https://doi.org/10.48047/AFJBS.6.5.2024. 9599-9666

AfricanJournalofBiological Sciences

"Navigating Pulmonary Fibrosis: Insights into Cytokines, Therapeutic Avenues, and Natural Solutions"

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Article History
Volume 6, Issue 5, 2024
Received: 10 May 2024
Accepted: 01 Jun 2024
Published : 20 Jun 2024
doi:*10.48047/AFJBS.6.5.2024. 9599-9666*

Abstract

Pulmonary fibrosis (PF) is a progressive and often fatal lung disease characterized by the accumulation of excessive extracellular matrix and scarring. Despite recent advancements with pirfenidone and nintedanib, which slow disease progression, effective treatments to halt or reverse PF remain elusive. This review explores the multifaceted role of cytokines in PF pathogenesis, focusing on transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), interleukins (ILs), and tumor necrosis factor-alpha (TNF-α). Understanding the intricate interplay between these cytokines is crucial for developing targeted therapeutic interventions. Additionally, we discuss emerging pharmacological strategies, such as PDGF receptor inhibitors and IL modulation, alongside natural solutions that may offer complementary approaches to managing PF. By elucidating the mechanisms underlying cytokine-mediated fibrotic alterations, this review aims to provide insights into potential avenues for improving PF treatment outcomes.

Keywords- Pulmonary Fibrosis, Cytokines, Natural Products, therapeutic targets, Covid-19.

Abbreviation- Pulmonary fibrosis(PF), Tissue inhibitor of metalloproteinase (TIMP),Yin Yang 1 (YY1), α-smooth muscle actin (α-SMA), Extracellular signal-regulated kinase (ERK), Type 2 congenital lymphocytes (ILC2), Jun N-terminal kinase (JNK), Matrix metalloproteinase (MMP), Mesenchymal progenitor cells (MPC), Extra cellular matrix (ECM), Epithelial mesenchymal transition (EMT), Focal adhesion kinase (FAK).

1. Introduction

Pulmonary fibrosis (PF) is a prevalent, advancing, irreversible, and ultimately deadly long-term lung condition marked by the accumulation of excessive extracellular matrix and scarring in the lungs, as mentioned by (Wan*et al.*, 2023). It leads to functional impairments, severe respiratory issues, and ultimately, mortality, with a median survival time of 2 to 4 years following diagnosis.(Hosseini*et al.*, 2021) mentioned that PF physiopathology is composed of three main processes: Alveolar epithelial lesions resulting from genetics and environment, vascular disorders involving neovascularization of nonfibrotic tissues, and oxidative stress induced by reactive oxygen species.

(Selvarajah*et al.*, 2023) pointed out in his studies that the approval of pirfenidone (Esbriet) and nintedanib (Ofev) marked a breakthrough in treating IPF by slowing its progression. However, they don't stop or reverse the disease and come with significant side effects.

(Wang*et al.*, 2021) reported that, the yearly incidence of IPF varies between 0.9 and 13.0 per 100,000 people globally, has a severely devastating clinical course, and has a significant socioeconomic impact.The average age of IPF patients is 65–70 years, with incidence rising with age globally. (Maher*et al.*, 2021) pointed out that thefactors contributing to the increase include aging populations, greater disease awareness, and improved diagnostics. IPF affects males more than females and is associated with risk factors like smoking, exposure to metal/wood dust, and genetic factors.

(Dhooria*et al.*, 2022) reported that the adjusted prevalence estimates for each country in the Asia-Pacific area ranged from 0.57 to 4.51 per 10,000 of the population; in European countries, they ranged from 0.33 to 2.51 per 10,000. In North America, the prevalence estimates ranged from 2.40 to 2.98 per 10,000. United States demonstrated adjusted prevalence of 2.40 per 10,000.[5] In 2022, there were 2,005 subjects enrolled in India for a study. Among them, 17.0% were identified as having IPF. The leading estimates for the raw national burden of IPF are in the range of 75,000 to 150,000 cases (in thousands), while the alternate estimates for IPF range from 46,000 to 91,000 cases (in thousands).

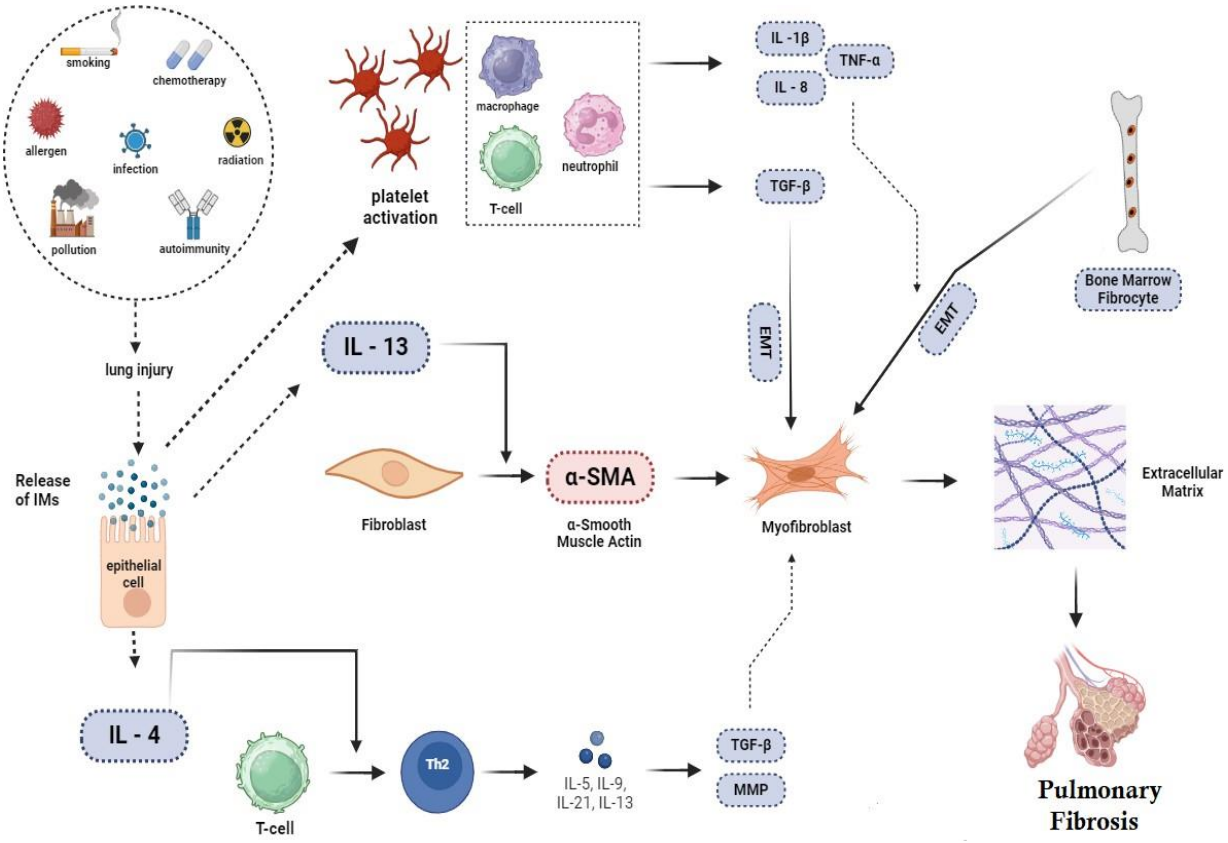

Figure 1. Pathogenesis of PF

2. Cytokines related with fibrotic alterations in the lung

2.1 TGF-β

TGF-β isoforms are key regulators ensuring the balance between appropriate inflammatory responses and avoiding excessive matrix production (fibrosis) or tissue destruction (emphysema or bronchiectasis). Sheppard(2006) mentioned in his studies that TGF-βacts as a chemotactic factor for macrophages and mast cells, enhancing their retention within the airway epithelium.

Zhangand Phan(2004) proposed that, TGF-β stimulates and differentiates various cell types, including mesenchymal cells, into myofibroblasts, which are key contributors to fibrotic lesions. Over time, these myofibroblasts replace eosinophils as the primary drivers of fibrosis progression.

Wilson & Wynn (2009) proposed that the activity of TGF-β is tightly regulated post-transcriptionally by latency-associated protein (LAP), which maintains TGF-β in an inactive state until release by agents commonly found in fibrotic conditions.(Santana*et al.*, 1995) addressed in his studies,the activated TGF-β induces the synthesis of several extracellular

matrix (ECM) molecules such as fibronectin, type 1 collagen, and tenascin. TGF-β not only promotes ECM production but also reduces matrix degradation by regulating protease and inhibitor expression.

(Sime*et al.*, 1997) reported that, the overexpression of active TGF-β1 in rats resulted in significant histopathological effects, including inflammatory cell accumulation dominated by mononuclear cells. The inflammation induced by TGF-β1 overexpression led to rapid pulmonary fibrosis, beginning around blood vessels and airways, and spreading throughout the lung interstitium, with increased fibroblast proliferation and ECM deposition extending to the pleural surface.

