

Modulation of PI3K/AKT Signaling Pathway by Chinese Medicine Research Progress in Treating Chronic Obstructive Pulmonary Disease

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Fei *et al.*: Mechanism of Action in Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease is a common respiratory disease characterized by persistent respiratory symptoms with incompletely reversible airflow limitation. Currently available treatments include oral or inhaled bronchodilators, oxygen therapy and surgery. However, these treatments are not effective enough in most cases, so it is clinically important to explore the mechanism of action and therapeutic strategies of chronic obstructive pulmonary disease in depth. The phosphatidylinositol 3-kinase/protein kinase B signaling pathway can play an important role in the occurrence and development of chronic obstructive pulmonary disease by regulating the release of inflammatory mediators and oxidative stress. Traditional Chinese medicine is characterized by holistic and comprehensive treatment of diseases, and has achieved good results in the prevention and treatment of chronic obstructive pulmonary disease in recent years. Traditional Chinese medicine monomers, active ingredients and their combinations can directly or indirectly regulate the phosphatidylinositol 3-kinase/protein kinase B signaling pathway by inhibiting the inflammatory response of the airway and alleviating oxidative stress, and play a protective role against chronic obstructive pulmonary disease with their multi-targeting, multi-component, and multi-pathway biologic advantages. Analyzing the research progress of traditional Chinese medicine at home and abroad in recent years, this article reviews the preventive role and mechanism of traditional Chinese medicine in regulating the phosphatidylinositol 3-kinase/protein kinase B signaling pathway in chronic obstructive pulmonary disease, and provides further theoretical basis for the study of the mechanism of clinical prevention and treatment of chronic obstructive pulmonary disease by traditional Chinese medicine.

Key words: Chinese medicine, chronic obstructive pulmonary disease, phosphatidylinositol 3-kinase/protein kinase B signaling pathway, signaling pathway

The onset of Chronic Obstructive Pulmonary Disease (COPD) is closely related to long-term exposure to hazardous gases or toxic particles^[1]. As one of the major global public health issues^[2], COPD is a common and frequent disease that seriously jeopardizes human health, and its prevalence and mortality rate are high. The global prevalence of COPD in people ≥ 40 y of age has reached 9 % to 10 %^[3], and the cause of death is in the 3rd place, and it is on the rise year by year, which has brought a heavy economic burden to the patients and their families as well as to the society^[4]. The stimulation of extrinsic factors affects the interactions between

different molecules, leading to extensive changes in the gene regulatory network of the lung epithelium and other related cells, which results in COPD damage^[5]. External signaling pathways influence COPD by rippling through the cell's gene regulatory network and shaping key cellular decisions and behaviors^[6]. A large body of literature confirms that the Phosphatidylinositol 3-Kinase/Protein Kinase B (PI3K/Akt) signaling pathway plays an important role in regulating the pathophysiological processes of COPD and is a key signaling pathway in the fight against COPD. The disease begins with alterations in the immune response, followed by chronic

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inflammation of the lungs and systemic body, which promotes COPD pathogenesis by producing excessive inflammatory factors causing airway remodeling and airflow limitation after persistent stimulation by extrinsic factors such as smoke^[7]. In recent years, with the deepening of the understanding of the multi-pathway and multi-target therapeutic effects of Traditional Chinese Medicines (TCM), the mechanism of action of TCM in the prevention and treatment of COPD has also been gradually exposed, and the upstream and downstream factors of the PI3K/Akt signaling pathway can be regulated by the relevant TCM, and affect the activity of the corresponding factors through different compositions. The PI3K/Akt signaling pathway has become an important target for the current and future prevention and treatment of COPD by Chinese medicine; however, there is no systematic review and summary in this field at home and abroad. In this paper, we focus on the progress of research related to the modulation of PI3K/Akt signaling pathway by TCM in the treatment of COPD in recent years, in order to improve the objective reference for the prevention and treatment of COPD by TCM.

COMPOSITION AND REGULATION OF THE PI3K/AKT SIGNALING PATHWAY

PI3K is a family of proteins that catalyze the phosphorylation of the 2-hydroxy terminus of phosphatidylinositol, and are classified as class I, class II, and class III based on the structure of the catalytic subunit, the type of binding subunit, and the lipid substrate. Among them, class I is the most widely studied and can be further subdivided into class IA, which includes PI3K Alpha (α), PI3K Beta (β) and PI3K Delta (δ), and class IB, which includes only PI3K Gamma (γ)^[8]. Class II includes PI3K-C2 α , PI3K-C2 β , and PI3K-C2 γ , and class III includes only VPS34^[9]. Interacting with growth factor receptors containing phosphorylated tyrosine residues, connexins, etc., PI3K heterodimers are activated by a change in conformation. First, the Receptor Tyrosine Kinase (RTK) located on the cell membrane undergoes oligomerization and auto phosphorylation upon stimulation by external factors, relieving the inhibitory effect of the PI3K regulatory subunit p85 on the catalytic subunit p110. Receptor phosphorylation then mediates the recruitment of a junction protein to facilitate the binding of PI3K, such as Insulin-Like Growth Factor (IGF), stimulating several downstream mediators of this signal^[10-12]. These mediators in turn

