International Journal of Clinical and Experimental Medicine Research, 2023, 7(2), 103-110
https: //www.hillpublisher.com/journals/ijcemr/
ISSN Online: 2575-7970
ISSN Print: 2575-7989

Progress in the Protective Mechanism of Salidroside in Chronic Obstructive Pulmonary Disease

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How to cite this paper: Ming Ruan, Ruicheng Hu. (2023) Progress in the Protective Mechanism of Salidroside in Chronic Obstructive Pulmonary Disease. *International Journal of Clinical and Experimental Medicine Research*, 7(2), 103-110.
DOI: 10.26855/ijcemr.2023.04.001

Received: January 20, 2023
Accepted: February 18, 2023
Published: March 15, 2023

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Abstract

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung disease that is persistent, repeatedly deteriorating airway obstruction due to respiratory abnormalities (bubuchitis, bronchiolitis) and/or alveolar abnormalities (emphysema). Salidroside, a widespread natural phenolic secondary metabolite found in Rhododiola, has several pharmacological effects. Relevant studies have shown that salidroside has protective effects in anti-diabetes, anti-cancer, anti-aging, heart and nerve protection, etc. Due to the limitations of clinical drug use in COPD, salidroside has multiple functions and low side effects, and its protective effect and mechanism of action on COPD have attracted increasing attention. By collecting relevant papers published in recent years, reviewed in the literature against oxidative stress, regulation of protease/anti-protease imbalance, anti-inflammatory, anti-bronchiolar and interstitial fibrosis, anti-telomere shortening, expounds the protective effect and mechanism of its effect in COPD, and provide reference for its clinical application. The clinical and experimental data are not sufficient, and the role and mechanism of salidroside need to be further studied.

Keywords

Salidroside, COPD, oxidative stress, protease/anti-protease, anti-inflammatory

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases [1]. Chronic obstructive pulmonary disease is currently one of the top three causes of death globally, with 90% of deaths occurring in low-income and middle-income countries [2]. The 2017 Global Burden of Disease Study (GBD) estimated the global point-in-time prevalence of COPD in 2017 was 3.92% [95%CI (3.52%, 4.32%)], and the fatality rate due to COPD was 42/100(4.72% of all-cause deaths). The estimated disability-adjusted life years (DALYs) rate was 1068.02/100,000. In the United States, the projected cost of treating COPD over the next 20 years is $800.09 billion, or about $40 billion per year [3]. Its high prevalence, high morbidity and mortality lead to increased personal, social and economic burdens, making COPD a major global health problem and an important public health challenge. With the increasing prevalence of smoking in developing countries and the increasing population aging in high-income countries, the prevalence of COPD is expected to rise over the next 40 years, with potentially over 5.4 million deaths from COPD and related diseases each year by 2060. Therefore, the prevention and treatment of COPD need to be paid necessary attention.

1. Current application status of clinical drugs in COPD

Some commonly used drugs include bronchodilators, corticosteroids, and/or antibiotics, mucolytic agents, and antioxidants. In addition to antibiotics, most COPD medications should be taken daily, usually for life. However, there are side effects of long-term use, for example, the main side effects of β 2 receptor agonists are rapid heartbeat, muscle tremors, and metabolic disorders; the side effects of anticholinergic drugs include dry mouth, blurred vision, urinary retention, postural hypotension, cognitive problems, and cardiac rhythm disorders; long-term use of glucocorticoids can induce and aggravate infection, causing hyperglycemia, osteoporosis, and even mental disorders [4-7]. Therefore, it is a major point of current research to find a drug that can be used for a long time with few adverse reactions.

2. The pharmacological effects of salidroside

Salidroside is the main active ingredient of the Tibetan medicine rhodiola (Rhodiola rosea L.), whose chemical name is hydroxyphenyl ethyl- β -D-glucoside, and whose glycoside element is hydroxyphenyl ethanol, namely tyrosol [8]. Traditional Chinese Medicine records that salidroside has the effects of anti-hypoxia, anti-fatigue, reducing pulmonary hypertension and anti-aging. Modern pharmacological studies have shown that salidroside is a promising environmental adaptation drug with low toxicity and few side effects. It has a wide range of pharmacological properties, including cardiovascular system and central nervous system activities, anti-hypoxia, anti-fatigue and anti-aging activities, anticancer activities, anti-inflammatory activities, antioxidant activities, antiviral and immune-stimulating activities, anti-diabetes activities, anti-osteoporosis activities, etc. It can be used for the treatment of diabetes, hypertension, pulmonary heart disease, coronary heart disease, rheumatism, depression and other chronic diseases, so it has attracted much attention [9-17].

