International Journal of Chronic Obstructive Pulmonary Disease

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

The Mechanism of Traditional Chinese Medicine and Natural Medicine in Treating Chronic Obstructive Pulmonary Disease

Lei Li[1,*], Xiao-Feng Liu[1,2,*], Zhi-Fang Cui[1], Heng Zou[1], Shu-Ling Liu[1,2], Hong-Wu Wang[1]

[1]Respiratory Disease Center, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, 101121, People's Republic of China; [2]Beijing University of Chinese Medicine, Beijing, 100029, People's Republic of China

*These authors contributed equally to this work

Correspondence: Hong-Wu Wang; Shu-Ling Liu, Respiratory Disease Center, Dongzhimen Hospital, Beijing University of Chinese Medicine, No. 116 Cuiping West Road, Tongzhou District, Beijing, 101121, People's Republic of China, Email wanghongwu2015@126.com; 553638521@qq.com

Ethnopharmacological Relevance: Chronic obstructive pulmonary disease (COPD) is one of the crucial chronic diseases that seriously endangers the health of residents in China. There is a complex mechanism of the pathogenesis of COPD, and no specific drugs are currently available to reverse the progressive decline in lung function during the natural course of COPD. Traditional Chinese Medicine (TCM) not only alleviates clinical symptoms, but also leads to fewer adverse reactions. However, the mechanism of action of TCM in COPD treatment remains unclear.

Aim: To summarize the mechanisms of action of Chinese herbal compounds and natural drugs in the treatment of COPD and identify potential signaling pathways and targets that can provide preclinical evidence for the treatment of COPD.

Methods: Literature was retrieved from the scientific databases PubMed, Web of Science, and CNKI, Wanfang Data Knowledge Service Platform, and VIP Chinese Science and Technology Journal from July 2007 to December 2023.

Results: This study introduced the specific pathways, targets and mechanisms of TCM in treating COPD from the perspectives of inhibiting inflammation, reducing oxidative stress, and regulating autophagy.

Conclusion: This study provides a comprehensive summary of the theories of Chinese medicine in treating COPD, which utilize multiple targets and pathways to display the advantages of Chinese medicine. This lays the foundation for further exploration of pathways related to Chinese medicine for the treatment of COPD.

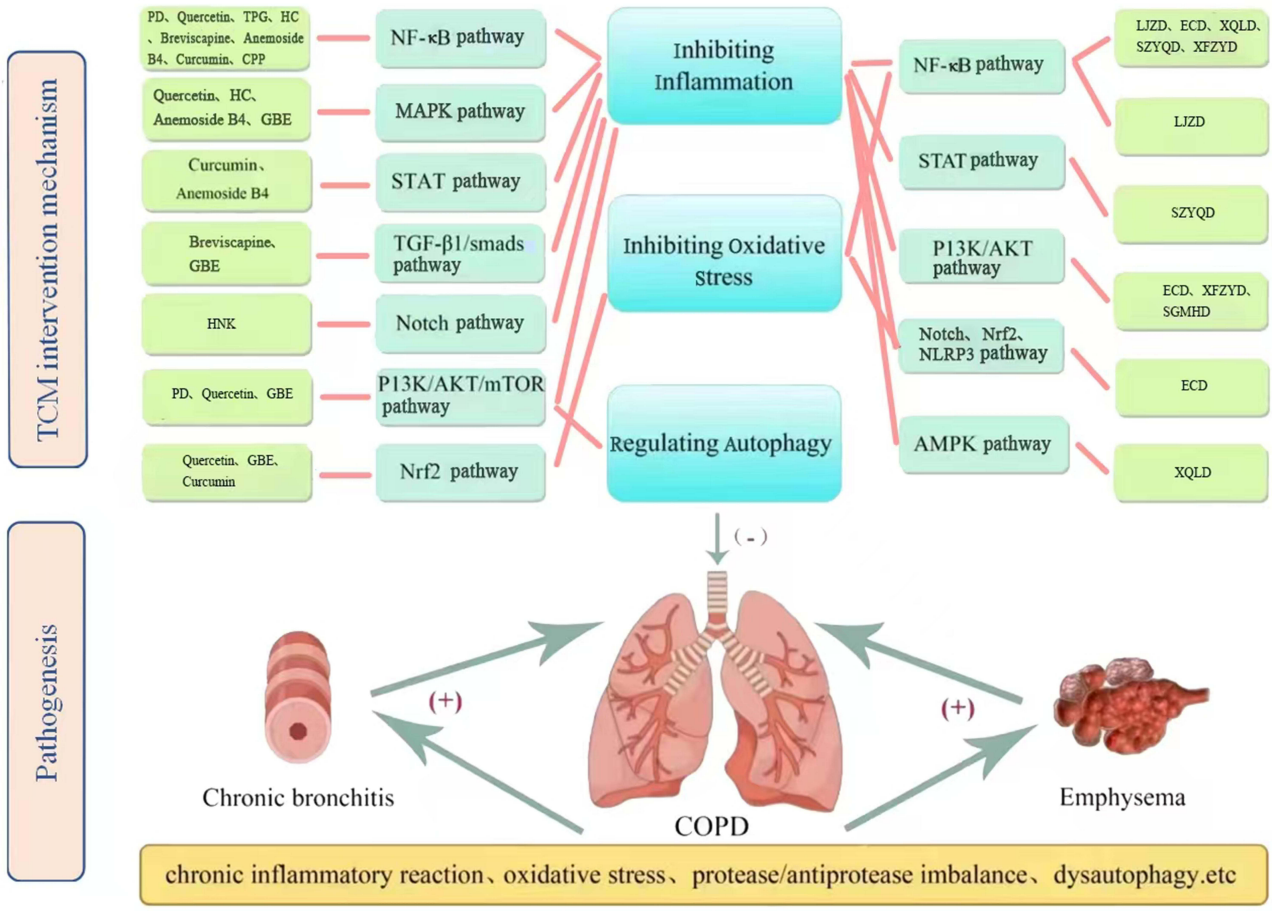
Keywords: chronic obstructive pulmonary disease, traditional chinese medicine, chinese herbal monomers, mechanism, therapeutic target pathway

Introduction

Chronic obstructive pulmonary disease (COPD) includes chronic bronchitis, emphysema, and small airway obstruction. Incompletely reversible airflow limitation, inflammation, excessive mucus secretion and bronchial mucosal epithelial lesions are the main pathological basis of the disease, which usually caused by extensive inhalation of deleterious particles or fumes.[1,2] COPD is a crippling disease with a high worldwide prevalence. It is the fifth-leading cause of death worldwide and estimated to become the third-leading cause of death by 2030.[3] And COPD has also become one of the leading causes of death in China.[4] As of 2017, 13.7% of people over the age of 40 in China were living with COPD.[5] Clinically, COPD is divided into acute exacerbation and stable periods, commonly treated with oxygen therapy combined with inhaled corticosteroids, bronchodilators, antibiotics, and other medications. In addition to the necessary medications, exercise and active patient counseling to quit smoking have also been emphasized.[1,6] Although these treatments can alleviate patients' symptoms of breathing difficulties to some extent, no specific drugs are available that can reverse the progressive decline in breathing ability during the natural course of COPD currently,[7] and the adverse reactions cannot be ignored.

Received: 5 February 2025
Accepted: 12 April 2025
Published: 26 April 2025

Graphical Abstract



Traditional Chinese medicine (TCM) has shown certain advantages in intervening in COPD, especially in playing a significant role during the stable phase.[8] TCM adheres to the principles of treatment, based on syndrome differentiation and a holistic approach. In treating diseases, the focus is on the individual rather than on the disease itself, and TCM can achieve good therapeutic effects. Previous research suggests that TCM may improve symptoms mainly by inhibiting airway inflammation and relieving oxidative stress, but its mechanisms of action remain unclear.[9,10] Therefore, this review summarizes the mechanisms of Chinese herbal monomers and compound formulas for the treatment of COPD. As of December 2023, we systematically searched two international authoritative databases, PubMed and Web of Science, as well as three Chinese core databases, China National Knowledge Network (CNKI), Wanfang Data Knowledge Service Platform, and VIP Chinese Science and Technology Journal Database. First, the keyword combination search strategy (COPD [Mesh] AND ("Chinese herbal monomers" OR "TCM") was used, and 2924 articles were initially obtained. Then, through supplementary search of keywords such as "mechanism" and "therapeutic target pathways" and based on the quick browsing of titles/abstracts, 192 articles focusing on the study of classical Chinese medicine compounds and monomers were screened. Further through the full text reading and quality evaluation, 95 high-quality papers meeting the research requirements were finally included.

TCM's Understanding of COPD

TCM has a history of more than 3,000 years, and although there was no explicit term "COPD" in ancient times, it falls under the category of "lung expansion" or "dyspnoea" according to its clinical characteristics. TCM considers COPD to be a disease of deficiency in the body coupled with pathogenic factors, and its pathogenesis is mainly related to deficiencies in the lungs, spleen,

and kidneys and is associated with phlegm and blood stasis. Hence, specific treatment methods include tonifying qi, strengthening the spleen, tonifying the lung and benefiting the kidney, eliminating phlegm, and transforming stasis. Many classic texts such as Treatise on Cold Pathogenic Diseases and Synopsis of the Golden Chamber clearly record the theories of TCM and the corresponding herbal prescriptions for COPD. In recent years, research on the treatment of COPD with TCM has become increasingly standardized. Clinical studies have shown that monomers of Chinese herbal medicines have been proven to control or improve COPD. We have summarized the monomers that have been proven to improve COPD in clinical practice (shown in Table 1). In addition, TCM herbal formulas can improve clinical symptoms and pulmonary function, and reduce acute exacerbations through methods such as tonifying the lung, strengthening the spleen, nourishing the kidney, promoting blood circulation to remove blood stasis, and resolving phlegm[11] (shown in Table 2).

Table 1 The Mechanism of Plant Medicine in Treating COPD

Plant Medicine	TCM	Mechanism	Signal Pathway	Cytokine Modulation
Polydatin	Reynoutria japonica	Suppressing inflammatory response	Inhibiting the PI3K/AKT/mTOR and the NF-κB signaling pathways[12–14]	Reducing the levels of TNF-α, IL-8 and IL-1β[12–14]
Honokiol	Magnolia officinalis	Suppressing inflammatory response	Inhibiting the Notch signaling pathways[15]	Reducing the Th1/Th2 and Th17/Treg ratios[15]
Quercetin	Ginkgo biloba	Promoting autophagy, inhibiting oxidative stress and suppressing inflammatory response	Inhibiting the PI3K/AKT/mTOR pathway,[16] activating the Nrf2 signaling pathway,[17] and inhibiting the NF-κB and MAPK pathways[18]	Inhibiting the expression of MDA and ROS,[17] reducing the levels of TNF-α, IL-1, IL-6, and MUC5AC[18,19]
Total Paeony Glycoside	Paeonia	Suppressing inflammatory response	Inhibiting the NF-κB pathways[20,21]	Reducing the levels of TNF-α, IL-1β, IL-6[20,21]
Houttuynia cordata	Houttuynia cordata	Suppressing inflammatory response	Inhibiting the NF-κB and MAPK pathways[22–24]	Reducing the levels of TNF-αand IL-6,IL-1β[22–24]
Breviscapine	Shortscape fleabane	Inhibiting inflammatory response	Inhibiting the NF-κB and TGF-β1/Smad2/3 pathways[25,26]	Reducing the levels of MMP-9, TGF-β and Smad3 mRNA, improving the levels of Smad 7 Mrna[25,26]
Anemoside B4	Pulsatilla chinensis	Regulating inflammatory response	Inhibiting the MAPK and the NF-κB pathways,[27,28] Inhibiting the IL-12/STAT4, activating the IL-4/STAT6 signaling pathways[29]	Reducing the levels of TLR4, MyD88, and MD2, as well as the expression of IL-12, T-bet, and STAT4 mRNA and protein, thereby inhibiting the immunological hyperactivity of Th1 cells;[27,28] increasing the expression of IL-4, GATA3, and STAT6 mRNA[29]
Ginkgo Biloba Extract	Ginkgo biloba	Inhibiting inflammation response, promoting autophagy and inhibiting oxidative stress	Inhibiting the P38 MAPK, TGF-β1/Smad[30,31]and PI3K/Akt/mTOR signaling pathways,[32] activating the Nrf2 signaling pathways[33]	Reducing the levels of TNF-α, TGF-β; Suppressing MUC5AC and EGFR levels, modulating the balance of MMPs/TIMPs;[30,31] inhibiting the expression of Akt, p-Akt, and mTOR;[32] increasing Nrf2 levels and upregulating HO-1[33]
Curcumin	Arisaema heterophyllum, Turmeric Root - tuber	Inhibiting inflammatory response and oxidative stress	Inhibiting the NF-κB and STAT signaling pathways,[34–37] activating the Nrf2 signaling pathways[34,38]	Reducing the levels of IL-1,IL-5,IL-6,IL-8, increasing IL-10 levels;[37]increasing the expression of γ-GCS,HO-1,GPX-1 and HDAC2[34,38]
Codonopsis Pilosula Polysaccharides	Codonopsis pilosula	Suppressing inflammatory response	Inhibiting the NF-κB signaling pathways[39]	Reducing the levels of TNF-α, IL-3, IL-6[39]

