Natural flavonoids for the treatment of chronic obstructive pulmonary disease: An overview

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Abstract

\<p\>Chronic obstructive pulmonary disease (COPD) has been a major global public health issue due to its high prevalence, disability, and mortality rates. The pathogenesis of COPD is complex and remains incompletely understood, compounded by a lack of specific and effective clinical therapies. Key pathophysiological mechanisms include oxidative stress, inflammation, programmed cell death, and fibrosis, influenced by external risk factors such as cigarette smoke and internal factors like immune deficiency. Natural flavonoids emerge as promising adjuvant treatments or potential drug candidates for COPD, attributed to their multi-target properties and low toxicity. This article provides an overview of various types and sources of natural flavonoids that exhibit therapeutic effects on COPD, their specific pharmacological actions and detailed mechanisms of action. This review aims to serve as a reference for adjuvant treatment strategies in daily dietary practices and to inspire novel drug candidates for COPD.\</p\>

Keywords: natural flavonoids; COPD; oxidative stress; inflammation; programmed cell death; fibrosis
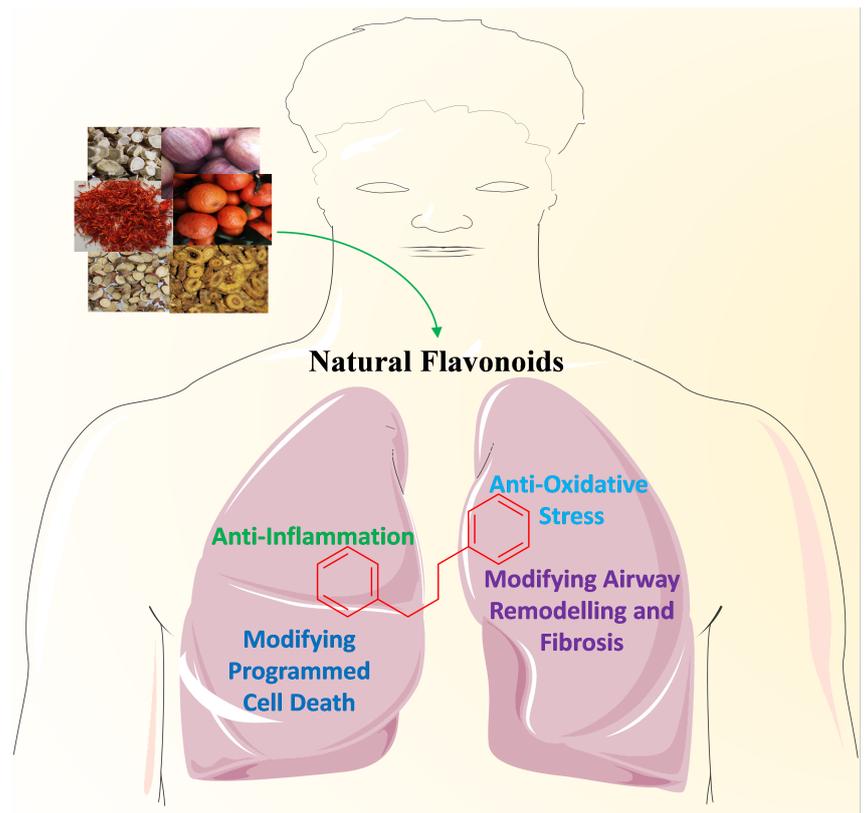
Highlights

<p>1. The effectiveness and diversity of traditional Chinese medicine in treating COPD promote the exploration of effective natural substances.</p><p>2. The structural diversity of natural flavonoids contributes to their ability to engage multiple pathways and mechanisms in the treatment of COPD.</p><p>3. The high safety and easy availability of natural flavonoids are significant advantages in both the prevention and treatment of COPD.</p>

Medical history of objective

<p>Extensive research on flavonoids in the treatment of COPD highlights the effectiveness of TCM for long-term management of lung diseases. For instance, the flower buds of *Tussilago farfara* L. were first documented in *"Shennong's Classic of Materia Medica"* (written during the Eastern Han Dynasty (25-220 C.E.)), which noted their ability to dissolve phlegm and relieve cough. Similarly, other ancient Chinese texts, such as *"Newly Revised Materia Medica"* (Jing Zhang et al. wrote in Tang Dynasty (659 C.E.)) and *"Compendium of Materia Medica"* (Shi-Zhen Li wrote in 1552-1578 C.E.), also recognized the same effects. Current pharmacological studies indicate that the flavonoids present in *Tussilago farfara* L. can combat COPD through various mechanisms, such as anti-inflammatory and anti-oxidative stress.</p>

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive condition defined by persistent airflow obstruction and debilitating respiratory symptoms, presenting a considerable public health challenge across the globe. This illness leads to significant health issues and increased death rates, highlighting its effect on healthcare systems and individuals' quality of life. A report published by the World Health Organization indicated that COPD has escalated to the status of the third cause of death worldwide [1]. Furthermore, COPD will continue to increase in tandem with the aging global population [2].

The main pathological features of COPD include airway inflammation, airflow limitation, excessive mucus production, and damage to lung tissue. These factors result in symptoms such as wheezing, coughing, and shortness of breath, often leading to acute exacerbations or even death. The lungs are damaged by exposure to cigarette smoke (CS), dust, biofuel exhaust, and pathogens [3, 4]. COPD often overlap with asthma and is often complicated by pulmonary hypertension and cardiovascular diseases, including systemic hypertension and atherosclerosis [5, 6]. Multiple theories have been used to elucidate the pathogenesis of COPD, including the regulation of local oxidative stress in the lungs, the degree of inflammation, the proteolytic homeostasis of the extracellular matrix (ECM), and the imbalance of autophagy and apoptosis [7-10]. Although the pathogenesis of COPD remains unclear, there is currently no specific treatment available. Palliative regimens focused on improving airflow limitation represent the primary clinical approaches. Thus, new strategies and drugs for blocking COPD development should be developed, and multiple pathological factors and targets should be considered.

Natural products are still a crucial source for drug screening and discovery because of their structural and functional diversity. Flavonoids are vital bioactive components found in natural plants, playing an essential role in maintaining health and alleviating diseases. Natural flavonoids are categorized based on their structural features and demonstrate various biological activities, including anti-inflammatory, antioxidative, cell-protective, antimicrobial, and ECM degradation [11, 12]. Furthermore, flavonoid intakes can not only alleviate COPD in experimental models but are also inversely associated with COPD incidence in smokers [13, 14]. Natural flavonoids, with the advantages of multi-target and low toxicity, have great potential in developing COPD drugs, but there are few reviews on the relevant content. The familiar sources of natural flavonoids and the mechanism of action in treating COPD are shown in Figure 1. This article mainly summarises the pharmacological effects and specific mechanisms of natural flavonoids on COPD and provides a reference for the adjuvant treatment of COPD in daily dietary life and opinions for identifying new prospective candidate drugs for COPD.

