Advances in Traditional Chinese Medicine Regulation of Mitochondrial Quality Control for Ischemic Stroke Treatment: A Postprint

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Date: 2023-12-11T00:00:00+00:00

Abstract

Ischemic stroke is the most common cerebrovascular accident and has increasingly become a serious global health problem. Dysregulation of mitochondrial quality control represents an important mechanism of neuronal death induced by cerebral ischemia, and maintaining mitochondrial function is crucial for promoting neuronal survival and improving neurological function. Mitochondrial quality control primarily involves mitochondrial oxidative stress, mitochondrial dynamics, mitophagy, mitochondrial biogenesis, and other aspects, constituting an essential condition for stabilizing normal mitochondrial structure and exerting normal mitochondrial function. In recent years, traditional Chinese medicine has attracted widespread attention from scholars for significantly improving clinical symptoms in ischemic stroke patients by regulating mitochondrial quality control through multiple angles, pathways, and targets, and by influencing mitochondrial structure and function. This article summarizes experimental studies and clinical observations in recent years on the application of active compounds from traditional Chinese medicine and traditional Chinese medicine formulas to regulate mitochondrial quality control in the treatment of ischemic stroke, further elucidates the pathogenesis of ischemic stroke, clarifies the regulatory mechanisms of traditional Chinese medicine on mitochondrial quality control, and summarizes the scientific connotations and deficiencies of traditional Chinese medicine in treating ischemic stroke, with the aim of providing certain ideas and methods for the further clinical application of traditional Chinese medicine in the treatment of ischemic stroke.

Full Text

Advances in Traditional Chinese Medicine Regulating Mitochondrial Quality Control in the Treatment of Ischemic Stroke

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Abstract

Ischemic stroke (IS) is the most common cerebrovascular accident and has become an increasingly serious global health problem. Mitochondrial quality control dysfunction represents a crucial mechanism underlying neuronal death induced by cerebral ischemia, and maintaining mitochondrial function is essential for promoting neuronal survival and improving neurological outcomes. Mitochondrial quality control primarily involves mitochondrial oxidative stress, mitochondrial dynamics, mitophagy, and mitochondrial biogenesis—processes that are vital for stabilizing normal mitochondrial structure and function. In recent years, traditional Chinese medicine (TCM) has attracted considerable scholarly attention for its ability to significantly improve clinical symptoms in IS patients by influencing mitochondrial structure and function through multi-perspective, multi-pathway, and multi-target regulation of mitochondrial quality control. This article systematically reviews recent experimental studies and clinical observations on the application of active compounds from Chinese herbs and TCM formulas in regulating mitochondrial quality control for IS treatment. We further elucidate the pathogenesis of IS, clarify the regulatory mechanisms of TCM on mitochondrial quality control, and summarize the scientific rationale and limitations of TCM in treating IS, aiming to provide insights and methodologies for the further clinical application of TCM in IS management.

Keywords: Ischemic stroke; Traditional Chinese medicine; Mitochondrial quality control; Research progress

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Ischemic stroke (IS) is the second leading cause of death and disability worldwide, resulting from interruption of cerebral blood flow due to thrombosis or embolism. Depending on the affected brain region, patients may present with various symptoms, with acute unilateral paresis and language dysfunction being the most common manifestations [1-2]. According to the American Heart Association's 2023 stroke statistics update, the absolute incidence of stroke increased

by 70% from 1990 to 2019, while the age-standardized incidence decreased by 17%; IS accounts for approximately 87% of all stroke cases and is characterized by high morbidity and decreasing age of onset [3]. As a severe global disease with rising incidence, IS urgently requires effective prevention and treatment strategies. TCM has a long history and rich clinical experience in treating IS. With the modernization of TCM, extensive research has been conducted both domestically and internationally on herbal monomers, active compounds, and TCM formulas, demonstrating unique advantages in improving clinical symptoms, reducing adverse reactions, and preventing recurrence.

Mitochondria, as the "powerhouses of the cell," play a critical role in maintaining cellular homeostasis following IS and are involved in neuronal autophagy and apoptosis. During cerebral ischemia, reduced blood supply and disrupted ATP synthesis destroy the cell's internal balance system. Cells can maintain homeostasis through mitochondrial quality control, which includes the mitochondrial protein response, fission and fusion, mitophagy, biogenesis, and intercellular transfer. These adaptive responses help preserve mitochondrial function and restore neurovascular unit homeostasis after IS [4-5].

