Exploring the Traditional Chinese Medicine Etiology and Pathogenesis of Alzheimer' s Disease Based on the Relationship Between "Deficiency-Stasis-Toxin" and Mitochondrial Autophagy: Postprint

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Abstract

The pathogenesis of Alzheimer' s disease (AD) is complex, and the role of mitochondrial damage in AD has become a current research focus. Under pathological conditions, dysfunction of mitochondrial autophagy leads to accumulation of damaged mitochondria, insufficient ATP production, release of free radicals and harmful substances, induces neuronal apoptosis, and exacerbates AD pathology. The "deficiency-stasis-toxin" pathomechanism permeates the entire course of AD onset and progression. AD originates from deficiency of the five viscera, subsequently giving rise to phlegm-turbidity and blood stasis, which over time brews toxic pathogenic factors that cloud the clear orifices, resulting in impairment of mental faculties. From the perspective of Traditional Chinese Medicine, the pathological mechanism of mitochondrial autophagy is closely related to the etiology and pathomechanism of "deficiency-stasis-toxin." Based on this relationship and integrating the "deficiency-stasis-toxin" pathomechanism theory, exploring Chinese medicinals that improve mitochondrial autophagy provides new insights for the treatment of AD with Traditional Chinese Medicine.

Full Text

Preamble

Exploring the Traditional Chinese Medicine Etiology and Pathogenesis of Alzheimer' s Disease Based on the Relationship between "Deficiency-Stasis-Toxin" and Mitophagy

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Abstract: The pathogenesis of Alzheimer' s disease (AD) is complex, and the role of mitochondrial damage in AD has become a current research hotspot. Under pathological conditions, dysfunctional mitophagy leads to the accumulation of damaged mitochondria, resulting in insufficient ATP production and continuous release of free radicals and harmful substances, which induces neuronal apoptosis and exacerbates AD pathology. The pathogenesis of "deficiency-stasis-toxin" runs throughout the entire course of AD. AD begins with deficiency and damage of the five organs, subsequently leading to phlegm turbidity and blood stasis. Over time, these transform into toxic pathogens that cloud the orifices, causing loss of mental faculties. From the perspective of Traditional Chinese Medicine (TCM), the pathological mechanism of mitophagy is closely related to the etiology and pathogenesis of "deficiency-stasis-toxin."Based on this relationship and combined with the pathogenesis theory of "deficiency-stasis-toxin," exploring Chinese medicines that improve mitophagy provides new ideas for TCM treatment of AD.

Keywords: Alzheimer' s disease; mitophagy; deficiency-stasis-toxin; Traditional Chinese medicine etiology and pathogenesis; mitochondria; review

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Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disease characterized by progressive cognitive dysfunction, with insidious onset and irreversible progression. Epidemiological surveys indicate that China currently has approximately 9.83 million AD patients, with prevalence roughly doubling every five years after age 60 [1], posing serious threats to public health and sustainable social development. The pathogenesis of AD is complex, with mainstream hypotheses including the amyloid-β (Aβ) cascade hypothesis, abnormal tau protein phosphorylation hypothesis, cholinergic hypothesis, neuroinflammation hypothesis, and oxidative stress hypothesis, yet the specific pathogenic mechanisms remain unclear and no cure exists. Mounting evidence demonstrates that mitochondrial damage is a key factor driving AD progression [2], with numerous damaged mitochondria observed in impaired neurons of both AD patients and animal models [2,3]. Some researchers have found that mitochondrial dysfunction occurs independently of Aβ deposition and intracellular tau protein hyperphosphorylation that leads to neurofibrillary tangle formation, and may even precede these pathological changes [4]. Mitophagy selectively degrades damaged mitochondria and serves as the primary mechanism for their clearance. Multiple studies have shown that regulating mitophagy can timely eliminate damaged mitochondria, thereby improving energy metabolism, calcium homeostasis, and oxidative stress damage, protecting neurons and ameliorating AD pathology [5,6].

In TCM, AD falls under the category of "dementia."Practitioners generally agree that dementia is located in the brain and represents a condition of root deficiency with branch excess, mixing deficiency and excess patterns. The root lies in organ deficiency, while the branch involves the intermingling of phlegm turbidity, blood stasis, and toxic pathogens. Due to natural aging, kidney essence gradually becomes deficient, organ function declines, leading to emptiness of the sea of marrow and loss of mental faculties, which subsequently generates pathological products including phlegm, stasis, and toxin. These products interact and affect organ function, creating a vicious cyclic network where root deficiency and pathogenic excess intertwine, forming the "deficiency-stasis-toxin" pattern. From a TCM theoretical perspective, the pathological changes and clinical outcomes triggered by mitophagy dysfunction share similarities with the evolution of the "deficiency-stasis-toxin" pathogenesis. This article focuses on the intrinsic connection between mitophagy dysregulation and "deficiency-stasis-toxin," analyzing the process of mitophagy in depth to elucidate the scientific connotation of AD' s "deficiency-stasis-toxin" pathogenesis from this microscopic perspective, thereby providing novel insights for research into AD pathogenic mechanisms.

