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Review article

Natural plant resource flavonoids as potential therapeutic drugs for pulmonary fibrosis

Meng-Chuan Wang

Department of Pharmacy, Affiliated Cixi Hospital, Wenzhou Medical University, China

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ABSTRACT

Pulmonary fibrosis is an enduring and advancing pulmonary interstitial disease caused by multiple factors that ultimately lead to structural changes in normal lung tissue. Currently, pulmonary fibrosis is a global disease with a high degree of heterogeneity and mortality rate. Nitidine and pirfenidone have been approved for treating pulmonary fibrosis, and the quest for effective therapeutic drugs remains unabated. In recent years, the anti-pulmonary fibrosis properties of natural flavonoids have garnered heightened attention, although further research is needed. In this paper, the resources, structural characteristics, anti-pulmonary fibrosis properties and mechanisms of natural flavonoids were reviewed. We hope to provide potential opportunities for the application of flavonoids in the fight against pulmonary fibrosis.

1. Introduction

Pulmonary fibrosis, a progressive pulmonary condition due to a culmination of interstitial lung disease, manifests through the early impairment of alveolar epithelial cells, subsequent unrestrained fibroblast proliferation, excessive accumulation of extracellular matrix (ECM) and ultimately results in respiratory failure, exhibits a staggering mortality rate ranging from 50% to 70% of patients [1,2]. In the clinic, in addition to nitidine and pirfenidone as specific drugs, glucocorticoids, cyclophosphamide and other immunosuppressive regulators are also utilized to slow the progression of pulmonary fibrosis. However, these drugs are accompanied by substantial adverse effects and exhibit limited efficacy in improving patient outcomes [3–5].

Flavonoids, a diverse group of polyphenolic compounds, are abundantly present in various parts of plants, including flowers, leaves, stems, and fruits [6]. Structurally, these compounds consist of a C6–C3–C6 carbon skeleton, while also featuring two aromatic rings linked together by a connecting chain composed of three carbon atoms, which can form a heterocyclic ring containing oxygen [7]. Based on the modes of heterocyclic substitution, flavonoids can be divided into chalcones, flavones, flavanols, flavanones, anthocyanidins, and others, highlighting their rich diversity and complexity [8]. Owing to their diverse biological activities, including anticancer, antidiabetic, antiviral, antibacterial, anti-inflammatory, protective mechanisms against autoimmune and antioxidant properties, natural flavonoids have garnered considerable interest as potential therapeutic agents [6,9]. Research has shown that traditional Chinese medicine monomer compounds, including flavonoids, alkaloids, glycosides, saponins, and polyphenols, have positive therapeutic effects on pulmonary fibrosis, among which flavonoids have great advantages and potential value [10]. Several natural flavonoids, such as quercetin, have been reported in clinical trials for the treatment of pulmonary fibrosis patients [10]. Additionally, silymarin has been applied in the clinic for treating liver fibrosis [11,12]. However, to our knowledge, a comprehensive understanding of these natural flavonoids that fight pulmonary fibrosis requires further exploration.

E-mail address: mengchuanwang1@163.com.

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In this paper, we systematically summarized the resources, structural features, latest progress and pharmacological mechanism of flavonoids in preventing and treating pulmonary fibrosis. Up to June 2023, a total of 32 natural flavonoids have been reviewed. Our objective has two main aspects: to evaluate the capacity of these natural compounds to prevent or slow the onset and progression of pulmonary fibrosis, and to identify promising candidates for future drug development.

2. The possible mechanism of pulmonary fibrosis

Pulmonary fibrosis can arise due to various factors, including drugs, chemicals, viruses, bacteria, and airborne particulate matter such as cigarette smoke and dust [13,14]. These factors contribute to the injury of alveolar epithelial cells, thereby instigating oxidative stress, evoking inflammatory responses, resulting in cellular apoptosis and related cascades of reactions [15]. This stage triggers the release of numerous cytokines and active substances, stimulating the proliferation and activation of myofibroblasts, ultimately leading to the formation of focal lung fibroblasts, collagen deposition, and extensive synthesis of ECM, ultimately resulting in pulmonary fibrosis [16,17] (Fig. 1).

Pulmonary fibrosis has long been considered a result of chronic inflammation. Upon tissue damage, epithelial cells respond by releasing inflammatory mediators, which in turn trigger a coagulation cascade with antifibrinolytic properties, ultimately leading to the formation of blood clots. As the inflammatory and proliferative stages evolve, chemokines and growth factors come into play, attracting and activating white blood cells to drive cellular proliferation [15]. Notably, these activated white blood cells secrete profibrotic cytokines, exacerbating the progression of fibrotic pathologies. Meanwhile, in this intricate process, the stimulated epithelial cells and myofibroblasts actively engage in producing specific cytokines and chemokines [15,17]. These molecular cues serve as recruitment signals for essential components of tissue repair, including neutrophils, macrophages, T cells, and eosinophils. The recruited immune cells become activated, working in tandem to clear debris, remove dead cells, and neutralize invading pathogens [17]. Remarkably, myofibroblasts exhibit an excessive capacity to generate a significant amount of extracellular matrix (ECM) protein during the early stages of inflammation. These cells serve as major contributors to the secretion of crucial fibrosis-related cytokines, including tumor necrosis factor-α (TNF-α), TGF-β1, and interferon-gamma (IFN-γ) [17].

Cellular redox status and the balance between oxidants and antioxidants play a crucial role in the progression of pulmonary fibrosis. The lungs, being directly exposed to atmospheric conditions, render these molecules as their more vulnerable to oxidative damage from reactive oxygen species (ROS) [15]. Furthermore, exogenous oxidants and air pollutants can induce the production of ROS and activate inflammatory cells, thereby triggering the generation of free radicals. Excessive levels of ROS and reactive nitrogen species (RNS) contribute to oxidative stress, resulting in cellular damage and impairing normal tissue repair processes [15]. NADPH oxidase (NOX) serves as the primary source of ROS, catalyzing the reduction reaction of O_2. Specifically, NOX4 is closely associated with myofibroblast activation and the regulation of the lung fibroblast phenotype. The recruitment and activation of inflammatory cells, such as neutrophils, macrophages, and eosinophils, culminate in the release of ROS and RNS, consequently promoting oxidative/nitrosative stress while dampening the activity of antioxidant enzymes. To counteract the effects of oxidative/nitrosative stress,

