Review Article

Advances in Pharmacological Actions and Mechanisms of Flavonoids from Traditional Chinese Medicine in Treating Chronic Obstructive Pulmonary Disease

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Chronic obstructive pulmonary disease (COPD) is a common respiratory disease with high morbidity and mortality. The conventional therapies remain palliative and have various undesired effects. Flavonoids from traditional Chinese medicine (TCM) have been proved to exert protective effects on COPD. This review aims to illuminate the poly-pharmacological properties of flavonoids in treating COPD based on laboratory evidences and clinical data and points out possible molecular mechanisms. Animal/laboratory studies and randomised clinical trials about administration of flavonoids from TCM for treating COPD from January 2010 to October 2020 were identified and collected, with the following terms: chronic obstructive pulmonary disease or chronic respiratory disease or inflammatory lung disease, and flavonoid or nature product or traditional Chinese medicine.

Pharmacokinetic studies and external application treatment were excluded. A total of 15 flavonoid compounds were listed. Flavonoids could inhibit inflammation, oxidative stress, and cellular senescence, restore corticosteroid sensitivity, improve pulmonary histology, and boost pulmonary function through regulating multiple targets and signaling pathways, which manifest that flavonoids are a group of promising natural products for COPD. Nevertheless, most studies remain in the research phase of animal testing, and further clinical applications should be carried out.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a devastating lung disease characterized by incomplete reversible air flow limitations that often develop progressively [1]. In the past few decades, COPD has been rifely accepted as a self-inflicted illness attributed to tobacco smoking. Although smoking is the major identified risk factor for COPD, one-third of worldwide patients are nonsmokers [2]. Furthermore, exposure to smoke from burning of biomass fuel and high levels of air pollution are also major environmental risk factors for COPD in many places around the globe [3]. Therefore, some researchers have suggested that COPD is the end result of lifelong, dynamic, and cumulative gene-environment interactions, which modulate the development, maintenance, and function of the lungs through complex and varied biologic mechanisms [4]. More than 3 million people die from COPD, which causes a major healthcare burden worldwide [5]. In 2014-2015, estimated overall prevalence of COPD was 13.6% among Chinese adults aged 40 years and above, indicating that COPD has become a dominating public health challenge in China [6]. Therefore, it is imperative to clarify the pathogenesis of COPD and take corresponding treatment measures.

COPD is a heterogeneous disease with intricate pathogenesis. There is endless inflammatory infiltration in the
airways, alveoli, and microvasculature of COPD patients [5]. Besides, impaired immune regulation plays a role in COPD, since inflammation and environmental damage in lungs expose some epitopes for the autoimmune attack [7]. Cell senescence generally leads to decreased proliferation with preserved metabolic activity, resulting in increased inflammation, reduced cell regeneration, and carcinogenesis [8]. In addition to the factors mentioned earlier, the fetal stage has been involved in the pathogenic of COPD, which might be programmed early in life [7]. Currently, a series of therapeutic strategies have been developed to inhibit or avoid the etiologic factors.

Treatment strategies for COPD include smoking cessation, physical activity, and pharmacotherapy. Thereinto, the mainstay of drug treatment for COPD involves inhaled long-acting β2 agonists (LABAs), long-acting muscarinic antagonists (LAMAs), inhaled corticosteroids, oral phosphodiesterase-4 inhibitors, and macrolides [5]. Although bronchodilator therapy (LABA, LAMA, or a combination of both) has been shown to be generally safe, there have been adverse cardiac events in clinical studies [9]. Inhaled corticosteroids are related to a higher risk of pneumonia in patients with severe COPD [10]. Phosphodiesterase-4 inhibitors have several side effects such as diarrhoea and nausea [5]. Therefore, novel strategies are needed for better therapeutic response and reduced side effects.

In recent years, an increasing number of studies have shown that flavonoids from traditional Chinese medicine (TCM) have certain protective effect on COPD [11–13]. Although there have been many research studies on flavonoids in treating COPD, the mechanisms of action of flavonoids are still not totally clear and few securable reviews illustrate the comprehensive and multiple pharmacological effects of flavonoids on COPD. Herein, this review aims to illuminate the pharmacologic actions and underlying mechanisms of TCM-derived flavonoids on COPD, based on experimental evidences as well as clinical data to lay the basis for subsequent research studies and developments of anti-COPD medications.

