A Review on Potential Therapeutic Effect of Natural Products with Targeted Mechanisms in the Treatment of Pulmonary Fibrosis

[A dissertation submitted to the Department of Pharmacy, Faculty of Allied Heath and Sciences, Daffodil International University, Dhaka. This report presented in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy.**]**

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APPROVAL

This Project paper, a review on "Potential therapeutic effect of natural products with targeted mechanisms for the treatment of pulmonary fibrosis" submitted to the Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, has been accepted as satisfactory for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy and approved as to its style and contents.

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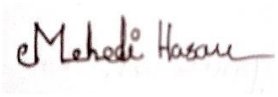
Declaration

I, with is, hereby declare that, this project is done by me under the guidance of Md Mizanur Rahman, Assistant Professor, Department of Pharmacy, Daffodil International University, in partial fulfillment of the requirements for degree of Bachelor of Pharmacy. The results embodied in this project have not been submitted to any other university or institute for the award of any degree.



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Certificate

This is to certify that the results of the investigation that are embodied in this thesis works are original and have not been submitted before in substance for any degree or diploma of this university. The entire present work submitted as a thesis work for the partial fulfillment of the degree of Bachelor of Pharmacy.

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- Mehedi Hasan Roni

To my Parents and Teachers,

The people who are constantly supportive of me in all aspects of my life

Abstract

Pulmonary fibrosis is an incurable end-stage lung disease that continues to be a global public health issue. Although some advances have been made in understanding the pathogenesis of pulmonary fibrosis, effective intervention methods remain limited. Natural products contain numerous biological activities and a high level of safety, which are essential elements in the prevention and treatment of pulmonary fibrosis. We summarized the processes and health advantages of natural products against pulmonary fibrosis in this review. These natural products target oxidative stress, inflammatory injury, epithelial-mesenchymal transition (EMT), fibroblast activation, extracellular matrix accumulation, and metabolic regulation via pathways involving the TGF-β Signaling pathway, anti-inflammatory and anti-oxidant properties, modulation of Cellular Signaling pathway and Inhibition of ECM deposition. We hope to develop novel methods for preventing and treating pulmonary fibrosis.

Keywords: Natural remedies; therapeutic targets; plant active ingredients; plant extracts; herbal medicine; pulmonary fibrosis

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Chapter One

Introduction

1.1. Introduction

Pulmonary fibrosis is the result of a number of progressive short-term and long-term lung illnesses. The average amount of time a person with pulmonary fibrosis lives after being diagnosed is only 3–5 years, and the average amount of time a person lives after a severe exacerbation is only 2–3 months. Symptoms of this disease include a dry cough and shortness of breath. (Richeldi et al., 2017) Epidemiological studies show that the number of people with lung fibrosis is rising every year.The tumor-like condition known as pulmonary fibrosis is now a major public health issue on a global scale. The main risk factors include age, smoking, environmental exposure, viral infection, and inheritance. (Kwapiszewska et al., 2018) Pirfenidone and nintedanib are primarily employed in the management of pulmonary fibrosis. Glucocorticoids are used to treat pulmonary fibrosis in addition to antioxidants, receptor inhibitors, and other drugs. These clinical medications' efficacy and side effects, however, are restricted. (Hutchinson et al., 2015) Even though early injury and immune disorders can be prevented and treated, pulmonary fibrosis is still incurable. Therefore, early disease prevention and correction of anomalous symptoms are essential for high-risk and suspected groups to delay the onset of clinical disease. The social and financial cost of the disease can also be lessened for the patient. Clinical drugs cannot be used to prevent disease because their main purpose is to treat it. Therefore, it is crucial to develop new interventional techniques that can treat and prevent pulmonary fibrosis. As a result of their anti-inflammatory, antioxidant, immune-regulating, and metabolic properties, natural medicines are increasingly frequently utilised in the prevention and treatment of cancer, cardiovascular disease, metabolic disease, and respiratory disease. (Papadopoulos et al., 2017) Numerous preclinical studies have demonstrated that several plant-derived natural products have both therapeutic and preventive effects on pulmonary fibrosis through a variety of mechanisms, including decreasing oxidative damage, decreasing inflammation, inhibiting fibroblast proliferation and activation, and resolving metabolic issues, suggesting that these substances have the potential to both stop the onset of pulmonary fibrosis and slow the clinical progression of this condition. (Chen et al., 2018) In this study, we provide fresh recommendations by describing the pharmacological processes of natural substances used in the prevention and treatment of pulmonary fibrosis.

1.2. Pulmonary Fibrosis Pathogenesis

The pathogenesis of pulmonary fibrosis is yet unknown. Typically, pulmonary fibrosis begins with abnormal tissue repair following injury. Inflammation and oxidative stress harm lung tissue while activating the body's repair and defence mechanisms. (Bahri et al., 2017)

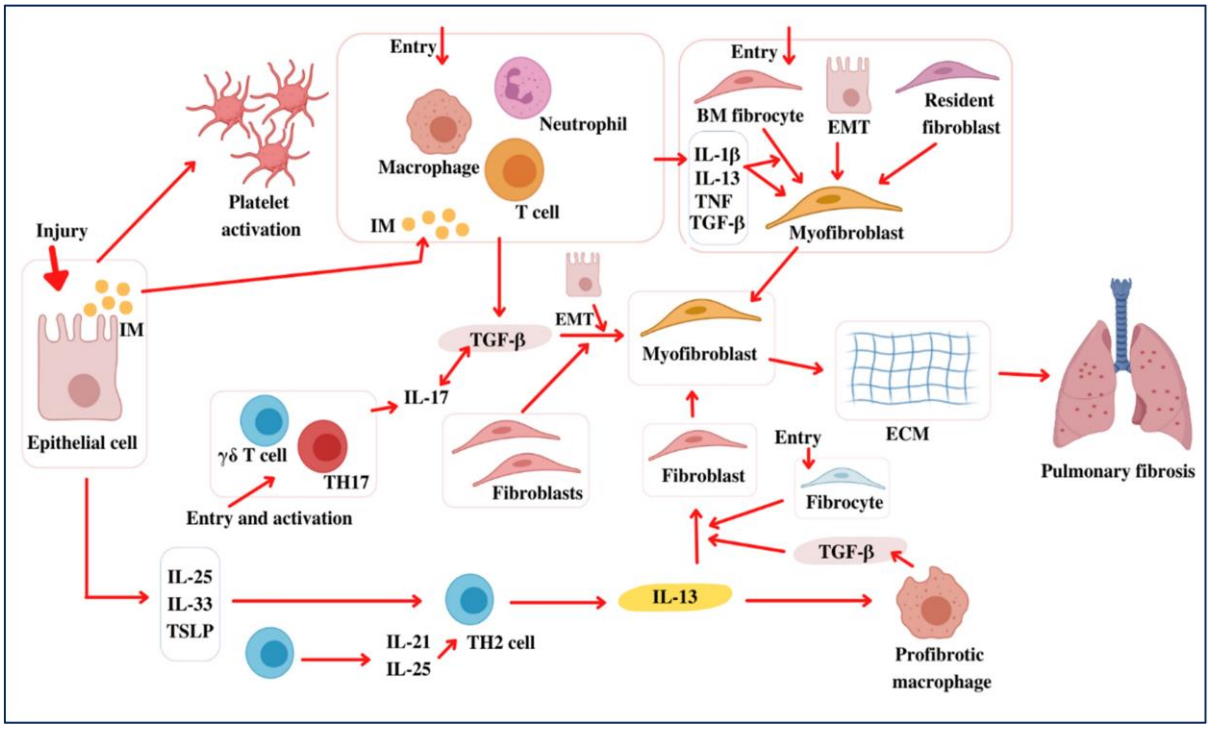

Figure 1: Pulmonary fibrosis pathogenesis. In response to lung injury, epithelial cells discharge inflammatory mediators (IMs), which trigger an antifibrinolytic coagulation pathway, activating platelets and resulting in the formation of blood clots. Activated leukocytes release profibrotic cytokines like TGF- β, IL-1, IL-1, IL-13, and TGF- β. The removal of infections and dead cells is also made possible by this, enabling neutrophils and macrophages. Afterwards, BM fibrocytes and local fibroblasts proliferate and develop into myofibroblasts, which secrete elements of the extracellular matrix (ECM). The ability to develop into fibroblasts and myofibroblasts is another feature of epithelial cells that have undergone EMT. Myofibroblasts support wound healing during the last redecorating and resolution stage, which results in wound contraction and blood vessel regeneration. When a stage of tissue regeneration is poor or when lung-damaging forces persist, fibrosis is frequently seen. Furthermore, TGF- β influences

epithelial cells, resulting in EMT and the development of myofibroblasts, which create ECM. TGF- β 1 promotes the growth of Th17 cells, which results in PF and intensifies inflammatory activity. Similar to this, epithelial cells produce IL-33, IL-25, and TSLP in response to injury, encouraging profibrotic Th2 responses. The cytokines IL-25 and IL-21, which support Th2 differentiation, are also produced by T cells. A profibrotic macrophage subset (PMS) can form and secrete TGF- β 1 and other mediators when Th2 cells generate IL-13. TGF- β1 fibroblasts can also be directly activated by IL-13 on its own. As a result, Th2 cytokines stimulate the production of collagen by bone marrow (BM) fibrocytes, which in turn stimulates fibrotic reactions. Myofibroblasts then appear in order to release ECM components, producing PF as a result. Although several PF manifestations, including those caused by particulate matter (like silica and asbestos), drugs (like bleomycin), bronchiolitis obliterans, radiation, and persistent graft-versus-host-induced PF, can be reliably established and studied in rodents, it is still unknown whether all experimental models accurately replicate the idiopathic aspect of the condition (Hasan et al., 2022)

1.3. Pulmonary Fibrosis Soluble Immune Modulators.

During an improperly controlled wound healing process, fibroblasts become pro-fibrotic and apoptosis-resistant myofibroblasts. Growth factors, cytokines, and chemokines all have an impact on the myofibroblasts' already robust activity. Pulmonary fibrosis is thought to be caused by a number of immune cells and soluble mediators, including neutrophils, phagocytes, fibrocytes, and T lymphocytes. (Kolahian et al., 2016)

1.3.1. Transforming Growth Factor-Beta-1 (TGF-β1)

TGF- β 1 is usually linked to the aetiology of PF. The formation of TGF- β based PF has been linked to activation of the ERK, MAPK, and phosphatidylinositol 3-kinase/Akt pathways. TGF- β 1 also increases the transcription of pro-collagen I and II by activating the serine/threonine kinase and Smad2/3 pathways. Furthermore, TGF- β 1 promotes fibroblast proliferation through vascular cell adhesion molecules 1 and fibroblast differentiation into myofibroblasts by activation of -SMA and galectin-3. Moreover, glycogen synthase kinase-3 mediates the differentiation of myofibroblasts that is stimulated by TGF- β 1. TGF- β 1-targeting treatments are being developed for the treatment of PF. The symptoms of PF have been demonstrated to be alleviated by

TGF- β 1 monoclonal antibodies, blocking the TGF- β 1 activator integrin protein v6, and blocking the TGF- β 1 type 1 receptor. Furthermore, paclitaxel-mediated miR-140 overexpression results in the TGF- β 1/Smad3 pathway being downregulated, which in turn decreases PF. (Hasan et al., 2022)

1.3.2. PDGF

Lung fibroblast survival and differentiation depend on the growth factor PDGF. In clinical IPF lung tissue, it has been discovered that macrophages and epithelial cells overexpress PDGF. In both BLM- and radiation-induced PF, the PDGF-tyrosine kinase inhibitor imatinib significantly reduced fibrosis. By concentrating on PDGFR, c-KIT, and Bcr-Abl, this was accomplished. Although encouraging results from preclinical research, imatinib unfortunately failed clinical studies. (Daniels et al.,2010) A novel PDGFR inhibitor called nintedanib has been introduced and has acquired FDA approval to supplement the treatment of IPF with pirfenidone. (Richeld et al., 2020)

1.3.3. IL-6, -8, and -37

Recent clinical evidence suggests that IL-6 and IL-8 levels are higher in acute exacerbated-IPF patients than in IPF patients. TGF- β levels dramatically differ depending on the course of an illness, although IL-4, IL-10, and IL-13 TGF- β levels do not. (Papiris et al., 2018) Treatment with the anti-inflammatory cytokine IL-37 decreased PF caused by BLM by lowering collagen deposition and inflammatory infiltration into the lungs. In contrast to enhancing IFN expression, lung tissue IL-37 treatment reduced the expression of MCP-1, IL-6, and TNF alpha. (Hasan et al., 2022)

1.4. Potential Therapeutic Targets of PF

The diagnosis, treatment, and prognosis of PF all have therapeutic targets that have been identified. Among the most important are cytokines, chemokines, growth factors, mediators of cell signalling, mediators of collagen remodelling, transcription factors, and mediators of other cellular processes. Figure 2 depicts potential PF treatment targets.

