



Review article

Innovative phytochemical-based drug delivery in the management of pulmonary fibrosis: A roadmap towards inhaled therapeutics

Shuet Li Wong^{a,1}, Jie Sin Gan^{a,1}, Gabriele De Rubis^{b,c}, Keshav Raj Paudel^{d,e},
Stewart Yeung^{b,c}, Dinesh Kumar Chellappan^a, Pei Sin Keng^{a,**}, Kamal Dua^{b,c,e,*}

^a Department of Life Sciences, School of Pharmacy, International Medical University, Bukit Jalil, 57000, Kuala Lumpur, Malaysia

^b Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Sydney, NSW, 2007, Australia

^c Faculty of Health, Australian Research Centre in Complementary and Integrative Medicine, University of Technology Sydney, Ultimo, Australia

^d Centre for Inflammation, Centenary Institute and University of Technology Sydney, Faculty of Science, School of Life Sciences, Sydney, 2007, Australia

^e Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun, India



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ABSTRACT

The long-lasting wounding of lung tissue that results in pulmonary fibrosis is a long-term, gradual lung condition that eventually impairs breathing and causes respiratory failure. For decades, people from a variety of cultures have used phytochemicals for their therapeutic benefits, providing a holistic and natural approach to treatment. Phytochemicals are well-known compound that consists of active ingredients that are extracted from plants and produces therapeutic effects in treating pulmonary fibrosis. In this review, the plants that were discussed to manage pulmonary fibrosis include *Quercetum*, chamomile, thyme, parsley, garlic, guava, broccoli, *Curcuma longa*, *Scutellariae radix*, *Erigeron breviscapus*, *Moraceae*, *Ruta graveolens*. Other than that, the mechanism of action of the type of pulmonary fibrosis and drug delivery through inhalation also discussed. The nanoparticles that can be used in drug delivery include liposomes, poly(lactic-co-glycolic acid), dextran, acetalated dextran, polymeric micelle, lyotropic liquid crystalline and polyethylene glycol (PEG).

1. Introduction

Pulmonary Fibrosis is a long-term lung condition that slowly affects the interstitium, dyspnea, lowering quality of life, and eventually leading to respiratory failure and death [1]. It originates from an aberrant wound healing process. This aberration encompasses a complex interplay of inflammatory responses, fibroblast activation, excessive collagen deposition, and impaired resolution mechanisms, ultimately leading to the progressive scarring and stiffening of lung parenchyma characteristic of pulmonary fibrosis. People with the condition are often between those in the age range of 50 and 70. Pulmonary fibrosis affects an estimated 13 to 20 per 100,000 individuals and around 30,000 to 40,000 fresh infections are identified globally each year [2]. In Australia, the prevalence of pulmonary fibrosis increases with 32.6–34.3 per 100,000 individuals while the incidence increases with 10.4–11.0 per 100,000 individuals each years and the mortality was estimated 5.9 to 6.2 per 100,000 individuals [3]. In addition, pirfenidone and nintedanib are

used as a current therapeutics strategies [4]. Pirfenidone is a modified pyridine that has antioxidant, anti-inflammatory and antifibrotic qualities. It suppresses the cytokine TGF- β , slows the fibrotic process by decreasing collagen formation, and lessens the rate at which the FVC declines [5]. Next, nintedanib is an intracellular tyrosine kinase inhibitor which inhibits signalling pathways associated with vascular endothelial growth factor receptor, fibroblast growth factor receptor 1–3, and platelet-derived growth factor receptor α and β by binding to adenosine triphosphate binding sites [6]. Fibroblast activity is reduced as a result of these effects on receptor tyrosine kinases. The two medications can both give the patient more comfort in a noticeably longer duration of time and halt the decline in FVC. However, using these medications may result in significant out-of-pocket expenses without affecting the disease's general course or its high death rate within three to five years after diagnosis [7]. Studies are being conducted to find out whether these tyrosine kinase inhibitors might not be beneficial since certain patients may not react to these medications and because of their cost and

* Corresponding author. Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Sydney, NSW, 2007, Australia.

** Corresponding author.

E-mail addresses: peisin_keng@imu.edu.my (P.S. Keng), kamal.dua@uts.edu.au (K. Dua).

¹ These two authors have contributed equally to the work.

adverse effect profile [8]. Therefore, medical plants can be used to replace pirfenidone and nintedanib for the pulmonary fibrosis therapy. Any plant that has chemicals in one or more of its organs that have medical value or that serve as building blocks for the creation of effective medications is considered medicinal plants [9]. However, some medicinal plants might have poor bioavailability which may not efficiently absorbed or utilized by the body when consumed orally. Other than that, some medicinal plants has poor solubility thus they do not dissolve in water and do not absorbed by the body [10]. In this review, we will discuss phytochemical-based drug delivery with the management of pulmonary fibrosis.

2. Types of pulmonary fibrosis

Pulmonary fibrosis can be triggered by allergens, chemicals and radiation, resulting in excessive inflammation and fibrosis [11]. The initiators of fibrosis include epithelial damage, inflammatory disorders, the transition from epithelial to mesenchymal (EMT), myofibroblast triggers, and repetitive damage to tissues. There are several type of pulmonary fibrosis such as pneumoconiosis, drug-induced interstitial lung disease (DILD), fibrotic hypersensitivity pneumonitis and idiopathic pulmonary fibrosis (IPF). Pneumoconiosis is a lung illness caused through inhaling organic or inorganic aerosol dusts and fibres. Patients are more likely to be exposed to these inhalants at work such as manufacturing department, coal mining and tunneling, hence it is classified as a job-related exposure illness. The three most common kinds of pneumoconiosis are asbestosis, silicosis, and coal miner's lung as they cover 90 % of pneumoconiosis cases [12,13]. As the particles promote inflammatory process and development of fibrosis in the lung, leading to permanent lung damage. Health care guidelines and workplace exposure control are the foundation of avoidance [14]. The breathing passages, respiratory parenchyma, mediastinum, pleura, pulmonary circulatory system, and neurological system can all be impacted by drug-induced lung injury. Interstitial lung disease is a particularly common kind of drug-induced lung damage (DILD). The most common modes of medication delivery for DILD are oral and parenteral, however the medicine delivery of nebulizer and intrathecal are additionally related to the condition. The risk of taking medication to treat interstitial lung disease can occur as an immediate or secondary pharmacological impact [15].

Other than that, fibrotic hypersensitivity pneumonitis (fHP) is also one of the fibrosing type of interstitial lung conditions which is triggered by inhaled antigenic exposures. It has similar impacts such as reduced quality of life and impaired respiratory function. The management of fibrotic hypersensitivity pneumonitis should begin with exposure remediation, with systemic immunosuppression and antifibrotic medication recommended in individuals with symptomatic or progressing illness. Moreover, nonpharmacologic and supportive therapy should be provided, and lung transplantation should be considered in situations with treatment-resistant, progressing sickness [16]. Interstitial lung disease (ILD) commonly linked with autoimmune such as systemic sclerosis-associated ILD or associated with connective tissue disease (CTD-ILD), such as rheumatoid arthritis-ILD [17,18]. IPF is a disease when gradual deterioration in pulmonary function. There are combination of genetic predisposition, environmental factors, and abnormal wound healing processes in the lungs that imply lung epithelial damage and dysfunction contribute to the pathogenic process.

Besides, growth factors and extracellular matrix-driven signalling may trigger several types of healing pathways, resulting in migration of inflammatory cells, a growth of fibroblasts, and the development of extracellular matrix, ultimately leading in tissue scarring. As a result, the changes in the biochemical and biomechanical characteristics of the extracellular matrix occurs, which in turn enhance profibrotic pathways in a "feed-forward cycle" [19]. Other than that, hypersensitivity pneumonitis (fHP) is also one of the fibrosing type of interstitial lung disease which is induced by inhaled antigenic exposures. It has similar impacts

such as reduced quality of life and impaired respiratory function. The management should begin with exposure remediation, with systemic immunosuppression and antifibrotic medication recommended in individuals with symptomatic or progressing illness. Nonpharmacologic and supportive therapy should be provided, and lung transplantation should be considered in situations with treatment-resistant, progressing sickness [16].

2.1. Mechanisms underlying pulmonary fibrosis

Pneumoconiosis is a job-related interstitial lung illnesses via inhaling aerosol dust particles in the lungs, resulting in respiratory failure [20]. The dust consists mostly of inorganic particles which involve coal mine dust, infused silicate dust, asbestos fabric, and untreated silicate dust. Besides, the clinical features of the illness include persistent fibrosis and inflammation of the respiratory tract and the inflammation can increase lung fibrosis lead to pneumoconiosis [21,22]. It has had a reasonably high prevalence in recent years [23,24].

