Review Article

Research Progress on *Astragalus* and its Active Ingredients in Treating Chronic Obstructive Pulmonary Disease

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The persistent restriction of airflow is a hallmark of chronic obstructive pulmonary disease. It includes alterations in lung tissue, emphysema, inflammation of the airways, and chronic bronchitis. Globally, chronic obstructive pulmonary disease is one of the leading causes of disability and death. Chronic obstructive pulmonary disease is categorized as lung distension, asthma syndrome and cough in traditional Chinese medicine, where the herb, *Astragalus* has tonic qualities, to bolster the body and ward off sickness. *Astragalus* has polysaccharides and saponins that lower inflammation, boost immunity, and lessen oxidative stress against chronic obstructive pulmonary disease. In order to aid in the development of novel chronic obstructive pulmonary disease treatments, this review focuses on the components and processes of *Astragalus*.

Key words: *Astragalus*, chronic obstructive pulmonary disease, astragaloside IV, interleukin

The defining features of Chronic Obstructive Pulmonary Disease (COPD) include limited airflow and other ongoing symptoms[1]. COPD is a disease that is growing more commonly which has rising death rates[2]. It is the 3rd most common cause of death in China among those over 40 with a frequency of 13.7 %[3]. Over $32 billion is spent annually on treating COPD in the United States of America (USA), which makes up a sizable amount of healthcare costs. In USA, the annual cost of treating COPD exceeds $32 billion, accounting for a significant portion of healthcare expenses[4]. As a result, COPD treatment has become a major social as well as medical concern.

Current treatments for COPD typically involve medications such as glucocorticoids and bronchodilators. However, these treatments have limitations, including the risk of drug resistance and high incidence of adverse reactions[5-8]. The medications only provide relief from symptoms and do not halt the progression of the disease. Traditional Chinese Medicine (TCM) is increasingly being used in the clinical management of COPD[9]. Studies have shown that combining *Astragalus* with conventional treatments for acute exacerbations of COPD can help regulate both humoral and cellular immunity in patients. Further research has indicated that *Astragalus* can lower levels of inflammatory markers in COPD patients, suggesting its potential to reduce inflammatory reactions in these individuals[10]. Hence, investigating the advantageous application of *Astragalus* is a crucial research avenue for both preventing and treating COPD in conventional Chinese medicine. This study investigates the *Astragalus* functions and methodically addresses its medicinal impact on COPD treatment. Proposals and creative approaches for managing COPD were introduced.

TCM PRINCIPLES OF *ASTRAGALUS*

TCM classifies COPD as a type of lung distension, asthma syndrome and cough. Ancient theories offer various perspectives for the causes and development of COPD. According to the book, Huangdi Neijing four syndromes namely, deficiency, fullness, asthma and cough with cold and heat as potential causes were identified.

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Accepted 29 July 2024
Revised 26 January 2024
Received 03 March 2023
Indian J Pharm Sci 2024;86(4):1210-1217

Physicians such as Zhang Zhongjing believed that external factors can trigger internal phlegm, resulting in COPD. Similarly, Chinese physician Chao Yuanfang from the Sui dynasty described the characteristics of stable COPD as calming evil and qi in the general treatise on causes and manifestations of all diseases[11,12]. Zhu Danxi, a physician belonging to the Yuan dynasty proposed that phlegm and blood stasis blocking qi are central to the pathogenesis of COPD, offering a new perspective[13]. Doctors belonging to the Ming and Qing dynasties generally believed that COPD can be caused by deficiencies in vital energy, external pathogens invading the lungs, combination of internal and external factors, and phlegm and blood stasis obstructing qi[14]. TCM believes that deficiency and damage to vital energy are the main causes of COPD. Investigators identified that deficiency of lungs, spleen and kidneys are the key internal factors contributing to recurrent COPD. According to the Huangdi Neijing theory, qi deficiency results in attacks from external factors highlighting the importance of low resistance in recurrent COPD[15]. Peng *et al*.[16] suggested that qi deficiency of lung and kidney are prevalent in stable COPD. *Astragalus* is known for its ability to tonify qi, enhance resistance, boost spleen qi to support yang, blood production, regulate lung qi to strengthen the body's exterior, tonify kidney qi to stabilize essence, reduce urination, promote diuresis to reduce swelling and improve qi for blood circulation[17]. According to the herbal pharmacology, *Astragalus* is considered as the best tonic which is effective in tonifying qi and protecting against pathogens[18]. Therefore, *Astragalus* is used in the treatment of COPD to enhance resistance, eliminate pathogenic factors, guide TCM diagnosis and treatment, and enhance its efficacy in different stages of COPD.