1.4.1. Targeted Antioxidative

Pathways It has been discovered that oxidative stress, which is predominantly brought on by the NADPH oxidase (NOX) enzymes that produce reactive oxygen species (ROS), is a contributing factor in idiopathic pulmonary fibrosis (IPF). Fibrotic tissue can

form in response to several different forms of NOX. The three NOX isoforms that are covered are NOX1, NOX2, and NOX4. TNF-alpha and other cytokines are produced more often as a result of the IPF's oxidative environment. Inducible nitric oxide synthase (iNOS), an enzyme that produces nitric oxide (NO) that is essential for the onset of idiopathic pulmonary fibrosis, is subsequently activated by this (Hasan et al., 2022)

1.4.2. Targeted Cell Signaling Pathways

The PI3K/Akt/mTOR pathway is essential for metabolism, cell growth, and survival. It has been demonstrated that blocking the PI3K/Akt pathway reduces TGF- β induced fibroblast proliferation and differentiation. Idiopathic pulmonary fibrosis (IPF) has been the subject of clinical investigations using the PI3K/Akt/mTOR pathway inhibitor olaparib (GSK2126458) In idiopathic pulmonary fibrosis (IPF), G-protein coupled receptors (GPCRs) are considered to stimulate profibrotic fibroblast promotion. Fibrotic lesions display increased ROCK activity in both rodent models of IPF and IPF patients. At the site of the damage, this results in profibrotic fibroblasts, epithelial cells, and endothelial cells. Immune cells in BAL fluid decreased in clinical trials using fasudil to inhibit ROCK, Knipe et alhaploinsufficiency .'s studies imply that ROCK1 and ROCK2 guard against BLM-related development. JNK, a member of the mitogen-activated protein kinase (MAPK) family, controls a number of cellular processes essential to the development of tumours and neurodegenerative diseases when it is triggered by cytokines and other stress stimuli. AEC, vascular endothelial cells, alveolar macrophages, smooth muscle cells, and lymphocytes have been observed to have an increase in phosphorylated JNK in patients with IPF. (Hasan et al., 2022) Due to CC 930's JNK inhibition's encouraging results in phase I clinical studies (NCT01203943) the drug is being tested in phase II trials.

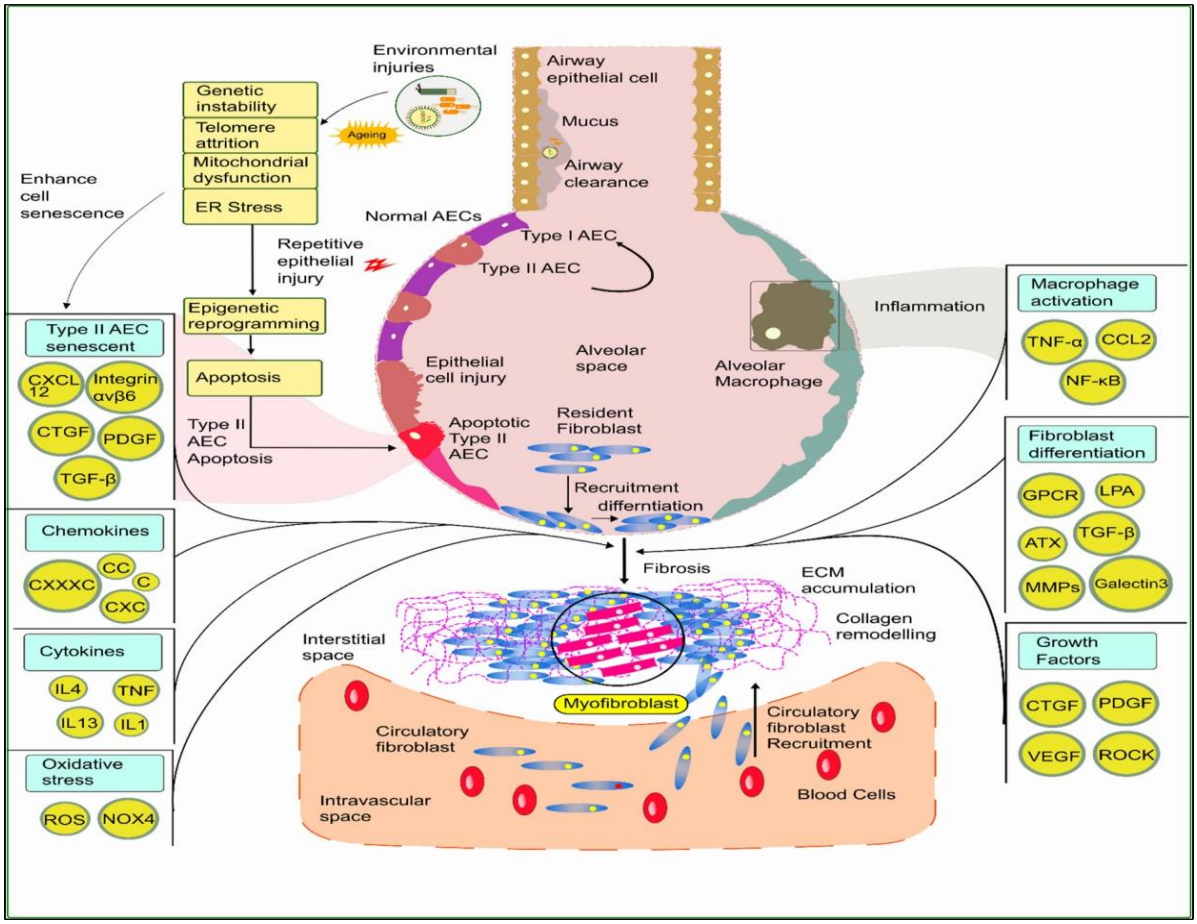

Figure 2: IPF mechanism-targeted therapies. Environmental micro-injuries, genetic and epigenetic influences, and microbial activity affect fibrosis and myofibroblast activation pathways and variables. This graphic shows how essential signaling molecules and variables interact, revealing IPF therapeutic targets discovered during years of research. (Lv et al., 2019)

1.4.3. Targeted Cytokines and Chemokines

Patients with IPF had a higher than normal level of interleukin-13. Age-related fibrosis development was also seen in a mouse model study. The experimental context, both in vitro and in vivo, reveals a complicated signalling network involving several interactions between macrophage CCL2 and TGF- and IL-13. In a mouse model of lung fibrosis, IL-13 (a Th2 cell cytokine) is shown to be beneficial. The lysyl oxidase (LOX) enzyme family promotes fibroblast expansion by deaminating between lysyl and hydroxylysine residues in type 1 collagen molecules. Premature senescence and increased cell proliferation are both signs of high LOX ligand (LOXL)-2 expression. By blocking LOXL-2 with the monoclonal antibody AB0024, the number of activated

fibroblasts is reduced, and the TGF- β signalling pathway is downregulated. (Hasan et al., 2022)

1.4.4. Targeted EMT Pathways

The transformation of epithelial cells into cell types with mesenchymal characteristics is characterised by changes in shape, increased motility, and the presence of mesenchymal markers such N-cadherin (CDH2), vimentin, and -SMA. The pathogenesis of IPF is further complicated by the epithelial-mesenchymal transition (EMT), which promotes the growth of myofibroblasts . As evidence of the significance of Wnt signalling in pulmonary fibrosis, neutralising antibodies against Wnt1-inducible signalling pathway protein-1 are used in mice treated with BLM to delay the onset of idiopathic pulmonary fibrosis . It has been suggested that wnt signalling could be a key therapy target for IPF. A critical factor in the development of pulmonary fibrosis is an imbalance in matrix metalloproteinases (MMPs), which encourages fibroblast proliferation and prolongs the process of ECM buildup . MMP inhibition as a secondary target may be advantageous for the management of IPF disease (Hasan et al., 2022)

1.4.5. Targeted Growth Factors

TGF- β, stimulates fibroblast proliferation, chemotaxis, and ECM deposition in epithelial, endothelial, and mesenchymal cells. IPF patients' BAL fluid has high levels of CTGF, a TGF-β inducer.

In a mouse model of fibrosis caused by BLM, anti-CTGF antibodies decreased the disease. FG-3019, a human anti-CTGF antibody, is being tested in IPF patients in a brand-new phase II study (clinicaltrials.gov ID NCT01890265). In IPF, levels of the tyrosine kinase receptor ligands PDGF, VEGF, and FGF are increased. When fibroblasts are stimulated by PDGF to release growth factors and ECM components, IPF begins to manifest. Profibrotic TGF-1, FGF, and TNF alpha are PDGF-dependent. The most common IPF inducers are CTGF, PDGF, VEGF, FGF, and TGF-1 and recent therapy advancements have focused on them because of their critical involvement in the pathogenesis of IPF. PDGF generates VEGF. (Hasan et al., 2022)

1.4.6. Targeted Transcription Factors

Mammals have four distinct isoforms of a family of transcriptional regulators called the forkhead box (FoxOs), which has a conserved DNA-binding domain. IPF progression can be stopped and the phenotypic change reversed by UCN-01 activation of FoxO3,

suggesting that FoxO3 may be a possible target for IPF treatment. FoxO3 is crucial in the development of myofibroblasts from fibroblasts because it restricts phenotypic changes. The TGF- β Smaddependent signalling cascade's controlling element, Smad, is helped to localise by Heat-Shock Protein (HSP)90. Myofibroblastic phenotypic changes in epithelial cell shape and ECM synthesis are brought on by TGF- β, the main cytokine in the EMT route of IPF formation, in conjunction with HSP90 (Hasan et al., 2022)

1.4.7. Others

In the family of pentraxins, pentraxin 2 (PTX-2) is arguably the most pivotal. PTX-2 is essential for innate immune system responses, such as monocyte, macrophage, and neutrophil binding, activation, and control. (Wuytset al., 2014)

Monocytes transform into macrophages with the help of PTX-2. PRM-151 (recombinant human PTX-2) has undergone a phase 1 trial (NCT01254409). Galectin-3 controls TGF- β receptor expression on amniotic epithelial cells and has an effect on TGF— β induced lung fibrosis. Galectin-3 is a -galactoside-binding lectin. Galectin-3 knockout BLM-treated rats showed significant changes in the course of fibrosis, with a reduction in lung collagen content and subsequent lung fibrosis. TGF- β has been demonstrated to prevent the activation of myofibroblasts, the epithelial-mesenchymal transition, and collagen I synthesis. (Mackinnon et al., 2012)

One transmembrane receptor that interacts with the cytoskeleton to initiate intracellular signalling is the integrin. Integrins control how cells adhere to each other and to the extracellular matrix (ECM). Type I and type II AECs express integrin v6 deterministically in the fibrotic regions, as shown by immunostaining of IPF lung tissues, and an elevated amount of v6 is linked to an increased risk of death. (Horan et al., 2008) According to low-dose therapeutic studies employing a BLM mouse model, applying a monoclonal antibody to v6 has the capacity to reduce fibrosis.

Chapter Two

Literature review

2. Literature review

- According to the findings of the most recent studies, pulmonary fibrosis (PF) is a form of lung illness that has a greater rate of mortality. Infections caused by viruses, radiation exposure, and harmful airborne contaminants are all possible contributors to the development of PF. Recurrent lung scarring is a hallmark of the condition known as idiopathic pulmonary fibrosis (IPF), which primarily impacts elderly patients and is linked to pneumonia. A wound healing process that is interrupted, as demonstrated by the dysregulated aggregation of extracellular matrix components, is the cause of the development of fibrotic scar tissue in the lungs. This condition is called fibrotic scarring. There are a number of potential causes, some of which include oxidative stress, changes in cell signalling, inflammation, and other similar processes. Both nintedanib and pirfenidone have been granted conditional approval as treatments for idiopathic pulmonary fibrosis (IPF). In addition, therapy options for PF that make use of natural items have demonstrated some promising results. In this study, we analysed the recently published literature and explored the prospective use of three types of natural products—isolated active compounds, crude plant extracts, and traditional medicine, which consists of combinations of diverse plant products—in the treatment of pulmonary fibrosis (PF). These natural compounds offer promise in the therapy of pulmonary fibrosis (PF) because they can reduce inflammation, oxidative stress, and the shift from endothelium to mesenchymal cells; they can also influence TGF-mediated cell signalling; and many other mechanisms. Based on the findings of the current research, the signalling pathways that are involved in the pathogenesis of PF as well as the potential opportunities for the use of natural product-based therapy to treat PF have been identified. (Hasan et al., 2022)
- There are few treatments that directly address the biology of fibrosis, despite the fact that fibrosis is a fatal clinical feature of many chronic diseases. Natural remedies are gaining popularity as fibrosis treatments. A greater understanding of the shared cellular and molecular processes underlying fibrosis facilitates the development of effective antifibrotic drugs. We discuss a variety of distinct profibrotic pathways and the natural substances that can be used to treat them.

Potential therapeutic targets include interleukin, ephrin-B2, Gas6/TAM, Wnt/-catenin, the hedgehog pathway, PPAR, lysophosphatidic acid, and connective tissue growth factor (CTGF). Inhibiting chronic inflammation, myofibroblast activation, epithelial-mesenchymal transition, and extracellular matrix production, natural products have been demonstrated to be effective in the treatment of fibrosis. Particularly, natural materials provide us with novel avenues to explore in our quest for antifibrotic drugs by inhibiting fibrosis in one organ while simultaneously targeting fibrosis in multiple others. (Chen et al., 2018)

- Pulmonary fibrosis (PF) is a long-lasting, progressive, and deadly lung disease that damages the interstitial lungs and makes it hard to breathe. The pathogenic route is made up of fibroblasts moving, multiplying, and changing into myofibroblasts. This causes extracellular matrix to build up and lung parenchyma to break down. Pirfenidone and nitedanib are the only antifibrotic drugs available, and they only stop the problem from getting worse, not better. In China, plant extracts and organic bioactive chemicals have been used to treat PF for more than 30 years. At the moment, both in vivo and in vitro research is being done on the use of phytotherapy to treat pulmonary fibrosis (PF) in rats with bleomycin (BLM)-induced lung inflammation, oxidative stress, and pulmonary fibrosis. In this review, we wanted to look at how different plant extracts have been used to treat PF and how they work to avoid it. (Bahri et al., 2017)

Chapter Three

Objective of the study

3. Objective of the study

3.1 General Objective

To find out the potential function of active plant components, plant extracts, and traditional herbal medicines in the treatment of pulmonary fibrosis (PF).

3.2 Specific objective

1. To know about pulmonary fibrosis (PF) & its pathogenesis
2. To know about potential therapeutic targets of PF
3. To learn about Soluble Immune Modulators of pulmonary fibrosis
4. To ascertain the diagnosis and natural treatment options of pulmonary fibrosis
5. To know how natural products prevent and treat pulmonary fibrosis by inhibiting inflammation

Chapter Four

Methodology

4. Methodology

4.1. Introduction

The exam is preceded by a literature review. Approximately 57 publications are reviewed for this study.

