

Traditional Chinese Medicine for Alzheimer's Disease: Current Evidence and Chemometric Approaches for Multi-Target Evaluation

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder for which there is currently no therapy that can fundamentally change the disease course. The limitations of single-target drugs have led the scientific community to turn to multi-target intervention strategies. In this context, traditional Chinese medicine (TCM) demonstrates potential in addressing the complex pathology of AD due to its "multi-component, multi-target, multi-pathway" overall regulatory characteristics. This review systematically reviews the current research status of TCM in the treatment of AD, with a particular focus on the evidence of its effects through multiple mechanisms such as reducing A β deposition, inhibiting excessive phosphorylation of Tau protein, regulating the cholinergic system, and alleviating neuroinflammation. Additionally, this article highlights how to utilize the "spectral efficacy relationship" combined with chemometrics methods (such as multiple regression, partial least squares regression, artificial neural networks, etc) to establish quantitative correlations between TCM chemical components and efficacy/clinical endpoints, thereby providing a methodological framework for evaluating the synergistic effects of TCM's multi-component interactions. The article also summarizes the evidence grades of currently commonly used TCM preparations in clinical practice and points out that future research needs to continuously deepen in areas such as standardized clinical endpoints, strict trial design, systematic safety assessment, and data-driven efficacy analysis. This review aims to provide theoretical references and research directions for integrating the holistic view of TCM with modern system analysis methods and promoting the development of multi-target treatment strategies for AD.

Keywords: Alzheimer's disease, traditional Chinese medicine, statistical methodology, spectrum-effect relationship, treatment status

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder affecting the elderly. According to Alzheimer's Disease International (ADI), approximately 13% of individuals over 65 years of age in developed countries are affected by AD, and the incidence rate is increasing annually. The World Health Organization projects that by 2050, the number of AD patients will approach 114 million,¹ inevitably imposing an increasing social and economic burden globally. The primary clinical manifestations of AD include progressive impairment of memory, motor, and language functions. Pathologically, AD is characterized by selective neuronal loss and degeneration in the hippocampus, cortex, and other brain regions, alongside a significant presence of senile plaques (SPs) and neurofibrillary tangles (NFTs) enriched with Tau protein. The pathogenesis of this disease is complex, with several proposed hypotheses including those related to amyloid β -protein (A β), Tau protein, cholinergic mechanisms, inflammation, oxidative stress, glutamate excitotoxicity, and calcium metabolism disorders. While modern medicine has yielded insights into the pathogenesis of AD, current treatment approaches remain largely palliative and often focus on single targets. This approach is problematic because long-term application of single-agent therapies often leads to drug resistance and significant side effects. Consequently, there is currently no disease-modifying treatment available using modern pharmaceuticals. In

recent years, research progress in Traditional Chinese Medicine (TCM) has become increasingly significant, offering new therapeutic approaches for various refractory diseases, particularly in the treatment of central nervous system disorders such as Alzheimer's disease, Parkinson's disease, stroke, and epilepsy. Numerous clinical studies have demonstrated that, compared to conventional Western medications, Chinese patent medicines can effectively alleviate symptoms in AD patients, improve cognitive function, enhance activities of daily living (ADL), reduce caregiver burden, and exhibit a favorable safety profile, thus attracting increasing attention. With the advent of modern medical big data and interdisciplinary approaches, the treatment of Alzheimer's disease with traditional Chinese medicine holds promising potential for the future.

This article aims to conduct a narrative review of the relevant fields. The cited literature was mainly selected by searching databases such as PubMed, Web of Science, and China National Knowledge Infrastructure (CNKI), and was based on a comprehensive review of key studies on Alzheimer's disease, traditional Chinese medicine treatment, and the methodology of efficacy-spectrum relationship in recent years.