2.2 PDGF

Platelet-Derived Growth Factor (PDGF) stands as a pivotal factor in numerous physiological processes, making it a focal point of research and therapeutic exploration.(Dadrich*et al.*, 2016)mentioned that, the PDGF family comprises of four subunits (PDGF-A,B, C,D), which activate PDGF receptor tyrosine kinases α and β, mediating their biological functions.

(Sasaki*et al.*, 2000)proposed that, PDGF, along with the cytokines causing inflammation, such as IL-1β and TNF-α, not only independently stimulates lung fibroblasts to generate MMPs like MMP-3 and MMP-9, crucial for breaking down extracellular matrix proteins, but also amplifies this effect when combined, leading to increased MMP production, cell proliferation, and chemotactic responses in lung fibroblasts.

(Sun *et al.*, 2016) highlighted in his studies that,different forms of PDGF are implicated in lung remodeling and fibrosis, with PDGF-BB signaling playing a crucial role in these processes.PDGF-BB activation correlates with lung fibroblast proliferation in fibrotic conditions.It induces PRMT1 (protein arginine methyltransferase 1) expression, vital for fibroblast proliferation control. Inhibiting PRMT1 may offer a therapeutic target for reducing fibrosis in chronic inflammatory lung diseases.

(Aono*et al.*, 2005) pointed out that therapeutic interventions utilizing imatinib, aninhibitor for PDGF-tyrosine kinase targeting PDGFR (PGDF receptor), c-KIT (Cellular-Kit Proto-Oncogene), and Bcr-Abl (Breakpoint Cluster Region-Abelson Oncogene), have shown substantial efficacy in mitigating fibrosis in both bleomycin-induced and radiation-induced PF.

2.3 Interleukin (IL)

ILs constitute a family of cytokines primarily synthesized by lymphocytes, monocytes, or macrophages, exerting their effects on various cell types. (Qin *et al.*, 2023) proposed that characterized by complexity in both structure and role, interleukins perform a major function in diverse processes, notably immune regulation and inflammation within pulmonary tissue.

(Klee*et al.*, 2016 and Passalacqua *et al.*, 2017) reported that during the onset of PF, IL-1,4,6, 11, 13 perform a major function by fostering the multiplication and accumulation of pulmonary fibroblasts, promotingECM accumulation, promoting collagen production, and contributing to the restoration of lung tissue. (Szikszet *al.*, 2015 and Huang *et al.*, 2002) mentioned that IL-7, 10,12, 18 exert a mitigating influence by suppressing inflammatory factors and regulating immunity.

(She *et al.*, 2021) suggested that interleukin levels exhibit variations not only amongst individuals with and without PF but also across various phases of PF.

(Wang *et al.*, 2023) discussed in his studies that, IL-1stands as a key player in the emergence and advancement of lung fibrosis, emanating chiefly from macrophages, monocytes, fibroblasts, and endothelial cells. (Osei *et al.*, 2020) mentioned in his studies that, IL-1α and IL-1β are key players in activating pathways that lead to fibrosis. Both of them are potent inflammatory molecules, triggering immune cell activation and recruitment to the lungs. This exacerbates the inflammatory response linked to fibrotic lung conditions. They promote the proliferation and activation of fibroblasts, causing an excess accumulation of ECM proteins like collagen, fibronectin, and periostin, hallmark features of pulmonary fibrosis.

(She *et al.*, 2021) suggested that IL-4 has contrasting effects on pulmonary fibrosis. It promotes collagen production and fibroblast differentiation to myofibroblasts through the activation of JNK/ERK pathway. Conversely, IL-4 also limits T cell inflammation, thus reducing lung injury. (Huax *et al.*, 2003) suggested thatincreased IL-4 levels are detected in lung injury-induced fibrosis models, implicating its involvement in disease progression.Analysis of bleomycin-induced lung injury in IL-4-deficient mice revealed heightened early pathological manifestations.

(Groves *et al.*, 2016) reported that,IL-6 performs a multifaceted function in fibrotic diseases.(Dawson *et al.*, 2021) suggested that IL-6 stimulates fibroblast proliferation via MAPK activation and exhibits profibrotic effects dependent on epigenetic regulation.

Furthermore, (Li *et al.*, 2022) mentioned in his studies that, IL-6 contributes to apoptosis resistance in myofibroblasts, leading to persistent accumulation of extracellular matrix (ECM). Moreover, IL-6 dysregulates autophagy, exacerbating fibrotic processes.

(NG *et al.*, 2019)proposed in his studies that,IL-11 promotes myofibroblast activation and ECM deposition in response to various profibrotic stimuli, including TGF-β1, PDGF, FGF2, and IL-13.(NG *et al.*, 2020) reported that,IL-11 exacerbates lung fibrosis when administered or overexpressed in mice, resulting in collagen accumulation, parenchymal disruption, and activation of invasive fibroblasts akin to those in IPF. Conversely, inhibiting IL-11 signaling via pharmacological or genetic interventions yields therapeutic benefits by reducing pulmonary fibrosis and associated pathological signaling pathways such as ERK and SMAD.

(Passalacqua *et al.*, 2017) reported that,IL-13 stimulates fibroblast proliferation and extracellular matrix synthesis, induces pro-fibrotic cytokines, and is associated with increased collagen production. Studies in mice have shown that IL-13 overexpression induces lung fibrosis, while its neutralization attenuates fibrosis in bleomycin-induced lung injury.(Nie *et al.*, 2017)reported that,Akt1 was implicated in mediating the release of IL-13, particularly under IL-33 treatment, which activates macrophages.

(Szikszet *al.*, 2015) demonstrated that, elevated IL-10 levels in silica-exposed mice lungs and bronchoalveolar lavage, coupled with increased lung inflammation in IL-10 knockout mice, highlight IL-10's role in mitigating pulmonary fibrosis, as demonstrated by genetic IL-10 delivery reducing TGF-β production in bleomycin-induced fibrosis models.

(Huang *et al.*, 2002) suggested that IL-7 induces Smad7 expression, resulting in the inhibition of TGF-β pathway activation. and collagen synthesis in PF fibroblasts.

Role of all the interleukins is depicted in table 1.

Table 1 Involvement of interleukins in PF.

Interleukin	Pro-Inflammatory/ anti-Inflammatory[a]	Pro-fibrotic/ anti-Fibrotic[b]	Mechanisms	References
IL-1α	▲	▲	Encourage fibroblast to adopt a pro-inflammatory phenotype and release cytokines.	(Huang *et al.*,2002)
IL-1β	▲	▲	(Huang *et al.*, 2002) Stimulates the influx of lymphocytes and neutrophils, resulting in lung fibrosis and inflammation. Stimulate fibroblasts by IL-1β to synthesize collagen and fibrin.	(Gasse *et al.*,2007)
IL-4	○	▲	Stimulate fibroblasts to express the collagen gene. Prompts myofibroblast transformation by stimulating JNK/ERK signalling.	(Sempowski *et al.*, 1996)
IL-5	○	▲	Facilitates lung eosinophil recruitment, triggering production of cytokines that cause fibrosis.	(Gharaee-Kermani*et al.*,1998)
IL-6	**Dual role**	▲	Released by polarised M2-like macrophages in the bleomycin-induced fibrotic milieu, combines with IL-4 & 13 to exacerbate fibrotic condition in mice. Plays a fibrogenic and fibrosis-inhibiting effect on macrophages in the late stages of PF and TIIAs in the early stages.	(Aumiller *et al.*,2013)

Table 1 Continued

Interleukin	Pro-Inflammatory/ Anti-Inflammatory[a]	Pro-fibrotic/ anti-Fibrotic[b]	Mechanisms	References
IL-7	○	▼	Mediates Smad7 activation via JAK/STAT signalling and produces fibrosis-inhibitory effect. Blocks phosphorylation of protein kinase C-δ induced by TGF-β in fibroblasts from lungs.	(Huang *et al.*,2002)
IL-8	○	▲	MPC-derived IL-8 autonomously stimulates the expansion, transformation and transit of MPCs. Moreover, via CXCR1/2 receptors it draws macrophages to fibroblastic focal points	(Yang *et al.*,2018)
IL-9	**Dual role**	▼	IL-9 protects against fibrosis of lung caused by Bleomycin and has anti-inflammatory properties. In order to prevent silica-induced lung fibrosis, macrophages produce more PGE2 when IL-9 is overexpressed. Mice that have had their lung fibrosis and inflammation caused by silica reduced when IL-9 is neutralised by a particular Ab.	(Sugimoto *et al.*, 2019)

IL-10	▼	▼	Prolonged overexpression of IL-10 can activate M2 macrophages, which in turn can lead to fibrosis.	(Kurosaki *et al.*, 2018)