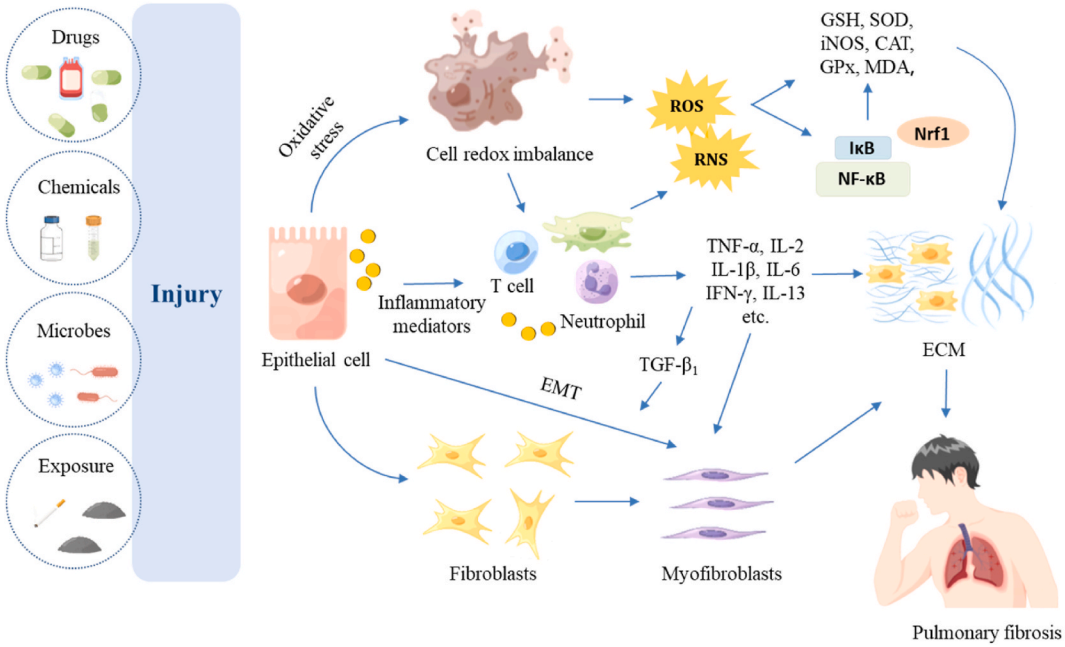

Fig. 1. The possible mechanism of pulmonary fibrosis. Drugs, chemicals, viruses, microbes, and exposure (cigarette smoke, dust or others) stimulate epithelial cells and cause superabundant inflammation, oxidative stress, EMT, and myofibroblast proliferation, resulting in excessive ECM accumulation and ultimately fibrosis. The source materials of the figure were from Figdraw.

cells initiate the activation of transcription factors, namely, Nrf2 and NF-κB, to adapt to these conditions [16]. The main indicators of this process include antioxidant enzymes, such as glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT) [17]. The accumulation of malondialdehyde (MDA) and reactive oxygen species (ROS) serves as indicators of oxidative damage.

EMT (epithelial-mesenchymal transition) is a crucial process implicated in the aberrant tissue remodeling observed in pulmonary fibrosis. EMT leads to the conversion of epithelial cells to mesenchymal cells, which is characterized by the loss of polarized epithelial phenotypes such as E-cadherin and the upregulation of mesenchymal markers such as vimentin and fibronectin [18]. TGF-β1 plays a key regulatory role, as fibroblasts derived from EMT contribute significantly to tissue fibrosis [19].

The pathogenesis of pulmonary fibrosis is complex and involves a network of molecular pathways that interact and influence the progression of the disease. Among these prominent orchestrators, the distinguished pathways of TGF-β/Smad, Wnt/β-catenin, PI3K/AKT, NF-κB, ERK, AMPK, JAK2/STAT, MAPK, and Nrf2 have emerged at the forefront of scientific scrutiny [18–23]. These pathways remain inactive in healthy individuals but become abnormally activated upon injury, triggering inflammation and oxidative stress and accelerating the progression of pulmonary fibrosis [24]. Therapeutic interventions targeting these signaling pathways as antioxidants, cytokine inhibitors and antifibrotic agents offer great potential for improving patient outcomes and enhancing the overall quality of life in pulmonary fibrosis patients.

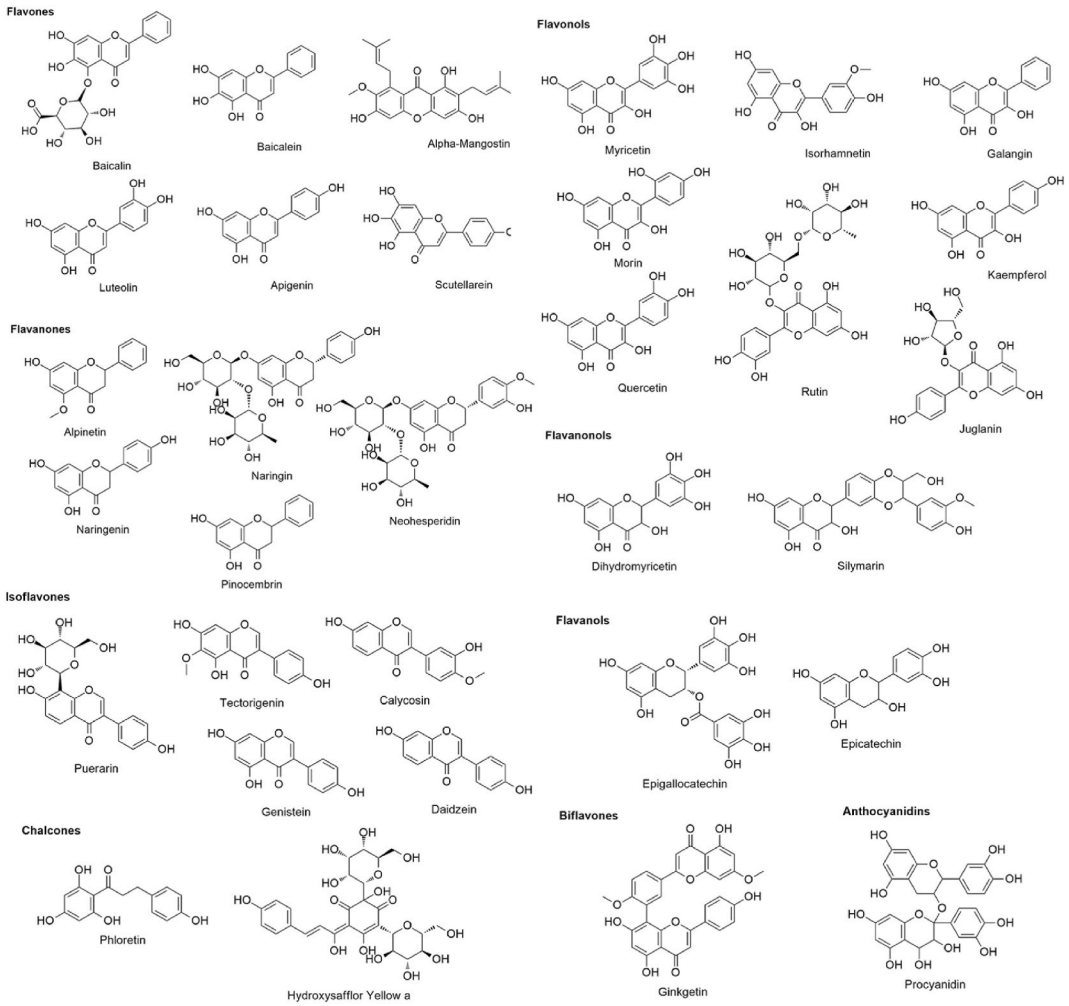

Fig. 2. Chemical structures of flavonoids against pulmonary fibrosis. The structural types of natural flavonoids against pulmonary fibrosis include flavonoids (Baicalin, Baicalein, Alpha-mangostin, Luteolin, Apigenin, Scutellarein), flavanones (Pinocembrin, Alpinetin, Neohesperidin, Naringenin, Naringin), flavonols (Morin, Myricetin, Isorhamnetin, Galangin, Quercetin, Rutin, Kaempferol, Juglanin), flavanonols (Silymarin, Dihydromyricetin), isoflavones (Puerarin, Tectorigenin, Calycosin, Genistein, Daidzein), chalcones (Phloretin, Hydroxysafflor yellow a), flavanols (Epicatechin, Epigallocatechin), biflavones (Ginkgetin) and anthocyanidins (Procyanidin).

3. Current status of the natural flavonoid for anti-pulmonary fibrosis

3.1. Flavones

3.1.1. Baicalin

Baicalin is one of the major bioactive components of *Scutellaria radix* and demonstrates a diverse range of therapeutic properties, including its ability to act as an antioxidant, reduce inflammation, combat infections, and inhibit tumor growth [25]. Recent investigations have revealed that baicalin exerts potent antifibrotic effects via the activation of the adenosine A2a receptor (A2aR), which is a novel inflammation regulator [26]. Specifically, A2aR activation suppressed TGF-β1 activation, downregulated ERK1/2 expression, and inhibited the pathological processes of BLM-induced pulmonary fibrosis [26]. Moreover, baicalin suppressed cyclin A, D, and E expression, inhibited fibroblast proliferation and notably elevated the intracellular Ca^{2+} concentration, concomitant with the transition of cells from the G0/G1 phase to both the S and G2/M phases [27]. In addition, baicalin prevented the upregulation of the connective tissue growth factor (CTGF) expression in rats with BLM-induced fibrosis [28]. These findings highlight the promising role of baicalin in mitigating the pathological processes that lead to fibrosis and provide critical insights of the process as a novel therapeutic candidate for lung fibrosis (Fig. 2).