From the perspective of traditional Chinese medicine, the material attribute of "Qi" is equivalent to mitochondria in modern medicine, and mitochondrial function corresponds to the role of "Qi" in TCM theory. Traditional Chinese medical theory posits that the root of all things lies in Yin and Yang. For the body, Yin represents the tangible material foundation, while Yang is the intangible source of motive force. As stated in *Suwen · Jingmai Bielun*: "When water and grains enter the stomach, their essence overflows and ascends to the spleen…" The spleen transforms and transports the essence of water and grains to generate body fluids and the Ying and Wei Qi needed by the human body. Body fluids fill the material foundation of the five viscera, while Ying and Wei Qi, through the lung's dispersing and descending functions, circulate throughout the body as the source of life activities. The continuous consumption and loss of Ying and Wei Qi during their circulation align closely with the concept of mitochondrial quality control. Based on this theoretical framework, this study systematically reviews recent literature on the regulation of mitochondrial quality control by TCM monomers, active compounds, and formulas in IS treatment, providing modern medical references for identifying therapeutic targets.

1. Mitochondrial Oxidative Stress

Oxidative stress refers to the excessive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) due to external or internal stimuli, leading to an imbalance between the oxidative and antioxidant systems that damages cellular macromolecules including sugars, lipids, proteins, and nucleic acids, thereby impairing normal cellular function and causing cell death. After IS, focal cerebral ischemia inhibits mitochondrial ATP production, affecting Na^+/K^+-ATPase and Ca^{2+}/H^+-ATPase functions. Increased intracellular Na^+, Ca^{2+}, and ADP content disrupts ion homeostasis and causes membrane de-

polarization, including changes in mitochondrial membrane potential (MMP) ($\Delta\Psi$m—a charge or electrical gradient) and transient excessive ROS release, resulting in mitochondrial oxidative stress and affecting mitochondrial quality control [6].

Yu et al. [7] found that oxymatrine could improve mitochondrial damage in IS rats by significantly enhancing Na^+/K^+-ATPase and Ca^{2+}/H^+-ATPase functions, reducing intracellular Ca^{2+} concentration, and inhibiting oxidative stress. Another study demonstrated that *Gastrodia elata* alcohol extract could improve mitochondrial respiratory function after cerebral ischemia-reperfusion (CI/R) injury, reduce MMP loss, decrease cytochrome C translocation to the cytoplasm, increase ATP levels, reduce oxidative stress and mitochondrial dysfunction, and inhibit apoptosis to protect neurons [8].

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a key antioxidant transcription factor activated by excessive ROS during oxidative stress. Nrf2 participates in multiple signaling pathways including Kelch-like ECH-associated protein 1, phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT), mitogen-activated protein kinase, nuclear factor- B (NF- B), and heme oxygenase-1 (HO-1) to inhibit oxidative stress after IS, maintain mitochondrial homeostasis, and alleviate CI/R injury [9]. Studies have shown that oxidative stress caused by mitochondrial dysfunction and energy metabolism failure after CI/R is a key factor contributing to poor IS outcomes. Piceatannol intervention can activate glycogen synthase kinase-3β to target and regulate Nrf2, causing Nrf2 phosphorylation that affects its nuclear export, ubiquitination, and degradation, thereby influencing antioxidant effects [10-11]. Another study confirmed that endothelial dysfunction caused by oxidative stress and neuroinflammation is a primary cause of brain cell damage and apoptosis in IS. Evodiamine can activate Nrf2 to induce oxidative and detoxifying enzyme expression that protects brain tissue, with HO-1 and NAD(P)H quinone dehydrogenase 1 (NQO1) being major antioxidant enzymes downstream of Nrf2. Evodiamine effectively intervenes in oxidative stress and inflammatory responses in IS through the Nrf2/HO-1/NQO1 pathway [12].

Shen et al. [13] found that resveratrol could regulate antioxidant enzyme transcription and expression through the Nrf2/antioxidant response element pathway, enhancing cellular antioxidant stress capacity and alleviating CI/R injury. Additionally, HO-1 is an inducible enzyme with antioxidant, anti-inflammatory, and neuroprotective effects. Studies show that prolonged, high-level expression at ischemic lesions leads to excessive ROS and RNS production, stabilization of hypoxia-inducible factor-1α (HIF-1α), and NF- B activation, causing mitochondrial dysfunction. In contrast, moderate HO-1 levels protect neurovascular function. The interaction between HO-1 and Nrf2 participates in oxidative stress responses, promoting glutathione peroxidase 4 (GPx4) and superoxide dismutase 2 (SOD2) production to exert neuroprotective effects [14].