Pathogenesis of COPD

COPD is a progressive respiratory condition defined by significant airflow limitation, mucus overproduction, chronic bronchitis, emphysema, or damage to the alveolar septal walls. These manifestations lead to symptoms such as wheezing, coughing, and dyspnea, which can result in acute exacerbations, hospitalisation, and even death [3].
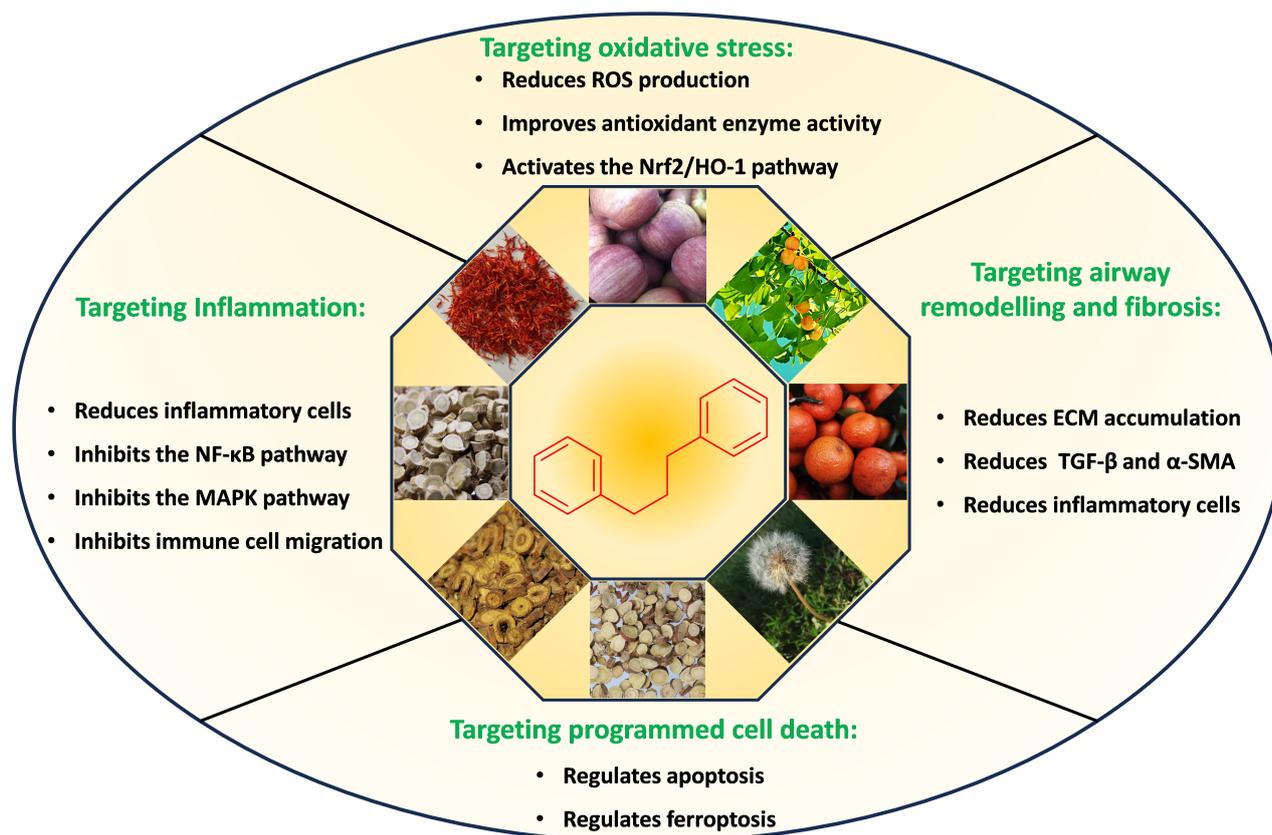
CS, pathogens, and various environmental exposures are significant external risk factors contributing to the development of COPD; notably, the removal of these risk factors has the potential to halt the pathological progression of the disease [4, 15]. Other factors, including genetics, gender, occupation, airway hyperresponsiveness, lung growth and development, and infections, also significantly contribute to the pathogenesis of COPD [3–5]. COPD is characterised by persistent inflammation and fibrosis of the small airways and the deterioration of lung parenchyma, also known as emphysema [18, 19]. COPD is complicatedly regulated by various biological mechanisms and their crosstalk, including oxidative stress, inflammation, ECM homeostasis, apoptosis, pyroptosis, and mucous cell hyperplasia [7, 20-24]. Among these, the regulation mechanism of oxidative stress and inflammation has attracted much attention in the field of COPD research and drug discovery, and airway remodelling and fibrosis are critical pathological features of late-stage COPD.

Oxidative stress

Increased oxidative stress in the lungs significantly drives the disease through various molecular mechanisms[25, 26]. The anatomical structure of the lungs makes them highly vulnerable to damage from environmental oxidative stress. Reactive oxygen species (ROS) from mitochondrial respiration and responses to lung infections also play a regulatory role. In individuals diagnosed with COPD, there is a notable increase in both the quantity and activation of alveolar macrophages, leading to higher levels of ROS, such as superoxide anions and H_2O_2 [6]. The same outcome can also be triggered by an increase in neutrophils, particularly during exacerbations [7]. In addition, lung epithelial cells also produce oxidative stress due to mitochondrial respiration [8]. Excessive ROS production is induced by both exogenous stimulation and internal inflammatory conditions.

Increased oxidative stress can activate several signalling pathways to drive the pathophysiology of COPD. Oxidative stress releases a large amount of oxidants, leading to the inactivation of anti-proteases and disrupting the protease-antiprotease balance in lung homeostasis, particularly affecting 1-antitrypsin [9]. The oxidative system is linked to the secretion of airway epithelial mucus, lead to the accumulation of ROS and induce high levels of mucus genes like mucin 5AC (*MUC5AC*) and mucin 5B (*MUC5B*) [10–12]. Epidermal growth factor receptor (EGFR) resided in oxidants-activated airway cells, which up-regulated the transcription of mucus genes during COPD development [34, 35]. Oxidative stress also triggers an inflammatory response in the lungs by influencing activator protein 1, an oxidant-sensitive transcription factor, and nuclear factor kappa-B (NF- B). These factors promote the expression of tumor necrosis factor-alpha (TNF-), interleukin-6 (IL-6), and interleukin-1 beta (IL-1) [13]. In addition, oxidative stress activates transforming growth factor- (TGF-) signalling pathways, leading to small airway fibrosis and increased expression of matrix metalloproteinase 9 (MMP9) [14], which also enhances elastolysis by inactivating 1-antitrypsin and secretory leukoprotease inhibitor, resulting in heightened neutrophil elastase activity and emphysema [15]. Moreover, corticosteroids play a significant role in suppressing pro-inflammatory gene expression [16]. However, oxidative stress can directly promote the phosphorylation and ubiquitination of histone deacetylase-2 (HDAC2) by activating phosphoinositide-3-kinase (PI3K)- [17], resulting in amplified inflammation and corticosteroid resistance [18].

Notably, nuclear factor erythroid 2-related factor 2 (Nrf2) will dissociate in oxidative stress response and transport to the nucleus to activate antioxidant gene transcription. Research indicates that the reduced self-protective mechanism in COPD patients is linked to decreased levels of Nrf2, leading to lower production of endogenous antioxidants. So, oxidative stress is a crucial mechanism of CS that initiates lung injury and inflammation and provides us with several targets, such as ROS and Nrf2, for drug discovery [19].

Targeting oxidative stress:
- Reduces ROS production
- Improves antioxidant enzyme activity
- Activates the Nrf2/HO-1 pathway

Targeting Inflammation:
- Reduces inflammatory cells
- Inhibits the NF-κB pathway
- Inhibits the MAPK pathway
- Inhibits immune cell migration

Targeting airway remodelling and fibrosis:
- Reduces ECM accumulation
- Reduces TGF-β and α-SMA
- Reduces inflammatory cells

Targeting programmed cell death:
- Regulates apoptosis
- Regulates ferroptosis

Inflammation and inflammatory cells

Inflammation drives the progression and exacerbations of COPD. In the airway lumen of COPD patients, inflammation is characteristic of increased numbers of macrophages, neutrophils, eosinophils, T cells, B cells, epithelial cells, endothelial cells, and fibroblasts [20]. The cells with different functions release different cytokines that work together to stimulate and maintain inflammatory levels and promote the progression and exacerbation of COPD.

CS stimulates both airway epithelial cells and macrophages to produce a range of chemotactic cytokines and chemokines, including IL-6, IL-8, C-X-C motif chemokine ligand (CXCL) 10, and CXCL9. These factors recruit neutrophils and CD8$^+$ T cells to the airway [21]. CD8$^+$ T cells are known to release perforins and granzymes, which contribute to tissue destruction and apoptosis. This process results in the production of pro-inflammatory proteases and cytokines, including IFN- and TNF-, which may play a significant role in the pathogenesis of emphysema [22]. IFN- secreted by Th1, CD8$^+$ cells, and B cells triggers a series of signalling cascades that induce macrophage polarized to M1 phenotype, which indeed produces pro-inflammatory cytokines. Such as, TNF- promotes leukocyte accumulation by modulating endothelial adhesion molecules, which release elastase and ROS to destroy alveolar epithelium [46, 47]. Proteases such as MMP and neutrophil elastase (NE), released by neutrophils and macrophages, degrade connective tissue and elastin in the alveoli, leading to both localized (centrilobular) and generalized (panlobular) emphysema. MMP levels were significantly increased in COPD patients with emphysema, contributing to ECM degradation and initiating airway tissue remodeling [23]. While CS-induced protease-antiprotease imbalance provokes airway inflammation for COPD pathogenesis, MMP and NE play crucial roles in the progression of emphysema and COPD [24]. Additionally, EGFRs can be activated by EGF released from neutrophils, or they may be indirectly activated through the mechanisms of oxidative stress [25]. Then, EGFRs activate mitogen-activated protein kinases (MAPK), which upregulate the expression of MUC5AC and MUC5B and lead to hyperplasia of goblet cells and submucosal glands, resulting in mucus hypersecretion and hyperplasia [26]. Moreover, macrophages and epithelials tend to secret TGF- to activate the fibrosis progress by proliferating epithelium, smooth muscle and fibroblasts. Thus, both the immune cells and airway epithelial cells are overly activated during the inflammation response and maintaining the stability of the pulmonary immune environment is a crucial problem in COPD treatment.