https://doi.org/10.2147/COPD.S518248

Table 2 The Mechanism of Herbal Formulas in Treating COPD

Herbal Formulas	Composition of Chinese Medicine	Mechanism	Signal Pathway	Cytokine Modulation
Liu Junzi Decoction	Dang Shen, Bai Zhu, Fu Ling, Ban Xia, Chen Pi, Gan Cao	Inhibiting inflammatory responses; Inhibiting oxidative stress	Inhibiting the NF-κB signal pathway[40–42]	Reducing IL-1β, IL-6, and TNF-α;[40,41] Reducing NOX4, MMP-9[43]
Xiao Qing Long Decoction	Ma Huang, Gui Zhi, Gan Jiang, Xi Xin, Shao Yao, Gan Cao, Wu Wei Zi, Ban Xia	Alleviating inflammatory responses and inhibiting oxidative stress	Inhibiting the NF-κB signal pathway;[44,45] Activating the AMPK/mTOR signaling pathway[46]	Reducing miR-145, CX3CL1, IL-6, IL-4[47],TLR4,MyD88mRNA[48]Reducing TGF-β1, MMP-9;[44,47] Reducing γ-GCS.[45] Increasing the expression of AMPK, mTOR and p-mTOR[46]
Erchen Decoction	Ban Xia, Chen Pi, Fu Ling, Gan Cao, Sheng Jiang, Wu Mei	Alleviating inflammatory responses; Inhibiting oxidative stress	Inhibiting the Midkine/Notch2/Hey1 signaling pathway[49]; Inhibiting the Jagged1/Notch1/Hes1 signaling pathway[50];Inhibiting the PI3K/Akt, NF-κB, NLRP3 signaling pathway;[51–53] Activating the Nrf2 pathway[51]	Downregulating downstream inflammatory mediators[51–53]
San Zi Yang Qin Decoction	Bai Jie Zi, Zi Su Zi, Lai Fu Zi	Inhibiting inflammatory responses	Inhibiting the STAT6-SPDEF-MUC5AC pathway[54] and the NF-κB pathway[55]	Reducing the expression of IL-4, STAT6, and protein of SPDEF, as well as the gene expression levels of STAT6 and MUC5AC,[54] Reducing hs-CRP, IL-6,TNF-α[56]
Xue Fu Zhu Yu Decoction	Tao Ren, Hong Hua, Dang Gui, Sheng Di Huang, Niu Xi, Chuan Xiong, Jie Geng, Chi Shao, Zhi Qiao, Gan Cao, Chai Hu	Inhibiting inflammatory responses	Inhibiting the PI3K/AKT pathway[57] and the NF-κB pathway[58]	Reducing the levels of TNF-α, IL-1β, IL-8, IL-17[58]
She Gan Ma Huang Decoction	Ma Huang, Sheng Jiang, Da Zao, Xi Xin, Kuan Dong Hua, Zi Wan, Ban Xia, Wu Wei Zi, She Gan	Inhibiting inflammatory responses	Inhibiting the EGFR/PI3K pathway[59]	Reducing TNF-α, IL-6, IL-1β, PI3K, EGFR mRNA and protein of PI3K and EGFR[59]

Mechanism of Action

The pathogenesis of COPD is mainly related to chronic airway inflammation, oxidative stress, and autophagy. Plant medicines and herbal formulas regulate these pathological mechanisms through multiple pathways and targets that can exert therapeutic effects in COPD (Figure 1).

Plant Medicine (Extracts or Active Constituents)

Polydatin

Polydatin (PD) is a monomeric polyphenol extracted from the rootstock of Polygonum cuspidatum. In the treatment of respiratory diseases, it primarily exhibits anti-asthmatic effects, inhibits fibrosis, reduces pulmonary edema, and alleviates lung injury, among other broad pharmacological actions. These properties are related to their antioxidant, anti-inflammatory, and improved pulmonary blood flow properties.[60] Studies have elucidated that PM2.5 exposure can trigger airway inflammation in macrophages, a process that may ultimately lead to the development of COPD. Long-term exposure to PM2.5, increases the number of macrophages and leukocytes in the lung, with increasing inflammatory cells

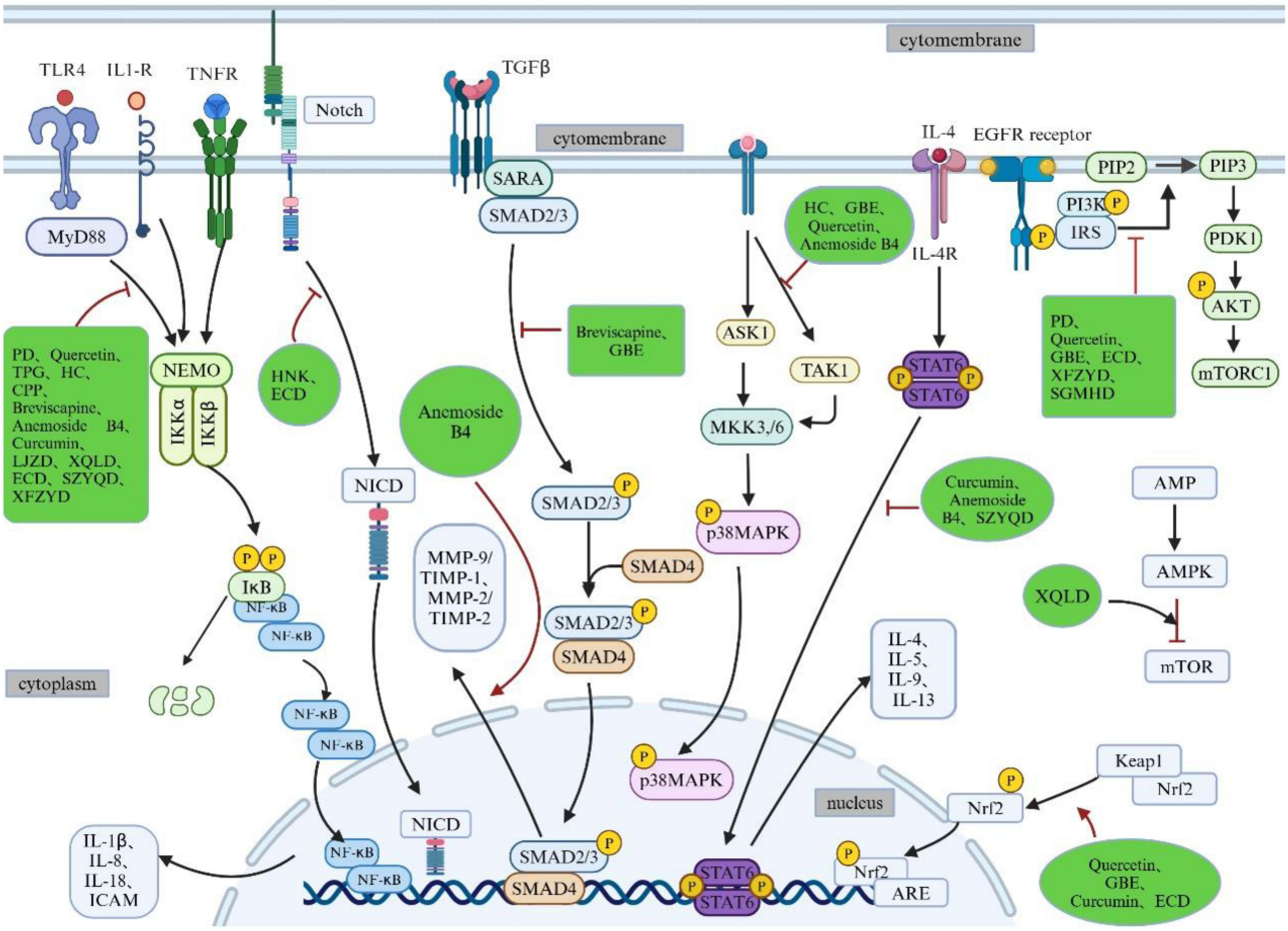


Figure 1 The mechanism of TCM monomer and compound in treating COPD. The characteristics of TCM monomers and prescriptions in the treatment of COPD are reflected in multi-target and multi-level regulation. (The green square and circle in the figure represent the TCM monomers and prescriptions participating in this pathway, and the continuous arrow lines represent the signal flow. The red arrow represents the activation effect, and the line similar to the "T" shape represents the inhibitory effect.).

and thickening of the alveolar walls. However, after eight weeks of polydatin administration, thickening of the alveolar walls and airway inflammation was reduced. The pro-inflammatory cytokine TNF-α and mRNA levels of IL-1β were decreased, indicating that polydatin can suppress airway inflammation.[61] Furthermore, by impeding the PI3K/AKT/mTOR and TLR4/NF-κB signaling pathways, polydatin effectively reduces the levels of inflammatory mediators, including TNF-α, IL-8, and IL-1β. This results in a decrease in airway inflammatory responses, improvement in lung and bronchial tissue morphology, and reduction in bronchial wall and smooth muscle thickness, thus exerting a protective effect against lung damage.[12–14]

Honokiol

Honokiol (HNK) is a bisphenol compound, possessing various biological activities, including anti-inflammatory, anti-tumor, antibacterial, anti-angiogenic, and the neuroprotective effect.[62,63] Its potential for treating COPD may be associated with its anti-inflammatory effects, inhibition of oxidative stress, and modulation of immune function. Cigarette smoke is a well-known culprit that can induce damage to airway epithelial cells, a pivotal step in the pathogenesis of COPD. Studies have shown that HNK exerts a significant anti-inflammatory action by reducing the expression and secretion of inflammatory cytokines (such as TNF-α, IL-1β, IL-6, and IL-8), thereby improving bronchial epithelial cell damage.[64,65] HNK also reduced lung injury by regulating oxidative stress. An increase in mitochondrial reactive oxygen species (ROS) production and decrease in mitochondrial ATP generation are considered key factors in the pathophysiology of COPD. CSE can increase ROS levels in bronchial epithelial (BEAS-2B) cells and inhibit mitochondrial function. However, HNK can counteract these detrimental

effects. It effectively lowers ROS levels and restores the normal function of mitochondria, thereby safeguarding the lung tissue.[63] In terms of immune regulation, experiments have demonstrated that HNK can correct the imbalance of Th1/Th2 and Th17/Treg cells to reduce the Th1/Th2 and Th17/Treg ratios in COPD mice by inhibiting the activation of the Notch signaling pathway in splenic T cells. Simultaneously, it suppresses the excessive inflammatory response triggered by the Th1/Th2 cell imbalance. This action weakens the immune response mediated by Th17 cells and enhances the immunosuppressive function of Treg cells. As a result, HNK contributes to the improvement of lung function, offering a promising therapeutic approach for managing COPD.[66]

Quercetin

Quercetin is a natural flavonoid that has many effects, including antioxidant anti-tumor, anti-infection, anti-inflammatory, and antiviral.[67] Quercetin has demonstrated its potential in multiple ways in the context of COPD. For instance, it has been found to enhance lung function in COPD mice. It promotes autophagy, which is a crucial cellular process, and remarkably suppresses the oxidative stress induced by CSE. It also enhances the survival rate of COPD cell models, suppresses apoptosis, regulates immunity, and reduces the levels of inflammatory factors and extracellular matrix damage-related factors.[15,68] This is mainly achieved through the regulation of the PI3K/AKT/mTOR, Nrf2, TLR4/ NF-κB and MAPK pathways.