Experimental studies have demonstrated that various TCM active components and formulas—including crocin [15], astragaloside, chlorogenic acid, scutellarin

[16], Yiqi Huoxue Formula [17], Gualou Guizhi Granules [18], Qingre Huayu Formula [19], Tianma Gouteng Decoction [20], and Buyang Huanwu Decoction [21]—can significantly alleviate oxidative stress damage in IS cells, stabilize MMP, and protect neurological function by regulating Nrf2/HO-1 signaling pathway expression.

Peroxisome proliferator-activated receptor γ coactivator-α (PGC-1α) is a master regulator of oxidative metabolism that affects mitochondrial energy production and ROS defense systems, and can upregulate Nrf2 to combat oxidative stress. Studies show that molecular mediators including PGC-1α, HIF-1α, c-MYC, silent information regulator 1 (SIRT-1), and AMP-activated protein kinase (AMPK) play important roles in regulating the glycolysis-mitochondria axis under ischemic and hypoxic conditions [22]. Zhang et al. [23] found that chikusetsusaponin could reduce ROS levels and mitochondrial damage and inhibit mitochondrial oxidative stress by activating AMPK and SIRT-1 to regulate PGC-1α. Pei et al. [24] discovered that resveratrol could regulate PGC-1α to reduce neuronal apoptosis and ROS production, and restore antioxidant levels and Na^+/K^+-ATPase to normal levels in the cortex and hippocampus. Applications of *Paeoniae Radix Rubra* [25], Huoxue Yangrong Formula [26], and Naoxin'an Capsule [27] have been shown to intervene in IS treatment by regulating PGC-1α.

2. Mitochondrial Dynamics

Mitochondrial dynamics, including fusion and fission, are central to mitochondrial quality control and essential for maintaining mitochondrial homeostasis and cell survival. After IS, increased mitochondrial fission and decreased fusion can be observed. These impaired mitochondrial dynamics lead to brain apoptosis and neuronal cell death [28].

2.1 Mitochondrial Fusion

Mitochondrial fusion proteins protect tissues or neurons from ischemic-hypoxic injury through pro-fusion functions, including optic atrophy 1 (Opa1), mitofusin 1 (Mfn1), and mitofusin 2 (Mfn2). Under CI/R conditions, upregulating Opa1 promotes mitochondrial fusion, reverses mitochondrial interconnection morphology, inhibits neuronal apoptosis, and reduces cerebral edema and infarct volume [29]. Mfn1 and Mfn2 are homologous proteins. Studies show that brain injury in IS rats may be caused by upregulation of mitochondrial E3 ubiquitin ligase 1, leading to mitochondrial dynamics instability and dysfunction through Opa1 SUMOylation and Mfn2 ubiquitination [5]. *Dipsacus asper* saponin B has been found to inhibit mitochondrial E3 ubiquitin ligase 1, reverse Mul1, and improve mitochondrial dynamics instability after IS by regulating dynamin-related protein 1 (Drp1) and Mfn2 protein expression [30].

Experimental studies have shown that Longhu Xingnao Granules can improve infarct area, alleviate cerebral ischemic injury, and correct mitochondrial dynam-

ics imbalance in IS rats by upregulating Opa1 and Mfn2 while downregulating mitochondrial fission protein 1 and Drp1 expression, thereby exerting neuroprotective effects [31]. Gao et al. [32] found that resveratrol could improve mitochondrial function and maintain neuronal viability through the AMPK-Mfn1 pathway. *Cornus officinalis* iridoid glycosides [33], crocin [34], and Sailuotong Capsule [35] can improve mitochondrial dynamics disorder by increasing Opa1 expression while inhibiting Drp1 expression.