2. Flavonoids in TCM

As the most common secondary metabolites, flavonoids are a large group of polyphenolic compounds and exist widely in plants as free aglycones or glycosides. The biosynthesis of flavonoids proceeds via the acetate pathway and the shikimate pathway [14]. Constructing from a 15-carbon skeleton, flavonoids are composed of two benzene rings connected by 3-carbon linking chain and mainly classified into flavones, flavonols, flavanone, flavanonol, flavan, flavanol, isoflavone, and chalcone [14].

Flavonoids have various functions both in plants and living organisms. The wide variety and high diversity of flavonoids are pivotal for plants to interact with the environment to defense both biotic and abiotic threats [15]. Flavonoids have a variety of biological properties such as antianaphylaxis [16], antibiosis [17], anti-inflammatory [18], vasodilatory [19], antimutagenic [20], and anticarcinogenic activities [21]. Recently, increasing research studies showed the protective effects of flavonoids on COPD through relieving symptoms and improving lung functions [22]. The pharmacological activities and structures of flavonoids for treating COPD are shown in Table 1 and Figure 1, respectively. The schematic diagram of poly-pharmacological properties of flavonoids is displayed in Figure 2.

3. Roles of Flavonoids on Chronic Obstructive Pulmonary Disease

3.1. Inflammation. COPD is a progressive inflammatory disease of the microvasculature, the alveoli, and the airways, in where inflammation-associated cells including macrophages, neutrophils, eosinophils, and dendritic cells are recruited to form the innate immune response [42]. In COPD, inflammatory tissue damage is endless. Therefore, relieving inflammation has a certain therapeutic effect on COPD.

Isolating from the root of Scutellariae radix, baicalin is an isoflavone and has various biological activities. To clarify the effects of baicalin on COPD, the rat model and cell models were established by using cigarette smoke (CS) and cigarette smoke extract (CSE), respectively. The results showed that baicalin reduced production of pro-inflammatory cytokines and had significant anti-inflammatory effects on COPD [23–25]. The anti-inflammatory effect is likely achieved via suppressing the nuclear factor-kappa B (NF-κB) pathway [23] and enhancing histone deacetylase 2 (HDAC2) activity [24].

Oroxylin A, a natural flavonoid isolated from the medicinal herb Scutellariae radix, has been proved to have anti-inflammatory and antioxidative properties [43]. Oroxylin A dose-dependently attenuated CS-induced inflammatory cytokine and chemokine production [26].

Liquiritin apioside is a main flavone from Glycyrrhizae radix et rhizoma. Liquiritin apioside was reported to attenuate tumor necrosis factor-α (TNF-α) and transforming growth factor-β (TGF-β) in human type II alveolar epithelial cell line (A549) [27]. Moreover, liquiritin apioside significantly inhibited goblet cells containing mucus in the atmosphere in a CS-induced mouse model [27].

Phloretin is a chalcone that exists in Crotonis fructus and Rubi fructus and possesses diverse biologic properties. Phloretin was reported to suppress the mucus hypersecre- tion and decrease inflammatory in a mice model induced by CS [28]. The results of in vitro experiment using NCI–H292 cells were consistent with in vivo experiments [28]. The anti-inflammatory effect is achieved via restraining phosphorylation of mitogen-activated protein kinase (MAPK) pathways [28]. The above data indicate that phloretin could be a potential therapy approach to COPD. However, it has not been approved for clinical use.

Hesperidin is a flavone with stable biological activity, which exists in various Chinese herbs such as Citrus reticulata, Schizonetetacia herba, and Chrysanthemi flos. In vivo, hesperidin was proved to mitigate inflammation in COPD mice by evaluating the levels of related cytokines in bronchoalveolar lavage fluid (BALF) and lung tissues [29]. The mechanism of action of hesperidin was associated
with NAD-dependent protein deacetylase sirtuin-1 (SIRT1)/PGC-1α/NF-κB signaling axis [29]. These data provide the laboratory evidence of hesperidin in treating COPD patients.

Silymarin is a flavonoid compound extracted from the *Silybl fructus*. Silymarin has been proved to alleviate lung inflammation by regulating extracellular signal-regulated kinase (ERK)/p38 MAPK pathways [30] and suppressing autophagy activation [31]. Silymarin might be an ideal agent treating inflammatory pulmonary diseases, but more clinical research studies are needed.