3.1.2. Baicalein

Baicalein, another bioactive constituent of *Scutellariae radix*, exhibits a diverse range of pharmacological properties, including potent anti-inflammatory, antioxidant, and antiviral effects [29]. Recent studies have demonstrated that baicalein effectively inhibited pulmonary fibrosis in vivo by restoring Sirt3 expression and then suppressing the TGF-β1/Smad signaling pathway [30]. Additionally, baicalein has been found to weaken BLM-induced pulmonary fibrosis by inhibiting miR-21, which is a key regulator of fibrosis development [31]. Using state-of-the-art SILAC-based proteomic technology, it was revealed that baicalein significantly decreased the expression of CTGF, which may be linked to the reduction in Smad2 phosphorylation in MRC-5 cells induced by TGF-β1 [32].

3.1.3. Alpha-mangostin

Alpha-mangostin, a potent natural product isolated from *Garcinia mangostana*, has been shown to significantly reduce oxidative stress in rats through activation of the AMPK pathway [33]. Alpha-mangostin effectively inhibited BLM-induced pulmonary fibrosis and activated primary lung fibroblasts, resulting in a marked decrease in the deposition of ECM [33].

3.1.4. Luteolin

Luteolin, a compound derived from *Lonicera japonica*, exhibits a remarkable dual role as an antioxidant and pro-oxidant, as demonstrated by compelling scientific evidence [34]. The profound influence of luteolin on neutrophil infiltration and the intricate regulation of proinflammatory cytokines in the bronchoalveolar lavage fluid of mice induced with bleomycin has great attention. Specifically, luteolin has been found to significantly inhibit the infiltration of neutrophils while effectively mitigating the elevation of TNF-α and IL-6 [35]. Additionally, luteolin was observed to significantly inhibit TGF-β1-induced expression of α-SMA, type I collagen, and vimentin in vitro using primary cultured mouse lung fibroblasts. Moreover, luteolin was found to be capable of effectively reversing EMT through the induction of E-cadherin, downregulation of N-cadherin, snail, vimentin, and contraction of the cytoskeleton in human alveolar epithelial-derived A549 cells [35].

3.1.5. Apigenin

Apigenin, a natural flavonoid extracted from *Turnera diffusa* and *Chrysanthemum morifolium*, is well known for its diverse biological activities, such as antioxidant, anti-inflammatory, antitumor, and antimicrobial properties [36]. Recently, published research has shown that apigenin has the ability to halt the advancement of pulmonary fibrosis [37]. Specifically, in a rat model induced by bleomycin, apigenin exhibited remarkable efficacy in suppressing the upregulation of hydroxyproline content, MPO activity, and crucial proinflammatory cytokine TNF-α and TGF-β levels while concomitantly enhancing SOD activity [37,38]. In mice exposed to BLM-induced pulmonary fibrosis, apigenin exerted a protective effect by inhibiting NF-κB/TGF-β-mediated lung EMT and collagen production [39]. Moreover, a recent investigation clarified the capacity of apigenin to effectively counteract the TGF-β1-induced expansion of hypercontractile myofibroblast clusters, characterized by their α-smooth muscle actin-positive phenotype, within the intricate tapestry of human bronchial fibroblast populations [40]. These compelling results shed new light on the potential of apigenin as a promising therapeutic agent for the prevention of fibrotic disorders.

3.1.6. Scutellarein

Scutellarein, a flavone extracted from *Erigeron breviscapus*, a traditional Chinese medicine, has been found to display potent therapeutic effects against pulmonary fibrosis [41]. Recent studies have uncovered the inhibition of fibroblast-to-myofibroblast differentiation via scutellarein through its effect on the TGF-β/Smad pathway and retarded cellular proliferation by inhibiting the PI3K/AKT pathway. Moreover, scutellarein promoted apoptosis of fibroblasts by modulating Bax/Bcl-2 in pulmonary fibrosis [41]. Furthermore, the profound anti-inflammatory and antifibrotic properties of scutellarein have been recently validated in a murine model induced by bleomycin. By intricately modulating the NF-κB/NLRP3 pathway, scutellarein consistently suppressed inflammation and effectively blocked the process of EMT [42]. These groundbreaking findings suggest that scutellarein may potentially act as a novel preventative or therapeutic agent for managing pulmonary fibrosis.

3.2. Flavonols

3.2.1. Morin

Morin, originally isolated from the Moraceae family, has displayed remarkable therapeutic benefits by inhibiting fibroblast transformation into myofibroblasts and ameliorating pathologic alterations in mice induced by bleomycin [43]. Moreover, studies have demonstrated its efficacy in suppressing TGF-β1-stimulated NIH-3T3 cells [44]. The underlying mechanism involved activating peroxisome proliferator-activated receptor-gamma (PPAR-γ), and morin inhibited the transformation of NIH-3T3 cells by inhibiting PPAR-γ [44]. Additionally, morin was found to inhibit glutaminolysis by downregulating the expression of glutaminase 1 (GLS1), a key enzyme involved in glutamine metabolism [44]. Furthermore, morin effectively attenuated inflammatory cellular infiltration, hydroxyproline content, and oxidative stress and reduced pathological changes in BLM-induced pulmonary fibrosis [45]. These findings provide critical insights into the mechanisms of the antifibrotic effects of morin.

3.2.2. Myricetin

Myricetin, a polyhydroxyflavonol compound initially isolated from *Myrica rubra* (Lour.) S. et Zucc., has been found to impede activation of lung fibroblasts in vitro and EMT by targeting heat shock protein (HSP) 90β in a mouse model induced by bleomycin [46,47].

3.2.3. Isorhamnetin

Isorhamnetin, a flavonol aglycone derived from *Hippophae rhamnoides* L and *Ginkgo biloba* L, has been shown to inhibit collagen deposition in vivo, reduce the expression of type I collagen and α-SMA, ameliorate both EMT and ERS, and activate the PERK signaling pathway in vivo [48,49]. Furthermore, isorhamnetin was also found to reverse the effects of both EMT and ERS in human bronchial epithelial cells and in A549 cells in vitro [49].

3.2.4. Galangin

Galangin, a flavonol, is present in high concentrations within the medicinal plant *Alpinia officinarum* and exerts antioxidant and free radical scavenging properties by modulating enzyme activities [50]. Galangin was found to reduce the increase in $CD4^{+}CD69^{+}$, $CD8^{+}CD69^{+}$ T cells, dendritic cells, and the presence of inflammatory cells in BLM-induced mice [51]. Furthermore, galangin has been demonstrated to inhibit EMT and fibroblast differentiation in vitro, further highlighting its significant therapeutic potential [51].