Autophagy is important for the treatment of chronic lung diseases. Inhibition of the PI3K/AKT/mTOR pathway in COPD mice promotes autophagy and reduces alveolar epithelial cell apoptosis.[69] Moreover, inhibiting this pathway can suppress the expression of inflammatory factors and airway remodeling, thereby improving COPD.[16,70,71]

When it comes to oxidative stress, quercetin's regulatory process is closely tied to the activation of the Nrf2 signaling pathway. In COPD mice treated with CSE, the levels of malondialdehyde (MDA) and ROS were elevated, yet quercetin managed to reverse this situation. It also alleviated the mitochondrial morphological alterations caused by cigarette smoke, safeguarding against lipid peroxidation.[72] High matrix metalloproteinase (MMP) levels are associated with the occurrence and progression of emphysema in COPD patients. Studies have found that quercetin prevents more serious destruction of the alveolar wall by inhibiting the levels of MMP induced by LPS, thereby slowing the progression of emphysema in mice.[73]

The TLR4/ NF-κB and MAPK pathways participate in the inflammatory response. Experiments have confirmed that quercetin inhibits the NF-κB and MAPK pathways in a CSE-induced mouse model by decreasing the levels of κB, IκB kinase, extracellular signal-regulated kinase (ERK), and p38 proteins, thereby inhibiting the activation of inflammatory factors. This ultimately alleviates COPD airway remodeling and prevents disease progression.[74] Additionally, by inhibiting the EGFR/PI3K/PKC/ AKT/NF-κB pathway, quercetin reduces the level of MUC5AC, inhibiting the excessive secretion of airway mucus.[17]

Furthermore, quercetin can also alleviate airway remodeling by regulating the balance of Th17 and Treg cells in COPD rats, significantly reducing the levels of the apoptotic proteins cytoC, Bax, Caspase-9 and Caspase-3, and affecting the activation of NF-κB p65, thus regulating cell apoptosis and other effects.[75]

Total Paeony Glycosides

Total Paeony Glycosides (TPG) are the main active component of red peony roots, including paeoniflorin, albiflorin, oxypaeoniflorin, benzoylpaeoniflorin, and apiopaeoniflorin.[18] They possess a broad spectrum of beneficial properties, demonstrating anti-cancer, anti-thrombotic, immune-enhancing, and protective capabilities in multiple vital organs including the heart, brain, liver, and kidneys.

In COPD treatment, TPG reduced inflammatory responses by reducing the TLR/MyD88/ NF-κB pathway. NF-κB is a key nuclear transcription factor downstream of TLR4 signaling that can promote the secretion of interleukins and other inflammatory factors, causing acute inflammatory responses and overexpression of inflammatory factors. Research investigations have unequivocally revealed that following TPG intervention, the levels of TNF-α, IL-1β, and IL-6 in COPD rats were reduced, along with decreased levels of TLR4, MyD88, and p-NF-κB p65. Moreover, experimental results showed that after applying TPG, the levels of apoptotic factors, such as Bcl-2, Bax, and Caspase-3, were reduced, indicating that TPG can inhibit inflammatory responses and decrease apoptosis of lung tissue cells, thereby improving lung damage.[18,19]

Houttuynia Cordata

Houttuynia has enjoyed a long history of extensive utilization as both a herbal remedy and a foodstuff since ancient times. The extract derived from Houttuynia cordata (HC) has been harnessed to combat a diverse array of diseases. Its pharmacological prowess primarily manifests in antiviral, anticancer, anti-allergic, anti-inflammatory capabilities.[76] In the realm of treating COPD, HC takes center stage with its remarkable anti-inflammatory function. This is accomplished by effectively suppressing the NF-κB and MAPK pathways. The NF-κB pathway occupies a pivotal position in modulating immunity and inflammation, while the MAPK pathway is equally crucial in orchestrating inflammatory reactions. When tissue damage occurs, the principal constituents of the MAPK subfamily, namely ERK, p38, and JNK spring into action and work in concert to regulate the inflammatory process.[20,21,77] Experiments have demonstrated that HC inhibits the TLR4/NF-κB and MAPK pathways to reduce the release of proinflammatory factors, thereby significantly reducing the levels of TNF-α, IL-6, and IL-1β. As a result, a marked improvement in lung function has been observed in rats afflicted with acute exacerbations of COPD, along with a pronounced alleviation of pathological lung damage. Such findings underscore the potential of HC as a valuable therapeutic agent for COPD.[22,23]

Breviscapine

Breviscapine represents a total flavonoid extract sourced from Shortscape fleabane. It harbors a range of pharmacological activities, such as ameliorating the body's hypercoagulable state, modulating oxidative stress responses, and tempering inflammatory reactions.[22] In the context of treating COPD, its therapeutic efficacy is manifested mainly through improving airway remodeling, bolstering the immune system, and decelerating the decline in lung function.

Airway epithelial cell proliferation is a key factor contributing to the thickening of the tracheal wall, airway remodeling, and hyperreactivity, all of which constitute central aspects of the pathogenesis of COPD. Research has shown that breviscapine can observably restrain the transcription and translation levels of the TNF-α/TNFR/NF-κB pathway in COPD model mice, thereby suppressing inflammatory responses.[24] Breviscapine inhibits the proliferation of airway smooth muscle cells (ASMC) mainly by suppressing the TGF-β1/Smad2/3 pathway, thereby inhibiting inflammatory responses and improve COPD airway remodeling.[78] Fibrotic airway remodeling reflects various chronic lung diseases, including COPD, characterized by basement membrane thickening and excessive deposition of fibrotic extracellular matrix (ECM) proteins (collagen, fibronectin, and laminin).[79] MMP-9 is a protease associated with COPD, and its primary physiological function is degradation of ECM components. An increase in MMPs can lead to degradation of the alveolar wall basement membrane and the occurrence of emphysema. Moreover, it promotes the proliferation of fibroblasts and smooth muscle cells through autocrine secretion. In this process, there is excessive activation of the TGF-β1/Smad2/3 pathway, while breviscapine can inhibit it to improve the deposition of ECM,[25,78] and by inhibiting the TNF-α/NF-κB pathway and reducing the levels of MMP-9, TGF-β, and Smad3 mRNA in the lung tissue of COPD rats, increasing the level of Smad7 mRNA, reducing the excessive multiplication of ASMC and the thickness of the bronchial wall and collagen fibers in COPD rats, thereby reducing airway resistance and inhibiting airway remodeling.[24,78] Breviscapine has therapeutic potential for AECOPD, as it can upregulate CD3+T cells, CD4+T cells, CD4+T/CD8+T ratio, immunoglobulin IgA, and immunoglobulin IgG content, and downregulate CD8+T cell content,[26,80] enhancing the body's immune function.

Anemoside B4

Anemoside B4 is one of the primary monomeric components of Pulsatilla chinensis and exhibits anti-inflammatory, antioxidant, and anti-apoptotic effects.[81] Its therapeutic role in treating COPD primarily involves alleviating inflammatory responses, regulating immunity, maintaining the balance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), and mitigating oxidative stress.

Chronic inflammation is a consistent feature throughout the development of COPD, with TNF-α being one of the earliest inflammatory cytokines released during the inflammatory response, which then promotes the release of other cytokines, such as IL-6 and IL-1β through cascading reactions. Studies have found that Anemoside B4 can reduce the release of inflammatory factors in lung tissues of COPD rats and inhibit the occurrence and development of COPD inflammation by suppressing the level of proteins in connection with the MAPK and TLR4/Myd88 pathways, reducing corresponding inflammatory factors such as TLR4, MyD88, and MD2.[82,83]

In terms of regulating anti-inflammatory immunity, Anemoside B4 achieves its effect by inhibiting IL-12/STAT4 pathway and promoting IL-4/STAT6 pathway. Transcription proteins (STATs) are signal transducers and activators, which play key

regulatory roles in various biological processes. CD4 T cells differentiate into Th1 cells by activating STAT4 through IL-12, and Th2 cells by activating STAT6 through IL-4. Experimental results from COPD rats treated with Anemoside B4 showed that it significantly reduced the expression of IL-12, T-bet, and the mRNA and protein of STAT4, thereby inhibiting the immunological hyperactivity of Th1 and increasing the levels of IL-4, GATA3, and STAT6 mRNA as well as the protein expression of STAT6, to enhance the immune function of Th2.[84]

Matrix metalloproteinases (MMPs) act a vital role in vivo as a series of enzymes capable of degrading extracellular matrix (ECM) components. Tissue inhibitors of metalloproteinases (TIMPs) are specific inhibitors of MMP activity that act as cell growth factors, promoting fibroblast proliferation and collagen synthesis, leading to ECM deposition and inhibition of its degradation.[81] Therefore, TIMPs are markers of airway fibrosis and reflect the airway repair and inflammatory processes. The MMP-9/TIMP-1 ratio was found to be the best predictive indicator of emphysema. Anemoside B4 significantly down-regulated the expression of MMP2, MMP12, and TIMP1 in lung tissues, increased the gene expression level of MMP9, and increased the MMP9/TIMP1 ratio, thereby alleviating the onset and progression of COPD.[81,84]

Additionally, Anemoside B4 can also improve the COPD oxidative irritable reaction, which is achieved by significantly reducing the expression of MDA and MPO in COPD lung tissues, enhancing GSH-PX enzyme activity, and balancing the content of oxidants and antioxidants,[81,83] thereby lessening the oxidative stress damage resulting from COPD.

Ginkgo Biloba Extract

Ginkgo biloba extract (GBE) is a mixture with unique pharmacological activities extracted from the TCM Ginkgo biloba, containing a lot of chemistry for example flavonoids, terpenoid lactones, and organic acids. It possesses major pharmacological effects, including antioxidant, free-radical scavenging, circulation improvement, antiplatelet aggregation, and neuroprotective functions.[27] In the treatment of COPD, GBE can effectively inhibit the infiltration of inflammatory cells in the alveolar pulmonary artery wall, proliferation of vascular smooth muscle cells, suppression of pulmonary vascular remodeling, and reduce airway inflammation,[28,29] which restrains the P38 MAPK, TGF-β1/Smad, PI3K/Akt/mTOR pathways, and activates the Nrf2 signaling pathway.