Naringenin is a plant-derived flavonone with a variety of biological activities. Naringenin was found to significantly decrease inflammatory cells and reduce the levels of

Table 1: The effects of flavonoids in TCM on chronic obstructive pulmonary disease.

<table>
<thead>
<tr>
<th>Flavonoids</th>
<th>TCM sources</th>
<th>Models</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baicalin (C21H18O11)</td>
<td>Scutellariae radix</td>
<td>CS-induced rat model; CS-induced mice model In vitro model using CSE-exposed type II pneumocytes CSE-induced human type II alveolar epithelial carcinoma cell line (A549 cells)</td>
<td>Inhibition of inflammation; prevention of pulmonary function [23]; reducing oxidative stress [24]; Prevention of inflammation [23]</td>
</tr>
<tr>
<td>Oroxylin A (C16H12O5)</td>
<td>Scutellariae radix</td>
<td>CS induced BEAS-2B bronchial epithelial cells and RAW264.7 cells</td>
<td>Alleviation of inflammation and oxidative stress [26]; Upregulation of Nrf2 expression and total cellular glutathione level [26]</td>
</tr>
<tr>
<td>Liquiritin apioside (C28H30O13)</td>
<td>Glycyrrhizae radix et rhizoma</td>
<td>CS-induced mouse model; In vitro model using CSE-exposed A549 cells</td>
<td>Inhibition of inflammation, myeloperoxidase activity, and increased SOD activity [27]; Attenuation of cytotoxicity, inflammation, and depleted GSH levels [27]</td>
</tr>
<tr>
<td>Phloretin (C13H14O5)</td>
<td>Crotonis fructus; Rubi fructus</td>
<td>CS-induced mice model; CSE-induced NCI-H292 cell model</td>
<td>Suppression of the mucus hypersecretion and inflammatory cell release [28]; Moderation of inflammatory cytokines and the phosphorylation of MAPK pathways [28]</td>
</tr>
<tr>
<td>Hesperidin (C28H34O15)</td>
<td>Citrus reticulata</td>
<td>CSE-induced mice model</td>
<td>Inhibition of inflammation and oxidative stress responses [29]</td>
</tr>
<tr>
<td>Silymarin (C25H22O10)</td>
<td>Silybl fructus</td>
<td>CS-induced mice model</td>
<td>Suppression of inflammation and oxidative stress [30]; Attenuation of autophagy [31]; Moderation of inflammatory cytokines and the phosphorylation of MAPK pathways [31]</td>
</tr>
<tr>
<td>Naringenin (C15H12O5)</td>
<td>Menthae herba</td>
<td>CS-induced mouse model; In vitro model using CSE-exposed A549 cells</td>
<td>Protecting pulmonary function and decreasing inflammatory cells and cytokines [32]; Suppression of inflammation [32]</td>
</tr>
<tr>
<td>Fisetin (C15H10O6)</td>
<td>Gleditsiae spina</td>
<td>CS-induced rat model</td>
<td>Inhibition of inflammation and oxidative stress; prevention of tissue damage [33]</td>
</tr>
<tr>
<td>Casticin (C19H18O8)</td>
<td>Viticis fructus</td>
<td>CS-induced C57BL/6 mice model</td>
<td>Inhibition of inflammatory cytokines and chemokines [34]</td>
</tr>
<tr>
<td>Isoliquiritigenin (C15H12O4)</td>
<td>Glycyrrhizae radix et rhizoma</td>
<td>CS-induced mice model</td>
<td>Reduction of the infiltration of inflammatory cells and cytokines; reversion of lung pathological injuries and oxidative stress levels [35]</td>
</tr>
<tr>
<td>Biochanin A (C20H12O5)</td>
<td>Trifolium pratense</td>
<td>Male Hartley guinea pigs and female BABL/c mice model PM 2.5-induced rat model</td>
<td>Suppression of inflammation response [36]; Amelioration of inflammation and oxidative stress [37]</td>
</tr>
<tr>
<td>Isoorientin (C22H20O11)</td>
<td>Anthopterus wardii</td>
<td>In vitro model using CSE-exposed human SAE cells</td>
<td>Anti-inflammatory activity [37]</td>
</tr>
<tr>
<td>Mangiferin (C19H18O11)</td>
<td>Anemarrhenae rhizoma</td>
<td>In vitro model using PAH-exposed BEAS-2B cells</td>
<td>Ameliorating oxidative stress, speeding up wound healing and restoring proliferation [38]</td>
</tr>
<tr>
<td>Quercetin (C15H10O7)</td>
<td>Polygoni avicularis herba</td>
<td>ACH-induced mice model Patients with COPD</td>
<td>Relieving precontracted airway smooth muscle [39]; Restoring corticosteroid sensitivity [40]</td>
</tr>
<tr>
<td>Genistein (C14H12O5)</td>
<td>Iridis tectori rhizoma</td>
<td>Patients with COPD</td>
<td>Suppression of the NF-κB, TNF-α, and MMP-9-associated pathways [41]</td>
</tr>
</tbody>
</table>
proinflammatory cytokines by restraining the NF-κB pathway in the BALF and serum of CS-induced BALB/c mice [32]. However, its role in COPD patients is not yet clear. Fisetin, a plant flavonoid present in *Gleditsia spina*, has been shown to be effective in lowering inflammation and oxidative stress associated with different disease conditions. Fisetin (25 or 50 mg) demonstrated a significant decrease in