3.2.5. Quercetin

Quercetin, derived from *Quercetum* (after Quercus, i.e., oak), displayed exceptional therapeutic potential for treating pulmonary fibrosis [52]. This flavonoid possessed remarkable antioxidant properties and prevented the oxidation of lipoproteins by clearing free radicals and chelated the transition of metal ions [52]. Studies have shown that quercetin can also attenuate BLM-induced pulmonary fibrosis in vivo through a spectrum of inflammatory cytokines, such as TNF-α, IL-1β, IL-6, IL-13, and PDGF-β, while concurrently strengthening the pivotal antifibrotic factor INF-γ [53,54]. Moreover, quercetin exerted a pneumoprotective effect in pulmonary fibrosis by enhancing antioxidant status, decreasing levels of inflammatory cytokines, reducing MMP-7 expression, and minimizing collagen accumulation [55]. Exciting new research has uncovered the potential of therapeutic benefits of quercetin in ameliorating inflammatory responses in an in vitro model consisting of BLM-triggered BEAS-2B cells. Specifically, this natural compound was shown to enhance the antioxidant response by significantly increasing Nrf2 activity while simultaneously reducing the expression of inflammatory factors [56]. Furthermore, quercetin has been revealed to influence promising efficacy in the reversal of apoptosis resistance triggered by death ligands through stimulating the expression of FasL receptors and caveolin-1 while simultaneously impeding AKT activation, which presents an innovative and potentially groundbreaking therapeutic strategy for the management of pulmonary fibrosis in aging mice [57]. Finally, quercetin was found to modulate macrophage polarity and mesenchymal-to-mesenchymal transition (MMT) by attenuating the TGF-β-Smad2/3 pathway [58]. These findings illustrated the vast therapeutic potential of quercetin in managing pulmonary fibrosis.

3.2.6. Rutin

Rutin, derived from the plant *Ruta graveolens*, has shown remarkable therapeutic promise in managing pulmonary fibrosis. It has been revealed that rutin significantly reduces the lung/body mass index, lactate dehydrogenase activity, macrophages, and lymphocytes in bronchoalveolar lavage fluid [59]. Moreover, rutin reduced the expression of TGF-β1 and other fibrosis-related biomarkers, including Col I, Col III, and α-SMA, while ameliorating histological changes and preventing collagen deposition, as evidenced by a reduction in lung hydroxyproline content [60]. Furthermore, rutin was found to significantly decrease malondialdehyde and nitric oxide content in lung tissue, while increasing glutathione content and superoxide dismutase activity, and enhance the total antioxidant capacity of serum [60].

3.2.7. Kaempferol

Kaempferol, first isolated from the rhizome of *Kaempferia galangal*, has been obtained as a pure product through extraction from tea, cauliflower, and other plants [61]. Researchers have discovered that kaempferol inhibited silica-induced pulmonary fibrosis by blocking inflammation [62]. Kaempferol partially reversed silica-induced LC3 lipidation [62]. In addition, the inhibitory effects of kaempferol on inflammation were countered through functional autophagy pathways, as evidenced by the ability of chloroquine, an autophagy-blocking agent, working to counteract these effects [62].

3.2.8. Juglanin

Juglanin, derived from the *crude Polygonum aviculare*, exerted a highly inhibitory effect against both the inflammatory response and cancer growth [63]. Studies have found that Juglanin restrains lung fibrosis by targeting the Sting pathway in both a mouse model and TGF-β1-incubated MRC-5 cells [64]. Additionally, it has been found that Juglanin exhibits protective properties in lung injury by inhibiting fibrosis and the inflammatory response through the inactivation of NF-κB pathways [65].

3.3. Flavanones

3.3.1. Pinocembrin

Pinocembrin, extracted from *Eucalyptus pressiana* subsp., exerts antioxidant, anti-inflammatory, anticancer and antifibrotic properties [66,67]. In a sheep model induced by bleomycin, pinocembrin significantly reduced the number of neutrophils, inflammatory cells, and immune-positive $CD8^+$ and $CD4^+$ T cells in bronchoalveolar lavage fluid [68]. In addition, pinocembrin significantly reduced the content of connective tissue in the lung segment. These findings demonstrate that pinocembrin has significant anti-inflammatory and antifibrotic remodeling effects.

3.3.2. Alpinetin

Alpinetin, a natural flavanone originating from *Alpinia intermedia* Gagnep [Zingiberaceae] plants in Japan, has demonstrated a significant ability to downregulate TNF-α, IL-1β, and IL-6 levels in LPS-induced inflammation [69,70]. Specifically, alpinetin exhibited profound effects on RAW 264.7 macrophages and lung injury mouse models, indicating promising potential for therapeutic applications [70,71].

3.3.3. Neohesperidin

Neohesperidin, a flavanone composed of hesperetin and disaccharide neohesperidoside, was obtained from the fruit of Huyou *(Citrus changshanensis)* [72]. Neohesperidin has been shown to possess remarkable antifibrotic properties. Primarily, neohesperidin mitigated the detrimental impact on alveolar epithelial cells, minimizing damage and preserving their integrity. The compound further unveiled its transformative potential by effectively reversing the differentiation process of myofibroblasts, which is intrinsic to the pathogenesis of fibrosis. Additionally, neohesperidin orchestrates a reduction in the excessive production of extracellular matrix and hinders the migration of fibroblasts, thereby impeding the progression of fibrosis [73]. Moreover, in vivo investigations have demonstrated Neohesperidin's potential to inhibit BLM-induced lung injuries and attenuate established pulmonary fibrosis within mice, thus, opening up new avenues for therapeutic interventions [73].

3.3.4. Naringenin

Naringenin, a prevalent flavane found grapefruit and oranges, as well as in various vegetables, has been shown to significantly mitigate BLM-induced pulmonary fibrosis and improve survival rates by modulating the immunosuppressive microenvironment [74]. Specifically, naringenin downregulated the expression of TGF-β1, reduced the proportion of $CD4^+CD25^+Foxp3^+$ regulatory T cells, and increased the abundance of activated effector T cells. These findings implicated naringenin as a potentially powerful immunomodulatory agent for inhibiting lung fibrosis and metastasis [75].

3.3.5. Naringin

Naringin, resulting from the combination of the flavanone naringenin, is a prominent and active constituent of traditional Chinese herbal medicines, including *Drynaria fortunei (Kunze) J. Sm., Citrus aurantium* L., and *Citrus medica* L. [76]. In rats with BLM-induced acute lung inflammation and fibrosis, naringin led to significant reductions in TNF-α, IL-1β, hydroxyproline content and MDA levels while increasing the activities of GSH-Px and SOD. These findings suggested the potential of naringin in mitigating inflammatory cytokine levels and preventing the formation of oxygen free radicals [77]. Furthermore, naringin was observed to effectively inhibit ERS levels and mitophagy-related gene expression while also downregulating ERS-downstream proteins. Intriguingly, this response appears to be partially mediated through the activation of the transcription factor (ATF) 3, along with the inhibition of the PTEN-induced kinase 1 (PINK1) transcription factor, which is suggestive of a key role for the ATF3/PINK1 signaling axis in regulating Naringin's immunomodulatory effects on respiratory function [78].

3.4. Flavanonols

3.4.1. Silymarin

Silymarin, popularly known as an extract from milk thistle (*Silybum marianum*), has been used for many centuries to treat liver diseases [79]. In recent years, several studies have proven that silymarin displays antioxidant and anti-inflammatory effects while acting as a modulator of signaling pathways [80]. Silymarin prevented collagen deposition and inflammation and is potentially protective in BLM-induced pulmonary fibrosis [81]. Silymarin exhibited a remarkable influence on pulmonary fibrosis, as evidenced by reduced deposition of collagen fibers and diminished pulmonary concentrations of hydroxyproline. Furthermore, significant alterations were observed in key molecular markers, with decreased levels of TGF-β1, fibronectin, and elevated levels of MMP-2 and IFN-γ [82].