1.2 Progressive Disease Development: Phlegm and Stasis as Critical Factors

Phlegm turbidity primarily forms when qi movement becomes impaired, obstructing the distribution of nutrients from food and grains. The spleen and stomach serve as the pivot for ascending, descending, entering, and exiting

within the body. In elderly individuals with organ deficiency, when spleen-stomach transformation and transportation functions become abnormal, spleen deficiency cannot effectively transform and transport water-dampness, leading to impaired fluid distribution, internal retention of water-dampness, and phlegm formation. Phlegm turbidity circulates with qi throughout the body, reaching everywhere and causing widespread disease. When phlegm turbidity clouds the orifices, it readily leads to loss of mental faculties and manifestations such as cognitive impairment. The *Danxi' s Methods of Treatment* from the Jin-Yuan period states: "For forgetfulness, most cases involve shortness of spirit, but some involve phlegm." The *Golden Cabinet' s Hidden Depths* also records: "Phlegm in the diaphragm causes mania, madness, and forgetfulness," both indicating that phlegm turbidity is an important factor causing forgetfulness. Wei Yilin created "Modified Poria Decoction" to treat symptoms of "phlegm confusing the pericardium, forgetfulness, loss of affairs, and speech like idiocy," further demonstrating that phlegm turbidity constitutes a significant pathological factor in AD.

With human aging, if spleen-kidney deficiency and phlegm turbidity obstruction cannot be promptly corrected, qi and blood continuously decline, blood flow slows or even stagnates, causing blood vessel stasis. Wang Qingren stated: "Whenever there is blood stasis, it also causes forgetfulness," indicating the relationship between blood stasis and forgetfulness. When blood stasis obstructs the brain orifices, qi and blood flow within the brain becomes unsmooth, easily leading to forgetfulness. Long-term development can cause dementia and even trigger emotional abnormalities such as mania. The *Treatise on the Origins and Symptoms of Diseases* mentions: "Those with blood stasis tend to be forgetful and do not wish to hear sounds," believing that long-standing blood stasis in the body causes forgetfulness. The *Classified Treatment* states: "If blood stasis is internal, there is forgetfulness like madness." The *Benevolent Direct Instructions* says: "When blood becomes pathogenic···if stored above, the person forgets," demonstrating that blood stasis is another important pathological factor in AD. Qi stagnation and blood stasis cause vessel congestion, which on one hand reduces and accumulates metabolic product clearance, and on the other hand prevents essential substances from reaching the brain orifices, leading to loss of mental faculties and AD-related manifestations of forgetfulness, dullness, and mania. Additionally, phlegm and stasis can mutually influence each other. The *Treatise on Blood Disorders* records: "When blood accumulation persists long, it can also transform into phlegm-water," and "blood stasis transforming into water also causes edema," proposing that blood stasis and phlegm-water combine to cause harm. In old age, when all organs decline, qi movement slows, water-fluid metabolism becomes impaired generating phlegm, and essence-blood congeals forming stasis. Phlegm and stasis intermix, clouding the orifices and causing loss of mental faculties, resulting in memory and cognitive impairments.

1.3 Mutual Influence of Deficiency, Phlegm, and Stasis Transforming into Toxin: Culminating in a Chronic Disease

"Endogenous toxic pathogens" refer to pathological products such as phlegm turbidity and blood stasis that arise from the body' s own organ-qi-blood decline or dysfunction and can cause physical damage [7]. The "toxin damaging brain collaterals" theory states that under the precondition of kidney essence deficiency and loss of brain marrow nourishment, phlegm and stasis subsequently form within the body, coagulate and transform into toxin, causing toxic pathogens to damage brain collaterals and destroy brain marrow, leading to the irreversible disease characteristics of AD [8]. Therefore, "toxin damaging brain collaterals" represents an important pathogenesis of AD. Viewing the entire disease course, deficiency, phlegm-stasis, and turbid toxin are not isolated in AD onset and progression. Deficiency creates conditions for phlegm-stasis generation, phlegm-stasis further transforms into turbid toxin, and turbid toxin in turn aggravates deficiency and phlegm-stasis. They interact as both cause and effect, perpetuating the disease with continuous complications, ultimately leading to AD.

