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RECENT ADVANCES IN THE NEUROPROTECTIVE EFFECTS OF TRADITIONAL CHINESE MEDICINE: FOCUS ON ACTIVE INGREDIENTS AND MECHANISMS OF ACTION IN ALZHEIMER'S DISEASE

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Abstract: Alzheimer's disease (AD) is a senile brain disease characterized by insidious onset and neurodegenerative pathology. According to reports from the World Health Organization, the global population of individuals affected by AD exceeds 55 million, with a new case occurring approximately every three seconds. This number is projected to exceed 150 million by the year 2050. Given the unclear pathogenesis of AD, there are currently no available etiological treatments. Traditional Chinese Medicine (TCM) is known for its multi-target therapeutic approach, which provides several advantages, including a variety of treatment methods, minimal side effects, and the capacity to coordinate effects across multiple targets and pathways. This makes TCM particularly significant for research focused on the prevention and treatment of AD. This paper utilizes TCM as a foundation to review recent research findings regarding its treatment of AD, including ganolearins A–D, ulmoidol (30), Ganoderma lucidum polysaccharide, Ganoderma sinense crude polysaccharide and so on. It identifies newly discovered active ingredients and treatment methods, with the aim of providing a theoretical basis for TCM approaches to AD and serving as a reference for drug development.
Keywords: Alzheimer's disease; Traditional Chinese Medicine; Active ingredient; Mechanism of action; Neuroprotection

1 INTRODUCTION

Alzheimer's disease (AD), a degenerative brain disorder, is primarily characterized by the gradual onset of dementia symptoms, predominantly affecting the elderly population [1]. As the condition advances, patients typically experience a continuous decline in memory and cognitive abilities, including logical reasoning [2]. This process not only significantly diminishes the patient's quality of life but also places considerable strain on the daily lives of their families. Although the impact of AD is extensive, our current understanding is still relatively limited. Due to the incomplete elucidation of its exact etiology and pathological processes, achieving etiological treatment for AD remains challenging. Clinically, only symptomatic treatments are available to slow the progression of AD currently. The research has revealed a series of complex mechanisms underlying AD, including the toxicity of beta-amyloid protein (Aβ), excessive phosphorylation of tau protein, neuroinflammation, glucose metabolism disorders, and dysregulation of the gut microbiota [2]. Currently, the third core feature of the pathogenesis of AD is neuroinflammation, which has become an important research focus in this field, along with the deposition of β-amyloid protein and the formation of neurofibrillary tangles (NFTs) [3].

AD is divided into several categories by the theory of Traditional Chinese Medicine (TCM), such as "dementia," "psychosis," "forgetfulness," "consumptive disease," and "dullness disease." One important internal mechanism that is thought to be responsible for the development of these ailments is the lack of kidney essence, as well as the dual deficiency of Qi and blood [4]. TCM's multi-target characteristics allow it to offer benefits including a range of treatment options and low side effects, and it has demonstrated remarkable effectiveness in treating the neuroinflammation linked to AD [5]. The principles of holistic control, syndrome differentiation, and treatment are all upheld in TCM treatment. It has the ability to precisely target a number of AD pathogenesis pathways, including neuroinflammation, as well as related targets within the cascade reactions that these mechanisms initiate. Either individual herbs or intricate formulations are used to do this, allowing for a thorough regulatory impact on the body that affects numerous targets and pathways [6]. TCM has a great deal of promise as a therapeutic strategy for reducing the clinical symptoms of AD and slowing its progression because of this special therapeutic mechanism.

In contemporary clinical practice, the primary pharmacotherapeutic agents for the management of AD encompass central cholinesterase inhibitors, glutamate receptor antagonists, and anti-amyloid monoclonal antibodies [7]. Lecanemab, memantine, donepezil, and galantamine are examples of medicines having well-established clinical applications [8]. Unfortunately, there are presently no viable treatments for Alzheimer's disease. They can only slow the disease's progression. Therefore, prevention remains the most effective technique for addressing this illness. This study provides an in-depth analysis of recent breakthroughs in AD pathogenesis and research on active TCM constituents for therapy. This work systematically lists various TCM active ingredients, such as ginsenosides and quercetum, along with their mechanisms of action, in order to provide distinct TCM therapeutic strategies for the treatment of AD, as well as to further research and clinical applications of integrated Chinese and Western medicine for AD.

