lung fibrocytes suggesting NSO can be used as an effective anti-inflammatory and anti-fibrotic agent. Carnosine present in this extract has been shown to reduce lipoxidation products and inhibit protein crosslinking. High levels of histidine during the NSO treatment could lead to the synthesis of carnosine, which promotes glycation of proteins and oxidative damage by its anti-inflammatory and antioxidant properties. Histological analysis determined that NSO-treated ones showed a rise in choline which was accompanied by extracellular matrix formation and structural disruption of the cell membrane in the alveoli [85].

Pistacia lentiscus

Pistacia lentiscus oil containing linoleic and palmitic acid as major constituents showed a protective effect against bleomycin-induced lung fibrosis by reversing all bleomycin-induced oxidative stress parameters like TGF-β, lipid peroxidation, superoxide dismutase and catalase disturbances by its antioxidant properties. The polyunsaturated fatty acids present in the extract acts as a major compound for exhibiting rich antioxidant properties [86].

Linum usitatissimum L.

The *Linum usitatissimum* L. herb is also known as flaxseed or linseed. Bleomycin administration followed by flaxseed oil treatment decreased the bleomycin-induced increased level of glucose, proline and glyceride rates in bronchoalveolar lavage fluid (BALF). The histological results showed a decline in inflammatory index and fibrosis score. This seed oil which constitutes linoleic, arachidonic, dihomo-γ-linoleic and docosapentaenoic acids significantly decreased the levels of thiobarbituric acid reactive substance in the rat lungs and raised levels of superoxide dismutase, catalase and fatty acids stimulating anti-inflammatory reactions in erythrocytes which showed that treatment with this oil significantly attenuated pulmonary damage induced by bleomycin [87].

Passiflora edulis

Passiflora edulis a purple passion fruit contains three major components quercetin-3-O-glucoside, cyanidin-3-O-glucoside and edulilic acid. Peel extract of this passion fruit attenuates bleomycin-induced pulmonary fibrosis. It has anti-inflammatory activity as indicated by a decrease in neutrophil accumulation and MPO activity in BALF and lung tissue respectively. Pre-treatment with this plant extract significantly restored bleomycin-induced reduction of superoxide dismutase activity and myeloperoxidase and increased hydroxyproline and collagen formation to normal showing its curative effects in treating pulmonary fibrosis [88].

Tanacetum parthenium

Parthenolide is a sesquiterpene lactone that can be extracted from feverfew (*Tanacetum parthenium*) shoots. Parthenolide via the NF-κB/Snail signalling pathway had been shown to attenuate bleomycin-induced pulmonary fibrosis. Parthenolide in a dose-dependent manner abridged the viability of lung fibroblasts. Wound healing assay determined its influence on the cellular migration of lung fibroblasts. Parthenolide-treated cells exhibited a delay in wound closure and inhibits the expression of transcription factors. Reduced inspiratory and expiratory resistance with a rise in dynamic compliance compared to mice treated with bleomycin suggested that parthenolide attenuates bleomycin-induced pulmonary fibrosis. The inflammatory cytokines like TNF-α, TGF-β and IL-4 decreased significantly in mice treated with parthenolide in a dose-dependent manner compared to untreated mice which showed that parthenolide inhibits the inflammatory responses which lead to pulmonary fibrosis. The parthenolide-treated groups exhibited a substantial reduction in collagen deposition. Parthenolide increased matrix metalloproteinase MMP1 [110] levels and decreased Col-1 collagenase [89]. Parthenolide inhibits IκB kinase which is an enzyme complex that is involved in proliferating the cellular response to inflammation; NFκB activation presents a vital part in regulating the immune response during infection in cystic fibrosis cells and mice [111].

Curcuma longa

Curcumin (diferuloylmethane), a polyphenol, is the major active component of turmeric which is a rhizomatous herbaceous perennial plant *Curcuma longa* that has antioxidant, anti-cancer, anti-inflammatory properties [112, 113]. Curcumin has the ability to suppress pulmonary fibrosis induced by bleomycin. Bleomycin causes a significant rise in total cell numbers, protein, angiotensin-converting enzyme and alkaline phosphatase activities in BALF and also increases TNF-α release by alveolar macrophages. Bleomycin also showed an increase in superoxide and nitric oxide in a cell culture medium and an increase in the lung hydroxyproline content. All the above-mentioned effects of bleomycin were reduced by curcumin [90]. Moreover, it stops proliferation of lung fibroblasts, myofibroblast differentiation and collagen secretion by IPF fibroblasts. Hence, these studies affirm that curcumin can be used in IPF treatment [114].