According to a recent analysis, the global frequency of pneumoconiosis, resulting from breathing in industrial pollen, grew by 61.5 % worldwide between 1990 and 2019 [12,13]. Pneumoconiosis had an all-age average occurrence percentage of 2.39 per 100,000 people in 2019 [12,13]. Between 2010 and 2022, the National Health Commission of China (NHC) recorded more than 271,000 cases of infection [12,13]. The necessity for strict precautions to limit silica accumulation in industries is highlighted by the recent increase in case numbers. According to epidemiological research, 90 % pneumoconiosis occurrences in China are caused by two common types including coal worker's pneumoconiosis (CWP), which is triggered by coal mine exhaust and silicosis, which is inhaled free crystalline silicon dioxide [25]. About 69.8 % (138,971) of all new cases of pneumoconiosis worldwide in 2019 were caused by silicosis. The quantity of reported incidences of silicosis was rising by 64.6 % from 84,426 in 1990 to 138,971 in 2019. The annual susceptibility rate (ASIR) to silicosis was 1.65 per 100,000 people globally, indicating significant variation. With 5.78 ASIR per 100,000 people, East Asia was found to have the highest [26].

Pneumoconiosis continues to be a serious national healthcare concern since there is an inadequate levels of dust protection. In work environments, an inability to diagnose the illness in its initial phases and a lack of appropriate therapies. Fresh diagnostic intruments and treatment targets offer promise for resolving pneumoconiosis' clinical difficulties, while numerous new research approaches, such as high volume omics equipment and rapidly expanding field of analytics equipment, allow for comprehensive investigation [27]. Particles that are not cleared by mucociliary action when these inhalants enter the lungs, then accumulate in the alveoli and bronchial tubes. The smaller particles are subsequently taken up by alveolar macrophages by ingestion. Throughout the process, cytokines that contribute to inflammation such as interleukin-1 and TNF- α and lysosomal enzymes are secreted, reactive oxygen species are produced as well as inflammatory signalling increases. These particle-carrying macrophages may cluster in the interstitium near the perivascular and peribronchiolar areas.

Growth factors are stimulated to start the fibrotic process when inflammation phase is over.

Then, in the interstitium, type 1 pneumocytes grow above them, encapsulating them. Fibroblasts are subsequently to generate ECM and matrix metalloproteinases, which promote fibrosis and tissue remodeling [14]. Fibrocytes will produce chemotaxis to promote inflammatory substances and chemical messengers, therefore amplifying immunological reaction [28]. In both simple and difficult disorders, IgG and IgA levels were elevated. Scar development results from an excessive production of fibronectin and gelatin [29].

The limitation of pneumoconiosis is that no treatment for pneumoconiosis and the prediction of the pneumoconiosis is weak during the fibrotic phase of the disease. Therefore, it is important to focus on which it is not possible for everyone to have lung disease even though they

inhale dust [30]. Individuals with pneumoconiosis are more likely to suffer from respiratory problems and die prematurely. Patients with pneumoconiosis often have emphysema or COPD [31]. People who smoke tobacco should be urged to stop. To reduce the sign and improve activity capacity, respiratory rehabilitation can be provided [14]. Respiratory retraining, low- or high-intensity exercise training, endurance training, and strength training are all commonly included in pulmonary rehabilitation regimens. Additionally, these initiatives could include dietary instruction, mood problem counselling, and health education [32].

One form of interstitial lung disease (ILD) that results from exposure to medications that generate inflammation and possibly interstitial fibrosis is called drug-induced ILD [33]. As more cases linked to drug exposure are documented, the clinical suspicion of DIILD increases. However, a definitive diagnosis requires ruling out other likely causes [34]. DIILD in cancer patients is predominantly linked to cytotoxic chemotherapy, targeted treatment, and immunotherapy [33].

There is still much to learn about the pathogenic mechanisms behind DIILD. A commonly accepted theory states that the causative drug affects the immune system by directly changing tissue-resident protein haptenic changes or deposition of antibody-antigen immune complexes which in turn triggers an inflammatory reaction [35]. Haptens are small chemical groups that cross-link B-cell receptors and do not elicit T-cell help by preventing them from inducing free-soluble antibody responses. When linked to a carrier protein, they become immunogenic because the protein has numerous hapten groups that may now cross-link B-cell receptors and activate T cells through peptides that are generated from the carrier protein [36].

An additional mechanism that has been suggested involves the direct toxic effects on endothelial and epithelial cells. This mechanism has been observed in patients who have developed lymphocytic alveolitis after receiving methotrexate or nitrofurantoin treatment, as well as in patients who have significant neutrophilia after receiving bleomycin, amiodarone, or phenytoin [37]. A few other agents can cause pulmonary injuries through their metabolism in the lungs include amiodarone, a phospholipase A2 inhibitor which can cause phospholipid accumulation in alveolar cells that can lead to degenerative and regressive alterations in lung macrophages and alveolar cells which include carmustine, nitrofurantoin, bleomycin and other agents can also increase endothelial permeability [37].

In addition, hypersensitivity pneumonitis (HP) is an immune-mediated interstitial lung disease (ILD) brought on by inhaling low-molecular-weight substances. There are two types of hypersensitivity pneumonitis which are non-fibrotic or acute and fibrotic or chronic [38].

The immunological pathways that lead to the development of HP was not fully known but mostly it may due to exposure to inhalation of low-molecular-weight chemicals which can cause granuloma formation, inflammation, irreversible damage and fibrosis [39]. Although the pathogenesis of hypersensitivity pneumonitis is unclear but the repetition of exposure based on its structures involved in antigen processing, and adjuvant modulatory factors may also cause fibrosis. Breathing in antigenic particles stimulates antigen-presenting cells such as activated macrophages and dendritic cells [39]. Next, the essential element for triggering immunological response is pattern recognition receptors such as toll-like receptors (TLRs). TLR-2 and TLR-6 are increased in murine mice models of HP and recognise diacyl lipopeptides and lipoteichoic acid on bacterial cell walls [40]. In the process of granuloma formation, TLR-6 takes an important role in the development of macrophages into epithelioid cells and multinucleated giant cells [41]. Other than that, it has also been discovered that other innate receptors such as TLR-9 and dectin-1 which stimulate the differentiation of Th17, which in turn causes more inflammation and fibrosis, and contribute to HP [42]. By moving to the lymph gland and stimulating the T-cell immune response, dendritic cells take part in the start of accommodative immunological response. Following an antigen challenge, the lung parenchyma of those with HP contains more dendritic cells [43].

Simultaneously, inhaled antigen attaches to IgG antibodies, starting the complement cascade and generating products such as C5, which can activate macrophages [44]. The HP diagnostic work-up may include serum IgG-specific antibodies. When exposed to foreign antigens, activated macrophages release chemotactic and pro-inflammatory factors, such as CCL-18 that draws lymphocytes and IL-18, MCP-1, TNF- α , IL-1, and IL-6 that increase B7 expression and significantly improve macrophages' ability to present antigens in response to inhaled antigens [45, 46]. A change in the inflammatory response from Th1 to Th2, the suppression of controlling T cells, and the overexpression of NKT cells all take part in the development of HP from an acute, inflammatory phase to a chronic, fibrotic one. Furthermore, it is unclear if fibrosis necessarily precedes an inflammatory phase or if fibrotic HP is more likely to exhibit distinct pathways common with other fibrotic lung illnesses. Through a decrease in Foxp3 expression, regulatory T-cell suppression promotes the growth of inflammation as well as the transition to a Th2 response [47]. Fibroblast proliferation and collagen synthesis are stimulated by Th2 cytokines, such as IL-4 and IL-13, as well as a reduce in Th1 chemokine receptor CXCR3 and an rise in Th2 chemokine receptor CCR4. Within each HP individuals, BAL fluid examination shows these kinds of alterations [48]. IL-17, which is generated by Th17 cells, neutrophils, and CD103+ expression on dendritic cells, also promotes fibroblast growth [49].

Scarring of the lungs associated with aging (ILD) of uncertain causes is known as idiopathic pulmonary fibrosis (IPF). It is characterised by scarring of lung that has no apparent aetiology. Typically, the illness worsens with time and has a dismal prognosis. The illness's hallmark symptoms include a non-productive cough and increasing dyspnea. Tests for pulmonary function often show reduced capacity to diffuse carbon monoxide and restrictive impairment [50]. It causes by exposing to tobacco smoke, dust and gastroesophageal reflux. Repeated damage to the alveolar epithelium starts off an immune system signalling cascade that results in fibrosis. Tissue remodelling may result from an aberrant immune response to the damage [51]. Numerous pathways are probably responsible for the onset. Although idiopathic instances account for the majority of cases, several genetic variables have been found to contribute to familial cases. Pulmonary fibrosis has been linked to mutations in the telomerase, surfactant and mucin genes. Another uncommon autosomal recessive disorder is Hermansky Pudlak syndrome, which is characterised by abnormalities in lysosome-related organelles that result in albinism, platelet abnormalities, and pulmonary fibrosis in many of the affected people [52].