regulate many downstream substrates involved in key processes such as cell growth, cell cycle, protein synthesis and cell death^[13]. The expression of PI3K and its downstream mediators is upregulated during COPD lung and airway remodeling^[14,15]. Differential expression of these signaling mediators hints at their dynamic regulation under pathological conditions. Dysregulation of PI3K signaling not only adversely affects the normal functioning of airway epithelial cells, but also affects alveolar immune cells, leading to excessive immune responses^[16,17]. This abnormally enhanced immune response leads to the chronic inflammation that characterizes COPD.

Akt, the major downstream effector molecule of PI3K, is a family of three serine-threonine kinases that are highly homologous to Akt1 (PKB), Akt2 (PKB β) and Akt3 (PKB γ)^[8,18]. Akt1 is universally expressed, whereas Akt2 is predominantly expressed in insulin-sensitive tissues such as Adipose Tissue (AT), liver and skeletal muscle, and Akt3 is expressed in the brain and testis^[19]. Akt consists of three structural domains; pH, the intermediate kinase, and the regulatory carboxy-terminal structural domain^[11]. When the PI3K/Akt pathway is activated, such as after insulin binding to Insulin Resistance (IR), the pH structural domain of Akt binds to PIP3 and phosphorylates Akt *via* threonine by enzyme 3 phosphorylation of Phosphatidylinositol-Dependent Protein Kinase 1 (PDK1), the mammalian Target of Rapamycin Complex (mTORC) 2, making Akt fully active. Activated Akt can regulate metabolism directly, by phosphorylating various metabolic enzymes or nutrient transport regulators such as Glucose Transporter Proteins (GLUTs), or indirectly, by activating important downstream effectors in cellular metabolic reprogramming, including mTORC1, Glycogen Synthase Kinase 3 (GSK3) and Forkhead Box O (FOXO) transcription factor family members, acetylases (Histone Deacetylases (HDACs)), Mitogen-Activated Protein Kinases (MAPKs), and S6 increase the production and secretion of CCL2 and CXCL8 chemokines, as well as Interleukin (IL)-6 and other pro-inflammatory cytokines, which in turn promote chronic inflammation^[20-23].

PI3K/AKT SIGNALING PATHWAY IS INVOLVED IN THE PATHOGENESIS OF COPD

Inhibition of the inflammatory response:

COPD is characterized by a persistent

inflammatory response and airflow limitation, which is mediated by inflammatory cells and inflammatory mediators, and affects the airways, lung parenchyma, and microvasculature of the lungs, etc. Macrophages, neutrophils, and lymphocytes are the main inflammatory cells involved in the development of COPD, which is characterized by the stimulation of the respiratory tract by external smoke particles and microorganisms, and the activation of Hypoxia-Inducible Factor-1 α (HIF-1 α), microRNA (miR)-203, and miRNA-101-3p.1, which can stimulate the activation of inflammatory cells in the respiratory tract. HIF-1 α , miR-203 and miRNA-101-3p.1 activation, can stimulate the activation of inflammatory cells in the respiratory tract, through the release of Tumor Necrosis Factor (TNF), IL, chemokines CCL2, CXCL8 and other inflammatory mediators to promote the inflammatory response. Activated inflammatory cells cause structural destruction of lung tissues by synthesizing and releasing a variety of proteases, such as elastase and histone protease, to promote the inflammatory response and airway remodeling in COPD. Barnes *et al.*^[26] found that macrophages in COPD patients not only release proteases to destroy lung tissues, but also produce Reactive Oxygen Species (ROS) that will induce an oxidative microenvironment and exacerbate the inflammatory response. Moreover, macrophages exhibit defective immune responses that are abnormally polarized toward the M2 phenotype^[24-26,19].

Mitigation of oxidative stress:

COPD is a progressive, multifactorial, and irreversible chronic disease, and oxidative stress is the main driver of chronic inflammation of the airways, destruction of the lung parenchyma, and decline in lung function in COPD, which is induced by a variety of environmental stimuli and endogenous factors, such as cigarette smoke, air pollutants, and microbial infections. Acute exacerbations of COPD have been associated with oxidative stress and oxidant/antioxidant imbalances in the blood^[27], and as the worsening of the disease and increasing inflammation, COPD patients have a significant increase in oxidants such as Hydrogen peroxide (H₂O₂), ROS, Reactive Nitrogen Species (RNS), and Malondialdehyde (MDA) in the alveolar fluid and blood, while antioxidants such as Superoxide Dismutase (SOD),

Glutathione (GSH), Glutathione Peroxidase (GSH-Px), and Catalase (CAT) are decrease and also reduces the expression of downstream antioxidant genes *via* Akt, which not only weakens the body's protection against oxidative stress, but also leads to alveolar destruction, progressive airway inflammation, and leukocyte infiltration^[28]. The mechanism by which oxidative stress leads to the development of COPD is complex, not only directly damaging airway epithelial cells, but also by inducing and exacerbating the inflammatory response and increasing the ability of protein hydrolases to hydrolyze matrix proteins, leading to ablation of lung tissue, enlargement of alveolar lumen, and accelerating the destruction of the lung parenchyma and interstitium^[29].