3.4.2. Dihydromyricetin

Dihydromyricetin, a flavonoid bioactive compound sourced primarily from *Ampelopsis grossedentata*, exhibits potent anti-inflammatory properties [83]. Dihydromyricetin has been shown to effectively mitigate lung inflammation by suppressing the infiltration of inflammatory cells and the secretion of inflammatory factors during early stages in a BLM-induced mouse model [84]. Moreover, dihydromyricetin ameliorated pulmonary fibrosis by enhancing pulmonary function and downregulating the expression of α-SMA and fibronectin via TGF-β1/Smad signaling pathways [84]. Dihydromyricetin has demonstrated a highly potent inhibitory effect against the abnormal migration and proliferation of myofibroblasts induced by TGF-β1 [85]. Through its profound regulation of fibroblast differentiation into myofibroblasts, dihydromyricetin mitigates the progression of pulmonary fibrosis in mice [85].

3.5. Isoflavones

3.5.1. Puerarin

Puerarin, an isoflavone, has been successfully extracted from *Pueraria lobata* and has received growing attention in the field of pulmonary fibrosis research [86]. By inhibiting fibroblast activation and migration, puerarin has demonstrated potency in regulating the JAK2-STAT3/STAT1 signaling pathway. Moreover, puerarin has also been found to induce apoptosis and inhibit the proliferation of human lung fibroblast HLF1 cells, upregulating caspase 3, downregulating Bcl-2, TGF-β1, and Smad3, and reducing the inflammatory factors IL-1, IL-2, and IL-4 [87]. These results suggested that puerarin may alleviate the inflammatory response resulting from pulmonary fibrosis and regulation of the TGF-β1/Smad3 pathway, indicating promising therapeutic potential.

3.5.2. Tectorigenin

Tectorigenin, a prominent compound derived from the rhizomes of the *Belamcanda chinensis* plant, is known for its anti-inflammatory properties [88]. Recent studies have demonstrated that tectorigenin effectively suppresses the proliferation of pulmonary fibroblasts. Tectorigenin boosted miR-338 expression, leading to the downregulation of LPA1 in BLM-induced rats [89]. Moreover, tectorigenin has been found to inhibit pulmonary fibrosis and airway inflammation in guinea pigs through modulation of the TGF-β1/Smad and TLR4/NF-κB signaling pathways [90].

3.5.3. Calycosin

Calycosin, the primary bioactive compound found within the root of *Astragalus membranaceus* (Fisch.) Bge, exhibited anti-inflammatory, antioxidative, neurological protection, antihyperglycemic, and hepatic protection effects [91]. A recent study demonstrated that calycosin effectively ameliorated the severity of fibrosis in BLM-induced mouse models by repressing EMT and blocking the AKT/GSK3β/β-catenin pathway [92]. Additionally, calycosin has demonstrated a highly potent inhibitory effect against inflammation and collagen deposition in BLM-induced mice while simultaneously enhancing the Nrf2/HO-1 pathway and inducing apoptosis [93]. Notably, calycosin promoted the upregulation of LC3, beclin1, and PINK1 and reduced p62 expression while amplifying the expression of LAMP1 and TFEB; thus, resulting in enhanced autophagy and the inhibition of lysosome enzyme release from ruptured lysosomes [93]. Furthermore, calycosin inhibited TGF-β1-induced EMT and alleviated pulmonary fibrosis by regulating the miR-375/YAP1 signaling pathway [94].

3.5.4. Genistein

Genistein, an isoflavone present in high quantities in soybeans, has been proven to mitigate pneumonitis/fibrosis caused by high-dose radiation exposure in mice [95]. The inhibitory action of genistein on EMT, occurred through the attenuation of the p38 and JNK signaling pathways and their associated transcription factors [96].

3.5.5. Daidzein

Daidzein, an isoflavone predominantly derived from soy plants, is known for striking structural resemblance to the human hormone estrogen, and consequently, it is commonly referred to as phytoestrogen [97]. In BLM-induced Wistar rats, daidzein was found to mitigate pulmonary fibrosis by attenuating inflammation through the reduction of the inflammatory cytokine TNF-α pathway [98]. This antifibrotic effect was achieved by downregulating protease-activated receptor 2, inhibiting inflammation, and inducing cell apoptosis, as evidenced by the modulation of Bcl-2, Bax, and caspase 3 [99].

3.6. Chalcones

3.6.1. Phloretin

Phloretin, a dihydrochalcone flavonoid found in high concentrations in apples and strawberries, has exhibited potent anti-inflammatory properties [100]. Studies have indicated that phloretin downregulates the levels of the proinflammatory cytokines COX-2 and ICAM-1 by blocking the NF-κB and MAPK pathways [100,101]. In addition, phloretin, as a robust antagonist of GLUT1 that regulates AMP-activated protein kinase, significantly inhibited the progression of BLM-induced lung fibrosis in vivo [102].

3.6.2. Hydroxysafflor yellow A

Hydroxysafflor yellow A, a chalcone of *Carthamus tinctorius* L., has been shown to significantly suppress TGF-β1-induced cell proliferation and migration [103]. Hydroxysafflor yellow A targeted TβRII in MRC-5 cells and reversed TGF-β1-activated cell overexpression of α-SMA, COL1A1, and FN, as well as the downregulation of Smad2, Smad3, and ERK [104,105]. Moreover, hydroxysafflor

yellow A effectively alleviated TNF-α-induced MRC-5 cell proliferation and inflammatory responses by modulating the NF-κB/AP-1 pathway [105]. An in vivo study demonstrated the potential of hydroxysafflor yellow A in improving pulmonary fibrosis by regulating E-cadherin [106]. Additionally, it has been proven that intravaginal injection of phytosomes containing Hydroxysafflor yellow A was a method to treat pulmonary fibrosis [107]. Mechanistic studies revealed that hydroxysafflor yellow A effectively hindered the activation of p38 protein in the MAPK-p38 pathway and inhibited the TGF-β/Smad3 pathway [108]. These dual actions resulted in a reduction in other related inflammatory factors, collagen deposition in mouse lungs, and the prevention of damage to the alveolar structure [108]. The findings emphasize the significant contribution of hydroxysafflor yellow A in the development of novel therapies for the treatment of pulmonary fibrosis.

3.7. Flavanols

3.7.1. Epicatechin

Epicatechin, a flavanol that is readily available in the diet and present in various sources, including tea, cocoa, vegetables, and cereals, has demonstrated potent antioxidant and anti-inflammatory activities [109]. In rats with BLM-induced pulmonary injury, epicatechin was found to exert protective effects during both the early and late phases of lung injury, as evidenced by the modulation of oxidative stress markers, such as the activities of superoxide dismutase, glutathione peroxidase, and catalase, as well as the levels of malondialdehyde and glutathione [110].

3.7.2. Epigallocatechin

Epigallocatechin, the primary bioactive component of catechins, was predominantly found in green tea leaves of *Camellia sinensis* [111]. In rats with BLM-induced pulmonary fibrosis, epigallocatechin was found to significantly enhance enzymatic and nonenzymatic antioxidants while reducing the W/D ratio, hydroxyproline, and lipid peroxidation marker levels. Histological observations also confirmed the potential of epigallocatechin in alleviating oxidative stress [112]. Additionally, a study revealed that epigallocatechin-3-gallate activated the Nrf2-Keap1 pathway, enhanced antioxidant activities and suppressed inflammation in rats with BLM-induced pulmonary fibrosis [113]. Furthermore, epigallocatechin was observed to reduce fibroblast proliferation and hydroxyproline levels while increasing the expression of MMPs 2 and 9 regulators [114].

3.8. Biflavones

3.8.1. Ginkgetin

Ginkgetin extracted from *Ginkgo biloba*, exerts ameliorative effects on oxidative stress and lung fibrosis, primarily through an AMPK-dependent signaling pathway [115].

