

# Research Progress on Chinese Medicine Regulation of Mitochondrial Damage for Intervention in Respiratory System Diseases

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## Abstract

Mitochondria are important organelles in cells for energy production, and mitochondrial damage caused by various reasons is an important factor promoting disease progression. Mitochondrial damage involves structural damage and mitochondrial DNA damage, which are closely related to the occurrence and development of respiratory system diseases. In recent years, a large number of studies have confirmed the significant role of mitochondrial damage in the progression of respiratory system diseases, which may be an important target for the treatment of respiratory system diseases with traditional Chinese medicine (TCM). This article reviews the role of TCM in regulating mitochondrial damage for intervention in respiratory system diseases such as chronic obstructive pulmonary disease, lung cancer, pulmonary fibrosis, acute lung injury, asthma, and pneumonia, aiming to provide a basis for the study of the pathogenesis and drug action targets of respiratory system diseases.

## Keywords

- ▶ mitochondrial damage
- ▶ respiratory system diseases
- ▶ TCM

## Introduction

Mitochondria are important semiautonomous organelles, serving as the energy metabolism center of eukaryotic cells. They can regulate cell signal transduction and maintain cellular function and homeostasis. Mitochondrial damage involves structural damage and mitochondrial DNA damage, playing an important role in promoting the progression of respiratory system diseases. A large amount of clinical and experimental data suggest that regulating mitochondrial damage may be an important target for traditional Chinese medicine (TCM) in treating respiratory system diseases.

In TCM, it is believed that respiratory system diseases are caused by factors such as invasion of external pathogenic

factors, improper diet, emotional imbalance, and overstrain, with complex pathogenesis and diverse patterns of syndromes. TCM treatment focuses on harmonizing the overall function of the organs to promote the smooth flow of qi and blood and achieve yin–yang balance. In recent years, significant progress has been made in the TCM intervention of respiratory system diseases by regulating mitochondrial damage. This article summarizes the role of TCM in regulating mitochondrial damage for intervention in respiratory system diseases such as chronic obstructive pulmonary diseases (COPDs), lung cancer, idiopathic pulmonary fibrosis (IPF), acute lung injury (ALI), and asthma, aiming to provide a basis for the study of the pathogenesis and drug targets of respiratory system diseases.

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## The Role of Mitochondrial Damage in the Occurrence and Development of Respiratory System Diseases

Mitochondria are important semiautonomous organelles, serving as the main site for aerobic respiration in cells and the energy metabolism center of eukaryotic cells. They mainly synthesize adenosine triphosphate (ATP), participate in aerobic respiration, and maintain human physiological functions. Mitochondria affects oxidative stress and immune responses by regulating calcium signals and their homeostasis, participating in cell differentiation, signal transduction, and apoptosis.<sup>1</sup> Mitochondrial damage refers to abnormal changes in mitochondrial structure and function, including large-scale loss of mitochondrial DNA, and changes in membrane structure, electron transfer function through the respiratory chain, mitochondrial transmembrane potential difference, etc.,<sup>2,3</sup> resulting in mitochondrial oxidative stress, mitochondrial autophagy, mitochondrial DNA mutations, telomere shortening, etc. A large number of studies have confirmed that mitochondrial damage plays an important role in the occurrence and development of respiratory system diseases.<sup>4–6</sup> Under the stimulation of factors such as hypoxia, infection, and cigarette smoke (CS), the body produces a large amount of oxygen free radicals which promote oxidative stress, disrupt oxidative phosphorylation, and mitochondrial homeostasis, leading to mitochondrial dysfunction, abnormal ATP generation, and consequently causing apoptosis of airway epithelial fibroblasts and increased mucus secretion and thus the occurrence and development of respiratory system disease.<sup>7</sup> In addition, a large amount of reactive oxygen species (ROS) can damage DNA, induce mtDNA mutations, and exacerbate cell death and mitochondrial damage.<sup>8</sup> Under exposure to smoke, ROS produced by mitochondria accelerates cell aging, and lung function indicators are related to telomere shortening.<sup>9</sup>

