

Review

Traditional Chinese Medicine for Airway Remodeling in Chronic Obstructive Pulmonary Disease: Mechanisms and Therapeutic Applications

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Abstract: Airway remodeling is a major structural substrate of progressive and largely irreversible airflow limitation in chronic obstructive pulmonary disease (COPD). It arises from an interconnected pathological network involving chronic inflammation, oxidative stress, epithelial-mesenchymal transition (EMT), extracellular matrix (ECM) deposition, and fibrosis. Within traditional Chinese medicine (TCM) theory, COPD is commonly characterized by a pattern of "root deficiency and branch excess," particularly phlegm and blood stasis obstructing the Lung. TCM interventions are characterized by holistic regulation and multi-target, multi-pathway actions and may therefore have potential to delay airway remodeling. This review summarizes the principal morphological changes and molecular signaling mechanisms underlying airway remodeling in COPD, discusses the correspondence between TCM pathogenesis concepts and modern pathological processes, and reviews evidence on Chinese herbal formulas, and bioactive constituents, with emphasis on the TGF- β 1/Smad, NF- κ B, Nrf2/HO-1, and related signaling pathways. The strength and limitations of the current evidence are further appraised to provide a theoretical basis and research framework for target identification, optimization of integrated intervention strategies, and clinical translation of TCM approaches for COPD airway remodeling.

Keywords: traditional Chinese medicine; chronic obstructive pulmonary disease; airway remodeling; mechanism; Chinese herbal medicine

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disorder characterized by persistent airflow limitation and respiratory symptoms such as cough, sputum production, and dyspnea, and is associated with high prevalence, disability, and mortality. Current evidence indicates that COPD affects more than 400 million people worldwide and remained the third leading cause of death in the 2023 Global Burden of Disease, Injuries, and Risk Factors Study (GBD) [1]. Modeling based on the Global Burden of Disease database further projects that the global number of COPD cases will approach 600 million by 2050, representing a 23% increase relative to 2020 [2]. Epidemiological surveys indicate that the prevalence of COPD among adults aged >40 years in China is approximately 13.6%, and China bears the highest absolute number of COPD-related deaths worldwide [1]. COPD is therefore not only a major global public health challenge but also a substantial medical and economic burden in China, underscoring the need for a more comprehensive understanding of its pathogenesis and for effective and affordable interventions.

Persistent airflow limitation is a defining feature of COPD, and airway remodeling is a key pathological substrate underlying its progressive and largely irreversible worsening. Current conventional pharmacotherapy relies primarily on bronchodilators and inhaled corticosteroids. These treatments can improve symptoms and lung function

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to some extent and reduce the risk of acute exacerbations; however, their principal effects remain the relief of bronchoconstriction and partial suppression of airway inflammation, with relatively limited impact on long-term lung-function decline. Moreover, clinical evidence that existing therapies can definitively halt or reverse established airway remodeling remains lacking. Long-term treatment also has limitations. β 2-adrenergic agonists may cause palpitations and tremor, anticholinergic agents commonly cause dry mouth, and inhaled corticosteroids may increase the risks of pneumonia and oropharyngeal candidiasis; treatment decisions must therefore balance expected benefits against potential harms [3]. Several novel agents directed at specific molecular targets have shown potential to suppress remodeling, but supporting clinical data remain insufficient and these agents have not become routine therapies. Accordingly, the development of additional safe and effective anti-remodeling strategies has considerable clinical relevance.

In the management of COPD, TCM employs a range of interventions, including orally administered herbal formulas, acupuncture, and acupoint application, on the basis of syndrome differentiation. An increasing body of research suggests that TCM may modulate inflammation, oxidative stress, and fibrotic processes through multiple targets and pathways, thereby offering potential advantages in delaying airway remodeling in COPD. However, its mechanisms of action and clinical evidence require further systematic synthesis and clarification.

2. Modern Biomedical Understanding of Airway Remodeling in COPD

Against this background, airway remodeling represents a central structural basis of progressive lung-function decline in COPD. Its pathological manifestations include airway epithelial injury, airway smooth muscle hyperplasia and hypertrophy, extracellular matrix deposition, mucous gland hypertrophy, and vascular remodeling. These processes are interrelated and collectively drive the progression of airflow limitation.