CHINESE MEDICINE'S UNDERSTANDING OF COPD

COPD is the name of a modern medical disease, according to the typical symptoms of long-term coughing, coughing up sputum and dyspnea, it should be categorized under the category of "lung distension" in Chinese medicine. "Lung distension" was first recorded in Huangdi Neijing-Lingshu. Scripture: "Lung distension is a person who is full of emptiness and wheezing and coughing", the pulse of the lung's hand taiyin is the movement that causes disease, the lungs are distended and puffed up with wheezing and coughing", The above article was the first to give a general description of the symptoms, pathogenesis, and treatment of lung distension, creating a precedent for the treatment of lung distension in Chinese medicine. Jin Gui Yao Lue: "Those who are asthmatic and agitated in the upper air, belonging to lung distension, wanting to wind and water, and cured by sweating", "Coughing and getting up in the air, this is lung distension, Yuemaijia Banxia decoction is the mainstay". "Lung distension, coughing up qi Xiaoqinglong plus gypsum soup is the main treatment", on the basis of Huangdi Neijing, Zhongjing Zhang, a medical sage, combined with his own clinical experience, made a more specific exposition on pulmonary distension. Among them, the image of "eyes like detachment" describes the phenomenon of bulbar conjunctiva and eyelid edema in patients with COPD during respiratory failure, "Fengshui" means that the pathogenesis of lung distension is external cold and internal drinking, and the wind and water are fighting each other. At the same time,

"sweating is the cure" means that lung distension can be treated by sweating. It is put forward in "The Theory of Pathogens and Stagnation" that "lung deficiency is slightly cold, resulting in cough... evil crouching leads to calmness, evil movement leads to upward movement of qi, and boredom leads to heartbreak, so it is called cough against qi", Yuanfang Chao supplemented the etiology of lung distension, considering "lung deficiency" as the basis of the disease, exogenous cold pathogen is the inducement, and lung qi stagnation and failure to declare and descend are the pathogenesis, and lung distension is innovatively divided into two stages; "pathogenic accumulation" and "pathogenic movement". Danxi's experiential therapy says "The person who is asthmatic and irritable in the upper body is lung distension", lung distention and cough, or left or right cannot sleep, this phlegm with blood stasis and qi stagnation and illness, Bai jie zi and Danxi Zhuput forward the pathogenic theory of phlegm and blood stasis and the corresponding prescription, which greatly improved the TCM theory of lung distension. In Ming and Qing Dynasties, Shoushi Baoyuan said, "People with lung distension are full of breath when they move, and they are short of breath and heavy" and the theory of "lung distension and cough, shortness of breath and rough breath" in Zhengzi Huibu basically continued and developed the theory of the previous generation of physicians. TCM takes the holistic view and evidence-based treatment as the starting point, and TCM is

characterized by multi-targets, multi-components, and multi-pathway effects, in which many TCM active ingredients and compound formulas can play an important role in COPD prevention and treatment by targeting the PI3K/Akt signaling pathway. Therefore, in-depth research on the pharmacology and molecular mechanism of TCM is beneficial to the development and progress of TCM in the prevention and treatment of COPD.

INTERVENTION OF PI3K/AKT SIGNALING PATHWAY BY TCM IN COPD

TCM extracts/active ingredients:

The active ingredients/extracts of TCM are the direct material basis for the efficacy of TCM in treating diseases. It has been found that the active ingredients/extracts of TCM that regulate the PI3K/Akt signaling pathway to prevent and treat COPD mainly include polyphenols, terpene glycosides, saponins, glycosides, flavonoids, ester glycosides, diterpenoids and aldehydes, etc., with flavonoids being the majority of the studies and the others being relatively few. Their main mechanism of action is to prevent and control COPD by inhibiting the levels of TNF- α and IL-6, IL-8, IL-1 β , ROS and Matrix Metalloproteinase-9 (MMP-9), and decreasing the expression of related proteins such as PI3K, AKT and mTOR. The specific mechanisms of action of the active ingredients/extracts of Chinese medicines in the treatment of COPD are summarized in Table 1.