**Figure 1:** Chemical structure of flavonoids for the treatment of chronic obstructive pulmonary disease.
inflammatory mediators such as TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), and interleukin (IL)-1β, IL-4, and IL-10 [44]. The anti-inflammatory mechanism of fisetin was related to suppressing the TNF-α-activated NF-κB cascade via targeting protein kinase C [33]. The involved proteins in NF-κB pathway that inhibited by fisetin are shown in Figure 3 [45].

Isolated from Viticis fructus, casticin is a flavone with various pharmacological effects. In a CS-induced murine model, administration of casticin significantly restrained the influx of inflammatory cells (macrophages, neutrophils, and lymphocytes) and reduced proinflammatory cytokines and chemokines in BALF [34]. These data suggest that casticin could be a promising candidate for suppressing lung inflammation in COPD.

Isoorientin, vitexin, and isovitexin are natural flavones including TNF-α, IL-2, IL-6, and IL-8 [37]. It was reported that isoorientigenin could attenuate CS-induced inflammatory cytokines levels (TNF-α, IL-1β) and the number of cells (neutrophils, and macrophages) in BALF via suppressing the NF-κB signaling pathway [48].

Biochanin A is a phytoestrogenic isoflavone of Glycyrrhiza radix et rhizoma, has various benefits including antioxidant, anti-inflammation, and antiapoptotic properties [35, 46, 47]. It was reported that isoorientigenin could attenuate CS-induced inflammatory cytokines levels (TNF-α, IL-1β) and the number of cells (neutrophils, and macrophages) in BALF via suppressing the NF-κB signaling pathway [48].

Oxidative stress refers to the over-generation oxides in the biological system when the organism is exposed to a harmful environment and has a significant driving role in the pathogenesis of COPD [50]. Oxidants consist of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and result from CS and inflammatory cells [51]. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that binds to antioxidant response element and originates the transcription of antioxidant genes in response to oxidative stress [34]. Hence, therapy directed towards increasing Nrf2-regulated antioxidants could be a therapeutic strategy for relieving the effects of oxidative stress in COPD.

From the literature mentioned above, flavonoids from TCM could inhibit inflammatory response both in vitro and in vivo mainly via suppressing TNF-α/NF-κB and MAPK signaling pathways.

3.2. Oxidative Stress. Oxidative stress is defined as the over-oxidation processes that increase ROS and RNS. ROS includes oxygen free radicals, such as superoxide anion, hydrogen peroxide, and singlet oxygen. RNS include nitric oxide and peroxynitrite. The two families of biomolecules are generated in the biological system when the organism is exposed to a harmful environment and has a significant role in the pathogenesis of COPD [50].

Oxidative stress refers to the imbalance between the generation of free radicals and the antioxidant defenses. Oxidants can be classified as reactive oxygen species (ROS) and reactive nitrogen species (RNS). Oxidants are generated under various conditions such as inflammation, infection, and stress. The main sources of ROS are mitochondria, endoplasmic reticulum, and NADPH oxidase. The main sources of RNS are inducible nitric oxide synthase (iNOS) and nitric oxide synthase (NOS).

The main mechanisms of flavonoids in COPD are shown in Figure 2 [49]. To date, there are many studies on the effects of flavonoids on COPD. However, more studies are needed to clarify their efficacy and safety.