Table 1 Continued

Interleukin	Pro-Inflammatory/ Anti-Inflammatory[a]	Pro-fibrotic/ anti-Fibrotic[b]	Mechanisms	References
IL-11	○	▲	Through the autocrine transmission of atypical ERK signal, IL-11 stimulates fibrin production and fibrosis. In vitro, IL-11 induces the transformation of fibroblast phenotype and amplifies ERK regulated collagen production.	(Ng *et al.*, 2019)
IL-12	○	▼	Th2 cells may become Th1 cells in response to IL-12, which would increase IFN-γ levels and inhibit fibroblasts from forming collagen.	(Keane *et al.*, 2001)
IL-13	○	▲	In IPF lung fibroblasts, IL-13 significantly boosts collagen I and α-SMA production. Controls the JNK signal.	(Guo *et al.*, 2015)

			Induces proliferation of fibroblast by blocking PGE2 synthesis and COX expression.	
IL-18	▲	▲	Upregulates Snail-1, α-SMA, and downregulates E-cadherin, IL-18 causes EMT and aids in bleomycin induced pulmonary fibrosis.	(Zhang*et al.*, 2019)

Table 1 Continued

Interleukin	**Pro-Inflammatory/ Anti-Inflammatory[a]**	**Pro-fibrotic/ anti-Fibrotic[b]**	**Mechanisms**	**References**
IL-22	▼	▼	Targets alveolar epithelia, inhibits EMT and has an anti-fibrotic impact.	(Liang*et al.*, 2013)
IL-23	○	▲	The generation of IL-17 by CD4+ T cells to induce PF is mediated by IL-23.	(Gasse*et al.*, 2011)
IL-25	○	▲	Facilitate fibroblast proliferation, differentiation, and collagen synthesis through interaction with IL-17BR. Fibrosis is encouraged by IL-25, which causes ILC2 to produce IL-13.	(Xu*et al.*, 2019)
IL-27	▼	▼	Release of IL-13 by ILC2 when triggered by IL-25, which causes fibrosis.	(Dong*et al.*, 2016)

IL-32 γ	▲	▼	Prevents fibrosis by blocking the activation of FAK and paxillin.	(Hong*et al.*, 2018)
IL-33	○	▲	Contribute to fibrotic process by producing M2 macrophages.	(Li*et al.*, 2014)
IL-37	▼	▼	Upregulates autophagy activity in affected lung tissue by increasing the level of LC3II.	(Kim*et al.*, 2019)

(a) Pro-inflammatory: ▲; anti-inflammatory: ▼ (b) Pro-fibrosis: ▲; anti-fibrosis: ▼; neither or unknown: ○

2.4 TNF α

Razzaque and Taguchi (2003)pointed out in his studies,TNF-α, a strong inducer of inflammation, is initially synthesized as a glycoprotein bound to the cell membrane and is cleaved into a biologically active 17-kDa monomeric peptide.

(Bolourani*et al.*, 2019) mentioned that,TNF-α, primarily released from M1 macrophages, alters the phenotype of macrophages and fibroblasts, promoting inflammation over tissue repair.Agostini and Gurrieri(2006) proposed that, TNF-alpha stimulates cellular interactions and cytokine/chemokine modulation. Moreover, TNF-alpha triggers fibroblast proliferation. (Bolourani*et al.*, 2019) reported that, even dormant fibroblasts respond to TNF-α, which stimulates the secretion of lumican and expression of integrins, perpetuating fibroblast activation in both autocrine and paracrine manners.

(Wan*et al.*, 2023) reported that, TNF-alpha induces the upregulation of vascular cell adhesion molecule. Furthermore, (Lin*et al.*, 2016) reported that, this includes the turning on of protein kinase C alpha (PKCα), resulting in the generation of oxidative molecules. ROS, in turn, activate MAPKpathways, including ERK1/2, p38 MAPK, and JNK1/2. This leads to the exacerbation of fibrotic condition.

(Hou*et al.*, 2018) reported that, in the model of pulmonary fibrosis induced by bleomycin, there is an elevation in TNF-alpha levels, accompanied by an increase in the expression of the NF-κB p65 subunit.

2.5 Chemokine (C-C motif) & (C-X-C motif) ligand (CCL & CXCL)

Cells producing cytokines are effectively attracted to injury sites by chemokine gradients. The CC and CXC chemotactic cytokine families have been extensively studied in fibrosis progression. (Suga*et al.*, 1999) mentioned in his studies, that people with IPF had higher levels of CCL2 in their blood and bronchoalveolar lavage (BAL) fluid.

(Sun*et al.*, 2011)reported that IL-10 can trigger macrophage activation via the CCL2/CCR2 pathway, resulting in fibroblast buildup and subsequent fibrotic degeneration.

(Muneesa*et al.*, 2021)highlighted in his studies that, CXCR3, the receptor for CXCL9, shows elevated expression near cells undergoing epithelial-mesenchymal transition (EMT) in IPF patients. Conversely, CXCL9 exhibits antifibrotic effects by inhibiting the TGF-β signaling pathway, reducing Smad2&3 phosphorylation in alveolar epithelial cells (AECs).

Agostini and Gurrieri(2006) proposed that, CXC chemokines, such as IL-8/CXCL8 and ENA-78/CXCL5, are elevated in PF and promote aberrant angiogenesis. This means that these chemokines contribute to the pathological vascular remodeling observed in PF.

Conversely,Agostini and Gurrieri(2006) mentioned in his studies, IP-10/CXCL10, exhibits fibrosis-limiting effects by attenuating fibroblast migration and reducing fibroblast accumulation. Additionally, IP-10/CXCL10 activates the chemokine receptor CXCR3, which performs a protective function in lung fibrosis by stimulating the production of interferon-gamma (IFN-γ).

Keane (2008) demonstrated that, experimental mice with pulmonary fibrosis induced by bleomycin, increased levels of CXCL2 and CXCL3 (ELR-positive) are associated with fibrosis, while decreased levels of CXCL10 and CXCL11 (ELR-negative) correlate with reduced fibrosis when administered exogenously.Furthermore, mice deficient in CXCR3 or CXCL10 exhibit increased mortality and progressive fibrosis, suggesting a protective role for these chemokines in limiting fibrosis.

3. COVID-19 and PF

At the forefront of COVID-19 stands SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), a virus surrounded by an envelope, known for its single-stranded, positive-sense RNA genome. (Guarino*et al.*, 2022; Cugno*et al.*, 2022 and Patrucco*et al.*, 2021)mentioned in his study that, this viral agent serves as the instigator of the ongoing pandemic. The primary avenue for human-to-human transmission has been predominantly attributed to respiratory droplets.(Hosseini*et al.*, 2020) discussed in his study that, SARS-CoV-2 is a coronavirus that is part of a family distinguished by its segmented RNA content and encapsulated form.Furthermore, (Tran*et al.*, 2022)reported that, the virus's spike protein, cleaved by various serine proteases, facilitates rapid transmission and infectivity.

3.1 Pathogenesis

In exploring the etiology of post-COVID-19 pulmonary fibrosis, two prominent theories have emerged: the "Two-hit hypothesis" positing a dual insult scenario involving genetic predisposition or pre-existing subclinical interstitial lung abnormalities, and the theory suggesting a direct effect of SARS-CoV-2on the profibrotic cascade, stated byAlrajhi NN, 2023.

3.1.1 "Two-hit hypothesis"

Alrajhi NN, 2023mentioned the "two-hit hypothesis" in his study, which suggests that the development of fibrosis involves two separate insults or triggers acting together. The first hit occurs when the virus along with other factors damage the pulmonary tissue. This initial insult affects either lungs already genetically predisposed to fibrosis or those with subclinical interstitial lung abnormalities (ILA), which are found in 7%–10% of people, in general. The second hit refers to additional insults or factors, such as prolonged mechanical ventilation, secondary bacterial infections, persistent inflammation, or other genetic and environmental factors. These secondary hits exacerbate lung injury and contribute to the progression of fibrosis, working in conjunction with the initial insult.

3.1.2 Direct effect of SARS-CoV-2 on the profibrotic cascade

(Tran*et al.*, 2022 and Alrajhi NN, 2023) addressed that, SARS-CoV-2 enters cells primarily through interaction with ACE2receptors, along with αvβ3 and αvβ6 integrins, which are located proximal to ACE2. Both elevated levels of ACE2 and αVβ integrins trigger activation of the fibrosis-promoting pathway, including the induction of TGF-β and the generation of reactive oxygen species.TGF-β drives fibroblasts to become collagen-producing myofibroblasts, responsible for accumulation of collagen. Reactive oxygen speciesexacerbate the inflammation process by inducing oxidative stress and activating pro-inflammatory signaling pathways.

4. Potential Targets for PF Therapy

A variety of treatment objectives have been recognized for addressing the course of therapy, diagnosis, and outlook of PF. Prominent therapeutic targets encompass oxidative stress, cell signalling mediators, growth factors, and transcription-related variables.

