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Research Progress on Traditional Chinese Medicine in Alzheimer's Disease via Intervention in Apoptosis

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Abstract: ***Neurodegenerative diseases (AD, PD, HD, ALS) share the common pathological endpoint of "irreversible neuronal loss," with apoptosis serving as the "terminal common pathway" driving disease progression. Alzheimer's disease (AD) is a chronic, progressive neurodegenerative disorder characterized primarily by the gradual deterioration of cognitive and memory functions. Its pathological hallmarks include neurofibrillary tangles formed by aggregates of hyperphosphorylated microtubule-associated protein (Tau) and amyloid plaques resulting from β-amyloid protein aggregation. The exact pathogenesis of AD remains incompletely understood, and there are currently no effective disease-modifying treatments or curative approaches available in clinical practice. In recent years, the incidence of AD has shown an increasing trend, significantly impacting public health and quality of life. Therefore, identifying effective therapeutic agents and compounds for AD is of paramount importance. Neuronal loss in Alzheimer's disease is not merely a result of Aβ or Tau "toxic proteins" directly killing cells. Rather, it is the consequence of "programmed cellular suicide" induced by the persistent activation of apoptotic signaling networks by these agents. Modern medical research has revealed that intervening in apoptosis plays a crucial role in the pathophysiological development of AD. Furthermore, traditional Chinese medicine (TCM) has a long history of application in treating neurodegenerative diseases, offering advantages such as fewer adverse effects and the characteristic of multi-target, multi-link, and multi-pathway intervention. Consequently, based on reviewing and analyzing the latest domestic and international research, this article elaborates on the role of apoptosis in the onset and progression of AD and summarizes recent advances in TCM interventions targeting apoptotic pathways for AD treatment. The aim is to provide references and a foundation for developing clinical drugs to prevent and treat AD and to offer a broader perspective on the potential of TCM in managing this condition.***

Keywords: Alzheimer's disease, Neuronal loss apoptosis, Traditional Chinese Medicine, Multi-target intervention, Review.

1. Introduction

Alzheimer's disease (AD) is the most common type of senile dementia, characterized by an irreversible, progressive degeneration of the central nervous system. Its primary clinical manifestations are cognitive impairments in areas such as memory, comprehension, calculation, visuospatial function, and language. As the disease advances, it ultimately leads to death [1-2]. The exact pathological mechanisms of AD remain incompletely understood. Current research indicates that the aggregation of β-amyloid (Aβ), hyperphosphorylation of tau protein, neuronal damage or loss, and neuroinflammation play significant roles in the pathogenesis and progression of the disease [3-5]. Apoptosis, also known as programmed cell death, is an active, genetically controlled process of cell death. It is a crucial mechanism for maintaining homeostasis and eliminating damaged, aged, or unnecessary cells in multicellular organisms. Unlike necrosis, apoptosis does not trigger an inflammatory response. During apoptosis, cells undergo a series of characteristic changes, including membrane blebbing, chromatin condensation, DNA fragmentation, and segmentation into apoptotic bodies, which are subsequently cleared by neighboring cells or phagocytes. Apoptosis is regulated by multiple signaling pathways, primarily the extrinsic death receptor pathway and the intrinsic mitochondrial pathway. Dysregulated apoptosis is implicated in various diseases, such as cancer, neurodegenerative disorders, and autoimmune diseases. Modern medical research has revealed that apoptotic signaling pathways play a pivotal role in the pathogenesis of AD. Abnormal activation of apoptosis intertwines with other pathological mechanisms—such as Aβdeposition, Tau pathology, and neuroinflammation—collectively driving neuronal death and cognitive decline [6]. Research progress in Western medicine for treating AD has been slow, with clinical outcomes often unsatisfactory. In contrast, studies on traditional Chinese medicine (TCM) for AD have deepened, revealing its characteristics of multi-link, multi-pathway, and multi-target holistic regulation. Notably, TCM has been found to treat AD and potentially prevent its recurrence by modulating the initiation and progression of apoptosis, offering novel therapeutic strategies and insights for AD prevention and treatment. Based on this, this article details the mechanisms by which intervention in apoptosis influences the pathophysiological processes after AD onset and reviews research progress on TCM regulation of AD through apoptosis modulation. It aims to provide a reference for the future application of these insights in the clinical diagnosis and treatment of AD.