Studies on the Pathogenesis of Alzheimer's Disease

AD is a complex neurodegenerative disorder with both genetic and sporadic forms. Its pathogenesis is characterized by the presence of A β plaques, hyperphosphorylated tau protein, NFTs, and neuroinflammation.² The amyloid cascade hypothesis, the prevailing theory of AD etiology, posits that A β is the primary risk factor in AD initiation and progression. In AD-affected brains, the overproduction of the A β 42 isoform is favored, leading to the formation of amyloid plaques.^{3,4} Notably, A β plaques are one of the two defining neuropathological features of AD and constitute the main components of senile plaques in patients.⁵ Researchers have long sought to reduce A β production, inhibit its aggregation, or enhance its clearance from the brain using various anti-A β agents in extensive clinical trials. However, these approaches have largely yielded disappointing results due to limited efficacy and adverse events.⁶ For instance, aducanumab, a novel disease-modifying anti-A β human monoclonal antibody developed for mild AD, has shown only modest clinical effects, rendering its potential benefit to patients uncertain.⁷

The Amyloid β -Protein Hypothesis

A characteristic pathological feature in the brains of AD patients is the presence of SPs. The main component of these plaques is A β , a peptide derived from the amyloid β -protein precursor (APP). Research has demonstrated that A β can induce neuron necrosis, apoptosis, and amyloidosis.⁸ A β primarily exists in two forms: A β 40 and A β 42. Although A β 42 constitutes less than 10% of total A β , it exhibits stronger toxicity and a greater propensity for deposition, leading to neurotoxicity.^{9–11} The proposed mechanism of A β neurotoxicity involves the formation of A β fibrils, which promote the production of intracellular free radicals. These radicals can damage organelles, membranes, and the cytoskeleton, potentially resulting in cell death.¹² Furthermore, studies have revealed that certain cell signaling pathways are closely associated with the pathological changes caused by amyloid β -protein deposits. These include the phospholipid-dependent protein kinase C (PKC) pathway, the cyclic adenylate-dependent protein kinase A (PKA) pathway, and the glycogen synthase kinase-3 (GSK-3) pathway. Notably, abnormalities in these pathways contribute to A β metabolism and Tau protein phosphorylation^{13–15} (Figure 1).

The Tau Protein Hypothesis

The adult human brain expresses six tau isoforms, comprising three isoforms with three microtubule-binding repeats (3R) and three with four repeats (4R).^{16,17} Aberrantly hyperphosphorylated tau protein exerts dual pathological effects. First, it aggregates to form NFTs. Second, it impairs microtubule assembly and stability due to reduced microtubule binding affinity, leading to structural abnormalities, neuronal dysfunction, and ultimately neuronal death.¹⁸ As a hallmark pathological feature of Alzheimer's disease, NFTs have been shown to demonstrate a stronger correlation with clinical disease severity than SPs across multiple studies.^{19,20}