The envisioned treatment targetsare outlined in Figure 2.

4.1 Oxidative stress

Oxidative stress plays a pivotal role in the pathogenesis of pulmonary fibrosis (PF), contributing to disease initiation and progression. Elevated levels of reactive oxygen species (ROS) lead to cellular damage and inflammationwithin the lungs, exacerbating tissue injury and promoting fibrotic remodeling. Understanding the intricate interplay between oxidative stress and PF pathogenesis is critical for developing targeted therapeutic interventions to mitigate disease progression and improve patient outcomes.

(Estornut*et al.*, 2022)reported that, enzymes like NOXs, MPO, xanthine oxidase, and NOS contribute to ROS/RNS production in the lungs.

[Chereshet *al.*, 2013;Kato and Hecker 2020] reported that,NOX oxidoreductases have a vital function in cellular mechanisms by catalyzing reductions that generate ROS, which are involved in signaling, microbial defence, and tissue damage. Particularly, NOX1, NOX2, and NOX4 are prominently implicated in the onset and progression of pulmonary fibrosis.

Research findings of (Amara*et al.*, 2010)suggests that NOX4 is essential in modulating the phenotype of pulmonary myofibroblasts in IPF, influencing the α-SMA protein levels and procollagen I, regulating Smad2/3 activation, and facilitating fibroblast migration in response to TGF-β1 and PDGF-BB.(Hecker*et al.*, 2012)reported that, mice lacking NOX4 were shielded from bleomycin-induced lung fibrosis due to reduced epithelial cell death, and inhibiting NOX4 lowered ROS production, protecting against apoptosis. Notably, NOX4 deficiency had minimal impact on inflammationafter bleomycin injury, indicating that NOX4 primarily affects fibrosis by regulating epithelial cell death rather than inflammation.

(Veith*et al.*, 2019) demonstrated that, NOX2, integral to the innate immune response, predominantly acts in phagocytic cells IPF. It contributes to alveolar epithelial cell death via ROS production, heightened in IPF patient neutrophils, indicating a specific role in these cells. NOX2 deficiency in mice protects against fibrosis induction, potentially involving non-immune cell NOX2 expression.

4.2 Cell Communication Pathways

4.2.1 TGF-β/Smad signalling cascade

The TGF-β/Smad signalling cascade is a versatile signalling cascade pivotal in inflammation, tissue repair, and fibrogenesis. Yan and Ping(2014) mentioned that, TGF-β/Smad signalling cascadeexerts a critical functionin a number of events, like as epithelial injury, myofibroblast expansion, maturation, and the production of ECM.

Miyazono (2009) discussed in his study, TGF-β binds to its receptors, forming a complexthat phosphorylates Smad2 and Smad3. Furthermore, Smad4 is produces a complex with the phosphorylated form of Smad3 and Smad2. This complex undergoes moves into the nucleus, which facilitates the activation of transcriptionalregulators associated with EMT and encourages the EMT process.

(Jiang*et al.*, 2014) pointed out that, directly targeting TGF-β is challenging due to its multiple physiological functions, thus understanding its downstream signaling pathways may offer insights for developing novel fibrotic disorder treatments.Study performed by (Shi*et al.*, 2014)indicates that various active compounds found in natural products have the potential to ameliorate PF by modulating the TGF-β/Smad signalling cascade.

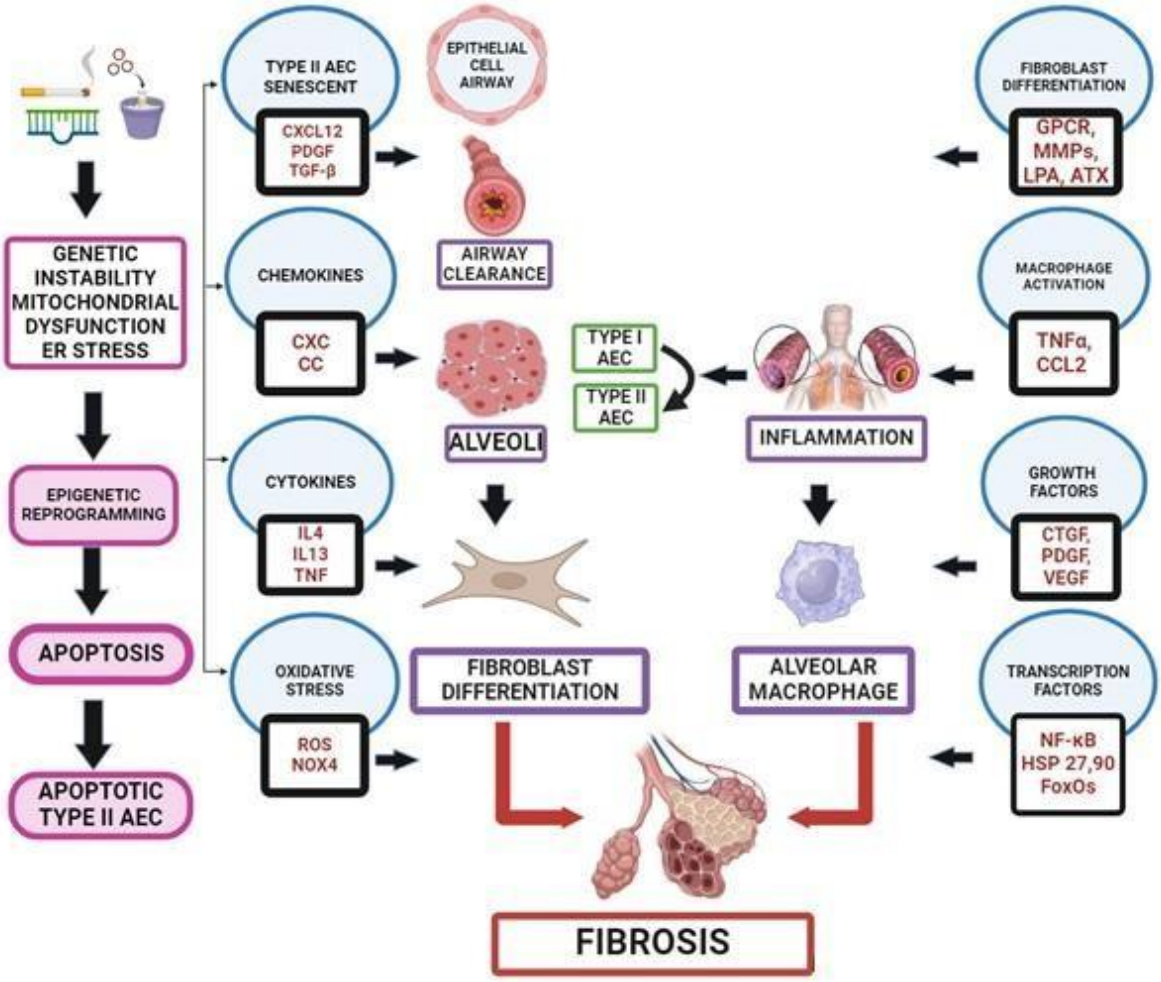

Figure 2. Envisioned treatment targets of PF

4.2.2 PI3K (Phosphoinositide 3-kinase) signalling cascade

PI3Ks are enzymes consisting of a regulatory subunit linked to a catalytic subunit, known as p110. (Margaria*et al.*, 2022) reported that, while p110α and p110β are widely expressed, p110δ and p110γ are specifically found in leukocytes.

Yan and Ping (2014) mentioned that, the PI3K-Akt signaling pathway has a fundamental significance in regulating cell proliferationand survival by preventing cellular suicide. Moreover, PI3K-Akt signaling interacts with various pathways such as VEGF, MAPK, and

focal adhesion, forming a complex network that regulates cell behaviour in pulmonary fibrosis.

Research performed by (Zhang *et al.*, 2016) suggeststhat bleomycin administration increased Akt phosphorylation without altering total Akt levels, indicating pathway involvement in lung fibrosis. Blocking PI3K/Akt with LY294002 inhibited BLM-induced p-Akt expression without affecting total Akt levels. This resulted in reduced inflammatory cell infiltration and proinflammatory cytokine levels while increase in anti-inflammatory cytokine IL-10. Furthermore, LY294002 treatment also suppressed myofibroblast expansion, fibronectin matrix formation, and collagen deposition, preserving lung compliance.

4.2.3 MAPK (Mitogen-Activated Protein Kinase) signalling cascade

MAP kinases (MAPKs) are crucial enzymes that relay signals from receptors on the cell surface to targets within the cell in response to various stimuli, mentioned by (Yoshida*et al.*, 2002) in his study.