TABLE 1: CHINESE MEDICINE EXTRACTS/ACTIVE INGREDIENTS AGAINST COPD BY MODULATING PI3K/AKT SIGNALING PATHWAY

Chinese medicine extracts/active ingredients	Categorization	Models	Target of action	Reference
<i>Ginkgo biloba</i> extract	Polyphenol	Wistar rats	↑IL-10, LC3 worker protein, Beclin1 mRNA expression, ↓PI3K p110a, Akt, p-Akt, mTOR, p-mTOR, PI3K, Akt, mTOR mRNA	[1]
Sodium tanshinone IIA sulfonate	Terpene glycoside	SD rats	↓Serum TNF- α , IL-1 β , IL-6, IL-8 and IL-18 levels, ↓lung tissue PI3K, AKT1 and mTOR protein expression levels	[34]
Sclerotin	Glycoside	Wistar rats	↓TNF- α , IL-6 levels, PI3K, AKT, mTOR protein expression	[36]
Ginsenoside Rg3	Saponins	BALB/C mice	Inhibits kinase phosphorylation, NF- κ B nuclear translocation, DNA binding, ↓TNF- α , IL-6, IL-8, IL-1 β , ROS, MMP9 production	[40]
Sodium fisetin	Aldehyde	Wistar rats	↓PI3K and AKT1 gene expression, ↑mTOR gene expression in lung tissue	[41]
Baicalin	Flavonoids	Balb/c mice	↑CXCR4, SDF-1, PPI3K/PI3KA2AR, ↓P-AKT/AKT	[42]

Puerarin	Flavonoids	PC12 cells	Activation of PI3K/AKT signaling pathway, ↓caspase-3 expression, ↓apoptosis	[44]
Puerarin	Flavonoids	HBECs cells	↓the expression of mitochondrial autophagy-related proteins PINK1 and park in to prevent mitochondrial autophagy and apoptosis in HBECs	[45]
Saffronin	Esteroids	C57BL/6 mice	↓IL-1 β , IL-6 and TNF- α levels, ↓pPI3K and p-Akt expression	[46]
Hesperidin	Flavonoids	ICR mice	↓AKT1, IL-6, VEGFA, MMP9, TP53 expression, ↑TP53 expression	[48]
Cryptotanshinone	Diterpene (chemistry)	U937 cells	↓Akt levels, ↑HDAC2 protein levels	[58]

Dan Shen has the effects of activating blood circulation, removing blood stasis, clearing menstruation and relieving pain, clearing the heart and removing vexation, cooling blood and eliminating carbuncle. It is used for chest paralysis and heart pain, epigastric and abdominal pain, accumulation of obstruction in the abdomen, heat paralysis and pain. The compendium of *Materia medica* includes promoting blood circulation, clearing the pericardium and treating hernia pain. Ben Jing (the scriptures); Evil Qi in the heart and abdomen, intestinal tinnitus as if walking on water, accumulation of cold and heat, breaking the syndrome and removing the obstruction in the abdomen, stopping vexation and fullness, and benefiting Qi. Bibliography; nourish blood, remove chronic diseases of the heart and abdomen, strong foot paralysis of the lumbar spine, and remove the wind and heat retention. Taking it for a long time will benefit people. Sodium tanshinone IIA sulfonate is a water-soluble substance obtained by sulfonation of the diterpene quinone compound tanshinone isolated from *Salvia miltiorrhiza* (*S. miltiorrhiza*), which possesses a variety of biological activities such as antioxidant, antibacterial and anti-inflammatory, anticoagulant effects and inhibition of airway remodeling^[30]. Wang *et al.*^[31] found that tanshinone IIA sodium sulfonate, an extract of *S. miltiorrhiza*, reduced serum TNF- α , IL-1 β , IL-6, IL-8, and IL-18 levels in aged COPD rats after animal experiments. The levels of PI3K, AKT1 and mTOR protein expression in lung tissues of the tanshinone IIA high-dose group were significantly lower than those of the model control group and the tanshinone IIA small-dose group in the medium-dose group. This suggests that tanshinone IIA sodium sulfonate can significantly improve the lung function of aged COPD rats, and its effect is related to its ability to reduce the body's inflammatory response and

regulate the expression of genes and proteins of PI3K/AKT signaling pathway. Cryptotanshinone is extracted from the root of *S. miltiorrhiza*, which can regulate intracellular signaling to inhibit the release of inflammatory factors, thus protecting cells and tissues. Xie *et al.*^[32] demonstrated that Cryptotanshinone pretreatment restored the sensitivity to dexamethasone in mice, and at the same time down-regulated the level of phosphorylated Akt, and up-regulated the level of HDAC2 protein by the experiments in human cells. Cryptotanshinone pretreatment reversed the decrease of HDAC activity in *cs*-stimulated U937 cells. Cryptotanshinone restores oxidative stress-induced corticosteroid sensitivity by inhibiting PI3K δ and is a potential drug for the treatment of corticosteroid-insensitive diseases such as COPD. Hu Zhang root has the effects of activating blood circulation and dispersing phlegm, dispelling wind and detoxifying toxins, reducing inflammation and relieving pain, and removing dampness-heat and jaundice, etc. It is recorded in Yunnan *Materia medica*; "Hu Zhang is used for attacking all kinds of swellings and poisons, stopping throat pain, facilitating urination, and walking through the meridians. The treatment of five gonorrhoea; white turbidity, hemorrhoid leakage, sore, women with red and white belt. Huperzin is a natural compound extracted from the root of *Huperzia serrata* with anti-inflammatory, antioxidant and antitumor effects. Zhou *et al.*^[33] proved by animal experimental studies that thujone glucoside can reduce the expression level of inflammatory factors TNF- α and IL-6, and inhibit the expression of PI3K, AKT, and mTOR proteins in thujone glucoside group of rats, which can prove that thujone glucoside can inhibit the PI3K/AKT/mTOR pathway in COPD rats, inhibit the inflammation in the airway, and play a protective role against lung injury.