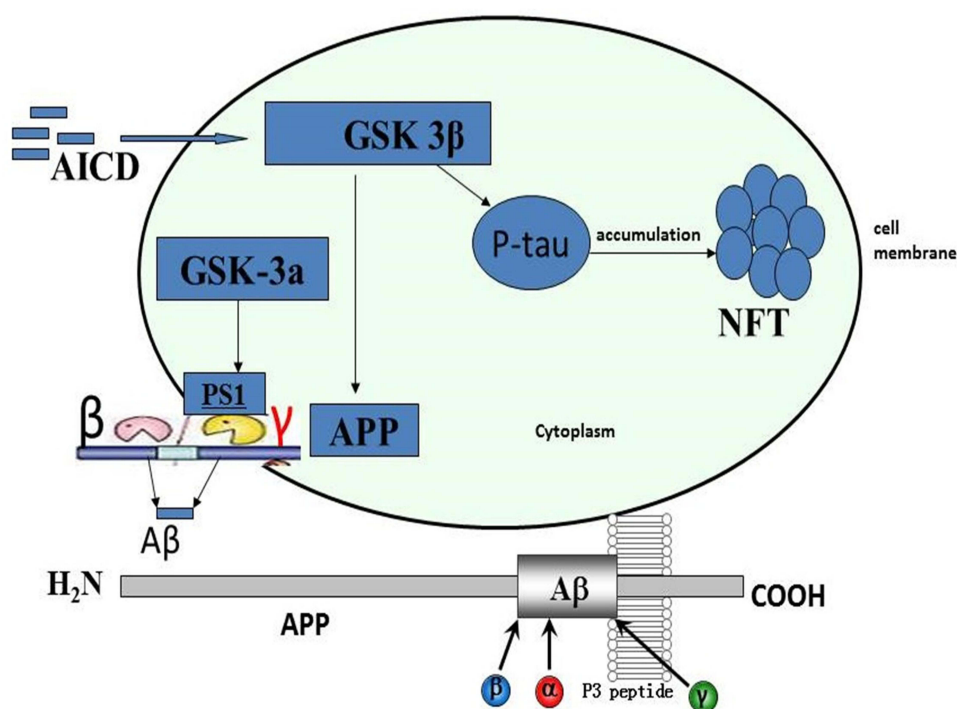


Figure 1 GSK-3 signaling pathway can simultaneously regulate A β production and Tau protein phosphorylation through a dual-channel mechanism.

Abbreviations: AICD, APP Intracellular Domain; GSK-3 β , Glycogen Synthase Kinase-3 β ; GSK-3 α , Glycogen Synthase Kinase-3 α ; P-tau, Phosphorylated Tau protein; PS1, Presenilin 1; APP, Amyloid β -Protein Precursor; A β , Amyloid β -protein; COOH, Carboxyl group.

The Cholinergic Mechanism Hypothesis

The cholinergic hypothesis proposes that AD originates from defects in brain neurotransmission, specifically involving damage to cholinergic neurons. This damage manifests as decreased activity of acetyl-cholinesterase (AChE) and choline acetyltransferase (ChAT), enzymes crucial for acetylcholine (ACh) metabolism. Consequently, ACh concentration diminishes, leading to reduced cholinergic activity. As ACh is essential for learning, memory, motor regulation, and sleep cycle control, its deficiency significantly contributes to cognitive impairment in AD patients.^{21–23}

The Inflammation Hypothesis

A β -mediated glial cell activation is a crucial factor in initiating the inflammatory response. Glial cells, which constitute the majority of cells in the central nervous system (CNS), interact extensively with neurons and immune cells.²⁴ Neuroinflammation is a hallmark of neurodegenerative diseases, characterized by its difficult-to-control nature and progressive deterioration into a chronic condition. Accumulating evidence suggests that the pathogenesis of AD extends beyond neuronal pathology, involving intricate interactions with the brain's immune mechanisms.^{25,26} Microglia, serving as the brain's immune sentinel cells, play a pivotal role in CNS immunity. These cells exhibit heightened activity in specific brain regions.²⁷ Upon activation, microglia release various immune and cytotoxic factors, including inflammatory cytokines (such as tumor necrosis factor- α (TNF- α) and nitric oxide (NO)), as well as reactive oxygen species.²⁸ Excessive production of these substances can lead to neuronal death. In addition to the aforementioned mechanisms, several other hypotheses have been proposed to explain AD pathogenesis, including those related to inflammation, oxidative stress, glutamate excitotoxicity, calcium metabolism disorders, and immune dysfunction.

Meanwhile, other novel disease-modifying therapies targeting A β have also made significant progress. For instance, lecanemab, a humanized monoclonal antibody that selectively targets A β fibrils, demonstrated in its pivotal Phase III clinical trial the ability to significantly clear amyloid plaques in the brain and, within 18 months, slowed the clinical decline of early Alzheimer's disease patients compared to the placebo by approximately 27%, bringing a clinically meaningful delay effect to patients. Donanemab, a monoclonal antibody targeting the N-terminal glutamylated form of

A β , also showed in its Phase III study that it can rapidly and significantly clear amyloid plaques and significantly slow down the cognitive and functional decline process in patients with early symptomatic AD. However, both of these antibody therapies have certain safety risks, among which amyloid protein-related imaging abnormalities is the most concerning adverse event. These advancements mark the continuous exploration of therapeutic strategies targeting the A β pathway, although they show potential in changing the disease course, the extent of their efficacy, long-term benefits, and safety management remain the key focuses of current research and clinical attention.