4.2. Research Design

We examined numerous electronic databases, including PubMed, Google Scholar, and the ISI Web of Science, for clinical and laboratory studies that support the use of natural products to treat pulmonary fibrosis. For referencing mendeley software was used

4.3. Method of Data Analysis

In this research included only English-language articles published between January 2010 and December 2022. The database contained a total of 110 records. Authors were asked to refrain from submitting review pieces, translations, overly informative compounds, and works published in languages other than English. Finally, the feasibility of bridging the gap between exploratory and clinical data was evaluated across 57 separate study studies.

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Chapter Five

Result & Discussion

5. Result

➢ Natural Products for Pulmonary Fibrosis with Targeted Mechanisms

Natural product-based therapeutic techniques for the treatment of pulmonary fibrosis (PF) have shown tremendous promise in both laboratory and clinical research. We examined what was written recently. Active compounds, the vast majority of which are secondary plant metabolites, are extracted from crude plant extract and traditional herbal medicine, which consists of mixtures of various plant parts (root, stem, fruits, etc.). Through their metabolic process, plants produce secondary metabolites, which are chemical molecules with no essential functions in plant growth or reproduction. In the treatment of pulmonary fibrosis, alkaloids, aristolactams, oxoaporphines, amides, indoles, ionones, flavonoids, benzenoids, steroids, and a variety of volatile oils, lipophilic diterpenes, tannins, essential oils, triterpenoid, phenolic compounds, xanthones, etc. all play significant roles. Table 1 summarizes the therapeutic potential of individual natural compounds against PF. In addition, Table 2 provides a summary of the organic and aqueous extracts of medicinal plants that have been demonstrated to treat PF ailment. Typically, decoction techniques, such as boiling plant portions such as stems, bark, leaves, and roots, are used to create traditional Chinese herbal remedies. There are validated decoction formulations for the treatment of PF disease in animals (Table 3).

5.1.1. Inhibition of the EMT Pathway

According to research and clinical trials, several active ingredients can reduce PF by preventing epithelial to mesenchymal cell transition. Alkaloids from Arenaria kansuensis called -carbolines are useful to cure BLM-induced PF mice. (Cui et al., 2019)

Carbolines considerably reduce inflammatory cell infiltration and the pulmonary index. The suppression of the nuclear factor-kappa B (NF-B) and EMT pathways was validated by additional in vitro experiments using TGF-induced A549 cells. Triterpenoid Celastrol, which was discovered to be beneficial in treating BLM-induced rats, was extracted from the root of Trpterygium wilfordii. (Divya et al., 2018)

Table 1: Active molecules isolated from secondary plant metabolites.

No	Source	Categories	Active compound	Experimental Model	Therapeutic Target	*Ref.*
1	*Arenaria kansuensis*	Alkaloid	β-carbolines	In vivo: mice with PF caused by BLM; in vitro: A549, RAW26	Blocking NF-B and p65 and preventing EMT	(Cui et al., 2019)
2	*Bletilla striata*	Dihydrophenanthrene	Coelonin	In vivo: BLM-induced PF rats	Anti-inflammatory and anti-fibrotic	(Jiang et al., 2019)
3	*Tripterygium wilfordii and Celastrus regelii.*	Triterpenoid	Celastrol	In vivo: BLM-induced PF rats; in vitro: A549 cells	TGF-β1/Smad2/3 inhibits EMT.	(Divya et al., 2018)
4	*Glycyrrhiza glabra*	Triterpenoid saponin glycoside	Magnesium isoglycyrrhizinate (MgIG)	Radiation-induced PF mice in vivo; human fetal lung fibroblasts-1 in vitro (HFL1)	p38MAPK/Akt/Nox4 inhibiting fibroblast differentiation.	(Yang etal., 2019
6	*Rhizomes of Curcuma zedoaria*	Curcuminoid	Curcumin and curcumol	n vitro: human lung fibroblast (HLF)	Autophagy-induced collagen inhibition.	(Chun-Bin et al., 2020)
7	*Gentianascabra, Gentiana lutea*	Secoiridoid glycoside	Gentiopicroside (GPS)	In vivo: BLM-induced PF mice; in vitro: A549 cells	Anti-inflammatory and anti-fibrotic via TGF-β-1	(Chen et al., 2018)
8	*Andrographis paniculata*	labdane diterpenoid lactone	Andrographolide	In vivo: lung fibrosis triggered by silica mic	Anti-inflammatory and EMT transition	(Karkale et al., 2018)
9	*Stephania tetrandra, S. Moore*	Alkaloid	Tetrandrine (TET-HP-βCD	In vivo: BLM-induced PF rat	Alleviating inflammation and fibrosis	(Sun et al., 2020)
10	*Polygonum aviculare*	Flavonoid	Juglanin	In vivo: BLM-induced PF mice	Signaling from the genes that stimulate interferon production (Sting) is blocked.	(Mansouri et al., 2019)
11	*Paeonia suffruticosa*	Phenols	Paeono	In vivo: BLM-induced PF mic	Stopping the signaling between MAPKs and Smad3.	(Liu et al., 2017)
12	*Magnolia officinalis*	Neolignan	Honokiol	In vivo: BLM-induced PF mice	Reducing EMT and TGF-/Smad signaling in culture and animal models.	(Pulivendala et al., 2020)
13	*Zingiber officinal*	Phenolics, Ketone	Zingerone	In vivo: BLM-induced PF rats	Changing how much TGF-1	(Gungor et al., 2020)

					and iNOS are produced.	
14	*Rabdosia japonic*	Diterpenoid	Glaucocalyxin	In vivo: BLM-induced PF mice	The blocking of leukocyte infiltration and the generation of proinflammatory cytokines.	(Yang et al., 2017)
15	*Rabdosia rubesecens*	Diterpenoid	Oridonin	In vitro: MRC5 cells, in vivo: BLM-induced PF mice	TGF/Smad pathway regulation.	(Fu et al., 2018)
16	*Vegetables*	Flavonoid	Apigenin	In vivo: BLM-induced PF mice	Anti-oxidative and PPARγ expression	(Chen & Zhao, 2016)
17	*Cruciferous vegetables*	Isothiocyanates	Sulforaphane	In vivo: BLM-induced PF mice; in vitro: A549 cell, MRC-5 cell	Inhibiting EMT transition	(Kyung et al., 2018)
18	*Salvia miltiorrhiza*	Phenolic acids	Salvianolic acid B	In vivo: BLM-induced PF rats; in vitro: MRC-5 cells	Reducing myofibroblast trans-differentiation via upregulation of Nrf2	(Liu et al., 2018)
19	*Citrus plant*	Flavonoid	Rutin	In vivo: BLM-induced PF mic	Reducing TGF-β1-α/SMA/Col I and III pathway	(Bai et al., 2020)
20	*Tea, coffee, cacao, etc*	Alkaloid	Caffeine	a surgically removed lung slice model ex vivo; lung epithelial and fibroblast cells cultured in vitro	Inhibiting TGF-β activation	(Tatler et al., 2016)
21	*Rhubarb*	Anthraquinone	Emodin	BLM-induced PF rats in vivo; alveolar epithelial cells in vitro	Inhibiting EMT transition, TGF-β1, p-Smad2/3	(Tian et al., 2018)
22	*Carthamus tinctorius*	Flavonoid	Hydroxysafflor yellow A (HSYA)	BLM-induced PF mice in vivo; A549 cells in vitro.	Inhibiting ECM deposition	(Jin et al., 2016)
23	*Pericarp of Citrus Reticulata*	Biological amine	4-methoxyphenethylamine	BLM-induced PF rats as an in vivo model; human embryonic lung fibroblast as an in vitro model	Reducing TGF-β1	(Zhou et al., 2016)
24	*Fruits*	Vitamin	Ascorbic Acid	the PQ-induced in vivo	Inhibiting IL-6, IL-17a, TGF-beta	(Rodrigues da Silva et al., 2018)

The suppression of EMT by HSP90 is also impacted by celastrol. Gambogic acid, a distinct xanthonoid compound derived from Garcinia hanburyi reverse EMT, was found

to be associated with decreased vimentin and increased cadherin in TGF- β 1-stimulated A549 and HPME cells.

Table 2: Therapeutic strategies for treating pulmonary fibrosis using plant extracts**.**

No	Formula	Source and Components	Experimental Model	Therapeutic Target	Ref.
1	Citrus alkaline extracts (CAE	*Pericarp of Citrus reticulata* (flavanone, alkaloid)	In vivo: BLM-induced PF mice; in vitro: primary murine lung fibroblasts	Preventing fibroblast senescence via activation of cyc-	(Feng et al., 2019)
2	Grape seed extracts	*Flavonoids, ascorbic acid (vitamin C), tocopherols, citric acid, limonoids, sterols, and minerals*	In vivo: BLM-induced PF mic	Inhibition of MMP-9 and TGF-β1	(Liu et al., 2017)
3	Myrtle	*Myrtus communis L*. (flavonoids, tannins, and essential oils)	In vivo: BLM-induced PF rats	Anti-inflammation and anti-oxidative	(Samareh Fekri et al., 2018)
4	Mixture of extracts	Rhodiola rosea L. (RRLroots)'s and rhizomes (phenylpropanoids, organic acids, and flavonoids))	In vivo: BLM-induced rats	TGF-β1 signaling transduction in lung tissues	(Qin et al., 2019)
5	Arenaria kansuensis	*Chinese herbal* (plant extracts)	In vivo: PQ-induced PF mic	Activation of Nrf2 pathway and the inhibition of NFkb/TGF-beta1/Smad2/3 pathway.	(Cui et al., 2021)
6	Tanshinone IIa	*Salvia miltiorrhiza* (plant extracts)	In vivo: silica-induced PF rats; in vitro: A549 and HBE cells.	Inhibition of EMT	(Feng et al., 2020)
7	B-peltoboykinolic acid	*Astilbe rubra* (plant extracts)	In vitro: A549 cells	Inhibition of EM	(Bang et al., 2019)
8	Aged garlic extract (AGE)	*Alluim sativum* (plant extracts)	In vivo: TiO2-induced toxicity	Attenuating hepatic inflammation and pulmonary fibrosis	(Moustafa & Hussein,2016)

Table 3: Traditional herbal medicine

No	Name	Components	Experimental Model	Therapeutic Target	Ref.
1	Chuanxiong Kangxian granules (CCKG)	*Combination of Chuanxiong and Kangxian*	In vivo: BLM-induced PF rats	Inhibition of oxidative stress and inflammation	(Shi et al., 2017)
2	Triptolide (TPL)	*Tripterygium wilfordii*	In vivo: PQ-induced PF mice	Binds with TGF-β and inhibits Smad3, E-	(Chen et al., 2017)

				cadherin, and Vimentin	
3	Xin jia xuan bai cheng qi decoction (XJXBCQ)	Rhei radix and rhizome, Gypsum fibrosum Trichosanthis pericarpium, Persicae semen, Semen armeniacae amarum, the teleophaga Eupolyphaga (in 10:3:2:5:3:3 ratio).	In vivo: BLM-induced PF rats; in vitro: MRC-5 cells	TGF-β1-Smad2/3 signaling	(Qin et al., 2019)
4	Radix puerariae extracts (RPES)	*Radix puerariae extracts (RPES)*	In vivo: PQ-induced PF mice	Fstl pathways and oxidative stress by inhibiting mir-21 expression	(Liu et al., 2016)
5	Renshen pingfei decoction (RPFS)	Anemarrhena asphodeloides, Lycium chinense, Morus alba, Panax ginseng, Glycyrrhiza uralensis, Asparagus cochinchinensis, and Citrus reticulata.	In vivo: BLM-induced PF rats	Downregulating TGF-β1/Smad3 signaling pathway	(Chen et al., 2016)
6	Yangyin Yiqi mixture (YYYQ	*Traditional Chinese medicine*	In vivo: BLM-induced PF rats	Suppressing TGF-β1/Smad signal pathway and EMT	(Meng et al., 2019)

Cruciferous vegetables create the isothiocyanate form of sulforaphane. To restore epithelial form in vitro, it inhibits BLM's induction of fibronectin, lowers the expression of transcription factors linked to EMT (Slug, Snail, and Twist), and raises E-cadherin levels. (Kyung et al., 2018) Emodin, an anthraquinone molecule, dramatically lowers lung deformation, cytokine expansion, and excessive collagen production. By boosting Nrf2 signaling, it inhibits p-IIB, NF-B, the EMT transition, TGF- β 1, and p-Smad2/3. (Tian et al., 2018)

Peltoboykinolic acid is a potent plant extract that targets the EMT pathway (Table 2). Astilbe rubra extract contains peltoboykinolic acid, which inhibits COL1 and fibronectin. Moreover, the whole plant ethanol extract of A. Rubra stops TGF- β 1 from causing EMT in A549 cells. In dichloromethane fractions, TGF- β 1-induced EMT inhibition is the strongest. Peltoboykinolic acid inhibits the Smad pathway that is triggered by TGF-1. (Bang et al., 2019)

5.1.2. Inhibition of TGF-β Signaling

The most common soluble immune mediator implicated in the formation of PF is TGF— β mediated signaling. There will therefore unavoidably be a large range of

tactics used to prevent TGF- β signaling. The Salviae miltiorrhza plant is the source of the polyphenol known as salvianolic acid B (SAB). In NIH/3T3 fibroblasts, it alters the expression of the fibrotic genes collagen and others. SAB (50g/mL) treatment reduced this proliferation without producing any obvious damage, although TGF— β sensitive MRC-5 fibroblasts increased their production of collagen type 1 alpha 1 (COL1A1) and COL1A2 by 240% and 170%, respectively. SAB dramatically decreased the expression of COL1A1, COL2A2, and COL3A1 that was stimulated by TGF-. E-cadherin expression was decreased by TGF- and TNF-, but this effect was mitigated by SAB. (Liu et al., 2016)