2.2 Mitochondrial Fission

Mitochondrial fission divides mitochondria into two smaller organelles, with Drp1 being the key regulator of fission. Upregulation of Drp1 during mitochondrial oxidative stress disrupts the balance between mitochondrial division and fusion, causing mitochondrial dysfunction and apoptosis. Downregulating Drp1 can protect mitochondrial morphology, reduce ROS production and oxidative stress, and decrease infarct area [36]. After IS, Drp1 activity increases significantly; activated Drp1 translocates to mitochondria, causing mitochondrial fragmentation and increasing the number of damaged mitochondria. Zeng et al. [37] found that luteolin could reverse this process and intervene in mitochondrial fission. Studies have shown that Ginkgo ketone ester significantly protects mitochondrial function in human neuroblastoma (SH-SY5Y) cells after hypoxia/reoxygenation (H/R) injury by reducing Drp1 expression levels, providing theoretical support for treating ischemic cerebrovascular disease [38]. Additionally, Buyang Huanwu Decoction has been shown to alleviate hippocampal neuron H/R injury and mitigate further ischemic damage by downregulating Drp1 expression in IS rats [39].

3. Mitophagy

Autophagy increases in mouse striatum and cortex after CI/R. While ROS are overproduced, mitophagy can clear damaged mitochondria and inhibit apoptosis, protecting neurons in ischemic brain injury [40]. Regulation of mitophagy primarily involves the PTEN-induced putative kinase 1/Parkin (PINK1/Parkin), B-cell lymphoma-2/adenovirus E1B-interacting protein 3/NIP3-like protein X (BNIP3/NIX), and FUN14 domain-containing protein-1 (FUNDC1) signaling pathways [41].

Studies show that baicalin can alleviate CI/R by regulating key protein expression in mitophagy pathways, including Parkin, BNIP3, and FUNDC1 [42]. *Cornus officinalis* iridoid glycosides [33] and Qingre Huayu Formula [43] can intervene in mitophagy and improve neurological function by reducing Bcl-2 homologous domain protein antibody (Beclin-1) and NIX expression in I/R rat brain tissue. Longhu Xingnao Granules [44] can treat IS by downregulating BNIP3 and Beclin-1 protein expression to promote mitophagy activation. Some scholars propose that moderate elevation of PINK1 and Parkin is protective against cerebral ischemia. Huazhuo Jiedu Huoxue Tongluo Formula has been verified to upregulate Parkin and PINK1 protein levels [45]. Berberine,

the active component of *Coptis chinensis* in the formula [46], and curcumin, the active component of *Curcuma longa* [47], are widely involved in mitophagy signaling pathways, helping restore normal function in damaged brain tissue cells. Xiaoxuming Decoction [48], quercetin [49], and Huoxue Rongluo Formula [50] primarily intervene in mitophagy and neuronal apoptosis by activating the Parkin/PINK1 pathway. Additionally, the PI3K/Akt signaling pathway has been identified as important for regulating mitophagy in brain tissue. Orientin [51] and geniposide [52] can inhibit excessive mitophagy activation by activating this pathway, thereby alleviating brain tissue damage and exerting neuroprotective effects.

4. Mitochondrial Biogenesis

Mitochondrial biogenesis involves degrading damaged mitochondria through autophagy to reduce energy consumption and provide raw materials, followed by synthesis from highly proliferative mitochondria to maintain cellular energy metabolism and normal mitochondrial function. This represents the final step in mitochondrial quality control. Mitochondrial biogenesis is one of the major endogenous protective mechanisms after IS, coordinating nuclear and mitochondrial gene expression during the cell cycle for mitochondrial proliferation and synthesis.

PGC-1α is a key regulator of mitochondrial biogenesis under hypoxic-ischemic conditions. It can be promoted by stress-induced molecules including ROS, Ca^{2+}, ADP/ATP, and NO, protecting neurons from oxidative stress by upregulating antioxidant protein expression and enhancing mitochondrial biogenesis [53]. PGC-1α induces Nrf1 and Nrf2 expression and transcription, increases mitochondrial transcription factor A (TFAM) expression and cell phosphorylation, after which TFAM promotes mitochondrial DNA and protein synthesis and generates new mitochondria by upregulating mitochondrial-encoded polypeptide expression and mtRNA replication [54-55]. Studies show that PGC-1α and Nrf1 expression levels decrease in astrocytes and neurons after CI/R, while chikusetsusaponin can enhance PGC-1α expression and deacetylation by activating AMPK and SIRT-1, increase antioxidant levels, reduce ROS levels and mitochondrial damage, and improve neurological function [56]. Some scholars found that Huoxue Rongluo Formula can promote ATP generation in ischemic brain tissue and improve neurological function by significantly upregulating PGC-1α, providing experimental evidence for TCM in IS prevention and treatment [28]. Others discovered that resveratrol can induce mitochondrial biogenesis through the PGC-1α/Nrf1/TFAM pathway, upregulating mitochondrial DNA content [57]. Additionally, curcumin [58] has been confirmed to protect cerebral mitochondrial biogenesis and exert antioxidant effects against IS through the PI3/Akt/GSK signaling pathway.

