2024 Volume 9, Issue 1
Journal of Medicines Development Sciences
ISSN: 2382-6371(Online)
ISSN: 2382-6363(Print)

Mechanism of TCM Intervention in Protease-Antiprotease Imbalance in Chronic Obstructive Pulmonary Disease: A Review

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Abstract:

The pathogenesis of chronic obstructive pulmonary disease (COPD) involves inflammation, oxidative stress, and protease-antiprotease imbalance. Among these, the protease-antiprotease imbalance is one of the main mechanisms of COPD. Increased protease can damage lung tissue by participating in inflammation, degrading the extracellular matrix, and remodeling the airways. In recent years, a large number of clinical trials and basic studies have been carried out with protease-antiprotease imbalance as a breakthrough point, accumulating fruitful results.

Keywords:

Chronic obstructive pulmonary disease
Protease-antiprotease imbalance
Pathogenesis
Clinical trial
Basic experiment
TCM
Research progress

Online publication: June 26, 2024

1. Introduction

In 2023, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) updated its definition, stating that Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous lung disease characterized by persistent and progressive airflow limitation due to abnormalities in the airways and/or alveoli. Currently, the World Health Organization reports that COPD is the third leading cause of death globally, with an estimated more than 5.4 million deaths per year attributed to COPD and its comorbidities by 2060 [1]. Epidemiological surveys indicate that the prevalence of this disease among people aged 40 and above in China is 13.7%, showing a continuous upward trend [2]. COPD often has an insidious onset and is frequently associated with multiple comorbidities, which can increase the incidence and mortality of COPD, resulting in a significant disease burden.

The imbalance between proteases and antiproteases is one of the critical mechanisms underlying the pathogenesis of COPD. It not only damages the integrity of the airway epithelium and participates in airway remodeling by excessively degrading the extracellular matrix (ECM) and epithelial junctional structures, but also promotes the aggregation of inflammatory cells and

selectively regulates inflammatory mediators, thereby exacerbating airway inflammation in COPD. This process is significant in driving the progression of COPD [3]. Therefore, regulating the protease-antiprotease imbalance is particularly important for the treatment of COPD. However, modern medicine has limited therapeutic options targeting this imbalance. Currently, alpha-1 antitrypsin augmentation therapy is used to slow down the deterioration of lung function in COPD patients, but there is still insufficient evidence of its benefits, and the high cost of treatment limits its clinical application [4]. Traditional Chinese medicine (TCM), with its broad range of targets, lasting efficacy, and few adverse reactions, holds an advantage in intervening in the pathogenic mechanism of the protease-antiprotease imbalance in COPD. In recent years, numerous clinical studies and basic experiments have been conducted in the field of TCM, focusing on the protease-antiprotease imbalance, and have yielded significant results. This article will elaborate on the mechanism of action of regulating the protease-antiprotease imbalance in COPD, exploring the perspectives of traditional Chinese medicine formulas, single herbs, and their active ingredients, aiming to provide an objective basis for the intervention of COPD with TCM.

2. COPD protease-antiprotease system

The proteases involved in the pathogenesis and progression of COPD mainly include exogenous proteases from pathogenic bacteria and endogenous proteases from neutrophils, macrophages, etc. Among them, neutrophil elastase (NE) and matrix metalloproteinases (MMPs) are most closely related to the pathogenesis of COPD [5].

2.1. Protease system

2.1.1. Neutrophil elastase (NE)

NE is mainly synthesized and secreted by neutrophils and is the primary protease in neutrophil primary granules, present at high concentrations within neutrophil azurophilic granules. The expression level of NE in normal lungs is very low, while it is significantly increased in COPD patients. NE mainly causes alveolar damage by degrading the extracellular matrix (ECM), leading to airway remodeling and lung parenchyma damage, and promoting local inflammatory responses. This perpetuates neutrophil inflammation and contributes to the pathogenesis of COPD [6].