Cordyceps sinensis

Cordyceps sinensis is a fungal species used in Chinese medicine. It reduces TGF-β1-dependent EMT by the presence of a soluble polysaccharide component in its crude extract [115]. Cordycepin (3′-deoxyadenosin), which is present in *Cordyceps sinensis* extract, is an adenosine analogue and the active ingredient, responsible for the reverse back mechanism of EMT [91, 116].

Salvia officinalis

Salvia officinalis is a well-reputed medicinal plant that consists of good amounts of phenolic compounds. Leaf extract of this plant was found to attenuate bleomycin-induced pulmonary fibrosis and oxidative stress in rats. The reduced catalase activity in bleomycin-induced rats was restored when compared with that of the control group with this treatment and also reported that it showed an effect on superoxide dismutase, lipid peroxidation, oxidative stress and fibrotic score which was decreased when given in specific content [92].

Silybum marianum L.

Silymarin extracted from *Silybum marianum* L., commonly known as milk thistle belongs to the family Asteraceae, alleviates bleomycin-induced lipid peroxidation and pulmonary toxicity. Silymarin induction to bleomycin-administered mice resulted in a significant reduction in thiobarbituric acid reacting substances, IL-6, TNF-α, myeloperoxidase activity. This treatment leads to a substantial rise in catalase and pulmonary glutathione, all favouring in reducing the impact of pulmonary fibrosis [93].

Oxalis corniculata

Oxalis corniculata, also known as creeping wood belongs to the family Oxalidaceae. It is used in the amelioration of CCl_4 induced pulmonary toxicity, and so, it can also be used to treat pulmonary fibrosis. This extract dose dependently prevented the alterations caused by carbon tetrachloride like thickening of alveolar walls, rupturing of the lung alveolar septa and causing damage to cells with the subsequent collapse of blood vessels due to the build up of degenerated blood cells [117]. It is a rich source of C-glycosyl flavones which are isovitexin, swertisin and isoorientin [95].

Phyllanthus emblica

Phyllanthus emblica leaf extract, due to the presence of polyphenolics and other active components, may have an important role in repairing the damaged lungs instigated with CCl_4 that induced production of free radicals and toxicity in the lungs in rats. The polyphenolic constituents present in methanolic leaf extract are gallic acid, kaempferol, caffeic acid and rutin. It constitutes pyrogallol as an antiproliferative compound [97]. Methanolic extract of the plant (dried) solid extract which constitutes total flavonoid and phenolic content is tested for its antioxidant potential by 1-diphenyl-2-picryl-hydrazyl (DPPH) radical scavenging activity, nitric oxide scavenging assay and lipid peroxidation assay. Sprague-Dawley male rats were taken to test the effect of plant extract on pulmonary fibrosis and stated that this has a significant role in repairing pulmonary fibrosis [98].

Angelica sinensis

Angelica Sinensis root extract which constitutes polysaccharides when given intragastrically to Sprague-Dawley rats that were previously treated with bleomycin to induce pulmonary fibrosis showed suppressed fibrogenesis and EMT [99].

Citrus reticulate

Citrus reticulate alkaline extract of pericarp given orally to bleomycin-induced Sprague-Dawley male rats had shown a preventive effect against pulmonary fibrosis by upregulation of MMP-9 expression and inhibition of the expressions of TNF-α and TIMP-1. Human embryonic lung fibroblasts are used for evaluating the inhibitory effect in vitro [100]. Flavanone glycosides namely hesperidin, narirutin and rutin are present in relatively large amounts in peel and rutin has antioxidant capabilities [101].

Houttuynia cordata

Houttuynia cordata, a herbaceous perennial plant, exhibits antiviral, anti-inflammatory, immunologic, antibacterial, antimutagenic, anticancer and antioxidative pharmaceutical activities. Various bioactive compounds present include thirteen amino acids of which six are essential amino acids, flavonoids, volatile oils and water-soluble polysaccharides [118]. The aqueous extract of this plant taken orally can have a protective effect on bleomycin-induced pulmonary fibrosis. IFN-γ and TNF-α which are increased in bleomycin-induced models were significantly suppressed after treatment with this plant extract [102].

