Using Traditional Chinese Medicine to Alleviate Chronic Obstructive Pulmonary Disease

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Abstract: Chronic obstructive pulmonary disease (COPD) is a common respiratory disease with high incidence in the world. Its main feature is that the lungs are affected by airflow obstruction. The disease can lead to impaired lung function in adults and cannot be completely cured. This paper expounds the pathogenesis of COPD, which can be alleviated by chemical methods and TCM methods. TCM treatment of COPD has the advantage of overall regulation, which can improve airway remodeling and alleviate the development of the disease. According to their structure, TCM therapeutic drugs can be divided into flavonoids, terpenoids, phenylpropanoids and alkaloids. On this basis, the article summarizes the advantages and disadvantages of common Chinese medicine administration methods, aiming to provide some reference and help when alleviating the disease.

Keywords: COPD; Flavonoids; Terpenoids; Alkaloids; Phenylpropanoids

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1. Introduction

COPD is a treatable progressive disease, which can cause chronic lung inflammation, excessive mucus secretion, airway remodeling and emphysema, resulting in some significant lung disease effects. Patients with COPD generally have symptoms of dyspnea, cough and expectoration, and may be accompanied by other symptoms of the body, such as fatigue, weight loss, loss of appetite and sleep disorders. Severe cases can also cause other complications of the body, affecting physical health. Now the traditional Chinese medicine treatment of the disease can effectively alleviate the symptoms and reduce the pain caused by the disease, but there is still no way to completely cure the disease.

2. The Pathogenesis of COPD

COPD is the result of the interaction of inflammatory cells such as macrophages, neutrophils, T lymphocytes, structural cells such as endothelial cells and epithelial cells, enzymes such as matrix metalloproteinases, cathepsins and inflammatory factors such as interleukin (IL) and tumor necrosis factor (TNF). COPD can be caused by viral infection and bacterial infection. Common pathogenic viruses include respiratory syncytial virus, coronavirus, adenovirus and human metapneumovirus. Common pathogens of bacterial infection include Pseudomonas aeruginosa, Klebsiella pneumoniae and Haemophilus influenzae[1]. In addition to infectious causes, non-communicable causes are related to long-term exposure to harmful particles gases. Smoking (passive or active) is the main cause of disease, and about 20% patients suffer from COPD due to smoking.

The activation of NF-κB signaling pathway is essential in the pathogenesis of COPD, It has an important influence on the regulation of human lung and regulates the activity of various cytokines. Under physiological conditions, NF-κB and its inhibitory protein IκB (IκB) are combined in the cytoplasm into an inactive state. When normal cells are stimulated by inflammatory cytokines, they can activate IκB kinase, so that IκB phosphorylation is degraded. NF-κB is transferred from the cytoplasm to the nucleus and binds to the κB site of the target gene, which can induce and enhance gene transcription expression, and then produce various biologically active cytokines to activate inflammatory cells, leading to increased inflammation process.

3. Treatment

In the treatment of COPD, bronchodilators, glucocorticoids, antibiotics, β2 adrenergic receptor agonists, theophylline and so on are usually used in clinical treatment[2]. These drugs can effectively relieve symptoms and achieve better results in acute exacerbation, but the long-term effect is not significant. Traditional Chinese medicine has the advantage of overall regulation in the treatment of COPD. The chemical components of traditional Chinese medicine have good anti-inflammatory activity, which can improve airway remodeling and alleviate the development of the disease. TCM drugs for relieving COPD can be divided into four types according to their components.
3.1. Flavonoids

It is a flavonoid compound based on the skeleton of 2-phenylchromone-4-one (2-phenyl-1-benzopyran-4-one). The basic mother nucleus is 2-phenylchromone compounds. They are widely found in fruits, vegetables, tea, wine, seeds or plant roots. Flavonoids have the effects of anti-oxidation, improve vascular disease, enhance gastrointestinal absorption, reduce their blood lipids, and increasing body resistance. They can also inhibit bacteria, viruses, and tumors, especially have significant antibacterial activity. Therefore, flavonoids play an increasingly important role as antibacterial drugs or antibacterial combination drugs in the antibacterial field[3]. For the treatment of COPD disease, there are several kinds of traditional Chinese medicine can be used for treatment.