GPS is a member of the secoiridoid glycoside family. GPS decreased the amount of hydroxyproline in the PF mice's lungs, which considerably decreased the levels of TNF- and IL-1 in BAL fluid. In the lungs of PF mice, GPS dramatically decreased TGF-1 and CTGF expression. Furthermore, GPS dose-dependently blocked the EMT pathway in an in vitro experiment utilizing TGF- 1-stimulated A549 cells. (Chun-Bin et al., 2020)

The phenolic substance gingerone originates in ginger. Interleukin-1 beta, malondialdehyde, tumor necrosis factor alpha, and collagen levels are all lowered (MDA). In PF-induced rats, superoxide dismutase (SOD) and glutathione peroxidase activity are both increased, likely as a result of ginger's ability to reduce TGF- 1 and iNOS production. The diterpenoid oridonin from Rabdosia rubesecens prevents the TGF- /Smad pathway from working. Oridonin both downregulates -SMA and COL1A1 expression in vitro and in vivo in TGF- stimulated MRC-5 cells and in BLM-induced PF mice. (Fu et al., 2018)

The activities of total cells, macrophages, lymphocytes, and lactate dehydrogenase in BAL fluid are all markedly decreased by the citrus flavonoid rutin. Nitric oxide elevated glutathione and superoxide dismutase (SOD) levels in PF-mice treated with rutin, whereas lung MDA was lowered. Moreover, decreased collagen deposition and lung hydroxyproline concentration are linked to lower expression of collagen type I, type III, and -SMA, as well as transforming growth factor beta 1. (Bai et al., 2020)

Caffeine was discovered to decrease TGF- activation in epithelial cells, but not in fibroblasts, in an ex vivo investigation using a precisely cut lung slice model. In a lung

slice model, caffeine administration for five days reduced fibrosis and decreased the expression of the -SMA gene. (Tatler et al., 2016)

By inhibiting the TGF- β /Smads pathway, the Arenaria kansuensis (AE) ethanol extract reduced the production of collagen and -SMA. Inhibiting the NF-kB/p65 pathway and inflammatory cytokines is another method that AE can lessen pulmonary inflammation. Also contributing to the reduction of oxidative stress were AE's effects on ROS levels, GSH levels, and SOD activity. (Cui et al., 2021) Salvia miltiorrhiza ethyl acetate (EASM) extract reduces oxidative stress in the lungs of BLM-treated mice by increasing Nrf2 and decreasing Nox4 levels. EASM decreased ROS production in fibroblasts by encouraging the breakdown of the kelch-like ECH-associated protein 1. (Keap1). Nrf2 knockdown decreased the anti-fibrotic effects of EASM in the lungs of mice treated with BLM. EASM decreased both the synthesis of ECM and the activation of myofibroblasts. (Peng et al., 2019)

In vivo, Xin Jia Xuan Bai Cheng Qi Decoction (XJXBCQ) treatment dramatically boosted Smad7 levels, lowered hydroxyproline levels, and improved lung function. On lung TGF- β1 protein expression, XJXBCQ had a markedly reduced effect. After TGF-β1 treatment, the MRC-5 cells were treated with XJXBCQ, which reduced the expression of -SMA, fibronectin, IL-17A, and IL-25. It was demonstrated that p-Smad2 was downregulated in a dose-dependent manner after XJXBCQ treatment of TGF- β 1-stimulated MRC-5 cells. Smad2 expression is decreased by XJXBCQ, whereas Smad7 expression is elevated, both at the mRNA and protein levels. (Qin et al., 2019)

When the Chinese herbal extract triptolide (TPL) binds to transforming growth factor beta, it prevents the EMT of lung epithelial cells (TGF- β). As a result of PQ-induced PF, the expression of vimentin was elevated whereas the expression of E-cadherin was downregulated. After TPL treatment, EMT was halted in its tracks, E-cadherin expression was increased, and vimentin levels were decreased. TGF- β binding to TPL caused TPL to inhibit the TGB1/Smad3 pathway. (Samareh et al., 2018) The favorable benefits of renshen pingfei decoction (RPFS) on lung damage, fibrosis, and function are brought about by a decrease in hydroxyproline content. Because to RPFS, the amounts of TGF- β1 and Smad3 mRNA and protein in lung tissue are decreased. Reduced levels of NF-B are found in rats' BAL fluid. It manages the level of SOD and

MDA in rat serum by blocking the TGF- β 1/Smad3-mediated intracellular signal transduction pathway. (Chen et al., 2016)

The levels of TGF- 1, CTGF, and hydroxyproline as well as the mRNA expression of TGF- β1, TRI, TRII, Smad3, -SMA, laminin, and collagen I were all significantly decreased after treatment with medium and high dosages of Yangyin Yiqi, ixture (YYYQ). Smad7 and E-cadherin expression, however, increased in the BLM and BLM treated with prednisolone groups following exposure to YYYQ. It was thought to be related to the downregulation of the TGF- β1/Smad and EMT signaling pathways. (Meng et al., 2019)

5.1.3. Anti-inflammatory and anti-oxidant properties

Some drugs can be used to treat PF by lowering oxidative stress and inflammation. It has been demonstrated that the dihydrophenanthrene chemical coelonin significantly inhibits the LPS-Apigenin, found in many plants, lowered inflammatory responses and oxidative stress. Apigenin lowers both hydroxyproline levels and the number of inflammatory cells. In addition, it raises the levels of SOD and PPAR in the lungs. In the lungs, it results in elevated levels of E-cadherin and Smad-7 and reduced production of NF-B, MMP-9, vimentin, and TGF- β. (Fu et al., 2018)

The alcohol glycoside rosavin from Rhodiola rosea reduces the quantity of inflammatory cells in BAL fluid as well as the expression of pro-inflammatory cytokines in lung tissue. Levels of hydroxyproline and malondialdehyde are also decreased. Lung tissue also showed increased levels of SOD and glutathione peroxidase activity. It has been established that Nrf2 overexpression and NF-kB p65, TGF- β1, and -SMA downregulation are the mechanisms by which rosavin-mediated fibrosis amelioration occurs. (Xin et al., 2019)

The terpenoid molecule glaucocalyxin A (GlnA) dramatically lowers lung collagen deposition and hydroxyproline concentration. Moreover, GlnA reduces the levels of pro-inflammatory cytokines in BAL fluid and reduces macrophage and neutrophil infiltration. (Yang et al., 2017)

The positive nutraceutical effect of aged garlic extract (AGE) in decreasing pulmonary fibrosis was confirmed in an animal model of TiO2-induced pulmonary and hepatic disease. One way AGE reduces TiO2-induced toxicity is via lowering pulmonary MMP-9, TIMP-9, TGF- β 1, collagen-1, and fibronectin mRNA. (Moustafa & Hussein,2016)

The methanolic extract of Myrtus communis significantly reduces lipid peroxidation, hydroxyproline content, and parenchymal inflammation (Myrtle). In PF mice, it increases catalase synthesis as well. (Samareh Fekri et al., 2018)

CAE regulates the senescence-associated secretory phenotype by repressing senescence in fibroblasts. Further mechanistic studies showed that CAE reduces lung fibroblast senescence through a P53-dependent mechanism and that CAE inhibits P53-dependent fibroblast senescence by activating cyclooxygenase-2. (Feng et al., 2019)

Rats with BLM-induced lung fibrosis are protected by Chuanxiong Kangxian granules (CCKG). When exposed to BLM, CCKG inhibits collagen deposition, oxidative stress, and inflammatory responses by downregulating the production of matrix metalloproteinase-2 (MMP-2) and -9 (MMP-9). (Shi et al., 2017)

5.1.4. Modulation of Cellular Signaling

The effects of magnesium isoglycyrrhizinate therapy on collagen synthesis, ROS production, and TGF—β1 elevation were all negative (MgIG). Nox4 and p38/MAPK/Akt expression was reduced in both vivo and in vitro as a result of MgIG treatment. Alpha-mangostin therapy in vivo significantly reduced the mRNA and protein levels of -SMA and Col 1. (-MG). The effects of -MG therapy were seen in the improvement of lung TGF— β1 expression and Smad 2/3 phosphorylation abnormalities. -MG also promotes AMPK-mediated inhibition of NOX4 expression and TGF- β1-induced trans-differentiation of lung fibroblasts, both of which reduce fibrogenesis. (Li et al., 2019) Centella asiatica has an essential component called madecacassoside, which profoundly modifies cellular transmission in the intestines. You can take it orally, but not intravenously. Madecacassoside has powerful anti-fibrotic properties when taken orally. Through increasing PPAR- mRNA, nuclear translocation, and DNA binding activity in madecacassoside-treated colonic epithelial cells, madecacassoside raises hepatocyte growth factor levels in colon tissue. (Xia et al., 2016)

5.1.5. Inhibition of ECM Deposition

Collagen, an essential component of the ECM, is deposited in the lungs, aiding the pathophysiology of fibrosis. As a result, ECM inhibition may prove to be a crucial therapeutic approach for pulmonary fibrosis. Curcuminoids like curcumin and curcumol inhibit autophagy, which in turn decreases ECM deposition. Treatment of human lung fibroblast cells with curcumin or curcumol in vitro dramatically decreased

the deposition of hydroxyproline, -SMA, Col-I, and Col-III. Furthermore, dose-dependent deregulation was observed for N-terminal pro-peptide for type I collagen (PINP), N-terminal pro-peptide for type III collagen, and prolyl-hydroxylase associated to ECM. (Chun-Bin et al., 2020)

The pulmonary collagen deposition is inhibited by the flavonoid hydroxysafflor yellow A (HSYA) from Carthamus tinctorius. In addition to lowering Smad3 phosphorylation (Jin et al., 2016) HYSA also lowers the increase in TGF- β, -SMA, and collagen I mRNA brought on by BLM. A biological amine termed 4-methoxy phenethylamine is found in the pericarp of citrus reticulate, and it prevents the breakdown of hydroxyproline in blood and lung tissue. Furthermore, TGF- β expression is inhibited. (Zhou et al., 2016) In paraquat-induced PF mice treated with ascorbic acid, immune cell infiltration, IL-17 and TGF- β secretion, and extracellular matrix (ECM) deposition were all significantly reduced. The antioxidant enzymes SOD and catalase are also increased by vitamin C. (Rodrigues da Silva et al., 2018) Radix puerariae extracts (RPEs) contain antioxidant and anti-inflammatory properties that lessen the severity of lung fibrosis brought on by PQ. RPE dramatically decreased the expression of miR-21 and Fstl 1 pathways, which both contribute to lung fibrosis. In vitro and in vivo studies have demonstrated that the Chinese herbal medicine Hong Jing Tian's small RNA (HJT-sRNA-m7) lowers fibrotic markers. The decoction contains the phosphocholines PC (18:0/18:2) and PC (16:0/18:2), which help cells absorb short RNAs. We discovered that gene expressions for -SMA, fibronectin, and collagen type I 1 (COL1A1) could all be effectively reduced using HJT-sRNA-m7. (Du et al., 2019)

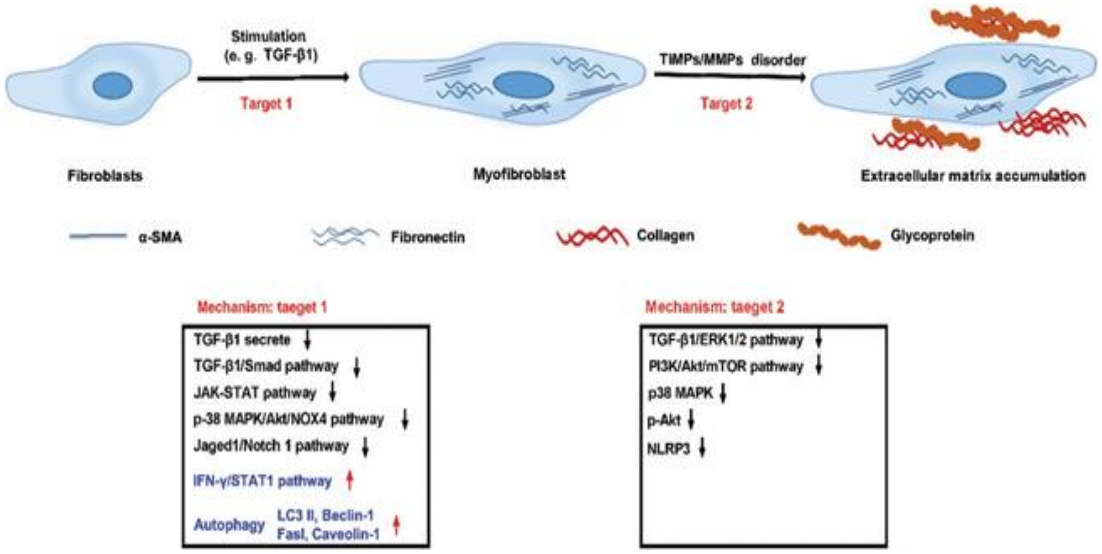

Figure 3: The activation of fibroblasts results in the accumulation of extracellular matrix. Inactive fibroblasts become active and begin to proliferate when they are stimulated by cytokines. These active fibroblasts subsequently differentiate into myofibroblasts, which produce a high quantity of extracellular matrix proteins, and cause an imbalance in the control of the matrix by TIMPs and MMPs, which ultimately results in an accumulation of extracellular matrix. (Wang et al.,2023)