PHARMACOLOGICAL ACTIVITIES OF *ASTRAGALUS*

Astragalus (Huangqi) was primarily mentioned in Shennong Bencao Jing (Chinese book on agriculture and medicinal plants) which is found in Shanxi, Gansu and Inner Mongolia[19]. Dried root of *Astragalus membranaceus* (Fisch.) contains polysaccharides, flavonoids, saponins, amino acids, trace elements and other active compounds[11,20-23]. *Astragalus* has been shown to have anti-inflammatory, antioxidant, immune-modulating, anti-tumor and blood sugar-regulating effects[24-26]. Therefore, *Astragalus* balances the level of protease and anti-proteases, improves immunity, decreases oxidative stress, facilitates airway remodeling and enhances balance in the treatment of COPD.

Reduction of oxidative damage:

Reactive Oxygen Species (ROS) and oxidative stress are produced excessively in patients with COPD because of their weakened antioxidant defensive mechanisms. The development of COPD into Acute Exacerbations (AE) of COPD is mostly dependent on oxidative stress, which is frequently triggered by hypoxia and infection[27]. AECOPD is primarily caused by the accumulation of oxidative stress which harms the lung tissues and body.

Astragaloside IV can reduce oxidative stress in COPD by lowering ROS levels and controlling the Nuclear factor erythroid-2 related factor 2/Heme Oxygenase-1 (Nrf2/HO-1) pathway. Studies by Shen *et al*.[28] have shown that astragaloside IV can help alleviate oxidative stress in COPD by reducing ROS levels and regulating the Nrf2/HO-1 axis. Additionally, Li *et al*.[29] discovered that TCM prescription containing raw *Astragalus* can activate the Kelch-like ECH-associated protein 1 (Keap1)-Nrf2-Antioxidant Responsive Element (ARE) pathway in COPD mice. This activation leads to an increase in Nrf2 expression, production of antioxidants, ultimately reducing oxidative stress and preserving lung function in mice. Feng *et al*.[30] found that in addition to standard treatment with Western medicine, combining *Astragalus* injection improved lung function in COPD patients, by increasing body's antioxidant capacity. This combination also increased the levels of antioxidant markers such as Superoxide Dismutase (SOD) and Glutathione Peroxidase (GSH-Px), while decreasing the expression of Malondialdehyde (MDA). This effectively enhances the body's antioxidant stress capacity. Similar antioxidant stress capacity was observed in mice injected by Qu *et al*.[31] where they discovered that *Astragalus* injection can reduce levels of Advanced Oxidation Protein Products (AOPP) and MDA in patients by inhibiting oxidative stress through reducing the accumulation of oxidative products.

Inhibition of inflammatory response:

Chronic inflammation in the airways, lung tissue and blood vessels is a common feature of COPD.

A major factor in the disease's progression is the production of inflammatory chemicals and cells, including T cells, neutrophils, and macrophages. Tumor Necrosis Factor-Alpha (TNF-α), Interleukin (IL)-6, IL-8 and other pro-inflammatory chemicals are implicated, whereas IL-10 possesses anti-inflammatory properties[32,33].