2 Relationship Between Mitophagy and AD Development

Mitochondria serve as the central hub of cellular life activities, functioning not only as the "power factory" providing cellular energy and deeply participating in intracellular energy supply, but also bearing the responsibility of a "death engine" regulating cell survival. They play core roles in multiple critical processes including calcium homeostasis, oxidative stress, apoptosis, and programmed necrosis. Once mitochondrial structure or function is damaged, it triggers severe consequences such as intracellular energy metabolism disorders, oxidative stress imbalance, and Ca^{2+} homeostasis disruption, further exacerbating neuronal damage [3]. Therefore, maintaining normal mitochondrial structure and function is crucial for AD.

Mitophagy selectively degrades damaged mitochondria and serves as the key pathway for clearing impaired organelles, with its functional status directly affecting cellular health. Mitophagy defects can lead to accumulation of damaged mitochondria, generating excessive reactive oxygen species (ROS) and damaging molecules that further injure mitochondria and cells, whereas excessive mitophagy causes massive mitochondrial loss, affecting energy supply to nerve cells [9]. Consequently, mitophagy is intimately related to AD. Throughout AD progression, mitophagy levels exhibit dynamic changes. In early-stage AD, although brain tissue has not yet shown obvious pathological changes and typical clinical symptoms are absent, studies have already discovered significantly elevated mitophagy levels in patient neurons. This phenomenon is considered a self-protective mechanism responding to mitochondrial dysfunction, attempting to maintain normal mitochondrial function and delay disease progression through enhanced autophagy [9]. However, as AD advances, various pathological changes continuously intensify and in turn inhibit mitophagy, causing autophagy levels to gradually decline. When the body' s autophagic capac-

ity cannot effectively clear the continuously increasing damaged mitochondria, neurons accumulate large numbers of functionally abnormal mitochondria. This abnormal mitochondrial accumulation becomes a critical turning point in AD deterioration, greatly accelerating disease progression and highlighting the driving role of mitophagy dysfunction in AD advancement [9].

2.1 Mitophagy Dysfunction Leading to Impaired Energy Metabolism

As the core hub of cellular energy metabolism, mitochondria play an irreplaceable role. They efficiently uptake nutrients such as glucose, fatty acids, and amino acids, synthesizing them into essential energy through the tricarboxylic acid cycle and oxidative phosphorylation—two closely linked biochemical processes—and store it as ATP to provide ample power for subsequent physiological activities. The brain, as a high-energy-consuming organ, is highly dependent on stable energy supply and is extremely vulnerable to energy metabolism abnormalities. In early-stage AD, characteristics include defects in cerebral glucose utilization and energy metabolism [10]. Using fluorodeoxyglucose positron emission tomography imaging, studies have observed significantly reduced glucose utilization in the hippocampus and cortex of AD patients, accompanied by structural changes in mitochondria in these regions, including reduced numbers and morphological swelling [11]. In 3xTg mouse experiments, expression of mitochondrial respiratory chain complex IV and activity of complexes II and III were found to decrease with AD progression [12], demonstrating the close relationship between AD and mitochondrial ATP energy metabolism. When mitophagy becomes abnormal, damaged mitochondria accumulate extensively in the brain or normal mitochondria are excessively cleared, resulting in reduced ATP generation or excessive consumption in neurons, creating an energy supply shortage in the brain that leads to neuronal dysfunction, memory loss, and cognitive decline [13]. Therefore, regulating mitophagy levels to maintain cerebral energy metabolism represents an important approach for TCM to alleviate AD damage.

2.2 Mitophagy Dysfunction Exacerbating Oxidative Stress Damage

In AD pathological progression, oxidative stress is an early event characterized by massive release of ROS and reactive nitrogen species, along with damage to antioxidant enzyme functions. Mitochondria serve as the primary source of ROS and play a key regulatory role in maintaining dynamic balance of oxidative stress levels in the body. Once mitophagy function is impaired, large numbers of functionally defective mitochondria accumulate in cells. These abnormal mitochondria continuously produce excessive ROS, far exceeding the clearance capacity of the antioxidant system. Excessive ROS causes multifaceted cellular damage: on one hand, it downregulates mitochondrial respiratory chain complex activity, disrupts mitochondrial oxidative phosphorylation, severely affects ATP synthesis, and leads to insufficient cellular energy supply [14]; on the other hand, ROS alters mitochondrial membrane permeability, causing re-

lease of cytochrome c from mitochondria into the cytoplasm, triggering Caspase cascade reactions that ultimately induce neuronal apoptosis and accelerate AD progression [15]. Notably, massive ROS production does not merely unidirectionally damage mitochondrial and cellular functions—it also further aggravates mitochondrial damage in return. Increased damaged mitochondria subsequently worsens mitophagy dysfunction, forming a continuously deteriorating positive feedback cycle that perpetually drives AD pathological processes. Therefore, regulating mitophagy levels to reduce oxidative stress damage represents an important strategy for TCM intervention in AD progression.