The Current Situation of AD Treatment and the Advantages of TCM Disadvantages in the Use of Treatment Involving Modern Western Medicine

European guidelines on AD treatment emphasize symptom management and delaying or preventing disease progression as key goals for evaluating treatment efficacy.²⁹ Globally, substantial financial resources are invested annually in developing AD treatments, with most targeting specific pathological mechanisms related to the disease. However, single-target therapies have shown limited efficacy, and to date, no drug has demonstrated significant effects in delaying disease progression or improving symptoms. Consequently, TCM, with its multi-component, multi-target, and multi-pathway approach, may offer a promising alternative for addressing this multifactorial disease with an unclear etiology and complex pathogenesis. The current clinical assessment mainly relies on a series of standardized cognitive and functional scales (such as the Mini-Mental State Examination MMSE, the Alzheimer's Disease Assessment Scale - Cognitive Part ADAS-Cog, the Clinical Dementia Rating CDR, etc), and given the common situation among elderly AD patients of taking multiple medications (polypharmacy), the safety, tolerability, and potential drug interactions of the treatment are crucial considerations in clinical decision-making.

TCM Has Its Own Advantages in the Intervention of Senile Dementia

In traditional Chinese medicine theory, “qi” can be understood as the functional energy that sustains life activities (vital energy or functional activity), “blood” represents the concrete material nourishment foundation (material nourishment), and “yin” and “yang” are the complementary principles that describe the relative states of bodily functions. For example, “yin” is associated with attributes such as nourishment, tranquility, and material storage, while “yang” is associated with attributes such as warmth, activity, and function promotion. In contrast to Western medicine, TCM has established distinct conceptual frameworks for understanding dementia through its unique diagnostic paradigm. Rooted in the foundational theories of the Huangdi Neijing, TCM attributes age-related cognitive decline to imbalances in vital substances (Qi, Blood, Yin, Yang) within the Five Zang organs - Heart, Liver, Spleen, Lung, and Kidney.³⁰ Contemporary research has highlighted TCM's emerging role in Alzheimer's disease intervention, particularly through its syndrome differentiation system. The TCM diagnostic protocol classifies senile dementia into five primary patterns: ① Kidney essence deficiency with marrow depletion; ② Yin deficiency of Heart and Liver; ③ Qi deficiency of Heart and Spleen; ④ Phlegm-turbidity clouding the orifices; and ⑤ Qi stagnation with blood stasis. Each syndrome manifests through specific symptom clusters quantified across three severity tiers (mild, moderate, severe). This diagnostic approach often integrates neurofunctional assessments, such as brain electrical activity mapping (BEAM), cerebral perfusion imaging, and cranial CT findings, complemented by biomarker analysis of cerebrospinal fluid acetylcholinesterase and tau protein levels.³¹ TCM formulations incorporate diverse medicinal materials with broad therapeutic indications, making them particularly suitable for managing diseases characterized by complex pathogenesis. There are several representative traditional Chinese medicines that have been used in clinical practice and have commercial formulations available in some countries or regions (Table 1). Although some clinical studies have shown that these formulations may have an improving effect on cognitive function, overall, high-quality, large-sample, long-term follow-up randomized controlled trials supporting their use for Alzheimer's disease are still relatively limited.

These formulations exhibit multi-component, multi-target mechanisms of action and demonstrate pleiotropic therapeutic effects. Given the multifactorial etiopathology of AD, TCM interventions offer distinct advantages through their capacity to simultaneously modulate multiple pathological pathways, as elaborated below.