3. Salidroside plays a protective role in COPD

The pathogenesis of COPD is still unclear, and it is generally believed to be related to oxidative stress, inflammation, protease/antiprotease imbalance and immunity decline. Oxidative stress, excessive protease production and apoptosis induced by biofuel smoke are the main factors of COPD. At present, a number of studies have suggested that salidroside has a protective effect on COPD. In this paper, the pathological mechanism of COPD proposed by GOLD was taken as the entry point to review and discuss the protective effect and its mechanism on COPD, in order to provide a basis for the clinical intervention of salidroside in COPD.

3.1 Resistance to oxidative stress

Oxidative stress refers to the imbalance between prooxidants and antioxidants, accompanied by the dysregulation of redox pathways and macromolecular damage. It is the main driving mechanism and an important amplification mechanism of COPD. Oxidative stress enhances the inflammatory activity in the lungs, further promoting the progression of COPD. Exogenous oxidants in cigarette smoke and air pollution, as well as endogenous production of reactive oxygen species by inflammatory cells and structural cells in the lungs, lead to increased pulmonary oxidative stress in COPD patients. Changes in the level of oxidative stress affect antioxidant defenses, affect autophagy/mitotic processes and the regulatory mechanisms of cell survival, and promote lung inflammation. Oxidative stress not only amplifies chronic inflammation, stimulates fibrosis and emphysema, but also causes corticosteroid resistance, accelerates lung aging, causes DNA damage, and stimulates the formation of autoantibodies [18]. Common factors that indicate the level of oxidative stress, include Malondialdehyde (MDA), Superoxide dismutase (SOD), and Myeloperoxidase (MPO) etc. MDA is one of the most important products of membrane lipid peroxidation, and is an important indicator of oxidation reaction, reflecting the level of oxidation. While SOD is an indicator of antioxidant, reflecting the level of antioxidant in the body. Therefore serum MDA and SOD can be used to assess the level of oxidative stress in vivo. Through a meta-analysis of the literature on sputum MPO in patients with COPD, it found that MPO levels in sputum of patients with stable COPD were increased, which was particularly obvious in the aggravation period compared with stable COPD patients. It is suggested that MPO in sputum can also be used as a non-invasive biomarker to assess the degree of airway inflammation and disease exacerbation [19]. The study of salidroside on cigarette smoke-induced COPD in mice found that, salidroside can improve the activity of serum SOD and reduce the content of serum MDA, thus inhibiting oxidative stress and playing a protective role in COPD [20]. By constructing an in vitro cell model of COPD, the study found that salidroside could significantly reduce the activity of ROS and MDA, and significantly increase the activity of intracellular T-SOD [21]. Oxidative stress is the main driving mechanism for chronic inflammation, disease progression, and exacerbation in COPD,

and induces corticosteroid resistance. In conclusion, studies have shown that salidroside can protect chronic obstructive pulmonary disease through oxidative stress. However, studies on the effects of salidroside on MPO and other oxidative stress factors are insufficient, and there is not enough evidence to confirm the effects of salidroside on MPO. There are more active components and signaling pathways of salidroside on COPD antioxidant stress, which need to be further studied.

3.2 Regulation of protease/antiprotease imbalance

In 1963, Laurell and Eriksson of Sweden proposed the hypothesis of protease-antiprotease imbalance, a classic mechanism of COPD, by discovering that α1-antitrypsin (α1-AT) deficiency is closely related to emphysema in youth [22]. It is suggested that the pathogenesis of COPD and emphysema is the result of an imbalance between the enzymes that degrade the extracellular matrix in the lung and the proteins that oppose this proteolytic activity [23].

Proteases can digest elastin and other protein structures on the alveolar walls, among which neutrophilelastase (NE) and matrixmetalloproteinases (MMPs) are representative. The antiprotease system can resist the effect of protease, one of the important alpha 1 - antitrypsin (α1-AT), secretory leukocyte protease inhibitors (SLP1), tissue inhibitors of metalloproteinases (TIMPs), etc. α1-AT is the most active of the antiprotease system in the human body, and evidence from experimental models of emphysema and individuals genetically lacking α1-AT strongly demonstrates that an imbalance between enzymes and inhibitors is important in the pathogenesis of tissue injury and COPD [24-26]. However, there are not enough papers and experimental basis to explain the effect of salidroside on α1-AT.