2.1.2. Matrix metalloproteinases (MMPs)

MMPs belong to the family of endopeptidases that rely on cofactors such as zinc and calcium for active degradation of the ECM. They are mainly synthesized and secreted by various cells including neutrophils, macrophages, and monocytes. Subtypes include MMP-7, MMP-9, MMP-10, MMP-12, and MMP-28. Their main function is to degrade and remodel the ECM [7]. Among them, MMP-9 has been widely studied in the pathogenesis of COPD and is considered the primary cause of airway remodeling in COPD. MMP-9 not only causes lung tissue damage by degrading the ECM but also promotes the extracellular migration and aggregation of neutrophils and participates in airway remodeling by activating and releasing related cytokines, thereby promoting the progression of COPD [8].

2.2. Antiprotease system

2.2.1. Alpha-1 antitrypsin (α1-AT)

α1-AT is mainly produced by hepatocytes and monocytes and is the most active member of the human antiprotease system, accounting for 92% of NE inhibition. During the progression of COPD, oxygen-free radicals produced and released by neutrophils and alveolar macrophages can significantly reduce the activity of α1-AT [9]. Its main role is to inhibit NE, reducing ECM elastin degradation and alveolar damage caused by NE. It also has immunomodulatory and anti-inflammatory functions [10].

2.2.2. Tissue inhibitors of metalloproteinases (TIMPs)

TIMPs are a group of metalloproteinase inhibitors mainly secreted by macrophages and endothelial cells. They include four family members: TIMP-1, TIMP-2, TIMP-3, and TIMP-4. Their main role is to inhibit the activity of MMPs. TIMP-1 is the most active among all subclasses and is a natural tissue inhibitor of MMP-9. The imbalance of MMP-9/TIMP-1 is an important mechanism in the occurrence of COPD. Studies have found that the imbalance of MMP-9/TIMP-1 plays a crucial role in inflammatory responses, extracellular matrix degradation, and vascular remodeling in the body [11].

3. Imbalance of protease-antiprotease in the progression of COPD

3.1. Imbalance of protease-antiprotease involved in the inflammatory response of COPD

The inflammatory response is one of the main pathogenic mechanisms of COPD, and the imbalance between proteases and antiproteases can exacerbate this inflammation. On the one hand, excessive proteases can upregulate intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), promoting neutrophil chemotaxis and infiltration. This, in turn, induces airway epithelial cells to release various inflammatory mediators such as interleukin-6 (IL-6) and interleukin-8 (IL-8), forming a cascade amplification network effect [12]. On the other hand, proteases can degrade the extracellular matrix (ECM) and basement membrane, allowing inflammatory cells to migrate through blood vessels and infiltrate into the airways, thus aggravating local inflammatory responses [13]. Additionally, neutrophil elastase (NE), as a mucus secretagogue for mucous gland cells and goblet cells, can increase mucin synthesis. Excessive mucus leads to the aggregation of pathogenic microorganisms, reducing local airway defense functions and exacerbating airway inflammation [14].

3.2. Imbalance of protease-antiprotease promotes airway remodeling in COPD

Airway remodeling is one of the fundamental pathological changes in COPD, and the imbalance between proteases and antiproteases can accelerate this process. Proteases such as NE and matrix metalloproteinases (MMPs) primarily degrade the ECM, causing abnormalities in ECM components and leading to increased collagen deposition. This is a key factor in airway wall thickening and airflow limitation [15]. Furthermore, these proteases can degrade the basement membrane, resulting in the loss of airway epithelial cell integrity and damage to alveolar and small airway structures, ultimately leading to airway remodeling [12,16]. Studies have shown that NE and MMP levels can simultaneously increase in COPD patients and are positively correlated with the severity of COPD [17]. NE and MMP can also exert synergistic destructive effects by eliminating each other's inhibitors, further aggravating lung tissue damage and persistent airway inflammation, leading to airway remodeling and reduced lung compliance [18]. The imbalance between NE/α1-AT and MMP/TIMP is a significant factor in COPD airway remodeling, and the imbalance of MMP/TIMP has been a recent research focus, considered a marker reflecting airway tissue damage and repair [11]. Under normal circumstances, these factors counteract and influence each other, maintaining a dynamic balance to preserve airway function. However, when stimulated by pathogenic factors, their imbalance leads to the onset of COPD [19].