2.1. Pathomorphological Features of Airway Remodeling

2.1.1. Airway Epithelial Injury and Remodeling

The airway epithelium, composed of multiple cell types, forms the first line of defense against inhaled harmful agents. Chronic exposure to cigarette smoke and other noxious particles increases reactive oxygen species (ROS), disrupts the oxidant-antioxidant balance, and induces oxidative stress, resulting in increased epithelial injury, apoptosis, and senescence. These events recruit inflammatory cells and promote persistent inflammation and tissue damage [4]. Under these conditions, COPD is associated with pathological epithelial remodeling, including basal-cell expansion, goblet-cell hyperplasia, squamous metaplasia, and abnormalities in ciliary structure and function. These changes impair epithelial barrier integrity and mucociliary clearance and thereby amplify airway inflammation [5,6]. Active epithelial-mesenchymal transition (EMT) is also observed in the airway epithelium of patients with COPD. During EMT, epithelial cells lose E-cadherin expression and acquire mesenchymal markers such as vimentin and α -smooth muscle actin (α -SMA), thereby promoting airway fibrosis and remodeling [7,8]. Chronic epithelial inflammation and repeated injury lead to aberrant repair responses and ultimately contribute to irreversible airway remodeling.

2.1.2. Hyperplasia and Hypertrophy of Airway Smooth Muscle Cells

Airway smooth muscle cells (ASMCs) are essential components of airway contractile function and also contribute to the production of inflammatory mediators, proteases, and growth factors. ASMC hyperplasia and hypertrophy correlate positively with the severity of airway-wall thickening and negatively with lung function [9]. Under chronic inflammatory activation in COPD, ASMCs can shift from a contractile to a proliferative phenotype, display enhanced migration, increase airway smooth muscle mass, and secrete multiple cytokines, chemokines, and matrix metalloproteinases (MMPs), thereby

further amplifying airway inflammation and remodeling [9-11]. Michaeloudes et al [12]. reported that COPD-derived ASMCs exhibit impaired mitochondrial function together with increased glycolysis and glutamine utilization. These metabolic changes support enhanced biosynthetic and antioxidant processes and may contribute to a metabolically driven hyperproliferative phenotype.

2.1.3. Extracellular Matrix Deposition and Airway Fibrosis

Abnormal deposition of extracellular matrix (ECM) is a major contributor to structural abnormalities of the airway wall, destruction of the lung parenchyma, and progression of airway fibrosis [13]. In healthy airway tissue, ECM synthesis and degradation are maintained in dynamic equilibrium. In COPD, however, this balance is disrupted, and structural proteins such as type I and type III collagen, fibronectin, and laminin accumulate within the basement membrane and submucosa, contributing to lung-function impairment and airway remodeling [13,14].

A central mechanism underlying disturbed ECM homeostasis is dysregulation of the MMP/tissue inhibitor of metalloproteinase (TIMP) system. Biomarker studies of bronchoalveolar lavage fluid and induced sputum from patients with COPD have shown increased levels of MMP-9 and MMP-12. Elastin degradation reduces elastic recoil and is closely associated with the development of emphysema [15]. Disruption of the MMP/TIMP balance further aggravates abnormal ECM degradation and remodeling. Fibroblasts and myofibroblasts are major sources of airway ECM, and fibroblast transdifferentiation is critical to the increase in ECM accumulation and airway remodeling in COPD [16]. Airway epithelial cells in COPD produce increased transforming growth factor- β 1 (TGF- β 1), generating a profibrotic microenvironment around the airways that promotes fibroblast activation, stimulates ECM deposition, and drives bronchial remodeling [17].

2.1.4. Mucous Gland Hypertrophy and Mucus Hypersecretion

Airway mucus hypersecretion is an important pathophysiological feature of COPD. Chronic exposure to harmful stimuli such as cigarette smoke, air pollution, and recurrent infection induces persistent airway inflammation and promotes goblet-cell hyperplasia and enlargement of submucosal glands. The resulting increase in mucus-secreting cells, acinar number, and relative thickness of the submucosal gland layer reflects remodeling of airway secretory structures [18]. MUC5AC and MUC5B are the major gel-forming mucins in airway mucus, and their expression is regulated by signaling pathways including EGFR/ERK, NF- κ B, and IL-13/STAT6 [19]. MUC5AC is secreted primarily by goblet cells of the surface epithelium and is closely associated with mucus hypersecretion and disease progression in COPD [20]. Excess mucus production together with impaired clearance promotes mucus-plug formation and small-airway obstruction. By facilitating pathogen colonization, persistent inflammation, and local hypoxia, mucus plugging can further exacerbate airway-wall thickening, smooth muscle remodeling, ECM deposition, and small-airway narrowing, creating a vicious cycle between mucus hypersecretion and structural remodeling and ultimately increasing the risks of acute exacerbation, hospitalization, and poor outcomes [21,22].