2 ETIOLOGY OF AD

2.1 Aβ Cascade Hypothesis

The aberrant accumulation of β-amyloid (Aβ) initiates AD, activating a cascade of pathogenic processes including tau protein hyperphosphorylation, neuroinflammation, and synaptic damage. That eventually leading to neuronal death and progressive cognitive impairment [9]. Aβ is a peptide that comes from the amyloid precursor protein (APP). APP is a transmembrane protein that is mainly expressed in neurons. Its physiological functions include synapse development, neural plasticity, cell adhesion, and signal transmission [10]. Under normal physiological circumstances, the α-secretase processing route cleaves APP, producing a membrane-anchored C83 fragment and soluble sAPPα, which has neuroprotective properties [11]. APP cleavage is changed in the clinical stage of AD, the first cleavage is carried out by β-secretase (BACE1) at the N-terminus of the Aβ domain inside APP, resulting in a membrane-bound C99 fragment [12]. The transmembrane region of the C99 fragment is next subjected to proteolytic cleavage by the γ-secretase complex, which releases Aβ peptides of different lengths, primarily Aβ40 and Aβ42 [11]. Aβ42 exhibits a significant tendency for aggregation and hydrophobicity [13]. Monomers aggregate into oligomers [14], which in turn aggregate into fibrous amyloid plaques , because to the hydrophobicity [15]. Inflammatory mediators released by excessive Aβ aggregation cause neuroinflammation, which in turn activates microglia and astrocytes.This activation creates a vicious cycle that worsens AD pathogenesis by encouraging more Aβ aggregation and generation [16]. There is clear pathological heterogeneity between the two types of AD, as tau can adopt distinct folds in the human brain in different diseases. [17].

2.2 Abnormal Modification of Microtubule-associated Protein Tau

Tau is a microtubule-associated protein that is essential to the physiological processes of neurons. Its primary role is to mediate microtubule-associated physiological functions and aid in intracellular microtubule assembly. It is also essential for controlling the intracellular transport of neurotransmitters and the development of neuronal axons [18]. Dysregulated tau protein function impairs neuronal development and repair and disrupts nerve impulse transmission across neurons [19]. Abnormal phosphorylation of tau protein is a mark pathogenic alteration in the brain neurons of AD patients [20]. Tau protein's innate disordered nature makes it susceptible to misfolding under pathological settings, exposing key motifs such as residues 275-280, which have been linked to vascular cognitive impairment. These misfolded motifs cause tau aggregation, which leads to the formation of neurofibrillary tangles (NFTs), a key clinical characteristic of AD [21]. Abnormal tau protein can spread trans-synaptically to undamaged brain areas, causing synaptic malfunction or loss, which leads to neuronal injury and progressive cognitive decline [21].

2.3 Oxidative Stress

Oxidative stress is a critical linked component in AD causation, which results from an imbalance between the organism's oxidative and antioxidant systems [22]. The primary oxidants in biological tissues are reactive oxygen species (ROS), whereas antioxidants consist mostly of enzymatic antioxidants such as superoxide dismutase (SOD) and non-enzymatic antioxidants such as vitamin C [23]. Given the brain's extraordinarily high oxygen consumption, a lack of antioxidant ability to combat the ensuing oxidants causes an accumulation of ROS. These excess ROS assault neuronal structures and biomolecules, disrupting cell membranes and eventually causing neuronal death [24]. Oxidative stress can trigger neuronal re-entry into the cell cycle, increase tau protein accumulation, and impede Aβ breakdown, resulting in Aβ buildup and neuroinflammation [24].

2.4 Cholinergic Receptor Deficiency

Short-term memory functions and synaptogenesis are supported by α7 nicotinic acetylcholine receptors (α7nAChRs) in the healthy brain.Research employing α7nAChR-deficient mice shows that receptor deficiency promote the generation of A β and abnormal aggregation of nAChRs. Additionally, it increases tau aggregation into NFTs and causes tau hyperphosphorylation by controlling glycogen synthase kinase-3β [25]. According to this, cholinergic receptor insufficiency may serve as a precursor to aberrant tau phosphorylation and Aβ buildup, collaborating with other harmful elements to promote the pathophysiology of AD [25].