4. Intervention of traditional Chinese medicine in the mechanism of protease-antiprotease imbalance

Based on symptoms such as wheezing, shortness of breath, chest fullness, and suffocation, COPD is categorized under "lung distension" and "dyspnea syndrome" in traditional Chinese medicine. The pathogenesis of COPD is generally characterized by deficiency in origin and excess in superficiality. The stable phase is dominated by deficiency, manifesting as deficiency of the lung, spleen, and kidney, or even deficiency of all three organs. The acute phase is primarily characterized by excess, with pathological factors such as turbid phlegm, fluid retention, and blood stasis. Targeting its etiology and pathogenesis, treatment focuses on strengthening the body's resistance in the stable phase and eliminating pathogenic factors in the acute phase. Clinically, methods such as clearing heat and resolving phlegm, promoting blood circulation and removing blood stasis, nourishing the lungs and kidneys, and warming the spleen and yang are often combined to achieve the effect of eliminating pathogenic factors and stabilizing the body. As stated in the "Su Wen: Sheng Qi Tong Tian Lun Pian," "When Yin and Yang are balanced and harmonious, the spirit and essence are governed. When Yin and Yang are separated, the vital essence is exhausted." Under physiological conditions, the body's Yin and Yang are in a dynamic balance state of mutual restraint and mutual growth, allowing the body's life activities to operate normally [20]. Similarly, proteases and antiproteases are in such a balance under physiological conditions. However, when proteases increase and antiproteases decrease, it leads to an imbalance of Yin and

Yang, triggering the progression of COPD. Traditional Chinese medicine follows the treatment principle of "replenishing deficiencies and reducing excesses" to regulate the imbalance of protease-antiprotease. On the one hand, it downregulates NE and MMP to inhibit inflammatory responses and delay airway remodeling. On the other hand, it upregulates α1-AT and TIMP to inhibit and deactivate NE and MMP, correcting the imbalance and delaying the decline in lung function.

4.1. Intervention of traditional Chinese medicine compounds in the imbalance mechanism of protease-antiprotease

Zhu *et al.* (2023) [21] observed the treatment of COPD with Ginseng Bufei Baoyuan Decoction and noninvasive positive pressure ventilation. The results showed that the levels of MMP-9 and Cyclooxygenase-2 (COX-2) in the medication group were lower than those in the control group, and the lung function indicators such as Peak Expiratory Flow (PEF), First Second Forced Expiratory Volume/Forced Vital Capacity (FEV1/FVC), and FEV1 were higher than those in the control group. This suggests that this formula has the effect of reducing MMP-9 and improving lung function. Lu *et al.* (2022) [22] used Shenqi Bufei formula to treat COPD and found that after using this formula, MMP-9, Vascular Endothelial Growth Factor (VEGF), neutrophils, and IL-8 decreased in COPD patients. This suggests that this formula inhibits inflammatory reactions and improves airway remodeling by reducing airway remodeling indicators such as MMP-9, while also playing a role in inhibiting vascular remodeling. Feng *et al.* (2022) [23] observed the effect of Xiefei Dingchuan Decoction on AECOPD and found that the levels of MMP-9, IL-6, CRP, and PCT decreased in AECOPD patients after using this formula. This suggests that this formula improves airway inflammation and airway remodeling in AECOPD through multiple targets and functions. Bufei Huoxue Capsule is a commonly used Chinese patent medicine in clinical practice, which has the functions of nourishing the lungs, tonifying the kidneys, replenishing Qi, and activating blood circulation.