2. Current Status of AD Treatment

2.1 Recent Advances in AD Drug Development

Current treatment options for AD include four approved symptomatic drugs: donepezil, rivastigmine, galantamine, and memantine. In 2023, the monoclonal antibody Lecanemab (brand name Leqembi), which targets Aβ plaques, was approved. While it has shown efficacy in reducing amyloid deposition in early AD, it carries risks such as amyloid-related imaging abnormalities (ARIA) and infusion reactions. Emerging immunotherapies, including donanemab and gantenerumab, also aim to clear Aβ plaques and delay Tau pathology; however, their long-term cognitive benefits are still under evaluation [7]. Innovative small-molecule drugs, such as F-SLCOOH, have demonstrated dual value in preclinical studies: functioning as a tracer for Aβ aggregates while also exerting therapeutic effects by activating autophagy pathways. The fluorescent probe F-SLOH has been shown in 5XFAD and 3xTg-AD mouse models to inhibit Aβ

aggregation, reduce levels of Aβ plaques/Aβ oligomers and Tau aggregates, enhance the clearance of APP/Tau metabolites via the autophagic-lysosomal pathway (ALP), mitigate neuroinflammation, and improve synaptic function and cognitive abilities [8]. Treatment strategies targeting Tau protein include Tau aggregation inhibitors and Tau vaccines. Neuroprotective agents, such as neurotrophic factors and BACE inhibitors, provide synergistic therapeutic effects by enhancing neuronal resilience and maintaining synaptic function [9-10]. Celastrol promotes autophagy-lysosome biogenesis by activating TFEB, facilitates TFEB nuclear translocation by inhibiting mTORC1, significantly reduces phosphorylated Tau aggregates in the brains of P301S Tau and 3xTg-AD mice, and effectively decreases phosphorylated Tau aggregation while improving cognitive function in AD models. This offers new insights for the treatment of Tauopathies [11]. APP overexpression promotes its binding to the Fe65 protein via the PTB2 domain, triggering Aβ secretion. Therefore, targeting and blocking the APP-Fe65 interaction has emerged as a novel therapeutic strategy. Engineered exosomes loaded with the autophagy inducer corynoxine B can specifically target APP-expressing cells and significantly improve cognitive function in AD mice [12]. Recent studies have found that caudatin, derived from Cynanchum otophyllum, can bind to the PPARα receptor, upregulate ALP expression to promote the clearance of Aβ and phosphorylated Tau, and improve cognitive behavior in AD models [13].

2.2 Emerging Trends in AD Treatment

Despite the significant unmet clinical needs in AD treatment, the number of drugs undergoing clinical trials for the disease remains limited. Between 2002 and 2012, only 244 AD therapeutic drugs were registered for clinical trials on ClinicalTrials. gov, with only memantine ultimately receiving approval—a success rate as low as 0.4% [14]. Even drugs developed based on the Aβ hypothesis, targeting points such as BACE1 inhibitors, anti-Aβ antibodies, RAGE receptors, PPARs, and 5-HT6 receptors, have largely failed in Phase III trials. β-secretase, a key enzyme in the amyloidogenic processing of APP, was once considered a promising target. However, three major BACE inhibitors have all failed: Verubecestat significantly reduced Aβ levels in blood, cerebrospinal fluid (CSF), and brain tissue but failed to slow symptom progression in the EPOCH trial for mild-to-moderate AD. The APECS trial for prodromal AD was terminated early due to a lack of efficacy, with the 40 mg dose group even accelerating cognitive decline and increasing adverse events [15]. Lanabecestat showed no efficacy in the AMARANTH (early AD) and DAYBREAK-ALZ (mild AD) trials and was associated with side effects such as psychiatric symptoms and weight loss [16]. Atabecestat, while lowering CSF Aβ levels, was discontinued due to hepatotoxicity, suggesting that BACE1 may not be an ideal target [17]. The anti-Aβ monoclonal antibody Solanezumab initially showed an increase in free Aβ levels in CSF, but the Phase III EXPEDITION series of trials failed to demonstrate cognitive improvement in patients with mild-to-moderate AD. Azeliragon, a RAGE inhibitor, showed cognitive improvement in Phase II trials for mild AD, but the Phase III STEADFAST trial was terminated due to ineffectiveness [18-19]. The diabetes drug pioglitazone, repurposed due to its PPAR-γ agonist activity, showed improved cerebral blood flow and cognition in small-scale studies but did not meet its primary endpoints in the Phase III TOMORROW trial [20]. The 5-HT6 receptor antagonist Idalopirdine showed limited efficacy as a monotherapy in Phase II trials but exhibited synergistic effects when combined with donepezil. However, the Phase III STAR trials (combining Idalopirdine with donepezil, rivastigmine, or galantamine) failed to demonstrate cognitive benefits from the combination therapy [21]. Similarly, Intepirdine, another drug in the same class, was discontinued after Phase III trials showed no significant efficacy, despite promising Phase II results [22-23]. Another current direction in AD research involves drug repurposing, focusing on drugs already approved by the U. S. Food and Drug Administration (FDA) for other indications. Drug repurposing offers a faster and more cost-effective development pathway for AD treatments but still faces significant challenges. The complexity and heterogeneity of AD substantially increase the difficulty of developing effective drugs. Although repurposed drugs come with established safety profiles, they may still cause unforeseen adverse effects, requiring additional clinical evaluation [24]. Furthermore, the complexity of intellectual property acquisition also hinders the redevelopment of existing drugs. Nevertheless, with advances in computational methods and a deeper understanding of disease pathology, drug repurposing has become a highly promising research strategy in the AD field.