The underlying mechanism of idiopathic pulmonary fibrosis (IPF) involves repeated subtle injuries to a genetically susceptible alveolar epithelium, leading to a breakdown in the process of alveolar re-epithelialization and repair [53]. Then, an array of cytokines and growth factors is secreted by activated cells within the alveoli, promoting the attraction, replication and transformation of lung fibroblasts into myofibroblasts [54]. This process causes the lung parenchyma to scar more severely, an excessive buildup of collagen, and irreversible function loss [54]. The development of pulmonary fibrosis suggests that a mutation in the IPF-associated surfactant protein C gene, which codes for a protein exclusive to alveolar type II (AT2) cells, can cause spontaneous lung fibrosis [55]. The intricacy of idiopathic pulmonary fibrosis is evident in the multitude of cells and signaling pathways involved. The development of IPF might encompass disrupted epithelial mending, compromised immune defense, cellular senescence, skewed immune reactions involving macrophage activation, fibroproliferative responses associated with irregular kinase activation, as well as the activation of pro-fibrogenic pathways downstream of transforming growth factor- β (TGF- β) [19]. Next, the factors that affect the function of AT2 cells in pulmonary fibrosis include telomere attrition, abnormal bioenergetics of mitochondria, and rised stress in endoplasmic reticulum [16]. AT2 cells play a crucial role in the restoration and healing of a damaged alveolus since they act as stem cells for the distal epithelium in the adult lung [17]. Normal tissue regeneration causes AT2 cells to move

into a pre-alveolar type 1 transitional cell state in which they show genes linked to senescence before they terminally mature into alveolar Type 1 cells. Pre-alveolar type 1 transitional cell accumulation may impede healthy alveolar regeneration, which may hasten the onset of fibrosis [18]. Idiopathic pulmonary fibrosis is mostly triggered by malfunctioning of the alveolar epithelium.

In addition, patients with idiopathic pulmonary fibrosis will cause the increase of scarring of the lungs with the increase of time. It will stop when the body's tissues and organs are no longer receiving adequate oxygen from the lungs. Idiopathic pulmonary fibrosis patients occasionally experience other severe lung diseases, such as lung cancer, pulmonary emboli, pneumonia, or elevated blood pressure in the blood arteries supplying the lungs [56]. The mechanisms underlying pulmonary fibrosis and different types of fibrosis discussed are summarized in Fig. 1.

2.2. Current treatment approaches for pulmonary fibrosis

For the current treatment for pulmonary fibrosis, there are two antifibrotic medications can be used which are pirfenidone and nintedanib that have been approved. A little chemical called pirfenidone is a modified pyridine that has antioxidant, anti-inflammatory and anti-fibrotic qualities. It suppresses the cytokine TGF- β , slows the fibrotic process by slowing down collagen formation, and lessens the rate at which the FVC declines [57]. The ASCEND study and two phase 3 CAPACITY studies demonstrated this. Over the course of a year of treatment, pirfenidone reduces the chance of hospitalisation for

respiratory-related issues [58]. Although skin rash, weight loss, nausea, and fatigue are common side effects of pirfenidone, there have also been reports of abnormal liver function, including elevated serum bilirubin and alanine aminotransferase (ALT/AST) [59]. As a result, patients receiving pirfenidone need to have their liver function regularly monitored [60].

Next, the intracellular tyrosine kinase inhibitor which is nintedanib inhibits signalling pathways associated with blood vessel growth factor receptor, fibroblast growth hormone receptor 1–3, and growth factor receptor from platelets α and β by binding to adenosine triphosphate binding sites. Fibroblast activity is reduced as a result of these effects on receptor tyrosine kinases [6]. INPULSIS phase 3 trials I and II demonstrated a noteworthy reduction in the FVC deterioration rate among PF patients, although the death rate stayed constant [61]. Medication can be used to control the adverse effects and the side effects mostly consist of nausea and diarrhoea. However, the treatment is not advised for people with severe liver disease and may cause hepatotoxicity in rare instances [62].

2.3. Therapeutic potential of phytochemicals in the treatment of pulmonary fibrosis

Pulmonary fibrosis can be treated with phytochemicals through pulmonary drug delivery. However, phytochemicals can be delivered through oral administration, topical application and rectal administration. Phytochemicals are well-known compound that consists of active ingredients that are extracted from plants and produces therapeutic effects in treating or preventing different form of diseases [63]. Phytochemicals can be extracted from different parts of the plants such as leaves, roots, bark and seeds. Different part within one plant might contain different active ingredients and produces different therapeutic effects. The examples of phytochemicals include korea red ginseng, flavonoids, red wine and broccoli sprout. The medical plants have more advantages than modern medicine.

Furthermore, the therapeutic management of fibrosis of the lungs involves the use of pulmonary medication routes of administration. Pulmonary drug delivery system is a method that administers the drugs directly into the lungs for respiratory conditions as it is targeted drug delivery [11]. The pulmonary delivery system used various inhalation devices to administer the drugs into lungs. The inhalers that can be used for management of pulmonary fibrosis involves nebulizers, a light spray inhalation device, airborne powder inhalation devices and metered-dose breathing devices. Metered-dose inhalers are always the first choice for the treatment of pulmonary disease [19]. Metered-dose inhaler is a nti-inflam inhaler with the release of medication as an aerosol when activated by a patient's inhalation while dry powder inhalers release the medication as a powdered form then dispersed in the lungs. Next, soft mist inhalers also deliver the medication as an aerosol but in the form of fine spray while nebulizer converts the liquid medication into a fine mist or an aerosol then inhaled by the patient.

Flavonoids are a complex group of polyphenolic compounds that are found in all sections of plants, including foliage, roots, and berries [64]. These compounds feature two rings of aromatic compounds bonded with a bridge chain that has three carbon atoms, which may produce a ring called a heterocyclic with the presence of oxygen. They also have a C6–C3–C6 carbon backbone (Wang et al., 2018). Based on heterocyclic substitution patterns, flavonoids are categorised as chalcones, flavones, ketones, flavanones, cyanide compounds, and others, highlighting their enormous complexity and diversity [65]. Because of their many metabolic activities which include anticancer, antiviral, antimicrobial, anti-inflammatory, autoimmune defensive processes and anti-oxidant properties—natural flavonoids have drawn a lot of interest as potential therapeutic agents [66]. Many chemical components used in traditional Chinese medicine, such as flavonoids, alkaloids, glycosides, saponins, and polyphenols, show positive medicinal benefits on alveolar fibrosis; however, flavonoids appear to offer the most potential benefit

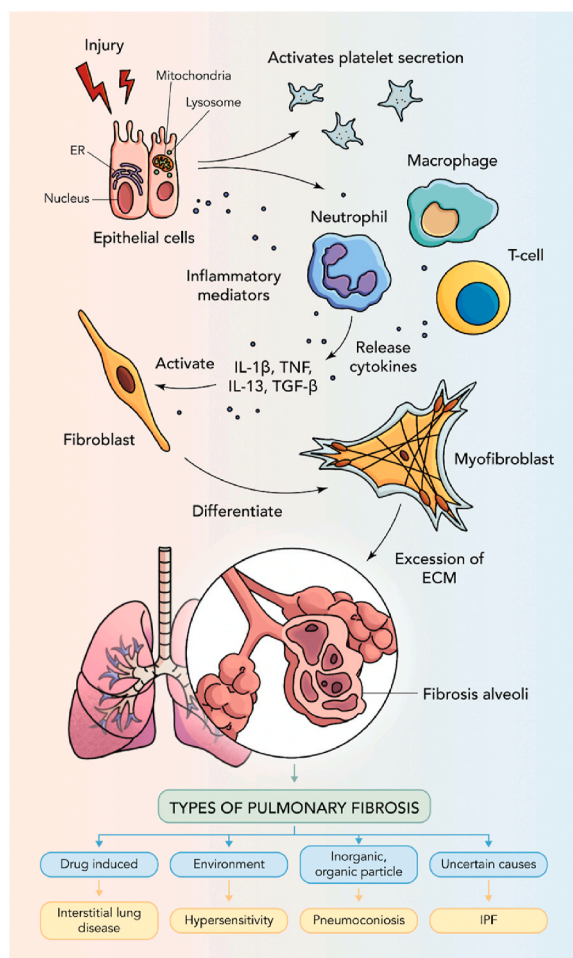


Fig. 1. Classification of the different types of pulmonary fibrosis and relative causing factors.