2.1.5. Airway Vascular Remodeling

Vascular remodeling of the airway wall is another pathological change of interest in COPD. Multiple studies have reported an increased airway vascular area and abnormalities in vessel number and microvascular architecture in patients with COPD, changes that are associated with airway remodeling, local inflammation, and airflow limitation [23,24]. Angiogenesis and vascular remodeling in a chronically inflamed airway may be accompanied by increased vascular permeability, which facilitates plasma-protein extravasation and inflammatory-cell recruitment and thereby amplifies local inflammation and contributes to airway-wall thickening. Vascular endothelial growth factor (VEGF) is a major driver of airway angiogenesis. In the oxidative, inflammatory, and hypoxia-like microenvironment induced by cigarette smoke exposure, hypoxia-

inducible factor-1 α (HIF-1 α) can be activated and enhance VEGF transcription, thereby promoting endothelial proliferation and neovascularization [25]. Endothelin-1 (ET-1) also promotes vascular smooth muscle contraction and proliferation through the ET-A receptor and contributes to remodeling of both the airways and pulmonary vasculature [26].

These pathomorphological changes do not occur in isolation. Rather, they represent structural consequences of the combined effects of inflammation, oxidative stress, and aberrant repair under chronic stimulation and are driven by an interconnected network of molecular signaling pathways. The major signaling mechanisms are summarized below.

2.2. Core Molecular Signaling Mechanisms of Airway Remodeling

Airway remodeling in COPD is not driven by a single signaling pathway; instead, it results from the combined effects of inflammatory amplification, oxidative stress, aberrant epithelial repair, matrix degradation, and immune-cell reprogramming under chronic exposure. Risk factors such as cigarette smoke, biomass smoke, particulate matter, and recurrent infection initially affect airway epithelial cells and innate immune cells. Subsequent crosstalk among the TGF- β 1/Smad, NF- κ B, Nrf2/HO-1, and EGFR pathways, the protease-antiprotease system, and non-coding RNA (ncRNA) regulatory networks ultimately manifests as goblet-cell metaplasia, mucus hypersecretion, basement-membrane alterations, smooth muscle hyperplasia, and peribronchiolar fibrosis.

2.2.1. TGF- β 1/Smad Signaling Pathway

The TGF- β 1/Smad pathway is regarded as an important profibrotic regulatory axis in COPD airway remodeling. Long-term tobacco-smoke exposure, oxidative stress, and persistent airway inflammation can cause epithelial injury and abnormal repair while increasing local TGF- β 1 expression or activation. Activated TGF- β 1 signals through the TGF- β RII/TGF- β RI receptor complex and initiates canonical Smad signaling. Smad2/3 is phosphorylated and forms a transcriptional regulatory complex with Smad4, which translocates to the nucleus and regulates the expression of ECM and profibrotic molecules, including collagen, fibronectin, and connective tissue growth factor (CTGF/CCN2) [27]. Sustained activation of TGF- β 1/Smad signaling promotes airway epithelial EMT, fibroblast-to-myofibroblast differentiation, ASMC proliferation, and abnormal ECM deposition, thereby contributing to small-airway wall thickening, luminal narrowing, and fixed airflow limitation [28].

2.2.2. NF- κ B Inflammatory Signaling Pathway

Nuclear factor- κ B (NF- κ B) is a key molecular link between chronic inflammation and airway remodeling. In resting cells, NF- κ B is sequestered in the cytoplasm in an inactive state through binding to inhibitor of κ B (I κ B). Upon stimulation by cigarette smoke, bacterial endotoxin, IL-1 β , and related factors, the I κ B kinase complex is activated, leading to phosphorylation and degradation of I κ B and release of NF- κ B. NF- κ B then translocates to the nucleus and induces the expression of numerous proinflammatory and remodeling-related molecules, including TNF- α , IL-6, IL-8, MMP-9, and MUC5AC [29]. By influencing epithelial injury and repair, mucus secretion, and fibroblast activation, NF- κ B contributes to structural changes in the small airways [30]. Some studies further suggest crosstalk between NF- κ B and TGF- β 1 signaling, through which both pathways participate in bronchiolar fibrosis and airway-wall thickening under chronic inflammatory conditions [31,32].