Shi *et al.* (2022) [24] found through animal experiments that the expression levels of TGF-β1, Smad2/3, Smad4, NE, αl-AT, and MMP-9 in rats were significantly reduced after intervention with Bufei Huoxue Capsule. It is speculated that its possible mechanism is to improve airway remodeling in COPD by inhibiting the TGF-β1/Smads signaling pathway and regulating the imbalance between protease and antiprotease. Liao *et al.* (2021) [25] confirmed that Weijing Decoction can inhibit airway remodeling in AECOPD model rats. Its mechanism is related to down-regulating the expression of MMP-9 and TIMP-1 mRNA in lung tissue and up-regulating the expression of Hyperplasia Suppressor Gene (HSG) in lung tissue. Shen *et al.* (2021) [26] stated that Bufei Wenshen Huoxue formula has a good clinical effect in treating patients with stable COPD. This formula improves the condition of COPD by inhibiting the production of inflammatory mediators such as IL-1, IL-8, and TNF-α, and regulating the imbalance of MMP-9/TIMP-1. Niu *et al.* (2021) [27] found that modified Erchen Decoction can reduce the content of MMP-2 and MMP-9, inhibit the expression of High Mobility Group Box 1 Protein (HMGB1) in rats, thereby improving lung tissue inflammation and delaying the process of airway remodeling in COPD model rats. Ma *et al.* (2020) [28] used Feixin Ning Decoction to intervene in COPD rats and found that this formula intervenes in airway remodeling by increasing TIMP-1 levels and inhibiting the expression of MMP-9 mRNA in lung tissue. Qinma formula is an empirical formula of National Medical Master Qiu Peiran. Ding *et al.* (2017) [29] stated that this formula can reduce the destruction of alveolar and tracheal structures in COPD, reverse the occurrence of airway remodeling, and improve respiratory function by reducing the content of TGF-β1, MMP-9, and TIMP-1 in model rats. Liao *et al.* (2022) [30] found that Compound Fu Er Cao mixture can reduce the content of MMP-2, MMP-9, TGF-β, and TIMP-1 in serum and alveolar lavage fluid, reduce the average thickness of bronchial wall and smooth muscle area, and improve pulmonary ventilation dysfunction.

Furthermore, some studies have shown that Qi Zhi Zhou Fei Granules [31], Shun Qi Hua Tan Formula [32], Tong Fu Ding Chuan Decoction [33], He Che Da Zao Capsule [34], Qing Fei Hua Tan Granules [35], Bu Zhong Yi Qi Decoction [36], and Ma Xing Xie Bai Powder [37] can also inhibit airway remodeling and reduce inflammatory responses by regulating the imbalance of protease-antiprotease systems, thereby improving COPD. The above evidence suggests that traditional Chinese medicine

compounds that intervene in the imbalance of protease-antiprotease in COPD have multi-target, multi-effect, and multi-pathway characteristics. They can not only regulate the secretion of inflammatory mediators and inhibit inflammatory responses but also improve airway remodeling and reduce lung tissue damage. Among the screened relevant literature, the imbalance of MMP9/TIMP-1 and the inflammatory response caused by this imbalance are current research hotspots in the protease-antiprotease system of COPD. Traditional Chinese medicine intervenes in the imbalance of MMP9/TIMP-1 while inhibiting the production of inflammatory mediators such as IL-1, IL-8, and TNF-α. The efficacy of the included traditional Chinese medicine compounds mainly focuses on clearing heat, resolving phlegm, nourishing Qi, activating blood circulation, tonifying the lungs, strengthening the spleen, and nourishing the kidneys. This is consistent with the pathogenesis characteristics of COPD, which involves a mixture of deficiency and excess and affects the lungs, spleen, and kidneys [38].