(Wang et al., 2023). Investigations conducted on individuals with respiratory fibrosis examined natural flavonoids, such as quercetin (Wang et al., 2023). Furthermore, calycosin's anti-inflammatory and liver protective actions have been utilized in the treatment of fibrosis in clinical settings (Gong et al., 2021). However, additional investigation is needed to fully comprehend these naturally found flavonoids that prevent lung cirrhosis.

The following section, we discuss some promising phytochemicals which have shown therapeutic potential for pulmonary fibrosis. These are also summarized in Table 1. Quercetin is a compound produced from *Quercetum* which has shown a great therapeutic promise for treating pulmonary fibrosis [66]. This flavonoid had outstanding antioxidant effects, preventing lipoprotein oxidation by removing free radicals and chelating metal ion transitions [66]. Chelating metal ions play an important role in antioxidant. According to the studies, quercetin can trigger Cu^{2+} and Fe^{2+} via catechol in its structure [67]. It works by binding Fe^{2+} and so prevent iron excess and oxidative damage in alcoholic liver disease by inhibiting Fe^{2+} -induced lipid peroxidation [68]. A chemiluminescence investigation able to prove that Fe^{2+} in compounds containing dihydroquercetin is inert, unable of catalysing the breakdown of hydrogen peroxide, and incapable of initiating further hydroxyl free radical formation. Consequently, quercetin can function as an antioxidant stressor via a variety of pathways and Fe^{2+} [69].

By inhibiting inflammatory mediators such $\text{TNF-}\alpha$, IL-1 β , IL-6, IL-13, and PDGF- β , quercetin is being reported to lessen BLM-induced the progression of lung in animals. Moreover, it increases INF- γ , an anti-fibrotic factor (Baowen et al., 2010). Additionally, by raising level of antioxidants, suppressing MMP-7 expression, inflammatory cytokine amounts, and reducing collagen formation, quercetin showed a pneumoprotective effect on lung inflammation (Verma et al., 2013). Quercetin possesses anti-inflammatory properties due to its ability to suppress inflammatory mediators and enzymes like lipoxygenase. By primarily targeting leukocytes and many intracellular signalling kinases and phosphatases, which are enzymes and membrane proteins frequently essential for a cellular specialised function, quercetin influences immunity and inflammation [70]. Perhaps via stabilising mast cell membranes, quercetin prevents the synthesis and release of histamine and other allergic and inflammatory chemicals [71]. Also, by promoting the synthesis of fast responses and caveolin-1 but combating protein kinase B (AKT) triggering, quercetin has been demonstrated to have promising efficacy in reversing apoptosis resistance induced by death ligands. This suggests an unexpected and probably unprecedented therapies to the remedy of pulmonary dysfunction in ageing animals [72]. It has been demonstrated that quercetin inhibits the TGF- β -Smad2/3 process, which lowers macrophage polarisation and the mesenchymal-to-mesenchymal transformation (MMT) (Geng et al., 2023). Researchers have confirmed quercetin has a great deal of therapeutic promise for treating pulmonary fibrosis.

Apigenin is a naturally occurring polyphenol that is obtained from *Chamomile morifolium* and *Turnera diffusa*. It is renowned due to multiple states medicinal properties, such as its antibiotics, anti-inflammatory, anti-oxidative, and cancer fighting abilities (Salehi et al., 2019). According to a released study, apigenin can stop pulmonary fibrosis from getting worse [73]. Apigenin markedly decreased the production of proinflammatory cytokines such as $\text{TNF-}\alpha$ and TGF- β , MPO action, and hydroxyproline loading in a bleomycin-induced animal model, but increased the function of SOD (Chen and Zhao 2016). By inhibiting NF- κ B/TGF- β -mediated lung epithelial growth and manufacture of collagen, apigenin shielded animals against BLM-induced lung inflammation [74].

A common belief is that the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) signalling pathway plays an active role in both proliferation and survival. Furthermore, the I κ B protein members control the members of the NF- κ B family [75]. In the cytoplasm, NF- κ B binds to I κ B in an inactive form as a heterodimer. IKK complex activation is brought on by a variety of signal molecules,

Table 1

A summary of plant species that can be used to treat pulmonary fibrosis.

Plants	Active constituent and effects	References
<i>Quercetum</i>	Quercetin improved bleomycin-induced lung fibrosis. Sphingosine-1-phosphate (S1P), initiation of required kinase, sphingosine kinase 1 (SphK1), and breaks down of enzyme, sphingosine-1-phosphate lyase (S1PL), increased in lung tissue and HELF cells with injection of bleomycin or TGF- β .	[73]
broccoli, mango, onion, basil, the herb parsley, and lavender	Apigenin controls multiple cellular processes, including oxygen consumption, ER suppression, and damage reaction in lungs	[141]
<i>Curcuma longa</i>	Curcumin has antioxidative and anti-inflammatory activities. Inhibition of histone acetyl transferase (HAT) activity, which is specific for the p300/CREB-binding protein	[78]
Scutellariae radix	Baicalein By decreasing the TGF- β 1/Smad signalling pathway and restoring Sirt3 expression, baicalein significantly reduced lung fibrosis in vivo. Furthermore, it has been discovered that baicalein attenuates BLM-induced lung fibrosis by blocking miR-21, an important regulator of the development of fibrosis. Baicalein dramatically reduced CTGF expression, which could be related to the TGF- β 1-induced decrease in phosphorylation of Smad2.	[80]
<i>Erigeron breviscapus</i>	Scutellarein Scutellarein inhibited the changes from fibroblasts to myofibroblasts by blocking the TGF- β /Smad pathway, and it also slowed down the growth of cells by blocking the PI3K/AKT pathway. Furthermore, in pulmonary fibrosis, scutellarein induced fibroblast death by modifying Bax/Bcl-2. Additionally, scutellarein's potent anti-allergic and antifibrotic qualities was validated in animals produced by bleomycin. Scutellarein modulated the NF- κ B/NLRP3 pathway to precisely suppress the onset of EMT and control inflammation.	[142]
<i>Moraceae</i>	Morin preventing fibroblast conversion to myofibroblasts and reducing pathologic changes, inhibiting NIH-3T3 cells activated by TGF- β 1, prevent NIH-3T3 cells from undergoing metamorphosis	[81]
<i>Ruta graveolens</i>	Rutin In bronchoalveolar lavage fluid, rutin significantly reduces the mass index of lung and body, macrophages, lymphocytes, and lactate dehydrogenase activity. Furthermore, rutin improves histological abnormalities and prevents collagen deposition, as evidenced by a decrease in lung hydroxyproline content. It also reduces the expression of fibrosis-related indicators such as TGF- β 1, Col I, Col III, and α -SMA.	[143]

including TNF, FasL, and TRAIL. This leads to I κ B α phosphorylation and proteasome destruction [76]. Following its release, NF- κ B moves into the nucleus. To prevent cell death, NF- κ B activates the target genes consist of prosurvival genes include Bcl-2, Bcl-xL, nti-infl, X-linked inhibitor of apoptosis protein (XIAP), genes associated to the cell cycle

(cyclin D1), VEGF, inflammatory cytokines, and genes that cause tumour metastasis (COX-2) [77]. According to a recent study (Wójcik et al., 2013), apigenin may proficiently restrict the TGF- β 1-induced cell growth of hypercontractile myofibroblast regions, which are identified by their α -smooth muscular actin-positive characteristics, underneath the complex assemblages associated with human airways ocytes. These compelling results shed new light on the potential of apigenin as a medicinal product for battling scarred disorders.

Curcumin, a polyphenolic compound derived from the rhizome of the *Curcuma longa* plant, has captured the attention of scientists, health enthusiasts, and medical practitioners worldwide. Through the inhibition of multiple routes for cells signalling, such as NF- κ B, STAT3, Nrf2, ROS, and COX-2, curcumin has antioxidative and anti-inflammatory activities. Its anti-inflammatory properties may possibly be attributed to curcumin's inhibition of histone acetyl transferase (HAT) activity, which is specific for the p300/CREB-binding protein. In this sense, curcumin block HAT, which suppresses the synthesis of IL-6 and TNF- α by monocytes. A crucial stage in fibrogenesis known as the epithelial-to-mesenchymal transition has been connected to HAT inhibition and IL-6 production [78].

Baicalin, a noteworthy bioactive constituent of *Scutellaria radix*, possesses an extensive array of therapeutic properties, especially the ability to function a natural antioxidant, reduce edoema, combat illness, and impede the expansion of tumors (Huang et al., 2019). Baicalin therapy balanced Th17 and Treg responses in a mouse model of silicosis, lowering inflammatory cell accumulation and clinical inflammatory and fibrotic alterations in lung tissues (Liu et al., 2015). When administered orally, baicalein significantly reduced the levels of miR-21, boosted TGF- β 1 and p-smad2/3 expression, and reduced lung tissue, hydroxyproline, and α -SMA (α -smooth muscular actin) levels. The buildup of collagen in the matrix of cells and the activation of myofibroblasts depend on these activities.

