Contents lists available at ScienceDirect

Digital Chinese Medicine

journal homepage: http://www.keaipublishing.com/dcmed

# Herbal remedies for Alzheimer's disease: neuroprotective mechanisms and cognitive enhancement potential

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ARTICLE INFO

*Article history*
Received 06 March 2025
Accepted 17 May 2025
Available online 25 June 2025

*Keywords*
Alzheimer's disease
Neuroprotective mechanisms
Medicinal plants
Phytochemicals
Oxidative stress

ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative condition characterized by memory loss and cognitive decline. Current drugs offer limited benefits and often cause side effects. Recently, interest has grown in medicinal plants for the treatment of AD due to their neuroprotective compounds. This review explores how herbal remedies may help AD, focusing on key plants including *Ginkgo biloba*, *Curcuma longa*, *Withania somnifera*, and *Panax ginseng*. These plants show promise in reducing inflammation, oxidative stress, and amyloid buildup. Their bioactive compounds, including flavonoids and alkaloids, may promote memory and slow AD progression. Despite these promising findings, the review also highlights significant challenges in translating preclinical success into clinical efficacy. Issues such as variability in plant composition, lack of standardized formulations, insufficient large-scale clinical trials, and regulatory hurdles continue to impede the integration of herbal therapies into mainstream AD treatment. Addressing these challenges through rigorous scientific validation and standardized protocols is essential for advancing the use of herbal medicine in neurodegenerative disease management.

## 1 Introduction

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disorder, predominantly affecting cognitive processes such as memory, attention, and executive function. As the most prevalent etiology of dementia globally, AD represents a critical and escalating public health challenge, particularly given the demographic shift toward an aging population [1]. Pathologically, AD is characterized by the deposition of extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein [2]. These neurotoxic aggregates lead to widespread neuronal damage and synaptic loss, resulting in a gradual decline in cognitive function and the ability to perform daily activities. This progressive degeneration ultimately causes severe cognitive impairment, greatly diminishing the quality of life for both patients and caregivers [3].

Despite several decades of intensive research into potential therapeutic interventions, the pharmacological management of AD remains suboptimal. Current treatment strategies, which are primarily based on acetylcholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists, offer limited symptomatic relief and fail to halt or reverse disease progression [4]. Moreover, these therapeutic agents are often associated

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Peer review under the responsibility of Hunan University of Chinese Medicine.

DOI: 10.1016/j.dcmed.2025.05.002
**Citation:** KIRUBAKARAN D. Herbal remedies for Alzheimer's disease: neuroprotective mechanisms and cognitive enhancement potential. Digital Chinese Medicine, 2025, 8(2): 183-195.

with notable side effects, such as gastrointestinal distress and cardiovascular complications, which further emphasize the need for novel, more effective, and safer treatment modalities. Consequently, there is an increasing demand for alternative and adjunctive therapeutic approaches that not only alleviate symptoms but also target the underlying pathophysiological mechanisms of AD more comprehensively and sustainably [5].

Recent research has considerably shifted focus to exploring the neuropharmacological potential of medicinal plants, which possess diverse bioactive compounds with antioxidant, anti-inflammatory, and neuroprotective properties [6]. Several herbal remedies have been shown to have the ability to modulate key molecular pathways involved in AD, including oxidative stress, neuroinflammation, cholinergic dysfunction, and the accumulation of misfolded proteins [7]. Specific herbs, such as *Ginkgo biloba*, *Bacopa monnieri*, *Curcuma longa*, *Withania somnifera*, and *Rosmarinus officinalis*, have garnered considerable attention due to their cognitive-enhancing effects and neuroprotective capabilities. Several herbal remedies show promise in supporting cognitive function in AD [8, 9].

This review aims to provide an exhaustive evaluation of the medicinal herbs that have been systematically studied for their therapeutic potential in AD. By critically examining their mechanisms of action, preclinical and clinical evidence, pharmacokinetic profiles, and safety considerations, this article seeks to offer a nuanced perspective on the feasibility of integrating herbal remedies as adjuncts into conventional pharmacological treatments [10, 11]. Additionally, the review outlines specific directions for future research, stressing the need for rigorous randomized controlled trials (RCTs) to establish standardized dosages, formulations, and long-term safety profiles of these herbal interventions. A comprehensive understanding of the synergistic effects between herbal remedies and existing pharmacotherapies could provide a more holistic and sustainable approach to managing AD in clinical practice [12].

## 2 Herbal plants targeted for AD treatment

Recent clinical and preclinical studies have identified several herbal remedies as promising candidates for the treatment of AD. These herbs are thought to exert therapeutic effects through multiple mechanisms, including reducing oxidative stress, inhibiting neuroinflammation, promoting neurogenesis, and modulating neurotransmitter systems [13]. The therapeutic potential of these herbs for AD treatment is summarized in Table 1 and Figure 1 (all figures in this article were created using BioRender.com).