5.2. Discussion

Globally, the number of people with pulmonary fibrosis is going up every year. Preventing and treating pulmonary fibrosis will do a lot to improve health and lessen the cost burden of the disease. Even though study into what causes pulmonary fibrosis is making progress, the exact causes are still unknown, and pulmonary fibrosis is still hard to treat. Pulmonary fibrosis can be caused by problems with the immune system, a lack of redox balance, and problems with how food and energy are used. Several signalling pathways and cytokines control important disease processes, such as the creation of extracellular matrix, the growth of fibroblasts, and EMT. Clinical treatments that focus on a specific part of the disease or how it works don't always work to reverse it. This could be a big reason why lung fibrosis is still not curable. Because of this, it is very important to find new ways to deal with the lack of pharmaceutical drugs. Still, it is very hard to make new medicines because we still don't know much about how lung fibrosis happens. Pulmonary fibrosis cases can be cut down by putting more focus on early diagnosis and prevention instead of treatment. This could help people feel better. Natural things fit well with these goals because they have many different biological uses and come from many different places. It's important because natural substances can affect many regulatory systems and networks at the same time. This makes them a good choice for healing pulmonary fibrosis, a disease that affects many parts of the body and has many different causes. Natural substances like bleomycin, trachea, paraquat, carbon tetrachloride, endotoxin, silica, and cigarettes have shown promise in avoiding and treating lung damage and pulmonary fibrosis in a wide range of animal species. From a mechanistic point of view, natural products can affect the Nox4-Nrf2 pathway, the NF-B pathway, the PI3K/Akt/mTOR pathway, the p38 MAPK/Akt/Nox4 pathway, the AMPK pathway, and others. All of these pathways are linked to the pathogenesis of pulmonary fibrosis. These substances have an effect on the pathogenetic processes that are known to cause pulmonary fibrosis. This means that

they can be used to avoid and treat it. This shows that natural products can help avoid and treat pulmonary fibrosis in a powerful way.As was already said, natural goods are made up of many different compounds, such as polyphenols, flavonoids, terpenoids, alkaloids, and other phytochemicals. All of these are good for lung fibrosis, especially in the early stages of inflammation and oxidative stress. In short, Fig. 3 shows how the molecules that make up a number of natural chemicals are arranged. Some of the active groups in these natural substances are the polycyclic benzene structures, the exposed carboxyl groups of polycyclic rings, the phenolic hydroxyl or carboxyl groups, and the conjugated double bond carboxyl groups. Polyphenols and flavonoids are the two most common types of natural substances that can stop or treat lung fibrosis. They are found in plants and help fight free radicals and inflammation. But the fact that terpenoids and glycosides have more complicated structures than polyphenols and flavonoids, which have been studied for a long time, does not mean that polyphenols and flavonoids are better at stopping lung fibrosis. Natural background amounts are not very high, biological functions are often lost during processing, and extraction and purification technology is still not very good. These chemical substances have a lot of promise and need to be looked into more.Even though natural goods have the benefits and possible uses we've already talked about, only a small number of them are used in clinical settings right now. Also, no one knows for sure what causes lung fibrosis. Prevention and treatment of pulmonary fibrosis seem to have effects that are hard to explain without a lot of research. It can't explain how natural chemicals affect pulmonary fibrosis in the way that drugs do. To get around the yield restriction bottleneck, future study should focus on developing the technology for extracting and purifying natural products, figuring out which natural products play the most important biological roles in complex systems, and using chemical synthesis. It is also important to know how lung fibrosis happens and what causes it. This will encourage doctors to use natural products and help explain how they can be used to avoid and treat pulmonary fibrosis. Even though they don't work as well as synthetic medicines, natural remedies are better at avoiding and treating pulmonary fibrosis when it is in its early stages. When using natural goods as medicine, it is also hard to get the safety and pharmacokinetic information needed to figure out the best dose. As people learn more about preventing illness and staying healthy, methods and management guidelines that make it easier to switch to and use natural products need to be raised and improved.

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Chapter Six

Conclusion

6. Conclusion

Pulmonary fibrosis is caused by structural deformities of the lungs. Recent clinical evidence suggests that SARS-CoV-2 survivors may have a pathophysiology comparable to that of PF. In this article, the immune-regulating mechanisms of PF are briefly discussed. Also presented are therapeutic targets that may prove useful in the future against PF. We analyzed recent research and clinical data (2015-2022) to determine the potential function of active plant components, plant extracts, and traditional herbal medicines in the treatment of pulmonary fibrosis (PF). Despite the abundance of studies examining the efficacy of natural substances for treating PF, the cohort weights are well-designed, with large sample sizes and extended follow-up. Is inadequate. To coordinate the release of anti-PF medication, each chemical must be approved for its specific target using cutting-edge drug discovery techniques such as in silico modelling, high-throughput screening, framework modelling and reconstruction, etc.

Chapter Seven

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7. Reference

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A Review on Potential Therapeutic Effect of Natural Products with Targeted Mechanisms in the Treatment of Pulmonary Fibrosis [A dissertation submitted to the Department of Pharmacy, Faculty of Allied Heath and Sciences, Daffodil International University, Dhaka. This report presented in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy.] Submitted To The Department of Pharmacy Faculty of Allied Health Sciences Daffodil International University Submitted By Mehedi Hasan Roni ID: 191-29-1472 Batch: 21th DSC-C Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University April, 2023 i Abstract Pulmonary fibrosis is an incurable end-stage lung disease that continues to be a global public health issue. Although some advances have been made in understanding the pathogenesis of pulmonary fibrosis, effective intervention methods remain limited. Natural products contain numerous biological activities and a high level of safety, which are essential elements in the prevention and treatment of pulmonary fibrosis. We summarized the processes and health advantages of natural products against pulmonary fibrosis in this review. These natural products target oxidative stress, inflammatory injury, epithelial-mesenchymal transition (EMT), fibroblast activation, extracellular matrix accumulation, and metabolic regulation via pathways involving the TGF-β Signaling pathway, anti-inflammatory and anti-oxidant properties, modulation of Cellular Signaling pathway, EMT pathway and Inhibition of ECM deposition. We hope to develop novel methods for preventing and treating pulmonary fibrosis. Keywords: Natural remedies; therapeutic targets; plant active ingredients; plant extracts; herbal medicine; pulmonary fibrosis ii Chapter & Serial NO Index Contents Page No Chapter-1 Introduction 1,1. Pulmonary Fibrosis Pathogenesis 1.2. Pulmonary Fibrosis Soluble Immune Modulators 1.2.1. Transforming Growth Factor-Beta-1 (TGF-β1) 1.2.2. PDGF 1.2.3. CCL2, 17, 18, and CXCL12 1.3. Potential Therapeutic Targets of PF 1.3.1. Targeted Antioxidative 1.3.2. Targeted Cell Signaling Pathways 1.3.3. Targeted Cytokines and Chemokines 1.3.4. Targeted EMT Pathways 1.3.5. Targeted Growth Factors 1.3.6. Targeted Transcription Factors 1.3.7. 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Introduction Pulmonary fibrosis is the result of a number of progressive short-term and long-term lung illnesses. The average amount of time a person with pulmonary fibrosis lives after being diagnosed is only 3–5 years, and the average amount of time a person lives after a severe exacerbation is only 2–3 months. Symptoms of this disease include a dry cough and shortness of breath. (Richeldi et al., 2017) Epidemiological studies show that the number of people with lung fibrosis is rising every year.The tumor-like condition known as pulmonary fibrosis is now a major public health issue on a global scale. The main risk factors include age, smoking, environmental exposure, viral infection, and inheritance. (Kwapiszewska et al., 2018) Pirfenidone and nintedanib are primarily employed in the management of pulmonary fibrosis. Glucocorticoids are used to treat pulmonary fibrosis in addition to antioxidants, receptor inhibitors, and other drugs. These clinical medications' efficacy and side effects, however, are restricted. (Hutchinson et al., 2015) Even though early injury and immune disorders can be prevented and treated, pulmonary fibrosis is still incurable. Therefore, early disease prevention and correction of anomalous symptoms are essential for high-risk and suspected groups to delay the onset of clinical disease. The social and financial cost of the disease can also be lessened for the patient. Clinical drugs cannot be used to prevent disease because their main purpose is to treat it. Therefore, it is crucial to develop new interventional techniques that can treat and prevent pulmonary fibrosis. As a result of their anti-inflammatory, antioxidant, immune-regulating, and metabolic properties, natural medicines are increasingly frequently utilised in the prevention and treatment of cancer, cardiovascular disease, metabolic disease, and respiratory disease. (Papadopoulos et al., 2017) Numerous preclinical studies have demonstrated that several plant-derived natural products have both therapeutic and preventive effects on pulmonary fibrosis through a variety of mechanisms, including decreasing oxidative damage, decreasing inflammation, inhibiting fibroblast proliferation and activation, and resolving metabolic issues, suggesting that these substances have the potential to both stop the onset of pulmonary fibrosis and slow the clinical progression of this condition. (Chen et al., 2018) In this study, we provide fresh recommendations by describing the pharmacological processes of natural substances used in the prevention and treatment of pulmonary fibrosis. 1.2. Pulmonary Fibrosis

Pathogenesis The pathogenesis of pulmonary fibrosis is yet unknown. Typically, pulmonary fibrosis begins with abnormal tissue repair following injury. Inflammation and oxidative stress harm lung tissue while activating the body's repair and defence mechanisms. (Bahri et al., 2017) Figure 1: Pulmonary fibrosis pathogenesis. In response to lung injury, epithelial cells discharge inflammatory mediators (IMs), which trigger an antifibrinolytic coagulation pathway, activating platelets and resulting in the formation of blood clots. Activated leukocytes release profibrotic cytokines like TGF-, IL-1, IL-1, IL-13, and TGF-. The removal of infections and dead cells is also made possible by this, enabling neutrophils and macrophages. Afterwards, BM fibrocytes and local fibroblasts proliferate and develop into myofibroblasts, which secrete elements of the extracellular matrix (ECM). The ability to develop into fibroblasts and myofibroblasts is another feature of epithelial cells that have undergone EMT. Myofibroblasts support wound healing during the last redecorating and resolution stage, which results in wound contraction and blood vessel regeneration. When a stage of tissue regeneration is poor or when lung- damaging forces persist, fibrosis is frequently seen. Furthermore, TGF- influences epithelial cells, resulting in EMT and the development of myofibroblasts, which create ECM. TGF- β 1 promotes the growth of Th17 cells, which results in PF and intensifies inflammatory activity. Similar to this, epithelial cells produce IL-33, IL-25, and TSLP in response to injury, encouraging profibrotic Th2 responses. The cytokines IL-25 and IL-21, which support Th2 differentiation, are also produced by T cells. A profibrotic macrophage subset (PMS) can form and secrete TGF- β 1 and other mediators when Th2 cells generate IL-13. TGF-1 fibroblasts can also be directly activated by IL-13 on its own. As a result, Th2 cytokines stimulate the production of collagen by bone marrow (BM) fibrocytes, which in turn stimulates fibrotic reactions. Myofibroblasts then appear in order to release ECM components, producing PF as a result. Although several PF manifestations, including those caused by particulate matter (like silica and asbestos), drugs (like bleomycin), bronchiolitis obliterans, radiation, and persistent graft-versus- host-induced PF, can be reliably established and studied in rodents, it is still unknown whether all experimental models accurately replicate the idiopathic aspect of the condition (Hasan et al., 2022) 1.3. Pulmonary Fibrosis Soluble Immune Modulators. During an improperly controlled wound healing process, fibroblasts become pro- fibrotic and apoptosis-resistant myofibroblasts. Growth factors, cytokines, and chemokines all have an impact on the myofibroblasts' already robust activity. Pulmonary fibrosis is thought to be caused by a number of immune cells and soluble mediators, including neutrophils, phagocytes, fibrocytes, and T lymphocytes. (Kolahian et al., 2016) 1.3.1. Transforming Growth Factor-Beta-1 (TGF-β1) TGF- β 1 is usually linked to the aetiology of PF. The formation of TGF- β based PF has been linked to activation of the ERK, MAPK, and phosphatidylinositol 3-kinase/Akt pathways. TGF- β 1 also increases the transcription of pro-collagen I and II by activating the serine/threonine kinase and Smad2/3 pathways. Furthermore, TGF- β 1 promotes fibroblast proliferation through vascular cell adhesion molecules 1 and fibroblast differentiation into myofibroblasts by activation of -SMA and galectin-3. Moreover, glycogen synthase kinase-3 mediates the differentiation of myofibroblasts that is stimulated by TGF- β 1. TGF- β 1-targeting treatments are being developed for the treatment of PF. The symptoms of PF have been demonstrated to be alleviated by TGF- β 1 monoclonal antibodies, blocking the TGF- β 1 activator integrin protein v6, and blocking the TGF- β 1 type 1 receptor. Furthermore, paclitaxel-mediated miR-140 overexpression results in the TGF- β 1/Smad3 pathway being downregulated, which in turn decreases PF. (Hasan et al., 2022) 1.3.2. PDGF Lung fibroblast survival and differentiation depend on the growth factor PDGF. In clinical IPF lung tissue, it has been discovered that macrophages and epithelial cells overexpress PDGF. In both BLM- and radiation-induced PF, the PDGF-tyrosine kinase inhibitor imatinib significantly reduced fibrosis. By concentrating on PDGFR, c-KIT, and Bcr-Abl, this was accomplished. Although encouraging results from preclinical research, imatinib unfortunately failed clinical studies. (Daniels et al.,2010) A novel PDGFR inhibitor called nintedanib has been introduced and has acquired FDA approval to supplement the treatment of IPF with pirfenidone. (Richeld et al., 2020) 1.3.3. IL-6, -8, and -37 Recent clinical evidence suggests that IL-6 and IL-8 levels are higher in acute exacerbated-IPF patients than in IPF patients. TGF- β levels dramatically differ depending on the course of an illness, although IL-4, IL-10, and IL-13 TGF- β levels do not. (Papiris et al., 2018) Treatment with the anti-inflammatory cytokine IL-37 decreased PF caused by BLM by lowering collagen deposition and inflammatory infiltration into the lungs. In contrast to enhancing IFN expression, lung tissue IL-37 treatment reduced the expression of MCP-1, IL-6, and TNF alpha. (Hasan et al., 2022) 1.4. Potential Therapeutic Targets of PF The diagnosis, treatment, and prognosis of PF all have therapeutic targets that have been identified. Among the most important are cytokines, chemokines, growth factors, mediators of cell signalling, mediators of collagen remodelling, transcription factors, and mediators of other cellular processes. Figure 2 depicts potential PF treatment targets. 1.4.1. Targeted Antioxidative Pathways It has been discovered that oxidative stress, which is predominantly brought on by the NADPH oxidase (NOX) enzymes that produce reactive oxygen species (ROS), is a contributing factor in idiopathic pulmonary fibrosis (IPF). Fibrotic tissue can form in response to several different forms of NOX. The three NOX isoforms that are covered are NOX1, NOX2, and NOX4. TNF-alpha and other cytokines are produced more often as a result of the IPF's oxidative environment. Inducible nitric oxide synthase (iNOS), an enzyme that produces nitric oxide (NO) that is essential for the onset of idiopathic pulmonary fibrosis, is subsequently activated by this (Hasan et al., 2022) 1.4.2. Targeted Cell Signaling Pathways The PI3K/Akt/mTOR pathway is essential for metabolism, cell growth, and survival. It has been demonstrated that blocking the PI3K/Akt pathway reduces TGF- β induced fibroblast proliferation and differentiation. Idiopathic pulmonary fibrosis (IPF) has been the subject of clinical investigations using the PI3K/Akt/mTOR pathway inhibitor olaparib (GSK2126458) In idiopathic pulmonary fibrosis (IPF), G-protein coupled receptors (GPCRs) are considered to stimulate profibrotic fibroblast promotion. Fibrotic lesions display increased ROCK activity in both rodent models