As a key player in each of the many stages leading to lung fibrosis, TGF- β 1 is a fundamental mediator in the development of lung fibrosis. This is because TGF- β 1 increases epithelial apoptosis, induces epithelial migration, suppresses epithelial cell proliferation, and drives epithelial-mesenchymal transition [72]. Furthermore, it promotes collagen synthesis, fibroblast proliferation, and prevents fibroblast death. It has been discovered that integrins, heterodimeric transmembrane proteins made up of α and β subunits, can bind with TGF- β 1 for activation purpose. TGF- β 1 is activated by the α v β 6 integrin, which is activated by cytoskeletal alterations [79].

According to recent research, baicalin has potent antifibrotic effects by stimulating the newly discovered inflammatory regulator, the adenosine A2a receptor (A2aR) [80]. According to Gao et al. [80], the activation of A2aR inhibited TGF- β 1 activation, ERK1/2 expression, and BLM-induced lung fibrosis. Baicalin also lowered the production of cyclin A, D, and E, fibroblast proliferation, and internal calcium quantity, all of which occurred at the same time as cells went from the G0/G1 to the S and G2/M phases (Zhao et al., 2020). likewise, in animals suffering BLM-induced inflammation, baicalin limited a spike of connective tissue growth factor (CTGF) levels (Jia et al., 2010).

Other than that, scutellarein is a traditional Chinese medicine and derived from *Erigeron breviscapus*. It has been shown to be effective against pulmonary fibrosis [81].

Numerous studies demonstrate that scutellarein inhibits the TGF- β /Smad route, which in turn inhibits fibroblast-to-myofibroblast development, and the PI3K/AKT system, which decreases cell division. Additionally, in respiratory fibrosis, scutellarein regulated Bax/Bcl-2 to promote fibroblast death [81]. Additionally, scutellarein's potent anti-inflammatory and antifibrotic properties were recently confirmed in a mouse model caused by bleomycin. According to Peng et al. [82], scutellarein suppresses irritation and EMT via controlling the NF- κ B/NLRP3 process [82]. These revolutionary findings imply that scutellarein might be used as a new prophylactic or therapeutic treatment for pulmonary fibrosis.

Originally belonging to the Moraceae family, morin has demonstrated remarkable medicinal benefits by halting the progression of fibroblasts into myofibroblasts and minimising the degenerative alterations that bleomycin causes in animals (Caselli et al., 2016).

The findings demonstrated that morin significantly reduced the pathologic changes and prevented fibroblasts from changing into myofibroblasts in the lungs of mice with PF caused by bleomycin as well as TGF- β 1 or hypoxia-stimulated NIH-3T3 cells [81].

Mechanistic investigations demonstrated that morin triggered the peroxisome proliferator activated receptor-gamma (PPAR- γ), and that the inhibitory effects of morin on the change of NIH-3T3 cells were greatly lessened by GW9662 or siPPAR- γ [81]. Furthermore, glutamine deprivation and GLS1 overexpression demonstrated that morin inhibited glutaminolysis by minimize the amount of glutaminase 1 (GLS1) [81]. The fibroblasts' transformation was stopped by morin when α -ketoglutarate (α -KG) and 2-hydroxyglutarate (2-HG) were replenished. However, TGF- β 1 and hypoxia did not cause the transformation of IDH2-knockdown fibroblasts, indicating that 2-HG was directly responsible for the action of morin. Then, it was shown that leucine and the KDM4A inhibitor inhibited the impact of morin, preventing the ubiquitination of DEPTOR. This was linked to KDM4A, an enzyme that was inactivated by 2-HG [81].

Rutin is an active component produced from *Ruta graveolens* plant, it has demonstrated tremendous therapeutic potential in treating pulmonary fibrosis. Studies have shown that rutin significantly reduces the number of macrophages, lymphocytes, lung volume, and lactate dehydrating enzyme activity in the bronchoalveolar lavage fluid [83]. Rutin improved modifications in histology and prevented the development of collagen by reducing the quantity of hydroxyproline in the lungs, and it also decreased TGF- β 1 alongside other fibrosis-related markers, such as Col I, Col III, and α -SMA [84]. Further, it proved that rutin significantly decreased pulmonary tissue levels of oxides of nitrogen and malondialdehyde while increasing serum antioxidant capacity, glutathione levels, and the enzyme superoxide dismutase capacity [84].

In this section we showcased the therapeutic potential, but none of these is clinically used to treat pulmonary fibrosis. This is caused by inherent issues with phytochemicals such as poor solubility and poor permeability, which limit their applicability. Because of quercetin's short biological half-life, biochemical unpredictability, difficult to dissolve in water, and low the absorption of nutrients it might not be as useful in the dietary supplement and medicine sectors [85]. Quercetin is a water-based substance that is slightly soluble in alcohol and highly dissoluble in the solvent dimethyl sulfoxide. At room temperature, the amount that dissolves in water is low [86]. For this reason, adding large amounts of quercetin directly into a dietary matrix that is dependent on water is challenging.

3. Type of nanoparticles

The issues of phytochemicals can be overcome by formulating phytochemicals in advanced drug delivery system. Nanoparticles can be used in delivering drug to treat pulmonary fibrosis. Nanoparticles are materials with at least one dimension less than 100 nm and the shape of the nanoparticles can be 0D, 1D, 2D or 3D [87]. Nanoparticles comprised three components which are surface layer, shell layer and the core [88]. Nanoparticle has better effect in treat pulmonary fibrosis as it allows targeted delivery which can be engineered to target specific cells or tissues in the body. The surface of the nanoparticle consists of ligands or antibodies allow the binding of receptors on targeted cells hence the therapeutic effects can be maximised while the side effects can be minimized. Next, most of the phytochemicals has poor solubility thus nanoparticles can encapsulate hydrophobic phytochemicals to enhance the solubility and allow better absorption of drug in the body.

Nanoparticles can be roughly classified into a number of types based on their size, shape, and chemical properties. The nanoparticles will be discussed to treat pulmonary fibrosis include liposomes, poly(lactic-co-

glycolic acid), dextran, acetalated dextran, polymeric micelle, lyotropic liquid crystalline and polyethylene glycol (PEG).

3.1. Liposomes

Liposomes are fluid-entrapped vesicles composed of hydrophobic and hydrophilic phospholipid molecules that can form bilayers. It is spherical lipid vesicles in range between 50 and 500 nm in diameter formed by emulsifying natural or synthetic lipids in an aqueous media [89]. A bilayer forms when two layers of oriented lipid molecules unite, with their hydrophobic sides in contact. Lipid molecules assemble into vesicles, encapsulating a fluid volume within lipid bilayers under certain conditions. Targeted drugs can be embedded in the fluid encapsulated by vesicles. Liposome nanoemulsions are commonly utilized in nanomedicine. Compared to biological membranes in the body, synthetic bilayers have better biocompatibility, stability and high drug loading efficiency [90], good bioavailability, and the safe excipients employed in formulations. Targeting can be achieved by chemically modifying the surface of the vesicle through the use of ligands or polymers.

The lipid composition greatly influences the characteristics of liposomes, including their particle size, rigidity, flexibility, stability, and electric charge [91]. Liposomes crafted from naturally occurring unsaturated phosphatidylcholine, like soybean phosphatidylcholine, exhibit high permeability but low stability. Conversely, liposomes composed of saturated phospholipids, such as dipalmitoyl phosphatidylcholine, result in rigid and impermeable bilayer structures [92].

The therapeutic efficiency administering via inhalation by aiding the interleukin receptors and leveraging its anti-fibrotic effects. It helps to control the severity of pulmonary fibrosis. The combination of colchicine and budesonide produce liposomal powder-like inhalants. Mannitol was served as carrier and the lyophilized liposome encapsulation rate ranged from 97.89 to 98.6 %. In addition, the approach decreased systemic level and provided extended drug retention at specific organs. With a lung deposition rate of 79.9 ± 1.5 % and low toxicity, naringin is used as an aerosol to improve lung mobility in pulmonary fibrosis therapy [74]. An inhaler used to nebulize paclitaxel liposomes was developed to treat rats with bleomycin-induced PF. The findings imply that paclitaxel liposomes breathed can stop severe PF. Compared to intravenous injection, inhalation is safer and has less systemic adverse effects [93].