From the literature mentioned above, flavonoids from TCM could inhibit inflammatory response both in vitro and in vivo mainly via suppressing TNF-α/NF-κB and MAPK signaling pathways.

Mangiferin ameliorated oxidative stress in vitro through inhibiting ROS level [38]. High-dose silymarin (50 mg/kg/day) administration prevented CS-induced elevation in MDA levels and decrease in SOD activities in vivo [30]. Fisetin significantly enhanced lung HO-1, GSH peroxidase-2, reduced GSH, SOD, nitric oxide (NO), and NFR2 levels in COPD.
3.3. Cellular Senescence. Defining as complete and irreversible loss of the replicative capacity in primary somatic cells, cellular senescence has participated in the pathogenesis of COPD [7, 49]. Senescent cells secrete multiple inflammatory proteins known as the senescence-associated secretory phenotype, leading to low-grade chronic inflammation, which further drives senescence [52]. Senescence influences lung structure and inflammatory cells, fibroblasts, and progenitors, making repair and regeneration insufficient [53].

It is clearly shown that mangiferin produced intense cytoprotective effect in bronchial epithelial cells (BEAS-2B) [38]. Furthermore, mangiferin sped up wound healing process and restored proliferation rate of bronchial epithelium [38]. Such protective effects of mangiferin stimulate further in vivo and clinical research. Oroxylin A could protect both epithelial cells and macrophages from damage by CS via activating the Nrf2 signaling pathway [26].

3.4. Corticosteroid Resistance. In contrast to many other inflammatory diseases, corticosteroids are largely ineffective in patients with COPD [40]. Peripheral blood mononuclear cells (PBMCs) from patients with COPD show corticosteroid insensitivity and oxidative stress reduces corticosteroid sensitivity in vitro [54, 55]. Corticosteroid insensitivity in COPD lungs explains why high doses of inhaled corticosteroids fail to slow disease progression or reduce mortality [56]. Therefore, increasing sensitivity of corticosteroids may be an effective therapeutic measure for COPD.

Quercetin is a naturally occurring flavone isolated from Polygoni avicularis herba. The in vitro model, quercetin (10 μM), was competent to restore CSE-induced corticosteroid insensitivity and activate adenosine monophosphate-
activated protein kinase (AMPK) pathways in the human mononuclear cell line U937 and peripheral blood mononuclear cells [40]. Therefore, combining with corticosteroids, quercetin had the potential to be a novel medication for treating COPD.

3.5. Pulmonary Histology. Following CS exposure, there are significant changes in the histology of lungs in experimental animals. In CS-exposed groups, the lung slices showed enhanced peribronchial inflammatory cell infiltration, airway epithelial cell hyperplasia, airway epithelium thickening, alveolar space collapse, interstitial edema, and lumen obstruction by mucus and cell debris. Fortunately, these changes can be alleviated by flavonoid treatment.

Baicalin relieved inflammatory cell infiltration and reduced both the mean linear intercepts and the destructive index [23, 25]. Oroxylin A weakened interstitial edema, dosage of inflammatory cells, and thickened alveolar wall [26]. Phloretin abated peribronchial inflammatory cell infiltration, airway epithelial cell hyperplasia, airway epithelium thickening, and lumen obstruction [28]. Hesperidin mitigated the infiltration level of inflammatory cells, alveolar space, and alveolar sacs [29]. Casticin alleviated inflammatory cell infiltration [34]. Similarly, isoliquiritigenin eased inflammatory cell infiltration and intra-alveolar edema [48].

3.6. Pulmonary Function. Biochanin A (20 mg/kg, orally) markedly relieved airway resistance ($R_L$), enhanced pause ($P_{exp}$), and increased lung dynamic compliance ($C_{dyn}$) values induced by methacholine in sensitized and challenged mice [36].

The whole-body plethysmography method was employed to evaluate the protective effect of naringenin on the pulmonary function of CS-exposed mice [32]. The results showed that naringenin significantly improved the parameters of breathing such as peak expiratory flow (PEF), peak inspiratory flow (PIF), and minute ventilation (MV).