By effectively inhibiting the P38 MAPK and TGF-β1/Smad pathways, GBE is able to bring down the levels of inflammatory cytokines like Tumor Necrosis Factor-α (TNF-α) and Transforming Growth Factor-β (TGF-β) in COPD rats. Moreover, it suppresses the protein expression of MUC5AC and Epidermal Growth Factor Receptor (EGFR) in lung tissue. As a result, it not only subdues both airway and systemic inflammatory responses, but also ameliorates pulmonary vascular remodeling and mitigates the excessive secretion of airway mucus.[85,86] At the same time, GBE can regulate the balance of MMPs/TIMPs, reduce the levels of MMP-9 and TIMP-1 in the lung tissue of COPD rats, and prevent and reduce lung tissue remodeling and fibrosis in COPD mice.[86]

The PI3K/Akt/mTOR pathway plays a critical role in regulating cell growth, proliferation, differentiation, autophagy, and apoptosis and is significant in COPD.[69] Alveolar macrophages are crucial for clearing bacteria on the alveolar surface and preventing infections caused by microorganisms; however, there is a defect in the autophagy function of macrophages in COPD patients.[87] Experiments have shown that compared to the model group, rats with COPD treated with GBE had reduced protein expression levels of PI3K p110α, Akt, p-Akt, mTOR, and p-mTOR in alveolar macrophages; increased LC3-II/LC3-I ratio; enhanced autophagy in macrophages; accelerated clearance of excess, damaged, and aged proteins and organelles; ensured normal macrophage function; and restrained abnormal aggregation of macrophages in the airways and lung parenchyma of COPD rats, thereby reducing macrophage-mediated inflammatory reactions, alveolar damage, and airway remodeling.[30]

The Nrf2 pathway plays a role in oxidative stress, and GBE activates the ERK, JNK, and p38 pathways by enabling the Nrf2 pathway, increasing Nrf2 levels, and achieving antioxidant, anti-apoptotic, and cytoprotective effects in COPD.[31]

Curcumin

Curcumin is a polyphenolic compound extracted from various ginger and aroids, and has anti-inflammatory, anti-oxidative, and anti-cancer effects. It improves COPD by regulating the balance between inflammatory and anti-inflammatory factors, oxidative stress, and equilibrium of Th17 and Tregs.[32]

In terms of anti-inflammation and angiogenesis inhibition, curcumin achieves this by inhibiting the TLR4/ NF-κB and STAT pathways.[32–34,88] Persistent inflammatory stimuli can lead to angiogenesis, with various inflammatory factors activating signal transduction and STAT pathways, upregulating angiogenic mediators such as VEGF, FGF-2, and HIF1, leading to blood vessel formation. Curcumin can suppress the level of NF-κB; downregulate inflammatory cytokines such as IL-1, IL-5, IL-6, and IL-8; upregulate anti-inflammatory factors such as IL-10; and suppress the STAT pathway, affecting the expression of PCNA in pulmonary arterioles. This significantly reduced airway inflammation and remodeling in rats with COPD, thereby improving lung function and reducing lung tissue damage.[34]

Regarding anti-oxidative stress, The Nrf2-ARE signaling pathway is currently the most important endogenous antioxidant stress pathway. Curcumin activates the Nrf2 pathway, inducing the expression of downstream genes such as γ-GCS, HO-1, and GPX-1. It also upregulates HDAC2 activity, reducing the activity of reactive oxygen species and superoxide radicals stimulated by inflammatory mediators, thereby exerting antioxidant effect.[32,35,36]

In immunomodulation, curcumin can correct the disorder of T cell subsets, regulate the Th17/Treg balance in COPD rats, increase IL-10 levels, decrease IL-17 levels, and downregulate CD4, CD25, and Foxp3 regulatory T cells, thereby exerting protective and therapeutic effects in COPD rats.[36]

Codonopsis Pilosula Polysaccharides

Codonopsis pilosula polysaccharides (CPP) are one of the primary active ingredients of Codonopsis pilosula, possessing anti-tumor, antioxidant, neuroprotective, immunomodulatory, and anti-inflammatory effects. Research indicates that CPP can regulate immunity[37] and enhance the defective phagocytosis of alveolar macrophages in COPD mice, as well as improve oxidative stress and inflammatory responses in COPD.

CPP exhibits remarkable efficacy in multiple aspects when it comes to dealing with COPD. Firstly, it significantly increases the ability of alveolar macrophages from COPD mice and those treated with PM2.5to phagocytose Escherichia coli. Secondly, it leads to a significant elevation in the levels of TAC and GSH-PX within the plasma, while concurrently reducing the concentration of malondialdehyde (MDA). Thirdly, CPP plays a crucial role in dampening local and systemic inflammatory responses by decreasing the levels of key inflammatory factors such as TNF-α and IL-3, thereby alleviating lung damage associated with COPD.[38] Additionally, CPP can inhibit the NF-κB pathway by downregulating NF-κB mRNA, suppressing NF-κB nuclear translocation, and reducing p-IκBα levels while upregulating IκBα mRNA, protein, and cytoplasmic NF-κB protein expression levels. It also increased CD3, CD4, and CD4/CD8 levels, inhibited T cell immunological derangement in COPD mice, enhanced immune function, and reduced airway phlegmonsis and lung tissue damages.[89]

Herbal Formula

TCM treatment is based on syndrome differentiation, tailored to meet the individual needs of patients. TCM practitioners prefer herbal formulas over single herbs. Herbal formulas are complex mixtures of various herbs rich in therapeutic compounds that interact with each other to maximize efficacy and minimize toxicity. Although there are many TCM diagnostic and treatment guidelines for COPD in China, their practical applications are not completely consistent, primarily because of the lack of high-level evidence-based medical evidence and unclear mechanisms of action. Recently, many domestic teams have made significant progress in their research on COPD treatment, and some promising herbal formulas have been shown to slow COPD progression, inhibit inflammatory development, improve airway remodeling, and mitigate the adverse reaction of oxidative stress.

Liu Junzi Decoction

The prescription for the Liu Junzi Decoction originated from Ming Dynasty physician Yu Tuan's Medical Correction, with ingredients comprising Dang Shen, Bai Zhu, Fu Ling, Ban Xia, Chen Pi, and Gan Cao. It is known for its benefits in replenishing qi, strengthening the spleen, drying dampness, and resolving phlegm.

In ancient times, a TCM formula called Liujunzi Decoction was used to treat COPD. This was mainly based on the theory of the interrelationship between internal organs in TCM. Usually, people with COPD have poor lung function. After a long time, it will even affect the spleen, and finally lead to weakness in both the spleen and the lung. The Liu

Junzi Decoction contains some medicinal herbs can strengthen the spleen and replenish qi, which means helping the spleen and lung to recover.

Moreover, patients with COPD often cough and expectorate phlegm. The pinellia and dried tangerine peel in the Liujunzi Decoction can play their roles. They can remove excess moisture in the body, dissolve phlegm, and make the qi flow smoothly, reducing the cough symptoms. So, the Liujunzi Decoction can not only treat lung diseases but also strengthen the body's healthy energy and improve the body's immunity, making patients feel better. In modern research Liu Junzi Decoction can suppress inflammatory responses, enhancing immune function, and improving pulmonary function. Modern pharmacological research has confirmed that Dang Shen extracts within the Liu Junzi Decoction inhibit airway inflammation in mice with COPD through the NF-κB pathway and regulate the immune function of COPD by downregulating inflammation.[90] The extracts of Bai Zhu, Fu Ling, Chen Pi, and Ban Xia exhibit many pharmacokinetic properties, including anti-inflammatory, antioxidant, immunomodulatory, and anti-tumor effects, which play an important role in the treatment of COPD.[39,91–93] Substances such as Pachymic acid, pachymic acid methyl ester, and Pachyman from Fu Ling, as well as Naringin, Hesperidin, and Naringenin from Chen Pi, can enhance the body's immunity and suppress the development of inflammatory responses. Bai Zhu mainly contains Atractylon, Mannan AM-3, Caryophyllene, and other substances, and Ban Xia extracts can reduce mucus secretion, regulate the release of MUC5AC, MMP-9, and NE in induced sputum, and promote sputum expulsion.[94–96]

Research findings have further indicated that certain modifications made to the Liu Junzi Decoction can trigger the activation of HDAC2.[40,41] By impeding the phosphorylation of IκB-α and NF-κB, it suppresses the NF-κB pathway, reduces the expression of the inflammatory factors IL-1β, IL-6, and TNF-α, and alleviates the infiltration of inflammatory cells in the airway tissue.[40–42] Furthermore, it can decrease the levels of airway remodeling markers, such as NOX4 and MMP-9. By doing so, it inhibits the process of airway remodeling and consequently improves lung function.[43] In addition, oxidative stress is known to exacerbate inflammatory reactions by activating the NF - κB signaling pathway. However, the Liu Junzi Decoction exhibits a dual protective mechanism. Not only does it restrain the phosphorylation of NF - κB, but it also curbs the formation of ROS. Simultaneously, it promotes the expression of antioxidant enzymes such as SOD and CAT, safeguarding the antioxidant enzyme system.[42] Liu Junzi Decoction can correct the imbalance between oxidation and antioxidation, reduce the positive expression rate of γ-GCS, and inhibit the expression of phosphorylated P38 to alleviate hypersecretory states in the airways, reduce the amount of airway secretion in COPD rats, decrease inflammatory reactions, and mitigate pathological damage to the airways and alveolus.[97,98]

Xiao Qing Long Decoction

The Xiao Qing Long Decoction, which has its origin in the renowned Treatise on Febrile Diseases, is renowned for its functions of dispelling cold, warming the lungs, and transforming retained fluids. In clinical practice, it is prevalently employed in the treatment of a variety of respiratory ailments, including COPD, bronchial asthma, and allergic rhinitis. Modern pharmacological investigations have unveiled that several ingredients within this decoction play crucial roles. Ma Huang, Gui Zhi, and Wu Wei Zi have been found to possess potent anti-inflammatory, antioxidant, antiviral, and anti-tumor properties specifically in the context of respiratory disease management.[99,100] For instance, cinnamaldehyde extracted from Gui Zhi, paeoniflorin from Shao Yao, glycyrrhizic acid and liquiritin from Gan Cao, and schisandrin from Wu Wei Zi have demonstrated the ability to suppress the expression of inflammatory cytokines, thereby effectively improving lung function.[101] Additionally, the polysaccharide compounds present in Ma Huang can skillfully modulate cytokines like TNF - α, IL - 6, and associated signaling pathways, while also fine - tuning the immune system.[102] This not only endows it with the capacity to combat the influenza virus but also bolsters overall immunity. Kaempferol from Xi Xin and β-sitosterol from Gan Jiang can inhibit the excessive secretion of airway mucus, alleviate airway obstruction and inflammatory responses, and ameliorate pulmonary ventilation.[103] Other components of the Xiao Qing Long Decoction, such as quercetin, luteolin, liquiritone, and naringin, participate in various immune responses and play key roles in inflammatory reactions, phagocytosis, and oxidative stress.[104]

The regulatory mechanism of the Xiao Qing Long Decoction in the treatment of COPD is complex and multifaceted, which includes anti-inflammatory effects, immune enhancement, autophagy regulation, suppression of oxidative stress, and alleviation of cell apoptosis. Xiao Qing Long Decoction can alleviate airway inflammation in COPD by lowering the

expression of inflammatory cytokines such as miR-145, CX3CL1, IL-6, and IL-4,[47] as well as TLR4 protein and TLR4/MyD88 mRNA expression,[48] thereby reducing lung tissue damage. In addition, it serves as a deterrent against airway remodeling by reducing the expression of TGF - β1 and MMP - 9,[44,47] and exert antifibrotic effects. Additionally, Xiao Qing Long Decoction increased IFN-γ and regulated Th1/Th2 cytokine levels in COPD patients, improving the immune response and boosting immunity.[105] Clinical studies have found that the Xiao Qing Long Decoction can improve the hypersecretory state of airway mucus in patients with stable COPD, reduce airway obstruction, and enhance pulmonary ventilation. This phenomenon is hypothesized to be linked to its inhibitory effect on MUC5AC oversecretion, which is mediated through the NF - κB/miR - 494 pathway.[106,107] Furthermore, a study confirmed the protective effect of Xiao Qing Long Decoction in COPD from an oxidation-antioxidation perspective. After treatment in a COPD rat model, there was a reduction in the levels of γ-GCS and NF-κB, indicating that Xiao Qing Long Decoction can correct the imbalance between oxidation and antioxidation, reducing inflammatory reactions.[45] Research has confirmed that Xiao Qing Long Decoction can activate the AMPK/mTOR signaling pathway, increasing the protein expression of AMPK, mTOR, and p-mTOR, and has a protective effect on inflammation and cell apoptosis in AECOPD mice.[46]

Erchen Decoction

The erchen Decoction, whose origin can be traced back to Taiping Huimin He Ji Ju Fang, comprises several herbal ingredients, namely Ban Xia, Chen Pi, Fu Ling, Gan Cao, Sheng Jiang, and Wu Mei. In clinical settings, it is frequently utilized in the treatment of chronic bronchitis and pulmonary emphysema, owing to its remarkable anti-inflammatory, antioxidative, and immune-boosting properties.

