

REVIEW ARTICLE

Phytochemicals as neurotherapeutics in Alzheimer's disease: Exploring plant-based interventions for emerging complex brain disorders

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and remains the most prevalent cause of dementia, accounting for approximately 60–70% of dementia cases worldwide and contributing substantially to disability and loss of independence in older adults. It is an increasing global health and economic burden. Its multifactorial, interconnected pathophysiology, including the deposition of amyloid- β (A β), hyperphosphorylation of tau, and neurofibrillary tangle (NFT) formation, as well as mitochondrial dysfunction and oxidative stress, makes treatment challenging because drugs targeting a single pathway often fail to cure or reverse the disease's root cause. Conventional pharmaceutical therapies such as cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists offer only symptomatic relief with significant side effects. Hence, in this context, phytochemicals have emerged as promising neurotherapeutic candidates, due to their multi-target effects and reduced side effects. This review highlights key plant-derived bioactive compounds, including withanolides, curcumin, bacosides, epigallocatechin-3-gallate, resveratrol, rosmarinic acid, limonene, caffeic acid, and lycopene, and their proposed mechanisms relevant to AD prevention and management. Most studies on these bioactive compounds are preclinical. These phytochemicals have the potential to reduce A β plaque formation and tau pathology and to enhance antioxidant defense. Using nanotechnology approaches, their bioavailability can be improved. Therefore, by integrating traditional medicine knowledge with advanced molecular technologies, the phytochemical-based therapy can become a promising treatment for AD.

Keywords: Alzheimer's disease; Phytochemicals; Neuroprotection; Amyloid- β ; Nanomedicine; Oxidative stress

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1. Introduction

Alzheimer's disease (AD) is a major neurological disorder with multiple causative factors. In 2019, approximately 55 million people worldwide were affected, and it is the

cause of approximately 70% of all dementia diagnoses. It is projected to rise to ~152 million by 2050.¹ With the increasing number of cases, the global economic burden for treating this disease is also likely to rise substantially over time. In 2019, the global cost of dementia was estimated at 1.3 trillion USD per year; by 2050, this cost could increase to 9.1 trillion USD annually.^{1,2} This disease shows a sex-specific pattern, with a higher prevalence in women than in men. The reason behind this pattern is not solely because women live longer than men. Additional contributors may include menopause-related hormonal changes, primarily decreased progesterone levels, genetic predispositions, and several additional biological and environmental influences.³

Treatment of AD is broadly divided into two categories: Pharmacological and non-pharmacological. Pharmacological treatment is again categorized into two types: (i) symptomatic agents, including cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and N-methyl-D-aspartate receptor antagonists (memantine), which modulate glutamate signaling to reduce excitotoxicity, and (ii) emerging disease-modifying pharmacological drugs, such as sodium oligomannate (GV-971), aducanumab, lecanemab, and donanemab (currently under review for market approval).^{4,5} Symptomatic drugs act by regulating neurotransmitters and therefore provide only symptomatic relief without curing or reversing the disease. In contrast, newer disease-modifying agents target crucial pathological hallmarks of the disease, such as amyloid- β (A β), while contributing to various undesirable side effects such as nausea, diarrhea, and constipation, memory loss, as well as, in rare cases, severe adverse effects including brain swelling, small brain bleeds, and stroke-like symptoms.⁶ Moreover, as this disease is multidimensional and affects multiple biological pathways simultaneously, drugs targeting a single pathway often fail to provide an effective cure.