3. Relationship Between Apoptotic Signaling Pathways and AD

3.1 Inflammation-Mediated Apoptosis

Studies have shown that neuroinflammation participates in the pathophysiological processes of AD by activating microglia and astrocytes [25]. The activation of microglia can counteract neuropathological damage induced by neuroinflammation in AD [26]. In the early stages of AD, even before the formation of senile plaques, activated microglia exert a neuroprotective effect by reducing Aβ deposition, effectively mitigating Tau protein hyperphosphorylation, and promoting the secretion of neurotrophic factors [27-28]. Research indicates that microglia play a dual role in the pathogenesis of AD. On one hand, a large number of activated microglia within senile plaques in patients exhibit phagocytic function, helping to clear Aβ aggregates through phagocytosis. Microglia also function through the expression of scavenger receptors, which are categorized into scavenger receptor class A (SR-A) and SR-B. These receptors aid in clearing apoptotic cells and protecting neurons, thereby slowing the progression of AD. On the other hand, excessive aggregation of Aβ and Tau proteins can activate the NLRP3 inflammasome, prompting microglia to shift from a resting state to a pro-inflammatory state. This leads to abnormal autophagy and the production of reactive oxygen species (ROS), further exacerbating the inflammatory response. Additionally, microglia cause neuronal damage and Aβ accumulation through Toll-like receptor (TLR) expression and abnormal activation of the complement system [29-30]. Consequently, sustained neuroinflammation leads to microglial activation, exacerbates Aβ deposition, and triggers neuronal damage. Aβ is a

significant neurotoxic factor that can activate microglia and initiate neuroinflammatory responses [31]. Other studies have shown that Tau oligomers and fibrils can provide sufficient stimulation to induce morphological changes in microglia and increase interleukin (IL) expression [32]. Different types of Aβ aggregates can activate microglia and release cytokines, leading to neuronal dysfunction and death [33]. Neuroinflammatory responses may play a driving role in the pathogenesis of AD, making anti-inflammatory therapy a potential treatment strategy. However, most large-scale clinical trials of anti-inflammatory drugs for AD have shown no significant improvement [34]. One randomized controlled clinical study indicated that non-steroidal anti-inflammatory drugs (NSAIDs) helped improve cognitive function in patients with mild-to-moderate AD carrying the ApoE4 allele [35]. Another study demonstrated that the use of NSAIDs before the onset of symptoms in AD patients had a protective effect on cognitive function, but their use after the onset of cognitive impairment was harmful [36].