Table 1 Overview of Some Traditional Chinese Medicine Formulations/Ingredients Used in Alzheimer's Disease Research and Their Main Effects

Traditional Chinese Medicine Formulations/Ingredients	Primary Components/Source	Mechanism of Action	Research Level
HS2 ³¹	Black Tiger Stem Extract	Reduce the mRNA levels of PS1 and BACE1, and decrease A β deposition	Preclinical research
EGb761 ^{32,33}	Ginkgo Leaf Extract	Affect the secondary structure of A β , inhibit the formation of β -sheet; promote the metabolism of α -secretase	Preclinical research and some clinical research
Morin ³⁴	Mulberry Leaf Extract	Inhibit the activity of GSK-3 β , reduce the excessive phosphorylation of Tau protein	Preclinical research
Nobiletin ³⁵	Citrus Peel Extract	Reduce oxidative stress, lower Tau protein phosphorylation	Preclinical research
Compound Zhizhi Powder ³⁶	Ginseng, Scutellaria, Acorus Tatarinowii, etc	Inhibit AChE activity, enhance ChAT activity, and increase the level of ACh in the brain	Preclinical research
Terandrine ³⁷	Pseudoephedrine	Inhibit the NF- κ B pathway, reduce the release of inflammatory factors	Preclinical research
Yokukansan ³⁸	Ginseng, Scutellaria, Acorus Tatarinowii, etc	Regulate neurotransmitters, anti-inflammatory, neuroprotection	Clinical research
Huperzine A ³⁹	Huperzine A	Reversible acetylcholinesterase inhibitor	Clinical research

Reducing the Deposition and Toxicity of A β

TCM demonstrates a multifaceted ability to reduce A β deposition and toxicity, reflecting the complex nature of A β -induced toxicity in AD. TCM and its active ingredients can delay AD progression through multiple mechanisms: interfering with A β production, promoting A β clearance, and preventing A β oligomer formation. For instance, HS2, a compound found in Kadsura Pepper Stem Extract, has been shown to reduce the mRNA levels of presenilin 1 (PS1) and β -site APP-cleaving enzyme (BACE1). Furthermore, HS2 decreased A β -induced senile plaques in the brain and improved learning and memory in a mouse model of AD.³¹ Additionally, EGb761, derived from Ginkgo biloba extract, can influence the secondary structure of A β . It chemically modifies the side chain of the A β 1-42 peptide, reducing the formation of β -sheet structures. This action inhibits A β aggregation and fibril formation.⁴⁰ Moreover, EGb761 has been shown to promote α -secretase metabolism, increase soluble APP (sAPP) production, and reduce A β and amyloid precursor protein (APP) levels.³²

Reducing Tau Protein Hyperphosphorylation

Aberrant phosphorylation of Tau protein, leading to neurotoxicity and NFT formation³³ is a key pathogenic mechanism in AD. Research by Gong et al demonstrated that Morin, a compound extracted from mulberry leaves, effectively inhibits the activity of glycogen synthase kinase-3 β (GSK-3 β), thereby reducing Tau protein hyperphosphorylation. Additionally, Morin mitigates A β toxicity and attenuates A β -induced Tau protein hyperphosphorylation.⁴¹ In a related study, Nakajima et al showed that nobiletin, extracted from tangerine peel, ameliorates age-related cognitive impairment, attenuates oxidative stress, and significantly reduces Tau protein phosphorylation in the senescence-accelerated mouse prone 8 (SAMP8) model.³⁴

Improving Neurotransmitter Function

Direct stimulation of muscarinic and nicotinic cholinergic receptors can improve cognitive function in AD patients. Fuzhisan, a Chinese herbal formula developed by De-Sheng Wang, consists of ginseng, Scutellaria baicalensis, Acorus tatarinowii, and other traditional Chinese herbs. Experimental studies have demonstrated that Fuzhisan can modulate the cholinergic system and improve cognitive function in mouse models of AD. Specifically, Fuzhisan was found to inhibit AChE activity, enhance ChAT activity, and increase ACh levels in the brain. These effects compensate for the loss of cholinergic neurons and the reduction in brain ACh content associated with AD, suggesting Fuzhisan's potential as a therapeutic intervention for the disease.³⁵