Ren Shen holds the title of the king of herbs, with functions such as anti-fatigue, improving heart disease and boosting immunity, and is commonly used in the treatment of respiratory, gastrointestinal and cardiovascular diseases. Ginsenosides are its main bioactive components, and in the treatment of respiratory diseases, ginseng and ginsenosides have been found to be effective in reducing inflammation and oxidative responses, including inhibition of kinase phosphorylation, N Nuclear Factor Kappa B (NF- κ B) nuclear translocation, Deoxyribonucleic Acid (DNA) binding, and the production of pro-inflammatory mediators (TNF- α , IL-6, IL-8, IL-1 β , ROS and MMP9)^[34]. More than 100 monomers have been identified from ginseng, among which Rg3 is a ginsenoside monomer with multiple pharmacological activities. Recent studies have found that ginsenoside Rg3 has therapeutic effects on airway diseases, for example, Rg3 can inhibit epithelial-mesenchymal transition and lung cancer invasion by regulating fucosylation of cancer cells as well as MAPK and NF- κ B signaling pathways^[35], and Rg3 can inhibit kinase phosphorylation, NF- κ B nuclear translocation, DNA binding, and pro-inflammatory mediator production by regulating PI3K/AKT/mTOR mediator production, to attenuate LPS-induced acute lung injury^[36], Guan *et al.*^[37], proved this view through animal experiments, and then showed that ginsenoside Rg3 has a certain degree of preventive effect on the occurrence of AECOPD by inhibiting the activation of the PI3K signaling pathway in the neutrophils, thus inhibiting neutrophil migration and reducing inflammation. There is a record of Fritillary in Yunnan *Materia medica*; it is used to treat lung pain, cough with pus and blood, phlegm with fishy odor, heat and toxicity of the large intestine, and cure hemorrhoids. It is believed that fritillary has the effect of clearing away heat and detoxification, eliminating pain and draining pus, and diuretic. Wu *et al.*^[38], intervened in Westar male rats with fritillaries extract sodium fisetin, and found that the lung tissue of mice in the sodium fisetin group showed a decrease in the expression of PI3K and AKT1 genes, and an increase in the expression of mTOR genes, which suggests that *Fritillaria* extract is able to alleviate the lung tissue injury in rats with COPD model, and the mechanism of *Fritillaria* may be related to its ability to down-regulate the expression of PI3K and AKT1 mRNA, and up-regulate mTOR

mRNA. Its mechanism may be related to its ability to down-regulate the expression of PI3K, AKT1 mRNA and up-regulate the expression of mTOR mRNA.

Astragalus, formerly known as Huangqi, was first published in Shennong Ben Cao Jing (Classic of the Materia medica of the Divine Husbandman), which recorded that it has the efficacy of generating fluids and nourishing the blood, and promoting stagnation and paralysis, which can be used for qi deficiency and weakness, internal heat and thirst, blood deficiency and atrophy, paralysis, and numbness, etc. Song *et al.*^[39] reported that astragali extract astragaloside (BA) could enhance the activity of A2AR and down-regulate the PI3K/AKT pathway induced by SDF-1, Cxcr4, PPI3K, p-AKT and PI3K/AKT *via* animal, formerly known as Huangqi, was first published in Shennong Ben Cao Jing (Classic of the *Materia medica* of the Divine Husbandman), which recorded that it has the efficacy of generating fluids and nourishing the blood, and promoting stagnation and paralysis, which can be used for qi deficiency and weakness, internal heat and thirst, blood deficiency and atrophy, paralysis, and numbness, etc. Song *et al.*^[39] reported that astragali extract astragaloside (BA) could enhance the activity of A2AR and down-regulate the PI3K/AKT pathway induced by SDF-1, Cxcr4, PPI3K, p-AKT and PI3K/AKT *via* animal experiments, PI3K, p-AKT/AKT-induced PI3K/AKT pathway. In another Polycyclic Aromatic Hydrocarbon (PAH) model, it was confirmed that BA (60 mg/kg, intraperitoneal injection) alleviated chronic hypoxia-induced PAH through the AKT pathway, and attenuated the effects on pulmonary vascular remodeling and cardiopulmonary injury. Puerarin is a flavone compound isolated from dried *Pueraria mirifica*, a TCM. Its medicinal value is attributed to its wide range of pharmacological properties such as vasodilatory, cardio protective, antioxidant, anti-apoptotic and IR reduction^[40]. Puerarin has a protective effect on cell damage caused by pathological factors, and it has been reported that puerarin significantly ameliorated TNF- α induced apoptosis in PC12 cells by decreasing the expression of caspase-3 through activating the PI3K/AKT signaling pathway^[41]. Wang *et al.*^[42], demonstrated that puerarin inhibited the mitochondrial autophagy-associated proteins PINK1, parkin expression, thus inhibiting the dephosphorylation of FUNDC1 to prevent