Baicalin was reported to increase the peak expiratory flow rate (PEFR), maximum ventilatory volume (MVV), and the forced expiratory volume in 0.3 s (FEV$_{0.3}$)/functional residual capacity (FRC) in CS-induced rat models [42]. Moreover, baicalin could significantly enhance the ventilatory parameters, including PEF, PIF, and MV in CS-exposed mice [25]. Compared with the group model, CS-induced rats treated with different concentrations of baicalin displayed an increased FEV$_{0.3}$/FRC ratio and vital capacity [24]. Moreover, administration of 40 mg/kg baicalin markedly prevented PaCO$_2$ augmentation and increased PaO$_2$ level [24]. These results indicated that baicalin exerts a lung function protection role in cigarette smoke COPD rats.

4. Roles of Flavonoids in Clinical Testing

Genistein is an isoflavone that exists in various Chinese herbs such as Iridis tectori rhizoma, Sojae Semen Praeparatum, and Sojae Semen Nigrum. Patients with COPD ($n=34$; age, 71.8 ± 9.0 years) were recruited to assess the effects of genistein on COPD [41]. In the supernatant of lymphocytes in COPD patients, the percentage of NF-$\kappa$B-positive cells and the concentrations of TNF-$\alpha$ and MMP-9 were markedly increased. Compared with control treatment, the levels of NF-$\kappa$B-positive cells, TNF-$\alpha$, and MMP-9 were reduced by genistein treatment. This clinical research indicated that genistein may provide a strategy for protecting patients with COPD.

Quercetin could inhibit acetylcholine chloride-induced continuous contractions in human bronchial airway smooth muscle strips, which indicated that quercetin could be developed as a bronchodilator [39]. Although quercetin has the potential to be a novel medication treating COPD, the safety of quercetin in patients with COPD is still not clear. A randomized clinical trial was performed to assess safety of quercetin [57]. COPD patients with mild-to-severe lung disease with FVE$_1$ ranging between >35% and <80% were recruited and administered with either placebo or quercetin at 500, 1000, or 2000 mg/day in a dose-escalation manner. The results showed that there are no quercetin-related severe adverse events in the patients based on evaluating lung function, blood profile, and COPD assessment test questionnaire. Therefore, quercetin was safely tolerated up to 2000 mg/day. However, the drawbacks of this trial are the small sample size and the short treatment time of quercetin. Hence, the safety of quercetin should be ascertained in a larger cohort of patients for a longer time.

5. Current Trends

COPD is an intractable respiratory disease with complicated pathogenic factors. Increasing studies have shown that flavonoids have certain therapeutic effects on COPD. Some of them exert a variety of pharmacological effects. For example, oroxylin A not only inhibits inflammation, oxidative stress, and cell senescence but also restores damaged lung tissue. Baicalin could relieve symptoms of COPD by restraining the levels of inflammation-associated cytokines and oxidative stress, enhancing pulmonary function. The above findings manifest that the protective effects of flavonoids are relevant to a multitarget mode action. Furthermore, many flavonoids could alleviate inflammation response and oxidative stress via regulating NF-$\kappa$B and Nrf2 signaling pathways, respectively. Based on the structure-activity relationship theory, the collective anti-inflammatory and antioxidant properties could be due to structural similarities. Consequently, exploiting the structural similarity may help to develop flavonoid-based novel lead compounds treating COPD.

However, most research studies on the treatment of COPD with flavonoids are still in the laboratory stage and there are few clinical studies on flavonoids. Consequently, the roles and safety of flavonoids on patients with COPD are vague, which greatly limits the application in the treatment of COPD. Based on the current situation, more clinical research studies are required to elucidate the efficacy and safety of flavonoids. In addition, we found that cigarette smoke or cigarette smoke extracts are commonly used in laboratories to trigger off oxidative stress and inflammation to establish COPD models; however, the pathogenesis of
COPD is intricate and about one-third of patients worldwide are nonsmokers. Consequently, the current modeling methods cannot adequately reflect the true situation of COPD patients and new methods are extremely needed to comprehensively show the pathological characteristics of COPD.

6. Conclusion

Flavonoids are the most diverse phenolic compounds and are broadly available in Chinese herb medicines, and therefore, COPD treatments with such natural compounds can be considered as a kind of promising alternatives. A mass of laboratory evidences have shown the beneficial effects of flavonoids on COPD pathogenesis via inhibiting inflammation, oxidative stress, and cellular senescence, restoring corticosteroid sensitivity, improving pulmonary histology, and boosting pulmonary function. Based on the above scenario, it is essential to establish a research platform to comprehensively uncover the interactions between flavonoids and genes in COPD.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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References

Evidence-Based Complementary and Alternative Medicine