3.1.1 Luteolin

Luteolin is a natural tetrahydroxyflavone compound. The data of Chen et al. showed that Luteolin can use its own antioxidant capacity to inhibit the activation of NF-κB and AP-1 dependent on oxidative repair, and also inhibit the expression of inflammation-related genes (TNF-α, IL-6, iNOS and COX-2), resulting in anti-inflammatory effects. It can alleviate the symptoms of dyspnea in patients with COPD and significantly improve lung function[4].

3.1.2 Naringenin

Naringenin is a natural flavonoid with a chemical name of 5,7,40-trihydroxyflavone. Liu et al. reported that naringenin can reduce the inflammatory response in cs-exposed mice and participate in inhibiting the expression of signaling pathways that produce COPD inflammation. Appropriate dose of naringenin can reduce the production of IL-8 and TNF-α in bronchoalveolar lavage fluid and serum of mice and reduce the level of matrix metalloproteinase (MMP)-9[5]. Zhang et al.’s article shown that oral administration of naringenin can improve lung injury by down-regulating radiation-induced IL-1β levels in mice. Therefore, naringenin can relieve the pain of COPD patients by inhibiting the inflammatory factors IL-8 and TNF-α[6].

3.1.3 Puerarin

Puerarin is the main bioactive component of Pueraria lobata. It is a kind of isoflavone compound with antipyretic, analgesic, anti-inflammatory and anti-tumor effects. Puerarin can inhibit the injury of human lung tissue caused by LPS[7]. Pan et al. established a COPD rat model and compared the inflammatory factors in alveolar lavage. The proportion of IL-1β, TNF-α and IL-6 decreased, which could reduce the occurrence of inflammation and protect lung function. Through the expression of PINK1-parkin pathway and apoptosis-related proteins in each group, it can be known that the activation of PINK1-parkin pathway leads to the continuous damage of mitochondria and excessive autophagy, resulting in apoptosis and COPD inflammation. Puerarin can induce mitophagy by regulating the pathway, inhibit the apoptosis of alveolar epithelial cells, and reduce the inflammatory response of COPD.

Polyphenols mainly delay the progression of COPD by regulating inflammatory mediators such as nuclear transcription factor kB, IL-8, and TNF-α.
3.2. Terpenoids

It refers to the presence of hydrocarbons and their oxygen-containing derivatives in nature with molecular formulas of isoprene units. Terpenoids are ubiquitous in nature and are mostly related to the composition of plant flavors, resins, pigments and other substances. Terpenoids have received extensive attention due to their important activities such as anti-cancer, anti-virus and anti-inflammation, so they can be used to relieve COPD symptoms[8]. Common Chinese herbal medicines in medicine are the following:

3.2.1 Andrographolide

Andrographolide is a diterpene lactone with biological activity, mainly extracted from andrographis paniculata[9]. Studies have confirmed that andrographolide can inhibit the biological activity of NF-kB, a transcription factor expressed by pro-inflammatory genes. It can induce and regulate genes such as TNF-α, IL-8 and IL-6, promote the transcription and translation of inflammatory cytokine mRNA, and cause inflammatory response[10]. Linder et al. pointed out that the median of serum MMP-9 in COPD patients is significantly higher than that in healthy people. The production of MMP-9 is mainly regulated by upstream TNF-α and NF-kB. Therefore, it is found that the pathway of inhibiting TNF-α and NF-kB-induced MMP-9 expression can be considered as an important pathway and potential therapeutic target for AECOPD inflammatory response[11].

3.2.2 Artesunate

Artesunate is contained in semi-synthetic artemisinin derivatives, artesunate is a widely existing bitter substance. Because of its various pharmacological effects, it has significant therapeutic potential in a variety of respiratory diseases, and also has a certain effect in the treatment of COPD. By establishing a Balb/c mouse model, Wang et al. found that airway resistance decreased after inhalation of artesunate aerosol in mice, and the traction of cultured ASMCs decreased after exposure to artesunate solution, inducing intracellular calcium flux. A certain dose of artesunate has a certain effect on improving airway resistance in mice and cultured ASMCs. Increasing the absorbed dose of artesunate can be a gradual expansion of the contracted bronchus and relieve the symptoms of COPD[12].