Novel targets provide a novel approach to treating PF and may be included in sophisticated drug delivery systems for targeted therapy [94]. A modified liposome with hyaluronic acid is particularly for receptor CD44, as it has been overproduced in pulmonary fibrotic cells [95]. The liposomes enhanced TGF- β mRNA but lowered transcripts of the anti-fibrotic VEGF, IL-1 β , and IL-12 pro-inflammatory cytokines.

To shield animals against bleomycin-induced PF, intratracheal administration of methyl-CpG-binding domain 2 (MBD2) siRNA liposomes was used. For loading siRNA, the produced liposomes' entrapment effectiveness was about 90 %. There was no evidence of the toxicity of siRNA inserted into liposomes on cell viability. For a minimum of seven days, the liposomes that were injected intratracheally kept building up in the lungs. Particularly the lungs exhibited NIRF signals; signals in other parts were lacking [93]. In formulations with reduced renal filtration, reduced reticuloendothelial system absorption and reduced enzymatic degradation, polyethylene glycol PEGylated liposomes may also be taken into consideration. PEGylated medications exhibit a longer half-life in vivo shows to improve their bioavailability [96]. Moreover, utilizing PEGylated liposomes for aerosolized drug delivery aids in improving the pharmacokinetic effectiveness of the medication, prolongs drug distribution in the lungs, and offers anti-fibrotic properties [97].

3.2. Poly(lactic-co-glycolic acid)

Poly(lactic-co-glycolic acid) is a copolymer synthesized through the

random ring-opening copolymerization of two different monomers: cyclic dimers of glycolic acid and lactic acid. Various catalysts like tin (II) 2-ethylhexanoate, tin (II) alkoxides, or aluminium isopropoxide are used in its preparation. In the polymerization process, consecutive monomeric units are linked together in PLGA through ester bonds, yielding a linear, amorphous aliphatic polyester product [98]. The ratio of monomers is commonly used to characterize different forms of PLGA. For instance, PLGA 50:50, which is extensively employed in nanotechnology, consists of a copolymer with a composition of 50 % lactic acid and 50 % glycolic acid. The predominant technique for producing PLGA nanoparticles is the single- or double-emulsion-solvent evaporation method. In the single-emulsion process, oil-in-water (o/w) emulsification is used, while the double-emulsion process involves a water-in-oil-in-water (w/o/w) approach. Water-soluble medications such as peptides, proteins, and vaccines are ideally encapsulated using the w/o/w approach, whereas water-insoluble pharmaceuticals like steroids benefit from the o/w method [99].

In exceptional cases, solid/oil/water (s/o/w) methods have been utilized with PLGA-based microspheres, particularly to enhance the loading of large water-soluble peptides. Briefly, the o/w approach entails dissolving PLGA in a water-immiscible, volatile organic solvent, followed by the addition of the drug into the polymer solution to create a dispersion of drug particles. This polymer-solvent-drug dispersion is then emulsified in a larger volume of water under appropriate stirring and temperature conditions, with the presence of an emulsifier like poly(vinyl alcohol) (PVA), to form an oil-in-water emulsion. PVA is utilized to stabilize the emulsion, ensuring modest particle diameters and consistent size distribution [83]. After removing the solvent through evaporation or extraction to solidify the oil droplets, the solid nanospheres are purified and gathered via filtration. They are then dried under appropriate conditions or subjected to lyophilization to yield the final injectable nanospheres with a free-flowing consistency [99]. PLGA NPs are colloidal systems that have a diameter of 10–1000 nm. The medicinal material is attached to the polymer matrix chemically, adsorbed, or entrapped within the NPs [84]. PLGA nanoparticles exhibit biodegradability due to the hydrolysis of ester bonds in the presence of water, resulting in the production of the original monomers, lactic acid and glycolic acid, which are metabolized as byproducts in the body's metabolic pathways. The degradation rate is influenced by the ratio of monomers. For instance, PLGA with a 50:50 ratio of lactic and glycolic acids degrades more rapidly than those with higher proportions of either monomer [100]. The degraded products are quickly metabolized by the body's Krebs cycle then eliminated [101]. Thus, the use of PLGA for medication delivery has very low systemic toxicity.

An examination of the pulmonary levels of IL-10 in lung tissue homogenates from various groups showed that rats administered bleomycin had significantly higher levels of the protein than control rats, but rats receiving with bleomycin + TQ-PLGA-PVA-NPs had significantly lower levels [102]. Rats injected with TQ-PLGA-PVA-NPs had a level of lungs of IL-10 of 22.19 ± 0.80 pg/mL, which was not significantly different from control rats. TGF- β 1 lung levels were substantially higher in bleomycin-treated rats than in control and bleomycin + TQ-PLGA-PVA-NPs treated rats [102]. On the other hand, TGF- β 1 levels in TQ-PLGA-PVA-NPs-treated rats were 204.5 ± 2.54 pg/mL, not significantly different from control rats [102].

3.3. Dextran

Dextran is an extracellular polysaccharide (EPS) synthesized by lactic acid bacteria or their enzymes when sucrose is present. It consists of a linear sequence of D-glucose units connected by α -(1 \rightarrow 6) bonds, with possible side chains of D-glucose attached by α -(1 \rightarrow 4), α -(1 \rightarrow 3), or α -(1 \rightarrow 2) linkages. If the molecular weight more than 40 kDa called dextrans, while molecular weight less than 40 kDa is called oligodextrans. Dextran's molecular weight and branching characteristics are determined by the generating strain, hence its qualities vary greatly

[103]. Dextran is commercially valuable because of its solubility, viscosity, heat and rheological qualities, which allow it to be employed in culinary, pharmaceutical, and analysis applications. The primary structure of dextran, featuring α -(1 \rightarrow 6) bonds, takes on a helical configuration, but the presence of branches (α -(1 \rightarrow 2), α -(1 \rightarrow 3), or α -(1 \rightarrow 4)) alters this conformation, causing the linear glucan structure to undergo repetitive folding [104].

Furthermore, the solubility and rheological characteristics of dextrans are connected to its molecular weight and branching. The solubility of dextrans relates to the interaction between molecules and water to form hydrogen bondings [105]. In some cases, dextran molecules would be fully soluble as there is interaction between hydroxyl group and water molecules with the presence of linear dextran molecules [106]. But, there is no direct association between molecular features and property variation [107]. However, despite their solubility, dextrans are classified as soluble EPS because of their propensity to absorb significant amounts of water and produce hydrogels [108].

The rheology and viscosity of the polymer change under an applied force due to the presence of hydroxyl groups that readily engage in hydrogen bonding with other molecules. These bonds break during shear forces [109]. The viscosity of dextran increases linearly with both its concentration and shear rate. This indicates that at low concentrations, it exhibits Newtonian behavior while at higher concentrations, it demonstrates non-Newtonian behavior. Newtonian fluids are fluids that exhibit constant viscosity regardless of the applied shear stress or shear rate while non-Newtonian fluid do not follow Newton's law of viscosity as the viscosity of the fluids can change with the applied stress or shear rate.

On the other hand, flexibility of the polymer will be influenced by temperature. At different temperatures gives different intermolecular tensions, crystallinity, and its size [110]. At low temperatures, linear amorphous polymers exhibit glass-like properties without flexibility due to the zero mobility [111]. At high temperature, they tend to become rubbery, and eventually melt [110].

During this phase, polymers reach the most flexible point. The high glass transition temperature (T_g) observed in crystalline polymers is attributed to the strong intermolecular forces present between the polymer chains. Short-chain polymers exhibit low melting temperatures (T_m) due to their limited entropy, whereas long-chain polymers are more rigid and possess higher entropies, resulting in higher melting temperatures [110].

Dextrans are employed because they mimic the colloidal osmotic pressure and viscosity of human blood when dissolved in a 6 % concentration of normal saline. Consequently, dextran serves as a plasma volume expander. For instance, Dextran 40 and 70, with molecular weights of 40 and 70 kDa respectively, are frequently used to manage shock or impending shock resulting from hemorrhage, burns, or trauma.

Furthermore, dextran finds application in gel filtration technology, as it can be easily cross-linked and formed into beads for use in gel filtration columns. For instance, Sephadex®, available in various porosities and bead sizes, offers characteristic molecular weight fractionation ranges. Sephadex® G-200, known for its highest porosity, is used to fractionate proteins ranging from 4 to 80 kDa, while Sephadex G-25 is suitable for fractionating peptides smaller than 5 kDa.

In neutral dextran gels, quaternized and carboxymethyl derivatives of dextran are commercially available for cation and anion exchange chromatography. Dextrans can be utilized to conjugate bioactive molecules like antibodies and hormones to extend circulation life and boost the in vivo stability and reduce antigenicity due to its hydrophilicity. The combination of dextran nanoparticles and insulin can be administered orally. This is because the nanoparticles can shield the insulin from the acid environment and control the release. Due to its hydrophilicity and functionalizable polymer, dextran can appear as surface modification in biosensor construction. It works by coating on sensor chips to decrease nonspecific analyte adsorption and improve surface ligand immobilisation, thus maximising biosensor sensitivity [111].