Studies have provided solid evidence that when the water decoction of Sheng Jiang is employed to intervene in a rat model of COPD, it can stimulate the expression of AQP1 protein while concurrently suppressing the expression of IL-8, IL-10, IL-13, TNF-α, and MUC5AC.[108] This dual action leads to a significant enhancement in the respiratory function of the rats.

The entire COPD process involves inflammatory responses, and the Erchen Decoction participates in controlling COPD inflammation through multiple pathways. Research has unearthed that the modified Erchen Decoction, with additional ingredients, exerts its anti-inflammatory effect by impeding the gene expression of crucial molecules within the Midkine/Notch2/Hey1[49] and Jagged1/Notch1/Hes1[50]signal transduction systems. It also inhibits the PI3K/Akt, TLR4/MyD88/ NF-κB p65, and NLRP3 signaling pathways; reduces the phosphorylation of NF-κB p65; and down-regulates the integration and liberation of downstream inflammatory factors HMGB1, CXCL-2, CXCL-3, and MCP-1. By doing so, it thwarts the chemotaxis and recruitment of inflammatory cells, thereby alleviating the inflammatory reactions in COPD, mitigating the pathological damage to lung tissue, and improving lung function.[51–53] Ying[109] et al found that Erchen Decoction with added ingredients improved lung function and inhibited airway inflammation in COPD rats by enhancing the protein and mRNA expression of β2AR in lung tissue, protein expression of β-arrestin2, and inhibition of IL-6 and NF-κB levels. Additionally, Erchen Decoction can activate the Nrf2 signaling pathway to achieve antioxidant effects, protect vascular endothelial and smooth muscle functions,[51] reduce the level of MUC5AC in patient sputum,[110] inhibit the hypersecretory state of airway mucus, reduce sputum production, and stimulate sputum discharge, which can improve lung function.

San Zi Yang Qin Decoction

The San Zi Yang Qin Decoction, originating from Jie Xiao Fang, is composed of Zi Su Zi, Bai Jie Zi, and Lai Fu Zi decoctions. It has the effects of warming the lungs to resolve phlegm and reducing qi to aid digestion. This effectively lowered the levels of inflammatory factors in the body and improved lung function. Key active constituents within the San Zi Yang Qin Decoction play significant roles. For instance, limonene diepoxide, arachidonic acid, and luteolin present in Zi Su Zi can modulate the proliferation and apoptosis of smooth muscle cells and epithelial cells in the upper respiratory tract, as well as orchestrating inflammatory and oxidative stress responses.[111] The common active ingredient β-sitosterol found in Bai Jie Zi, Zi Su Zi, and Lai Fu Zi has an inhibitory effect on inflammatory reactions, reducing pro-inflammatory factors such as IL-6 and TNF-α and increasing the level of the anti-inflammatory factor IL-10.[112,113]

Clinically, the San Zi Yang Qin Decoction is generally not used alone but is often combined with other TCM compounds, such as Si Junzi Tang and Kuan Xiong Li Fei Tang. Research by Li Ya Lan[114] and others found that San Zi Yang Qin Decoction combined with Si Junzi Decoction can inhibit the STAT6-SPDEF-MUC5AC pathway and reduce serum levels of inflammatory factors. This leads to a reduction in serum levels of inflammatory factors such as IL-4, as well as the expression levels of STAT6 and SPDEF proteins and STAT6 and MUC5AC genes in lung tissue. Consequently, it alleviates inflammatory reactions, ameliorates airway mucus hypersecretion, and safeguards the structural integrity of the lung tissue. Kuan Xiong Li Fei Decoction combined with San Zi Yang Qin Decoction regulates the TLR4/ NF-κB signaling pathway by reducing the serum expression of TLR4 and NF-κB[54] and downregulates the systemic inflammatory cytokines hs-CRP, IL-6, and TNF-α,[55] thereby reducing systemic inflammatory responses and improving lung ventilation function.

Xue Fu Zhu Yu Decoction

Xue Fu Zhu Yu Decoction, which originated from Yi Lin Gai Cuo, is composed of a combination of multiple medicinal herbs, namely Tao Ren, Hong Hua, Dang Gui, Sheng di Huang, Niu xi, Chuanxiong, Jie Geng, Chi shao, Zhi Qiao, Gan Cao, and Chai hu. This decoction is renowned for its remarkable efficacy in invigorating blood circulation to eliminate blood stasis and promoting qi movement to relieve pain. Modern pharmacological investigations have shed light on the specific mechanisms and effects of its constituents. For instance, the aqueous extracts of Hong Hua have been found to possess the ability to impede platelet aggregation and augment fibrinolysis. Tao ren contains amygdalin and amygdalase, which have a sedative effect on the respiratory center, as well as anti-inflammatory, anti-allergic, antitussive, and expectorant effects, inhibits vascular smooth muscle contraction, reduces peripheral vascular resistance, decreases platelet surface activity, and inhibits platelet aggregation. Ferulic acid, an important component present in Dang Gui, can enhance peripheral circulation. Moreover, it exhibits sedative, anti-inflammatory, anti-hypoxic, and antibacterial properties in vitro.[56]

Xue Fu Zhu Yu Decoction can delay the pathological progression of airway remodeling in COPD, which have in connection with upregulating the VEGF-VEGFR2 pathway, inducing endothelial cell proliferation, and promoting angiogenesis.[115] Network pharmacology suggests that Xue Fu Zhu Yu decoction can also improve the inflammatory response and ventilatory impairment by intervening in the PI3K/AKT pathway.[57] The inflammatory response in COPD is related to the high expression of proteins, such as TLR4, MyD88, and NF-κB. Xue Fu Zhu Yu decoction can control the inflammatory response in COPD; it can inhibit the TLR4/MyD88/ NF-κB signaling pathway and reduce the release of inflammatory factors such as TNF-α, IL-1β, IL-6, IL-8, and IL-17.[116]

She Gan Ma Huang Decoction

She Gan Ma Huang Decoction originates from Jin Gui Yao Lue and is composed of Gan, Huang, Jiang, Xin, Wan, Hua, Zao, Xia, and Zi. It warms the lungs to resolve fluids, directing qi downward to expel phlegm. Clinically, it is frequently employed in the treatment of COPD, pulmonary heart disease, and other relevant medical conditions.Modern pharmacological research indicates that the fat-soluble substances in She Gan, such as tectoridin, irisolidone, tectorigenin, and irigenin, as well as flavonoids such as quercetin and kaempferol, terpenes such as aster ketone and coltsfoot flower ketone found in Zi wan and Kuan Dong Hua, lignans from Xi Xin, gingerols, volatile oils, diarylheptanoids from Sheng jiang, sugars, saponins, triterpenes, vitamins from Da Zao, alkaloids from Ban Xia, and total lignans from Wu Wei Zi, all contribute to anti-inflammatory, antibacterial, antiviral, cough relief, and asthma suppression impact.[58,117–121] Clinically, it has been found that She Gan Ma Huang decoction integrated with Western medicine significantly improves COPD therapy, effectively enhancing patients' lung function. Its potential theory is probably associated with the inhibition of the EGFR/PI3K pathway, reducing the release of inflammatory factors such as TNF-α, IL-6, and IL-1β, as well as the levels of PI3K and EGFR mRNA and the protein levels of PI3K and EGF, thereby reducing lung damage.[122]

Discussion

The high heterogeneity of COPD has limited progress in treatment options and there is currently no definitive cure. The pathogenesis of COPD is complex, diverse, and interrelated. At present, although some molecular targeted therapeutic

drugs have proven effective in animal experiments, the multi-directional signaling pathway is not only targeted at a certain mechanism; therefore, the therapeutic effect on COPD is still unknown.[59,123,124] However, multi-element, multi-pathway, and multi-target TCM can completely avoid this problem. Simultaneous regulation of multiple signaling pathways has unique advantages.

TCM therapy for COPD has many advantages, including personalized treatment, holistic concepts, multi-component and multi-target therapeutic effects, high safety, and increasingly rich clinical and experimental research data. By searching the Chinese and English literature from the past 20 years, this article summarizes the mechanism of TCM monomers, extracts, and herbal recipes in the treatment of COPD. The molecular mechanism of TCM action on COPD mainly involves inhibition of airway inflammation, inhibition of oxidative stress, improvement of immune function, and regulation of autophagy, which can inhibit airway remodeling, reduce airway mucus secretion, and alleviate lung damage. TCM has great potential for treating COPD as it can simultaneously regulate multiple pathways, exerting synergistic effects to achieve therapeutic effects. For example, LJZT can inhibit COPD inflammation and oxidative imbalance by interfering with the NF-κB pathway. SZYQT can inhibit airway inflammation through both the NF-κB and STAT signaling pathways, fully reflecting the multi-target approach of TCM, which greatly improves pulmonary function and respiratory symptoms of COPD and comprehensively controls the course of the disease in multiple directions. This paper summarizes studies on the pathogenesis of the intervention of various signaling pathways by TCM monomers and herbal formulas in COPD, which helps to develop insights into the pathophysiological mechanism of COPD from different angles, comprehensively recognize the complex pathological process of COPD, and provide a diagnosis and treatment basis for future TCM treatments of COPD. It can more accurately understand the actual effect of TCM in curing COPD, optimize the treatment plan, and improve the treatment effect.

At present, no serious adverse reactions caused by TCM in curing COPD have been reported, and its clinical application may be safe, providing a new choice for the treatment of intervention in COPD. Further research is needed on the mechanism of TCM treatment for COPD, which may promote the effective combination of TCM and modern medicine treatment strategies. The precise diagnosis and treatment technology of western medicine, combined with the overall conditioning and individualized treatment advantages of TCM, may be able to better meet the treatment needs of patients with COPD.

Conclusion

TCM exerts its therapeutic effects on COPD through the unique advantages of multiple targets and pathways and serves as an alternative complementary option. The mechanism of action warrants further investigation.