mitochondrial autophagy, and inhibiting Cigarette Smoke Extract (CSE)-induced mitochondrial autophagy and apoptosis in Human Bronchial Epithelial Cells (HBECS) by activating the PI3K/AKT/mTOR signaling pathway. Saffron has the efficacy of activating blood circulation and removing blood stasis, cooling the blood and detoxifying the toxin, and relieving depression and tranquilizing the mind. It is recorded in the Justice of the *Materia medica* that Tibetan saffron, which is used to lower the rebellious Qi, opens the knot and eliminate blood stasis, is still similar to Sichuan saffron, but its power is more powerful than that of Sichuan saffron. Xie *et al.*^[43], demonstrated that saffron reduced the level of pro-inflammatory mediators in BAL fluid and lung tissues through the significant reduction of inflammatory factors IL-1 β , IL-6, and TNF- α in animal experiments. PI3K and p-Akt expression was significantly up-regulated by cigarette smoke but significantly reversed by saffron, suggesting that saffron reduces the level of pro-inflammatory mediators in BAL fluid and lung tissues. Reversed by saffronin, suggesting that the protective effect of saffronin may be dependent on the PI3K/AKT pathway for the treatment of COPD. Chenpi (aged peel) is the dried peel of citrus (*Citrus reticulata*, Blanco) after aging treatment. Chenpi is not only a dietary supplement, but is also used to treat respiratory disorders by regulating qi, strengthening the spleen, drying dampness, resolving phlegm and relieving cough. Modern pharmacological studies have shown that chenpi has anti-inflammatory, anticancer, antioxidant and phlegm-thinning properties^[44]. Hesperidin is a candidate compound of chenpi, Zhou *et al.*^[45] found that hesperidin inhibits AKT1, IL-6, Vascular Endothelial Growth Factor A (VEGFA), MMP9 protein expression and up-regulates TP53 protein expression by participating in the PI3K-

Akt signaling pathway, which reduces the risk of progression of COPD to lung cancer.

Chinese medicine compound prescription:

With the inheritance and development of TCM, more and more studies have found that traditional Chinese medicine prescriptions also play an important role in the treatment of COPD patients. According to the existing studies, Chinese herbal remedies targeting the PI3K/Akt signaling pathway for COPD prevention and treatment are mainly based on basic research, and fewer clinical studies have been carried out. In this paper, we summarize the compound prescriptions of Qingfei Huatan decoction, Bufe Yishen formula, Yiqi Gubiao pill, Erchen Jiawei formula and Yiqi Huayin Qing Re formula, Jianpi Bushen formula, Wen shen Yiqi granule, Bushen Fang Chuan formula, Xuefu Zhuyu decoction, and Louqin Zhisou decoction. Most of the drugs are used to nourish yin, benefit qi, activate blood circulation, and promote the circulation of blood. A variety of drugs work together to inhibit the production of pro-inflammatory cytokines such as IL-6 and IL-17A in BALF through activation of the PI3K/Akt pathway, down-regulate the expression of related proteins such as NE, MCP-1, PI3k, MMP, and AKT, and reduce apoptosis, oxidative stress, inflammation, and airflow restriction brought about by the secretion of high airway secretions, airway infections, and damage to the structure of the lungs, thus improving COPD. The specific mechanism of action of Chinese herbal medicine compound in treating COPD is detailed in Table 2. Qu *et al.*^[46] used Qingfei Huatan decoction to intervene the COPD model rats induced by cigarettes, and found that Qing fei Huatan decoction could regulate and inhibit TNF- α and IL-1 β , down-regulate the expression of HDAC2, mRNA and reduce the expression of HDAC2 protein.

TABLE 2: MECHANISMS OF ACTION OF HERBAL COMPOUNDS AND PREPARATIONS IN THE TREATMENT OF COPD *via* PI3K/AKT SIGNALING PATHWAY

Compound prescription	Constitute	Models	Target of action	Reference.
Qing fei Hua tan decoction	Sang Bi Pi, Huang Qin, Gua Lou Pi, Zhe Bei Mu, Xing Ren, Su Zi, Fa Ban Xia, Fu Ling, Yu Xing Cao, Gua Lou Rer and Gan Cao Pian	SPF grade model rats	\uparrow IL-10,LC3worker protein,Beclin1 mRNA expression, \downarrow PI3K p110a, Akt,p-Akt,mTOR,p-mTOR,PI3K,mTORmRNA expression	[50]
Bufe Yi Shen formula	Ren Shen, Chen Pi, Huang Qi, Yin Yang Huo and Dan Pi	SD rats	\downarrow CD34 protein positive expression, \downarrow VEGF, VEGFR2, ET-1m RNA expression, VEGF/PI3K/Akt pathway related protein expression	[51]