Fibrosis

Most types of chronic lung injury, primarily COPD, can induce fibrosis in the lungs, which occurs during the airway remodelling phase induced by persistent inflammatory stimulation and irreversible lung injury. Initially targeted at susceptible lung cells, recurring injuries caused by viruses, cigarette smoke, and others provoke epithelial cell death. Repairing the injuries increased vascular permeability, allowing fibrinogen and fibronectin to format a provisional matrix. Meanwhile, recurring injuries promote bronchiolar and alveolar epithelial cell migration and proliferation, including the aberrant-activated epithelial cells producing diverse epidermal growth factors (EGF) and chemokines to encourage the response. MMP1 and MMP7 are significant contributors to the migration of epithelial cells [27]. Following the migration of fibroblasts and fibrocytes to the sites of injury, these cells release MMP2 and MMP9, which activate TGF 1. This activation subsequently facilitates epithelial-mesenchymal transition and promotes the differentiation of fibroblasts into myofibroblasts [28]. Myofibroblasts secrete ECM accumulation in the foci, mainly fibrillar collagens and alpha smooth muscle actin (-SMA), and can provoke additional epithelial apoptosis through different signalling ways [52, 53].

In addition, lipopolysaccharide (LPS) and smoke stimulation can also promote the occurrence of epithelial-mesenchymal transition (EMT) by up-regulating NF- B signalling, toll-like receptor 4 (TLR4)/c-Jun N-terminal kinase (JNK) signalling, and forkhead box O signalling [29]. Pulmonary fibrosis, a final stage of COPD, is a critical phase to prevent COPD from developing into a pulmonary malignant disease.

Flavonoids in COPD regulation

Traditional Chinese medicine possesses distinctive advantages in the treatment of COPD due to its inherent natural properties and demonstrated efficacy. Noteworthy, flavonoids, as the principal constituents of natural ingredients, offer outstanding anti-inflammatory and antioxidant properties, prompting significant interest and attention in scientific and industrial domains. Flavonoids can be categorized into 7 subgroups based on their structural variances, which include chalcones, flavones, flavonoid glycosides, Isoflavones, catechins (flavanols), biflavones and others. We have summarized 28 flavonoids that have

been used in the treatment of COPD and divided them into 6 categories, which can be visualized in Figure 2.

The different biological activities of flavonoids depend on the three rings C6-C3-C6 essential backbone and different substitution groups. In addition, we have made a detailed summary of the natural sources of flavonoids in order to provide a reference for the public's daily diet. The leading information can be seen in [30–97].

The use of natural compounds and traditional Chinese medicine for managing COPD has been increasingly recognised. Patients with COPD should consider integrating these treatments into their overall care plan. Specifically, flavonoids have the potential to regulate imbalances in protease-antiprotease activity, immune function, lung function changes, blood flow, and serum markers by addressing airway and lung inflammation, improving airway remodelling, reducing airway reactivity, and modulating oxidative-antioxidant processes. Below, we summarise the potential efficacy of flavonoids in the treatment of COPD by discussing the specific mechanisms of action of these compounds. The detailed experimental verification can be found in [30–97].

Flavonoids targeting oxidative stress

Targeting ROS and antioxidative enzymes. Oxidative stress accelerates the pathogenesis of COPD [98]. Harmful substances such as CS can cause inflammatory cells such as neutrophils and macrophages to accumulate in the lungs, producing large amounts of ROS [99]. In turn, ROS stimulates the expression of various inflammatory mediators in the lungs and results in hyper-mucus secretion by airway epithelial cells [125, 126], aggravating the development of COPD.

Flavonoids have been reported to prevent and inhibit lung injury by scavenging free radicals. Flavonoids enhance intrinsic antioxidant capacity by increasing the levels and activities of antioxidant enzymes such as catalase, superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px), while also inhibiting ROS-generating enzymes like xanthine oxidase. For example, puerarin reversed mitochondrial membrane potential levels and ATP levels and decreased ROS content in cigarette smoke extract (CSE)-stimulated human bronchial epithelial cells (HBECs) [81]. Baicalin exerted an antioxidant role in CS-induced COPD mice by enhancing SOD, haem oxygenase 1 (HO-1) and reducing malondialdehyde (MDA) levels [65]. Liquiritin inhibited oxidant stress by increasing the SOD levels of the lung in CS-induced ICR mice [76]. Biochanin A increased the levels of antioxidant enzymes such as GSH-Px and decreased MDA, lactate dehydrogenase and alkaline phosphatase in a rat model of $PM_{2.5}$ exposure [80]. Apigenin enhanced the activation of silent information regulator 1 (SIRT1), nicotinamide adenine dinucleotide (NAD+), and the NAD+/NADH ratio in H_2O_2-induced WI-38 cells [36]. By regulating the balance between the antioxidant and ROS-generating enzymes, the flavonoids above can alleviate lung tissue lesions in COPD.

Targeting Nrf2/HO-1. Nrf2 serves as a pivotal transcription factor that governs the expression of genes associated with antioxidant activity. In patients with COPD, low levels of Nrf2 can diminish the body's antioxidant capacity [100]. Under normal conditions, Kelch-like ECH-associated protein 1 sequesters Nrf2 in the cytoplasm. However, under oxidative stress, Nrf2 is released and translocated to the nucleus, where it initiates the transcription of various antioxidant genes, including glutathione (GSH), glutathione peroxidase 4 (GPX4), nicotinamide adenine dinucleotide phosphate (NADPH), NADPH quinone dehydrogenase 1, HO-1, 6-phosphogluconate dehydrogenase, thioredoxin, and the glucocorticoid receptor (GR) [128, 129].

Various flavonoid monomers have been shown to have protective effects on airway epithelial cells and inflammatory cells. In summary, flavonoids were found to inhibit oxidative stress and inflammatory responses by targeting Nrf2 in different cell types, including epithelial cells, macrophages, and lung cancer cells, The mechanism of action can be visually illustrated in Figure 3. Casticin enhanced SOD activity but decreased ROS and MDA by regulating Keap1-Nrf2/antioxidant response element signalling way in H_2O_2-induced BEAS-2B cells [53]. Oroxylin A reduced the inflammatory response by increasing Nrf2 levels in CS-damaged RAW 264.7 cells [37]. Luteolin decreased total ROS and mitochondrial ROS concentrations by inhibiting CYP2A13 expression while simultaneously increasing Nrf2 levels in CSE-treated A549 cells [55].

In mice and rat models of COPD, various flavonoids have likewise been proved to inhibit the development of COPD by modulating Nrf2-related oxidative stress to attenuate lung damage

and inflammatory responses. In a four-days CS-induced mouse model, Oroxylin A increased GSH, GR, GPx-2 and HO-1 levels by promoting Nrf2 binding to antioxidant response element [37]. In a CS-induced mouse model, isoliquiritigenin reduced MDA levels by enhancing the expression of Nrf2 and HO-1 [32]. Fisetin was demonstrated to prevent lung damage and attenuate oxidative stress and inflammation via Nrf2-mediated antioxidant factors in CS-induced rat model, including decreasing inflammatory cytokines such as IL-4, IL-1 , TNF- and increasing antioxidant enzymes such as SOD, GSH [48]. Epicatechin repressed the production of ROS by enhancing the Nrf2-induced anti-oxidant enzyme and then reduced IL-18 and IL-1 levels by inhibiting the NLRP3-Caspase-1 pathway in the CS-induced rat [84]. Luteolin inhibited oxidative stress by decreasing the TRPV1 and CYP2A13 proteins while increasing SIRT6 and Nrf2 levels in CSE-treated A549 cells and CS- and LPS-induced COPD mice [55]. Additionally, flavonoids could target Nrf2 and reverse dexamethasone tolerance during COPD treatment. Quercetin was reported to reverse the dexamethasone-tolerance in CSE-induced U937 cells by activating adenosine 5'-monophosphate-activated protein kinase (AMPK) and Nrf2 signalling way [40].

Total flavonoids of natural plants have also been reported to inhibit oxidative stress in COPD by targeting Nrf2. Dandelion total flavonoids improved lung function and reduced oxidative stress-induced lung damage by upregulating antioxidant enzymes such as SOD and GSH in mice exposed to CS, linked to the activation of the Nrf2 signaling pathway [97].

Flavonoids targeting inflammation

Inflammation is a vital component in the initiation and advancement of COPD. The infiltration of neutrophils demonstrates a positive correlation with the severity of airflow obstruction. Harmful substances induce the respiratory tract epithelium to secrete inflammatory cytokines and chemokines. Likely, TNF- facilitates leukocyte migration and accumulation by stimulating pulmonary endothelial cells, releasing lysosomal enzymes, elastase, and ROS, all detrimental to endothelial cells and the alveolar epithelium [101]. IL-6 activates neutrophils, releasing NE and ROS, which damage alveolar surfactants, increase pulmonary vascular permeability, and induce pulmonary edema [102]. Additionally, monocyte chemotactic protein-1 and macrophage inflammatory protein-1 serve as chemoattractants, recruiting inflammatory cells such as macrophages and lymphocytes into inflamed tissues.