2.5 Genetic Factors

Certain differences between AD patients' and unaffected people's DNA have been found using molecular probe techniques. The condition may become more likely to develop if genes like *ZDHHC21* and *CHCHD2* are mutated [26]. According to research, family early-onset AD can result from mutations in genes such the amyloid precursor protein gene, *presenilin 1* (*PSEN1*), and *presenilin 2* (*PSEN2*) [27]. Genetic variations such alpha-2-macroglobulin (*A2M*) and *apolipoprotein E* ε4 (*APOE* ε4) greatly increase the risk of sporadic AD in the general population [28–30]. *CHCHD2* is a mitochondrial protein with many functions that regulate respiratory chain complex production as well as the mitochondrial apoptosis pathway. CHCHD2 and CHCHD10 proteins, which are homologous proteins with 54% identity in amino acid sequence, belong to the mitochondrial coiled-coil-helix-coiled-coil-helix (CHCH) domain protein family

and have been found to be linked to neurodegenerative diseases [31]. Furthermore, a recently discovered novel pathogenic pathway for AD is *ZDHHC21* mutation-induced aberrant protein palmitoylation, which causes familial AD in Chinese cohorts [26].

3 ACTIVE INGREDIENTS OF TCM FOR TREATING AD

3.1 Terpenoids

Several terpenoids and terpenoid derivatives have been shown to be effective against AD, including carvone, ginkgolide B, salidroside, astragaloside IV, ginsenoside, tenuifolin, *Gynostemma pentaphyllum*, and Ganoderma triterpenes [32]. Plant-derived triterpenoids have anti-inflammatory, antioxidant, and other therapeutic qualities, making them interesting candidates for treating AD (Table 1). Triterpenoids, such as *Ganoderma* triterpenes and ginsenosides, can help AD patients by altering critical pathways such as neuroinflammation, oxidative stress, autophagy, mitochondrial dysfunction, and endoplasmic reticulum stress. *Ganoderma lucidum* contains significant amounts of triterpenoids, which could act as natural anti-inflammatory agents or functional meals to help prevent, delay, and treat AD [33]. Pathological tau protein is eliminated as a result of the efficient autophagy activation provided by the *ganoderma* triterpenes ganoapplin A and ganoapplin B [34]. To encourage the removal of Tau proteins, ganolearins A–D, which are produced from *Ganoderma* triterpenes, trigger the AMPK-ULK1 autophagy pathway [35]. By regulating key signaling pathways related to inflammation, triterpenoids extracted from *Poria* can reduce the incidence of Alzheimer 's disease. Additionally, it improves memory function by reducing oxidative stress, preventing tau hyperphosphorylation and neuronal death, and controlling the cholinergic system [36-37]. Gypenoside XLVI, a dammarane-type triterpenoid saponin found in *Gynostemma pentaphyllum*, has been shown to have therapeutic potential for AD by considerably improving learning and memory deficits in the 3×Tg-AD mouse model of the disease [38]. From the *Eucommia ulmoides* leaf extract's ethyl acetate fraction, thirty-eight chemicals were separated and identified. The nortriterpenoid ulmoidol showed the most anti-neuroinflammatory effect among them [39-41].

3.2 Flavonoids

Quercetin, genkwanin, dihydromyricetin, myricetin, myricitrin, puerarin, and the total flavonoids from *Drynaria fortunei* are examples of active flavonoids that are used to treat AD. By regulating the apoptosis-related proteins Bcl-2 and Bax and altering the PI3K/Akt signaling pathway, quercetin has neuroprotective effects [42]. By lowering intracellular ROS, improving mitochondrial dysfunction, and lowering tau hyperphosphorylation, genkwanin has neuroprotective benefits [43]. *Ampelopsis grossedentata's* dihydromyricetin exhibits strong research promise because to its biological activities, which include antioxidant, anti-inflammatory, and neuroprotective properties [44].

Extracted from *Pueraria lobata*, puerarin has neuroprotective, antioxidant, and anti-inflammatory properties [45]. Research shows that puerarin works better than β-sitosterol to improve cellular AD models. Puerarin dramatically increases NOS3 protein expression in AD cells at 100 μM, indicating that NOS3 might be a possible target for puerarin's advantageous effects in AD [45]. In hydrocortisone-induced model mice, osteopractic total flavone may have neuroprotective properties against AD. The ER pathway mediates this possible therapeutic effect, which reduces brain tissue damage by upregulating the expression of the proteins NMDAR1 and GluR2 and downregulating that of CaMKII [46].