2.2.3. Oxidative Stress and the Nrf2/HO-1 Pathway

Cigarette smoke contains abundant reactive oxygen species that can directly damage DNA, proteins, and lipids in airway epithelial cells while simultaneously activating inflammatory pathways and aggravating abnormal epithelial repair. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a central transcription factor in the endogenous response to oxidative stress. Under physiological conditions, Nrf2 binds to Kelch-like ECH-associated protein 1 (Keap1) and is targeted for ubiquitin-mediated degradation. During oxidative stress, modification of critical cysteine residues in Keap1 permits Nrf2

accumulation and nuclear translocation. Nrf2 then binds antioxidant response elements and induces antioxidant enzymes such as heme oxygenase-1 (HO-1), superoxide dismutase (SOD), and glutathione peroxidase (GPx) [33,34]. In patients with COPD, the capacity for Nrf2 nuclear translocation is reduced, accompanied by lower pulmonary expression of Nrf2 protein and downstream target genes. This shifts the oxidant-antioxidant balance toward oxidative stress and further accelerates epithelial injury and remodeling [35].

2.2.4. EGFR Signaling Network

Aberrant activation of epidermal growth factor receptor (EGFR) signaling is an important driver of mucus hypersecretion and epithelial remodeling in COPD [36]. EGFR can be activated by multiple ligand-dependent and ligand-independent stimuli. Activation of its intracellular tyrosine kinase domain initiates the Ras-Raf-MEK-ERK cascade and transcriptionally upregulates mucin genes such as MUC5AC [37]. EGFR signaling can also activate the PI3K/Akt pathway, increase EMT-related transcription factors, suppress epithelial-marker expression, and promote mesenchymal-marker expression [38]. Extensive crosstalk exists between EGFR and TGF- β 1 signaling, and their combined activity promotes EMT and accelerates the transition of airway epithelial cells toward a mesenchymal phenotype [39].

2.2.5. Protease-Antiprotease Imbalance

Protease-antiprotease imbalance is a classical pathogenic mechanism in COPD. Neutrophil elastase (NE) can directly hydrolyze elastin, collagen, and fibronectin, thereby compromising airway structural integrity. NE can also activate airway epithelial cells through protease-activated receptor 2 (PAR-2), enhance the secretion of chemokines such as IL-8, recruit additional neutrophils, and further promote inflammation and epithelial apoptosis [40,41]. α 1-Antitrypsin is the major physiological inhibitor of NE; inherited deficiency or oxidative inactivation induced by smoke exposure can accelerate airway remodeling in a subset of patients with COPD [42,43].

2.2.6. ncRNA-macrophage Regulatory Axis

Immune regulation mediated by ncRNAs represents an important upstream mechanism linking chronic inflammation with structural remodeling. ncRNA networks comprising microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) may participate in COPD airway remodeling by regulating macrophage polarization, inflammatory-mediator release, and related processes [44]. Macrophages are major immune cells within the COPD airway microenvironment and can shift toward proinflammatory M1 or alternatively activated M2 phenotypes in response to specific environmental stimuli. M1 polarization can amplify epithelial injury and matrix degradation, whereas M2 polarization can promote fibroblast activation, collagen deposition, and angiogenesis [45,46]. Multiple ncRNAs have been implicated in regulating this polarization balance. Current evidence indicates that miR-125a promotes COPD progression by inducing M1 macrophage polarization [47], whereas miR-146a and miR-223 exert negative regulatory effects that may constrain excessive inflammation and help maintain macrophage homeostasis [48,49]. lncRNAs and circRNAs can also function through competing endogenous RNA (ceRNA) mechanisms by sequestering specific miRNAs and thereby relieving inhibition of key nodes in the TGF- β /Smad, STAT3, MAPK, and related pathways [50]. Macrophage-derived exosomes may serve as important vehicles for intercellular ncRNA transfer, delivering miRNAs or lncRNAs to airway epithelial cells, smooth muscle cells, and fibroblasts, where they can induce EMT, airway smooth muscle proliferation, and ECM deposition and thereby contribute to chronic inflammation and progressive airway remodeling [51,52].