Flavonoids possess strong anti-inflammatory properties in various inflammatory diseases, effectively inhibiting the onset and progression of COPD. Additionally, flavonoids play a significant role in addressing respiratory diseases closely linked to inflammation. We will focus on the anti-COPD effect of flavonoids and their related mechanisms of action, including their relationship with NF- B signalling pathway, MAPK signalling pathway, EGFR signalling pathway, and immune cells migration. The different mechanisms of action that flavonoids protect COPD can be seen intuitively in Figure 4.

Targeting NF- B pathway. The activation of the NF- B pathway is believed to play a pivotal role in inflammatory diseases, including airway and pulmonary inflammation. Under normal conditions, NF- B remains inactive in the cytosol, as it is bound to the inhibitor kappa B (I B). Upon stimulation of airway epithelial receptors, I B kinase is activated, leading to the phosphorylation of I B or I B . This phosphorylation results in the dissociation of I B or I B from NF- B. Subsequently, NF- B (comprising p50 and p65 subunits) translocates to the nucleus, where it activates the expression of genes encoding inflammatory cytokines and chemokines, such as *TNF-* , *IL-1* , and *IL-6* [103]. Notably, activated NF- B in the lung tissue of COPD patients were significantly elevated, while I B levels were notably reduced [104]. Furthermore, the inhibition of the NF- B pathway led to a decrease in the presence of respiratory mucus, specifically MUC5AC and MUC5B [105].

Researchers have identified a range of natural products that modulate NF- B signalling in COPD, acknowledging NF- B's significance in chronic inflammatory conditions. Casticin was reported to inhibit the apoptosis and pro-inflammatory cytokines (TNF- , IL-6, IL-1 , and IFN-) production by down-regulating p-p65 but increasing Nrf2 in LPS-induced BEAS-2B cell [52]. Epigallocatechin gallate diminished the lipid peroxidation, ROS production and inflammation mediator levels (COX-2, NADPH oxidase 4 (NOX4), NOS2, IL-6 and IL-8) by suppressing the activation of NF- B pathway in CSE-stimulated airway epithelial cells [85]. Baicalin inhibited

Chalcones

Phloretin
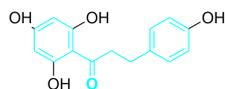
Isoliquiritigenin
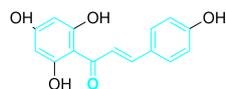
Hydroxysafflor yellow A
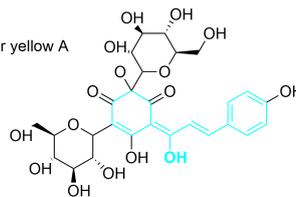
Flavones

Apigenin

Oroxylin A
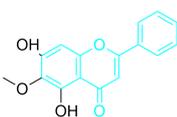
Scutellarein

Quercetin

Fisetin

Myricetin

Casticin

Luteolin

Naringenin

Hesperetin

Flavonoid glycosides

Baicalin

Astragalin

Icariin

Liquiritin apioside

Tilianin

Isoflavones

Formononetin

Biochanin A

Puerarin

Catechins

Epicatechin

Epigallocatechin Gallate

Other flavonoids

Silibinin

Silymarin

ginkgetin

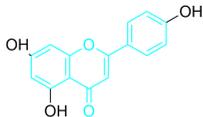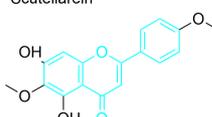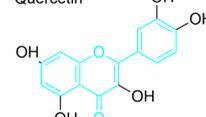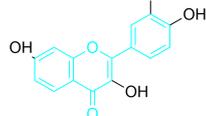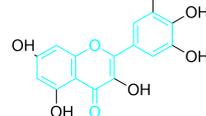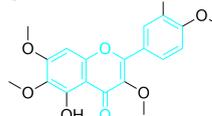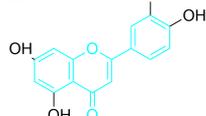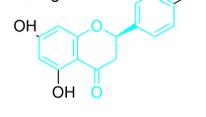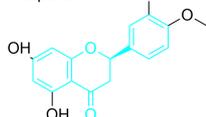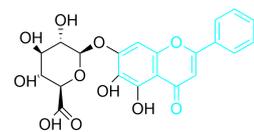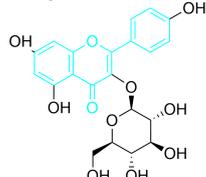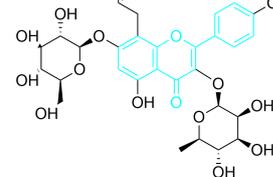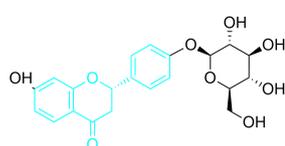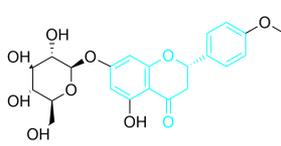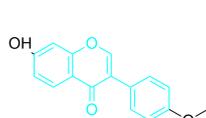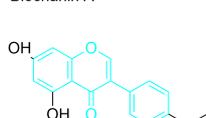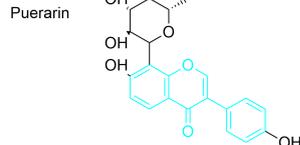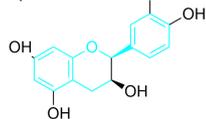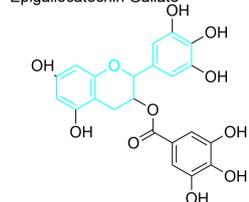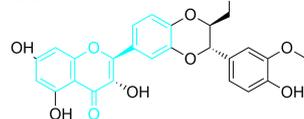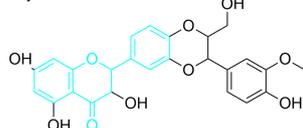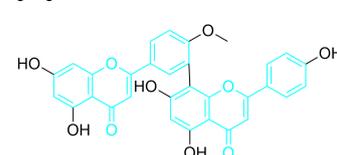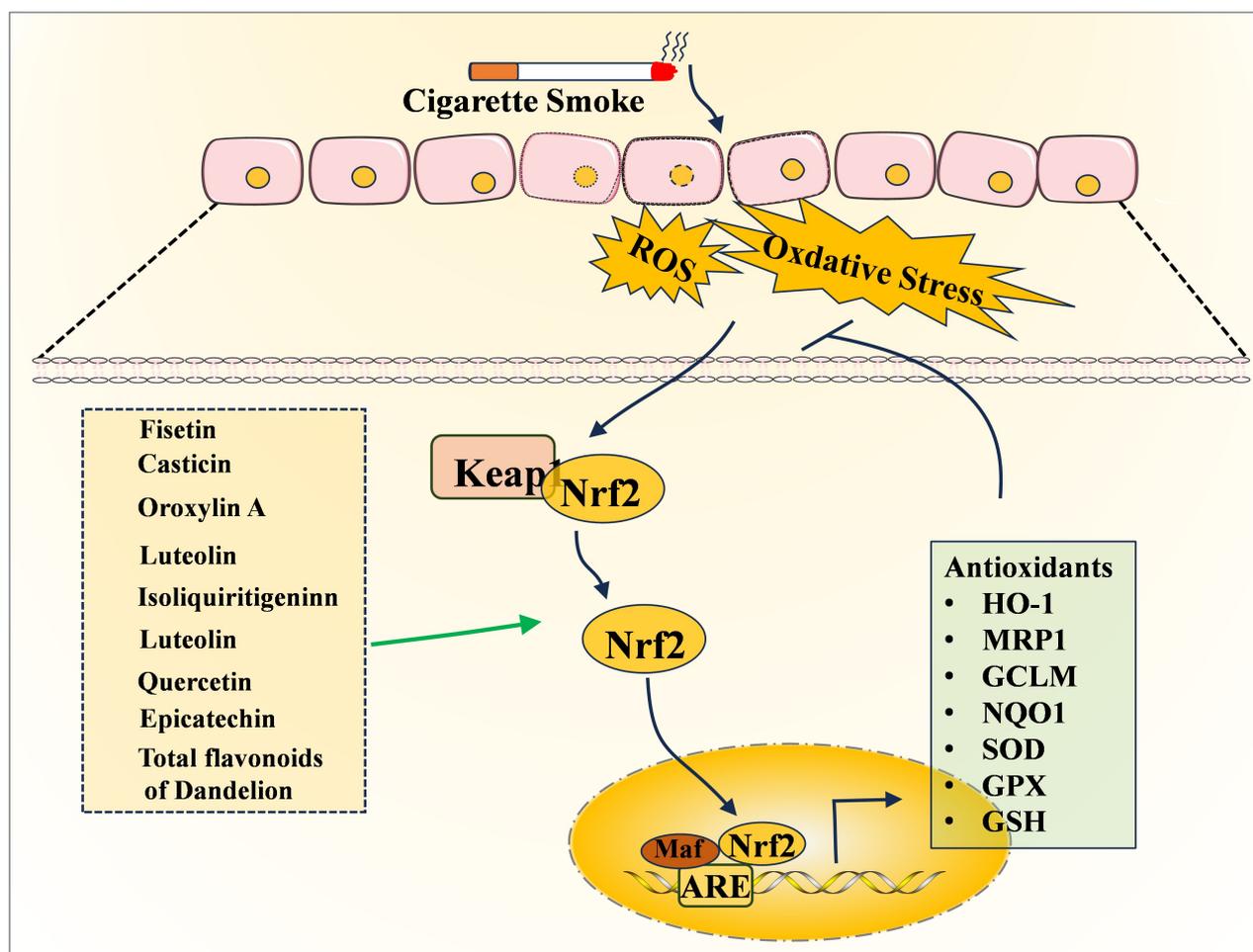the TNF-, IL-8, and MUC5AC levels by decreasing NF-B p65 phosphorylation in IL-1-induced NCI-H292 cells [69], in CSE-induced type II pneumocytes and in CS-exposed rat [63]. In a CS-induced mouse model, Isoliquiritigenin reduced the phosphorylation of p65 and I B, attenuating the inflammatory response and reducing the inflammatory factors [32]. Casticin improved lung function and reduced the number of white blood cells, neutrophils, and macrophages and the level of leptin, C-reactive protein, and pro-inflammatory cytokines by inhibiting the NF-B and iNOS pathway [51]. Taxifolin significantly suppressed elevated IL-1, IL-6 and TNF- levels in COPD mouse lung tissue and CSE-treated HBECs by inhibiting the phosphorylation p65 NF-B [62].