## Research Status of Traditional Chinese Medicine Regulation of Mitochondrial Damage in Intervening Respiratory System Diseases

### Traditional Chinese Medicine Regulation of Mitochondrial Damage in Treating Chronic Obstructive Pulmonary Diseases

COPD is a preventable and treatable disease characterized primarily by persistent airflow limitation, with high morbidity and mortality rates. Epidemiological investigations show that COPD became the third leading cause of death globally in 2020, which imposes a heavy economic burden, with annual economic losses exceeding 100 billion U.S. dollars.<sup>10–12</sup> Mitochondrial damage caused by factors such as tobacco smoke, air pollutants, and hypoxia is closely related to the occurrence and the development of COPD.<sup>13,14</sup> TCM has obvious advantages in treating COPD, and the mechanisms involve intervention in inflammation, oxidative stress, mitochondrial damage, etc. The Chinese herb Hongjingian (*Rhodiola crenulata* Radix et Rhizoma)

is mild in nature, enters the lung and heart meridians, and has the effects of tonifying qi and activating blood circulation, dredging the meridians, and relieving asthma. Its extract salidroside can improve lung function, muscle strength, body weight, and enhance ATP activity in COPD rats, alleviate mitochondrial damage, and thus improve the prognosis of COPD.<sup>15,16</sup> Baicalin, an extract of Chinese herbs, is a flavonoid compound with anti-inflammatory, antipyretic, and antiallergic effects. Studies have found that baicalin can significantly inhibit mitochondrial damage and cell iron apoptosis and improve COPD induced by lipopolysaccharide (LPS) or CS in mice.<sup>17</sup> The supplemented Sijunzi decoction is a famous prescription for treating “asthma,”<sup>18</sup> which can increase the activity of succinate dehydrogenase in skeletal muscles of COPD model mice, alleviate mitochondrial structural damage and oxidative stress, and enhance energy metabolism.<sup>19</sup> Animal experiments and clinical results have also confirmed that the compound Chinese herbs Bufei Jianpi Granules can effectively improve the skeletal muscle function of COPD rats, reduce the frequency of acute exacerbations in COPD patients with lung-spleen qi deficiency by improving mitochondrial quantity and function, improve lung function, and enhance quality of life.<sup>20</sup> The TCM treatment method of “cultivating earth (spleen) to generate metal (lung)” borrows the theory of the mutual generation of the five elements, using spleen-tonifying and qi-benefiting prescriptions to reinforce lung qi, which is used as an adjuvant treatment for lung qi deficiency.<sup>21</sup> Research by Feng et al<sup>22</sup> has shown that the TCM compound prescription of “cultivating earth (spleen) to generate metal (lung)” can significantly improve lung alveoli, diaphragm muscles, and mitochondrial damage in COPD rats, relieve respiratory muscle fatigue, enhance mitochondrial function, and reduce the occurrence of respiratory failure.

### Traditional Chinese Medicine Regulation of Mitochondrial Damage in Treating Lung Cancer

Lung cancer is a malignant tumor of the bronchial gland or mucosa, with increasing incidence and mortality rates year by year, and is one of the most serious threats to human health and life among malignant tumors.<sup>23</sup> Mitochondrial damage is closely related to the metabolic patterns of tumors, and factors such as mitochondrial membrane damage and oxidative stress can lead to tumor invasion and metastasis.<sup>24,25</sup> Panoxadiol is a novel antitumor drug isolated from the Chinese herb *Renshen* (*Ginseng Radix et Rhizoma*), which is an important active ingredient of ginseng.<sup>26</sup> Li et al<sup>27</sup> used panoxadiol on lung cancer A549 cells and found that panoxadiol could reduce the mitochondrial membrane potential of lung cancer cells, promote mitochondrial damage of lung cancer cells, induce apoptosis of lung cancer cells, and delay the progression of lung cancer. Fangji (*Stephaniae Tetrandrae Radix*) has anti-inflammatory, analgesic, and antioxidant effects. Fangchinoline is a monomer extracted from the dried roots of Fangji (*Stephaniae Tetrandrae Radix*), which can delay the development of tumors by inducing mitochondrial apoptosis and blocking the cell cycle.<sup>28,29</sup> Chen et al<sup>30</sup> found that fangchinoline can