of IPF and IPF patients. At the site of the damage, this results in profibrotic fibroblasts, epithelial cells, and endothelial cells. Immune cells in BAL fluid decreased in clinical trials using fasudil to inhibit ROCK, Knipe et alhaploinsufficiency .'s studies imply that ROCK1 and ROCK2 guard against BLM-related development. JNK, a member of the mitogen- activated protein kinase (MAPK) family, controls a number of cellular processes essential to the development of tumours and neurodegenerative diseases when it is triggered by cytokines and other stress stimuli. AEC, vascular endothelial cells, alveolar macrophages, smooth muscle cells, and lymphocytes have been observed to have an increase in phosphorylated JNK in patients with IPF. (Hasan et al., 2022) Due to CC 930's JNK inhibition's encouraging results in phase I clinical studies (NCT01203943) the drug is being tested in phase II trials. Figure 2: IPF mechanism-targeted therapies. Environmental micro-injuries, genetic and epigenetic influences, and microbial activity affect fibrosis and myofibroblast activation pathways and variables. This graphic shows how essential signaling molecules and variables interact, revealing IPF therapeutic targets discovered during years of research. (Lv et al., 2019) 1.4.3. Targeted Cytokines and Chemokines Patients with IPF had a higher than normal level of interleukin-13. Age-related fibrosis development was also seen in a mouse model study. The experimental context, both in vitro and in vivo, reveals a complicated signalling network involving several interactions between macrophage CCL2 and TGF- and IL-13. In a mouse model of lung fibrosis, IL-13 (a Th2 cell cytokine) is shown to be beneficial. The lysyl oxidase (LOX) enzyme family promotes fibroblast expansion by deaminating between lysyl and hydroxylysine residues in type 1 collagen molecules. Premature senescence and increased cell proliferation are both signs of high LOX ligand (LOXL)-2 expression. By blocking LOXL-2 with the monoclonal antibody AB0024, the number of activated fibroblasts is reduced, and the TGF- β signalling pathway is downregulated. (Hasan et al., 2022) 1.4.4. Targeted EMT Pathways The transformation of epithelial cells into cell types with mesenchymal characteristics is characterised by changes in shape, increased motility, and the presence of mesenchymal markers such N-cadherin (CDH2), vimentin, and -SMA. The pathogenesis of IPF is further complicated by the epithelial-mesenchymal transition (EMT), which promotes the growth of myofibroblasts . As evidence of the significance of Wnt signalling in pulmonary fibrosis, neutralising antibodies against Wnt1-inducible signalling pathway protein-1 are used in mice treated with BLM to delay the onset of idiopathic pulmonary fibrosis . It has been suggested that wnt signalling could be a key therapy target for IPF. A critical factor in the development of pulmonary fibrosis is an imbalance in matrix metalloproteinases (MMPs), which encourages fibroblast proliferation and prolongs the process of ECM buildup . MMP inhibition as a secondary target may be advantageous for the management of IPF disease (Hasan et al., 2022) 1.4.5. Targeted Growth Factors TGF- β, stimulates fibroblast proliferation, chemotaxis, and ECM deposition in epithelial, endothelial, and mesenchymal cells. IPF patients' BAL fluid has high levels of CTGF, a TGF-β inducer. In a mouse model of fibrosis caused by BLM, anti-CTGF antibodies decreased the disease. FG-3019, a human anti-CTGF antibody, is being tested in IPF patients in a brand-new phase II study (clinicaltrials.gov ID NCT01890265). In IPF, levels of the tyrosine kinase receptor ligands PDGF, VEGF, and FGF are increased. When fibroblasts are stimulated by PDGF to release growth factors and ECM components, IPF begins to manifest. Profibrotic TGF-1, FGF, and TNF alpha are PDGF-dependent. The most common IPF inducers are CTGF, PDGF, VEGF, FGF, and TGF-1 and recent therapy advancements have focused on them because of their critical involvement in the pathogenesis of IPF. PDGF generates VEGF. (Hasan et al., 2022) 1.4.6. Targeted Transcription Factors Mammals have four distinct isoforms of a family of transcriptional regulators called the forkhead box (FoxOs), which has a conserved DNA-binding domain. IPF progression can be stopped and the phenotypic change reversed by UCN-01 activation of FoxO3, 8 ©Daffodil International University suggesting that FoxO3 may be a possible target for IPF treatment. FoxO3 is crucial in the development of myofibroblasts from fibroblasts because it restricts phenotypic changes. The TGF- β Smaddependent signalling cascade's controlling element, Smad, is helped to localise by Heat-Shock Protein (HSP)90. Myofibroblastic phenotypic changes in epithelial cell shape and ECM synthesis are brought on by TGF- β, the main cytokine in the EMT route of IPF formation, in conjunction with HSP90 (Hasan et al., 2022) 1.4.7. Others In the family of pentraxins, pentraxin 2 (PTX-2) is arguably the most pivotal. PTX-2 is essential for innate immune system responses, such as monocyte, macrophage, and neutrophil binding, activation, and control. (Wuytset al., 2014) Monocytes transform into macrophages with the help of PTX-2. PRM-151 (recombinant human PTX-2) has undergone a phase 1 trial (NCT01254409). Galectin- 3 controls TGF- β receptor expression on amniotic epithelial cells and has an effect on TGF—β induced lung fibrosis. Galectin-3 is a -galactoside-binding lectin. Galectin-3 knockout BLM-treated rats showed significant changes in the course of fibrosis, with a reduction in lung collagen content and subsequent lung fibrosis. TGF- β has been demonstrated to prevent the activation of myofibroblasts, the epithelial-mesenchymal transition, and collagen I synthesis. (Mackinnon et al., 2012) One transmembrane receptor that interacts with the cytoskeleton to initiate intracellular signalling is the integrin. Integrins control how cells adhere to each other and to the extracellular matrix (ECM). Type I and type II AECs express integrin v6 deterministically in the fibrotic regions, as shown by immunostaining of IPF lung tissues, and an elevated amount of v6 is linked to an increased risk of death. (Horan et al., 2010) According to low-dose therapeutic studies employing a BLM mouse model, applying a monoclonal antibody to v6 has the capacity to reduce fibrosis. Chapter Two Literature review 2. Literature review According to the findings of the most recent studies, pulmonary fibrosis (PF) is a form of lung illness that has a greater rate of mortality. Infections caused by viruses, radiation exposure, and harmful airborne contaminants are all possible contributors to the development of PF. Recurrent lung scarring is a hallmark of the condition known as idiopathic pulmonary fibrosis (IPF), which primarily impacts elderly patients and is linked to pneumonia. A wound healing process that is interrupted, as demonstrated by the dysregulated aggregation of

extracellular matrix components, is the cause of the development of fibrotic scar tissue in the lungs. This condition is called fibrotic scarring. There are a number of potential causes, some of which include oxidative stress, changes in cell signalling, inflammation, and other similar processes. Both nintedanib and pirfenidone have been granted conditional approval as treatments for idiopathic pulmonary fibrosis (IPF). In addition, therapy options for PF that make use of natural items have demonstrated some promising results. In this study, we analysed the recently published literature and explored the prospective use of three types of natural products—isolated active compounds, crude plant extracts, and traditional medicine, which consists of combinations of diverse plant products—in the treatment of pulmonary fibrosis (PF). These natural compounds offer promise in the therapy of pulmonary fibrosis (PF) because they can reduce inflammation, oxidative stress, and the shift from endothelium to mesenchymal cells; they can also influence TGF-mediated cell signalling; and many other mechanisms. Based on the findings of the current research, the signalling pathways that are involved in the pathogenesis of PF as well as the potential opportunities for the use of natural product-based therapy to treat PF have been identified. (Hasan et al., 2022) There are few treatments that directly address the biology of fibrosis, despite the fact that fibrosis is a fatal clinical feature of many chronic diseases. Natural remedies are gaining popularity as fibrosis treatments. A greater understanding of the shared cellular and molecular processes underlying fibrosis facilitates the development of effective antifibrotic drugs. We discuss a variety of distinct profibrotic pathways and the natural substances that can be used to treat them. Potential therapeutic targets include interleukin, ephrin-B2, Gas6/TAM, Wnt/- catenin, the hedgehog pathway, PPAR, lysophosphatidic acid, and connective tissue growth factor (CTGF). Inhibiting chronic inflammation, myofibroblast activation, epithelial-mesenchymal transition, and extracellular matrix production, natural products have been demonstrated to be effective in the treatment of fibrosis. Particularly, natural materials provide us with novel avenues to explore in our quest for antifibrotic drugs by inhibiting fibrosis in one organ while simultaneously targeting fibrosis in multiple others. (Chen et al., 2018) Pulmonary fibrosis (PF) is a long-lasting, progressive, and deadly lung disease that damages the interstitial lungs and makes it hard to breathe. The pathogenic route is made up of fibroblasts moving, multiplying, and changing into myofibroblasts. This causes extracellular matrix to build up and lung parenchyma to break down. Pirfenidone and nitedanib are the only antifibrotic drugs available, and they only stop the problem from getting worse, not better. In China, plant extracts and organic bioactive chemicals have been used to treat PF for more than 30 years. At the moment, both in vivo and in vitro research is being done on the use of phytotherapy to treat pulmonary fibrosis (PF) in rats with bleomycin (BLM)-induced lung inflammation, oxidative stress, and pulmonary fibrosis. In this review, we wanted to look at how different plant extracts have been used to treat PF and how they work to avoid it. (Bahri et al., 2017) Chapter Three Objective of the study 3. Objective of the study 3.1 General Objective To find out the potential function of active plant components, plant extracts, and traditional herbal medicines in the treatment of pulmonary fibrosis (PF). 3.2 Specific objective 1. To know about pulmonary fibrosis (PF) & its pathogenesis 2. To know about potential therapeutic targets of PF 3. To learn about Soluble Immune Modulators of pulmonary fibrosis 4. To ascertain the diagnosis and natural treatment options of pulmonary fibrosis 5. To know how natural products prevent and treat pulmonary fibrosis by inhibiting inflammation Chapter Four Methodology 4. Methodology 4.1. Introduction The exam is preceded by a literature review. Approximately 57 publications are reviewed for this study. 4.2. Research Design We examined numerous electronic databases, including PubMed, Google Scholar, and the ISI Web of Science, for clinical and laboratory studies that support the use of natural products to treat pulmonary fibrosis. For referencing mendeley software was used 4.3. Method of Data Analysis In this research included only English-language articles published between January 2010 and December 2022. The database contained a total of 110 records. Authors were asked to refrain from submitting review pieces, translations, overly informative compounds, and works published in languages other than English. Finally, the feasibility of bridging the gap between exploratory and clinical data was evaluated across 57 separate study studies. . Chapter Five Result & Discussion 5. Result ‣ Natural Products for Pulmonary Fibrosis with Targeted Mechanisms Natural product-based therapeutic techniques for the treatment of pulmonary fibrosis (PF) have shown tremendous promise in both laboratory and clinical research. We examined what was written recently. Active compounds, the vast majority of which are secondary plant metabolites, are extracted from crude plant extract and traditional herbal medicine, which consists of mixtures of various plant parts (root, stem, fruits, etc.). Through their metabolic process, plants produce secondary metabolites, which are chemical molecules with no essential functions in plant growth or reproduction. In the treatment of pulmonary fibrosis, alkaloids, aristolactams, oxoaporphines, amides, indoles, ionones, flavonoids, benzenoids, steroids, and a variety of volatile oils, lipophilic diterpenes, tannins, essential oils, triterpenoid, phenolic compounds, xanthones, etc. all play significant roles. Table 1 summarizes the therapeutic potential of individual natural compounds against PF. In addition, Table 2 provides a summary of the organic and aqueous extracts of medicinal plants that have been demonstrated to treat PF ailment. Typically, decoction techniques, such as boiling plant portions such as stems, bark, leaves, and roots, are used to create traditional Chinese herbal remedies. There are validated decoction formulations for the treatment of PF disease in animals (Table 3). 5.1.1. Inhibition of the EMT Pathway According to research and clinical trials, several active ingredients can reduce PF by preventing epithelial to mesenchymal cell transition. Alkaloids from Arenaria kansuensis called -carbolines are useful to cure BLM-induced PF mice. (Cui et al., 2019) Carbolines considerably reduce inflammatory cell infiltration and the pulmonary index. The suppression of the nuclear factor-kappa B (NF-B) and EMT pathways was validated by additional in vitro experiments using TGF-induced A549 cells. Triterpenoid Celastrol, which was discovered to be beneficial in treating BLM-induced rats, was extracted from the root of Trpterygium wilfordii. (Divya