3.9. Anthocyanidins

3.9.1. Procyanidin

Procyanidin, also known as proanthocyanidins and condensed tannins, is ubiquitous in flowers, nuts, fruits, bark, and seeds of various plants [116]. Procyanidin possesses a multitude of properties, including antioxidant, antibacterial, anti-inflammatory, and antitumor activities [116]. Recent research has highlighted the potential of procyanidin in mitigating the effects of fluoride toxicity. In a study, procyanidin was shown to reduce F accumulation, enhance antioxidant defense mechanisms, and suppress oxidative stress in F-treated rats [117]. Additionally, proanthocyanidin was observed to prevent radiation-induced differentiation of fibroblasts into myofibroblasts by inhibiting the p38/MAPK/Akt/Nox4 pathway to regulate mitochondrial ROS production, ATP production, lactate release, and glucose consumption [118].

4. Prospect strategies of modification and derivatives of natural flavonoids for anti-pulmonary fibrosis

Natural products have displayed remarkable pharmacological activities, which is intriguing to researchers in drug discovery [119]. Nonetheless, their utilization as clinical therapeutics is impeded by intrinsic challenges such as intricate structural compositions, physical characteristics, limited bioavailability, and other associated impediments [119–121]. Consequently, there is an imperative need to unravel the full clinical potential of natural flavonoids and their derivatives through systematic modification strategies, particularly targeting their anti-pulmonary fibrosis efficacy.

In the quest for novel therapeutics, modified baicalin has entered a phase II clinical trial as a potential treatment for adult influenza [122]. Beyond its primary application, baicalin plays a critical role in screening anti-SARS coronavirus type 2 compounds, and demonstrating exciting prospects for drug development [122]. Moreover, research has led to the discovery of a Baicalin analog, specifically modified at the 6th position of the A ring, which significantly activates the NF-κB signaling pathway [123]. Concurrently, investigations into alpha-mangostin modifications targeted at the C-3 and C-6 hydroxyl groups have shown promising results by effectively reducing cytotoxicity while also preserving acetylcholinesterase inhibitory activity [124]. Furthermore, the explorations into luteolin derivatives have identified compounds featuring a hydrophobic substituted benzyl group within the B ring, along with hydrogen or methyl groups attached to the 7-OH group, as displaying superior inhibitory activity compared to luteolin itself [125]. Despite its clinical potential, quercetin faces challenges such as poor water solubility, rapid in vivo clearance, rapid metabolism, and low bioavailability, limiting its use in medical practice [126]. To address these limitations, extensive efforts have yielded numerous

Table 1
Natural plant resource flavonoids as potential therapeutic drugs for pulmonary fibrosis.

Categories	Name	Molecular formula	Source	Experiment Model	Therapeutic Target	Reference
Flavones	Baicalin	$C_{21}H_{18}O_{11}$	*Scutellaria radix*	In vivo: BLM-induced mice (120 mg/kg), Female wistar rats (50 mg/kg)), Male SD rats (6, 12.5, 50 mg/kg).	1.Enhanced adenosine A2a receptor andinhibited ERK1/2 signaling pathway. 2. Blocked the up-regulation of CTGF expression. 3.Inhibited PI3K/AKT pathway.	[25–28]
	Baicalein	$C_{15}H_{10}O_5$	*Scutellariae radix*	In vivo: BLM-induced ICR mice (100 mg/kg), SD rats (50, 100 mg/kg). In vitro: TGF-β1-induced human fibroblast MRC-5 cell (1, 10 μM).	1.Downregulated Sirt3 expression, then inhibited TGF-β1/Smad signalling pathway. 2.Repressed the levels of miR-21and inhibited TGF-β/Smad pathway. 3.Inhibited type I collagen production by downregulating CTGF levels.	[29–32]
	Alpha- mangostin	$C_{24}H_{26}O_6$	Mangosteen (*Garcinia mangostana*)	In vivo: BLM-induced Male C57BL/6 mice (10 mg/kg). In vitro: Mouse primary lung fibroblasts (50,100 nM)	1. Reduced oxidative stress through the AMPK pathway. 2. Decreased the deposition of ECM.	[33]
	Luteolin	$C_{15}H_{10}O_6$	*Lonicera japonica*	In vivo: BLM-induced male C57BL/6 mice (10 mg/kg). In vitro: human A549 cells, primary cultured mouse lung fibroblasts (25 μM).	1.Delayed collagen deposition. 2. Reduced α-SMA, type I collagen, and vimentin expression.	[34,35]
	Apigenin	$C_{15}H_{10}O_5$	*Turnera diffusa* and *Chrysanthemum morifolium*	In vivo: BLM-induced SD rats (25 mg/kg), male Wistar rats (10, 15, 20 mg/kg). In vitro: Pulmonary cells/human lung fibroblast populations (10 μM).	1.Reduced the levels of TNF-α and TGF-β cytokines. 2.Suppressed hydroxyproline content, MPO activity and restored SOD activity. 3.Ednhanced antioxidant ability and PPARγ expression, impeded lung epithelial to mesenchymal transition and collagen production by NF-κB/TGF-β pathway. 4.Supressed TGF-β1 induced fibroblast-to-myofibroblast transition.	[36–40]
	Scutellarein	$C_{15}H_{10}O_6$	*Erigeron breviscapus*	In vivo: BLM-induced C57BL/6 mice (10 mg/kg), male BALB/c mice (30, 60, 90 mg/kg). In vitro: A549 and rat lung epithelial RLE-6TN cell line (0.1, 0.2, 0.4 mM). Human pulmonary fibroblasts (10 μM).	1.Altered the differentiation, proliferation, and apoptosis of fibroblasts. 2.Suppressed inflammation and EMT via NF-κB/NLRP3 pathway.	[41,42]
Flavonols	Morin	$C_{15}H_{10}O_7$	Moraceae	In vivo: BLM-induced Male C57BL/6 mice (25, 50, 100 mg/kg).	1.Regulated PPAR-γ-glutaminolysis-DEPTOR pathway. 2.Attenuated the infiltration of inflammatory cells, hydroxyproline content and oxidative stress	[43–45]
	Myricetin	$C_{15}H_{10}O_8$	*Myrica rubra*	In vivo: BLM-induced C57BL/6 mice (25, 50, 100 mg/kg).	Inhibited TGF-β signaling via targeting HSP90β.	[46,47]
	Isorhamnetin	$C_{16}H_{12}O_7$	*Hippophae rhamnoides* L and *Ginkgo biloba* L	In vivo: BLM-induced male C57 mice (10, 30 mg/kg). In vitro: Human A549 cells and HBECs(25, 50, 100 μM).	Attenuated EMT, ERS and the activation of PERK pathway.	[48,49]

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Table 1 (*continued*)