(Wang*et al.*, 2021)discussed that, the MAPK family members areassociated in modulating TGF-β1 triggered signaling pathways and are significant regulators of epithelial-mesenchymal transition (EMT).Saleem(2024) pointed out that, the MAPK signaling pathways, including p38, ERK, and JNK, controlscellular homeostasis.Furthermore, (Yoshida*et al.*, 2002) mentioned that, while p38 MAPK and JNK respond to environmental stress and inflammation, promoting apoptosis and cytokine expression, ERK is activated by growth signals, supporting cell proliferation and survival.

Ye and Hu(2021)pointed out that, TGF-β1 activates the MAPK family, particularly ERK1/2, which phosphorylates and activates p90RSK. This influences Smad signaling, indicating crosstalk between MAPK and Smad pathways. These interactions contribute to myofibroblast differentiation, EMT/EndMT (Endothelial mesenchymal transition), and fibrogenesis in IPF.

(Antoniou*et al.*, 2010)highlighted that, therapeutic intervention aimed at modulating MAPK signaling has demonstrated potential efficacy in addressing both idiopathic pulmonary fibrosis (IPF) and cancer, underscoring its importance as a prospective therapeutic avenue [86].

4.2.4 Wnt/β-catenin signalling cascade

Study conducted by (Shi*et al.*, 2017) suggests that, the Wnt/β-catenin cascade hinges on Wnt binding to its coreceptors, LRP5 or LRP6, and a member of the FZD family. This interaction triggers cytosolic β-catenin accumulation.

Yan and Ping (2014) mentioned that, the Wnt/β-catenin signaling cascade interacts with TGF-β, synergistically contributing to the progression of IPF. TGF-β activates Wnt/β-catenin signaling via ERK1/2 phosphorylation, inhibits GSK-3β activity, and promotes cellular matrix accumulation and β-catenin nuclear translocation. This pathway also regulates cell apoptosis, crucial in scar repair during pulmonary fibrosis.

(Andersson-Sjöland*et al.*, 2016) pointed out that, in lung endothelial cells, the onset of Wnt/β-catenin communication triggers a shift from vascular-associated fibroblasts to cells with characteristics similar to myofibroblasts.This transition results in the accumulation of ECM and increased tissue stiffness, thereby assisting in the development of PF.Additionally, (Cao*et al.*, 2020) highlighted that, suppressing the Wnt signalling pathway led to the inhibition of myofibroblast differentiation, ultimately ameliorating PF lesions [89].

Research findings of (Königshoff*et al.*, 2017) reveal increased expression of genes targeted by the Wnt pathway in IPF lungs, suggesting its activation. Observation of β-catenin staining in ATII cells and fibroblasts further supports the activation of Wnt signaling.

4.2.5 ROCK (Rho-associated coiled-coil-forming protein kinase) signalling cascade

The ROCKis essential for tissue repair process, because it promotes actomyosin contraction and actin assembly, which reformulate cytoskeletal components, as suggested by Julian and Olson (2014).

(Shimizu*et al.*, 2014) pointed out that, elevated ROCK activity is seen in fibrotic lesions from both mice models and people with IPF. At the area of injury, this heightened activity triggers the endothelial and epithelial cells as well as fibroblast, to become profibrotic.

(Knipe*et al.*, 2018) it was found that both ROCK isoforms, ROCK1 and ROCK2, assist in the advancement of PF in the bleomycin mouse model. Additionally, the study revealed that a

reduction in the activity of each isoform has a preventive impact against PF caused by bleomycin.

4.3 Growth Factors

Growth factors play a significant role in pulmonary fibrosis. Key growth factors implicated in pulmonary fibrosis include TGF-β, PDGF, VEGF and CTGF.

TGF-β is central to the pathogenesis of IPF, promoting EMT in alveolar epithelial cells and severe pulmonary fibrosis, as per (Sureshbabu*et al.*, 2011).

(Abdollahi*et al.*, 2005) mentioned that,the PDGF family binds to PDGFR-a and PDGFR-b, activating their tyrosine kinase activity to modulate cellular functions.(Nishioka*et al.*, 2013) suggested that, increased PDGF-A expression in mice models and presence of PDGF-BB and PDGF-AA in rats, promote lung fibroblast growth. PDGF isoforms, especially PDGF-B, are implicated in lung fibrosis. Enhanced PDGF expression in IPF patients suggests its role in fibrotic lung diseases.

(Chong*et al.*, 2023) pointed out that, inhibiting PDGF-BB with Imatinib or APB5 reduces PF, while Nintedanib, an approved treatment, targets PDGFR and other receptors, limiting fibroblast activity. Further investigation into platelet-derived factors in PF is crucial.

Additionally, Imatinib/Gleevec, SU9518, and SU11657, inhibitors of PDGF signaling, notably decreased lung fibrosis in a radiation-induced mouse model, pointed out by (Abdollahi*et al.*, 2005).

Vascular endothelial growth factor (VEGF) has various actions directly related to the pathogenesis of IPF, including promoting epithelial multiplication and preventing programmed death of epithelial cells, mentioned by (Roberts*et al.*, 2007). Furthermore,(Farkas*et al.*, 2009) mentioned that, because of its ability to shield endothelial cells, VEGF is also essential in preventing vascular alteration. On the other hand,(Lee*et al.*, 2004) mentioned that, type-2 inflammation is linked to VEGF, which may amplify pre-existing fibrogenic reactions.

(Farkas*et al.*, 2009) mentioned that, in idiopathic pulmonary fibrosis, VEGF decreases while PEDF increases, impacting fibrosis and angiogenesis. Despite reduced VEGF, TGF-β1 can still stimulate it, potentially worsening fibrosis and angiogenesis.

A recent experiment performed by (Kasuya*et al.*, 2021), demonstrates that VEGF overexpression focused at the lungs significantly reduces buildup of collagen, mortality, death of epithelial cells and histological signs of tissue remodelling when exposed to bleomycin.

(Isshiki*et al.*, 2021) discussed that, CTGF, referred to as CCN2(cellular communication factor 2), is involved in fundamental biological functions such as ossification, neovascularization, and wound healing. Furthermore, CTGF investigation is directed towards tissue fibrosis, where elevated levels are noted in different fibrotic conditions affecting organs like the kidney, heart, liver, skin, and lungs.Effendiand Nagano(2022) pointed out that, CTGF expression is regulated by physiological and pathological factors at transcriptional, post-transcriptional, and translational levels.CTGF serves diverse roles, including signal transduction initiation, cytokine regulation, ECM turnover, and modulation of cytokine and growth factor activity.

(Vanstapel*et al.*, 2021) suggested that, including the kidney, liver, heart, and lungs, CTGF upregulation in IPF, observed in fibroblasts, broncho-alveolar lavage, plasma, and lung tissue. Animal models confirm increased CTGF levels in fibroblasts, promoting a profibrotic environment, even in lungs resistant to fibrosis induction.

(Bickelhaupt*et al.*, 2017) demonstrated that, FG-3019 (an anti-CTGF antibody) administration transiently improved lung remodeling in mice exposed to radiation, enhancing health and lifespan.

Future studies could explore CTGF-targeting therapies for PF linked to COVID-19 or other causes, offering potential treatment avenues.

4.4 Transcription factors

Transcription factors performs a crucial function in pulmonary fibrosisby modulating the expression of genes involved in fibrotic processes. Transcription factors like TGF-β, NF-κB, STAT3, HIF-1, FOXOs, HSP27, and Smad proteins are key drivers of pulmonary fibrosis.

(Yu*et al.*, 2020) mentioned that,the NF-κB pathway encompasses two branches: the canonical and non-canonical pathways. The canonical pathway responds to various stimuli, activating NF-κB through IκB (Inhibitor of κB) protein phosphorylation mediated by IKK (IκB Kinase). The non-canonical pathway, triggered by specific TNF (Tumor Necrosis Factor) receptors,

involves NIK (NF-κB Inducing Kinase) accumulation due to TRAF3 (TNFR-associated factor 3) degradation, leading to p100 phosphorylation and NF-κB activation.

(Titan *et al.*, 2017) pointed out that, *in vitro* experiments show time-dependent NF-κB expression and EMT marker induction in human epithelial cells. *In vivo* studies demonstrate that repetitive NF-κB pathway stimulation causes airway epithelial cell morphological changes, intensifying airway fibrosis.

(Knight*et al.*, 2011)mentioned that, STAT3 is a crucial transcription factor, existing in two isoforms: STAT3a and STAT3b. While STAT3a is essential for cell viability, STAT3b acts as a dominant negative factor.(Pedroza*et al.*, 2016) pointed out that, in pulmonary fibrosis, STAT-3 activation, driven mainly by IL-6 and TGF-β, is crucial for disease progression. Further he stated that, elevated STAT-3 phosphorylation in lung tissue promotes fibrosis by regulating cell survival, migration, proliferation, and differentiation.

(Pechkovsky*et al.*, 2012) stated that, in pulmonary fibrosis, STAT3 regulates fibroblast function, where constitutively phosphorylated STAT3 is linked to reduced expression of α-SMA, Thy-1/CD90, and α-v β-3 integrin.