Reducing the Immune Inflammatory Response

AD may represent an immune inflammatory reaction caused by the excessive activation of immunoreactive cells in the central nervous system. Research suggests that drugs that inhibit or block central nervous system immune inflammation may play an important role in the prevention and treatment of AD. In a study by He et al, pretreatment of microglia with A β ³⁶ demonstrated that tetrandrine could reduce the A β -induced expression of interleukin-1 β , TNF- α , and phosphorylated NF- κ B p65. Their findings also showed that tetrandrine reduced the neurotoxicity of microglia while maintaining its neuroprotective effect. This research aligns with growing evidence indicating that neuroinflammation plays an essential role in the pathogenesis of AD.⁴² Astrocytes and microglia serve as the primary resident cells responsible for the brain's immune/inflammatory response.⁴³ In AD, misfolded and aggregated proteins can bind to microglia and astrocytes, triggering an innate immune response. This response is characterized by the release of inflammatory cytokines, ultimately leading to chronic neuro-inflammation and promoting AD progression.⁴⁴

Combining AD with Multiple Therapeutic Targets and Multiple Clinical Symptoms to Seek Statistical Methods for the TCM Efficacy Scale

TCM prescriptions often incorporate a variety of Chinese herbs. By integrating the complexity of TCM with advanced data analysis methods, researchers can evaluate the efficacy of TCM on different targets in AD using the “spectrum-effect relationship” approach. This methodology holds promise for effectively treating AD with TCM.

The spectrum-effect relationship approach has been widely applied in TCM research, including pharmacodynamic studies, drug compatibility assessments, processing technology improvements, and pharmacodynamic predictions. It has also been used to elucidate the pharmacodynamics and pharmacological mechanisms of both single herbs and herbal formulas in TCM.^{37,45} The validity of these data analysis methods significantly impacts the accuracy and reliability of spectrum-effect modeling. With the advent of big data technologies, an increasing number of spectrum-effect analyses have emerged. Therefore, the selection and application of appropriate data analysis algorithms are crucial for effective spectrum-effect modeling.

Artificial neural networks, grey relational analysis, and correlation analysis can all be employed to investigate the relationship between active ingredients and the pharmacological efficacy. These analytical methods enable the establishment of connections between the chromatographic profiles of TCM and the drug efficacy, thereby elucidating the pharmacodynamic properties of bioactive constituents. Through these approaches, researchers can quantify associations between specific components and the therapeutic outcomes and establish robust spectrum-effect relationships. However, precise identification of bioactive constituents requires advanced statistical modeling techniques, such as multiple linear regression analysis and partial least squares regression. Well-constructed regression models provide quantitative measures of individual components' contributions to overall pharmacological activity. This multi-component targeting approach is particularly valuable in addressing the complex pathological mechanisms associated with AD, where single-target therapies often prove inadequate. Integrating computational network pharmacology with multivariate statistical analysis allows for systematic evaluation of drug actions at both the organismal and molecular levels. This combined methodology not only accelerates drug discovery but also advances our understanding of TCM's fundamental principles, particularly regarding the mechanistic basis of herbal formula efficacy (Figure 2).

The workflow of spectral efficacy relationship analysis in the TCM-AD research is as follows: Firstly, the acquisition and standardization of chemical fingerprint profiles: Analyze multiple batches of compound Y extracts using techniques such as high-performance liquid chromatography (HPLC), obtaining their chromatographic fingerprints; After peak alignment, baseline correction, and normalization, a chemical feature matrix with samples as rows and the response of common chromatographic peaks as columns is formed. The second step, the definition and quantification of pharmacodynamic endpoints: Select indicators closely related to AD pathology as endpoints, such as quantifying the content of A β 42 in brain tissue homogenates by ELISA, or evaluating spatial learning and memory ability through behavioral tests (such as the Morris water maze), and standardizing all endpoint data. The third step, data integration and preprocessing: Connect the chemical feature matrix with the pharmacodynamic endpoint data, perform necessary centralization and scaling; Through coefficient of variation analysis or preliminary correlation screening, reduce the interference of noise