Categories	Name	Molecular formula	Source	Experiment Model	Therapeutic Target	Reference
	Galangin	$C_{15}H_{10}O_5$	*Alpinia officinarum*	In vivo: BLM-induced C57BL/6 mice (25 mg/kg). In vitro: Human A549 and NIH3T3 cells (50 μM).	1.Diminished the increase of $CD4^+CD69^+$, $CD8^+CD69^+$ T cells and dendritic cells. 2.Reduced the residence of inflammatory cells. 3.Inhibited EMT and fibroblast differentiation.	[50,51]
	Quercetin	$C_{15}H_{10}O_7$	*Quercetum* (after *Quercus*, i.e., oak)	In vivo: BLM-induced male Wistar rats (50 mg/kg), C57BL/6 mice (30, 100 mg/kg). In vitro: The human bronchial epithelial cell line BEAS-2B, Primary Pulmonary Fibroblasts (15 μg/ml). Mouse macrophage cells (50 μM).	1.Increased antioxidant capacity, reduced inflammatory cytokines, MMP-7 expression and collagen accumulation. 2. Boosted the antioxidant response by increasing Nrf2 activity. 3. Induced cell apoptosis through promoting the expression of FasL receptor and caveolin-1. 4.Regulated macrophage polarity and the MMT through the TGF-β-Smad2/3 pathway.	[52–58]
	Rutin	$C_{27}H_{30}O_{16}$	*Ruta graveolens* L.	In vivo: BLM-induced SD rats (50, 100 mg/kg).	Reduced expressions of TGF-n1 and other biomarkers (Col I, Col III, and α-SMA).	[59,60]
	Kaempferol	$C_{15}H_{10}O_6$	*Kaempferia galangal*	In vivo: Silica-induced C57BL/6 mice (150 mg/kg).	1.Inhibited pulmonary inflammation. 2.Restored silica-induced LC3 lipidation without increasing the p62 levels.	[61,62]
	Juglanin	$C_{20}H_{18}O_{10}$	*Crude Polygonum aviculare*	In vivo: BLM-induced male C57BL/6J mice (80 mg/kg). In vitro: The MRC-5 cells, Mouse alveolar type II epithelial MLE-12 cell (40 μM).	Suppressed inflammation and fibrosis through targeting sting pathway.	[63–65]
Flavanones	Pinocembrin	$C_{15}H_{12}O_4$	*Eucalyptus pressiana* subsp.	In vivo: BLM-induced sheep (50 mg/kg).	1.Reduced neutrophils, inflammatory cells, immune positive CD8+and CD4+T cells in bronchoalveolar lavage. 2.Reduced the content of connective tissue.	[66–68]
	Alpinetin	$C_{16}H_{14}O_4$	*Alpinia intermedia* Gagnep	In vivo: LPS-induced male BALB/c mice (50 mg/kg). In vitro: Raw 264.7 cells (80, 160, 240 μg/ml).	1.Reduced TNF-α, IL-6 and IL-1β level. 2.Modulated cytokine responses by inhibiting NF-κB and MAPKs.	[69–71]
	Neohesperidin	$C_{28}H_{34}O_{15}$	*Citrus changshanensis*	In vivo: BLM-induced male C57BL/6J mice (20 mg/kg). In vitro: NIH-3T3 cell line, mouse fibroblast, (5, 10, 20 μM).	Inhibited TGF-β1/Smad3 signaling pathway.	[72,73]
	Naringenin	$C_{15}H_{12}O_5$	grapefruit and oranges	In vivo: BLM-induced female C57BL/6 mice (100 mg/kg).	Improved the immunosuppressive environment and reducing regulatory T cells.	[74,75]
	Naringin	$C_{27}H_{32}O_{14}$	*Drynaria fortunei* (Kunze) J. Sm. (DF), *Citrus aurantium* L. (CA) and *Citrus medica* L. (CM)	In vivo: BLM-induced male Wistar-albino rats, male C57BL/6 mice (50 mg/kg).	1.Decreased TNF-α and IL-1β activity, hydroxyproline content and MDA level, increased Glutathione peroxidase and SOD activities. 2. Regulated endoplasmic reticulum stress and mitophagy through the ATF3/PINK1 signaling axis.	[76–78]
Flavanonols	Silymarin	$C_{25}H_{22}O_{10}$	*Silybum marianum*	In vivo: amiodarone-induced male albino rats (100 mg/kg).	1.Suppressed inflammation, improved antifibrosis and antioxidant capacity. 2. Inhibited MMP-2 and IFN-γ.	[79–82]

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Table 1 (*continued*)

Categories	Name	Molecular formula	Source	Experiment Model	Therapeutic Target	Reference
	Dihydromyricetin	$C_{15}H_{12}O_8$	*Ampelopsis grossedentata*	In vivo: BLM-induced male C57BL/6 mice (50, 100 mg/kg). In vitro: Primary mouse lung fibroblasts, Primary human lung fibroblasts (100 μM, 200 μM, 300 μM).	1.Inhibited the infiltration of inflammatory cells and the secretion of inflammatory cytokines via TGF-β1/Smad pathways. 2.Regulated the STAT3/p-STAT3/GLUT1 pathway.	[83–85]
Isoflavones	Puerarin	$C_{21}H_{20}O_9$	*Pueraria lobata*	In vivo: BLM-induced male C57BL/6 mice (14 mg/kg). In vitro: Murine embryo fibroblast NIH-3T3 cell line, Human lung fibroblasts HLF1 cell line (200 μg/ml, 400 μg/ml, 600 μg/ml).	1.Inhibited the fibroblasts activation and migration through JAK2- STAT3 STAT1 pathway. 2.Alleviated the inflammatory response by regulating the TGF-β1/Smad3 pathway.	[86,87]
	Tectorigenin	$C_{16}H_{12}O_6$	*Belamcanda chinensis*	In vivo: BLM-induced male SD rats (50 mg/kg), ovalbumin-sensitized guinea pigs (10, 25 mg/kg). In vitro: Cultured pulmonary fibroblasts, Murine macrophage RAW 264.7 cells (10 μM, 100 μM, 500 μM).	1.Prevented inflammation through decreasing the expression of COX-2 and PGE2. 2.Inhibited the proliferation of pulmonary fibroblasts. 3.Enhanced miR-338* expression, then downregulated LPA1.	[88–90]
	Calycosin	$C_{16}H_{12}O_5$	*Astragalus membranaceus* (Fisch.) Bge	In vivo: BLM-induced male C57BL/6 mice (7, 14 mg/kg). In vitro: MLE-12 cells, Human BEAS-2B cell line (10–80 μM).	1. Inhibited EMT through suppressing the AKT/GSK3β/β-catenin pathway. 2.Suppressed oxidative stress, apoptosis, and enhanced autophagy. 3.Regulated the miR-375/YAP1 pathway.	[91–94]
	Genistein	$C_{15}H_{10}O_5$	Soybeans	In vivo: Whole thorax lung irradiation induced C57 L/J mice (200 mg/kg).	1.Improved survival and reduced morbidity. 2.Inhibited EMT through suppressing p38 and JNK pathways.	[95,96]
	Daidzein	$C_{15}H_{10}O_4$	Soy plants	1. In vivo: BLM-induced Wistar rats (0.2 mg/kg).	2.1.Attenuated inflammation. 3.2.Reduced the expression of Proteinase activated receptor 2 and inhibited inflammation. 4.3.Induced apoptosis.	[97–99]
Chalcones	Phloretin	$C_{15}H_{14}O_5$	Apples and strawberries	In vivo: BLM-induced male C57BL/6 mice (10 mg/kg). In vitro: The A549 cell line (3–100 μM).	1.Inhibited COX-2 and ICAM-1 expression via blocking NF-κB and MAPK pathways. 2.Inhibited glucose transporter 1 (GLUT1)–induced glycolysis.	[100–102]
	Hydroxysafflor yellow A	$C_{27}H_{32}O_{16}$	*Carthamus tinctorius* L.	In vivo: BLM-induced male C57BL/6 mice (120 mg/kg), male Wistar rats (35.6, 53.3, 80.0 mg/kg). In vitro: The MRC-5 human fetal lung fibroblasts (5, 15, 45 μmol/L).	1.Blocked TGF-β1 by binding to TGF-β type II receptor (TβRII). 2.Inhibited TGF-β1/Smad and ERK/MAPK pathways. 3.Inhibited NF-κB/AP-1 pathway. 4.Regulated α-SMA and E-cadherin. 5.Alleviated inflammation. 6.Inhibited the activation of p38 protein in the MAPK-p38 pathway.	[103–108]
Flavanols	Epicatechin	$C_{15}H_{14}O_6$	Tea,cocoa, vegetable, fruits, and cereals	In vivo: BLM-induced male NMRI mice (25, 50, 100 mg/kg).	Reduced oxidative stress, inflammation and fibrosis.	[109,110]
	Epigallocatechin	$C_{22}H_{18}O_{11}$	*Camellia sinensis*	In vivo: male albino Wistar rats (20 mg/kg).	1.Alleviated the oxidative stress. 2.Augmented antioxidant	[111–114]