3. TCM Understanding of the Pathogenesis of COPD Airway Remodeling

Within TCM, COPD is generally discussed under disease categories such as "lung distension" (feizhang), "cough" (kesou), "panting syndrome" (chuanzheng), and "phlegm-

fluid retention" (tanyin). Modern TCM physicians commonly summarize its pathogenesis as "deficiency of the Lung, Spleen, and Kidney as the root, with phlegm and blood stasis obstructing the Lung as the branch." Lung deficiency impairs dispersing and descending functions; Spleen deficiency impairs transportation and transformation and gives rise to phlegm-dampness; and Kidney deficiency weakens the reception of qi. Deficiency of these three organ systems can therefore promote internal retention of phlegm-turbidity and disturbance of qi movement. Persistent phlegm obstruction may in turn impair blood circulation, resulting in combined phlegm and blood stasis obstructing the Lung collaterals. The structural changes that characterize COPD airway remodeling—including epithelial injury, goblet-cell hyperplasia, mucus hypersecretion, airway-wall thickening, fibroblast activation, and ECM deposition—show conceptual correspondence with TCM patterns such as "root deficiency and branch excess," "phlegm-turbidity congesting the Lung," and "phlegm and blood stasis obstructing the Lung."

TCM pathogenesis elements can be conceptually aligned with several modern pathological components of COPD airway remodeling and thereby provide a theoretical framework for TCM intervention. Deficiency of the Lung, Spleen, and Kidney is considered to persist throughout the disease course. Lung-qi deficiency, characterized by weakened exterior defense and impaired protective and reparative functions, corresponds conceptually to recurrent airway epithelial injury, abnormal repair, and EMT. Spleen-qi deficiency leads to impaired transportation and transformation and internal generation of phlegm-dampness and can be related to goblet-cell hyperplasia, mucus hypersecretion, and mucus-plug formation. Kidney deficiency with impaired reception of qi is associated with a prolonged disease course and may be conceptually linked to the chronic progression of airway smooth muscle hyperplasia and airway-wall remodeling. Phlegm-turbidity, regarded as a central pathological product, obstructs the Lung collaterals and parallels mucus hypersecretion and luminal obstruction. Blood stasis obstructing the collaterals is associated with abnormal ECM deposition, pulmonary vascular remodeling, and microcirculatory disturbance. Persistent interaction between phlegm and blood stasis is considered to promote fibroblast activation, collagen deposition, and airway fibrosis, thereby contributing to airway-wall thickening and irreversible airflow limitation. This network of "root deficiency and branch excess" conceptually echoes the previously described processes of inflammatory amplification, oxidative stress, disturbed matrix metabolism, and aberrant repair and provides the TCM pathophysiological rationale for the multi-target interventions discussed below.

Based on the TCM concept of "root deficiency and branch excess," treatment follows the principles of reinforcing healthy qi, eliminating pathogenic factors, and addressing both the root and the manifestations. During the stable phase, deficiency of the Lung, Spleen, and Kidney predominates, while pathological products such as phlegm-turbidity and blood stasis remain in the Lung collaterals. Treatment therefore focuses on strengthening the body's vital functions while also resolving phlegm and removing blood stasis. Common therapeutic methods include tonifying the Lung and augmenting qi, strengthening the Spleen and resolving phlegm, and tonifying the Kidney to support qi reception. Lung-qi deficiency is treated by tonifying Lung qi, consolidating the exterior, and securing the Lung; Spleen deficiency with abundant phlegm is treated by strengthening Spleen qi, drying dampness, and resolving phlegm; and Kidney deficiency with impaired qi reception is treated by tonifying the Kidney and assisting qi reception, warming the Kidney to relieve wheezing, or nourishing the Kidney and securing the Lung. When phlegm and blood stasis coexist and obstruct the Lung collaterals, methods for resolving phlegm, dispersing accumulation, invigorating blood, and unblocking the collaterals are added to reduce airway obstruction and delay disease progression.

Recent studies suggest that a range of Chinese herbal formulas and bioactive constituents may affect multiple processes relevant to COPD, including inflammation, oxidative stress, mucus hypersecretion, abnormal ECM deposition, and structural airway remodeling. This multi-component, multi-target, and multi-pathway mode of action

provides a modern pharmacological rationale for the use of TCM in COPD and for its potential role in delaying airway remodeling.