The plant *Scutellaria barbata* has antibacterial, antioxidant, and anticancer properties.Its active ingredients are flavonoids, which show promise in the treatment of ovarian and lung adenocarcinomas. According to recent research, *Scutellaria barbata* suppresses microglial (MG) proliferation and modifies the expression of pro-inflammatory factors and nitric oxide synthase activity to prevent Aβ complex-induced neuroinflammation. Its flavonoid concentration is responsible for its anti-AD therapeutic and preventative activities [47-48]. One of the most researched phytochemicals, luteolin, has neuroprotective properties. By blocking acetylcholinesterase activity, controlling the production and aggregation of Aβ, altering Tau protein phosphorylation and brain glucose metabolism, and exhibiting anti-inflammatory, antioxidant, and anti-apoptotic properties, it produces these effects in the context of AD [49].

3.3 Polysaccharides

Physalis alkekengi fruit, deproteinized *Vitis vinifera*, *Ganoderma lucidum*, and *Schisandra chinensis* are a few examples of medicinally active polysaccharides used to treat AD.*Ganoderma lucidum* reduces oxidative stress damage, improves immunological function loss, and lessens AD symptoms. In $AlCl_3$/D-gal-induced AD animal models, studies on *Ganoderma lucidum* polysaccharide (GLP) and *Ganoderma sinense* crude polysaccharide (GSP) showed that GSP was noticeably more effective than GLP in reducing cognitive impairments and dementia-related behaviors. This improvement included less memory loss, more time spent investigating new things, and improved spatial exploration [50]. Two fractions, GSP1 and GSP2, were produced by the separation and purification of GSP. GSP1 reversed AD-induced gut microbiota dysbiosis, increased the abundance of potentially beneficial bacteria (including taxa that produce short-chain fatty acids), significantly improved dementia-associated behavioral and pathological symptoms, and effectively attenuated cerebral Aβ deposition in $AlCl_3$/D-gal-induced AD model mice [50]. Furthermore, GSP1 may also influence AD progression through the gut-brain axis. Furthermore, by modifying the expression levels of antioxidant enzymes, polysaccharides obtained from deproteinized *Vitis vinifera* 'Thompson Seedless' reduce oxidative

damage caused by $A\beta_{1-42}$, showing promise as a therapy for AD [51]. By reducing tau protein phosphorylation in the brain, *Lycium chinense* polysaccharides improved learning and memory impairments in AD combined with type 2 diabetes mellitus (AD+T2DM) model mice [52].

Four separate fractions were obtained from the fractionation of *Schisandra chinensis* polysaccharides (SCP). In AD rats, all pure polysaccharide fractions dramatically restored intestinal barrier integrity, reduced neuroinflammation, and enhanced learning and memory in a dose-dependent manner. However, the SCP2 group showed the most notable efficacy [53]. By blocking the TLR4/NF-κB/NLRP3 pathway, SCP2 reduces neuroinflammation and has neuroprotective effects [53]. Fucoidan has the potential to be used in the development of natural product-based AD therapies, as evidenced by animal trials showing that it dramatically reduced scopolamine-induced cognitive impairment, decreased Aβ deposition, and activated the Nrf2/TLR4/NF-κB neuroprotective pathway [54].

Table 1 The Main Active Components of TCM in the Treatment of AD and its Mechanism of Action

Traditional Chinese medicine	Active ingredient	Category	Specific mechanism	Literature
Ganoderma lucidum	*Ganoderma* triterpenes	Terpene	the AMPK-ULK1 autophagy pathway	[34, 35]
Panax ginseng	ginsenosides		Activation of NLRP3↓→cleaved caspase-1↓ →TNF-α↓	[33]
Poria	*Poria cocos* triterpenes		BACE1↓→APP↓→Aβ↓; GSK-3β↓;NF-κB pathway↓ →TNF-α↓IL-1β↓IL-6↓; ROS↓	[38]
Gynostemma pentaphyllum	Gypenoside XLVI		NLRP3↓→NLRP3↓→speck-like pro↓;PPM1A /NLRP3/tau axis↓ & PPM1A /nuclear factor -κB/CX3CR1 pathway	[39]
Eucommia ulmoides	nortriterpenoid Ulmoidol (30)	Flavonoid	Aβ↓;NF-κB pathway↓→TNF-α↓IL-1β↓IL-6↓	[40, 41]
Rutin	Quercetin		PI3K/AKT pathway change Bcl-2/Bax→caspase-3↓→ Aβ↓;GSK-3β↓CDK5↓MAPKs↓→Tua pro	[42]
Genkwa Flos	Genkwanin		NF-κB pathway↓ →TNF-α↓ IL-6↓ ; ROS↓ RNS↓	[43]
Ampelopsis grossedentata	Dihydromyricetin		BACE1↓ →Aβ↓ ;NF-κB pathway →TNF-α↓ IL-6↓;AChE↓;ROS↓ RNS↓	[44]
Pueraria lobata	Puerarin		NOS3↑	[45, 46]
Davallia mariesii	Osteopractic total flavone		NMDAR1↑GluR2↑CAMKII↓→Prot-ecting the nerves	[47]
Scutellariae Barbatae Herba	*Scutellaria barbata* flavonoids		Aβ↓;MG↓;NOS↓TNF-α↓IL-6↓	[48, 49]
Reseda odorata L.	Luteolin		AChE↓;Aβ↓;Tua pro	[50]
Ganoderma lucidum	GSP1	Polysaccharides	Aβ↓;Intestinal flora↑;the gut-brain axis way	[51]
Schisandra chinensis	SCP2		TLR4/NF-κB/NLRP3 pathway↓→ TNF-α↓ IL-1β↓ IL-6↓ ;Aβ↓; MG↓	[54]
Sargassum pallidum	Fucoidan		Aβ↓;NRf-2/TLR4/NF-kB pathway↑ → protecting the nerves	[55]
Lycium chinense	Polysaccharides of *Lycium chinense*		ROS↓RNS↓ ;GSK-3↓	[53]