effectively regulate the production of ROS caused by mitochondrial damage, alleviate epithelial-mesenchymal transition of non-small cell lung cancer, inhibit tumor cell invasion and migration, and exert anticancer effects. Yinxingye (Ginkgo Folium) has the effects of astringing the lung to relieve cough and drying dampness to stop diarrhea, mainly used for chest tightness, heart pain, phlegm panting, and cough. Ginkgetin is a natural bis-flavonoid compound extracted from ginkgo,<sup>31</sup> which can intervene in the cancer process by enhancing the loss of mitochondrial membrane potential induced by cisplatin, increasing the generation of mitochondrial ROS and apoptosis in lung cancer cells.<sup>32</sup>

### Traditional Chinese Medicine Regulation of Mitochondrial Damage in Idiopathic Pulmonary Fibrosis (IPF)

IPF is a chronic, progressive, and fibrotic interstitial lung disease, which is the main pathological manifestation of end-stage respiratory system disease. The core pathological change of IPF is the aging and injury to alveolar epithelial cells.<sup>33,34</sup> Mitochondrial damage and autophagy defect are associated with the development of pulmonary fibrosis, with increased mitochondrial autophagy, abnormal phenotype of mitochondrial enlargement, increased ROS production, and cell apoptosis leading to increased sensitivity of alveolar epithelial cells to pressure and fibrosis occurrence.<sup>35,36</sup> Rougui (Cinnamomi Cortex), also known as Guipi, is a Chinese herb with warm property and the efficacy of warming the middle energizer to dispel cold, regulating qi and alleviating pain. Scholars have used cinnamaldehyde to intervene in a hydrogen peroxide-induced IPF mice model, and the experimental results showed that cinnamaldehyde can significantly increase the level of superoxide dismutase (SOD), matrix metalloproteinase, and ATP in IPF mice. It also restores mitochondrial structure by regulating the PINK/Parkin signaling pathway, inhibits mesenchymal stem cell apoptosis, maintains the ability of mesenchymal stem cells to repair alveolar epithelium, regulates cell proliferation and migration, and participates in the pathological process of IPF.<sup>37</sup> Researchers have confirmed that No.2 TCM compound prescription Feibi prescription can reduce ROS level in alveolar epithelial cells, protect mitochondrial function, regulate antioxidant enzyme expression, alleviate mitochondrial damage, and inhibit cell apoptosis in a ROS-induced pulmonary fibrosis model.<sup>38</sup> Naringin is a dihydroflavonoid compound found in naringoside, which has significant anti-inflammatory, analgesic, and blood viscosity reducing effects.<sup>39</sup> Wei et al<sup>40</sup> investigated the impact of naringin on IPF and found that in a bleomycin-induced mice model of IPF, naringin exhibited anti-inflammatory and antioxidant effects, inhibited mitochondrial autophagy, maintained mitochondrial homeostasis, and alleviated cell apoptosis, thereby intervening in the progression of IPF.

### Traditional Chinese Medicine Regulation of Mitochondrial Damage in Acute Lung Injury

Acute Lung Injury (ALI) refers to acute hypoxemic respiratory insufficiency caused by various direct or indirect factors,