Currently, the balance of MMPs/TIMPs is considered as a marker reflecting the dynamic balance of airway tissue destruction and repair, which is usually associated with the pathogenesis of the disease. Excessive expression of MMPs degrades tissue structure, while excessive TIMPs may lead to excessive tissue repair. Sun J et al. found that MMP-8, MMP-9, and MMP-12 mRNA were up-regulated more than 7-fold, but not TIMP-1 and TIMP-4 in response to cigarette smoke extract (CSE) [27]. Multiple studies have confirmed that the genetic diversity of MMP-1, MMP-7 [28], MMP-9 [29-31], MMP-12 [32] are associated with COPD. Salidroside has been found to inhibit the expression of MMP-2 and MMP-9 in airway epithelial smooth muscle cells (ASMCs) stimulated by PDGF [33]. Relevant studies have found that salidroside can prevent ventilation-induced lung injury by inhibiting the expression of MMP-9 [34]. The effect of salidroside on TIMPs has not been fully supported. The studies on protease/antiprotease by salidroside need further improvement.

3.3 Anti-inflammatory effects

COPD is characterized by chronic bronchitis, chronic airway obstruction, and emphysema, leading to a progressive, irreversible decline in lung function. Inflammation is central to the development of COPD. Inflammatory cells release inflammatory mediators and destructive enzymes, especially infiltrating immune cells, which further cause progressive lung destruction and airway remodeling. Airway remodeling includes hyperplasia of airway epithelium, thickening of the reticular basement membrane, collagen deposition, peribronchial fibrosis, transition of airway epithelium to interstitium, and bronchial smooth muscle cell proliferation.

3.3.1. Inflammatory cells

COPD has been shown to be associated with chronic inflammation, primarily affecting the lung parenchyma and peripheral airways, resulting in irreversible and progressive airflow limitation. This inflammation is characterized by increased numbers of alveolar macrophages, neutrophils, lymphocytes (mainly TC1, Th 1 and Th 17 cells) and of congenital lymphocytes recruited from the circulation [35-40]. Neutrophils are the key inflammatory cells in the pathogenesis of COPD, and the increase of neutrophils in sputum and blood is a typical feature of all COPD patients. They have also been reported as a marker of COPD severity. Compared with the number of neutrophils, the percentage of neutrophils has diagnostic significance for COPD and AECOPD. Macrophages are widely involved in different pathogenesis of COPD and are important members of the pathogenesis. A variety of cells, such as lung innate immune cells, can not only act as upstream cells of macrophage activation and proliferation, but also be recruited by macrophages and migrate into the cells. This "recruitment" and "recruitment" relationship forms a complex "inflammatory grid", which promotes the progression of inflammation in COPD. Studies have shown that salidroside inhibits activation of proinflammatory macrophages induced by lipopolysaccharide ethanol through Notch signaling pathway [41]. Studies on ALI/ARDS model of SD rats under salidroside showed that salidroside regulates the inflammatory pathway of alveolar macrophages by influencing the secretion of miRNA-146a exosomes from lung epithelial cells [42]. At present, the study of salidroside on inflammatory cells in COPD pa-

tients, especially neutrophils, is very limited, and the inflammatory effect of salidroside on COPD needs to be further improved.

3.3.2. Inflammatory mediators

Inflammatory cells are activated by cigarette smoke and other inhaled irritants (such as biomass fuel smoke) to produce inflammatory mediators, which epithelial cell produce including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukins-6 (IL-6), granulocyte-macrophage colony-stimulating factor (GM-CSF) and chemochemical factor (C-X-C motif) ligand 1 (CXCL8), Small airway epithelial cells express transforming growth factor-β (TGF) - β et al. Macrophage production including TNF- α, CXCL1, CXCL8, chemokine ligand 2 (CCL2), leukotriene B4 (LTB 4) and reactive oxygen species (ROS). And some studies have shown that activated macrophages from COPD patients release more inflammatory mediators, ROS and elastolytic enzyme than normal macrophages [35]. Through the analysis of sputum of patients with COPD and relavant in vivo and in vitro experiments, it has been found that salidroside can inhibit the expression of NF-kB and related inflammatory molecules in alveolar macrophage (AM) by promoting the expression of miR-146a in exosomes secreted by lung epithelial cells. The expressions of IL-1, TNF-α, IL-6 and IL-8 in salidroside +miR-146a antagonist group were significantly up-regulated [42]. In addition, it has been found that in mice and their spleen cells subjected to salidroside, salidroside can reduce the secretion of IL-2 and IFN-γ by TH1 cells, and IL-4, IL-5 and IL-10 by TH2 cells [43]. Luo et al. found that the salidroside (20 and 40 mg/kg) group significantly reduced the amount of TNF-α, IL-6 and IL-1β in lung samples and serum, suggesting that salidroside can inhibit the inflammatory response in serum and lung tissue [44]. salidroside has a wide range of effect on inflammatory cells and inflammatory mediators. It can not only be used for the treatment of COPD, but also has certain effects on other acute and chronic diseases.