Furthermore,(Prêle*et al.*, 2012) mentioned in his study that, STAT3 activation affects how fibroblasts behave, leading to changes like decreased proliferation, modified expression of genes involved in cell death, and shifts in cell surface markers like Thy-1/CD90 and integrin αvβ3.

Hypoxia, a common feature in fibrotic tissues, affects different cell types due to insufficient oxygen levels and activates the hypoxia-inducible factor (HIF)-1, which plays a crucial role in fibrosis.(Goodwin*et al.*, 2018)mentioned that, under aerobic conditions, HIF-1αis degraded, but in low oxygen levels, it teams up with HIF-1β to activate genes for adapting to hypoxia, including shifting metabolism to anaerobic glycolysis. Furthermore, (Aquino-Gálvez*et al.*, 2019) stated that hypoxia-induced accumulation of HIF-1α&2α, particularly pronounced in IPF, suggests a shift towards anaerobic metabolism akin to cancer cells.

(Ueno*et al.*, 2011) stated that, in pulmonary fibrosis, TGF-β triggers PAI-1 transcription via HIF-1 deposition, emphasizing the role of HIF-1 in alveolar macrophages and its potential as a therapeutic target.

(Wang*et al.*, 2017) proposed that Hsp27 actively participates in the fibrotic progression by regulating the differentiation of lung fibroblasts through pathways such as Smad3 and

ERK.(Sontake*et al.*, 2017) mentioned that, Hsp90 serves as a facilitator of fibroblast activation, and inhibiting the ATPase activity of Hsp90 has been demonstrated to lessens the severity of PF.

(Altintas*et al.*, 2016) mentioned that, the FoxOs constitutes a conserved DNA-binding site present in family of transcriptional regulators including four isoforms in mammals: FoxO1, FoxO3, FoxO4, and FoxO6. Activation of FoxO3 through UCN-01 has been observed to reverse phenotypic alterations and impede the advancement of idiopathic pulmonary fibrosis. This implies that FoxO3 may be a fresh and viable target for the treatment of IPF.

5. Plant sources as therapeutic agents

Natural compounds are valued for their ability to influence metabolism, combat oxidative stress, reduce inflammation, and modulate the immune system, as per (Mijatović*et al.*, 2018). (Bahri *et al.*, 2017) stated that, numerous preclinical investigations have demonstrated that numerous natural products derived from plants possess both preventive and therapeutic properties against PF. These effects are achieved through various mechanisms, including the reduction of oxidative stress, attenuation of inflammation, inhibition of fibroblast multiplication and stimulation, and normalization of biochemical reactions.

These results imply that, in clinical settings, these natural compounds may be able to prevent the beginning of PF and decelerate its progression.

5.1 Alkaloids

(Hosseini*et al.*, 2021) stated that, alkaloids are basic chemicals that frequently have a ring like structure with one or more nitrogen atoms. In their protonated state, they are water-soluble owing to their primary nature under acidic conditions. However, in a neutral form, they tend to be lipophilic, particularly under alkaline conditions.

Role of all the reported alkaloids are given in table 2.

Table 2Plant sources containing alkaloids as their active constituents and their effects.

CHEMICAL GROUP	SOURCE	ACTIVE CONSTITUENT	EFFECTS	REFS.
ALKALOIDS	*Tripterygium wilfordii Hook. f*	Isorhynchophylli-ne	Anti-inflammatory	(Qiu*et al.*, 2020)
	Sophorae flavescens radix	Matrine	Suppresses TGF-β, Smad 2&3 signalling.	(Li *et al.*, 2020)
	Indigo naturalis	Indirubin	Suppresses TGF-β1, Smadsignalling.	(Wang *et al.*, 2020)
	Chelidonii herba	Chelerythrine	Activation of Nrf2, ARE signaltransduction.	(Peng *et al.*, 2021)
	Coptidis rhizoma	Berberine	Activation of PPAR-γ.	(Guan *et al.*, 2018)
	Amaryllidaceae	Lycorine	Inhibition of NLRP3 expression.	(Liang*et al.*, 2020)
	Leonuri herba	Leonurine	Upregulates AKT signalling.	(Zhu *et al.*, 2021)
	Arenaria kansuensis	β-carboline alkaloids	Inhibit NF-κB /p65 phosphorylation; Suppress MCP-1; Inhibits TNF-α, IL-6 and IL-1β;	(Cui *et al.*, 2019)

			Suppress EMT.	
	Stephania tetrandra	Tetrandrine	Suppresses secretion of α-SMA,fibronectin, vimentin, and type 1 collagen. Inhibit fibroblast proliferation.	(Liu *et al.*, 2021)

Table 2 Continued

CHEMICAL GROUP	SOURCE	ACTIVE CONSTITUENT	EFFECTS	REFS.
ALKALOIDS	Tea, coffee, etc.	Caffeine	Inhibits basal expression of α-SMA gene; Downregulates TGF-β1.	(Tatler*et al.*, 2016)
	Nelumbo nucifera Gaertn	Isoliensinine	Decreases Hydroxyproline content, lung histological injury, MDA; Increases SOD; Downregulates TNF-α, TGF-β1.	(Xiao*et al.*, 2005)

5.2 Flavonoids

Flavonoids are polyphenolic compounds characterized by a 15-carbon skeleton. Their bioactivity stems from various structural features, including hydroxyl groups (-OH) and other substituents, such as methoxy (-OCH3) and glycosyl moieties (-O-R), which can modulate their antioxidant, anti-inflammatory, and antifibrotic properties.

(Wen*et al.*, 2021)highlighted in his study that, natural flavonoids are of great interest as potential therapeutic agents due to their diverse physiological effects, including anticancer, anti-inflammatory, autoimmune protection, and antioxidant properties. Furthermore, (Wang*et al.*, 2023) pointed out that,numerous natural flavonoids, including quercetin, have been investigated in clinical trials for their potential efficacy in treating patients with PF.

Role of all the reported flavanoids is given in table 3.

Table 3Plant sources containing flavonoids as their active constituents and their effects.

CHEMICAL GROUP	SOURCE	ACTIVE CONSTITUENT	EFFECT	REFS.
FLAVONOIDS	*Scutellariae radix*	Biacalein	Regulate CaMKII, PI3K & AKT signalling; Prevent EMT; Inhibit miR-21.	(Zhao*et al.*, 2020)
	Various fruits and vegetables	Quercetin	Suppresses ROS production; Modulate Smad and β-catenin pathways.	(Takano*et al.*, 2020)
	Erigeron breviscapus	Scutellarin	NF-κB, NLRP3 signalling regulation; Inhibition of PI3K, Akt signalling.	(Peng*et al.*, 2020)
	Citrus aurantium L *Citrus fruits*	Hesperidin	Reduction of TGF-β, Smad 2&3 and NF-κB signalling.	(Ren*et al.*, 2019) (Zhou*et al.*, 2019)

	Alpiniae ofcinarum rhizoma	Galangin	Suppress EMT.	(Wang*et al.*, 2020)
	Aronia melanocarpa	Cyanidin-3 galactoside	Inhibit TGF-β, mTOR signalling.	(Cui*et al.*, 2022)
	Hippophae fructus	Isorhamnetin	Suppress EMT.	(Zheng*et al.*, 2019)
	Ampelopsis grossedentata	Dihydromyricetin	Suppresses TGF-β1 Signalling; Regulation of STAT3, p- STAT3 signalling.	(Xiao*et al.*, 2021)

Table 3Continued.

CHEMICAL GROUP	SOURCE	ACTIVE CONSTITUENT	EFFECT	REFS.
FLAVONOIDS	*Camptotheca acuminata Decne*	Hyperoside	AKT, GSK3b signalling regulation.	(Huang*et al.*, 2020)
	Myrica rubra Sieb	Myricetin	Smad and non-Smad signalling regulation.	(Li*et al.*, 2020)
	Aurantii fructus immaturus	Neohespridin	TGF-β, Smad3 signalling inhibition.	(Guo*et al.*, 2019)
	Astragali radix	Biacalin	Increases SOD.	(Chang*et al.*, 2021)
	Erigeron breviscapus	Scutellarin	NF-κB, NLRP3 signalling regulation.	(Peng*et al.*, 2020)
	Various plant sources	Epicatechin	Reduces inflammation and oxidative stress.	(Shariati*et al.*, 2019)

		Pinocembrin	TLR4, NF-κB & NLRP3 signalling inhibition.	(Gan*et al.*, 2021)
	Rhodiolae crenulatae radix	Rutin	Suppresses TGF-β1; Inhibits α- SMA, Col I&III production.	(Bai*et al.*, 2020)
	Juglans	Juglanin	Sting suppression	(Sun*et al.*, 2020)

Table 3Continued.