The intervention indicators of various TCM monomers, active compounds, and formulas on IS through mitochondrial quality control are detailed in Table 1 and Table 2 .

5. Summary and Outlook

In current TCM treatment of IS through mitochondrial quality control regulation, herbs primarily attributed to the spleen, liver, and kidney meridians are commonly used. Traditional medical theory holds that strengthening spleen transportation, tonifying kidney essence, and soothing liver qi can increase the "Qi" circulating throughout the body and improve its channels, allowing unobstructed flow and recovery from various symptoms. The treatment principles of supplementing qi, activating blood, resolving stasis, and dredging collaterals correspond to the concept of "Qi" in TCM theory and mitochondria in modern medicine, further confirming the scientific basis of TCM intervention for IS.

This review reveals that TCM regulates mitochondrial quality control in IS mainly through experimental research on mitochondrial oxidative stress, fusion and fission, mitophagy, and mitochondrial biogenesis. Regarding mitochondrial oxidative stress, TCM primarily reduces ROS and RNS levels, improves Na^+/Ca^{2+}-ATPase and Ca^{2+}/H^+-ATPase activities, decreases cellular Ca^{2+} concentration, reduces MMP loss, and regulates expression of related factors and enzymes including Nrf2, HIF-1α, and HO-1 to alleviate mitochondrial oxidative stress. In mitochondrial dynamics, TCM improves mitochondrial function by upregulating fusion proteins (Opa1, Mfn1, Mfn2) and downregulating the key fission regulator Drp1. For mitophagy, TCM reduces brain damage by regulating PINK1/Parkin, Bnip3/NIX, FUNDC1, and PI3K/Akt signaling pathways to inhibit excessive mitophagy. In mitochondrial biogenesis, TCM promotes mitochondrial synthesis and improves neurological function by regulating the key regulator PGC-1α and signaling pathways such as PGC-1α/Nrf1/TFAM and PI3/Akt/GSK. Experimental studies have verified the therapeutic effects of numerous TCM monomers, active components, and formulas on IS through mitochondrial quality control, though further exploration of other agents is needed.

This systematic review clarifies that TCM can influence mitochondrial quality control by regulating oxidative stress responses, mitochondrial fusion/fission, mitophagy, and mitochondrial biogenesis-related factor expression, thereby exerting therapeutic effects in IS by reducing brain damage and improving neurological function. However, current research has several limitations: (1) Most published studies are preliminary explorations focusing on animal experiments, requiring multi-level, multi-angle, and multi-dimensional investigation; (2) Clinical studies are scarce and lack standardized, systematic clinical trials; (3) Reports on TCM regulating mitochondrial quality control predominantly feature experimental studies on herbal monomers and compounds, with fewer on TCM formulas, limiting clinical application; (4) Experimental studies mostly focus on single signaling pathways/regulators with limited detection indicators and lack pharmacokinetic support, necessitating future multi-pathway, multi-target research; (5) There is a lack of unified TCM diagnostic and treatment standards, and further discussion is needed on integrating TCM etiology, pathogenesis, and treatment principles with modern medical understanding to elucidate the connection between traditional theory and modern medicine and enhance clinical

efficacy.

In summary, this article systematically reviews the mechanisms and treatment protocols of TCM regulating mitochondrial quality control in IS, identifies existing deficiencies, clarifies the impact of mitochondrial quality control on IS pathogenesis, and provides new insights for TCM treatment of IS through mitochondrial quality control regulation. This further confirms that TCM exerts therapeutic effects through multi-target, multi-pathway, and multi-channel actions, offering novel directions for future experimental research and clinical application.

Author Contributions: SU Ziwei was responsible for conceptualization, literature collection and organization, table preparation, and manuscript writing; MA Yan and ZHOU Yanzhang contributed to manuscript revision; ZHOU Zhiliang was responsible for conceptualization, manuscript revision, quality control, and overall supervision.

Conflict of Interest: The authors declare no conflict of interest.

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(Received: August 28, 2023; Revised: November 12, 2023)

Note: Figure translations are in progress. See original paper for figures.