Yi qi Gu Biao pill	Dang Shen, Fu Xiao Mai, Chao Bai Zhu, Fa Ban Xia, Chen Pi, Zi Su Zi, Yi Bei Mu, Fu Ling, Fang Feng, Yi Yi Ren, Kuan Dong Hua, Huang Qin and Pi Pa Ye	Wistar rats	↑p-IGF-1R, p-PI3K, p-AKT, p-GSK3 protein levels, ↓ PTEN, p-mTOR protein levels	[52]
Er chen Jia wei formula	Dang Shen, Jiang Ban Xia, Chao Zi Su Zi, Ku Xing Ren, Chen Pi, Fu Chao Bai Zhu, Ma Huang, Ting Li Zi, Fu Ling, Shan Yao, Gui Zhi, Fu Chao Zhi Ke and Di Long	SD rats	↓protein expression of p-PI3K, p-Akt, ↑ protein expression of p-Nrf2	[53]
Yi qi Hua yin Qing Re formula	Mi Ma Huang, Huang Qin, Sang Bai Pi, Shi Gao, Qing Ban Xia, Fu Ling, Dang Shen, Chao Bai Zhu, Gan Jiang, Xi Xin, Wu Wei Zi, Hou Po, Xing Ren and Zhi Gan Cao	Wistar rats	↓ IL-1B, IL-4, IL-6, TNF-α levels	[54]
Jian pi Bu shen formula	Dang Shen, Chao Bai Zhu, Chao Zhi Ke, Chen Pi, FU Ling, Sha Ren, Shu Di, Shan Yu Rou, Chao Shan Yao, Bu Gu Zhi, Zi Ying Shi, Zhi Huang Jing, Sheng Huang Qi and Zhi Gan Cao	C57BL/6 mice	↓NEDD4, PI3k, AKT levels, ↑ PTEN protein expression	[55]
Wen shen Yi qi granule	Huang Qi, Tu Si Zi, Zi Shi Ying, Chong Lou and E Zhu	SD rats	↓the ratio of p-AKT/AKT, p-mTOR/mTOR and inhibit PNCA protein expression	[56]
Bu Shen Fang Chuan formula	Fu Zi, Tu Si Zi, Yin Yang Huo, Bu Gu Zhi, Shan Yao, Sheng Di, Shu Di and Chen Pi	SD rats	↓ TNF-α, IL-6 concentrations, attenuate NF-κB activation and glucocorticoid receptor downregulation	[57]
Xue fu Zhu yu decoction	Tao Ren, Hong Hua, Dang Gui, Sheng Di Huang, Niu Xi, Chuan Xiong, Jie Geng, Chi Shao, Zhi Ke, Gan Cao and Chai Hu	Cyber pharmacology	Improvement of oxidative stress and inflammatory response, alleviation of airway remodeling and impaired ventilation, correction of hypercapnia and hypoxemia	[58]
Lou qin Zhi sou decoction	Gua Lou Pi, Huang Qin, Lian Qiao, Lou Lu, Zhe Bei Mu, Qing Ban Xia, Qian Hu and Jie Geng	Wistar rats	↓MUC5AC mRNA expression, ↓phosphorylated EGFR, pi3k, Akt levels. ↓ IL-6, IL-17A levels, ↓NE, MCP-1 secretion, reverse Th17 and Treg key transcription factor ROR	[59]
Tiao bu Fei shen formula	Dang Shen, Yin Yang Huo, Huang Qin, Ban Xia, Jie Geng, Xing Ren, Dan Shen, Gan Cao, Huang Qi, Shan Zhu Yu, Shu Di Huang, Zhe Bei Mu and Ai Di Cha	COPD cell models	↑ expression levels of GRα and HDAC2, ↓expression of PAKT1	[60]

It is suggested that Qingfei Huatan decoction can treat COPD by regulating the expression of inflammatory factors and related proteins in PI3K/Akt/mTOR pathway. Zhang *et al.*^[47] used CSE combined with repeated bacterial infections to establish a stable COPD rat model. After treatment, the results showed that Bufe Yishen component could obviously improve the lung function of rats, reduce the thickening of pulmonary vascular wall, reduce the positive expression of Cluster of differentiation (CD) 34 protein in pulmonary

small vessels, and reduce the expressions of VEGF, VEGFR2, ET-1mRNA and VEGF/PI3K/Akt pathway related proteins in lung tissue. Dan *et al.*^[48] used Yiqi Gubiao pill to intervene the COPD rat model established by inhaling smoke and intratracheal instillation of LPS, and found that Yiqi Gubiao pill could increase p-IGF-1R and p-PI response in lung tissue samples of COPD rats. Er Chen Tang Jiawei recipe reduces the protein expression of p-PI3K and p-Akt^[49], and increases the protein expression of p-Nrf2, so as to reduce the

lung inflammation and oxidative stress of COPD rat model with phlegm and turbidity blocking lung.