### 2.1 *Ginkgo biloba*

*Ginkgo biloba*, a plant with a long history of use in traditional Chinese medicine, has become one of the most explored herbs for cognitive health. Its therapeutic effects are primarily attributed to its antioxidant and anti-inflammatory properties [14]. It contains bioactive

**Table 1** Herbal remedies for the treatment of AD

| Herb | Bioactive compound | Mechanism | Therapeutic use | Reference |
|---|---|---|---|---|
| *Panax ginseng* | Ginsenosides | Enhances energy, reduces fatigue | Fatigue, stress reduction | [13] |
| *Lavandula angustifolia* | Linalool, linalyl acetate | Modulates GABA receptors | Anxiety, headaches | [13] |
| *Echinacea purpurea* | Alkamides, echinacosides | Stimulates immune response | Colds, respiratory infections | [14] |
| *Mentha piperita* | Menthol | Relaxes smooth muscles | Digestive issues | [13, 14] |
| *Ginkgo biloba* | Flavonoids, terpenoids | Enhances blood flow, antioxidant effects | Memory, cognitive enhancement | [15] |
| *Curcuma longa* | Curcumin | Anti-inflammatory, antioxidant | Joint pain, inflammation | [16, 17] |
| *Allium sativum* | Allicin | Antibacterial, antiviral | Cardiovascular health | [17] |
| *Withania somnifera* | Withanolides | Modulates cortisol, adaptogenic | Stress, anxiety management | [18] |
| *Hypericum perforatum* | Hypericin | Inhibits neurotransmitter reuptake | Depression, mood disorders | [18, 19] |
| *Bacopa monnieri* | Bacosides | Modulates neurotransmitters | Memory enhancement | [20] |
| *Matricaria chamomilla* | Apigenin, bisabolol | Binds benzodiazepine receptors | Anxiety, sleep disorders | [21] |
| *Silybum marianum* | Silymarin | Antioxidant, hepatoprotective | Liver health | [20, 21] |
| *Aloe barbadensis* | Acemannan, anthraquinones | Promotes wound healing | Skin care | [20, 21] |
| *Ocimum sanctum* | Eugenol, ursolic acid | Modulates stress response | Stress relief | [22, 23] |
| *Rhodiola rosea* | Rosavins, salidroside | Adaptogenic, reduces stress | Fatigue, cognitive support | [24, 25] |
| *Valeriana officinalis* | Valerenic acid | Increases brain activity | Insomnia, anxiety | [26, 27] |
| *Cinnamomum verum* | Cinnamaldehyde | Improves insulin sensitivity | Blood sugar regulation | [28, 29] |
| *Salvia officinalis* | Rosmarinic acid, flavonoids | Modulates acetylcholine | Cognitive improvement | [30, 31] |
| *Huperzia serrata* | Huperzine A | Inhibits acetyl cholinesterase | Cognitive enhancer | [32, 33] |

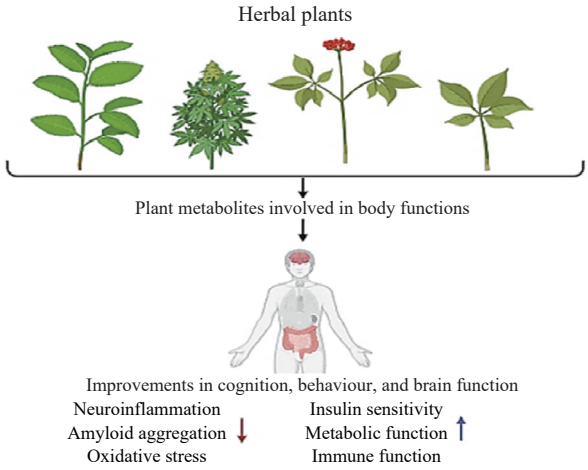


**Figure 1** Herbal plants target the treatment of AD

flavonoids and terpenoids that help protect neurons from oxidative damage and reduce neuroinflammation, which is crucial in AD pathology. One of its primary mechanisms of action is the inhibition of platelet-activating factor (PAF), which improves cerebral blood flow, ensuring better oxygen and nutrient delivery to neurons. Clinical findings on its efficacy in AD have yielded mixed results [15]. Recent improvements in memory, attention, and daily functioning among AD patients suggest that *Ginkgo biloba* may offer modest cognitive benefits. However, other clinical trials have not consistently shown significant improvements, emphasizing the need for more rigorous, large-scale studies to determine the herb's true effectiveness and therapeutic role in AD treatment. Despite these mixed results, *Ginkgo biloba* remains of interest due to its neuroprotective properties and potential to enhance cerebral blood flow [16].

### 2.2 *Curcuma longa*

*Curcuma longa*, commonly known as turmeric, has gained substantial attention in the context of AD due to its active compound, curcumin, which possesses powerful anti-inflammatory and antioxidant properties [17]. The effects of curcumin on AD are multifaceted: it not only helps to reduce amyloid plaque accumulation by modulating the enzymes responsible for Aβ formation but also acts as a potent free radical scavenger, thereby reducing oxidative stress and neuronal damage [18]. Furthermore, curcumin affects critical signalling pathways involved in neuroinflammation and neuronal survival, including the nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, increasing its neuroprotective capacity. Preclinical studies suggest curcumin can reduce amyloid plaque load, promote neurogenesis, and modulate inflammatory responses in the brain. However, the low bioavailability of curcumin, which means that only a small portion of the compound reaches the brain when administered orally, remains a considerable challenge for its widespread clinical use [19].