From the perspectives of minimizing adverse effects and enabling multi-target modulation, phytochemicals derived from medicinal plants have emerged as potential alternatives or adjuncts to conventional therapy.^{7,8} Traditional medical systems have utilized plant-based remedies to enhance memory, cognition, and overall brain health. Modern pharmacological and molecular research has begun to validate ancient practices by demonstrating that phytochemicals exhibit multitargeted mechanisms of action. Although numerous phytochemicals have been investigated for their neuroprotective potential, the existing literature remains fragmented. Most studies focus on individual compounds or isolated pathways, often *in vitro* or preclinical models, without systematically comparing their multitargeted therapeutic relevance in AD. Furthermore,

limited efforts have been made to integrate preclinical findings to evaluate phytochemicals in the context of safety profiles and their advantages over conventional pharmacological agents. As a result, there is a lack of a comprehensive framework to identify the most promising phytochemicals based on the strength of evidence and translational potential for AD management. This review aims to address that gap by providing a consolidated and critical evaluation of the most extensively studied phytochemicals with the strongest preclinical and emerging clinical evidence. This review focuses on: (i) summarizing phytochemicals' multitargeted mechanisms of action across crucial AD-related pathological pathways, (ii) comparing their therapeutic potentials, limitations, and safety profile, and (iii) highlighting their relevance as an alternative strategy to current treatments. By integrating molecular, preclinical, and clinical evidence, this review aims to bridge the existing knowledge gap and guide future research toward rational development of phytochemical-based interventions for AD.

2. Literature search methodology

This review used a structured, predefined search strategy to ensure comprehensive coverage of the relevant literature on phytochemicals with neuroprotective roles in AD. A systematic search of peer-reviewed studies was carried out across major scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. Search terms combined keywords such as "Alzheimer's disease," "phytochemicals," "neuroprotection," "amyloid- β ," "tau phosphorylation," "oxidative stress," "nanomedicine," and "neuro-inflammation." Only studies published in English from 2000 to the present were included, capturing both foundational studies and the most recent advancements in phytochemical-based neuro-therapeutics. The search results were screened manually to identify studies relevant to phytochemical-based neuroprotective mechanisms in AD. The inclusion criteria were peer-reviewed original research and review articles reporting mechanistic data, preclinical (*in vitro/in vivo*) findings, or clinical trial results in AD. Exclusion criteria were non-peer-reviewed sources, studies unrelated to neurodegeneration, insufficient mechanistic or experimental evidence, and non-English publications. Based on these criteria, 90 articles were selected for this review.

3. Pathophysiology of AD

AD is a multifactorial neurodegenerative disorder involving various interconnected pathological mechanisms (Figure 1). Major hallmarks of the disease include the abnormal deposition of A β plaques and the formation of NFTs through hyperphosphorylation, oxidative stress,