In addition, glucocorticoid drugs are often used to improve airflow limitation and attenuate the inflammation of COPD in clinical, which usually induces drug tolerance at the same time. Several kinds of flavonoids decreased the inflammation levels and reversed the glucocorticoid drug tolerance at the same time. In CS exposure mice and pig models, naringenin not only significantly improved the pulmonary function but decreased the accumulation of inflammatory cells and pro-inflammatory cytokines such as IL-8, TNF-, and MMP9 by inhibiting phosphorylation of NF-B but increasing GR, which indicate that naringenin enhances the corticosteroid sensibility [48, 82]. Icariin demonstrated a significant reduction in inflammation, airway remodelling, and ROS production that is induced by CSE. Furthermore, it alleviated glucocorticoid resistance through the down-regulation of the Nrf2 and NF-B signalling pathways [73].

Flavonoids can directly act on the NF-B pathway to improve COPD inflammation. However, as a core pathway, its upstream regulators, including toll-like receptors (TLRs) and sirtuins, also regulate its activation.

TLRs are a family of receptors that detect pathogens and tissue damage. Among them, TLR2 recognizes lipoteichoic acid from gram-positive bacteria, and TLR4 is activated by LPS and other endogenous ligands [106], which were reported to be up-regulated and activated during COPD initiation and development, especially in the COPD co-infection model. Upon stimulation, myeloid differentiation primary response gene 88 recruits the interleukin-1 receptor-associated

kinase (IRAK) family member IRAK4 to TLRs and induces the phosphorylation of IRAK1, which subsequently activates the NF-B pathway [107]. In CS and LPS co-induced COPD rat model, baicalin reduced TLR2 and TLR4, followed by lowering MYD88, phosphorylation of p65, and increasing phosphorylation of I Ba [70], Total flavonoids of *Trollius altaicus* downregulated TLR4 to reduce the activation of IRAK-1, thereby reducing the activation of the NF-B and reducing IL-1, IL-6, IL-8, TNF- [95]. In long-term cs-exposed rats, casticin reduced TLR4 expression to inhibit the NF-B phosphorylation and increase the I B phosphorylation level, thereby reducing inflammation [51]. TLRs are crucial targets of flavonoids in inhibiting COPD-associated inflammation, especially in infection-associated COPD development.

SIRT1, one of seven-number families with different subcellular localisations and functions, is the first sirtuin that regulates inflammatory, oxidative stress, autophagy, and apoptosis, which can inhibit the activation of NF-B. The heightened inflammatory response may reduce SIRT1 levels in patients with COPD [108], and a high level of SIRT1 inhibits inflammatory reactions in lung cells stimulated by CS [109]. Quercetin increased SIRT1 levels to reduce inflammatory responses and oxidative stress in mice with COPD induced by LPS and elastase [39]. Myricetin reduced IL-6 and IL-8 levels in TNF--induced A549 cells by regulating the SIRT1/NF-B pathway [49]. Hesperetin alleviated inflammation and oxidative stress responses by SIRT1/PGC-1a/NF-B signalling axis in CES-induced COPD mice [59]. Besides, total flavonoids of *Scutellaria baicalensis* Georgi also inhibited inflammatory and oxidative stress by increasing SIRT1 and PGC-1a levels in CS- and LPS- co-induced mice models [93].

There are also several other targets for flavonoids to regulate NF-B during COPD inflammation, such as protein kinase C (PKC), peroxisome proliferator-activated receptor, HDAC2 and NOX4. Fisetin has been reported to directly bind to PKC, preventing the activation of NF-B and the expression of IL-8 in HEK293T and NCI-H292 cells induced by TNF- [47]. Icariin promoted lung function and reduced TNF- and IL-6 levels in bronchoalveolar lavage fluid and
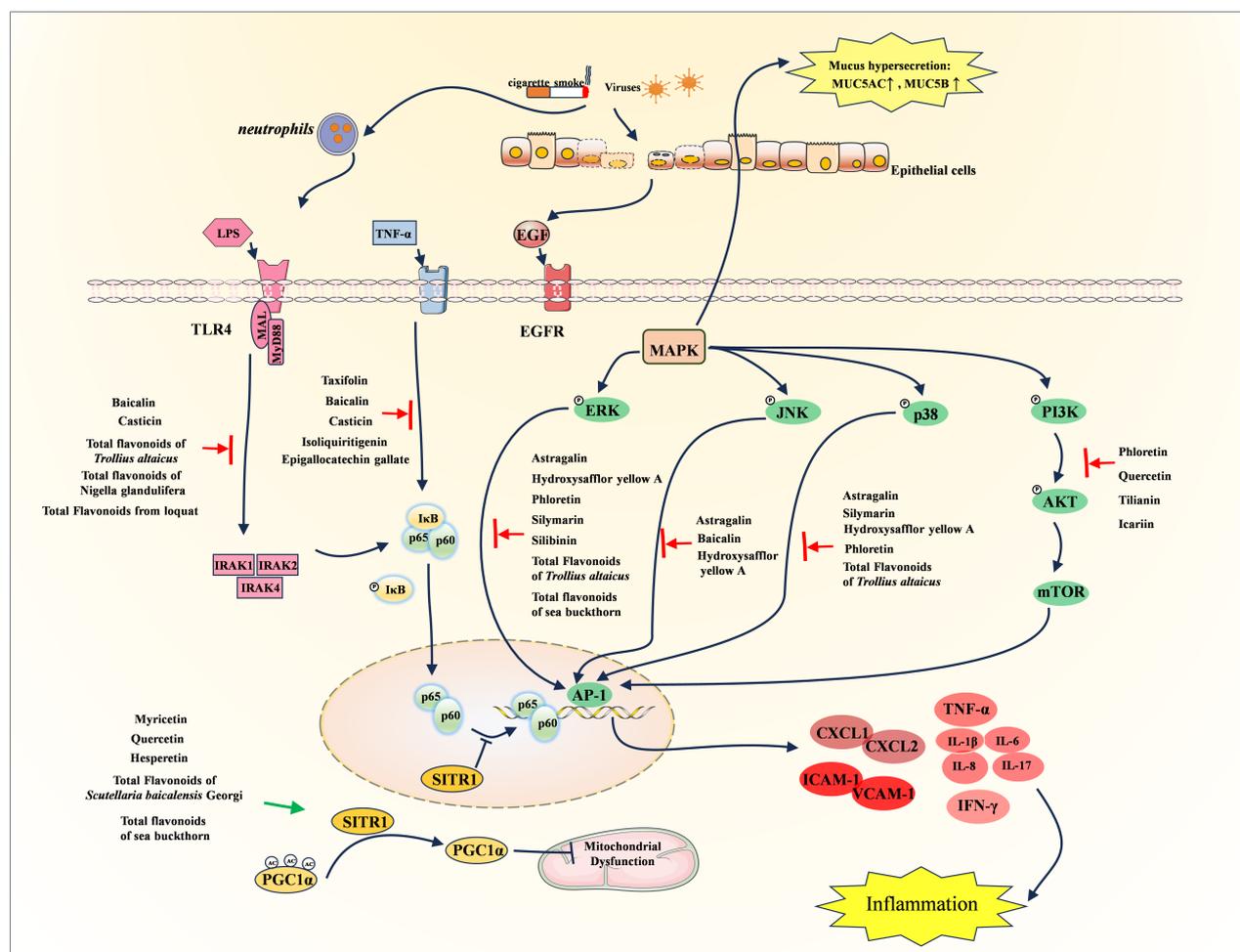
serum of COPD rat model, and indeed up-regulated the peroxisome proliferator-activated receptor expression and inhibited the activation of p65 of lung and epithelial cells [75]. Baicalin treatment markedly attenuated the inflammatory effects through down-regulating airway inflammatory infiltration and decreasing the inflammatory factors (the levels of TNF- and IL-1) in CS/CSE-exposed rats and cells, which attributed to the enhancement of HDAC2 protein expression and inhibition of NF-B or even targeting its downstream effector PAI-1 [89, 92]. Luteolin reduces inflammation and oxidative stress via the NOX4-mediated NF-B pathway in CS-induced cell and mice [54].