### 2.3 *Bacopa monnieri*

*Bacopa monnieri*, also known as Brahmi, is a revered herb in Ayurvedic medicine, which is used primarily to strengthen memory and cognitive function. The herbs primary bioactive compounds, bacosides, are thought to improve neurotransmission, particularly by enhancing acetylcholine signaling, a neurotransmitter crucial for memory and learning. *Bacopa monnieri* also indicates strong antioxidant properties that protect neurons from oxidative damage, a key contributor to the progression of AD [20]. Clinical trials have demonstrated that *Bacopa monnieri* can significantly improve memory, attention, and cognitive performance in both healthy individuals and those experiencing cognitive decline. In patients with AD, *Bacopa monnieri* has been shown to reduce anxiety and enhance cognitive function. Preclinical studies further support its neuroprotective role, particularly against oxidative stress induced neuronal damage. Collectively, these findings underscore *Bacopa monnieri* potential as a therapeutic agent in the management of AD [21, 22].

### 2.4 *Withania somnifera*

*Withania somnifera*, which is commonly known as ashwagandha, is an adaptogenic herb traditionally used in Ayurvedic medicine for its stress-reducing and general health-promoting properties. Recent study has highlighted its neuroprotective potential in AD [23]. The primary mechanism of ashwagandha in AD is linked to its modulation of stress hormones, especially cortisol, which exhibits elevated levels in neurodegenerative conditions. By reducing chronic stress, ashwagandha may lower neuroinflammation, a key contributor to the progression of AD [24]. In addition to modulating stress responses, ashwagandha demonstrates potent antioxidant properties, which protect neurons from oxidative damage and promote neurogenesis. Animal studies have demonstrated that ashwagandha can reduce cognitive decline, improve memory, and prevent stress-induced brain damage. While human studies are still limited, preliminary data suggest that ashwagandha may enhance memory and support cognitive function in aging individuals, making it a promising candidate for the treatment of AD [25].

### 2.5 *Rosmarinus officinalis*

*Rosmarinus officinalis* (rosemary) is a commonly used culinary herb that has gained attention for its potential cognitive enhancing properties. It contains rosmarinic acid, a bioactive compound with both antioxidant and anti-inflammatory effects [26]. Rosmarinic acid has been shown to protect neurons from oxidative stress and reduce inflammation in the brain, two critical factors involved in AD. Moreover, rosemary may improve blood

circulation to the brain, further supporting cognitive function and protecting against neurodegeneration. Preliminary studies suggest that rosemary may enhance memory and concentration. One study indicated that inhaling rosemary essential oil improved cognitive performance in healthy individuals, although further clinical research is needed to establish its efficacy in patients of AD [27, 28].

### 2.6 *Salvia officinalis*

*Salvia officinalis* (sage) is another herb known for its memory enhancing effects and has been used in traditional medicine for centuries. Its effectiveness in AD is largely attributed to its ability to inhibit acetyl cholinesterase, the enzyme responsible for breaking down acetylcholine [29, 30]. Acetylcholine is a neurotransmitter that plays a vital role in memory and learning, and its depletion is a hallmark of AD. By preventing the breakdown of acetylcholine, sage plays a beneficial role in increasing acetylcholine levels in the brain, thus enhancing cognitive function [31, 32]. Clinical trials have shown that sage can significantly improve memory and cognitive performance in individuals with mild to moderate AD, with some studies also demonstrating a reduction in behavioral symptoms. The acetylcholinesterase inhibition of sage and cognitive enhancing properties make it a valuable herb in treating AD [33].

## 3 Mechanisms of herbal remedies in AD

Herbal remedies have been employed in traditional medicine for centuries, owing to their therapeutic potential in managing various health conditions, including neurodegenerative diseases such as AD [34]. Recent study has elucidated the multifaceted mechanisms through which specific herbs exert neuroprotective and cognitive enhancing effects, providing promising adjunctive strategies for AD management [35]. AD, a progressive neurodegenerative disorder, is characterized by multiple intertwined pathogenic processes that contribute to cognitive decline, memory loss, and behavioral changes. These include the accumulation of neurotoxic proteins, oxidative stress, chronic neuroinflammation, and disturbances in neurotransmitter systems [36]. The interaction between these mechanisms plays a central role in the pathophysiology of AD, leading to synaptic dysfunction, neuronal loss, and cognitive impairments (Figure 2 and Table 2).