Abbreviations

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; Akt, Protein kinase B; AMPK, Adenosine 5,-monophosphate (AMP)-activated protein kinase; AQP1,Aquaporin 1; ASMC, airway smooth muscle cells; Bax BCL-2 associated X protein;.Bcl-2, B-cell lymphoma/leukemia-2; Caspase-3, Cysteine-aspartic protease-3; CAT, Catalase; COPD, chronic obstructive pulmonary disease; CNKI, China National Knowledge Infrastructure; CPP, Codonopsis pilosula polysaccharides; CSE, cigarette smoke extract; cytoC, cytochrome c; ECD, Erchen decoction; ECM, extracellular matrix; EGF, epidermal growth factor; EGFR, epithelial growth factor receptor; ERK, extracellular signal-regulated kinase; FGF-2, basic fibroblast growth factor 2; GSH-Px, glutathione peroxidase; GBE, ginkgo biloba extract; HC, Houttuynia cordata vapor extract; HDAC, histone deacetylase; HIF, hypoxia-inducible factor; HMGB, high mobility group box; HO-1, Heme Oxygenase-1; IFN-γ, Interferon γ; IL, Interleukin; JNK, Jun N-terminal kinase; LC3, light chain 3; LJZD, Liu Junzi Decoction; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractantprotein-1; MDA, malondialdehyde; MMP, matrix metalloproteinase; MPO, myeloperoxidase; Muc5AC, mucin gene 5AC; MyD88, myeloid differentiation factor 88; NF-κB, Nuclear factor-κB; NOX4, NADPH Oxidase 4; Nrf2 Nuclear factor erythroid 2-related factor 2; PCNA Proliferating Cell Nuclear Antigen; PD polydatin; PI3K/AKT/mTOR phosphatidylinositol-3-kinase/AKT/mammalian target of rapamycin; γ-GCS: γ-glutamyl-cysteine synthetase; ROS, reactive oxygen species; SGMHD She Gan Ma Huang Decoction; SOD Superoxide Dismutase; SPDEF, SAM pointed domain containing Ets transcription factor; STAT signal transducer and activator of transcription; SZYQD,

Three-Seed Filial Devotion Decoction; TAC Total anti-oxidative capacity; TGF-β transforming growth factor β; TLR4 Toll-like receptor 4; TIMP matrix metalloproteinase-inhibitor; TNF-α, tumor necrosis factor-α; Treg Regulatory T; TPG total paeony glycoside; VEGF, Vascular endothelial growth factor; XFZYD Xue Fu Zhu Yu Decoction; XQLD, Xiao Qing Long Decoction.

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas, took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was sponsored by National Natural Science Youth Fund Project (82305155).

Disclosure

The authors have no competing interests in this work.

References

1. Guo P, Li R, Piao TH, Wang CL, Wu XL, Cai HY. Pathological mechanism and targeted drugs of COPD. *Int J Chron Obstruct Pulmon Dis*. 2022;17:1565–1575. PMID: 35855746; PMCID: PMC9288175. doi:10.2147/COPD.S366126
2. Soriano JB, Polverino F, Cosio BG. What is early COPD and why is it important? *Eur Respir J*. 2018;52(6):1801448. PMID: 30309976. doi:10.1183/13993003.01448-2018
3. Jagana R, Bartter T, Joshi M. Delay in diagnosis of chronic obstructive pulmonary disease: reasons and solutions. *Curr Opin Pulm Med*. 2015;21(2):121–126. PMID: 25575363. doi:10.1097/MCP.0000000000000133
4. Zhou M, Wang H, Zeng X, et al. Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: a systematic analysis for the global burden of disease study 2017. *Lancet*. 2019;394(10204):1145–1158. doi:10.1016/S0140-6736(19)30427-1
5. Wang C, Xu J, Yang L, et al. Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): a national cross-sectional study. *Lancet*. 2018;391(10131):1706–1717. Epub 2018 Apr 9. PMID: 29650248. doi:10.1016/S0140-6736(18)30841-9
6. Katzenberg G, Deacon A, Aigbirior J, Vestbo J. Management of chronic obstructive pulmonary disease. *Br J Hosp Med*. 2021;82(7):1–10. Epub 2021 Jul 20. PMID: 34338012. doi:10.12968/hmed.2020.0561
7. XiaoLei Z, Chen W. Emphasize the screening and management of chronic obstructive pulmonary disease. *Chin J Health Manag*. 2015;9(4):250–253,10.3760/cma.j.issn.1674–0815.2015.04.003.
8. World Federation of Chinese Medicine Societies. International Clinical Practice Guideline of Chinese Medicine Chronic Obstructive Pulmonary Disease. *World Chin Med*. 2020;15(7):1084–1092. doi:10.3969/j.issn.1673-7202.2020.07.026
9. Huang P, Lin X, Liu Y, Hou Z. The efficacy and safety of combined traditional Chinese and western medicine in the treatment of chronic obstructive pulmonary disease complicated with respiratory failure: a systematic review and meta-analysis study. *Ann Palliat Med*. 2022;11(3):1102–1111. PMID: 35365040. doi:10.21037/apm-22-272
10. Rahman MM, Bibi S, Rahaman MS, et al. Natural therapeutics and nutraceuticals for lung diseases: traditional significance, phytochemistry, and pharmacology. *Biomed Pharmacother*. 2022;150:113041. Epub 2022 May 6. PMID: 35658211. doi:10.1016/j.biopha.2022.113041
11. QuanYing H, CuiLing F. Expert consensus on integrated traditional Chinese and western medicine management for chronic obstructive pulmonary disease. *Chin General Pract*. 2023;26(35):4359–4371.
12. Shi FH, Chen ZR. Effects of polydatin on PI3K/AKT/mTOR pathway and airway inflammation in rats with chronic obstructive pulmonary disease. *Drug Eval Res*. 2020;43(10):1983–1987.
13. Jin XF, Xu ZJ, Wang WT, Xu YX, Zhang XL. The regulative effects of polydatin on toll-like receptor 4 signal transduction pathway in lung ischemia/reperfusion injury in rabbits. *Zhongguo Ying Yong Sheng Li Xue Za Zhi*. 2009;25(1):41–44. Chinese. PMID: 21186612.
14. Zhou Y, Yu Y, Cheng WT. Effects of polydatin on airway inflammation and TLR4/ NF-κB signaling pathway in rats with chronic obstructive pulmonary disease. *Pharmacol Clin Chin Materia*. 2019;35(02):35–40. doi:10.13412/j.cnki.zyyl.2019.02.008
15. Lee KH, Yoo CG. Simultaneous inactivation of GSK-3β suppresses quercetin-induced apoptosis by inhibiting the JNK pathway. *Am J Physiol Lung Cell mol Physiol*. 2013;304(11):L782–9. Epub 2013 Apr 5. PMID: 23564507. doi:10.1152/ajplung.00348.2012
16. Zhang LX, Tian YG, Zhao P, Feng SX, Han XX, Li JS. Network pharmacology analysis uncovers the effect on apoptotic pathway by Bu-Fei formula for COPD treatment. *J Ethnopharmacol*. 2022;289:115022. doi:10.1016/j.jep.2022.115022
17. Wu XP, Tao YZ, Liu L, Han J, Liu WJ, et.al. Quercen reduces airway mucus hypersecretion in rats based on EGFR signaling pathway. *Guizhou Univ School oMed*. 2022;38(08):940–945.
18. Xu HH, OuYang SY, Chen LL. Therapeutic effect of total paeony glucosides on chronic obstructive pulmonary disease model rats. *Chin J New Drugs Chin J Clin*. 41(09):561–565. doi:10.14109/j.cnki.xyylc.2022.09.10
19. Heng H, Zhihong Z, Gangcheng Z., et.al. The effect of total peony glycosides on inflammation and apoptosis of lung tissue in chronic obstructiVe pulmonary rats through NF-KB pathway. *J Hubei Univ Chin Med*. 2022;24(03):16–20.

20. Shingnaisui K, Dey T, Manna P, Kalita J. Therapeutic potentials of Houttuynia cordata Thunb. against inflammation and oxidative stress: a review. *J Ethnopharmacol*. 2018;220:35–43. doi:10.1016/j.jep.2018.03.038
21. Chun JM, Nho KJ, Kim HS, et al. An ethyl acetate fraction derived from Houttuynia cordata extract inhibits the production of inflammatory markers by suppressing NF-κB and MAPK activation in lipopolysaccharide-stimulated RAW 264.7 macrophages. *BMC Complement Altern Med*. 2014;14:234. doi:10.1186/1472-6882-14-234
22. Li H, Xing XY, Wang YX. Effects of Houttuynia Cordata Extract on Lung Function of COPD Acute Exacerbation Rats and Regulation TLR4/NF-κB Signal Pathway. *Acta Chin Med*. 2021;36(04):807–812. doi:10.16368/j.issn
23. YuH LLC, Tan MX. Effects of houttuynia cordata extract on ACE2 and p38MAPK pathway in lung tissue for rats with chronic obstructive pulmonary disease. *J Sichuan Trad Chin Med*. 2018;36(08):34–39.
24. Shi LL, Han WN, Wang Q. Xu NN.The effect of breviscapine on the proliferation of airway smooth muscle cells in COPD rat models. *J. Xinjiang Med. Univ*2021;44(07):788–793.
25. Wang SY, Zhao Q, Yang X. Clinical efficacy of Breviscapine injection on stale COPD and its effect on TGF-β1 content and TβRI,Smad2,Smad3 expression levels. *Mol Diagn Ther*. 2023;15(02):335–338+343.
26. Liu YP, F ZX, P JX, et al. Analysis of clinical effect and immunoglobulin level of breviscapine in patients with acute exacerbation of chronic obstructive pulmonary disease. *Shanxi Med J*. 2021;45;13:1577–1579.
27. Zhang PF, Liao LJ, Deng Z, et al. Research progress of pharmacological effects and clinical application of ginkgo biloba extract. *Liaoning JTrad Chin Med*. 2017;44(02):426–429. doi:10.13193/j.issn.1673-7717.2022.10.041
28. Tan YP, Wang CH, Meng DS, et al. The inhibitory effects of ginkgo biloba extract on airway and vascular remodeling in rat model of chronic obstructive pulmonary disease. *Chin J Respir Crit Care Med*. 2008;(04):274–276+262+32.
29. Zhang HL, Tan YP, Li KC, et al. Effect of ginkgo extract on inflammatory reaction in rats with chronic obstructive pulmonary disease. *J Guangxi Univ Chin Med*. 2021;15(04):40–44.
30. Guo DW, Zhang PF, Ren MJ, et al. Mechanistic of ginkgo biloba extract in the prevention and Treatment of COPD:regulating autophagy in alveolar macrophages via PI3K/Akt/mTOR signaling pathways. *Chin General Pract*. 2023;26(03):293–303.
31. Hsu CL, Wu YL, Tang GJ, et al. Ginkgo biloba extract confers protection from cigarette smoke extract-induced apoptosis in human lung endothelial cells: role of heme oxygenase-1. *Pulm Pharmacol Ther*. 2009;22(4):286–296. Epub 2009 Feb 28. PMID: 19254777. doi:10.1016/j.pupt.2009.02.003
32. Qin K. Guo XJ.Research progress on the mechanism of curcumin in treating chronic obstructive pulmonary disease. *Chin J Respir Critical Care Med*. 2020;19(02):193–197.
33. Yuan J, Liu R, Ma Y, Zhang Z, Xie Z. Curcumin attenuates airway inflammation and airway remolding by inhibiting NF-κB signaling and COX-2 in cigarette smoke-induced COPD mice. *Inflammation*. 2018;41(5):1804–1814. doi:10.1007/s10753-018-0823-6
34. Wu Y, Shi SF. Potential molecular biological mechanism of TCM in preventing and treating airway remodeling of COPD.J. *Info on Trad Chin Med*. 2021;38(03):69–72.
35. Deng HJ, Yu HP, Xia H, et al. Investigating the role and mechanism of oxidative stress in the pathogenesis of chronic obstructive pulmonary disease based on the Nrf2/ARE/HO-1 pathway. *Southern Med Univ Zhujiang Hospital*. 2021.
36. Lin XG, Tan L, Huang W, et al. Effect of curcumin on helper T cells 17 and regulatory T cells in rats with chronic obstructive pulmonary disease. *J Beijing Univ Trad Chin Med*. 2017;40(01):31–35.
37. Zou YF, Zhang YY, Fu YP, et al. A polysaccharide isolated from codonopsis pilosula with immunomodulation effects both in vitro and in vivo. *Molecules*. 2019;24(20):3632. doi:10.3390/molecules24203632
38. Chu X, Liu XJ, Qiu JM, et al. Effects of Astragalus and Codonopsis pilosula polysaccharides on alveolar macrophage phagocytosis and inflammation in chronic obstructive pulmonary disease mice exposed to PM2.5. *Environ Toxicol Pharmacol*. 2016;48:76–84. doi:10.1016/j.etap.2016.10.006
39. Min F, Ziming J, Ming W, et al. Effectiveness of Fuling and its extracts against spleen deficiency in rats tonifying spleen. *J Tradit Chin Med*. 2023;43(3):501–506. doi:10.19852/j.cnki.jtcm.2023.03.002
40. Cao YH, Zhu JF, Huang HF. Clinical observation on the treatment of acute stage of chronic obstructive pulmonary disease with TCM directional transdrug based on HDAC2. *J Yunnan Tradit Chin Med Materia Med*. 2022;43(01):35–40.
41. Lu F, Wang SC, Lu SY. Effect of Liujunzi Decoction on endogenous anti-inflammatory system function in rats with chronic obstructive pulmonary disease and its mechanism. *J CJGMCM*. 2015;30(10):2101–2103.
42. Zhou R, Luo F, Lei H, et al. Liujunzi Tang, a famous traditional Chinese medicine, ameliorates cigarette smoke-induced mouse model of COPD. *J Ethnopharmacol*. 2016;193:643–651. Epub 2016 Sep 19. PMID: 27660011. doi:10.1016/j.jep.2016.09.036
43. Chen M, Zhou JP, Wang YG. Clinical study on yupingfeng powder and liujunzi decoction in the treatment of acute exacerbation of chronic obstructive pulmonary disease of phlegm-dampness and pulmonary-obstruction based on the theory of spleen invigorating and lung benefiting. *J Evaluation Analysis Drug-Use Hospitals of China*. 2020;20(08):949–952+956.
44. Cao DR. Effects of Xiaoqiongtang decoction on airway inflammation and airway remodeling in patients with COPD. *J Med J West China*. 2009;21(04):575–577.
45. ZhangW LG, Zhang XY. Xiao qing long decocition's Influence on NF-κB and γ-GCS of COPD model rats. *J Zhejiang Univ Tradit Chin Med*. 2006;05:457–458+460.
46. Huang Q, Yang H, Zhang C, et al. Xiao qing long decoction protects the lungs of AECOPD Mice through the AMPK/mTOR signaling pathway. *Evid Based Complement Alternat Med*. 2020;2020. doi:10.1155/2020/9865290
47. Zhang MC, Du SB, Fan L. Clinical effects of xiaoqinglong decoction combined with conventional treatment on patients with chronic obstructive pulmonary disease in acute phase due to external cold and internal fluid. *J Tradit Chin Med*. 2022;44(01):78–82.
48. Yan LL, Zhang HY, Yang AD. Effect of supplemented xiaoqinglong decoction on mrna expression of TLR4, MyD88 and SocS1 in lung tissue of rats with chronic obstructive pulmonary disease. *J Lishizhen Med Materia Med Res*. 2015;26(08):1879–1881.
49. Hu WH, Shang LZ, Xie WY. Modified erchentang alleviates inflammation in chronic obstructive pulmonary disease via Midkine/Notch2/Hey1 Signaling Pathway in Rats. *Chin J Exp Tradit Med Formulae*. 2023;29(16):12–21. doi:10.13422/j.cnki.syfjx.20230741
50. Shang LZ, Ji S, Li YY. Anti-inflammatory mechanism of modified erchentang on chronic obstructive pulmonary disease through jagged1/Notch1/Hes1 signaling pathway. *Chin J Exp Tradit Med Formulae*. 2023;29(09):109–118,10.13422/j.cnki.syfjx.20230109.