CHEMICAL GROUP	SOURCE	ACTIVE CONSTITUENT	EFFECT	REFS.
FLAVONOIDS	Lonicera japonica	Luteolin	Suppresses neutrophil infiltration in BALF, collagen deposition & TGF-β1 expression; Inhibits αSMA expression, type I collagen; Retains epithelial morphology; Reduces Smad3 phosphorylation.	(Chen*et al.*, 2010)
	Oroxyli semen	Chrysin	TGF-β1 signalling inhibition.	(Kseibati*et al.*, 2020)
	Silybi fructus	Silibinin	Decreases IL-1β, IL-6, TNF-α in BALF & pulmonary tissue; Suppresses TGF-β and p-smad2/3expression in pulmonary tissue; Reduces collagen-I and fibronectin levels in the lungs; Decreases α-SMA expression in pulmonary tissue;	(Ali*et al.*, 2021)

Table 3Continued.

CHEMICAL GROUP	SOURCE	ACTIVE CONSTITUENT	EFFECT	REFS.
FLAVONOIDS	*Ampelopsis grossedentata*	Dihydromyricetin	Downregulates TGF-β1/Smad signaling pathways; Suppresses Expression of α-SMA and fibronectin.	(Xiao*et al.*, 2021)
	Rhododendron brachycarpum	Hyperoside	AKT, GSK3b signalling regulation.	(Huang*et al.*, 2020)
	Epimedii folium	Icariin	Suppresses hippo signalling.	(Du*et al.*, 2021)
	Scutellaria baicalensis	Biacalein	Suppresses CTGF expression.	(Sun*et al.*, 2020)
	Rhodiolae crenulatae radix	Rutin	Reduces expression of TGF- β1. Suppresses α-SMA; Prevent collagen deposition; Decreases lung hydroxyproline level.	(Bai*et al.*, 2020)
	Artemisia annua L	Dihydromyricetin	Suppresses TGF-β1, Smad signalling.	(Xiao*et al.*, 2021)
	Glycyrrhizae radix	Isoliquiritigenin	Suppresses PI3K, AKT & mTOR Signalling.	(He*et al.*, 2020)
	Rhizoma Kaempferiae	Kaempferol	Anti-inflammatory action.	(Liu*et al.*, 2019)

Table 3Continued.

CHEMICAL GROUP	SOURCE	ACTIVE CONSTITUENT	EFFECT	REFS.
FLAVONOIDS	*Hippophae fructus*	Isorhamnetin	EMT suppression.	(Zheng*et al.*, 2019)
	Radix Puerariae	*Radix puerariae* extracts	Suppress oxidative stress induced by paraquat.	(Liu*et al.*, 2015)
	Various herbs and vegetables	Apigenin	Reduces TGF-β, TNF-α, Hydroxyproline content. Increases SOD.	Chen and Zhao (2016)

TLR4- Toll-like receptor 4; GSK3B- Glycogen Synthetase Kinase 3beta;

5.3 Glycosides

Glycosides, found in plants, are studied for potential therapeutic effects in pulmonary fibrosis.

(Chen*et al.*, 2022) demonstrated in his study that, loganin and morroniside, iridoid glycosides, displayed protective effects against lung injury and fibrosis by reducing inflammationand regulating signaling pathways. They also decreased collagen deposition, suggesting their potential as therapeutic agents for lung diseases.

Role of all the reported glycosides are given in table 4.

Table 4 Plant sources containing glycosides as their active constituents and their effects.

CHEMICAL GROUP	SOURCE	ACTIVE CONSTITUENT	EFFECT	REFS.
GLYCOSIDE	*Rhei radix et rhizoma*	Rhapontin	TGF-β/Smad signalling regulation.	(Tao *et al.*, 2017)
	Mangifera indica L.	Mangiferin (Polyphenol glycoside)	Inhibits TGF-β1, Smad 2&3 signalling.	(Jia*et al.*, 2019)
	Prunus armeniaca semen amarum	Amygdalin	Downregulates TGF-β1, Smad 2&3 signalling.	(Wang*et al.*, 2019)
	Gentianae radix et rhizoma	Gentiopicroside	Anti-inflammatory.	(Chen*et al.*, 2018)
	Rosmarinus officinalis	Carnosol	Anti-infammatory. Antioxidant.	(Kalantar*et al.*, 2021)
	Dioscorea polystachya Turczaninow	Dioscin	Promotes autophagy in alveolar macrophages.	(Du*et al.*, 2019)
	Pterocypsela laciniata	Lettuce glycoside B	Decreases fatality rates; Lowered MDA levels; Boosted SOD and other antioxidant enzyme function; Normalized serum concentrations of TGF-β1, IL-6, and	(Zhou*et al.*, 2022)

			TNF-α.	

Table 4 Continued

CHEMICAL GROUP	SOURCE	ACTIVE CONSTITUENT	EFFECT	REFS.
GLYCOSIDE	*Trigonella foenum-graecum* (Fenugreek)	Trigonelline	Inhibition of NF-κB/NLRP3/IL-1β signaling; Deactivation of S1P/Hippo signaling; Reduction of EMT, cellular apoptosis, and senescence.	(Zyeda*et al.*, 2024)
	Bletilla striata	Coelonin	Inhibition of IL-1β,6; Suppresses TNF-α; Suppression of NF-κB activity.	(Jiang*et al.*, 2019)

5.4 Polyphenols

Natural antioxidants called polyphenols are gaining attention for their potential to prevent and cure several illnesses, including cancer. Furthermore,these substances' antifibrotic properties have been studied. For example,(Li*et al.*, 2013)mentioned that flavonoids obtained from the Chinese plant Hedysari Radix decrease the advancement of PF.

Additionally,(Impellizzeri*et al.*, 2015)pointed out that polyphenols reducinginflammationand oxidative stress have been reported, which includes resveratrol, quercetin, and grape leaf extract high in dihydroquercetin. These substances show reduction in NF-κBp65 relocation and down-regulation of COX2 (cyclo-oxygenase-2) in mice exposed to bleomycin.

Role of all the reported polyphenols are given in table 5.

Table 5 Plant sources containing polyphenols as their active constituents and their effects

CHEMICAL GROUP	SOURCE	ACTIVE CONSTITUENT	EFFECT	REFS.
POLYPHENOLS	*Polygoni cuspidati rhizoma et radix*	Polydatins	TGF-β1/Smad signaling inhibition.	(Liu*et al.*, 2020)
	Schisandra chinensis fructus	Schisantherin A	Downregulates ERK signalling.	(Zhuang*et al.*, 2020)
		Schisantherin B	Suppresses WNT signalling.	(Wang*et al.*, 2020)
	Ferulae resina	Ferulic acid	Blocks TGF-β1, Smad3 signaling.	(Ali*et al.*, 2021)
	Vaccinium spp	Pterostilbene	TGF-β1 signalling inhibition.	(Peng*et al.*, 2021)
	Salviae miltiorrhizae radix et rhizoma	Salvianolic acid B	Anti-infammatory and antioxidant.	(Liu*et al.*, 2018)
	Rhei radix et rhizoma	Sinapic Acid	Blocking of NF-κB/ NRF2/HO-1 signalling	(Raish *et al.*, 2020)
	Zingiberis rhizoma recens	Zingerone	Impacts signalling of iNOS and TGF-β1.	(Gungor*et al.*, 2020)
	Gallnut	Gallic acid derivative	Anti-inflammatory antioxidant.	(Rong*et al.*, 2018)

	Mangifera indica	Mangiferin	Blocking TGF-β1, Smad 2&3 signaling.	(Jia*et al.*, 2019)

Table 5 continued

CHEMICAL GROUP	SOURCE	ACTIVE CONSTITUENT	EFFECT	REFS.
POLYPHENOLS	*Rosmarinus offcinalis*	Rosmarinic acid	Blocks RhoA/Rock signaling.	(Zhang*et al.*, 2020)
	Kaempferiae rhizoma	Alpha-Mangostin	Regulates AMPK signaling.	(Li*et al.*, 2019)
	Rhei radix et rhizoma	Chrysophenol	Downregulates Wnt & β-catenin signaling.	(Qi*et al.*, 2020)
	Grape	Resveratrol	Controls AP-1 and MAPK signalling.	(Wang*et al.*, 2018)
	Kaempferiae rhizoma	Alpha-Mangostin	Controls the MAPK & AP-1 signalling.	(Li*et al.*, 2019)
	Lonicerae japonicae fos	Chlorogenic acid	Suppresses endoplasmic reticulum stress.	(Wang*et al.*, 2017)
	Asarum heterotropoides	Asarinin	Activates PPARγ; Downregulates TGF-β, AKT & MAPK signalling.	(Zeng *et al.*, 2023)
	Various plant sources	Quercetin	Regulation of Smad and β-catenin signalling;	(Takano*et al.*, 2020; and Veith*et al.*, 2017)

CHEMICAL GROUP	SOURCE	ACTIVE CONSTITUENT	EFFECT	REFS.
	Glycine max (Linn.) Merr	Phloretin	AMPK activation	(Cho*et al.*, 2017)

Table 5 continued

POLYPHENOLS	*E. prostrata*	Wedelolactone	AMPK, TGFβ1 & Raf-MAPK pathway activation; Suppress fibroblast proliferation.	(Yang*et al.*, 2019)
	Green tea	EpigallocateChin-3- gallate	Reduces collagen deposition and MDA levels; Increases SOD activity; Balances serum levels of inflammatory cytokines.	(You*et al.*, 2014)
	Grape	Proanthocyanidin	Suppresses inflammatory responses, edema, fibrosis severity and extension; Reduces accumulation of inflammatory cells, iNOS staining, and hydroxyproline levels.	(Agackiran*et al.*, 2012)

Table 5 Continued

CHEMICAL	SOURCE	ACTIVE	EFFECT	REFS.