Liu *et al*.[34] used network pharmacology and molecular docking to identify 44 active components in the *Astragalus-Paeonia* combination that target COPD. In cell experiments, quercetin and kaempferol were found to reduce the secretion of IL-8 and Matrix Metalloproteinases (MMP)-9, indicating their potential therapeutic effects on COPD. Ao *et al*.[35] discovered that *Astragalus* injection can decrease IL-8 levels while increase IL-10 levels in COPD rats, leading to reduced inflammation. In COPD mice which were given *Astragalus* injection, the quantity of white blood cells and neutrophils as well as their proportion in Bronchoalveolar Lavage Fluid (BALF) also reduced, indicating the plant's efficacy in reducing airway inflammation in COPD patients. Zhang *et al*.[36] also demonstrated that *Astragalus* injection can decrease inflammation by inhibiting IL-6 production through activation of the Adenosine-Monophosphate-activated Protein Kinase/ mammalian Target of Rapamycin (AMPK-mTOR) pathway. Additionally, Zhou *et al*.[37] discovered that a high dose of Shenqi Tiaoshen formula shown strong anti-inflammatory impact by suppressing Nuclear Factor Kappa B (NF-κB) signaling pathway significantly decreased the expression of NF-κB p65, phospho (p)-NF-κB p65 and MMP-9 proteins in mouse lung tissues, as well as lowered levels of inflammatory factors IL-1β, IL-6 and TNF-α in COPD mice, suggesting its anti-inflammatory effects.

To find ligands and receptors, researchers used PubChem, based on the three-Dimensional (3D) similarity procedure; further we used Kyoto Encyclopedia of Genes and Genomes (KEGG) mapper to predict powerful targets, which has similar property principle stating that molecules with similar structures should have the same bioactivities. A higher hybrid score indicates that the query and target molecules are more closely aligned in terms of form and chemotype identities.

Enhancing immunity:

In a study conducted by Deng *et al*.[37], it was observed that elderly patients with stable COPD showed significant improvements in lung function, exercise tolerance and respiratory health markers after receiving *Astragalus* injection at the Zusanli acupoint along with pulmonary rehabilitation training. Patients exhibited enhanced levels of antimicrobial peptide IL-37, Cluster of Differentiation ($CD3^+$) T lymphocytes, $CD4^+$ T lymphocytes, and $CD4^+/CD8^+$ ratios, while levels of inflammatory markers TNF-α, IL-6 and C-Reactive Protein (CRP) decreased[38]. The research results indicate that a comprehensive treatment strategy significantly improves pulmonary function, motor coordination, immune system response and overall respiratory stability in patients with COPD. Liao *et al*.[39] in their research, observed and examined 140 patients who were stable with COPD. When *Astragalus* injection alongside the Bufei Yishen formula and Western medicinal methods were used, eir collective efficacy exceeded that of solely Western medical treatments. The combined treatment ed considerably lower levels of Procalcitonin (PCT), high-sensitivity (hs)-CRP and $CD8^+$, but significantly higher levels of Forced Expiratory Volume in the first second (FEV1), Forced Vital Capacity (FVC), Immunoglobulin (Ig) A, IgM, IgG and $CD4^+$ levels of FEV1, FVC, IgA, IgM, IgG, and $CD4^+$ were found to be significantly high in combination treatment group, while levels of $CD8^+$, PCT and hs-CRP were significantly lower. This suggests that the combination treatment enhanced lung function, improved immune response and reduced inflammation in COPD patients.

Likewise, studies also discovered that patients suffering from COPD with deficiencies in the lungs, kidneys and kidneys along with blood stasis syndrome experienced improved treatment results with *Astragalus*-danshen formula when combined with thiotropion breathing[39]. The patient group exhibited effective enhancements in clinical manifestations, immune responses and pulmonary performance.

Regulation of apoptosis:

Apoptosis, involving programmed cell death triggered by diverse factors, is frequently observed in models of COPD. Principal genes implicated in apoptosis encompass Fatty Acid Synthase (FAS) ligand, TNF-α, tumor protein (p53), B cell lymphoma-2 (Bcl-2) and caspase. Growth

in both alveolar epithelial and endothelial cells, along with increased Vascular Endothelial Growth Factor (VEGF) levels, contributed to diminishing the apoptosis in pulmonary vascular endothelial cells within models of COPD.