Carthamus tinctorius L.

Carthamus tinctorius L. is a bushy herbaceous annual or winter annual widely known as safflower or false saffron is used as a traditional medicine for various health conditions [119]. Hydroxysafflor yellow A (HSYA) is an active component extracted from aqueous extract of this plant. In mice, it had been known to attenuate bleomycin-induced pulmonary fibrosis. HSYA reduced the lung consolidation area, collagen deposition, TGF-β1, α-SMA and collagen I mRNA levels. It repressed the increase of Smad3 phosphorylation, expression of α-

SMA and expression of collagen I mRNA brought by TGF-β1 that facilitate EMT [103].

Eriobotrya japonica

Eriobotrya japonica, a loquat, is a large evergreen shrub which contains triterpene acids that can be used as a prophylactic for treating pulmonary fibrosis due to its antifibrosis effect. Triterpene acids present constitute oleanolic acid, euscaphic acid, arjunic acid and ursolic acid. The antifibrosis effect of these triterpene acids of loquat was determined in bleomycin-treated rats. These triterpene acids of loquat showed a reduction of collagen content in the lung parenchyma and decreased the number of cells. These decreased TNF-α mRNA and TGF-β1 expression in the model group suggest that these could downregulate TNF-α mRNA expression and TGF-β1 [104].

Centella asiatica

Centella asiatica herbs contain madecassoside, a triterpenoid saponin which ameliorates bleomycin-induced pulmonary fibrosis in mice by reducing the deposition of collagen. It decreased TGFβ1 and α-smooth muscle-acting expressions and also inhibited the Smad2 and Smad3 phosphorylations in the lung tissues. It attenuated oxidative damage and inflammation by reducing total leukocytes in the BALF and also reducing malondialdehyde level, myeloperoxidase activity and increasing SOD activity and glutathione level in lung tissues. Thus, madecassoside ameliorates pulmonary fibrosis by preventing extracellular matrix deposition, which might be achieved mainly through oxidative stress, attenuating inflammation and resultant overexpression of TGFβ1 [105]. In this way, plants can be used in treating IPF. The therapeutic effect of plants on various factors and pathways leading to IPF is tabulated in Table 4.

Isoquinoline alkaloids

Isoquinoline alkaloids are tyrosine-derived plant alkaloids with an isoquinoline skeleton. Among them, benzylisoquinoline alkaloids form an important group with potent pharmacological activity. Biosynthesis of isoquinoline alkaloids proceeds via decarboxylation of tyrosine or DOPA to yield dopamine, which together with an aldehyde (4-hydroxyphenylacetaldehyde) derived from tyrosine convert to reticuline, an important precursor of various benzylisoquinoline alkaloids. Among various isoquinoline alkaloids like berberine, magnoflorine, tetrahydropalmatine and jatrorrhizine are synthesized in plants belonging to the families Papaveraceae, Berberidaceae, Fumariaceae, Menispermaceae, Ranunculaceae and Rutaceae, and Annonaceacan plays an important role to treat pulmonary fibrosis by acting on specific inflammatory factors and by acting on various metabolic processes that commonly leads to pulmonary fibrosis.

Berberine

Berberine is an isoquinone plant alkaloid, which is a quaternary ammonium salt formed from the protoberberine group. Benzyl isoquinoline alkaloids found in plants are known for their broad range of pharmacological activities to treat multiple diseases [120]. Berberine can be used to treat idiopathic pulmonary fibrosis. Administration of berberine significantly improved bleomycin-induced histological alterations by decreasing the inflammatory cell infiltrate in bronchoalveolar lavage fluid (BALF). Berberine had significantly blocked the accumulation of collagen with an equivalent decline in the level of hydroxyproline. Bleomycin induced activation of nuclear factor kappa β (NF-β) which controls the expression of IL-1β and TNF-α gene in monocytes and macrophages is inhibited by berberine. It repressed its downstream target inducible nitric oxide synthase (iNOS) [121]. Outstandingly, berberine showed target attenuation of key pro-fibrotic mediator, TNF-α and TGF-β1against bleomycin-induced fibrosis by activating Nrf2 and suppressing fibrotic events mediated by NF-β and TGF-β1 [76]. Various signals are carried by serine/threonine kinase receptors through the cell surface towards the intracellular mediators by the TGF-β superfamily member known as Smads which upon initiation causes their translocation from the cytoplasm towards the