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Table 1 (*continued*)

Categories	Name	Molecular formula	Source	Experiment Model	Therapeutic Target	Reference
				In vitro: Human foetal fibroblast cell line WI-38 (0–150 μmol/L).	activities and inhibited inflammation through Nrf2-Keap1 pathway. 3.Inhibited fibroblast activation and collagen accumulation.	
Biflavones	Ginkgetin	$C_{32}H_{22}O_{10}$	*Ginkgo biloba*	In vivo: BLM-induced male ICR mice (25, 50 mg/kg).	Regulated the transdifferentiation of mouse lung fibroblasts and the oxidative stress by activating AMPK, reduced ECM deposition.	[115]
Anthocyanidins	Procyanidin	$C_{30}H_{26}O_{13}$	Flowers, Nuts,Fruits and Bark	In vitro: Human fetal lung fibroblasts (2.5, 5, 10 μg/ml).	Inhibited p38MAPK-Akt-Nox4 pathway.	[116–118]

synthetic quercetin derivatives through chemical manipulations involving phenolic hydroxyl and/or C-4 carbonyl groups, A-ring and B-ring functionalization, and metal complexation, leading to significant advances in overcoming the aforementioned shortcomings [126].

The meticulous modification of natural flavonoids and their derivatives stands as an essential trajectory in the quest for heightened anti-pulmonary fibrosis therapeutics. The transformation of natural flavonoids into derivatives through chemical derivatization provides an avenue to explore new chemical space. By strategically manipulating functional groups or introducing specific moieties, as the resulting derivatives can exhibit optimal interactions with their target proteins, thereby modulating key signaling pathways involved in fibrotic processes. Capitalizing on the vast potential of natural products through systematic modification strategies offers a compelling pathway to advance the treatment landscape for pulmonary fibrosis.

5. Conclusion

In this paper, the structural characteristics and anti-pulmonary fibrosis mechanisms of 30 natural flavonoids, including 6 flavones, 5 flavanones, 8 flavanols, 2 flavanonols, 5 isoflavones, 2 chalcones, 2 flavanols, 1 biflavone and 1 anthocyanidin, were systematically

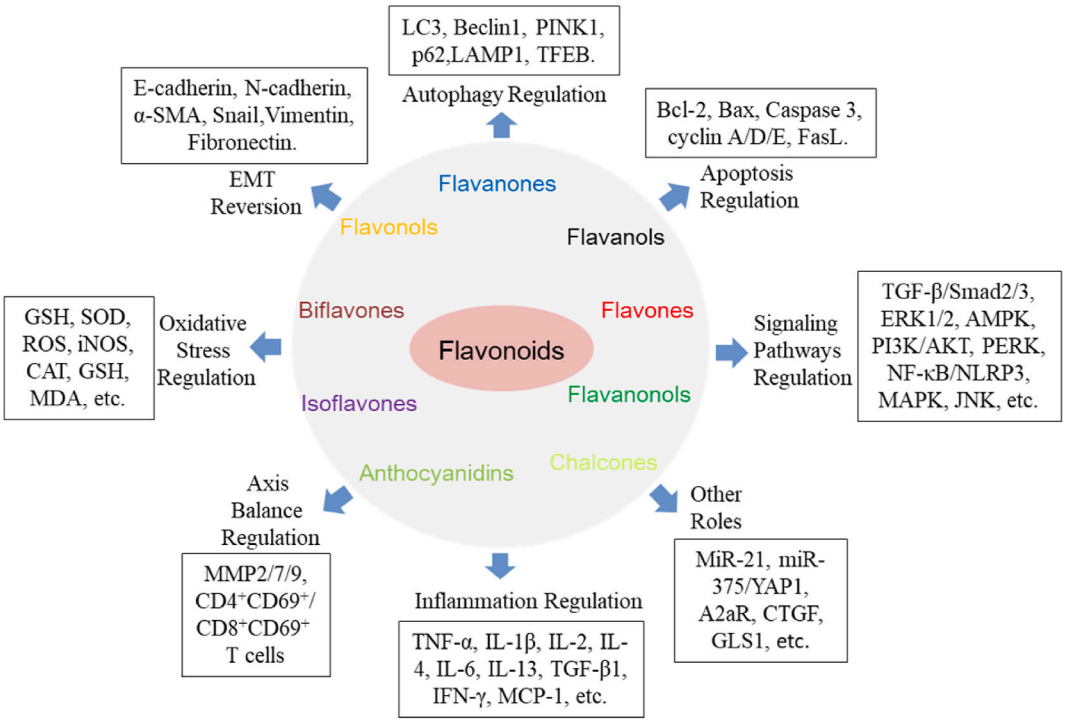

Fig. 3. The regulatory effect of flavonoids on pulmonary fibrosis. Inflammation, oxidative stress, EMT, cell apoptosis, autophagy, axis balance and other processes are involved. The natural flavonoids in pulmonary fibrosis include flavones, flavanones, flavonols, flavanonols, isoflavones, chalcones, flavanols, biflavones and anthocyanidins.

reviewed (Table 1) (Fig. 2). Both in vivo and in vitro experiments effectively demonstrated the potent anti-pulmonary fibrosis properties of these flavonoids. Their remarkable activities encompass a wide range of beneficial effects, including anti-inflammatory and antioxidant capabilities, regulation of EMT, induction of fibroblast apoptosis, targeted modulation of transcription factors such as CTGF, and influence over various cell signaling pathways, which significantly ameliorated pulmonary fibrosis in rats or mice. In addition, these key cell signaling pathways target ERK1/2, PI3K/AKT, AMPK, PPAR-γ-glutaminolysis-DEPTOR, TGF-β/Smad2/3, NF-κB/NLRP3, HSP90β, PERK, Nrf2, MAPK, STAT3/p-STAT3/GLUT1, AKT/GSK3β/β-catenin, miR-375/YAP1, JNK, ATF3/PINK1 and the p38/MAPK/Akt/Nox4 regulatory axis (Fig. 3).

Furthermore, COVID-19 has been a global epidemic caused by SARS CoV-2 [127]. SARS CoV-2 mainly invades and damages lung organs, leading to lung inflammation, which can lead to acute respiratory distress syndrome (ARDS), thus causing pulmonary fibrosis [128]. Research has shown that approximately 17.2% to 31% of patients might develop ARDS, leading to pulmonary fibrosis, as patients who died from COVID-19 had fibrosis changes in their lungs [129,130]. The mechanism of COVID-19-induced cytokine storm and ARDS is similar to that of pulmonary fibrosis [128]. Therefore, pulmonary fibrosis has become an important risk factor for the deterioration of COVID-19. In China's treatment, traditional Chinese medicine can be used to improve the clinical symptoms of patients with COVID-19 in the recovery period and promote the absorption and regression of pulmonary inflammation, which is of great significance to the recovery of patients' condition, prognosis and improvement in quality of life [131]. Commonly used traditional Chinese medicines include *Astragalus membranaceus* (containing baicalin and quercetin), *Pericarpium citri reticulatae* (containing *hesperetin), and liquorice* (containing liquiritin *and isoliquiritigenin)*, showing the therapeutic potential of these flavonoids [131,132]. Moreover, in this paper, we found that dihydromyricetin is an effective inhibitor of SARS-CoV-2 and prevents BLM-induced pulmonary inflammation and fibrosis in mice [84].

In conclusion, the results of this review provide valuable insights on the potential of natural flavonoids as alternative drugs for the prevention or treatment of pulmonary fibrosis. Nevertheless, further work is necessary, including the utilization of advanced drug discovery tools such as computer-aided design and high-throughput screening to confirm the target specificity for each compound. Structural modifications of the compounds should also be explored. Additionally, conducting standardized clinical trials and evaluating potential side effects are crucial steps in determining their efficacy and safety.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

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

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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