GROUP		**CONSTITUENT**		
POLYPHENOLS	*Atractylodes lancea*	Rikkunshito	Suppresses IL-1β & 6 and TGF-β1 expression; Improves survival rate; Downregulates NF-κB signaling pathway.	(Tsubouchi *et al.*, 2014)
	Salviae miltiorrhiza	Salvianolic acid B	Mitigate oxidative damage & prevent programmed death of endothelial cells; Modulates MAPK as well as NF-κB signaling cascades.	(Liu*et al.*, 2018)
	Curcuma longa.	Curcumin	Inhibits COX-2, NF-κB-p65, and fibronectin expression; Suppresses NF-κB-p105 expression; Minimizes mRNA levels of PDGF, CTGF, NFκB, MMP.	(Shaikh*et al.*, 2020)

Table 5 Continued

CHEMICAL GROUP	SOURCE	ACTIVE CONSTITUENT	EFFECT	REFS.
POLYPHENOLS	*Tamarindus indica*	Procyanidins	Regulates Nox4 and p38 MAPK expression. Reduces oxidative stress Suppresses collagen deposition	Ameeramja and Perumal (2018)
	Date palm	Date palm sap	Increases SOD and CAT Decreases MDA and hydroxyproline Lung architecture improvement	

5.5 Terpenoids

Plants emit a wide range of volatile organic compounds, predominantly terpenes and terpenoids, which are significant plant secondary metabolites. These compounds, formed by linking isoprene units, possess diverse biological activities.(Kim*et al.*, 2020)pointed out that, recent investigations have uncovered new terpenes and terpenoids, broadening the spectrum of potential chemotherapeutic agents for clinical trials.

(Nguyen*et al.*, 2012) mentioned that, based on the chemical structure, terpenoids may be categorized into numerous groups, such as monoterpenes, sesquiterpenes, diterpenes, and triterpenes.

(Zhang*et al.*, 2022) highlighted that,total terpenoids of *I. japonica* alleviated LPS-induced lung damage by targeting TLR4 and Nrf2 pathways, reducing inflammationand oxidative stress. It inhibited COX-2 and phosphorylation of p65, p38, ERK, and JNK via MAPK/NF-κB, independently of TLR4, while activating Nrf2 pathway proteins through Nrf2 receptor activation.

Furthermore,(Xie*et al.*, 2023)demonstrated that,Glycyrrhizic acid (GA), extracted from the herbal medicine *Glycyrrhiza uralensis Fisch.* effectively mitigates BLM-induced lung

fibrosis and inhibits epithelial-to-mesenchymal transition (EMT). Utilizing GA via nebulized inhalation holds potential for treating pulmonary fibrosis clinically, as it suppresses the TGF-β/Smad pathway.

Role of all the reported terpenoids are given in table 6.

Table 6 Plant sources containing terpenoids as their active constituents and their effects.

CHEMICAL GROUP	SOURCE	ACTIVE CONSTITUENT	EFFECT	REFS.
TERPENOIDS	*Andrographis herba*	Andrographolide	Suppresses TGF-β1, Smad 2&3 and Erk 1&2 signalling; AKT, mTOR signalling regulation; Prevents ECM deposition.	(Li*et al.*, 2020)
	Tripterygium wilfordii Hook. f	Triptolide	FAK, calin signalling regulation; EMT suppression.	(Zhang*et al.*, 2019)
	Rabdosia japonica	Glaucocalyxin	Reduces lung macrophage and neutrophil infiltration; Suppresses release of proinflammatory cytokines in lung tissue and BALF; Suppresses NF-κB activation.	(Yang*et al.*, 2017)
	Azadirachta indica	Nimbolide	Suppresses TGF-β/Smad signaling; Inhibits EMT; Reduces collagen; Alters autophagy	(Goud*et al.*, 2019)

			signaling proteins.	

Table 6 Continued

CHEMICAL GROUP	SOURCE	ACTIVE CONSTITUENT	EFFECT	REFS.
TERPENOIDS	Atractylodis rhizoma	Atractylon	Modulation of TGFBR2 expression.	(Zeng*et al.*, 2021)
	Pyrethrum parthenium (L.) *Sm*	Parthenolide	NF-κB, Snail signalling inhibition.	(Li*et al.*, 2018)
	Curcuma aromatica Salisb	Curdione	TGF-β, Smad3 signalling inhibition.	(Liu*et al.*, 2020)
	Gynostemma pentaphyllum (Thunb.) Makino	Gypenoside	AKT, mTOR, c-Myc signalling inhibition.	(Liu*et al.*, 2022)
	Siratia grosvenorii	Mogrol	TGF-β1 and AMPK signaling regulation.	(Liu*et al.*, 2021)
	Atractylodis rhizoma	Atractylodin	TGF-β1, Smad signaling inhibition.	(Chang*et al.*, 2021)
	Multiple plant sources	Hederagenin	Regulates Ras/JNK/NFAT4 axis	(Ma*et al.*, 2020)
	Podocarpus nagi	Nagilactone D	TGF-β/Smad3 signaling inhibition.	(Li*et al.*, 2020)
	Andrographis herba	Andrographolide	AKT/ mTOR signaling regulation.	(Li*et al.*, 2021)

Table 6 Continued

CHEMICAL GROUP	SOURCE	ACTIVE CONSTITUENT	EFFECT	REFS.
TERPENOIDS	Birch bark	Betulinic acid	Wnt/β-catenin signaling inhibition.	(Li*et al.*, 2021)
	Atractylodis rhizoma	Atractylenolide III	Nrf2/NQO1/ HO-1 signalling activation.	Huai and Ding. (2020)
	Siratia grosvenorii	Mogrol	TGF-β1 and AMPK signaling regulation.	(Liu*et al.*, 2021)
	Aucklandiae radix	Costunolide	Anti-oxidative and anti-inflammatory effects; Reduces IL-6 and NF-KB expression; Inhibits α-SMA and collagen transcription; Downregulates Smad2 signaling pathway and NOX4 expression.	(Li*et al.*, 2019)
	Artemisia annua L.	Dihydroartemisnin	Anti-inflammatory; Inhibit TGF-β1, JAK2, phosphorylated JAK2, STAT3, and phosphorylated STAT3 activity;	(You*et al.*, 2022)

		Suppress alveoliinflammation; Mitigates lung damage and fibrosis.

Table 6 Continued

CHEMICAL GROUP	SOURCE	ACTIVE CONSTITUENT	EFFECT	REFS.
TERPENOIDS	Citrus fruits	D-limonene	Suppression of PI3K, AKT, NF-κB p65 signalling cascade; Protection against lung fibrosis by Bleomycin.	(Yang*et al.*, 2021)
	Rabdosiae rubescentis herba	Oridonin	TGF-β/ Smad signaling regulation.	(Fu*et al.*, 2018)
	Siraitia grosvenorii	Mogroside IIIE	Reduces Nitric Oxide release in macrophages; Reduces MPO; Downregulates TLR4, MyD88, MAPK signalling pathway.	(Tao*et al.*, 2017)
	Centella asiatica	Asiatic acid	Reduces TGF-β1 expression in lung tissues; Decreases Collagen, α-SMA, and TIMP-1 level; Inactivate Smads and ERK1/2 signaling pathways;	(Dong*et al.*, 2017)

		Decreases $NLRP_3$ inflammasome.

6. Conclusion

This review underscores the intricate involvement of cytokines in pulmonary fibrosis, shedding light on potential therapeutic avenues and emphasizing the need for further research in this complex field.Through exploring both conventional therapeutic avenues and emerging natural solutions, it provides a holistic perspective on managing this challenging condition. By bridging traditional and innovative approaches, this comprehensive analysis opens doors to promising directions for research and clinical practice in the realm of pulmonary fibrosis.

Acknowledgments:

We are thankful to the chairman, management, principal, teaching and non-teaching staff of Acharya & BM Reddy College of Pharmacy, Bengaluru for providing us with necessary support throughout our review submission.

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