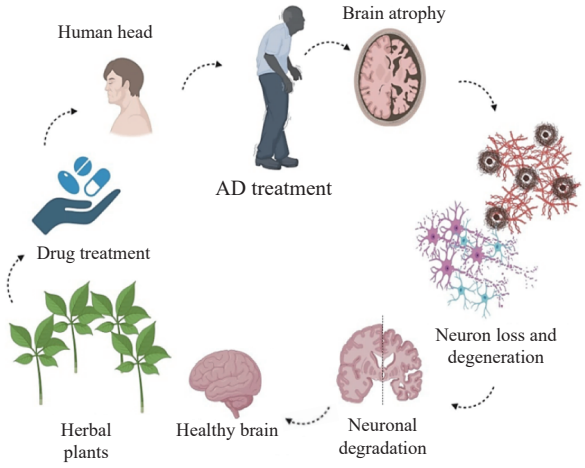


**Figure 2** Overview of the pathophysiological mechanisms in AD and its herbal treatment

**Table 2** Pathophysiological features of AD and their role in cognitive mechanisms

| Feature | Description | Mechanism | Reference |
|---|---|---|---|
| Amyloid plaques | Extracellular Aβ deposits | Accumulation and aggregation between neurons | [34, 35] |
| Tau tangles | Intracellular tangles | Tau protein abnormalities | [36, 37] |
| Neuroinflammation | Activation of microglia | Triggered by amyloid plaques and tau tangles | [38] |
| Neuronal death | Neuron loss in critical brain areas | Induced by amyloid plaques | [39] |
| Synaptic dysfunction | Loss of synaptic connections | Impaired synaptic signalling | [40] |
| Cholinergic dysfunction | Reduced brain acetylcholine | Loss of basal forebrain cholinergic neurons | [41] |
| Vascular changes | Blood-brain barrier disruption | Vascular dysfunction contributes to amyloid build-up | [42, 43] |
| Genetic factors | Presence of genetic risk variants | Promotes amyloid plaque formation | [44-46] |
| Mitochondrial dysfunction | Impaired energy metabolism | Leads to oxidative stress and neuronal damage | [47-49] |

### 3.1 Amyloid plaques and herbal modulation

A defining feature of AD is the accumulation of amyloid-beta plaques in the brain, which are derived from the amyloid precursor protein (APP) through enzymatic cleavage (Figure 3). Under normal conditions, Aβ is typically cleared from the brain, but in AD, it aggregates into insoluble plaques that disrupt synaptic communication and induce neurotoxicity [37]. These plaques activate microglial cells, triggering a cascade of inflammatory responses that further damage neurons and accelerate disease progression. Herbal remedies, such as *Curcuma longa* and *Ginkgo biloba*, have indicated the potential in inhibiting Aβ aggregation, thereby preventing plaque formation [38]. *Curcuma longa*, with its active compound curcumin, has demonstrated the ability to disrupt Aβ fibril

formation and facilitate its clearance from the brain. Similarly, *Ginkgo biloba* has been shown to exhibit Aβ modifying activity, contributing to the reduction of amyloid plaque burden and offering neuroprotective benefits for patients with AD [39].

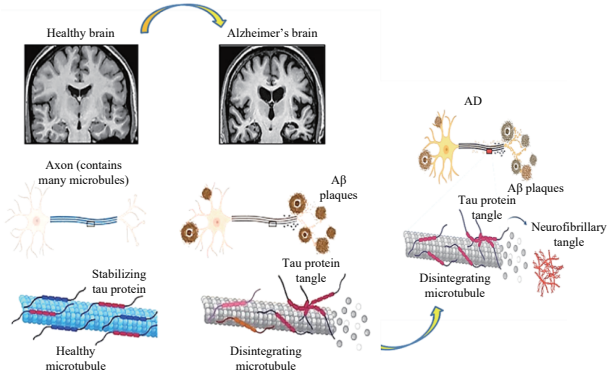


**Figure 3** General mechanisms involved in the pathology of AD

### 3.2 Hyperphosphorylation and neurofibrillary tangles

Another hallmark of AD is the accumulation of NFTs, which are primarily composed of hyperphosphorylated tau protein (Figure 4). Tau, a microtubule-associated protein, stabilizes neuronal microtubules and supports intracellular transport. In AD, tau undergoes abnormal phosphorylation, causing detachment from microtubules and the formation of insoluble tangles that disrupt neuronal function [40]. This process impairs intracellular transport mechanisms, which results in neuronal dysfunction and ultimately contributes to neuronal death. Herbal compounds, such as those derived from *Withania somnifera* (ashwagandha), have been shown to modulate tau phosphorylation. *Withanolides*, the active constituents in ashwagandha, may help reduce tau hyperphosphorylation, thereby preventing tangle formation and preserving microtubule stability [41].

Chronic neuroinflammation is a considerable factor

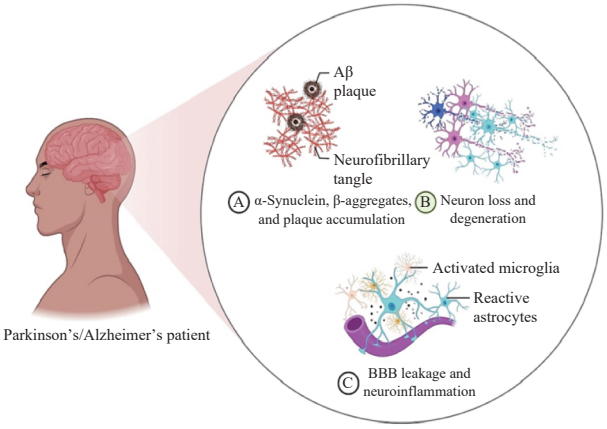


**Figure 4** Hyperphosphorylation and neurofibrillary tangle formation in an AD

BBB, blood brain barrier.