Astragaloside IV has been demonstrated in studies to significantly and dose-dependently increase apoptosis in the lung tissues of COPD-affected rats. This substance can reduce inflammation and apoptosis in the lungs of COPD-affected mice, as evidenced by its inhibition of caspase-3 and caspase-12 expression[36,40]. Furthermore, studies by Wang[41] have demonstrated that astragaloside IV can upregulate p-Akt expression while inhibiting caspase-3 and caspase-9 expressions. Cellular experiments have demonstrated that astragaloside IV can hinder apoptosis while boosting ROS and pro-inflammatory factors in IL-8-activated diaphragm cells, indicating its promise as a remedy for COPD diaphragm impairment.

Regulation of protease and antiprotease balance:

COPD manifests as obstructive air passages, ongoing bronchitis or emphysema. Disparity in proteases and antiproteases may result in emphysema and further damage to lung tissues[12]. Proteases such as Neutrophil Elastase (NE) and MMP decompose proteins and elastic fibers in the lungs, whereas antiproteases like α1-antitrypsin, Secretory Leukocyte Protease Inhibitor (SLPI) and Tissue Inhibitors of Metalloproteinases (TIMP) block this disintegration[42].

Research indicates that treating *Astragalus* with polysaccharides lower alveolar walls, diminishe the penetration of inflammatory cells, lower expression of Myeloperoxidase (MPO), MMP-9 and TIMP-1, generally enhancing airway remodeling and lung fibrosis[43]. Zhao *et al*.[44] discovered that *Astragalus* Polysaccharides (APS) decreased hydroxyproline in pulmonary tissues, also suppressed MMP-9 protein in COPD rats, aided in harmonizing the creation and breakdown of Extracellular Matrix (ECM) and ameliorated inefficient airway restructuring and lung scar tissue.

Airway remodeling:

In COPD patients, airway blockages are primarily caused by the remodeling, inflammation and epithelial-mesenchymal shift resulting from ECM accumulation. Enzymes involved in altering and inflating air passages are discharged upon encountering detrimental substances.

Consequently, inflammatory cells infiltrate the air passages, boosting the expression of MMP-2, MMP-9 and MMP-12[45].

Levels of Secretory (S) IgA, Transforming Growth Factor-Beta (TGF-β) 1, TGF VEGF and VEGF were reduced in rats suffering from COPD that received treatment with *Astragalus* and atractylodes decoction[46]. The inference is that *Astragalus* and atractylodes diminish cysteine and cysteine in pulmonary tissue, alleviate inflammation and infection and lower TGF-β1 and VEGF levels to decelerate the restructuring of the airways and blood vessels. Research has shown that the use of *Astragalus* can decelerate COPD progression through diminishment of bronchiolitis thickness and inflammatory cells in the bronchial lining.

In COPD patients, airway blockages are primarily caused by the remodeling, inflammation and epithelial-mesenchymal shift resulting from ECM accumulation. Enzymes instrumental in altering and inflating air passages are discharged upon encountering detrimental substances. As a result, inflammatory cells migrate into the respiratory tract, elevating the levels of MMP-2, MMP-9 and MMP-12 in cases of COPD. The alteration of the inflammatory airway, accumulation of ECM and the change from Epithelial Mesenchymal Transition (EMT) play significant roles in obstructing airflow. Damaged compounds initiate the secretion of inflammatory agents like TNF-α, IL-8 and CXC chemokines, resulting in the invasion of inflammatory cells and the increase of MMP-2, MMP-9 and MMP-12 levels, contributing to airway inflammation and restructuring in COPD, airway remodeling caused by inflammation, ECM deposition EMT is a significant factor contributing to airflow obstruction. Harmful substances trigger the release of inflammatory mediators such as TNF-α, IL-8 and CXC chemokines, leading to infiltration of inflammatory cells and upregulation of MMP-2, MMP-9 and MMP-12, which play a role in airway inflammation and remodeling[45].