2.3 Mitophagy Dysfunction Aggravating Ca^{2+} Homeostasis Imbalance

In neuronal signal systems, the Ca^{2+} signaling system constitutes an important component, participating in regulation of action potential generation and conduction, synaptic vesicle release, and synaptic plasticity. Mitochondria are key organelles for Ca^{2+} storage, and their dysfunction can inhibit Na^{+}-Ca^{2+} exchange, causing intracellular Ca^{2+} overload [16]. When mitophagy is impaired, damaged mitochondria cause massive Ca^{2+} retention within neuronal cells, altering intracellular mitochondrial permeability, reducing mitochondrial membrane potential, and exacerbating mitochondrial damage. Over time, chronic Ca^{2+} overload destroys mitochondrial membrane potential, triggers expression of apoptosis-related proteins in the brain, promotes excessive cell death, damages brain cells, and ultimately causes memory impairment, initiating AD [17,18]. In AD, mitophagy dysfunction and Ca^{2+} homeostasis imbalance interact as both cause and effect, jointly driving disease occurrence and development. In-depth investigation of their relationship not only provides deeper understanding of AD pathological mechanisms but also offers potential therapeutic targets for future drug development.

3.1 Pathological Products of Mitophagy Dysfunction as Manifestations of "Deficiency-Stasis-Toxin"

Under normal physiological conditions, mitophagy can precisely identify and clear damaged mitochondria through multiple pathways such as PINK1/Parkin, effectively preventing release of cytotoxic substances and thereby avoiding neuronal apoptosis. However, during AD pathogenesis, due to organ deficiency, impaired qi movement, and abnormal metabolism, mitophagy function becomes dysregulated. At this point, damaged mitochondria cannot be promptly cleared and massively release ROS and pro-apoptotic substances. From a TCM perspective, these pathological products precisely match the characteristics of "phlegm" and "toxin,"and can be categorized as such. ROS not only inhibits mitochondrial respiratory chain activity, leading to reduced ATP generation ("deficiency"), but also disrupts intracellular metabolism and transport, promoting accumulation of metabolic products (such as Aβ and phosphorylated tau protein) and forming a "stasis" pathological state. These "phlegm," "toxin," "deficiency," and "stasis" elements intertwine and form a vicious cycle. On one hand, they promote

oxidative stress, induce neuronal apoptosis, and directly damage the nervous system; on the other hand, as phlegm turbidity and blood stasis pathological products cannot be cleared long-term, they interact and further transform into toxin, causing severe damage to brain collaterals—precisely the typical pathological features of AD. Therefore, pathological products generated by mitophagy dysfunction highly correspond with "deficiency-stasis-toxin," representing its microscopic manifestation. Regulating mitophagy to clear "stasis-toxin" and repair "deficiency" may provide new therapeutic strategies for AD.

3.2 Pathological Changes of Mitophagy Dysfunction Mirroring the Dynamic Evolution of "Deficiency-Stasis-Toxin"

Studies have shown that in early-stage AD patients' brains, decreased glucose metabolism rates and mitochondrial morphological changes already appear, powerfully demonstrating that AD onset is accompanied by energy metabolism abnormalities [11]. When mitophagy dysfunction occurs, it triggers severe consequences. On one hand, excessive mitochondrial clearance directly reduces ATP generation, causing insufficient energy supply to neurons and exacerbating AD pathological damage. From a TCM perspective, this insufficient ATP synthesis represents one of the internal mechanisms generating deficiency patterns. On the other hand, when mitophagy is abnormal, damaged mitochondria cannot meet cellular energy demands, leading to increased free radical production [19]. Mitochondrial free radicals are primarily superoxide anions that disrupt intracellular oxidative stress balance, induce neuronal apoptosis, and accelerate AD onset. Notably, the process from gradual mitochondrial free radical accumulation to ultimate cellular damage highly resembles the TCM process of phlegm-stasis transforming into toxin and damaging brain collaterals. In TCM theory, long-term phlegm-stasis accumulation interacts and transforms into toxin that damages brain collaterals, triggering various brain diseases, AD being one of them. From a microscopic perspective, pathological changes produced by mitophagy dysfunction closely match the dynamic evolution trajectory of the TCM "deficiency-stasis-toxin" pathogenesis. Therefore, linking mitophagy dysfunction with the "deficiency-stasis-toxin" pathogenesis will facilitate deeper TCM understanding of AD and open new avenues for AD research and treatment.