3.2.3 Gentiana

Shiwei gentian flower has the effects of resolving phlegm and relieving asthma. It is used to treat cough and yellow sticky phlegm caused by phlegm-heat obstructing lung. In Peng et al. ’ s experiment, by taking Shiwei Longdanhua capsule combined with salmeterol fluticasone, it was concluded that Shiwei Longdanhua could reduce the levels of inflammatory factors ( TNF-α, CRP, PCT ) in patients, improve the TCM syndromes of phlegm-heat obstructing lung syndrome, enhance the lung function of patients, thereby improving the lung ventilation function, effectively improving the airway inflammation response of patients, and alleviating the clinical symptoms of patients.

Terpenoids mainly relieve the symptoms of COPD by improving the respiratory diseases of patients.
3.3. Alkaloids

Alkaloids are a class of basic organic compounds. Most of them have complex cyclic structures[13]. The alkaloids have a certain optical rotation and absorption spectrum, mostly colorless crystalline, and a few are liquid[14]. The structural diversity and biological activity of alkaloids can be deeply understood by transcriptomics and genomics methods combined with metabolomics data[15]. Alkaloid Chinese medicinal materials for the treatment of COPD are mostly the following:

3.3.1 Ephedra sinica

Ephedra sinica is a herbaceous plant. Its stems and roots are dried and used as medicine. It is a traditional Chinese herbal medicine. It can extract alkaloids, pseudoephedrine and other components to make Chinese patent medicine or compound preparation. In 1885, Yongjing separated ephedrine from ephedra, which has the effects of sweating, dispersing cold, dispersing lung and relieving asthma, diuresis and detumescence[16]. The experimental results showed that ephedra polysaccharide had a protective effect on airway and lung inflammation. Ephedra polysaccharide reduced the expression of TNF-α, IL-6, IL-8 and MMP-9, and also reduced the expression of Smad2 / 3. Therefore, ephedra polysaccharide alleviated airway and lung inflammation by regulating inflammatory factors and signaling pathways[17].

3.3.2 Berberine

The main active structure of berberine is isoquinoline alkaloids. It has many characteristics such as anti-pathogenic bacteria and anti-oxidation. Wang et al found that CSE could increase the proportion of inflammatory cells in BALF, improve the score of pneumonia inflammation. By using berberine, it was found that it can inhibit the activity of TGF-β1 / Smads signaling pathway, which has the opposite mechanism of action for CSE-induced COPD mice and has a therapeutic effect[18]. Therefore, high-dose berberine can be used to treat COPD.

Alkaloids alleviate lung diseases caused by COPD by reducing the expression of TGF-β1, Smad2 and Smad3.

3.4. Phenylpropanoids

It refers to the natural organic compound group with one or several C6-C3 units in the basic parent nucleus. Phenylpropanoids are synthesized from cinnamic acid pathway, and the key precursor of biosynthesis is p-hydroxycinnamic acid. Because of its unique structure, phenylpropanoids have good biological activities in antioxidant, antibacterial, antiviral, anti-tumor, immune regulation, cardiovascular and endocrine regulation, so they can be used to treat COPD.

3.4.1 Schisandra

Schisandrae Chinensis Fructus is the mature fruit of the Magnoliaceae plant Schisandrae Chinensis Fructus. It has the effects of astringent and astringent, benefiting qi and generating fluid, tonifying kidney and calming heart. It can be used to treat long-term cough, deficiency and asthma, fluid injury and thirst, internal heat and diabetes. Wang et al. found that the mortality rate of cells in rats treated with SchA was lower than that of
unused cells after primary culture of rat cortical neurons, indicating that SchA can improve cell viability[19]. In addition, Zhang et al. have shown that SchA has a therapeutic effect on mice induced by CSE combined with LPS. A certain dose of SchA can inhibit the expression of inflammatory factors. SchA can play an anti-inflammatory role in the treatment of COPD.

3.4.2 Asarum

Asarone is the extract of Asarum, the main component of which is α-asarone. It has the effects of relieving asthma, relieving cough and expectorant, sedation and spasmolysis[20]. The study of asarone in the treatment of acute exacerbation of COPD can significantly reduce IL-4 and IL-8, improve the symptoms and signs, and improve the lung function of patients. Inflammatory cytokines IL-4 and IL-8 are closely related to airway and lung inflammation, which reflects the degree of airway inflammation in COPD to a certain extent. Observations have shown that asarone is effective in treating acute exacerbation of COPD and can significantly improve the lung function of patients. The mechanism of action is related to the expression of inflammatory factors[21].