Table 4 The therapeutic effect of plants on various factors and pathways leading to IPF

S. no.	Pathway responsible for IPF	Compounds responsible and effect of plant extracts	
		Increase	Decrease
1.	Oxidative stress regulations	GSH, CAT, SOD, GPx	ROS, MDA, NOS, NO, MPO
2.	Autophagy inhibition		LC3A, beclin
3.	Signalling pathway regulation	Nrf2-Keapl	TGF-β1/Smads; ROS/MAPK; NF-kB
4.	EMT reversion	E-Cadherin	Vimentin, α-SMA, Snail
5.	Inflammation regulation		TNF-α, IL-1β,4,6,8,10,13,17,18
6.	Fibrotic regulation		MMP-2,9; collagen, Smad 2/3; TIMP
7.	Other roles	IFN-γ	PDGF, hydroxyproline

nucleus to control gene expression [122, 123]. Non-Smad and Smad signalling cascades, mediated by TGF-β1, act as chief players in accelerating pulmonary fibrosis of which berberine eased the raised expression of fibrotic markers, fibronectin, α-smooth muscle actin (α-SMA) and collagens I and III and reversed structural changes induced by bleomycin in the lungs and inhibited the bleomycin-induced increase in p-Smad 2/3 and enriched Smad 7 expression. It obstructed the activation of focal adhesion kinase (FAK) and phosphatidylinositol 3-kinases (PI3K/Akt). Protein kinase B known as Akt is a serine/threonine-specific protein kinase that plays a crucial role in cell proliferation, apoptosis, transcription, glucose metabolism and cell migration. Berberine targeted inhibition of dysregulated Smad and FAK-dependent PI3K/Akt mTOR signalling axis (mammalian target of rapamycin) reduced the fibrotic effects of bleomycin [124]. Berberine had been shown to act against dysregulation induced by bleomycin with a successive rise in phosphatase and tensin homologue (PTEN) expression. PTEN through the action of its protein product phosphatase acts as a tumour suppressor gene where it is involved in the regulation of the cell cycle by preventing cells from rapid growth and division. It plays a crucial role in cell cycle arrest, apoptosis and possibly cell migration [125]. Epithelial PTEN controls fibrosis and acute lung injury by regulating the integrity of alveolar epithelial cells. Inactivation of PTEN exacerbates the TGFβ1-induced interruption of tight junctions in epithelial cells of the lungs [126, 127]. Berberine initiating autophagy is supported by the rise in Beclin-1 and LC3-II levels with enriched autophagosome formation. In general, LC3-II and Beclin-1 expressions in two major types of lung cancer which are adenocarcinoma and squamous cell carcinoma, in which both mRNA and protein levels of LC3-II and Beclin-1 which are autophagy-related genes were considerably reduced in lung cancer tissues suggesting autophagy may be involved in the pathogenesis of lung cancer [128]. Berberine through downregulation of matrix metalloproteinases (MMP) will inhibit pulmonary metastasis in B16F-10 melanoma cells. B16-F10 cells are used to develop a primary tumour model [129]. MMPs produced by metastatic cells have a main role in the degradation of the basement membrane, which is crucial for the invasiveness of metastatic cells. Berberine significantly suppressed tumour nodule formation induced by B16F-10 melanoma, boosted the survival of tumour-bearing mice and decreased various biochemical parameters associated with lung metastasis [130]. Berberine shows protective effects on lung injury induced by radiation means of intercellular adhesion molecular-1(ICAM-1) and TGFβ1in patients with lung cancer [131].

Azithromycin is an acid-stable macrolide antimicrobial drug which can be orally administered [132]. It reduces lung inflammation in mice suffering from cystic fibrosis and increases its survival [133]. This antibiotic attenuates the virulence of *Pseudomonas aeruginosa*, weakens its capability to form biofilms of fully polymerized alginate and upturns its sensitivity to complement and stationary-phase killing [134]. *P. aeruginosa* is one of the major opportunistic pathogens which can cause chronic lung infection, cystic fibrosis. Cystic fibrosis is initiated by a mutation in the conductance regulator gene in the transmembrane which encrypts a cyclic AMP-regulated chloride ion channel [135]. The formation of biofilm promotes cystic fibrosis development and limits the antimicrobial efficacies of current antibiotics. Berberine in a gut-dependent manner with azithromycin shows synergistic activity against *P. Aeruginosa* isolated from a patient's lung with cystic fibrosis in vitro and in vivo [136].