SUMMARY AND OUTLOOK

In recent years, the involvement of the PI3K/Akt signaling pathway and its mechanism of action have been widely reported in the study of COPD. As a classical signaling pathway regulating the release of inflammatory mediators, activation of inflammatory cells, airway remodeling, oxidative stress, and other biological activities, PI3K/Akt signaling plays an important role in suppressing airway inflammatory responses, alleviating oxidative stress, and other pathological processes through the regulation of key factors such as TNF- α , IL-6, IL-8, IL-1 β , ROS, MMP9, PI3K, AKT, and so on. MMP9, PI3K, AKT and other key factors play important regulatory roles in inhibiting airway inflammatory responses, alleviating oxidative stress and other pathological processes.

Currently, Chinese medicine extracts/active ingredients, and complexes have achieved good results in treating COPD through the PI3K/Akt signaling pathway, and the mechanism of action of related drugs has also been studied. Therefore, this paper reviewed the connection between the PI3K/Akt signaling pathway and the pathogenesis of COPD, as well as the studies on active ingredients/extracts/complexes of TCM to prevent and control the progression of COPD by interfering with the PI3K/Akt signaling pathway, and found that the PI3K/Akt signaling pathway has a role in mitigating the inflammatory response in the airway by inhibiting airway inflammatory response, alleviating the oxidative stress, inhibiting the value-added of inflammatory factors and related proteins, and alleviating the airflow limitation and airway inflammation caused by smoke and hypoxia, etc., and that these mechanisms are interconnected and interact with each other.

It has been shown that genetics, epigenetics, gender, immune system and microbiome are considered as background or susceptibility factors^[50], while cigarette smoke, air pollution, biomass smoke and microbial infections are risk factors^[51]. Risk factors mainly induce oxidative stress, altered immune responses^[52,53], as various oxidative stresses, altered immune responses can induce chronic inflammation in the lungs and throughout the body. After exposure to smoke, other pollutants or oxidants airway epithelium

can secrete mucus and release inflammatory mediators for defense against smoke attack, but the release of excessive inflammatory mediators due to persistent stimulation can lead to airway remodeling and airflow limitation, promoting COPD pathogenesis^[7]. It is now clear that PI3K has a role in inflammatory cell recruitment and activation in the inflammatory response of COPD, and is accompanied by the secretion of various pro-inflammatory cytokines and chemokines. The PI3K/Akt signaling pathway plays an important role in mitigating airway inflammation induced by smoke and hypoxia by inhibiting airway inflammatory responses, alleviating oxidative stress, and inhibiting, directly or indirectly, the value-added of inflammatory factors and related proteins. Important role and these mechanisms are interconnected and interact with each other.

In conclusion, it was found that Chinese medicine monomers and combinations can prevent the induction of mitochondrial autophagy, apoptosis, oxidative stress, and immune response by inhibiting the PI3K/Akt signaling pathway, and achieve cyto protection, which provides a new way of thinking for the treatment of COPD. Most of the Chinese medicines used in the treatment of COPD through the regulation of PI3K/Akt signaling pathway are based on "warming the lungs and kidneys, expelling drinks and removing blood stasis", which reflects the concept of "combination of tonic and tonic" in Chinese medicine, warming the kidneys and boosting yang, transforming the cold drinks and removing the stasis of blood, and then all the symptoms will be relieved. The Chinese medicines that are used more frequently are Huang Qin, Dang Shen, Ban Xia, Fu Ling, Chen Pi, Gan Cao, Huang Qi *et al.*^[54-60] which are of good application value and prospect in the prevention and control of COPD, providing the direction of the use of Chinese medicine in the treatment of COPD, providing new ideas and methods for the treatment of COPD, which is of certain significance, and providing theoretical foundations for the use of medicines in the future clinic and the direction of the research of COPD. However, the clinical effectiveness of Chinese medicine in treating COPD has been confirmed and widely accepted, but the research on the mechanism of PI3K/Akt signaling pathway on COPD is still in the early stage, and there are fewer clinical studies on the treatment of COPD through this pathway, and the

intervention in the PI3K/Akt signaling pathway in the treatment of COPD is mostly confined to the animal experiments and the cellular level, so the development of related clinical research is the direction of future research. Therefore, the development of related clinical studies is the direction of future research. Secondly, Chinese medicine extracts and compound formulas have complex compositions, many targets, and uncertain molecular mechanisms. In the future, we can utilize network pharmacology, high-throughput mass spectrometry, bioinformatics, multi-omics analysis and molecular docking to further study the material basis of PI3K/Akt signaling pathway of traditional Chinese medicine to prevent and treat COPD, and to further research on the pharmacological substances and mechanisms of action.

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