in the development and progression of AD (Figure 5). Normally, microglia and astrocytes in the brain play key roles in immune defense and maintaining neuronal homeostasis [42]. However, in AD, these glial cells become overactivated, leading to the excessive release of inflammatory cytokines, reactive oxygen species (ROS), and other cytotoxic molecules [43]. This persistent inflammation exacerbates neuronal injury, impairs synaptic function, and accelerates the accumulation of Aβ and tau aggregates. Herbal remedies with anti-inflammatory properties, such as *Curcuma longa* (turmeric), *Withania somnifera* (ashwagandha), and *Rosmarinus officinalis* (rosemary), have demonstrated the ability to modulate neuroinflammatory pathways [44]. Curcumin, the active compound in *Curcuma longa*, inhibits the NF-κB signalling pathway, a central regulator of inflammatory gene expression. Similarly, withanolides in *Withania somnifera* have indicated potential in reducing cytokine levels and suppressing the activation of pro-inflammatory enzymes, thus mitigating neuroinflammation and offering neuroprotective effects [45].

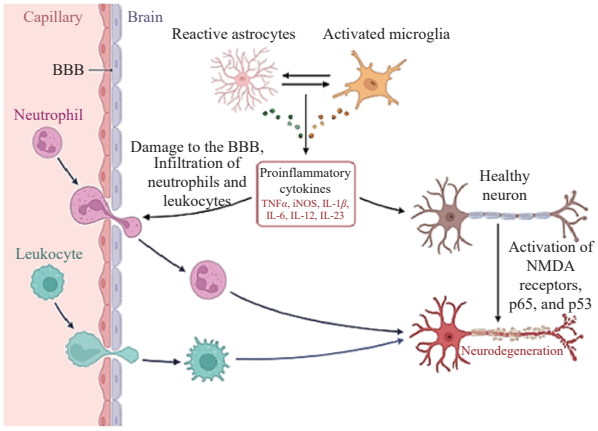


**Figure 5** Roles of astrocytes and microglia in neurodegeneration

### 3.3 Oxidative stress and antioxidant mechanisms

Oxidative stress is another critical factor causing neuronal damage in AD. The brain, with its high metabolic rate and abundance of polyunsaturated fatty acids, is highly vulnerable to oxidative damage [46]. Free radicals, such as ROS, can induce lipid peroxidation, protein damage, and DNA damage, all of which contribute to the pathogenesis of AD [47]. Herbal remedies, which are rich in antioxidant compounds, such as *Curcuma longa* (curcumin) and *Bacopa monnieri* (bacopa), can neutralize free radicals and restore the balance between oxidants and antioxidants [48]. These herbs demonstrate potent antioxidant activities, scavenging ROS, and reducing the oxidative damage that brings about the formation of amyloid plaques and tau tangles. By enhancing the brain's endogenous antioxidant defense, herbal compounds may

aid in alleviating oxidative stress, offering a neuroprotective effect that may slow the progression of AD [49].

### 3.4 Specific mechanisms of herbal remedies in AD

As a progressive neurodegenerative disorder, AD is featured with extracellular deposition of Aβ plaques, intracellular NFTs composed of hyperphosphorylated tau protein, synaptic degeneration, and sustained neuroinflammation [50] (Figure 6 and 7). Herbal remedies, those rooted in traditional medicinal systems such as Ayurveda, traditional Chinese medicine (TCM), and Kampo in particular, have gained increasing attention due to their pleiotropic biological activities, lower adverse effect profiles, and long-standing ethno pharmacological use [51].

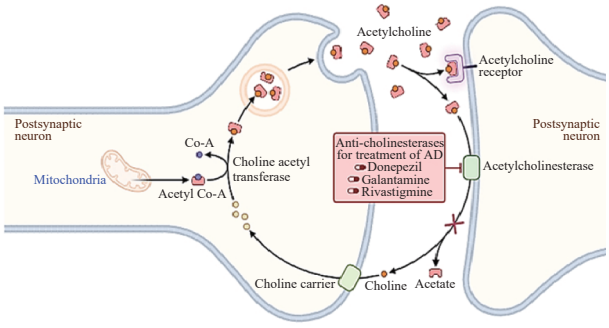


**Figure 6** Anti-cholinesterase mechanism in AD

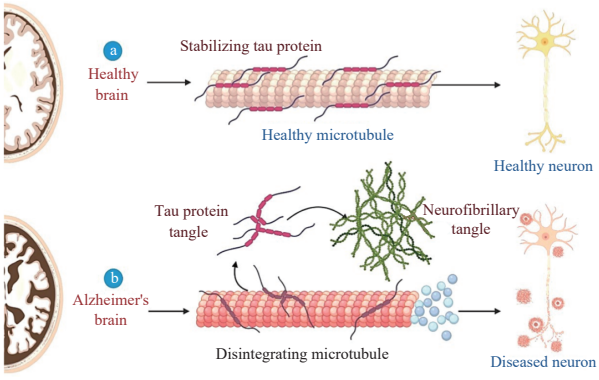


**Figure 7** Brain mechanisms in AD

**3.4.1 Inhibition of Aβ aggregation and promotion of clearance** One of the central pathogenic features of AD is the accumulation of neurotoxic Aβ oligomers and plaques, which were primarily derived from APP through sequential cleavage by β-secretase (BACE1) and γ-secretase. Several herbal compounds have demonstrated efficacy in disrupting Aβ production, aggregation, and deposition [52]. Curcumin, a polyphenol from *Curcuma longa*, exhibits a high binding affinity for Aβ aggregates and disrupts β-sheet-rich fibril structures, facilitating microglial-mediated phagocytosis of plaques. Ginsenosides derived from *Panax ginseng* reduce Aβ generation by modulating secretase activity and promoting non-amyloidogenic APP processing via α-secretase. Likewise, epigallocatechin-3-gallate (EGCG), a catechin from *Camellia sinensis* (green tea), inhibits Aβ oligomerization and boosts clearance through proteasomal and autophagic pathways in preclinical AD models [53].