A study demonstrated that orally administered *Astragalus* and atractylodes decoction reduced the levels of SIgA, SIgC, TGF-β1 and VEGF in rats with COPD compared to the experimental group[46-51]. The inference is that *Astragalus* and atractylodes diminish cysteine in pulmonary tissue, alleviate inflammation and infection and lower TGF-β1

and VEGF levels to decelerate the restructuring of the airways and blood vessels. Research has shown that the use of *Astragalus* can decelerate COPD progression through the diminishment of bronchiolitis thickness and diminishment of inflammatory cells in the bronchial lining.

Research has also shown that *Astragalus* treatment reduces the number of inflammatory cells in the bronchial mucosa, thins the smooth muscle of the bronchioles and may delay or prevent disease progression in COPD rats by reducing airway remodelling.

MECHANISM OF ACTION OF ACTIVE INGREDIENTS IN *ASTRAGALUS*

For treating COPD, polysaccharides and saponins which are the crucial elements of *Astragalus* play a vital role. It has been demonstrated that these components are efficacious in the management of COPD. Delving into the distinct workings of *Astragalus* in managing COPD might spark ideas for subsequent research on *Astragalus* compound formulations in COPD therapy. Researching these processes might lead to the development of novel COPD medications.

APS:

Astragalus contains active substances called APS that have therapeutic effects on conditions such as diabetes, cancer, inflammation, and immunosuppression. APS are important active compounds found in *Astragalus* that have been shown to have therapeutic effects on various diseases such as diabetes, cancer, inflammation and immunosuppression. Research confirms that APS can treat COPD by enhancing immune responses and reducing inflammation and it influences the immune system by acting on T and B cells, macrophages, dendritic cells and cytokines. APS helps to reduce inflammation and promote lung tissue healing by regulating the inflammatory responses (Table 1).

Astragalus saponins:

Studies have indicated the efficacy of *Astragalus* saponins in treating the primary bioactive factor, COPD. This chemical exhibits qualities that are antitumor-preventive, immune-modifying, anti-inflammatory and antioxidant. Contemporary drug research indicates that astragaloside IV possesses properties that are anti-tumor, immune-modifying, anti-inflammatory and antioxidant[52,53]. Medicinal impacts of astragaloside IV in treating COPD involve enhancing antioxidant functions, inducing lung cell apoptosis and reducing inflammation mechanisms; information in Table 2, encompasses animal/cell models, biological impacts and action mechanisms used in COPD therapies.

TABLE 1: SPECIFIC ANIMAL/CELL MODELS, BIOLOGICAL EFFECTS AND MECHANISMS OF APS IN TREATING COPD

Dosage	Animal/cell model	Biological effect	Mechanism	References
400, 600 and 800 mg/kg	COPD rats	↑ Proplatelet megakaryocyte and Mean Platelet Volume (MPV) while ↓ total megakaryocyte, IL-1β, IL-8, TNF-α, Toll-Like Receptor 4 (TLR4), NF-κB protein expression, IL-1β, IL-8 and TNF-α messenger Ribonucleic Acid (mRNA)	Inhibition of supressing TLR4/ NF-κB pathway to reduce inflammatory response in COPD rats and increased MPV, which decreases with increasing inflammation severity	[47]
50, 200 µg/ml	PBMC from COPD patients	↓ IL-6, MMP-9, TNF-α, Prostaglandin E2 (PGE2), TLR4 and NF-κB mRNA	Inhibition of supressing TLR4/ NF-κB pathway to modulate inflammatory response, promoting lung tissue repair	[48]
100, 200 and 400 mg/kg	COPD Sprague-Dawley (SD) rats	↓ IL-8, TNF-α and Partial pressure of Carbon dioxide ($PaCO_2$) while IL-10, Interferon-Gamma (IFN-γ) FEV1 and FEV1/Peak Expiratory Flow (PEF) ratio, Partial pressure of Oxygen (O_2) and pH ↑	Inhibition of lung tissue damage, reduction of IL-8 and TNF-α in serum and lung tissue, increase in IL-10 and IFN-γ, improvement in VE, PEP, FEV1, pH, PaO_2, and reduction in $PaCO_2$	[49]
40 mg/kg	Male Wistar rats	↑ FEV0.2, FEV0.2/Forced Vital Capacity (FVC) while ↓ hydroxyproline, MMP-9, TIMP-1 and MMP-9/TIMP-1 levels	Inhibition of MMP-9 and TIMP-1 expression in COPD rat lung tissue	[50]