3.2 Interaction Between Aβ and Apoptotic Signaling Pathways

Aβ deposition is one of the core pathological features of AD. Aβ can directly bind to neuronal surface receptors (such as RAGE), activate downstream signaling pathways, lead to intracellular calcium homeostasis imbalance and increased oxidative stress, thereby triggering apoptosis. Studies have found that in the hippocampus of APP/PS1 mice, knockout of the RAGE gene resulted in a 48% reduction in Cyto-c release, a 55% decrease in Caspase-3 activity, and a 42% reduction in neuronal loss rate [37]. Furthermore, traditional Chinese medicine formulas such as Huanglian Jiedu Tang (Coptis Detoxification Decoction) and the compound ginsenoside Rg1 have been demonstrated to simultaneously inhibit the RAGE-ROS axis and enhance Akt phosphorylation, achieving a "dual-axis therapeutic" effect [38]. Concurrently, Aβ can also indirectly promote apoptosis by inhibiting insulin signaling pathways (such as the PI3K-Akt pathway), thereby reducing the protective effects on neurons [39]. A published report indicates that both intracerebral insulin sensitizers (intranasal insulin) and Akt allosteric activators (SC79) can restore Akt phosphorylation, reduce Bax translocation, and result in a 38% decrease in hippocampal neuronal apoptosis rate in AD mice [40].

3.3 Tau Protein Abnormalities and Apoptosis

Hyperphosphorylation of Tau protein, leading to the formation of neurofibrillary tangles (NFTs), constitutes another critical pathological hallmark of AD. Aberrant Tau protein can activate apoptosis-associated proteins, such as Caspase-2, thereby inducing neuronal apoptosis [41]. Furthermore, Tau protein can promote cytochrome c release by impairing mitochondrial function, subsequently activating the intrinsic apoptotic pathway [42]. In the AD brain, Tau phosphorylation levels at residues including Ser202, Thr205, Ser214, Ser396, and Ser404 are elevated by 4 to 5-fold, causing its dissociation from microtubules and resulting in a loss of "track stability" function [43]. Recent research further reveals that Tau can directly or indirectly push neurons toward programmed cell death. In 3xTg-AD mice, the expression level of CypD in the hippocampus at 12 months of age positively correlates with Tau oligomer levels (r=0.81). CypD gene knockout reduces neuronal apoptosis by 40% [44]. Additionally, in SH-SY5Y cells, Tau knockdown significantly attenuates etoposide-induced P53 stabilization and Caspase-3 activity, leading to a 50% reduction in the apoptotic rate. This demonstrates that Tau acts as a "rheostat" for P53-dependent apoptosis following DNA damage [45]. In summary, Tau pathology propels neurons from structural damage to apoptotic demise through three major pathways: "microtubule disassembly–transport paralysis," "oligomer–mitochondrial pore," and "DNA damage–P53." Its oligomeric form acts as the pro-apoptotic toxic species, whereas NFT fibrils may represent a relatively inert "protective trash can" [44]. Targeting phosphorylation, oligomerization, or downstream nodes in the mitochondrial-genomic cascade offers novel and precise intervention points for anti-apoptotic therapy in AD.

4. Intervention of Traditional Chinese Medicine (TCM) on Alzheimer's Disease by Regulating Apoptotic Signaling Pathways

4.1 Intervention of Traditional Chinese Medicine (TCM) Monomeric Compounds in Alzheimer's Disease Based on Apoptotic Signaling Pathways

1) Phenolic Esters Salidroside is the primary active component of Rhodiola rosea and exhibits a variety of pharmacological effects. Studies have shown that salidroside possesses anti-inflammatory, antioxidant, anti-fatigue, anti-aging, free radical scavenging, and immunomodulatory properties [46]. Research by Jia Xin et al. experimentally confirmed that Rhodiola rosea may improve the structure and function of cortical neurons by activating the BDNF/TrkB signaling pathway, scavenging free radicals, reducing the synthesis and release of inflammatory factors, inhibiting inflammatory responses and apoptosis, and enhancing synaptic plasticity, thereby mitigating neuronal damage [47].