Total flavonoid extract also has the effect of inhibiting the NF-B pathway. For example, total flavonoids from *Nigella glandulifera* relieved the pathological state, inhibited the infiltration of neutrophils and macrophages into the lung and decreased levels of TNF- and IL-8 via the NF-B pathway [91]. Total flavonoids from loquat (*Eriobotrya japonica*) leaves alleviated oxidative stress-induced lung injury, emphysema and inflammation by inhibiting NF-B and JNK phosphorylation [94].

Targeting MAPK pathway. MAPKs represent a diverse family of kinases that are critical components of various signal transduction pathways. The MAPK family comprises four subfamilies: extracellular regulated protein kinases (ERK)1/2 (extracellular signal-regulated kinases 1 and 2), ERK5, JNKs, and p38s (p38 MAPKs). Notably, p38 MAPK is activated in response to environmental stress and inflammatory stimuli. Of its subtypes, p38 is particularly abundant in inflammatory cells [110]. Moreover, elevated levels of p38 MAPK have been detected in the airways and sputum of COPD patients [111]. Furthermore, it has been demonstrated that pathogens can augment MUC5AC mucin secretion by activating the p38 MAPK pathway while simultaneously inhibiting the PI3K-Akt pathway [112].

In mice exposed to CS, astragalin demonstrated an ability to attenuate inflammation and oxidative stress induced by pulmonary thrombus. This effect was mediated by a reduction of PAR-1 and PAR-2, which subsequently inhibited the production of ROS and the expression of COX-2, iNOS, and ICAM-1. The mechanism involved the inhibition of the ERK, p38, and JNK signalling pathways [72].

Silymarin significantly alleviated the thickening of the airway epithelium and infiltration of peribronchial inflammatory cells (including total cells, macrophages, and neutrophils) while also reducing levels of pro-inflammatory factors such as TNF- , IL-1 , and IL-8 by attenuating the phosphorylation of ERK and p38 in CS-exposed mice, the results were also proved in CSE-induced Beas-2B cells [113, 114]. The total flavonoids of *Trollius altaicus* protected lung function by inhibiting the activation of p38 and ERK in CS-induced mice [96].

Bacterial infection stands as a primary culprit behind acute exacerbations of COPD. These exacerbations correlate with a notable rise in both airway and systemic inflammation [113]. Flavonoids alleviate the pathological inflammation associated with COPD combined with bacterial infection by inhibiting the activation of MAPKs. Appling LPS/CSE-induced acute exacerbations of COPD mouse models, researchers discovered that: Hydroxysafflor yellow A decreased levels of IL-6, IL-1 , and TNF- by inhibiting the phosphorylation of ERK, p38, and JNK, and to inhibit inflammatory mediator by decreasing levels of p-p38 and p-p65, as well as in platelet-activating factor (PAF)-stimulated HSAECs [59, 60]; Baicalin reversed elevated levels of IL-8, IL-6, TNF- and MUC5AC which is associated with the inhibition of JNK activation [66]; Silibinin inhibited the expression of MUC5AC, IL-6, and IL-1 by suppressing the activation of ERK and specificity protein 1, as well as in CS condensate-stimulated NCI-H292 cells [86]. Total flavonoids of sea buckthorn inhibited expression of IL-1 , IL-6, CXCL1, prostaglandin E2, cyclooxygenase-2, and MUC5AC through the inhibition of the ERK, PI3K/Akt, and PKC pathways, as well as in LPS/CSE-induced HBE16 cells [92].

Targeting EGFR pathway. The EGF and its receptor (EGFR) are essential for causing and promoting various cell growth, proliferation, and transformation processes. Patients with COPD have higher levels of EGFR in their lungs compared to smokers without COPD symptoms [114]. This suggests that EGFR plays a significant role in the development of COPD. The increased EGFR levels are linked to the growth of airway epithelial goblet cells and more mucus production [25]. EGFR activation initiates key signaling pathways, including PI3K/protein kinase B (AKT)/mTOR, RAS/MEK/ERK, and MAPK

p38 [115].

Flavonoids inhibit the activation of the EGFR signalling pathway, making them promising for treating lung diseases. In CS-exposed mice and CSE-induced NCI-H292 cells, phloretin decreased EGFR phosphorylation, reducing ERK phosphorylation and p38 expression and decreasing mucin expression and inflammation [30]. In the LPS-induced airway mucus hypersecretion rat model, quercetin reduced the expression level of MUC5AC by inhibiting the activation of the EGFR, as evidenced by decreased levels of p-EGFR/EGFR, p-PI3K/PI3K, p-PKC/PKC, p-AKT/AKT, and NF- B [44]. Additionally, in EGF-stimulated H292 cells or A549 cells, tilianin also reduced MUC5AC expression by modulating the expression of AKT, ERK, and p38 in EGF-stimulated NCI-H292 human airway epithelial cells. However, it did not affect A549 cells [77]. Furthermore, icariin was shown to promote lung function and reduce pro-inflammatory cytokines by inhibiting the phosphorylation of PI3K, AKT, and p38 [74].

Immune cells migration. The inflammatory process of COPD is characterized by the persistent migration of inflammatory cells from the blood vessels to the lungs. This includes neutrophils, macrophages, and T cells, which produce a plethora of cytokines that exacerbate inflammation.

Casticin was found to inhibit immune cell infiltration in the lungs, including neutrophils, macrophages, and lymphocytes. This effect was accompanied by a downregulation of TNF- , IL-6, IL-1 , and monocyte chemotactic protein-1 levels in bronchoalveolar lavage fluid of CS-exposed mice [50]. Phloretin was shown to reduce the level of CXCL1, a neutrophil chemoattractant, which was induced by nontypeable *Haemophilus influenzae* in a COPD model of infection [31]. Quercetin improved the lung function and alleviated goblet cells metaplasia and emphysematous by down-regulating the inflammation mediators levels (such as CXCL-1, CXCL-10, TNF- , IFN- IL-13 and IL-17A) and infiltration of immune cells (such as leukocytes, total lymphocytes, CD11b$^+$CD11c$^+$ macrophages, neutrophils and CD8$^+$T cells) in both CS-induced and rhinovirus/CS-induced COPD mice [66, 70]. Quercetin also improved epithelial regeneration and reduced TGF- , IL-6 and IL-8 airway basal cells of COPD patients [46]. Tilianin inhibited neutrophil infiltration in the lung by affecting CXCL2, IL-17/STAT3 signal pathways in the COPD mice model [78]. Ginkgetin decreased CCL2 levels by downregulating the c/EBP signalling pathway in CSE-induced A549 cells, which is associated with immune cell migration such as macrophages [90]. Additionally, naringenin inhibited the M1 polarization of macrophages induced by extracellular vesicles from CSE-induced epithelial cells and reduced inflammatory cells and myeloperoxidase in CS-exposed guinea pigs [81, 83]. Additionally, naringin has a protective effect on NEP activity by reducing SP and the expression of the NK-1 receptor, thereby relieving the cough symptoms in CS-exposed guinea pigs [79].

Flavonoids targeting airway remodelling and fibrosis

There is currently insufficient data on how flavonoids affect the anti-COPD fibrosis process. These studies primarily focus on the formation and degradation of ECM and the process by which fibrotic cells are formed. Figure 5 offers more detailed insights into the specific mechanisms of action involved.