with decreased lung volume, ventilation/perfusion mismatch, and decreased lung compliance as the pathophysiological features.<sup>41</sup> ALI is closely related to mitochondrial damage and abnormal level of mitochondrial mtDNA.<sup>42</sup> Increased production of mitochondrial oxygen free radicals, imbalance of mitochondrial calcium homeostasis, and changes in mitochondrial permeability all affect ALI. Xuanfei Baidu prescription is a classical Chinese medicine prescription with precise clinical efficacy, which can clear the lung and resolve dampness, clear heat and eliminate pathogens, purge the lung, and remove toxin.<sup>43</sup> Studies have reported that Xuanfei Baidu prescription can inhibit mitochondrial dysfunction in LPS-induced ALI model mice, suppress mtDNA synthesis and replication, reduce the expression level of inflammatory factors, and alleviate the clinical symptoms of ALI and coronavirus disease 2019 patients.<sup>44</sup> Chuanxinlian (Andrographis Herba) is bitter in flavor and cold in property, with the effects of protecting the liver and gallbladder, clearing heat and removing toxin, as well as antibacterial and anti-inflammatory effects.<sup>45</sup> Its effective component, dehydroandrographolide (Deh), reduces ROS generation by inhibiting the protein kinase B (Akt)/nuclear factor E2-related factor 2 (Nrf2) pathway, inhibits mitochondrial damage, and may be a potential drug for treating ALI.<sup>46</sup> Tangeretin, a flavonoid compound, has anti-inflammatory and neuroprotective effects.<sup>47</sup> In studies related to the treatment of ALI induced by sepsis, tangeretin can inhibit ROS-mediated inflammasome activation, maintain mitochondrial homeostasis in LPS-induced ALI model mice, alleviate excessive mitochondrial fission, and thus achieve the purpose of treating ALI.<sup>48</sup> Huangqin (Scutellariae Radix) is a heat-clearing and dampness-drying herb with the effects of clearing heat and drying dampness, purging fire and detoxifying, stopping bleeding, and calming the fetus. Baicalein, as the most abundant monomer in Huangqin (Scutellariae Radix), has a significant clinical application value in antiviral, antibacterial, and anti-inflammatory effects.<sup>49</sup> Recent studies have confirmed that baicalein can alleviate lung injury severity and delay the progression of ALI by regulating mitochondrial damage induced by mitochondrial division protein Drp1, downregulating the expression level of inflammatory factors and ROS production.<sup>50</sup>

### Traditional Chinese Medicine Regulation of Mitochondrial Damage in Asthma

Asthma is a common chronic heterogeneous disease of the respiratory system characterized by airway inflammation. Its clinical features primarily include airway hyperresponsiveness and airway remodeling. The pathogenesis of asthma is complex, requiring long-term standardized and individualized treatment.<sup>51</sup> Asthmatic patients accumulate airway inflammatory cells for an extended period, leading to elevated oxidative stress level, damaging epithelial cell mitochondrial function and homeostasis.<sup>52,53</sup> Numerous studies at home and abroad have found that apigenin has antitumor, cardiovascular protection, and antiviral effects.<sup>54</sup> It can regulate the ROS-apoptosis signal-regulating kinase 1 (ASK1)-mitogen-activated protein kinase (MAPK) pathway

to reduce airway epithelial cell apoptosis, enhance cell vitality and mitochondrial function, and inhibit inflammation and oxidative stress.<sup>55</sup> The extract salidroside from the root of Hongjingtian (*Rhodiola Crenulatae Radix et Rhizoma*) can enhance immune function and has anticancer and antioxidant effects.<sup>56</sup> Shan et al<sup>57</sup> found that salidroside can effectively increase mitochondrial membrane potential, decrease ROS level and cell apoptosis levels, and improve asthma progression in bronchial epithelial cell model induced by PM<sub>2.5</sub>. Chinese herb Mudanpi (*Moutan Cortex*) has the effects of clearing heat, cooling blood, promoting blood circulation and removing blood stasis. Its main components, paeonol and paeoniflorin, have anti-inflammatory, antipyretic, and antithrombotic effects.<sup>58,59</sup> Studies have found that paeonol and paeoniflorin can effectively improve lung injury induced by ovalbumin (OVA) in mice and participate in asthma processes by inhibiting the expression of inflammatory factors, restoring mitochondrial membrane potential and mitochondrial metabolic activity and inhibiting mitochondrial autophagy.<sup>60</sup> The TCM prescription Bushen Yiqi prescription has the effects of tonifying qi and kidney, promoting blood circulation and resolving masses. Research shows that Bushen Yiqi prescription has a positive effect on the mouse model with chronic asthma. It can reduce the generation of ROS and inhibit the expression of the inflammatory factor nuclear factor- $\kappa$ B (NF- $\kappa$ B), lower nitric oxide (NO) expression levels in lung tissue, improve bronchial epithelial mitochondrial structure and ATP level in the lung, alleviate airway remodeling in the asthma model to relieve asthma symptoms.<sup>61</sup>