4.2. Single herbs and their components intervening in the imbalance mechanism of protease-antiprotease

Bai Ling Capsule is composed of fermented Cordyceps sinensis powder and is a commonly used drug for respiratory systems. Xue *et al.* (2018) [39] found through clinical trials that after taking Bai Ling Capsule, COPD patients had significantly reduced serum levels of TGF-β, MMP-9, and the MMP-9/TIMP-1 ratio. The BODE index of the patients decreased, and clinical symptoms improved. Ginkgo extract is derived from *Ginkgo biloba* leaves. Modern pharmacology has found that it has anti-inflammatory, free radical scavenging, and cardio-cerebrovascular circulation-improving effects [40]. Yang *et al.* (2018) [41] confirmed that it can not only reduce the expression of MMP-9 and TIMP-1 in the lung tissue of COPD rats but also improve airway remodeling and inhibit the occurrence of pulmonary fibrosis in COPD rats by regulating the proportional balance of MMP-9 and TIMP-1. *Polygonum cuspidatum* has the effects of promoting blood circulation to relieve pain, clearing heat and draining dampness, resolving phlegm, and relieving cough. Modern pharmacological research has found that it has the effects of relieving cough and expectoration, lowering blood pressure and lipid levels, anti-inflammation, and anti-oxidation [42]. Huang *et al.* (2017) [43] found that it can intervene in the imbalance of MMP-9/TIMP-1 in rats at the protein and gene levels, thereby slowing down airflow limitation, improving lung function, and playing a role in preventing and treating COPD. *Tetrastigma hemsleyanum* has the effects of clearing heat and detoxifying, dispelling wind and resolving phlegm, promoting blood circulation, and relieving pain. It is used in folk medicine to treat febrile convulsions, pneumonia, hepatitis, and other diseases [44]. Jiang *et al.* (2016) [45] stated that the water extract of *Tetrastigma hemsleyanum* can down-regulate the expression of MMP-9 and TIMP-1 in COPD rats, regulate the imbalance of MMP-9/TIMP-1, thereby intervening in airway remodeling and delaying disease progression. *Astragalus polysaccharides* are the main active ingredients of Astragalus. Modern pharmacological research has confirmed their effects on regulating immunity, lowering blood sugar, and anti-tumor activities [46].

Yu *et al.* (2012) [47] demonstrated that they can improve lung tissue damage and lung function by inhibiting the expression of MMP-9 and TIMP-1 in the lung tissue of COPD rats, and found a negative correlation between FEV0.2/FVC and the ratio of MMP-9/TIMP-1. Curcumin is a lipophilic polyphenol extracted from traditional Chinese medicine turmeric, which has various pharmacological effects such as anti-inflammatory, anti-infection, anti-oxidation, and anti-tumor activities [48]. Zhang *et al.* (2022) [49] found that curcumin can not only reduce the content of TNF-a, IL-1β, and IL-6 in lung tissue to inhibit inflammatory responses, but also down-regulate the expression of Caspase-3, MMP-9mRNA, reduce the expression of TLR4, MyD88 protein, and the phosphorylation level of IkBa. Additionally, it increases SOD activity and reduces NF-kBp65 nuclear translocation. It is speculated that its mechanism of action may be related to inhibiting the activation of the TLR4/NF-KB signaling pathway. Zhou *et al.* (2021) [50] discovered that curcumin can reduce IL-8, TGF-a, and neutrophil ratios. Besides inhibiting the inflammatory response by suppressing the IL-8/MUC5AC pathway, it can also lower MMP-2 and MMP-9 levels to protect the airways. *Reineckea carnea* is one of the traditional herbal medicines commonly used by ethnic groups such

as Tujia and Miao in southwest China. It has the functions of clearing the lungs, relieving cough, cooling blood and stopping bleeding, detoxifying, and relieving sore throat. Modern pharmacology has confirmed its anti-inflammatory, cough-relieving, phlegm-resolving, and analgesic effects [51]. Chen *et al.* (2020) [52] stated that after intervention with the water extract of *Reineckea carnea*, cytokines and inflammatory mediators such as IL-1B, IL-6, COX-2, and Prostaglandin E_2 (PGE2) in the serum of COPD mice decreased to varying degrees. The expression of MMP9 was reduced, inflammatory cell infiltration was decreased, and no significant abnormalities were observed in the airway structure. The airway resistance, airway elastic resistance, and main airway resistance of the mice were all reduced, while dynamic compliance was increased.