4. Research Progress on TCM Interventions for COPD Airway Remodeling

4.1. Chinese Herbal Formulas

4.1.1. Classical Formulas

Bufei Decoction consists of Renshen (ginseng), Huangqi (Astragalus), Shudihuang (prepared Rehmannia root), Ziwan (Aster root), Sangbaipi (mulberry root bark), and Wuweizi (Schisandra fruit) and is traditionally used to tonify the Lung and augment qi. A clinical study by Yao et al [53]. reported that this formula reduced MMP-9 and increased TIMP-1 levels in patients with COPD, findings interpreted as indicating attenuation of airway remodeling. Erchen Decoction combined with Sanzi Yangqin Decoction contains prepared Banxia (Pinellia rhizome), Chenpi (tangerine peel), Fuling (Poria), Zisuzi (Perilla fruit), Baijiezi (mustard seed), Laifuzi (radish seed), and related ingredients and is traditionally used to dry dampness, resolve phlegm, direct qi downward, and relieve wheezing. Xing and Chen [54] reported that this combination reduced IL-17 and IL-33 levels and decreased expression of NGF, bFGF, VEGF, and MMP-9 in COPD rats, with associated improvements in airway remodeling and inflammation. Jinshui Liuju Decoction, composed of Danggui, Shudihuang, Chenpi, Banxia, Fuling, and honey-processed Gancan, is traditionally used to nourish yin, resolve phlegm, and strengthen the Spleen to support the Lung. In experimental COPD, the formula reduced MUC5AC secretion and goblet-cell hyperplasia, attenuated mucus hypersecretion, and thereby delayed small-airway remodeling [55].

4.1.2. Empirical and Modified Formulas

Bufei Nashen Pills, composed primarily of Huangqi, Huangjing, Roucongrong, and Xuduan, are used to tonify the Lung and Kidney. In COPD rats, the formula inhibited activation of the PI3K/AKT/HIF-1 pathway, reduced TGF- β 1, IL-6, IL-8, MMP-9, and TIMP-1 levels, modulated the disturbed MMP/TIMP balance, and reduced ECM deposition, thereby improving airway structural remodeling and lung function [56]. Qibai Pingfei Capsules contain Huangqi, sun-dried ginseng, Chuanxiong, Xiebai, Tinglizi, and other herbs and are formulated according to the principles of augmenting qi, strengthening the root, resolving phlegm, and removing blood stasis. In COPD rats, the preparation downregulated pulmonary HIF-1 α and COX-2 protein expression, reduced TNF- α , alleviated inflammatory infiltration of the bronchial lumen and alveolar walls, and improved lung function [57]. Fang et al [58]. additionally reported reduced Rho kinase expression in lung tissue and pulmonary arteries, together with attenuation of pulmonary vascular remodeling. Xie et al [59]. found that Buyuan Decoction modulated NLRP3 inflammasome signaling, reduced pulmonary pathological injury and airway collagen deposition, and thereby improved airway remodeling.

Chinese herbal formulas may exert coordinated effects across multiple targets, pathways, and biological levels, and thus show potential for modulating molecular mechanisms of airway remodeling while improving symptoms and lung function in COPD. However, the current evidence is derived largely from animal studies or small clinical studies and is limited by short treatment durations, heterogeneous outcome measures, and inadequate standardization of herbal preparations. Future work should include large, well-designed randomized controlled trials with long-term follow-up and should incorporate lung function, exacerbation outcomes, and direct indices of airway structure. At present, these formulas are more appropriately considered adjuncts to standard therapy rather than replacements for established treatment.

4.2. Bioactive Constituents of Chinese Herbal Medicines

Research on bioactive constituents of Chinese herbal medicines for COPD has expanded in recent years and includes polysaccharides, flavonoid glycosides, sterols, alkaloids, and other compounds. Most current evidence comes from animal studies, cell

experiments, and network pharmacology, suggesting that some constituents may influence airway-remodeling-related pathology by reducing inflammation and oxidative stress and by correcting abnormalities of matrix metabolism.