10, 20 and 40 mg/kg	Male COPD SD rats	↑ HO-1 mRNA and protein levels	Increase in HO-1 expression; APS improves lung tissue damage in COPD rats through HO-1-mediated antioxidant action	[50]
10, 20 and 40 mg/kg	Male COPD SD rats	↓ Hydroxyproline levels and MMP-9 expression	Reduction of hydroxyproline levels in lung tissue, inhibition of MMP-9 protein content in COPD rat lung tissue, balancing ECM synthesis and degradation	[51]

Note: (↑): Increase and (↓): Decrease

TABLE 2: BIOLOGICAL EFFECTS AND MECHANISMS OF ASTRAGALOSIDE IV IN TREATING COPD

Dosage	Animal/cell model	Biological effect	Mechanism	References
25, 50, 100, 200, 400 and 800 µg/ml	A549 cells	↓ ROS levels, apoptosis rate, ↑ SOD, Nrf2 mRNA, HO-1 mRNA levels and Nrf2 and HO-1 protein expression	Enhances cell viability, SOD levels, Nrf2, HO-1 mRNA and protein expression; reduces ROS, MDA levels, and apoptosis rate	[28]
2, 5 and 10 mg/kg	Male COPD SD rats	↓ Apoptosis rate, caspase-3 and 12 expression	Reduces Endoplasmic Reticulum (ER) stress-mediated apoptosis in lung tissue, decreases caspase-3 and 12 expression, alleviates lung cell apoptosis and bronchial inflammation in COPD rats	[54]
3 and 9 mg/ml	Male COPD SD rats	↓ Found in Inflammatory Zone (FIZZ1) 1 protein, TNF-α expression, FIZZ1 mRNA and TNF-α mRNA expression	Reduces airway inflammation in COPD by downregulating FIZZ1 and TNF-α expression, inhibits airway remodeling	[55]
10, 20 and 40 mg/kg	Female C57BL/6 mice	↓ Diaphragm cell apoptosis, caspase-3 and 9 expression, and ↑ p-Akt expression	Inhibits diaphragm cell apoptosis induced by COPD, significantly reduces caspase-9 and 3 expression, significantly increases p-Akt expression, activates p-Akt to inhibit caspase-9 and 3 expression	[41]

COPD is an irreversible lung condition that may lead to severe complications like pulmonary heart disease and respiratory failure[55]. Research is underway on TCM's capacity to hinder and manage COPD, emphasizing *Astragalus* as an essential component in managing the disease. Scientists have pinpointed multiple treatment routes for *Astragalus* in COPD, including diminishing oxidative stress, managing inflammatory responses, enhancing immunity, controlling cell demise, harmonizing enzyme functions and averting respiratory harm. These findings offer valuable insights into *Astragalus membranaceus* potential for COPD treatment. *Astragalus* contains active ingredients that are effective for treating COPD[56].

CONCLUSION

Study indicates that substances like APS and saponins adjust signaling routes including NF-κB, Phosphoinositide 3-Kinase (PI3K)/Akt and Nrf2/HO-1, playing an important role in reducing inflammation, oxidative stress, apoptosis and enhancing protease/antiprotease balance and restructuring of airways in those with COPD. Nonetheless, additional research is required to examine the possible advantages of using more active components in *Astragalus* for treating COPD. Yet, the prospective advantages of additional active ingredients in *Astragalus* for managing COPD warrant additional research. To sum up, a comprehensive grasp of *Astragalus*' function in preventing and treating COPD requires additional scientific studies to advice on creating novel *Astragalus* medicines, resource allocation and clinical application.

Acknowledgements:

This work is supported by Lanzhou Science and Technology Bureau Social Development Project (2022-2-47, 2023-2-17)

Author's contributions:

Aijun Zhao and Hongli Wang are the co-authors who have contributed equally to this study.

Conflict of interests:

The authors declare no conflict of interests.

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