ECM degradation. Proteases are key in remodelling tissue and promoting inflammation [23]. An imbalance between proteases and anti-proteases disrupts ECM, which is essential for maintaining the dynamic integrity of organs. MMPs, serine proteases, and caspases are the three main elastase types responsible for hydrolysis peptides and other proteins. MMP-2, MMP-8, MMP-9, and NE are most involved in emphysema and COPD [49, 145-147]. Among them, MMPs are a prominent and influential family. Tissue inhibitors of metalloproteinases (TIMPs) are endogenous inhibitors of MMPs; usually, TIMP-1 inhibits active MMPs, and TIMP-1 binds to pro-MMP-9 to prevent the activation of pro-MMP-9. However, under harmful conditions, the combination of TIMP-1 and pro-MMP-9 dissociates by NE action, and MMP-3 activates pro-MMP-9 to MMP-9 [116]. NE, cathepsin G, and proteinase-3 are three main types of serine proteases that are also destroyed by degrading ECM components of lung tissue [117]. ECM degradation releases collagen and elastin, which attract immune cells and cause ongoing airway inflammation in the lungs.

In CS-exposed mice, quercetin [39], naringenin [57], hesperidin [60], and baicalein all downregulated MMP9 levels and reduced inflammation [65]. Baicalein also reduced TIMP-1, MMP2, MMP9, and MMP8 [64]. In CSE-induced BEAS-2B cells, icariin reduced the expression of MMP-9 and TIMP1 [73]. Thus, flavonoids inhibited ECM degradation and maintained alveolar integrity in the early phase of COPD development.

Fibrosis. In patients with COPD, airway epithelial cells show higher levels of TGF- 1 expression, which contributes to fibrotic airway remodelling and a decline in lung function [118]. TGF-activates TGFBR, promoting the phosphorylation of Smad2/3. The phosphorylated Smad2/3 subsequently binds to Smad4, initiating the transcription of genes related to airway remodellings, such as -SMA and collagen. This process alters the EMT [119]. Additionally, TGF-signalling upregulates MMPs, facilitating EMT and resulting in the degradation and destruction of lung tissue. Furthermore, TGF- induces the EGF/EGFR signalling pathway, which synergistically promotes EMT-related phenotypic changes. TGF- 1 also stimulates the activity of neutrophils, macrophages, and mast cells.

Hydroxysafflor yellow A reduced the expression of TGF- 1 in a rat model of LPS-CS co-infection and alleviated pulmonary fibrosis by decreasing the accumulation of -SMA and collagen I, thereby improving lung function [33]. In four-day CS-exposure mice, liquiritin apioside reduced inflammatory response and TGF- 1 level. The same results were performed in CSE-induced A549 [76]. In a three-month CS-exposed mouse model, quercetin also reduced TGF- 1 and -SMA in the lungs [42]. In the CS-exposed mouse model, silibinin decreased collagen accumulation by modulating the TGF- 1/p-Smad 2/3 signalling axis and simultaneously attenuated the expression of inflammatory factors [87]. Besides, in the LPS-CS co-induced rat model, total flavonoids of *Trollius altaicus* were shown to decrease TGF- 1 levels [95]. Both short-term and long-term exposure to smoke can result in lung inflammation and cellular damage, leading to the production of TGF- 1, implicating the initiation of pulmonary fibrosis. However, flavonoids, such as hydroxysafflor yellow A, liquiritin apioside, quercetin, silibinin, and total flavonoids of *Trollius altaicus* may help prevent the progression of COPD to pulmonary fibrosis by reducing TGF- . Compared with the anti-inflammatory and antioxidant studies of flavonoids, there are few studies on anti-pulmonary fibrosis, and most of them only reduce TGF- , which suggests that more extensive and in-depth research is needed.

Flavonoids targeting programmed cell death

Targeting apoptosis. Apoptosis is a physiological or pathological response of cells to various stimuli, including DNA damage, oxidative stress, and inflammation. This process is complex and tightly regulated by multiple genes, such as the *Bcl-2* family, the caspase family, the oncogene *C-myc*, and the tumour suppressor gene *P53*, as well as by various molecular signals, including the death receptor pathway and the mitochondrial pathway [120]. Research shows that the apoptosis (cell death) of lung structural cells is a crucial factor in the development of COPD. In patients with COPD, there is an observed increase in the apoptosis of alveolar epithelial and endothelial cells. This increase cannot be compensated for by the proliferation of structural cells, leading to the destruction of lung tissue and the development of emphysema [121].

Flavonoids have been reported to act as positive protectors against apoptosis in the pathogenesis of COPD. For instance, baicalin has been shown to inhibit the expression of HSP72 and alleviate apoptosis in CSE-treated MLE-12 cells, which are mouse lung type II epithelial cells [66]. Additionally, baicalin mitigates the apoptosis of LPS- or CSE-induced 16HBE cells by increasing Bcl-2 and CyclinD1 but increasing B-cell lymphoma 2-associated X (Bax) and P21 [92, 93, 96]. Taxifolin inhibited apoptosis by suppressing Bax and CCP3 levels and increasing Bcl-2 levels in COPD mouse lung tissue and CSE-treated HBECs [62]. Hesperetin is capable of suppressing the protein expression of AKT1, IL6, VEGFA, and MMP9 while up-regulating the protein expression of TP53, thereby impeding COPD to lung cancer [60]. Furthermore, flavonoids regulate autophagy-related apoptosis. Puerarin has been demonstrated to inhibit FUNDC1-mediated mitochondrial autophagy and CSE-induced apoptosis in human bronchial epithelial cells by activating the PI3K/AKT/mTOR signalling pathway [81]. Puerarin also protects lung function and inhibits apoptosis by down-regulating the Bax level and up-regulating Bcl-2 in the lung, a process that depends on the PINK1-parkin signalling pathway mediated mitophagy [82]. Moreover, formononetin can attenuate CS-induced inflammation, endoplasmic reticulum stress, and apoptosis in bronchial epithelial cells through the inhibition of AhR/CYP1A1
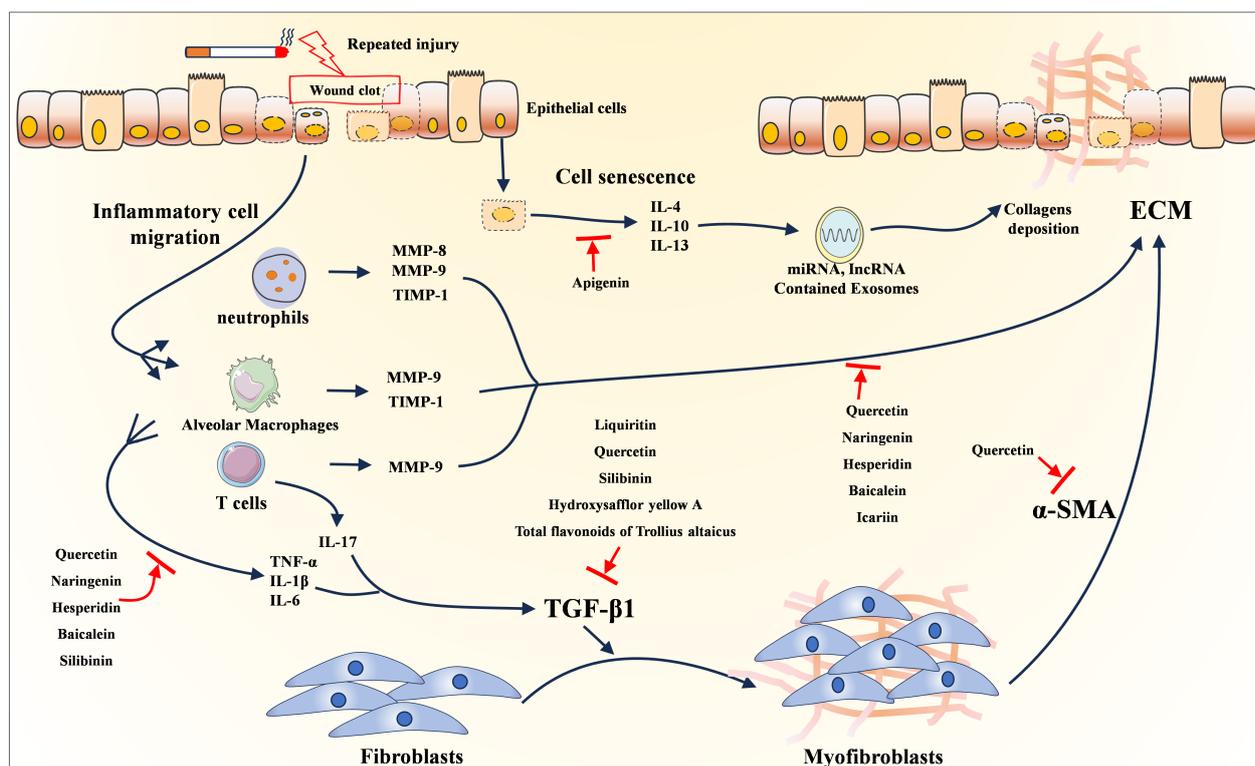
and AKT/mTOR signalling pathways [83]. In addition, flavonoids inhibit apoptosis associated with inflammation. Biochanin A has been shown to reduce PM2.5-induced apoptosis and the production of pro-inflammatory factors, such as TNF- , IL-2, IL-6, and IL-8 [80].