### Traditional Chinese Medicine Regulation of Mitochondrial Damage in Pneumonia

Pneumonia is mainly caused by pathogens such as bacteria and viruses, leading to infectious inflammation of the alveoli, distal airways, and lung interstitium. It can occur at any age, and the severity of the disease depends on the patient's immunity and the degree of inflammation.<sup>62,63</sup> Similar to ALL, inflammation and oxidative stress are key pathological factors. Mitochondrial damage and excessive ROS production can cause mitochondrial dysfunction, resulting in changes in mitochondrial membrane permeability and transmembrane potential, the release of cytochrome C from mitochondria into the cytoplasm, and leading to cell apoptosis.<sup>64,65</sup> Glycyrrhizic acid is one of the extracts of Gancan (*Glycyrrhizae Radix et Rhizoma*), with certain anticancer and antiviral effects.<sup>66</sup> Guan et al<sup>67</sup> showed that in the carbapenem-resistant *Klebsiella pneumoniae* (CRKP)-induced human lung epithelial cell model by activating Nrf2 expression glycyrrhizic acid can promote antioxidant protein production, inhibit the expression of inflammatory factors, and alleviate mitochondrial damage and cell apoptosis, thus reducing lung tissue damage caused by CRKP infection. Huanglian (*Coptidis Rhizoma*) mainly functions to clear heat, dry dampness, purge fire, and detoxify. It is commonly used clinically to treat diarrhea, vomiting, ulcers, swelling, and pain.<sup>68</sup> Berberine, also known as berberine alkaloid, isolated from Huanglian (*Coptidis Rhizoma*), has broad-

spectrum antibacterial effects. Liu et al<sup>69</sup> found that berberine can significantly inhibit the activation of NLRP3 inflammasomes in a model of macrophage inflammation induced by influenza virus infection, increase mitochondrial membrane potential, reduce mitochondrial oxidative stress response and mitochondrial damage, and effectively relieve pneumonia. The TCM prescription Tongfu Yiqi Huoxue decoction combined with alveolar lavage can exert a stable effect on pneumonia sepsis. Its effective ingredients, astragaloside and ligustrazine, have anti-inflammatory and antioxidant effects, which can repair mitochondrial homeostasis, inhibit peritoneal inflammation and significantly improve clinical symptoms of pneumonia sepsis patients.<sup>70</sup>