3.4 Anti-bronchiolar and interstitial fibrosis

COPD patients have bronchiolar fibrosis, small airway remodeling, leading to persistent airway obstruction, and small airway remodeling in smokers leads to airflow obstruction. The pathogenesis of small airway remodeling is unknown, but it is generally believed that inflammation caused by smoking leads to abnormalities of the bronchioles and alveoli. Tobacco smoke is the driving factor, and the effects of smoke on small airway include mediating airway inflammatory response, mucus secretion and airway obstruction, and tissue injury in the lung. Meanwhile, it has been suggested that small airway remodeling is caused by smoke-induced production of airway wall growth factors rather than inflammation [45]. Relevant experiments showed that smooth muscle hyperplasia and airway collagen deposition were significantly reduced after salidroside intervention in rats, suggesting that salidroside can improve airway remodeling in COPD rats, possibly by regulating PPAR-γ/TGF-β1/Smad signaling pathway [46]. Studies have found that salidroside treatment in COPD rats, especially high dose treatment, significantly alleviates and eliminates lung function damage caused by smoking-induced emphysema and COPD, and reduces skeletal muscle atrophy associated with COPD in rats in a dose-dependent manner [47]. Excessive production of growth factors may play a role in small airway restriction, airway occlusion, and emphysema in COPD, but the studies are incomplete. Therefore, the effect of salidroside on peribronchiolar and interstitial fibrosis and the appropriate dosage need to be further studied, but current studies suggest that saildroside may be a promising candidate for designing new therapies for intervention in smoking-related COPD.

3.5 Anti-telomere shortening

Telomeres are repetitive nucleotide sequences (TTAGGG) located at the ends of chromosomes that protect the cap during cell division and prevent the loss of critical DNA and the fusion of chromosomes. Shortening occurs at each time a cell divides, but is counteracted by telomerase. Telomerase is an enzyme complex that maintains telomere length. It is composed of telomerase reverse transcriptase (TERT), telomerase RNA component (TERC) and dyskerin protein. During each cell division, telomeres become shorter, and the cells reach the senescence stage when shorter telomeres disrupt the telomere structure [48]. A large observational study found that short telomeres in circulating white blood cells were associated with decreased lung function, although the independent effect of COPD was relatively small once adjusted for age and smoking. Shorter telomeres were also found in the alveolar epithelial cells and endothelial cells of patients with emphysema, although this was also seen in smokers with normal lung function [49]. Studies have found that mice with short telomerase and short telomeres are more prone to emphysema after long-term exposure to cigarettes, and cell senescence in these animals is correspondingly increased [50]. Experiments on knockout mice have shown that knockout TERT and TERC can lead to replicative aging of alveolar cells and low degree pneumonia, with increased IL-1, IL-6, CXCL8(IL-8), and CCL2, suggesting

that telomere shortening can lead to COPD like lung disease [51]. A 10-year prospective study found that patients with the most telomere shortening had poorer alveolar gas exchange, lung hyperinflation, and clinical outcomes during follow-up compared with patients with less telomere shortening, and patients with the lowest telomere length had a higher risk of all-cause death [52]. Genetic determinants of telomere length may increase the susceptibility to COPD, but may also increase its comorbidities, such as cardiovascular diseases and metabolic diseases, which provide a common mechanistic link between these diseases. At present, there are insufficient data on the role of salidroside on telomeres in COPD, and further studies is needed.

In addition, many studies have shown that salidroside has anti-cancer, anti-apoptosis, anti-virus, anti-depression, anti-osteoporosis and other effects [53-57].

4. Summary and Outlook:

In conclusion, certain achievements have been made in the research on the role of salidroside in COPD, suggesting that salidroside can play a protective role in COPD through anti-oxidative stress, regulation of protease/anti-protease imbalance, anti-inflammatory, anti-bronchial and interstitial fibrosis, and anti-telomere shortening. However, due to the limitations of the current pharmaceutical level and the experimental technology level, there are still many effects and mechanisms of salidroside in COPD. At present, the effect of salidroside on COPD is mostly limited to the research and discussion of the mechanism in vivo and in vitro in animals. As a drug, clinical studies on the treatment of COPD are rarely reported, and a large number of clinical data research support is still needed. The effective dose range of salidroside active ingredients has also not been systematically studied. Finally, there are few studies on the pharmacokinetics, and the absorption, distribution, metabolism and excretion of drugs are not fully defined. All of these will be the focus of future studies. As a drug with low toxicity, small side effects and multiple function, salidroside has great application prospects, and its application value needs to be further developed. The study of the role and mechanism of salidroside action in COPD may provide a broader opportunity for them as therapeutic means to help in the treatment of COPD and other chronic airway diseases.

Funding

Project of Hunan Provincial Administration of Traditional Chinese Medicine (201197).

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