Polysaccharides are among the most extensively studied classes of bioactive constituents in COPD. Astragalus polysaccharide, lentinan, and Dendrobium polysaccharides have shown immunomodulatory, anti-inflammatory, and antioxidant activities [60]. In COPD models, Astragalus polysaccharide has been reported to upregulate HO-1, suppress TLR4/NF- κ B signaling, and regulate MMP-9 and TIMP-1 expression, thereby improving ECM metabolic disturbances associated with an altered MMP-9/TIMP-1 ratio [61,62]. Wang et al [63]. reported that Perilla leaf polysaccharide may improve airway inflammation and remodeling in COPD rats through the Wnt/PCP pathway. Collectively, polysaccharides show promise for preventing or attenuating COPD airway remodeling through control of inflammation, reduction of oxidative stress, and regulation of ECM metabolism. However, substantial heterogeneity in polysaccharide source, dose, and experimental models makes direct comparison of effect magnitude difficult.

Flavonoid glycosides and triterpenoids have also been investigated in relation to airway inflammation and remodeling in COPD. Icariin has been reported to increase IL-10, reduce the proinflammatory mediators IL-8 and TNF- α , modulate the MMP-9/TIMP-1 ratio, improve ECM metabolic balance, and attenuate pulmonary fibrosis through inhibition of TGF- β /Smad signaling [64-66]. Ligustrum lucidum fruit contains compounds such as nuzhenide, oleanolic acid, and ursolic acid; related studies suggest that these constituents can influence TGF- β /Smad signaling, reduce TGF- β 1 and Smad3 expression, increase Smad7, and inhibit ASMC proliferation and collagen deposition [67]. However, direct primary evidence for Ligustrum lucidum fruit or its isolated compounds in COPD airway remodeling remains limited, and some conclusions are extrapolated from studies in asthma, pulmonary fibrosis, and other related conditions.

Among sterol compounds, stigmasterol isolated from Coix seed has been studied in COPD model rats. It increased PPAR γ expression, reduced the alveolar macrophage M1/M2 ratio, and improved inflammatory-cell infiltration and alveolar structural injury. These effects were attenuated by a PPAR γ antagonist, suggesting that stigmasterol may act in part through PPAR γ -mediated regulation of macrophage polarization [68]. However, the study primarily assessed lung injury and immunometabolic outcomes and did not directly evaluate airway-remodeling-specific endpoints such as airway-wall thickness, collagen deposition, or goblet-cell metaplasia. The effects of stigmasterol on airway remodeling therefore require validation in studies specifically designed around these endpoints.

With respect to alkaloids and other small molecules, Datura flower has been proposed to regulate multiple aspects of COPD pathology, including cell survival, apoptosis, inflammation, and airway remodeling, through the PI3K-Akt pathway. Available data suggest reduced inflammatory-mediator release, potential cytoprotective effects, decreased ASMC proliferation and collagen deposition, and reduced angiogenesis and vascular permeability [69]. Importantly, Datura flower contains tropane alkaloids such as scopolamine and hyoscyamine, has a narrow therapeutic window, and can cause anticholinergic toxicity. Excessive exposure may lead to dry mouth, mydriasis, tachycardia, and central nervous system symptoms and can be life-threatening in severe cases. Existing studies are based largely on network-pharmacology predictions and preliminary experimental validation, and the effective and safe dose ranges, in vivo metabolic characteristics, and long-term safety remain uncertain. Clinical translation should therefore be approached cautiously and evaluated under strict dose control and toxicity monitoring rather than promoted without adequate evidence. A water extract of processed Arisaema has also been reported to inhibit PI3K/AKT phosphorylation, reduce TNF- α , IL-6, and IL-1 β , and exert anti-inflammatory and lung-protective effects [70].

From a translational perspective, although the current literature provides mechanistic clues for multi-target regulation, the overall evidence remains preclinical and

is insufficient to support definitive therapeutic recommendations. Animal and cell models frequently use short-term inflammation or lung injury as major endpoints, which differ substantially from the long-term, heterogeneous, and incompletely reversible process of airway remodeling in patients with COPD. Some studies assess signaling pathways and inflammatory mediators but do not include clinically relevant structural or functional endpoints such as airway-wall thickness, collagen deposition, smooth muscle hyperplasia, mucous gland remodeling, or sustained changes in lung function. Considerable heterogeneity also exists in compound purity, extraction methods, dosing, treatment duration, and model construction. In addition, some conclusions are based on network-pharmacology predictions or indirect evidence from asthma and pulmonary fibrosis, creating a risk of mechanistic over-extrapolation and overestimation of efficacy. For high-molecular-weight constituents such as polysaccharides, *in vivo* absorption, tissue distribution, and the actual material basis of pharmacological activity remain incompletely defined, and isolated active compounds cannot be assumed to be equivalent to complete formulas or crude medicinal materials. Future research should strengthen quality control, pharmacokinetic characterization, and dose-response evaluation, verify causal mechanisms using pathway inhibition or gene-knockout approaches, and adopt standardized airway-remodeling endpoints with longer follow-up. Before clinical implementation, hepatotoxicity, nephrotoxicity, long-term safety, and interactions with conventional therapies such as bronchodilators and inhaled corticosteroids should be carefully evaluated. High-quality randomized controlled trials stratified by patient phenotype or endotype are also needed.