4 "Tonifying Deficiency, Resolving Phlegm, Activating Blood, and Detoxifying": A Novel TCM Therapeutic Strategy for AD from the Mitophagy Perspective

4.1 Theoretical Compatibility Between Mitophagy and TCM Tonifying Deficiency, Resolving Phlegm, Activating Blood, and Detoxifying

The pathological mechanism of mitophagy is intimately associated with the "deficiency-stasis-toxin" etiology and pathogenesis in TCM. Based on "deficiency-stasis-toxin" theory, integrating traditional TCM understanding of AD with modern medical mitophagy is crucial for elucidating AD pathogenesis, clinical

prevention and treatment, and identifying effective intervention drugs. This integration also opens new pathways for further explaining the TCM theoretical connotation of "deficiency, phlegm, stasis, toxin" in AD, promoting more breakthroughs in TCM AD research and advancing integrated Chinese-Western medicine treatment of AD.

Mitophagy is the key mechanism for mitochondrial renewal in AD neurons. Its regulatory mechanism not only effectively prevents damaged mitochondria from releasing harmful substances, thereby reducing cellular toxic stress, but also plays an important role in maintaining intracellular mitochondrial homeostasis. Cleared mitochondrial components can be recycled by the body to help generate new organelles and provide energy. The treatment principle of tonifying deficiency, resolving phlegm, activating blood, and detoxifying—guided by the "deficiency-stasis-toxin" pathogenesis—aims to improve energy deficiency, clear harmful substances, and restore unobstructed blood flow, ultimately achieving the state of "yin-yang equilibrium." This demonstrates certain compatibility between mitophagy regulatory mechanisms and the theoretical connotation of tonifying deficiency, resolving phlegm, activating blood, and detoxifying. Based on this compatibility, utilizing this therapeutic principle to regulate mitophagy, thereby reducing ROS release, improving neuronal energy metabolism, inhibiting neuronal apoptosis, and ultimately ameliorating AD pathology, possesses a solid theoretical foundation. This compatibility point may become a crucial breakthrough for integrated Chinese-Western medicine to overcome AD challenges, opening new therapeutic pathways.

4.2 Chinese Herbs Based on Tonifying Deficiency, Resolving Phlegm, Activating Blood, and Detoxifying Play Important Roles in Improving AD Mitophagy

In recent years, modern research has continuously focused on TCM interventions for AD, revealing that numerous Chinese herbs with tonifying deficiency, phlegm-resolving, blood-activating, and detoxifying effects significantly regulate mitophagy-related indicators and improve AD progression. Ginseng, a traditional qi-tonifying medicine, contains the active component ginsenoside Rg1 that can upregulate the PINK1/Parkin pathway and significantly increase expression of downstream adaptor targets NDP52 and OPTN to enhance mitophagy levels, playing a key role in neuroprotection [20]. Ligustilide from *Chuanxiong* improves neuronal injury by regulating the PINK1/Parkin mitophagy pathway [21]. Research shows that β-asarone extracted from the phlegm-resolving and orifice-opening herb *Acorus tatarinowii* can activate PINK1-Parkin-mediated mitophagy, thereby improving learning, memory, and cognitive dysfunction in APP/PS1 mice [22]. Experimental studies have found that *Ginseng-Notoginseng-Chuanxiong* extract stimulates mitophagy through the AMPK pathway, effectively preventing high glucose and palmitate-induced mitochondrial ROS production [23]. The blood-tonifying, blood-activating, spleen-strengthening, and dampness-resolving formula *Danggui Shaoyao San*

can clear damaged mitochondria through PINK1-Parkin-mediated mitophagy, improve mitochondrial function, and exert neuroprotective effects [24]. The turbidity-resolving, toxin-detoxifying, blood-activating, and collateral-dredging formula upregulates mitophagy-related proteins PINK1 and Parkin expression to exert cerebral protective effects [25].

As TCM research in the field of mitophagy gradually deepens, exploring and screening Chinese herbs and compounds that regulate mitophagy and revealing their mechanisms for improving AD have become frontier hotspots in TCM research, with broad future development prospects.

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