**3.4.2 Tau protein stabilization and anti-hyperphosphorylation** Intraneuronal accumulation of hyperphosphorylated tau disrupts microtubule stability, impairs axonal transport, and forms NFTs. Herbal bioactives have shown potential in modulating tau phosphorylation and stabilizing cytoskeletal dynamics [54]. Baicalin, a flavone glycoside from *Scutellaria baicalensis*, and withanolides derived from *Withania somnifera* (ashwagandha) attenuate tau hyperphosphorylation by inhibiting the activity of tau kinases such as glycogen synthase kinase (GSK)-3β and cyclin-dependent kinase 5 (CDK5). These compounds also upregulate phosphatases including PP2A, which restore the physiological phosphorylation state of tau and preserve neuronal microtubule integrity [55].

**3.4.3 Antioxidant activity and redox homeostasis** Oxidative stress plays a pivotal role in AD pathogenesis by inducing lipid peroxidation, protein oxidation, and mitochondrial dysfunction. Herbal antioxidants act both as direct free radical scavengers and modulators of redox-sensitive transcription factors [56]. Resveratrol derived from *Vitis vinifera*, rosemary extract derived from *Rosmarinus officinalis*, and EGb761, a standardized extract of *Ginkgo biloba* activate the nuclear factor erythroid 2-related factor 2 (Nrf2) signalling pathway. This leads to upregulation of phase II detoxifying and antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase, hence mitigating oxidative neuronal injury and supporting mitochondrial function [57].

**3.4.4 Anti-inflammatory and immunomodulatory effects** Chronic neuroinflammation, mediated by overactivated microglia and astrocytes, exacerbates AD pathology through the sustained release of inflammatory cytokines and reactive species. Herbal agents such as curcumin, glycyrrhizin from *Glycyrrhiza glabra* and ginsenosides suppress neuroinflammation by inhibiting key inflammatory transcription factors, including NF-κB and MAPKs. These compounds reduce the expression of pro-inflammatory mediators such as interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and inducible nitric oxide synthase (iNOS), thus preserving neuronal viability and function [58].

**3.4.5 Enhancement of cholinergic neurotransmission** Deficits in cholinergic neurotransmission, primarily owing to the degeneration of basal forebrain cholinergic neurons and decreased levels of acetylcholine (ACh), are closely associated with cognitive impairment in AD. Huperzine A, a naturally occurring alkaloid from *Huperzia*

*serrata*, is a potent, reversible acetylcholinesterase (AChE) inhibitor that increases synaptic ACh concentration. In addition, *Bacopa monnieri* facilitates cholinergic function by upregulating choline acetyltransferase (ChAT) and reducing oxidative stress in cholinergic neurons, supporting cognitive processes such as learning and memory [59].

**3.4.6 Promotion of neurogenesis and synaptic plasticity** Cognitive resilience in AD is closely linked to neurogenesis and synaptic plasticity, especially in the hippocampus. *Withania somnifera* has been shown to promote neurite outgrowth, dendritic branching, and synaptic density. Likewise, *Centella asiatica* (gotu kola) stimulates neuronal regeneration and synaptic connectivity by increasing the expression of brain-derived neurotrophic factor (BDNF) and other neurotrophic factors. These effects contribute to improved long-term potentiation (LTP) and synaptic signalling, which is critical for memory consolidation [60].

**3.4.7 Mitochondrial protection and enhancement of energy metabolism** Mitochondrial dysfunction and impaired bioenergetics are early events in AD, promoting synaptic degeneration and neuronal apoptosis. Herbal compounds, such as salvianolic acid B from *Salvia miltiorrhiza,* preserve mitochondrial membrane potential, improve ATP synthesis, and inhibit cytochrome c release. These effects strengthen mitochondrial resilience to oxidative stress and prevent caspase-mediated apoptotic pathways, supporting neuronal survival and metabolic homeostasis [61].

## 4 Future directions and challenges

### 4.1 The need for more rigorous clinical trials to validate efficacy

To advance the use of herbal remedies in the treatment of AD, it is essential to conduct more comprehensive clinical trials, as shown in Table 3. Although preclinical studies and some smaller clinical trials have indicated promising results, the overall evidence supporting these herbal treatments remains limited [62]. These trials should evaluate the effectiveness of herbal remedies across diverse patient populations and various stages of the disease. Given the progressive nature of AD, it is important to assess the long-term impact of these treatments, as extended follow-up periods will provide valuable insights into their potential to slow disease progression or raise quality of life. Additionally, future studies should incorporate biomarkers, such as brain imaging, genetic markers, and protein levels, to obtain a more precise understanding of how herbal remedies affect AD at the molecular and cellular levels [63, 64].