51. Niu H. Exploring the intervention of modified erchentang on pulmonary vascular remodeling in the model of COPD rats which were belong to phlegm interferes with the lung based on PI3K/Akt / Nrf2 pathways. *Henan Univ Chin Med*. 2022. doi:10.27119/d.cnki.ghezc.2022.000180
52. Shang LZ, Ji S, Wang GQ. Mechanism of modified erchentang on signaling pathway of TLR4/MyD88/ NF-κB in Lung tissue of rats with chronic obstructive pulmonary disease. *Chin J Exp Tradit Med Formulae*. 2019;25(23):65–72. doi:10.13422/j.cnki.syfjx.20192203
53. Shang LZ, Ji S, Wang GQ. Effect of modified erchentang on NLRP3 inflammasome expression in peripheral blood mononuclear cells (PBMCs) of rats with chronic obstructive pulmonary disease. *Chin J Exp Tradit Med Formulae*. 2019;25(23):56–64. doi:10.13422/j.cnki.syfjx.20192204
54. Xiao QL, Cao KK. Clinical efficacy of kuan xiong li fei decoction and san ZI yangqin decoction in the treatment of acute exacerbation of chronic obstructive pulmonary disease with phlegm dampness blocking lung type and its impact on TLRs / NF-κB signal pathway. *J Chin J Clin Rational Drug Use*. 2022;15(30):26–29.
55. Huang XY, Zhang R, Zhao JY. The effects of kuan xiong li fei decoction combined with san zi yangqin decoction on pulmonary function and serum inflammatory cytokines in elderly patients with acute exacerbation of chronic pulmonary disease. *J Emerg Trad Chin Med*. 2015;24 (12):2109–2112.
56. He RQ, Li MX. Observation on curative effect of xue fu zhu yu decoction in treating pulmonary heart disease and heart failure.J. *Chin Comm Doctors*. 2010;12(02):74.
57. Hu Y, Lan Y, Ran Q, Gan Q, Huang W. Analysis of the clinical efficacy and molecular mechanism of xuefu zhuyu decoction in the Treatment of COPD based on meta-analysis and network pharmacology. *Comput Math Methods Med*. 2022;2022:2615580. PMID: 36479314; PMCID: PMC9720234. doi:10.1155/2022/2615580
58. Ling Y, Chen JP. Ye Q.Research progress of shoot stem and predictive analysis of its quality markers. *J Chin Herbal Med*. 2022;53 (05):1595–1608.
59. Wang C, Zhou J, Wang J, et al. Progress in the mechanism and targeted drug therapy for COPD. *Signal Transduct Target Ther*. 2020;5(1):248. PMID: 33110061; PMCID: PMC7588592. doi:10.1038/s41392-020-00345-x
60. XiaoDan Y, YaHao L, Zhang PeiCheng, et al. Research progress on the pharmacological effects of polydatin in the prevention. and Treatment of respiratory diseases. *Pharmaceutical J Chin People's Liberation Army*. 2018;34(05):436–439.
61. Yan XD, Wang QM, Tie C, et al. Polydatin protects the respiratory system from PM2.5 exposure. *Sci Rep*. 2017;7:40030. PMID: 28067267; PMCID: PMC5220290. doi:10.1038/srep40030
62. Munroe ME, Arbiser JL, Bishop GA. Honokiol, a natural plant product, inhibits inflammatory signals and alleviates inflammatory arthritis. *J Immunol*. 2007;179(2):753–763. PMID: 17617564. doi:10.4049/jimmunol.179.2.753
63. Ramesh S, Govindarajulu M, Lynd T, et al. SIRT3 activator Honokiol attenuates β-Amyloid by modulating amyloidogenic pathway. *PLoS One*. 2018;13(1):e0190350. PMID: 29324783; PMCID: PMC5764272. doi:10.1371/journal.pone.0190350
64. Li F, Ye C, Wang X, Li X, Wang X. Honokiol ameliorates cigarette smoke-induced damage of airway epithelial cells via the SIRT3/SOD2 signalling pathway. *J Cell Mol Med*. 2023;27(24):4009–4020. Epub 2023 Oct 5. PMID: 37795870; PMCID: PMC10746946. doi:10.1111/jcmm.17981
65. Munroe ME, Businga TR, Kline JN, Bishop GA. Anti-inflammatory effects of the neurotransmitter agonist Honokiol in a mouse model of allergic asthma. *J Immunol*. 2010;185(9):5586–5597. Epub 2010 Oct 1. PMID: 20889543; PMCID: PMC3197781. doi:10.4049/jimmunol.1000630
66. Li B, Gan DK, He LL. Honokiol inhibits immune imbalance and provides lung protection in mice with chronic obstructive disease through the Notch signaling pathway. *Chin J Comp Med*. 2022;32(4):86–93.
67. Du LN, Shan JJ, Wang SC. Advances in application of quercetin for respiratory system disease. *JSHJTCM*. 2012;46(08):93–95. doi:10.16305/j.1007-1334.2012.08.024
68. Ding M, He F, Bao M. To explore the mechanism of Yupingfeng powder in treating chronic obstructive pulmonary disease based on network pharmacology and cell experiments. *Chinese Trad Patent Med*. 2024;46(7):2407–2414.
69. Wang H, Liu Y, Wang D, et al. The upstream pathway of mTOR-mediated autophagy in liver diseases. *Cells*. 2019;8(12):1597. doi:10.3390/cells8121597
70. Xu XY, Li Z, Pan MY. Pentanmethylquercetin ameliorates cigarette smoke extract induced acute exacerbation of chronic obstructive pulmonary disease. *J Human Univ Chin Med*. 2022;42(08):1283–1288.
71. Ganesan S, Unger BL, Comstock AT, et al. Aberrantly activated EGFR contributes to enhanced IL-8 expression in COPD airways epithelial cells via regulation of nuclear FoxO3A. *Thorax*. 2013;68(2):131–141. Epub 2012 Oct 25. PMID: 23099361; PMCID: PMC6712980. doi:10.1136/thoraxjnl-2012-201719
72. Liu X, Ma Y, Luo L, et al. Dihydroquercetin suppresses cigarette smoke induced ferroptosis in the pathogenesis of chronic obstructive pulmonary disease by activating Nrf2-mediated pathway. *Phytomedicine*. 2022;96:153894. doi:10.1016/j.phymed.2021.153894
73. Ganesan S, Faris AN, Comstock AT, et al. Quercetin prevents progression of disease in elastase/LPS-exposed mice by negatively regulating MMP expression. *Respir Res*. 2010;11(1):131. doi:10.1186/1465-9921-11-131
74. Li LY, Zhang CT, Zhu FY, et al. Potential natural small molecular compounds for the treatment of chronic obstructive pulmonary disease: an overview. *Front Pharmacol*. 2022;13:821941. doi:10.3389/fphar.2022.821941
75. Zhang TM. Machanism of QGG from descurainia sophia on airway inflammation and remodeling in COPD rats. *Chin Traditional Herbal Drugs*. 2019;50(04):910–917.
76. Kumar M, Prasad SK, Hemalatha S. A current update on the phytopharmacological aspects of Houttuynia cordata Thunb. *Pharmacogn Rev*. 2014;8(15):22–35. doi:10.4103/0973-7847.125525
77. Arthur JS, Ley SC. Mitogen-activated protein kinases in innate immunity. *Nat Rev Immunol*. 2013;13(9):679–692. doi:10.1038/nri3495
78. Du F, He G, Chen DG. Effects of Breviscapine on airway remodelng in rats with chronic obstructive pulmonary disease model. *Hebei J TCM*. 2017;39(7):1069–1073. doi:10.3969/j.issn.1002-2619.2017.07.027
79. van der Velden JL, Wagner DE, Lahue KG, et al. TGF-β1-induced deposition of provisional extracellular matrix by tracheal basal cells promotes epithelial-to-mesenchymal transition in a c-Jun NH-terminal kinase-1-dependent manner. *Am J Physiol Lung Cell mol Physiol*. 2018;314(6):L984–L997. doi:10.1152/ajplung.00053.2017
80. Gu WY, Gao QR, Geng ZQ. A meta-analysis of RCTs: effect of breviscapine on immunologic in AECOPD. *J Emerg Trad Chin Med*. 2019;28 (11):1916–1919+1924.