Magnoflorine

Magnoflorine is a quaternary benzylisoquinoline alkaloid of the aporphine structural subgroup which has been extracted from numerous species of the Menispermaceae family. It is an aporphine alkaloid, i.e. (S)-corytuberine in which the nitrogen has been quaternized by an additional methyl group. It has a role as a plant metabolite. It is an aporphine alkaloid and a quaternary ammonium ion. It is derived from (S)-corytuberine [137]. Acute lung injury (ALI) which is known worldwide as a severe respiratory disease accompanied by symptoms which include sepsis, neutrophilia and lung inflammation produced by bacteria, trauma, pneumonia and lipopolysaccharide. ALI is induced by various groups of stimulants like an endotoxin released from Gram-negative bacteria which cause intravascular coagulation, leukocytosis and endotoxic shock in mice. The results of histopathological changes and MPO activity showed that magnoflorine considerably alleviated the lung injury induced by lipopolysaccharides (LPS). Quantitative polymerase chain reaction (qPCR) analysis showed that this alkaloid dose-dependently reduced the pro-inflammatory cytokines IL-6, IL-1β and TNF-α expression. Immunofluorescence assay showed that LPS-induced levels of Toll-like receptor 4 (TLR4) were inhibited by magnoflorine treatment. The Western blotting technique used in order to detect the expression of MAPK and NF-kB signalling pathways exhibited that this alkaloid reduced the levels of phosphorylated p38, p65, extracellular signal-regulated kinase(ERK), c-Jun amino-terminal kinases (JNK) and nuclear factor of kappa light polypeptide gene enhancer in β cell inhibitor alpha (IkBα), which indicate that magnoflorine could protect against LPS-induced inflammation in ALI at least partially by inhibiting TLR4 mediated MAPK and NF-kB signalling pathways. ERK's

role in cell division and of these enzyme inhibitors are being discovered as anticancer agents. The JNKs are critical regulators of transcription and p38 MAPKs are initiated by environmental stresses and inflammatory cytokines can contribute to autoimmunity and asthma [138, 139].

Tetrahydropalmatine

Tetrahydropalmatine (THP), an isoquinoline alkaloid is found in various plant species, significantly reduces the harmful effects of radiation and oxidative modification in the lungs. THP lessened the lung injury by inhibiting lung inflammation, apoptosis, cell recruitment in BALF and its protein levels, decreasing THP collagen content of lung tissues thus showing the protective effect of THP treatment for pulmonary fibrosis [140].

Jatrorrhizine

Jatrorrhizine is a protoberberine alkaloid [141]. Jatrorrhizine in thioacetamide-traumatized rat liver has been testified to have an anti-inflammatory effect and proven to recover blood flow as well as inducing mitotic activity. Jatrorrhizine has antifungal and antimicrobial activities. This alkaloid noncompetitively binds to the active site and inhibits monoamine oxidase [142]. It plays an acute neuroprotective role in apoptosis brought by H_2O_2 through its anti-oxidative actions and can be used as a novel therapeutic for its increased bioavailability to treat Alzheimer's disease [143, 144].

Thus, Isoquinoline alkaloids enable the reduction of pulmonary fibrosis by acting on various mechanisms that lead to the development of the disease. As a result, isoquinoline alkaloids can be used in prophylactic or therapeutic treatment for pulmonary fibrosis.