2) Glycosides Curculigoside, extracted from the rhizome of Curculigo orchioides, is a phenolic glycoside compound that functions as a potent antioxidant. It exhibits anti-inflammatory, antioxidant, and immunomodulatory effects [48-49]. Research indicates that curculigoside may enhance learning and memory abilities in dementia model rats by activating the BDNF/TrkB signaling pathway. This activation subsequently triggers downstream signaling molecules, including PI3K, MAPK/ERK, and phospholipase Cγ (PLCγ) pathways. It upregulates the expression of ERK and Bcl-2 proteins in hippocampal tissue while inhibiting the expression of Bcl-2-associated X protein (Bax). These effects collectively suppress neuronal apoptosis, promote neuronal survival and neurogenesis, and enhance synaptic plasticity [50].

3) Terpenoids Ligustri Lucidi Fructus is the dried ripe fruit of the evergreen tree Ligustrum lucidum (Oleaceae). It is traditionally used to tonify the liver and kidneys, improve vision, darken hair, nourish Yin, and promote longevity. Modern research indicates that Ligustri Lucidi Fructus possesses physiological functions such as antioxidant, anti-inflammatory, anti-aging, and immunomodulatory effects. Oleanolic acid is one of its active components,

exhibiting various biological activities and physiological functions. A study by Lin Ling et al. demonstrated that the diterpenoid monomer crocin can upregulate the expression of BDNF and TrkB proteins in hippocampal tissue, thereby improving learning and memory abilities in rats [51]. Research by Chen Weirong confirmed that the pentacyclic triterpenoid saponin extract Polygalae Radix total saponins can significantly increase the expression of BDNF and its receptor TrkB in the hippocampal CA1 region of AD model rats and enhance synaptic plasticity, which may be associated with its improvement of cognitive function [52].

4) Sterols Ginsenosides belong to triterpenoid glycoside compounds and are a class of traditional Chinese medicine monomers found in low abundance but with high biological activity in ginseng. They exhibit anti-inflammatory, antioxidant, and anti-apoptotic effects [53]. Research has confirmed that ginsenoside Rg1 can ameliorate brain tissue damage in AD model rats and inhibit neuronal apoptosis [54]. Wu et al. elaborated on the mechanisms of ginsenoside Rg1 and its deglycosylated derivatives in treating AD. They involve the inhibition of Aβ aggregation and Tau protein phosphorylation, enhancement of synaptic function, and reduction of inflammation and apoptosis, which are mediated through the regulation of multiple signaling pathways [55].

5) Coumarin compounds possess a range of pharmacological effects, including antioxidant, antitumor, antibacterial, antiviral, anti-inflammatory, and neuroprotective activities, and are widely used in clinical practice [56]. Meranzin hydrate (MH), one of the active components isolated from Citrus aurantium, exhibits multiple physiological activities. Studies have demonstrated that meranzin hydrate can alleviate pathological damage in the hippocampus of rats, inhibit apoptosis, increase neuronal cell counts, and modulate neurotransmitter balance in AD model rats [57].

5. Summary

This review provides a detailed exploration of the critical role of apoptosis in Alzheimer's disease (AD) as an entry point. It systematically summarizes the potential effects of traditional Chinese medicine (TCM) herbal formulas, proprietary TCM medicines, and TCM monomers in regulating this signaling pathway. A comprehensive analysis of their possible mechanisms for intervening in AD is presented, offering a theoretical foundation for the clinical application of TCM in AD treatment. Although TCM has demonstrated broad application prospects and significant potential in intervening in apoptosis for AD prevention and treatment, several challenges remain: (1) Both herbal medicines and proprietary TCM formulas exert their effects on AD by modulating apoptotic signaling pathways and their downstream cascades. However, identifying the specific active components responsible for this regulation remains difficult. (2) Current related research is primarily confined to animal experiments and in vitro cellular studies. There is a lack of clinical trial evaluations in human subjects, and research focusing on the recovery phase of AD is relatively scarce. (3) Existing studies mainly concentrate on formulas, extracts, and monomers. Research on single herbs and TCM component-based drugs is insufficient, indicating a need for a more stratified and comprehensive research approach. Therefore, building upon current research, further investigation is warranted. This includes clarifying the critical points at which TCM interventions targeting apoptosis exert their effects and elucidating their precise mechanisms of action. Additionally, exploring the potential of other characteristic TCM modalities to regulate relevant signaling pathways for AD treatment may provide novel insights and strategies for the clinical prevention, treatment, and drug development of AD within the TCM framework.

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