4 COMPARISON BETWEEN TCM AND CONVENTIONAL THERAPEUTIC DRUGS

4.1 Mechanism of Action

TCM's mode of action has advantages over Western medicine in the treatment of AD.Through mechanisms like heat shock protein activation, oxidative stress and inflammation modulation, and gut-brain axis regulation, TCM's distinctive multi-target strategy allows for synergistic benefits [55]. On the other hand, traditional pharmaceutical treatments for AD usually focus on a single pathway: memantine serves as an NMDA receptor antagonist, whereas donepezil just inhibits acetylcholinesterase.Neither directly addresses the control of tau phosphorylation or Aβ production [56]. Aducanumab and other monoclonal antibodies that target Aβ clearance are controversial in clinical settings and ineffective in repairing synaptic damage [57].

4.2 Efficacy and Safety

Since AD is a neurological condition, it requires ongoing medical care. TCM offers substantial benefits for such long-term treatment plans because of its natural multi-target effects and good safety record. Additionally, research suggests that integrating TCM with Western therapy could lessen the negative effects of traditional medications. When used with chemical medications like donepezil, for instance, TCM may be more successful than chemical medications alone at improving patients' cognitive impairment and lowering the risk of side effects like urticaria and sleeplessness [58].

4.3 Treatment Philosophy

The treatment philosophy of TCM integrates a systemic perspective, holism, and pattern differentiation-based treatment. The primary goals of current therapy approaches, which emphasize preventive measures, are to reduce symptoms and halt the progression of AD because the pathophysiology of the illness is yet unknown. With its ability to delay the beginning of disease and support health maintenance and recovery, TCM has intrinsic advantages in preventive medicine. This offers substantial research opportunities for AD therapy and prevention [59]. A foundation for dietary intervention is also provided by the TCM idea of the homology of medicine and food, which is extremely pertinent to the prevention and treatment of AD [60].

5 CONCLUSION AND OUTLOOK

In conclusion, the pathophysiology of AD, a neurodegenerative disease that poses a serious risk to the health of the aged, is still poorly understood, and the available clinical treatments for it have serious drawbacks. TCM's theoretical underpinnings provide special benefits for the treatment of AD. Through multi-component, multi-target herbal formulae, its therapeutic strategies—which emphasize "holistic regulation" and "syndrome differentiation and treatment (bian zheng lun zhi)"—execute synergistic effects. The clinical efficacy of traditional Chinese medicine in treating AD is currently not fully supported by evidence-based medicine. Nonetheless, further research is necessary to fully understand the complex mechanisms of action and the pharmacological underpinnings of important bioactive components.

Clarifying the targets and signaling pathways of TCM's mechanisms of action, examining how it integrates with other therapeutic modalities, and examining the processes underlying TCM's holistic regulatory effects within the intricate pathophysiology of AD should be the top priorities of future study. In order to clarify the mechanisms of TCM in the treatment of AD from a variety of viewpoints and biological levels, future research should use biomedical methodologies such as pharmacology, network pharmacology, immunology, bioinformatics, and data analytics. Research on the scientific analysis and processing methods of TCM formulations, as well as on combination treatment approaches that combine TCM and Western medicine, should be stepped up at the same time. This seeks to lessen harmful side effects while increasing therapeutic efficacy.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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