Targeting ferroptosis. Ferroptosis, a form of regulated cell death, is driven by an excessive accumulation of iron, ROS, and lipid peroxides. This process leads to a decrease in GSH and the inactivation of GPX4 [122]. Ferroptosis is increasingly recognised as a critical factor in COPD, with levels elevated in free iron, lipid peroxidation, and inflammatory responses in mice, which are reversed by the overexpression of the GPX4 [123]. GPX4, a negative regulator of ferroptosis, was significantly downregulated in HBECs, which correlates with exacerbations of airway obstruction. Additionally, acyl-CoA synthetase long-chain family member 4 (ACSL4) has been identified as a significant contributor to sensitivity to ferroptosis and was significantly upregulated [124]. Furthermore, Nrf2 plays a protective role by inhibiting ferroptosis through the scavenging of ROS and the promotion of GSH synthesis [125].

Scutellarein may help treat COPD by inhibiting ferroptosis through iron chelation and interaction with the enzyme arachidonate 15-lipoxygenase, which is involved in fatty acid oxidation. Besides, scutellarein significantly inhibited Ras-selective lethal small molecule 3-induced ferroptosis and mitochondria injury [38]. Dihydroquercetin significantly inhibited the ferroptosis induced by CS through the Nrf2-dependent signalling pathway. It notably impeded the increasing of lipid peroxidation and morphological changes in the mitochondria by up-regulating SLC7A11, GPx4, and SOD by down-regulating MDA and ROS [61]. Naringenin increased the extracellular vesicles miR-23a-3p level of CSE-induced alveolar macrophages and inhibited lung epithelial ferroptosis by targeting ACSL4 [58]. Thus, flavonoids could alleviate the ferroptosis-induced injury and oxidative stress by chelating iron and activating the downstream anti-oxidant pathway during the progression of COPD.

Flavonoids' safety

Flavonoids have a long history of consumption in diets with high-rich flavonoids, and a high intake of flavonoids has not caused any side effects. As a result, it is unlikely that dietary sources could provide doses sufficient to cause mutations or cytotoxicity. However, pharmacological and clinical experiments have shown that a variety of flavonoid preparations have certain toxicity, consult Table 3 [68, 158-171] for additional details. For example, chalcones, such as isoliquiritigenin has mortality and malformationand [126], hydroxysafflor yellow A has

a slight nephrotoxicity in long term [127]; Flavone glycosidescertain, baicalin has certain renal toxicity [128]. Isoflavones, such as puerarin has the severity of adverse drug reactions depends on the choice of infusion solvent [129], not the dosage of puerarin, formononetin has mortality at acute dose 300 mg/kg and LD50 at 103.6 mg/kg [130]. Bisflavonoid, such as ginkgetin has potential hepatic and renal toxicity [131]. There are tens of thousands of types of flavonoids, and the safety of each flavonoid compound is extensive, so it is of great significance to investigate the side effects of daily flavonoid supplementation.

Conclusion and prospect

Natural flavonoids are a class of compounds commonly found in various foods, and herbs derives its properties from a wide range of plants, including apples, celery, bayberry, citrus, tea, and ginkgo, as well as astragalus and licorice. A significant body of research exists regarding the flavonoid content in different food sources. Among the flavonols and flavones, quercetin is the most prevalent compound which is particularly abundant in onions and tea. Other noteworthy flavonoids include kaempferol, myricetin, as well as the flavones apigenin and luteolin.

COPD is a prevalent and fatal chronic lung disease that poses a significant burden on global healthcare systems. Despite its high incidence, the mechanisms underlying the development of COPD remain elusive, and there are currently no drugs available to prevent or reverse its initiation and progression. As discussed in this review, flavonoids can target multiple pathways to inhibit the development of COPD, including regulating oxidative stress by targeting ROS and Nrf2/HO-1, reduce inflammation by targeting NF- B, MAPK, and EGFR pathway, remodel airway by reducing ECM and fibrosis, and regulate programmed cell death by targeting apoptosis and ferroptosis. All of this indicates that flavonoids offer unique advantages in drug discovery and adjuvant therapy but also suggests that foods rich in flavonoids can be used to prevent the occurrence of COPD.

The structure of flavonoids is both complex and diverse. As discussed in this review, the structures of flavonoids exhibiting therapeutic effects on COPD vary significantly. Notably, the number and position of hydroxyl groups influence flavonoids' activity and mechanism of action, with the ortho-hydroxyl group playing a particularly critical role. Additionally, glycosylation represents another important structural feature that impacts efficacy. However, research related to COPD has not thoroughly and specifically addressed the structure-activity relationships of flavonoids. Elucidating these relationships, along with conducting structural modifications and

optimisations, is essential for guiding the development of anti-COPD drugs.

A variety of flavonoids have been developed into pharmaceuticals, cosmetics, and health foods, such as ginkgo flavonoids, tea polyphenols, and puerarin. Flavonoids as dietary supplements are not regulated as strictly as drugs, do not need to be reviewed by the FDA, and are not thoroughly evaluated for potential toxicity. When people use these drugs, cosmetics, or health foods, the recommended intake of flavonoids is much higher than in the daily diet, usually at the gram level. Therefore, people need to pay attention to the dosage when supplementing with additional flavonoid preparations to avoid adverse reactions.

Many flavonoid compounds, as well as flavonoid-rich diets and medications, are utilized in clinical treatments, demonstrating their relative safety for human health, only quercetin has explicitly been tested in clinical trials for treating COPD [43]. Consequently, which flavonoid is most suitable for COPD therapy remains unclear, underscoring the need for further preclinical and clinical research. Currently, there have been only two clinical trials involving quercetin and a flavonoid-rich diet for COPD [13, 14]. Nonetheless, numerous other clinical trials have established the safety of flavonoids, which can serve as a reference for conducting trials related to COPD. In addition, the combination of flavonoid compounds with other drugs is also an important strategy.

This article provides a comprehensive overview of flavonoids employed in the treatment of COPD. It delineates their primary sources, structural classifications, and the various mechanisms of action and therapeutic targets. This information serves as a crucial reference for the dietary management and treatment strategies for patients suffering from COPD. Furthermore, it offers valuable insights for researchers concerning structural attributes, pharmacological effects, and potential toxicities. Additionally, the article establishes a foundation for future clinical trials aimed at advancing the treatment methodologies for COPD.

Author contributions

Shi PL collected documents and wrote the manuscript; Zhang GX, Wang PY, and Liu ZQ helped with information collection and manuscript editing; Zheng BQ revised the manuscript for important content and the manuscript preparation and editing.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

COPD, chronic obstructive pulmonary disease; CS, cigarette smoke; ROS, reactive oxygen species; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; NF-B, nuclear factor kappa-B; TNF-, tumor necrosis factor-alpha; TGF-, transforming growth factor-; IL-6, interleukin-6; IL-1, interleukin-1 beta; MMP9, matrix metalloproteinase 9; HDAC2, histone deacetylase-2; PI3K, phosphoinositide-3- kinase; Nrf2, nuclear factor erythroid 2-related factor 2; CXCL, C-X-C motif chemokine ligand; NE, neutrophil elastase; MAPK, mitogen-activated protein kinase; EGF, epidermal growth factor; LPS, lipopolysaccharide; TLR4, toll-like receptor 4; JNK, c-Jun N-terminal kinase; SOD, superoxide dismutase; GSH, glutathione; GSH-Px, glutathione peroxidase; HO-1, haem oxygenase 1; MDA, malondialdehyde; SIRT1, silent information regulator 1; NAD+, nicotinamide adenine dinucleotide; GPX4, glutathione peroxidase 4; NADPH, nicotinamide adenine dinucleotide phosphate; GR, glucocorticoid receptor; CSE, cigarette smoke extract; IB, inhibitor kappa B; HBECs, human bronchial epithelial cells; TLRs, toll-like receptors; IRAK, interleukin-1 receptor-associated kinase; PKC, protein kinase C; NOX4, NADPH oxidase 4; TIMP, tissue inhibitors of metalloproteinase; EMT, epithelial-mesenchymal transition; -SMA,

alpha smooth muscle actin; ERK, extracellular regulated protein kinases; AKT, protein kinase B.

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