3.4. Acetalated dextran (Ac-DEX)

Acetalated dextran (Ac-DEX) is among the most thoroughly investigated dextran derivatives. The acetalation of dextran occurs through a reaction with 2-methoxypropene, catalyzed by pyridinium p-toluenesulfonate (PPTS). Following the acetalation process of the hydroxyl groups on dextran, the resulting product (Ac-DEX) becomes insoluble in water but soluble in organic solvents [112]. Moreover, these acetal groups are prone to undergo acidic hydrolysis, resulting in the production of dextran, methanol, and acetone as degradation products [112]. Ac-DEX has been selected for drug encapsulation via precipitation and emulsion methods because of its hydrophobic nature and its ability to dissolve in organic solvents. Besides, it allows the drug to be released in the stomach as it acts as an acid-triggered degradation such as endosomal compartments, and tumour microenvironments [113].

Ac-DEX comprises both linear acetal groups and cyclic acetal groups. Over 80 % of the hydroxyl groups undergo reactions with linear acetal groups. Conversely, the formation of cyclic acetals offered a thermodynamic advantage during synthesis. With prolonged reaction times, cyclic acetals eventually reacted with linear ones [114]. The balance between cyclic and acyclic acetals is a critical structural aspect of Ac-DEX, as it impacts the polymer's degradation rate. Acyclic acetals degrade rapidly, yielding methanol and acetone, while cyclic acetals degrade more slowly, primarily producing acetone [114]. Thus, ratio of cyclic to acyclic acetal influences the Ac-DEX degradation half-life.

Ac-DEX-based therapeutic delivery systems for anti-tumor applications have been developed to enhance the effectiveness of chemotherapy, photodynamic treatment, and the advancement of chemimmunotherapy. Typically, Ac-DEX is formulated into nanoparticles (NPs) in these delivery systems, through which drugs are transported to tumors either by passive accumulation exploiting the enhanced permeability and retention (EPR) effect or by active targeting achieved through the attachment of specific tumor-targeting ligands. Subsequently, the pH-responsive degradation within the acidic tumor microenvironment triggers drug release, facilitating the eradication of cancer cells [115,116].

The utilization of Ac-DEX for delivering chemotherapeutic drugs aims primarily to enhance the solubility and bioavailability of poorly soluble pharmaceuticals while reducing systemic adverse effects compared to free drugs. The surface of pH-responsive Ac-DEX nanoparticles (NPs) will be coated with PEG through an encapsulation process [115]. The PEG-conjugated Ac-DEX carrier has great inherent in delivering extremely toxic medicines for antitumor treatment.

The zinc-doped copper oxide NPs with a core structure that are enclosed in SpAcDEX and have a conjugated 3-(cyclooctylamino)-2,5,6-trifluoro-4-[(2-hydroxyethyl)sulfonyl] benzenesulfonamide (VD1142) ligand on the surface are an additional example of delivering hazardous anticancer medicines [117]. The zinc-doped copper oxide NPs' prickly nature enabled them to physically rupture lipid membranes, exhibiting notable cytotoxicity [117]. Zinc-doped copper oxide nanoparticles (NPs) were enclosed in SpAcDEX to improve biological stability and safety [117]. Moreover, the system gained pH responsiveness via the polymer coating. The SpAcDEX shell disintegrated in the acidic endosomal environment during endocytic absorption, revealing the prickly NPs that broke through the endosomal membrane and fled into the cytoplasm [117].

Moreover, SpAcDEX will generate a nanocomposite for chemimmunotherapy by blending a non-genotoxic chemical, Nut3a, with a cytokine that stimulates antigen-presenting cells, granulocyte-macrophage colony-stimulating factor (GM-CSF) [118]. The nanoparticles were observed to maintain the pH-responsive release of Nut3a for cancer cell eradication, along with exhibiting endosomal escape characteristics. This behavior is attributed to the "proton sponge" effect induced by the cationic amine groups present in SpAcDEX [118]. The presence of GMCSF in the system gives an efficient antitumor immune response, which functioned as a complement to Nut3a's particular

toxicity towards wild-type p53 cancer cells while minimize the perniciousness to immune cells [118].

Apart from chemotherapeutic drugs and immunostimulants, Ac-DEX-derived polymers can serve as carriers for delivering photosensitizers in photodynamic cancer therapy, such as 5,10,15,20-tetraphenyl-21H,23H-porphyrine (TPP), within folic acid-functionalized SpAcDEX [119]. The attachment of folic acid onto the NP surface increased its uptake by HeLa-KB cells that overexpress the folate receptor α in vitro. Nevertheless, even SpAcDEX without folic acid conjugation exhibited substantial cellular uptake, likely due to nonspecific binding [119]. By using folic acid functionalized SpAcDEX NPs, photodynamic treatment may selectively and effectively target cancer cells overexpressing folic acid receptor α .

Spermine modification can potentially enhance the targeted delivery of therapeutic agents to the lungs. Spermine is a polyamine compound that has been shown to accumulate in tissues undergoing fibrosis. By attaching spermine to dextran, a biocompatible and biodegradable polymer, it may facilitate the delivery of drugs or therapeutic agents specifically to the fibrotic areas of the lungs. Spermine modified Ac-DEX (Spermine-Ac-DEX) was evaluated to transport siRNA. The novel approach has the added advantages of regulated payload release that is responsive to physiologically appropriate acidity conditions, along with easy production and biocompatibility. Acid-sensitive systems are very useful because they can release cargo when endosomal acidity occurs during cellular absorption. Spermine-modified dextran is produced by the acid-catalyzed hydrolysis of spermine-Ac-DEX then subjected to further in vivo enzymatic metabolism [109]. It undergoes additional chemical transformations catalyzed by enzymes present within the organism's body.

The customised design of spermine-Ac-DEX particles explains their capacity to go past several cellular barriers and serve as an effective siRNA delivery system.

Based on the design, the encapsulated siRNA should be shielded from enzymatic and chemical destruction by the particle composition. The cationic properties of Spermine-Ac-DEX enable the encapsulation of siRNA within particles and could potentially enhance cellular absorption by facilitating improved interaction between the particles and the negatively charged cell membranes. Once inside the cells, the siRNA may be released from the particles as a result of polymer hydrolysis occurring in the acidic endolysosomal compartment. Endosomal escape can occur through the amine moieties' "proton sponge" action or through the decomposition of the spermine-Ac-DEX material, which increases endosomal osmotic pressure.

In summary, spermine-Ac-DEX particles function as a delivery system that efficiently and less toxically delivers siRNA to cancer cells. Spermine-Ac-DEX is a safe and efficient gene delivery technology that combines the appealing qualities of polymeric particles with cationic polymers. The spermine modification of Ac-DEX made it easier to generate particles that had a high loading efficiency and could encapsulate siRNA. An in vitro study demonstrated that particles have the capability to dose-dependently decrease luciferase expression in HeLa-luc cells with minimal cytotoxicity. Spermine-Ac-DEX exhibits appealing novel transfection and biodegradability properties in contrast to what has been previously stated or documented gene delivery materials then it can also be readily modified [120].

3.5. Polymeric micelles

The example of nanoparticle includes polymeric micelles are nanoscale and have a core-shell structure. They are created when amphiphilic block copolymers self-assemble in an aqueous solution [121]. Amphiphilic molecules exist independently in diluted aqueous solutions and amphiphiles function as surfactants to lower surface tension at the air-water interface [122]. When polymeric chain concentrations are greater than the critical micellar concentration (CMC), stability of the micelle is maintained. The most crucial factor in determining the

thermodynamic stability of micelles is the CMC value. Hence, polymeric micelle with low molecular weight surfactants has higher kinetic stability and can be used as drug delivery system. Moreover, drug can be encapsulated in the micelle during the formation. Polymeric micelles are intriguing carriers for various administration routes due to their tiny size, ease of manufacture, and good solubilization qualities. In order to decrease adverse effects, they can increase drug bioavailability and allow drug delivered in a controlled or targeted order [123].

Polymeric micelles facilitate drug release either through drug diffusion from intact micelles or micelle breakdown. In either scenario, micelles must possess robust thermodynamic and kinetic stability to prevent uncontrolled drug release during delivery. Therefore, block copolymers conjugated with a lipid molecule were synthesized because it allows decrease in the CMC can be attained by increasing the length of the hydrophobic section of the unimer [121].