5. Discussion and Future Perspectives

5.1. Strengths of the Current Research Landscape

Research on TCM interventions for COPD airway remodeling has developed a growing theoretical and experimental basis. A key potential advantage is the multi-component, multi-target nature of TCM formulas, which may simultaneously regulate pathways such as TGF- β 1/Smad, NF- κ B, and PI3K/Akt/mTOR. This profile is potentially relevant to the multifactorial mechanisms of airway remodeling, including inflammation, oxidative stress, and fibrosis. Available clinical studies also suggest generally acceptable tolerability, particularly when TCM is used as an adjunct to conventional therapy. However, these findings require confirmation in larger, multicenter trials.

5.2. Current Problems and Limitations

Several limitations continue to hinder clinical translation. Most mechanistic studies rely on cigarette-smoke- or lipopolysaccharide-induced animal models, which cannot fully reproduce the heterogeneity of COPD across disease stages, inflammatory phenotypes, and comorbidities. Therefore, extrapolation to clinical practice remains limited.

The active material basis and molecular targets of many herbal formulas are also incompletely defined. Although network pharmacology and molecular docking provide useful hypotheses, experimental validation remains insufficient, while variability in herb sources, processing, and batch composition may reduce reproducibility. In addition, many clinical trials are limited by small sample sizes, short follow-up, and methodological weaknesses. Most studies emphasize lung-function outcomes rather than direct structural indicators of airway remodeling, leaving the evidence for specific anti-remodeling effects incomplete.

5.3. Future Directions

Future studies should integrate TCM theory with advanced experimental and clinical technologies. More clinically relevant models, including organoids, patient-derived primary cells, and multicellular co-culture systems, may help clarify relationships between TCM syndrome patterns and airway remodeling. Mechanistic research should strengthen causal target validation using single-cell sequencing, spatial transcriptomics,

and multi-omics approaches. These methods may help define the cellular and molecular basis of TCM concepts such as phlegm, blood stasis, and deficiency of the Lung, Spleen, and Kidney. A multidimensional evaluation framework is also needed. Quantitative CT, functional imaging, and artificial-intelligence-based image analysis could be combined with airway-remodeling biomarkers and TCM syndrome assessments to establish more objective outcome measures.

Finally, large, multicenter, randomized controlled trials should incorporate structural biomarkers, quantitative imaging, and standardized TCM syndrome criteria. Stratification by syndrome type, imaging phenotype, and molecular phenotype may further improve the rigor and translational relevance of TCM interventions for COPD airway remodeling.

6. Conclusion

Airway remodeling is a central structural basis of progressive and difficult-to-reverse airflow limitation in COPD and is driven by an interconnected network involving chronic inflammation, oxidative stress, EMT, abnormal ECM deposition, and fibrosis. Within the TCM framework of "root deficiency and branch excess," therapeutic strategies emphasize reinforcing healthy qi, eliminating pathogenic factors, resolving phlegm, and removing blood stasis. Chinese herbal formulas, bioactive constituents, acupuncture, and acupoint application have been reported to regulate key pathways such as TGF- β 1/Smad, NF- κ B, Nrf2/HO-1, and PI3K/Akt through multiple targets and pathways, with potential effects on airway-wall thickening, collagen deposition, mucus hypersecretion, and smooth muscle proliferation. However, current evidence is derived predominantly from preclinical studies and small clinical investigations. The conceptual mapping between TCM pathogenesis and modern pathological mechanisms requires further refinement, and substantial gaps remain in evidence quality and clinical translation. Future research should combine TCM theory with organoid systems, multi-omics technologies, and quantitative imaging; conduct high-quality, stratified clinical studies; and develop evaluation frameworks that integrate TCM characteristics with objective modern endpoints, thereby advancing TCM research on COPD airway remodeling from mechanistic exploration toward evidence-based translation.

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