et al., 2018) Table 1: Active molecules isolated from secondary plant metabolites. No Source 1 Arenaria kansuensis 2 Bletilla striata Categories Alkaloid Dihydrophena nthrene Active compound β-carbolines Coelonin Experimental Model Therapeutic Target Ref. In vivo: mice with PF caused by BLM; in vitro: A549, RAW26 Blocking NF-B and p65 and preventing EMT (Cui et al., 2019) In vivo: BLM-induced PF rats Anti- inflammatory (Jiang et al., 2019) and anti- fibrotic 3 Tripterygiu Triterpenoid Celastrol In vivo: BLM- TGF- (Divya et m wilfordii induced PF rats; in β1/Smad2/3 al., 2018) and vitro: A549 cells inhibits EMT. Celastrus regelii. 4 Glycyrrhiza Triterpenoid Magnesium Radiation-induced p38MAPK/Akt/ (Yang glabra saponin isoglycyrrhizi PF mice in vivo; Nox4 inhibiting etal., glycoside nate (MgIG) human fetal lung fibroblast 2019 fibroblasts-1 in vitro differentiation. (HFL1) 6 Rhizomes Curcuminoid Curcumin n vitro: human lung Autophagy- (Chun- of Curcuma and curcumol fibroblast (HLF) induced Bin et al., zedoaria collagen 2020) inhibition. 7 Gentianasc Secoiridoid Gentiopicrosi In vivo: BLM- Anti- (Chen et abra, glycoside de (GPS) induced PF mice; in inflammatory al., 2018) Gentiana vitro: A549 cells and anti- lutea fibrotic via TGF-β-1 8 Andrograp labdane Andrographol In vivo: lung fibrosis Anti- (Karkale his diterpenoid ide triggered by silica inflammatory et al., paniculata lactone mic and EMT 2018) transition 9 Stephania Alkaloid Tetrandrine In vivo: BLM-Alleviating (Sun et tetrandra, (TET-HP- induced PF rat inflammation al., 2020) S. Moore βCD and fibrosis 10 Polygonum Flavonoid Juglanin In vivo: BLM- Signaling from (Mansour aviculare induced PF mice the genes that i et al., stimulate 2019) interferon production (Sting) is blocked. 11 Paeonia Phenols Paeono In vivo: BLM- Stopping the (Liu et al., suffruticosa induced PF mic signaling 2017) between MAPKs and Smad3. 12 Magnolia Neolignan Honokiol In vivo: BLM- Reducing EMT (Pulivend officinalis induced PF mice and TGF- ala et al., /Smad 2020) signaling in culture and animal models. 13 Zingiber Phenolics, Zingerone In vivo: BLM- Changing how (Gungor officinal Ketone induced PF rats much TGF-1 et al., 2020) 14 Rabdosia Diterpenoid Glaucocalyxi japonic n In vivo: BLM- induced PF mice 15 Rabdosia rubesecens 16 Vegetables 17 Cruciferous vegetables 18 Salvia miltiorrhiza Diterpenoid Flavonoid Isothiocyanate s Phenolic acids Oridonin Apigenin Sulforaphane Salvianolic acid B In vitro: MRC5 cells, in vivo: BLM- induced PF mice In vivo: BLM- induced PF mice In vivo: BLM-induced PF mice; in vitro: A549 cell, MRC-5 cell In vivo: BLM- induced PF rats; in vitro: MRC-5 cells 19 Citrus plant Flavonoid Rutin In vivo: BLM- induced PF mic 20 Tea, coffee, cacao, etc 21 Rhubarb 22 Carthamus tinctorius 23 Pericarp of Citrus Reticulata 24 Fruits Alkaloid Anthraquinone Flavonoid Biological amine Vitamin Caffeine Emodin Hydroxysafflo r yellow A (HSYA) 4- methoxyphen ethylamine Ascorbic Acid a surgically removed lung slice model ex vivo; lung epithelial and fibroblast cells cultured in vitro BLM-induced PF rats in vivo; alveolar epithelial cells in vitro BLM-induced PF mice in vivo; A549 cells in vitro. BLM-induced PF rats as an in vivo model; human embryonic lung fibroblast as an in vitro model the PQ-induced in vivo and iNOS are produced. The blocking of leukocyte infiltration and the generation of proinflammato ry cytokines. TGF/Smad pathway regulation. Anti-oxidative and PPARγ expression Inhibiting EMT transition Reducing myofibroblast trans- differentiation via upregulation of Nrf2 Reducing TGF-β1- α/SMA/Col I and III pathway Inhibiting TGF- β activation Inhibiting EMT transition, TGF-β1, p- Smad2/3 Inhibiting ECM deposition Reducing TGF-β1 Inhibiting IL-6, IL-17a, TGF- beta (Yang et al., 2017) (Fu et al., 2018) (Chen & Zhao, 2016) (Kyung et al., 2018) (Liu et al., 2018) (Bai et al., 2020) (Tatler et al., 2016) (Tian et al ., 2018) (Jin et al., 2016) (Zhou et al., 2016) (Rodrigu es da Silva et al., 2018) The suppression of EMT by HSP90 is also impacted by celastrol. Gambogic acid, a distinct xanthonoid compound derived from Garcinia hanburyi reverse EMT, was found to be associated with decreased vimentin and increased cadherin in TGF- β 1- stimulated A549 and HPME cells. Table 2: Therapeutic strategies for treating pulmonary fibrosis using plant extracts. No Formula 1 Citrus alkaline extracts (CAE 2 Grape seed extracts 3 Myrtle 4 Mixture extracts of 5 Arenaria kansuensis Source and Components Pericarp of Citrus reticulata (flavanone, alkaloid) Flavonoids, ascorbic acid (vitamin C), tocopherols, citric acid, limonoids, sterols, and minerals Myrtus communis L. (flavonoids, tannins, and essential oils) Rhodiola rosea L. (RRLroots)'s and rhizomes (phenylpropanoids, organic acids, and flavonoids)) Chinese herbal (plant extracts) Experimental Model In vivo: BLM- induced PF mice; in vitro: primary murine lung fibroblasts In vivo: BLM- induced PF mic In vivo: BLM- induced PF rats In vivo: BLM- induced rats In vivo: PQ- induced PF mic 6 7 8 Tanshinone IIa B- peltoboykinolic acid Aged garlic extract (AGE) Salvia miltiorrhiza (plant extracts) Astilbe rubra (plant extracts) Alluim sativum (plant extracts) In vivo: silica- induced PF rats; in vitro: A549 and HBE cells. In vitro: A549 cells In vivo: TiO2-induced toxicity Therapeutic Target Preventing fibroblast senescence via activation of cyc- Inhibition of MMP-9 and TGF- β1 Anti- inflammation and anti-oxidative TGF-β1 signaling transduction in lung tissues Activation of Nrf2 pathway and the inhibition of NFkb/TGF- beta1/Smad2/3 pathway. Inhibition of EMT Inhibition of EM Attenuating hepatic inflammation and pulmonary fibrosis Ref. (Feng et al., 2019) (Liu et al., 2017) (Samareh Fekri et al., 2018) (Qin 2019) et al., (Cui 2021) et al., (Feng 2020) et al., (Bang 2019) et al., (Moustafa & Hussein,2016) Table 3: Traditional herbal medicine No Name Components 1 2 Triptolide (TPL) Tripterygium wilfordii Chuanxiong Kangxian granules (CCKG) Combination Chuanxiong Kangxian of and Experimental Model In vivo: BLM-induced PF rats In vivo: PQ- induced PF mice Therapeutic Ref. Target Inhibition of (Shi et al., oxidative stress 2017) and inflammation Binds with TGF- (Chen et β and inhibits al., 2017) Smad3, E - 3 Xin jia xuan bai cheng qi decoction (XJXBCQ) 4 Radix puerariae extracts (RPES) 5 Renshen pingfei decoction (RPFS) 6 Yangyin Yiqi mixture (YYYQ Rhei radix and rhizome, Gypsum fibrosum Trichosanthis pericarpium, Persicae semen, Semen armeniacae amarum, the teleophaga Eupolyphaga (in 10:3:2:5:3:3 ratio). Radix puerariae extracts (RPES) Anemarrhena asphodeloides, Lycium chinense, Morus alba, Panax ginseng, Glycyrrhiza uralensis, Asparagus cochinchinensis, and Citrus reticulata. Traditional Chinese medicine In vivo: BLM- induced PF rats; in vitro: MRC-5 cells In vivo: PQ- induced PF mice In vivo: BLM- induced PF rats In vivo: BLM- induced PF rats cadherin, and Vimentin TGF-β1- Smad2/3 signaling Fstl pathways and oxidative stress by inhibiting mir-21

expression Downregulating TGF-β1/Smad3 signaling pathway Suppressing TGF-β1/Smad signal pathway and EMT (Qin et al., 2019) (Liu et al., 2016) (Chen et al., 2016) (Meng et al., 2019) Cruciferous vegetables create the isothiocyanate form of sulforaphane. To restore epithelial form in vitro, it inhibits BLM's induction of fibronectin, lowers the expression of transcription factors linked to EMT (Slug, Snail, and Twist), and raises E-cadherin levels. (Kyung et al., 2018) Emodin, an anthraquinone molecule, dramatically lowers lung deformation, cytokine expansion, and excessive collagen production. By boosting Nrf2 signaling, it inhibits p-IIB, NF-B, the EMT transition, TGF- β 1, and p-Smad2/3. (Tian et al., 2018) Peltoboykinolic acid is a potent plant extract that targets the EMT pathway (Table 2). Astilbe rubra extract contains peltoboykinolic acid, which inhibits COL1 and fibronectin. Moreover, the whole plant ethanol extract of A. Rubra stops TGF- β 1 from causing EMT in A549 cells. In dichloromethane fractions, TGF- β 1-induced EMT inhibition is the strongest. Peltoboykinolic acid inhibits the Smad pathway that is triggered by TGF-1. (Bang et al., 2019) 5.1.2. Inhibition of TGF-β Signaling The most common soluble immune mediator implicated in the formation of PF is TGF— β mediated signaling. There will therefore unavoidably be a large range of tactics used to prevent TGF- β signaling. The Salviae miltiorrhza plant is the source of the polyphenol known as salvianolic acid B (SAB). In NIH/3T3 fibroblasts, it alters the expression of the fibrotic genes collagen and others. SAB (50g/mL) treatment reduced this proliferation without producing any obvious damage, although TGF— β sensitive MRC-5 fibroblasts increased their production of collagen type 1 alpha 1 (COL1A1) and COL1A2 by 240% and 170%, respectively. SAB dramatically decreased the expression of COL1A1, COL2A2, and COL3A1 that was stimulated by TGF-. E- cadherin expression was decreased by TGF- and TNF-, but this effect was mitigated by SAB. (Liu et al., 2016) GPS is a member of the secoiridoid glycoside family. GPS decreased the amount of hydroxyproline in the PF mice's lungs, which considerably decreased the levels of TNF- and IL-1 in BAL fluid. In the lungs of PF mice, GPS dramatically decreased TGF- 1 and CTGF expression. Furthermore, GPS dose-dependently blocked the EMT pathway in an in vitro experiment utilizing TGF- 1-stimulated A549 cells. (Chun-Bin et al., 2020) The phenolic substance gingerone originates in ginger. Interleukin-1 beta, malondialdehyde, tumor necrosis factor alpha, and collagen levels are all lowered (MDA). In PF-induced rats, superoxide dismutase (SOD) and glutathione peroxidase activity are both increased, likely as a result of ginger's ability to reduce TGF- 1 and iNOS production. The diterpenoid oridonin from Rabdosia rubesecens prevents the TGF- /Smad pathway from working. Oridonin both downregulates -SMA and COL1A1 expression in vitro and in vivo in TGF- stimulated MRC-5 cells and in BLM-induced PF mice. (Fu et al., 2018) The activities of total cells, macrophages, lymphocytes, and lactate dehydrogenase in BAL fluid are all markedly decreased by the citrus flavonoid rutin. Nitric oxide elevated glutathione and superoxide dismutase (SOD) levels in PF-mice treated with rutin, whereas lung MDA was lowered. Moreover, decreased collagen deposition and lung hydroxyproline concentration are linked to lower expression of collagen type I, type III, and -SMA, as well as transforming growth factor beta 1. (Bai et al., 2020) Caffeine was discovered to decrease TGF- activation in epithelial cells, but not in fibroblasts, in an ex vivo investigation using a precisely cut lung slice model. In a lung slice model, caffeine administration for five days reduced fibrosis and decreased the expression of the -SMA gene. (Tatler et al., 2016) By inhibiting the TGF- β /Smads pathway, the Arenaria kansuensis (AE) ethanol extract reduced the production of collagen and -SMA. Inhibiting the NF-kB/p65 pathway and inflammatory cytokines is another method that AE can lessen pulmonary inflammation. Also contributing to the reduction of oxidative stress were AE's effects on ROS levels, GSH levels, and SOD activity. (Cui et al., 2021) Salvia miltiorrhiza ethyl acetate (EASM) extract reduces oxidative stress in the lungs of BLM-treated mice by increasing Nrf2 and decreasing Nox4 levels. EASM decreased ROS production in fibroblasts by encouraging the breakdown of the kelch-like ECH-associated protein 1. (Keap1). Nrf2 knockdown decreased the anti-fibrotic effects of EASM in the lungs of mice treated with BLM. EASM decreased both the synthesis of ECM and the activation of myofibroblasts. (Peng et al., 2019) In vivo, Xin Jia Xuan Bai Cheng Qi Decoction (XJXBCQ) treatment dramatically boosted Smad7 levels, lowered hydroxyproline levels, and improved lung function. On lung TGF- β1 protein expression, XJXBCQ had a markedly reduced effect. After TGF-β1 treatment, the MRC-5 cells were treated with XJXBCQ, which reduced the expression of -SMA, fibronectin, IL-17A, and IL-25. It was demonstrated that p-Smad2 was downregulated in a dose-dependent manner after XJXBCQ treatment of TGF- β 1-stimulated MRC-5 cells. Smad2 expression is decreased by XJXBCQ, whereas Smad7 expression is elevated, both at the mRNA and protein levels. (Qin et al., 2019) When the Chinese herbal extract triptolide (TPL) binds to transforming growth factor beta, it prevents the EMT of lung epithelial cells (TGF- β). As a result of PQ-induced PF, the expression of vimentin was elevated whereas the expression of E-cadherin was downregulated. After TPL treatment, EMT was halted in its tracks, E-cadherin expression was increased, and vimentin levels were decreased. TGF- β binding to TPL caused TPL to inhibit the TGB1/Smad3 pathway. (Samareh et al., 2018) The favorable benefits of renshen pingfei decoction (RPFS) on lung damage, fibrosis, and function are brought about by a decrease in hydroxyproline content. Because to RPFS, the amounts of TGF- β1 and Smad3 mRNA and protein in lung tissue are decreased. Reduced levels of NF-B are found in rats' BAL fluid. It manages the level of SOD and MDA in rat serum by blocking the TGF- β 1/Smad3-mediated intracellular signal transduction pathway. (Chen et al., 2016) The levels of TGF- 1, CTGF, and hydroxyproline as well as the mRNA expression of TGF- β1, TRI, TRII, Smad3, -SMA, laminin, and collagen I were all significantly decreased after treatment with medium and high dosages of Yangyin Yiqi, ixture (YYYQ). Smad7 and E-cadherin expression, however, increased in the BLM and BLM treated with prednisolone groups following exposure to YYYQ. It was thought to be related to the downregulation of the TGF- β1/Smad and EMT signaling pathways. (Meng et al., 2019) 5.1.3. Anti-inflammatory and anti-oxidant properties Some drugs can be used to treat PF by lowering oxidative stress and inflammation. It has been demonstrated that the