**Table 3** Challenges and limitations in AD diagnosis and herbal treatment

| Category | Challenge/limitation | Reference |
|---|---|---|
| Diagnosis | Early detection is difficult in biomarkers and imaging are costly | [62-64] |
| Understanding | Incomplete knowledge in disease progression varies | [65-68] |
| Treatment options | Treatments are symptomatic of potential side effects | [68-71] |
| Research | Limited animal models in the lack of large-scale trial resources | [72-75] |
| Caregiving | High caregiver burden of need for specialized care | [76-78] |
| Awareness & education | Mental health stigma in low public awareness | [79-83] |
| Technology | Low use of assistive technologies | [84-88] |
| Social impact | Disruption of relationships and daily life | [89-94] |

A major challenge with herbal remedy in the treatment of AD is the low bioavailability of many active compounds. For instance, curcumin from turmeric and bacosides from *Bacopa monnieri* are often poorly absorbed by the body, which limits their therapeutic efficacy. To overcome this limitation, it is crucial to develop more bioavailable formulations [65]. Innovations such as nanoparticles and nanoemulsions can enhance the solubility and absorption of herbal compounds, making them more readily available for therapeutic use [66]. These advanced formulations can slow the metabolic breakdown of active compounds, thereby prolonging their circulation in the bloodstream. This extended bioavailability enhances their neuroprotective efficacy, which may translate into improved clinical outcomes for AD. Ultimately, such strategies could maximize the therapeutic potential of herbal remedies against AD [67].

Exploring combined therapies that pair herbal remedies with conventional pharmaceutical treatments presents an exciting avenue for future research. Current medications for AD, such as acetylcholinesterase inhibitors (including donepezil and rivastigmine) and glutamate regulators, provide symptomatic relief but do not slow disease progression [68]. Combining herbal remedies with these medications could yield synergistic effects, enhancing overall treatment outcomes [69]. For instance, *Ginkgo biloba* may complement cholinesterase inhibitors by improving cognitive function and reducing cognitive decline when used together. Similarly, the anti-inflammatory properties of curcumin could boost the

neuroprotective effects of pharmaceutical drugs [70, 71].

This combined approach could target multiple pathways in AD, such as reducing oxidative stress, managing inflammation, and preventing amyloid plaque formation. Personalized medicine continues to evolve, developing treatment plans tailored to an individual's genetic, biochemical, and clinical profile will be vital for optimizing AD management [72]. Personalized approaches can help identify which herbal remedies are most effective based on a patient's genetic predisposition, biomarker status, and treatment response. Certain genetic variants, such as the apolipoprotein E4 (APOE4) allele, can increase an individual's susceptibility to AD. By considering a patient's unique genetic makeup, healthcare providers may be able to identify herbal treatments that are most likely to yield positive outcomes [73]. Additionally, integrating biomarkers such as Aβ, tau, and neuroinflammation markers into clinical practice can guide treatment decisions and monitor the effectiveness of herbal remedies by assessing their influence on key AD-related processes [74].

### 4.2 Research limitations in herbal treatments of AD

The herbal therapies for AD have shown promising preclinical potential, but several key limitations in the current body of research hinder their bench-to-bedside translation (Table 3). These challenges merit the need for more systematic, standardized, and evidence-based research [75]. A primary limitation lies in the lack of standardization of herbal preparations. Herbal remedies are derived from botanicals whose chemical compositions are highly variable due to differences in species, geographical origin, cultivation methods, harvest time, and extraction techniques [76]. Such variability affects the concentration, stability, and bioavailability of bioactive compounds, resulting in inconsistent therapeutic efficacy across studies. Without standardized protocols for formulation and quality control, it becomes difficult to replicate findings or assess treatment outcomes reliably [77]. Another major constraint is the limited number of well-designed clinical trials. While numerous *in vitro* and animal studies demonstrate the neuroprotective, anti-inflammatory, and cognitive benefits of herbal extracts, human trials are often small in scale, short in duration, and methodologically limited [78]. Most studies involve narrow patient populations, reducing the generalizability of findings. Moreover, the complex and multifactorial nature of AD encompassing Aβ accumulation, tau pathology, oxidative stress, neuroinflammation, and synaptic loss poses difficulty in isolating the specific effects of herbal compounds without robust, multifaceted clinical evaluations [84].

Potential herbal drug interactions also represent a critical but underexplored area of concern. Patients with AD, who are typically elderly and often on multiple medications for comorbid conditions, may be at risk of adverse interactions when herbal treatments are used concurrently with standard pharmaceuticals [79]. Certain herbal compounds can alter drug metabolism, especially through modulation of cytochrome P450 enzymes, potentially affecting the efficacy or toxicity of co-administered drugs [80]. Regulatory challenges and lack of quality control further complicate the clinical adoption of herbal therapies. Unlike conventional pharmaceuticals, herbal products are not always subject to rigorous regulatory scrutiny, leading to inconsistencies in purity, potency, and safety [81]. Contamination with heavy metals, adulterants, or variable active compound content is not uncommon in commercial herbal formulations. The lack of regulation reduces confidence in the reliability of herbal products and underscores the need for stricter quality assurance and regulatory oversight [82, 83]. Finally, while the mechanistic understanding of herbal compounds in AD is expanding, it remains largely preliminary. Although bioactive compounds such as *curcumin, ginsenosides, Bacopa monnieri*, and *Ginkgo biloba* show promise in modulating key AD-related pathways such as amyloid aggregation, tau phosphorylation, oxidative damage, and neuroinflammation, the exact molecular mechanisms remain insufficiently characterized. More in-depth mechanistic studies are warranted to elucidate their cellular targets and optimize therapeutic strategies [85, 86].