Conclusion

This review emphasizes on the beneficial effects of plants and their bioactive compounds that can be used for treating IPF where these plants' bioactive compounds exhibit prophylactic or therapeutic properties providing us a natural source to treat pulmonary fibrosis, replacing the use of synthetic drugs that cause side effects. To determine the effects of various bioactive compounds for treating pulmonary fibrosis, In vitro studies were performed on model organisms (mice, rat) which are induced with pulmonary fibrosis. Effects of plants and the bioactive compounds on pulmonary fibrosis were determined by measuring the extent of inflammation, collagen formation and oxidative stress. A wide range of factors which regulates pulmonary fibrosis such as hydroxyproline, collagen-I, NF-kB, PDGF, MMP-9, MCP-1, TIMPs, iNOS, α-SMA, IκB, MAPK, PTEN, ICAM-1, TGF-β, TNF-α, IFN and interleukins; SOD, catalase and glutathione-S-transferase; and MPO, MDA, ROS and RNS levels in pulmonary fibrosis-induced model organisms before and after administration of plant extract were measured. Bioactive compounds present in various plants which include isoquinoline alkaloids like berberine, magnoflorine, tetrahydropalmatine and jatrorrhizine present in plants *Mahonia aquifolium*, *Tinospora cordifolia*; β-caboline alkaloids present in *Arenaria kansuensis*; polysaccharides in *Angelica Sinensis*; lactones like ellagic acid present in *Punica granatum*; flavonoids in *Passiflora edulis*, *Silybum marianum*, *Oxalis corniculata*, *Phyllanthus emblica*, *Citrus reticulate*, *Carthamus tinctorius* L; triterpene acids in *Eriobotrya japonica*, *Centella asiatica*; fatty acids in *Pistacia lentiscus*, *Linum usitatissimum*; and catechins like epigallocatechin-3-gallate (EGCG) in *Camellia sinensis* possesses beneficial properties in treating IPF. Hence, the plants and their bioactive compounds mentioned above provide a promising therapeutic approach for IPF treatment.

Abbreviations

IPF: Idiopathic pulmonary fibrosis; ECM: Extracellular matrix; EMT: Epithelial mesenchymal transition; TNF-α: Tumour necrosis factor alpha; IL: Interleukins; TGF-β: Transforming growth factor beta; MCP-1: Monocyte chemo attractant protein; IP-10: Interferon-gamma-inducible protein; ROS: Reactive oxygen species; Th 17: T helper cells; M1 and M2: Macrophages 1 and macrophages 2; MMP: Matrix metalloproteinases; PDGF: Platelet-derived growth factor; Th2: T helper type 2; IFN-γ: Interferon gamma; WISP-1: WNT1-inducible-signalling pathway protein 1; WNT: Wingless-related integration site; PTEN: Phosphatase and tensin homologue; PI3Ks: Phosphoinositide 3-kinases; BLM: Bleomycin; CCl_4: Carbon tetrachloride; TIMP-1: Tissue inhibitor of metalloproteinase 1; MMP-9: Matrix metallopeptidase 9; SOD: Superoxide dismutase; MPO: Myeloperoxidase; MDA: Malondialdehyde; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; α-SMA: Alpha-smooth muscle actin; EGCG: Epigallocatechin-3-gallat; AE2: Anion exchange protein 2; RNS: Reactive nitrogen species; CXCL: Chemokine (C-X-C motif) ligand; PCEB: *Pistacia chinensis* bark; BALF: Bronchoalveolar lavage fluid; DPPH: 1-Diphenyl-2-picryl-hydrazyl; HSYA: Hydroxysafflor yellow A; DOPA: Dihydroxyphenylalanine; NF-β: Nuclear factor kappa β; iNOS: Inducible nitric oxide synthase; FAK: Adhesion kinase; PI3K/Akt: Phosphatidy linositol 3-kinases; mTOR: Mammalian target of rapamycin; LC3-II: 1A/1B-light chain 3; ICAM-1: Intercellular adhesion molecular-1; ALI: Acute lung injury; AMP: Adenosine monophosphate; LPS: Lipopolysaccharides; qPCR: Quantitative polymerase chain reaction; TLR4: Toll-like receptor 4; ERK: Extracellular signal regulated kinase; JNK: c-Jun amino-terminal kinases; IkBα: Nuclear factor of kappa light polypeptide gene enhancer in β cell inhibitor alpha; MAPK: Mitogen-activated protein kinases; THP: Tetrahydropalmatine; TIMP: Tissue inhibitor of metalloproteinases; Nrf2: Nuclear factor erythroid 2-related factor 2; Keap1: Kelch ECH associating protein 1; GPx: Glutathione peroxidase; CAT: Catalase; GSH: Glutathione; TBARS: Thiobarbituric acid reactive substances; POD: Peroxidase; NO: Nitric oxide; GST: Glutathione-S-transferase; lncRNA DANCR: Differentiation antagonizing non-protein coding RNA; CTGF: connective tissue growth factor

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