3.4.3 Arctium

It is a dry and mature fruit of burdock, a 2-year-old herbaceous plant of Compositae. It is odorless, slightly spicy and slightly numb tongue after bitter taste. It has the effects of evacuating wind-heat, ventilating lung and removing phlegm, relieving sore throat, detoxifying and detumescence. It is not suitable for cold, qi deficiency and loose stool. Arctigenin is an anti-inflammatory component extracted from Arctium. Arctigenin inhibited the expression of iNOS and the activation of MAPK in RAW264.7 macrophages. In view of these findings, Zhang et al. found that Arctigenin can regulate MAPKs, HO-1 and iNOS. However, the role of signaling pathways needs further study (22). In conclusion, Arctigenin has an effect on lung disease and oxidative damage caused by COPD, and can be used to alleviate COPD.

Phenylpropanoids inhibit the expression of inflammatory factors by improving lung symptoms and treat COPD symptoms.

4. Treatment modalities

Traditional Chinese medicine treatment has the advantages of overall dialectical thinking and multi-target, multi-channel, multi-link intervention and individual treatment. Some traditional Chinese medicine has obvious anti-inflammatory effect on COPD, which is in line with the principle of COPD treatment. The effectiveness and safety of traditional Chinese medicine treatment are also recognized by clinicians. Therefore, it can be divided into oral treatment, atomization treatment and external treatment according to its treatment methods. Through these three methods, the symptoms can be significantly alleviated. Each method has its own obvious advantages, but also has different shortcomings, as shown in table 1.
Tab.1 Advantages and disadvantages of different treatment modalities

<table>
<thead>
<tr>
<th>Treatment methods</th>
<th>Advantage</th>
<th>Disadvantage</th>
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<tbody>
<tr>
<td>Oral medication</td>
<td>1. The administration method is simple; 2. It does not directly damage the skin or mucosa, and has painless and non-invasive characteristics.</td>
<td>1. Unconsciousness or coma patients should not be used; 2. Some drugs can produce adverse gastrointestinal stimulation.</td>
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<tr>
<td>Atomization treatment</td>
<td>1. Inhaled drugs can be directly into the respiratory tract, its dosage is only one-tenth of other ways of administration, significantly reducing the side effects of drugs; 2. Humidify the airway, dilute sputum, can be widely used in various respiratory diseases; 3. For some virus-based, self-healing diseases, aerosol inhalation therapy can significantly and quickly reduce symptoms and shorten the course of disease.</td>
<td>1. Don’t eat as much as possible half an hour before aerosol inhalation treatment to prevent the liquid from stimulating the airway during inhalation and causing vomiting; 2. Atomization inhalation may lead to accidental aspiration choke into the trachea.</td>
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<tr>
<td>Acupoint application</td>
<td>1. The method is simple, does not require complex, sophisticated medical equipment, parts are easy to identify, easier to learn and master; 2. Safety, small side effects, traditional Chinese medicine sticking on the body surface, no internal medicine to bring bitter taste and gastrointestinal reactions.</td>
<td>1. Acupoint application has a certain stimulating effect on the skin, and sometimes it can cause local skin redness, itching, burning, pain, etc., and may even have adverse reactions such as blisters. 2. Slow effect, it is easy to repeat the disease effect in general.</td>
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5. Summary and prospect

At present, there is no complete cure for COPD. Chinese herbal medicines containing flavonoids, terpenoids, phenylpropanoids and alkaloids can be selected for treatment to improve the symptoms and relieve the pain of patients. In addition, COPD can be prevented by self-restraint.

(1) Quit smoking. Studies have shown that smoking cessation can reduce the risk of disease and improve physical health. For patients who have been ill, smoking cessation can also alleviate the symptoms and effectively avoid further deterioration of the disease.

(2) Inoculation. The main vaccines for this disease are influenza and Streptococcus pneumoniae vaccines, including polysaccharide conjugate vaccines and polysaccharide vaccines. Vaccination with this vaccine significantly reduces the risk of illness and the severity of illness.

(3) Self-management. A self-management program for COPD patients shows that hospitalization rates can be significantly reduced by receiving disease education, learning breathing and coughing skills, practicing energy conservation in daily activities, learning symptom prevention and control, and improving lifestyles (including nutrition and exercise). Patients can be treated safely at home to reduce the demand for hospital beds(23).
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