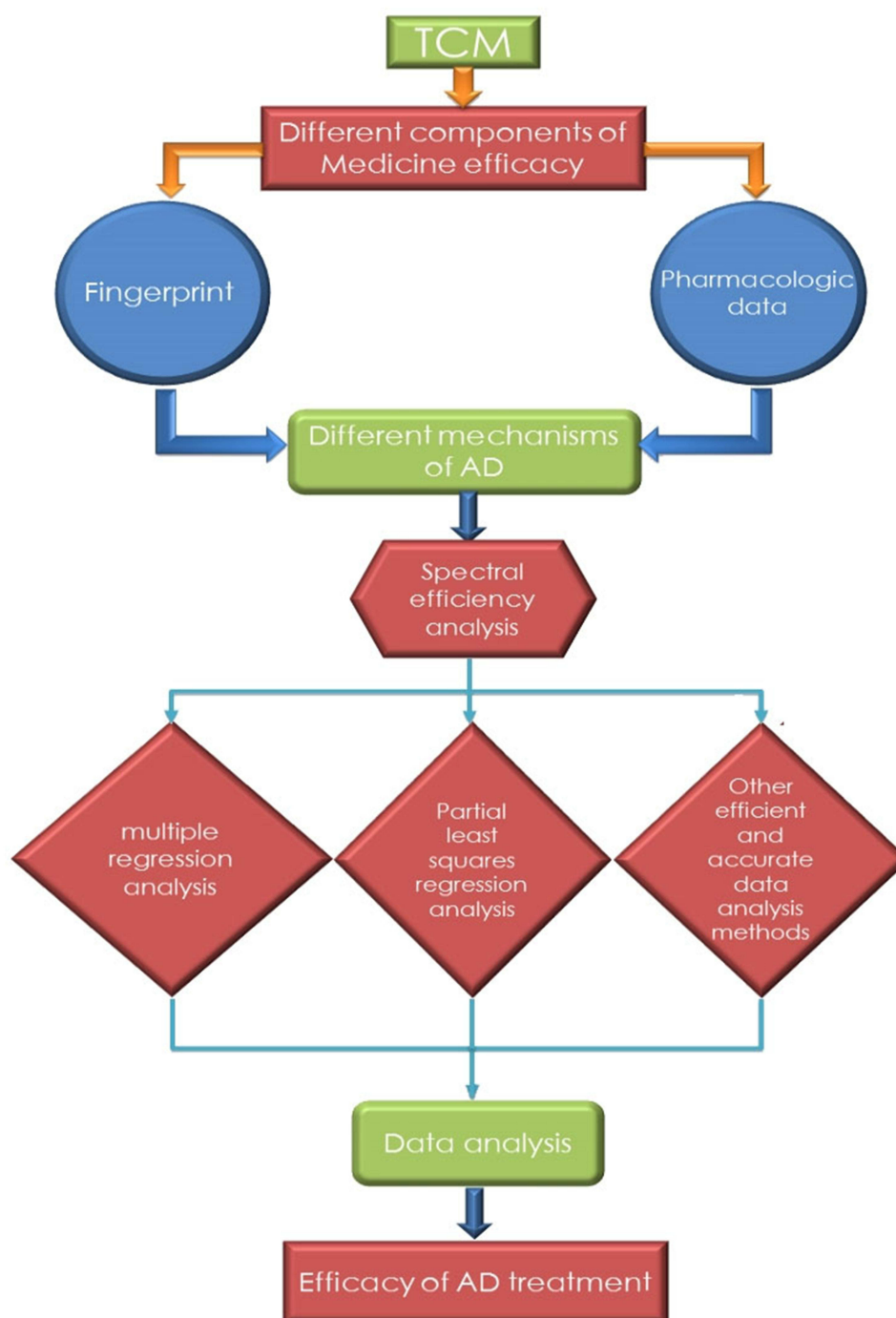


Figure 2 By combining the complexity of TCM with various data analysis methods, it is possible to evaluate the efficacy of different target therapies for AD by using the "spectrum-effect relationship" of TCM.