dihydrophenanthrene chemical coelonin significantly inhibits the LPS-Apigenin, found in many plants, lowered inflammatory responses and oxidative stress. Apigenin lowers both hydroxyproline levels and the number of inflammatory cells. In addition, it raises the levels of SOD and PPAR in the lungs. In the lungs, it results in elevated levels of E-cadherin and Smad-7 and reduced production of NF-B, MMP-9, vimentin, and TGF- β. (Fu et al., 2018) The alcohol glycoside rosavin from Rhodiola rosea reduces the quantity of inflammatory cells in BAL fluid as well as the expression of pro-inflammatory cytokines in lung tissue. Levels of hydroxyproline and malondialdehyde are also decreased. Lung tissue also showed increased levels of SOD and glutathione peroxidase activity. It has been established that Nrf2 overexpression and NF-kB p65, TGF- β1, and -SMA downregulation are the mechanisms by which rosavin-mediated fibrosis amelioration occurs. (Xin et al., 2019) The terpenoid molecule glaucocalyxin A (GlnA) dramatically lowers lung collagen deposition and hydroxyproline concentration. Moreover, GlnA reduces the levels of pro-inflammatory cytokines in BAL fluid and reduces macrophage and neutrophil infiltration. (Yang et al., 2017) The positive nutraceutical effect of aged garlic extract (AGE) in decreasing pulmonary fibrosis was confirmed in an animal model of TiO2-induced pulmonary and hepatic disease. One way AGE reduces TiO2-induced toxicity is via lowering pulmonary MMP- 9, TIMP-9, TGF- β 1, collagen-1, and fibronectin mRNA. (Moustafa & Hussein,2016) 25 ©Daffodil International University The methanolic extract of Myrtus communis significantly reduces lipid peroxidation, hydroxyproline content, and parenchymal inflammation (Myrtle). In PF mice, it increases catalase synthesis as well. (Samareh Fekri et al., 2018) CAE regulates the senescence-associated secretory phenotype by repressing senescence in fibroblasts. Further mechanistic studies showed that CAE reduces lung fibroblast senescence through a P53-dependent mechanism and that CAE inhibits P53-dependent fibroblast senescence by activating cyclooxygenase-2. (Feng et al., 2019) Rats with BLM-induced lung fibrosis are protected by Chuanxiong Kangxian granules (CCKG). When exposed to BLM, CCKG inhibits collagen deposition, oxidative stress, and inflammatory responses by downregulating the production of matrix metalloproteinase-2 (MMP-2) and -9 (MMP-9). (Shi et al., 2017) 5.1.4. Modulation of Cellular Signaling The effects of magnesium isoglycyrrhizinate therapy on collagen synthesis, ROS production, and TGF—β1 elevation were all negative (MgIG). Nox4 and p38/MAPK/Akt expression was reduced in both vivo and in vitro as a result of MgIG treatment. Alpha-mangostin therapy in vivo significantly reduced the mRNA and protein levels of -SMA and Col 1. (-MG). The effects of -MG therapy were seen in the improvement of lung TGF— β1 expression and Smad 2/3 phosphorylation abnormalities. -MG also promotes AMPK-mediated inhibition of NOX4 expression and TGF- β1-induced trans-differentiation of lung fibroblasts, both of which reduce fibrogenesis. (Li et al., 2019) Centella asiatica has an essential component called madecacassoside, which profoundly modifies cellular transmission in the intestines. You can take it orally, but not intravenously. Madecacassoside has powerful anti- fibrotic properties when taken orally. Through increasing PPAR- mRNA, nuclear translocation, and DNA binding activity in madecacassoside-treated colonic epithelial cells, madecacassoside raises hepatocyte growth factor levels in colon tissue. (Xia et al., 2016) 5.1.5. Inhibition of ECM Deposition Collagen, an essential component of the ECM, is deposited in the lungs, aiding the pathophysiology of fibrosis. As a result, ECM inhibition may prove to be a crucial therapeutic approach for pulmonary fibrosis. Curcuminoids like curcumin and curcumol inhibit autophagy, which in turn decreases ECM deposition. Treatment of human lung fibroblast cells with curcumin or curcumol in vitro dramatically decreased the deposition of hydroxyproline, -SMA, Col-I, and Col-III. Furthermore, dose- dependent deregulation was observed for N-terminal pro-peptide for type I collagen (PINP), N-terminal pro-peptide for type III collagen, and prolyl-hydroxylase associated to ECM. (Chun-Bin et al., 2020) The pulmonary collagen deposition is inhibited by the flavonoid hydroxysafflor yellow A (HSYA) from Carthamus tinctorius. In addition to lowering Smad3 phosphorylation (Jin et al., 2016) HYSA also lowers the increase in TGF- β, -SMA, and collagen I mRNA brought on by BLM. A biological amine termed 4-methoxy phenethylamine is found in the pericarp of citrus reticulate, and it prevents the breakdown of hydroxyproline in blood and lung tissue . Furthermore, TGF- β expression is inhibited. (Zhou et al., 2016) In paraquat-induced PF mice treated with ascorbic acid, immune cell infiltration, IL-17 and TGF- β secretion, and extracellular matrix (ECM) deposition were all significantly reduced. The antioxidant enzymes SOD and catalase are also increased by vitamin C. (Rodrigues da Silva et al., 2018) Radix puerariae extracts (RPEs) contain antioxidant and anti-inflammatory properties that lessen the severity of lung fibrosis brought on by PQ. RPE dramatically decreased the expression of miR- 21 and Fstl 1 pathways, which both contribute to lung fibrosis. In vitro and in vivo studies have demonstrated that the Chinese herbal medicine Hong Jing Tian's small RNA (HJT-sRNA-m7) lowers fibrotic markers. The decoction contains the phosphocholines PC (18:0/18:2) and PC (16:0/18:2), which help cells absorb short RNAs. We discovered that gene expressions for -SMA, fibronectin, and collagen type I 1 (COL1A1) could all be effectively reduced using HJT-sRNA-m7. (Du et al., 2019) Figure 3: The activation of fibroblasts results in the accumulation of extracellular matrix. Inactive fibroblasts become active and begin to proliferate when they are stimulated by cytokines. These active fibroblasts subsequently differentiate into myofibroblasts, which produce a high quantity of extracellular matrix proteins, and cause an imbalance in the control of the matrix by TIMPs and MMPs, which ultimately results in an accumulation of extracellular matrix. (Wang et al.,2023) 5.2. Discussion Globally, the number of people with pulmonary fibrosis is going up every year. Preventing and treating pulmonary fibrosis will do a lot to improve health and lessen the cost burden of the disease. Even though study into what causes pulmonary fibrosis is making progress, the exact causes are still unknown, and pulmonary fibrosis is still hard to treat. Pulmonary fibrosis can be caused by problems with the immune system, a lack of redox balance, and problems with how food and energy are used. Several signalling pathways and cytokines control important disease processes, such as the creation of extracellular

matrix, the growth of fibroblasts, and EMT. Clinical treatments that focus on a specific part of the disease or how it works don't always work to reverse it. This could be a big reason why lung fibrosis is still not curable. Because of this, it is very important to find new ways to deal with the lack of pharmaceutical drugs. Still, it is very hard to make new medicines because we still don't know much about how lung fibrosis happens. Pulmonary fibrosis cases can be cut down by putting more focus on early diagnosis and prevention instead of treatment. This could help people feel better. Natural things fit well with these goals because they have many different biological uses and come from many different places. It's important because natural substances can affect many regulatory systems and networks at the same time. This makes them a good choice for healing pulmonary fibrosis, a disease that affects many parts of the body and has many different causes. Natural substances like bleomycin, trachea, paraquat, carbon tetrachloride, endotoxin, silica, and cigarettes have shown promise in avoiding and treating lung damage and pulmonary fibrosis in a wide range of animal species. From a mechanistic point of view, natural products can affect the Nox4-Nrf2 pathway, the NF-B pathway, the PI3K/Akt/mTOR pathway, the p38 MAPK/Akt/Nox4 pathway, the AMPK pathway, and others. All of these pathways are linked to the pathogenesis of pulmonary fibrosis. These substances have an effect on the pathogenetic processes that are known to cause pulmonary fibrosis. This means that 28 ©Daffodil International University they can be used to avoid and treat it. This shows that natural products can help avoid and treat pulmonary fibrosis in a powerful way.As was already said, natural goods are made up of many different compounds, such as polyphenols, flavonoids, terpenoids, alkaloids, and other phytochemicals. All of these are good for lung fibrosis, especially in the early stages of inflammation and oxidative stress. In short, Fig. 3 shows how the molecules that make up a number of natural chemicals are arranged. Some of the active groups in these natural substances are the polycyclic benzene structures, the exposed carboxyl groups of polycyclic rings, the phenolic hydroxyl or carboxyl groups, and the conjugated double bond carboxyl groups. Polyphenols and flavonoids are the two most common types of natural substances that can stop or treat lung fibrosis. They are found in plants and help fight free radicals and inflammation. But the fact that terpenoids and glycosides have more complicated structures than polyphenols and flavonoids, which have been studied for a long time, does not mean that polyphenols and flavonoids are better at stopping lung fibrosis. Natural background amounts are not very high, biological functions are often lost during processing, and extraction and purification technology is still not very good. These chemical substances have a lot of promise and need to be looked into more.Even though natural goods have the benefits and possible uses we've already talked about, only a small number of them are used in clinical settings right now. Also, no one knows for sure what causes lung fibrosis. Prevention and treatment of pulmonary fibrosis seem to have effects that are hard to explain without a lot of research. It can't explain how natural chemicals affect pulmonary fibrosis in the way that drugs do. To get around the yield restriction bottleneck, future study should focus on developing the technology for extracting and purifying natural products, figuring out which natural products play the most important biological roles in complex systems, and using chemical synthesis. It is also important to know how lung fibrosis happens and what causes it. This will encourage doctors to use natural products and help explain how they can be used to avoid and treat pulmonary fibrosis. Even though they don't work as well as synthetic medicines, natural remedies are better at avoiding and treating pulmonary fibrosis when it is in its early stages. When using natural goods as medicine, it is also hard to get the safety and pharmacokinetic information needed to figure out the best dose. As people learn more about preventing illness and staying healthy, methods and management guidelines that make it easier to switch to and use natural products need to be raised and improved. 29 ©Daffodil International University . . . Chapter Six Conclusion 6. Conclusion Pulmonary fibrosis is caused by structural deformities of the lungs. Recent clinical evidence suggests that SARS-CoV-2 survivors may have a pathophysiology comparable to that of PF. In this article, the immune-regulating mechanisms of PF are briefly discussed. Also presented are therapeutic targets that may prove useful in the future against PF. We analyzed recent research and clinical data (2015-2022) to determine the potential function of active plant components, plant extracts, and traditional herbal medicines in the treatment of pulmonary fibrosis (PF). Despite the abundance of studies examining the efficacy of natural substances for treating PF, the cohort weights are well-designed, with large sample sizes and extended follow-up. Is inadequate. To coordinate the release of anti-PF medication, each chemical must be approved for its specific target using cutting-edge drug discovery techniques such as in silico modelling, high-throughput screening, framework modelling and reconstruction, etc. Chapter Seven References 7. Reference Bahri, S., Ben Ali, R., Abidi, A., & Jameleddine, S. (2017). 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