The above evidence suggests that single herbs and their active ingredients mainly play a role in reducing airway remodeling and protecting lung tissue by lowering MMP-9 and inflammatory mediator levels and regulating the imbalance of MMP-9/TIMP-1. Through screening the literature, it was found that this research direction mostly involves *Cordyceps sinensis*, Astragalus, *Ginkgo biloba*, *Polygonum cuspidatum*, turmeric, *Tetrastigma hemsleyanum*, *Reineckea carnea* and their active ingredients. These traditional Chinese medicines include tonifying, blood-activating, heat-clearing, and phlegm-resolving herbs, which are related to the pathogenesis of COPD with a mixture of deficiency and excess, and pathological products such as phlegm, heat, and blood stasis. Single herbs and their ingredients are more straightforward than compound formulas of traditional Chinese medicine, and their action pathways in the body are relatively clear. This facilitates the study of precisely targeted regulation of traditional Chinese medicine and is one of the important ways to promote traditional Chinese medicine.

5. Conclusion

In summary, traditional Chinese medicine has a definite effect on regulating the imbalance of protease-antiprotease in COPD. This article summarizes the impact of traditional Chinese medicine compounds, single herbs, and their active ingredients on the imbalance of protease-antiprotease in COPD over the past ten years, systematically and comprehensively explaining their mechanism of action. After summarizing the clinical research and basic experiments of traditional Chinese medicine, it was found that traditional Chinese medicine compounds can play a role in regulating the imbalance of protease-antiprotease in COPD through multiple targets and pathways such as clearing heat and resolving phlegm, promoting blood circulation and dredging meridians, strengthening the spleen and nourishing Qi, and tonifying the lungs and nourishing the kidneys. This, to some extent, compensates for the lack of Western medicine treatment options targeting protease-antiprotease imbalance. Modern pharmacological research has confirmed that single Chinese herbal medicines and their active ingredients often have anti-inflammatory, anti-infective, immune-modulating, antioxidant, and phlegm-resolving effects, which align with the pathogenesis of COPD, including airway inflammation, oxidative stress, immune dysregulation, and high secretion of airway mucus.

The mechanisms of traditional Chinese medicine's intervention in protease-antiprotease imbalance can be summarized as follows:

(1) It reduces the content of MMP and NE, inhibits the aggregation of neutrophils and the release of inflammatory mediators, and reduces inflammatory infiltration and direct damage to lung tissue;

(2) It increases the content of a1-AT and TIMP, inhibits and inactivates proteases, and plays a role in protecting airway tissue;

(3) It reduces MMP and NE proteases while increasing al-AT and TIMP protease inhibitors, regulating the imbalance of MMP/TIMP and NE/al-AT, intervening in airway remodeling, and delaying the progression of COPD.

However, there are limitations in the research on the intervention of protease-antiprotease imbalance by traditional Chinese medicine:

(1) There is still a lack of deep exploration of specific mechanisms targeting protease-antiprotease imbalance. Future research can focus on the relationship between proteases, protease inhibitors, and related inflammatory mediators and molecular signaling pathways, with the aim of deeply exploring the impact of

protease-antiprotease imbalance on COPD.

(2) Traditional Chinese medicine compounds are complex systems composed of multiple components, with multi-target and multi-effect characteristics. However, the active ingredients are not clear, and there is a lack of research on pharmacokinetics and pharmacodynamics. In the future, multi-omics and biological effect methods can be used to explore the material basis for the efficacy of drugs, providing objective support for the efficacy of traditional Chinese medicine.

(3) Research on single Chinese herbal medicines mainly focuses on basic experiments, and there is a lack of human trials. Moreover, there are very few single Chinese herbal medicines that have been developed into drugs. In the future, extraction, separation, and purification techniques of traditional Chinese medicine can be used to clarify the active ingredients of single herbs, laying a technical foundation for the development of single herbs into drugs.

Funding

National Natural Science Foundation of China (Project No.: 82205036); Science and Technology Innovation Project of China Academy of Chinese Medical Sciences (Project No.: C12021A01102); Scientific Research Project of Wangjing Hospital, China Academy of Chinese Medical Sciences (Project No.: WJYY2020-20)

Disclosure statement

The authors declare no conflict of interest.

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