### Traditional Chinese Medicine Regulation of Mitochondrial Damage in Other Respiratory System Diseases

Various functional disorders like damage of mitochondrial protein synthesis are closely related to the progression of respiratory system diseases such as pulmonary arterial hypertension (PAH), acute respiratory distress syndrome (ARDS), and pneumoconiosis. Abnormal elevation of pulmonary artery pressure is a lethal pathological and physiological state, manifesting symptoms of dyspnea, fatigue, angina pectoris, etc.,<sup>71</sup> which can lead to right heart failure. Studies have shown that mitochondrial dysfunction and DNA damage are involved in the remodeling of pulmonary vasculature and right ventricle in PAH.<sup>72,73</sup> Dilong (*Pheretima*), a Chinese herb used to soothe wind and relieve convulsions, mainly functions to clear heat and arrest convulsions, dredge collaterals, relieve asthma, and promote diuresis. Liu et al<sup>74</sup> found that the extract of Dilong (*Pheretima*) can down-regulate the protein expression of NLRP3 in lung tissue of PAH rats, reduce oxidative stress and inflammation levels in pulmonary artery endothelial cells, alleviate apoptosis, improve mitochondrial functional damage, and thus inhibit pulmonary vascular remodeling and PAH. Magnolol, an important component of the Chinese herb Houpo (*Magnoliae Officinalis Cortex*), has remarkable pharmacological anti-inflammatory, antibacterial, antioxidant, and anticancer effects.<sup>75</sup> Chen et al<sup>76</sup> studied the effect of magnolol on LPS-induced ARDS and found that when magnolol acts on pulmonary microvascular endothelial cells, the expression level of mitochondrial-dependent Sirt3 protein is upregulated, AMP-activated protein kinase (AMPK) pathway is activated, further inhibiting apoptosis of pulmonary microvascular endothelial cells and alleviating ARDS. A pneumoconiosis is a group of diseases characterized by diffuse nodular or reticular fibrosis in lung tissue caused by long-term inhalation of inorganic mineral dust during occupational activities or in living environments.<sup>77</sup> Catalpol, extracted from the root and rhizome of Dihuang (*Rehmanniae Radix*) in the Scrophulariaceae family, has extensive pharmacological anticancer, anti-inflammatory, and hypoglycemic effects.<sup>78</sup> Through tracheal injection of quartz dust to establish a rat model of pneumoconiosis, it was found that by regulating the peroxisome proliferator-activated receptor- $\gamma$  coactivator 1 $\alpha$  (PGC-1 $\alpha$ )/Nrf1 and mitochondrial

transcription factor A (TFAM) pathways, catalpol can effectively protect the exercise capacity and skeletal muscle function of model rats, enhance the ATP level of gastrocnemius muscle, restore mitochondrial membrane potential, and inhibit oxidative stress indicator malondialdehyde level. These studies indicate that improving mitochondrial function and alleviating oxidative stress may be potential pathways for catalpol in the treatment of pneumoconiosis.<sup>79</sup>

## Summary and Prospect

Various factors such as environmental pollution and aging population increasingly affect the development of respiratory system diseases globally, seriously affecting people's physical and mental health. The incidence and mortality of diseases of COPD, lung cancer, asthma, and IPF have been increasing year by year. In recent years, there have been numerous reports on the relationship between mitochondria and diseases, involving research studies on mitochondrial autophagy, mitochondrial damage, mitochondrial dynamics, etc., which play a positive role in studying the pathogenesis, early prevention, and intervention of the diseases. For the past few years, the effectiveness of TCM in regulating mitochondrial damage to intervene in diseases has been widely confirmed, especially in the treatment of respiratory system diseases. However, the mechanism of TCM regulation of mitochondrial damage to intervene in respiratory system diseases is still not very clear, and it lacks relevant clinical trial data. There are still many problems in the research, for instance: (1) the components of Chinese materia medica are complex and diverse, making it difficult to accurately evaluate the effects of different components on mitochondrial damage; (2) whether TCM treatment methods such as Tuina, guiding technique, and acupuncture can affect the progression of diseases by regulating mitochondrial damage; (3) research studies on TCM regulation of mitochondrial damage still focus on animal cell experiments and lack clinical trial data, which is not sufficient to guide clinical medication; and whether the therapeutic principles of TCM syndrome differentiation and treatment can be combined with regulating mitochondrial function to explore more individualized treatment plans for clinical application. Therefore, further exploration is needed on the research of TCM regulation of mitochondrial damage to intervene in respiratory system diseases.

### CRedit Authorship Contribution Statement

Haibo Li: Writing—original draft, and investigation. Jingfan Yang: Investigation. Yanqin Qin: Conceptualization, writing—review and editing, and funding acquisition. Tiantian Liu: Writing—review and editing.

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### Conflict of Interest

The authors declare no conflict of interest.

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