By considering the role of micelle in the subcellular delivery of pharmaceuticals to a particular target, a number of internalisation pathways spots should be elucidated [124]. Based on the micelle interaction with cellular membrane, endocytosis is the primary mechanism for internalising microbes. It is followed by uptake in cells and endosome transit to ultimately reach the cytoplasm of the cell [125]. Other than that, some polymeric micelles are typically broken down in lysosomes or disassembled in the plasma membrane thus they are internalised in their intact form [125]. In another way, micelles have the ability to enter cells directly, but they can also release the drug outside of cells or be taken up as disaggregated unimers, which causes the drug to accumulate in other locations such as the plasma membrane or different cellular compartments [126].

Taraxasterol (TA) is a promising anti-IPF medication because of its anti-inflammatory, antioxidant, and lung-protective properties. However, TA's preventive efficacy against IPF has not been shown, and its low solubility in water limits its therapeutic applicability. This research indicated that TA could inhibit the transforming growth factor- β 1 (TGF- β 1)/Smad signaling pathway, thereby halting the epithelial-mesenchymal transition (EMT) and migration of A549 cells. To enhance the water solubility and effectiveness of pulmonary administration of TA, we developed TA-loaded methoxy poly(ethylene glycol)-poly(D,L-lactide) (mPEG-PLA)/D- α -tocopheryl polyethylene glycol succinate (TPGS) mixed polymeric micelles (TA-PM). Then, TA-PM was administered once every two days for three weeks, using a Micro-Sprayer® Aerosolizer to assess its therapeutic benefits on bleomycin (BLM)-induced IPF animals. The findings showed that BLM-induced lung tissue inflammation, oxidative stress, and fibrosis were dramatically reduced by inhaled TA-PM. In addition, TA-PM demonstrated a good safety profile and significant pulmonary deposition and retention upon pulmonary delivery. In summary, the research highlights the inherent in inhaling TA-PM as a therapeutic intervention for IPF, hence offering a fresh avenue for its practical use [127].

3.6. Lyotropic liquid crystalline

An developing category of nanosystems called lyotropic liquid crystalline nanoparticles is designed to transport a variety of pharmaceutically active substances, including hydrophilic or hydrophobic medications and biotherapeutics (peptides, proteins, and nucleic acids). Most of them exhibit highly organized two- or three-dimensional nanostructures containing hydrophilic aqueous channels embedded within lipid matrices, forming hexagonal or cubic mesophases [128, 129]. In contrast to other lipid and polymeric nanocarriers, lyotropic liquid crystalline nanoparticles provide several advantages. These include the capacity to encapsulate multiple drugs, a larger internal lipid bilayer-water interfacial surface that enhances drug entrapment efficiency, the capability to regulate and target drug release via matrix architecture and functional modifications, and potentially lower toxicity due to the biodegradable nature of the lipids utilized [130]. A steric stabiliser capable of ensuring sustained colloidal stability in aqueous

environments over an extended period is necessary for these nano-systems. A steric stabiliser works to preserve the internal architecture of a particle while preventing unfavourable interactions between it and preventing aggregation occurrences [131].

In recent years, the usage of LLCs for medicine distribution has grown in prominence. They are administered either as bulk phases or as colloidal nanoparticles and can be utilized as protein, peptide, and nucleic acid delivery nanosystems. Water-soluble medications can be encapsulated in the polar region of lyotropic liquid crystalline, while liposoluble medications can be encapsulated between the hydrocarbon chains. Lyotropic liquid crystalline (LLQ) are incredibly adaptable platforms. The payloads can be released continuously because of the LLCs' high viscosity. Aqueous channels in LLCs have the potential to release therapeutic compounds, albeit this is reliant on the properties of the medicine [132]. LLC may also be stimulus-sensitive as they will release their payloads in response to specific stimuli. Due to the LLC's thermodynamic stability, the encapsulated medicine can be released when stimuli cause the thermodynamic stable structure to change into an unstable one, which facilitates the payloads' release whenever needed [133]. An further option would be to include substances or agents that respond to environmental variations, such pH or magnetic fields, to create stimuli-sensitive LLCs that can undergo reversible transformation in response to this stimulus and release the cargo.

3.7. Polyethylene glycol (PEG)

There are four categories of polymer-based drug delivery methods including polymeric drugs, polymer-protein conjugates, polymer-drug conjugates, and polymeric micelles [134]. Polymers can also undergo emulsification to generate nanoscale particles capable of encapsulating pharmaceuticals. Polymeric drugs typically consist of natural polymers with antiviral or anticancer properties. Among these, PEG is commonly employed in protein conjugates due to its high water solubility, excellent biocompatibility, and ability to enhance drug solubility and efficacy through conjugation. Polyethylene glycol (PEG) attachment refers to the process of PEG molecule covalently linking to another molecule, often a drug or a biological entity. Hence, PEG attachment has limited the drug clearance in kidneys and increasing receptor-mediated absorption by cells. As a result, it increases the drug's half-life and minimises dose frequency. Additionally, the conjugation of polymers with drugs seeks to enhance the solubility and specificity of low molecular weight medications. Moreover, polymeric micelles are frequently composed of amphiphilic polymers, which self-assemble into micelles in solution and encapsulate drugs within them.

IPF pathogens are linked to the aging of Alveolar Epithelial Type 2 (AEC2) cells. Arctiin (ARC), a significant bioactive substance derived from the traditional Chinese herb *Fructus arctii*, possesses potent properties that combat inflammation, senescence, and fibrosis. The fundamental processes behind ARC's possible therapeutic benefits on IPF remain unclear. DSPE-PEG bubble-like nanoparticles (ARC@DPBNPs) that are encased in ARC was created to enhance ARC hydrophilicity and attain optimal pulmonary delivery effectiveness [135]. A bleomycin (BLM)-induced pulmonary fibrosis paradigm was established in C57BL/6 mice in order to evaluate the anti-senescence characteristics of AEC2 and the impact of ARC@DPBNPs on lung fibrosis [136].

In the meanwhile, AEC2-related p38/p53 signalling was found in the lungs of IPF patients, BLM-induced mice, and an A549 senescence model. The result of ARC@DPBNPs' effects on p38/p53/p21 was evaluated in both in vivo and in vitro. Besides, ARC@DPBNPs prevented BLM-induced AEC2 senescence. In the pulmonary tissues of IPF patients and in lung fibrosis induced by BLM [137]. In both in vivo and in vitro, ARC@DPBNPs prevented BLM-induced AEC2 senescence [138]. In the lung tissues of individuals with IPF, senescent AEC2, and BLM-induced lung fibrosis, the p38/p53/p21 signalling axis was markedly activated. By blocking the p38/p53/p21 pathway, ARC@DPBNPs reduced lung fibrosis and AEC2 degradation [138].

4. Conclusions and future perspectives

Pulmonary fibrosis stands as one of the most severe interstitial lung conditions, marked by a grim prognosis. Its emergence as a complication in COVID-19 patients underscores the critical need for targeted therapeutics capable of reversing or potentially curing the disease [139]. Currently, available treatments for pulmonary fibrosis rely on systemic administration, resulting in significant toxicity, adverse effects, and low patient adherence. The development of effective inhaled medications is underway; however, existing inhaled anti-fibrosis agents are plagued by high toxicity, rapid clearance, and non-specific lung distribution [140].

In conclusion, this study highlights the potent effect of phytochemicals in managing pulmonary fibrosis through inhaled drug delivery. The phytochemicals can prevent the conversion of fibroblast to myofibroblast by inhibiting the secretion of profibrotic cytokines. Utilizing the varied pharmacological attributes of phytochemical presents potential benefits, such as precise delivery to the lungs, minimized systemic adverse effects, and improved treatment effectiveness. Nonetheless, additional investigation is required to clarify the mechanisms, refine formulations, and tackle obstacles linked to phytochemical-based drug administration in the management of pulmonary fibrosis. By persistently exploring and translating findings into clinical practice, incorporating phytochemicals into inhalable formulations shows significant potential for advancing personalized and enhanced therapeutic approaches for individuals with pulmonary fibrosis.

CRedit authorship contribution statement

Shuet Li Wong: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Jie Sin Gan:** Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **Gabriele De Rubis:** Validation, Visualization, Writing – review & editing. **Keshav Raj Paudel:** Validation, Visualization, Writing – review & editing. **Stewart Yeung:** Validation, Visualization, Writing – review & editing. **Dinesh Kumar Chellappan:** Conceptualization, Supervision, Visualization, Writing – review & editing. **Pei Sin Keng:** Conceptualization, Project administration, Supervision, Visualization, Writing – review & editing. **Kamal Dua:** Conceptualization, Project administration, Supervision, Visualization, Writing – review & editing.

Declaration of competing interest

The authors of the manuscript submitted to the journal "Journal of Drug Delivery Science and Technology", have no conflict of interest to declare.

Data availability

No data was used for the research described in the article.

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