81. Ma HM. Effect of cigarette smoke on the occurrence and transformation of COPD to lung cancer and the intervention mechanism of anemoside B4. *JXZC*. 2021. doi:10.27180/d.cnkigjxzc.2021.000296
82. He J, Yuan R, Cui X, et al. Anemoside B4 protects against Klebsiella pneumoniae- and influenza virus FM1-induced pneumonia via the TLR4/Myd88 signaling pathway in mice. *Chin Med*. 2020;15:68. doi:10.1186/s13020-020-00350-w
83. Ma H, Zhou Z, Chen L, Wang L, Muge Q. Anemoside B4 prevents chronic obstructive pulmonary disease through alleviating cigarette smoke-induced inflammatory response and airway epithelial hyperplasia. *Phytomedicine*. 2022;107:154431. doi:10.1016/j.phymed.2022.154431
84. Wang LL, Chen LY, Ma HM, et al. Study on effect of anemoside B4 in improving COPD rats by regulating IL-12/STAT4 and IL-4/STAT6 signaling pathways. *China J Chin Materia Med*. 2021;46(14):3660–3671. doi:10.19540/j.cnki.cjcmm.20210304.401
85. Yang XM, Zhang B, Zhang PF, et al. Based on P38MAPK signaling pathway to explore the Effects of ginkgo biloba extract in intrevention of airway mucus high secretion a vascular remodeling in COPD rats. *Prog Mod Biomed*. 2023;23(09):1624–1630+1641. doi:10.13241/j.cnki.pmb.2023.09.005
86. Zhang PF, Guo DW, Liao LJ. The effect of ginkgo biloba extract on the signal pathway of COPD. *Asia-Pacific Tradit Med*. 2022;18(06):198–202.
87. Monick MM, Powers LS, Walters K. Identification of an autophagy defect in smokers' alveolar macrophages. *J Immunol*. 2010;185(9):5425–5435. doi:10.4049/jimmunol.1001603
88. Zhang R, Chen YF, Li LL, et al. Improvement effect and mechanism of curcumin on chronic obstructive pulmonary disease in rats. *Chin J New Drugs Clin Remedies*. 2022;41(08):495–501. doi:10.14109/j.cnki.xyylc.2022.08.09
89. Lin XL, Fang C, Ke WQ. Codonopsis pilosula polysaccharides regulate NF-κB signaling pathway to alleviate T cell immune disorders and airway inflammation in rats with chronic obstructive pulmonary disease. *Tianjin J Trad Chin Med*. 2021;38:06):788–793.
90. Li N. Ginseng extract (ginseng total saponins) on chronic obstructive pulmonary disease type lung spleen-deficiency rats immune function and mechanism of NF-κB signaling pathway. *CUCM*. 2015.
91. Zhu B, Zhang QL, Hua JW, et al. The traditional uses, phytochemistry, and pharmacology of Atractylodes macrocephala Koidz. *A Review J Ethnopharmacol*. 2018;226:143–167. doi:10.1016/j.jep.2018.08.023
92. Yu X, Sun S, Guo Y, et al. Citri reticulatae pericarpium (Chenpi): botany, ethnopharmacology, phytochemistry, and pharmacology of a frequently used traditional Chinese medicine. *J Ethnopharmacol*. 2018;220:265–282. doi:10.1016/j.jep.2018.03.031
93. Yang LJ, Gao H, Luo W, et al. Research progress and prospect of pinellia ternate.J. *Anhui Agricultural Sci Bulletin*. 29;02:33–38.
94. Zhang LF, Duan B, Liu F, et al. Effect and mechanism of shenling baizhu powder in the treatment of stable chronic obstructive pulmonary disease. *J Liaoning J Tradl Chin Med*;2021;272:113927
95. Peng X, Liu J, Luan Z. pathogenesis of airway mucus hypersecretion in chronic obstructive pulmonary disease and intervention of tradition chinese medicine: a review. *Chin J Exp Tradit Med Formulae*. 2023.30:228–39
96. Chen XM, Tait AR, Kitts DD. Flavonoid composition of Orange peel and its association with antioxidant and anti-inflammatory activities. *Food Chem*. 2017;218:15–21. doi:10.1016/j.foodchem.2016.09.016
97. Zhang W, Shao YM, Zhang XY. Effect of Liujunzi Decoction on expression of nuclear factor κB and γ-glutamylcysteine synthase in rats with chronic obstructive pulmonary disease. *Jiangsu J Trad Chin Med*. 2007;04:57–59.
98. Zhong YQ, Xu GL, Wang XF. Xionggui Liujunzi Decoction decreases the airway mucus hypersecretion in rats with COPD. *J Tradit Chin Med Sci*. 2017;39(08):1577–1581.
99. Li X, Zhao JH, Wu WX. Research prograss on chemical constituents and pharmacological effects of ramulus cinnamomi. *J Acta Chin Med Pharmacol*. 2023;51(05):111–114.
100. Zhang D, Hu S, Li W, et al. Schisandra A ameliorates cigarette smoke extract and lipopolysaccharide-induced oxidative stress in lung epithelial cells. *J Thorac Dis*. 2020;12(3):394–402. doi:10.21037/jtd.2020.01.24
101. Chen KL, Fu ZF, Huang QS. Chemical composition analysis of xiaoqinglong decoction and its effect on mice with acute exacerbation of chronic obstructive pulmonary disease. *J Tradit Chin Med*. 2022;44(12):4037–4040.
102. Liu CY, Cong ZF, He MY. Research progress on ma huang (Ephedrae Herba) treating respiratory diseases and predictive analysis of quality markers. *J Chin Arch Trad Chin Med*. 2022;40(10):175–181+277.
103. Huang P, Huang T, Li D, et al. Molecular mechanism of xixin-ganjiang herb pair treating chronic obstructive pulmonary disease-integrated network pharmacology and molecular docking. *Evid Based Complement Alternat Med*. 2021;2021:5532009. doi:10.1155/2021/5532009
104. Wang YF, Xia XL, Ma YP. A study on the mechanism of the Xiaoqinglong decoction on chronic obstructive pulmonary sisease based on network pharmacology and molecular docking. *J Clinl J Chin Med*. 2021;13(22):1–10.
105. Jiang GW, Zang M. Effect of Xiaoqinglong Decoction on Th1/Th2 cytokines in patients with acute exacerbation of chronic obstructive pulmonary disease. *J Zhejiang J Trad Chin Med*. 2013;48(11):788–790.
106. Chen N, Yang Q. Effect of xiao qing long decoction on MUC5AC and QOL of patients with airway mucus hypersecretion. *J Tradit Chin Med*. 2020;37(05):106–109.
107. Peng M, Liu Y, Chen Y, et al. Mechanism of xiao qing long decoction and qing qi hua tan pills in improving pathological airway mucus based on nuclear factor-κB /microRNA-494 signaling regulation of mucin 5AC and cystic fibrosis transmembrane conductance regulator. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue*. 2022;34(8):831–836. doi:10.3760/cma.j.cn121430-20220310-00234
108. Yang S, Li LL, Wen P. Study on Intervention effect of ginger on chronic obstructive pulmonary disease rats with cold fluid in the lung syndrome. *J World Chin Med*. 2018;13(04):803–807.0.
109. Xie WY, Wang JY, Bao YS. Effect of modified erchentang on β2AR/β-arrestin2 signaling pathway in rats with chronic obstructive pulmonary disease. *Chin J Exp Tradit Med Formulae*. 2019;25(23):34–40. doi:10.13422/j.cnki.syfjx.20192337
110. Sun GL. Clinical study of erchen decoction combined with sanziyangqin decoction in the treatment of AECOPD patients with phlegm turbidities and lung obstruction syndrome and its effect on MUC5AC in sputum. *J China Med Univ*. 2022.
111. Wang Y. Chen Q.Based on network pharmacology, the mechanism of action of Sanzi Yangqin decoction in the treatment of chronic obstructive pulmonary disease was explored. *J Chin Trad Patent Med*. 2022;44(07):2386–2390.
112. Wan JM. Research progress on the traditional chinese medicine seed of white mustard. *J Chin J Ethnomed Ethnopharm*. 2014;23(11):20–22.
113. Valerio M, Awad AB. β-Sitosterol down-regulates some pro-inflammatory signal transduction pathways by increasing the activity of tyrosine phosphatase SHP-1 in J774A.1 murine macrophages. *Int Immunopharmacol*. 2011;11(8):1012–1017. doi:10.1016/j.intimp.2011.02.018

114. Li YL, Ma JL, Li Y. Effects of si junzi decoction combined with san zi yan qin decoction on hypersecretion of airway mucus in mice with COPD based on the method of treating lung and spleen together. *J Emerg Trad Chin Med*. 2023;32(05):777–780+800.
115. Yang JX, Yuan JL. Guan HS.Intervention of drug for invigorating blood circulation and eliminating stasis on airway remodeling of COPD rat model. *J Mod J Integrated Trad Chin Western Med*. 2013;22(23):2524–2526+2619.
116. Wang HL, Liu H, Ni HB. Effects of Xue Fu Zhu Yu decoction on inflammatory factors and TLR4/MyD88/NF—κB signaling pathway in COPD model mice. *J Emerg Trad Chin Med*. 2022;31(05):769–772.
117. Cai YJ, Shi XL, Liu HY. Effective components and pharmacological effects of Aateris Radix. *J Tradit Chin Med Sci*. 2023;42(02):39–42.
118. Lin X, Li CY, Jia MT. Research progress on chemical constituents and pharmacological effects of kuan dong hua (Farfarar Flos) and prediction and analysis of its quality markers. *J Chin Arch Trad Chin Med*. 2023;41(05):131–140.
119. Li QH, Shan Y XX. Research progress of she gan ma huang decoction and predictive analysis on its Q-markers. *J China J Chin Materia Med*. 2023;48(08):2068–2076.
120. Nie QH, Fan FY. Effects of she gan ma huang decoction and albuterol on pulmonary function and quality of life in patients with COPD. *J Tradit Chin Med*. 2020;41(02):180–182.
121. Wang SM, Ma J, Jin YM. Clinical observation on modified she gan ma huang tang plus symbicort in treating the acute attack of asthma-chronic obstructive pulmonary disease overlap syndrome. *J Nanjing Univ Tradit Chin Med*. 2017;33(05):535–537.
122. Xie LY, Liu L, Jin J. Protective effect of She gan ma huang decoction on lung tissue of rats with chronic obstructive pulmonary disease and regulation of EDFR/PI3K signaling pathway. *J China Medical Herald*. 2020;17(21):12–16+29+198.
123. Wechsler ME. Current and emerging biologic therapies for asthma and COPD. *Respir Care*. 2018;63(6):699–707. PMID: 29794205. doi:10.4187/respcare.06322
124. Riera-Martínez L, Cànaves-Gómez L, Iglesias A, Martin-Medina A, Cosío BG. The Role of IL-33/ST2 in COPD and its future as an antibody therapy. *Int J mol Sci*. 2023;24(10):8702. doi:10.3390/ijms24108702