## 5 Future safety and efficacy considerations

As the interest in herbal remedies for AD continues to grow, future research must prioritize the rigorous assessment of both safety and efficacy to support their integration into mainstream clinical practice [87, 88]. Although multiple herbal compounds exhibit neuroprotective and cognitive enhancing properties in preclinical studies, their clinical viability depends on overcoming several translational challenges. A key aspect of future development is the establishment of comprehensive safety profiles for herbal compounds and their standardized formulations [88, 89]. Long-term toxicity data, dose-dependent adverse effects, and potential interactions with conventional AD medications must be systematically evaluated. This is particularly critical given the target elderly population, who often present with polypharmacy and increased susceptibility to metabolic and hepatic alterations [90, 91]. The development of pharmacovigilance systems specific to botanical therapies will be essential in identifying and managing herb-drug interactions and adverse events [92].

On the efficacy front, well-powered, randomized controlled trials (RCTs) with standardized dosage, validated cognitive outcome measures, and long-term follow-up are needed to confirm the therapeutic benefits

observed *in vitro* and *in vivo* [93, 94]. Emphasis should be placed on trials that reflect real-world patient heterogeneity, including diverse genetic, lifestyle, and comorbidity backgrounds [95, 96]. Additionally, the use of biomarkers such as amyloid PET imaging, cerebrospinal fluid tau levels, and markers of oxidative stress and neuroinflammation can help establish mechanistic correlations between herbal interventions and AD pathology[97,98]. The application of modern pharmacological tools including network pharmacology, metabolomics, and molecular docking will promote our understanding of the multitarget actions of herbal compounds and may facilitate the identification of novel bioactive constituents [99]. Furthermore, nanotechnology-based delivery systems could improve the bioavailability and brain-targeting efficiency of poorly soluble herbal extracts, thereby optimizing therapeutic efficacy [100, 101]. Finally, regulatory frameworks must evolve to support the safe and ethical use of herbal medicines in AD care. Implementation of Good Manufacturing Practices (GMP), quality assurance protocols, and standardization of herbal extracts are essential to ensure consistency, reproducibility, and patient trust[102].

## 6 Conclusion

The findings of this review highlight the urgent need for innovative approaches in addressing the escalating prevalence of AD. Herbal remedies, used in traditional medicine for a long time, show promising neuroprotective and cognitive enhancing properties that merit further investigation. This review has examined several key herbs, including *Ginkgo biloba, Bacopa monnieri, Curcuma longa, Withania somnifera*, and *Rosmarinus officinalis*. The combined properties of these herbs suggest that they could serve as valuable complementary treatment options for individuals with AD, which potentially enhance cognitive function and mitigate disease progression. However, it is crucial to emphasize that further research is warranted. Rigorous clinical trials are required to thoroughly assess the efficacy and safety of these herbal interventions and to explore their possible integration with conventional therapies. Such studies in the future will clarify optimal dosages, treatment regimens, and mechanisms of action, ultimately leading to improved management strategies for AD. By deepening our understanding of these natural substances, we can better harness their therapeutic potential and strengthen outcomes for those with this condition.

## Acknowledgements

The authors extend appreciation to the Department of Pharmacology, Saveetha Medical College and Hospital, Saveetha University, Chennai, Tamil Nadu 602105, India.

## Competing interests

The authors declare no conflict of interest.

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# 草药疗法治疗阿尔茨海默病的神经保护机制与认知增强潜力综述

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**【摘要】**阿尔茨海默病（AD）是一种进行性神经退行性疾病，主要表现为记忆丧失和认知功能下降。当前药物疗法疗效有限，且常伴随副作用。近年来，基于药用植物中神经保护活性化合物的发现，越来越多的研究关注用于治疗 AD 的药用植物。本文综述了对 AD 治疗有潜在作用的药用植物，主要包括银杏、姜黄、睡茄和人参。这些药用植物在减少炎症、氧化应激和 β-淀粉样蛋白沉积方面显示出治疗潜力，其所含的生物活性化合物，如黄酮类和生物碱，可能有助于促进记忆并延缓 AD 的进展。然而，将临床前成功转化为临床疗效仍面临重大挑战，如植物成分不稳定、无统一标准制剂、缺乏大规模临床试验及监管障碍等问题，均阻碍了草药疗法应用于主流 AD 治疗方案。通过严格的科学验证和标准化治疗方案以解决上述挑战，对于推动药用植物在神经退行性疾病管理中的应用至关重要。

**【关键词】**阿尔茨海默病；神经保护机制；药用植物；植物化学成分；氧化应激