variables on modeling. The fourth step, multivariate statistical modeling: Use methods such as partial least squares regression (PLS-R) to establish a quantitative model between chromatographic peak intensity (X variable) and pharmacodynamic endpoints (Y variable). By calculating variable importance in projection (VIP) values, potential active chromatographic peaks that contribute significantly to the model can be identified. The fifth step, model validation and overfitting prevention: To ensure the reliability and generalization ability of the model, a strict validation process must be carried out: (1) Determine the optimal latent variable number using k-fold cross-validation to prevent overfitting due to

excessive variables; (2) Divide the data into training set and independent test set, use the training set to build the model, and evaluate its external predictive performance (such as calculating the root mean square error of prediction RMSEP) on the test set; (3) Conduct permutation tests, repeat modeling by randomly shuffling the pharmacodynamic data to confirm that the significance of the original model is superior to random results. The sixth step, model interpretation and biological association: The final model not only can predict efficacy but also can reveal positive or negative associations between key chromatographic peaks and efficacy through loadings plots, regression coefficients, etc. These key peaks can be linked to specific compounds through subsequent mass spectrometry identification, thereby linking statistical analysis results with potential biological mechanisms (such as inhibiting A β aggregation or reducing neuroinflammation), achieving a systematic interpretation from chemical fingerprints to biological activity.^{38,39}

Summary

AD arises from complex interactions within biological networks, not from a single gene or protein. Dysfunction in these networks leads to abnormalities at multiple levels, including genes, proteins, organelles, cells, neurotransmitters, and the cellular environment. Western medicine's single-target approach to AD treatment has shown limited efficacy. In contrast, TCM compounds, with their complex compositions and diverse effects, can act on multiple levels through various mechanisms. Currently, our understanding of TCM's efficacy is multifaceted, largely due to varying perspectives on its material basis, research objectives, academic backgrounds, and methodologies. Therefore, it is crucial to identify chemical components that correlate with clinical efficacy, embody TCM's multi-component, multi-target approach, and enable the study of AD from multiple angles. This will provide a more effective and reliable foundation for AD treatment strategies.

The core of establishing a spectrum-effect relationship lies in mapping the chemical fingerprint of TCM to its pharmacology and clinical efficacy. Given the complexity of TCM components and the diverse hypotheses regarding AD mechanisms, numerous interactions may exist between multiple factors, necessitating multidimensional data analysis. In the era of big data, life sciences face the challenge of enhancing the efficiency and rigor of research. A significant challenge in studying TCM's efficacy in AD treatment is the need to identify active ingredients, elucidate their pharmacodynamic properties, establish robust spectrum-effect relationships, and explore potential mechanisms of action. To facilitate this, we propose the creation of a comprehensive database where researchers can upload pharmacological and pharmacodynamic data. Statistical analysis experts could then access this data to investigate TCM pharmacodynamics and develop new treatments for various diseases using efficient and accurate data analysis methods. The application of such methods will undoubtedly accelerate TCM research in AD and related fields.

In conclusion, the multi-component and multi-target treatment strategies of traditional Chinese medicine offer a promising perspective for addressing the complex pathological mechanisms of Alzheimer's disease. The development of methods such as spectral efficacy relationships and stoichiometry provides feasible paths for scientifically explaining its mechanism of action. However, it is also necessary to be aware that there are still some key challenges in this field at present: First, most high-level clinical evidence for the intervention of traditional Chinese medicine is still insufficient lacking large-scale, long-term, and well-designed clinical trial data support; Second, in the context of elderly patients and the use of multiple drugs simultaneously, the long-term safety, adverse reaction monitoring, and interactions between traditional Chinese medicine and conventional Western medicine have not been fully and systematically evaluated. Therefore, future research should not only promote high-quality clinical validation but also attach great importance to safety evaluation in the real world and rational drug use guidance, so as to provide a safer, more effective, and more scalable integrated treatment plan combining traditional Chinese and Western medicine for Alzheimer's disease.⁴⁶

The evidence summarized in this review indicates that various traditional Chinese medicines and their active components have demonstrated the potential to intervene in AD through multiple pathways such as regulating A β metabolism, Tau phosphorylation, cholinergic system, and neuroinflammation in preclinical studies. At the same time, we objectively point out that translating these findings into confirmed clinical benefits still requires more rigorous large-scale clinical trials that measure with consensus clinical endpoints (such as ADAS-Cog, CDR-SB) to verify.

Disclosure

The authors report no conflicts of interest in this work.

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