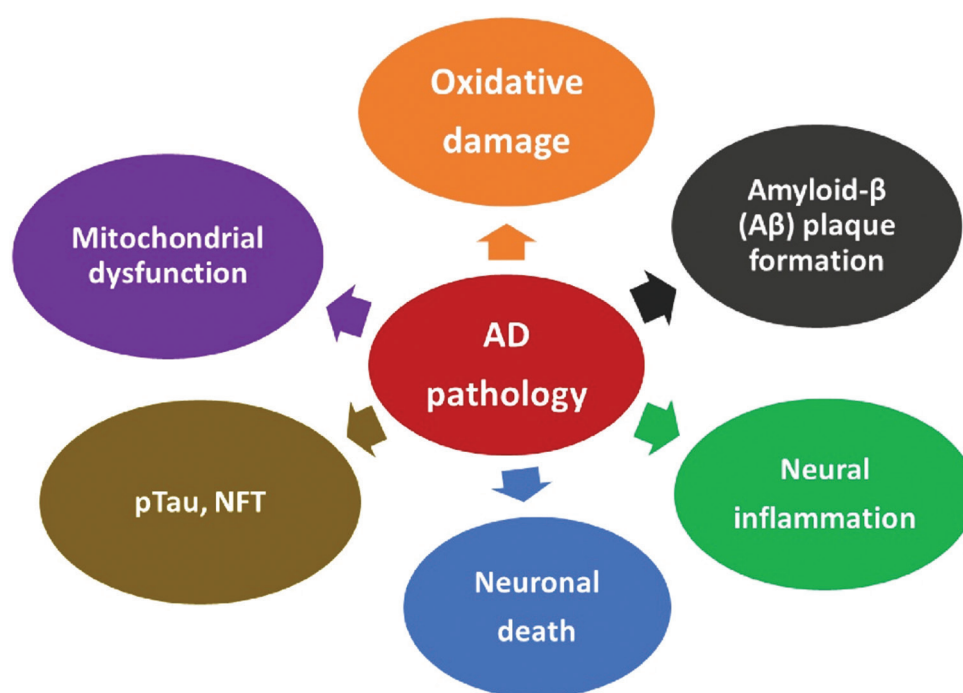


Figure 1. Major pathological features of Alzheimer's disease (AD). The interconnected pathological events involved in AD include: A β (amyloid- β) plaque formation, tau hyperphosphorylation (ptau) and neurofibrillary tangle (NFT) development, oxidative stress, mitochondrial dysfunction, neuro-inflammation, and neuronal loss.

mitochondrial dysfunction, and neuro-inflammation, ultimately leading to neuronal death.

3.1. A β plaque formation

A β peptides are formed when the amyloid precursor protein (APP), a single-pass transmembrane protein abundantly present in neurons, undergoes enzymatic cleavage. APP can be metabolized through two alternative routes. The first, known as the non-amyloidogenic pathway, is considered neuroprotective because it does not produce toxic A β peptide. In this route, the enzyme α -secretase cleaves APP, producing a soluble extracellular fragment (sAPP α) and a membrane-bound remnant, C83. Subsequent cleavage of C83 by γ -secretase leads to the formation of non-toxic P3 peptide and APP intracellular domain.^{9,10} In a healthy brain, this pathway contributes to neuronal protection, reduction of oxidative damage, cognitive function, memory enhancement, and synaptic plasticity. In this condition, low or no A β is produced, or if produced, it remains as soluble monomers that support brain health through a well-regulated A β clearance mechanism. In AD, the normal processing of APP is altered, favoring a toxic amyloidogenic pathway, in which β -secretase initiates cleavage at a different site, producing soluble APP β and C99 fragment (Figure 2). The subsequent action of enzyme γ -secretase on the C99 fragment generates excessive A β peptides (mainly A β 40 and A β 42).^{11,12} These

peptides are prone to aggregation, leading to the formation of oligomers, fibrils, and plaques in the extracellular space. This aggregation disrupts synaptic communication by dysregulating calcium homeostasis, elevating oxidative and mitochondrial stress, and activating glial cells, thereby contributing to neuronal damage and synaptic loss and ultimately leading to a decline in cognitive function.¹³

3.2. Aberrant tau hyperphosphorylation and toxicity

Tau is a protein that exists in six isoforms in the adult human brain, generated by alternative splicing of the *MAPT* (microtubule-associated protein tau) gene. Tau stabilizes microtubules, particularly in neurons. In healthy individuals, tau plays a critical role in axonal transport, synaptic function, signaling, memory, and cognition.^{14,15} Its activity is regulated by controlled phosphorylation and dephosphorylation at specific serine and threonine residues, mediated by kinases, such as glycogen synthase kinase-3 (GSK3 β), cyclin-dependent kinase 5 (CDK5), and mitogen-activated protein kinase, and the protein phosphatase 2A (PP2A). In AD, the balance between kinase and phosphatase activity is disrupted.¹⁶ Kinases, including GSK3 β and CDK5, are overexpressed, and PP2A phosphatase expression is reduced, leading to hyperphosphorylation (at more than 80 serine/threonine sites of tau). A β oligomers are implicated in the hyperphosphorylation of tau, potentially through

the activation of kinases, such as GSK3 β and CDK5.¹⁷ Hyperphosphorylated tau loses affinity for microtubules, detaches, and destabilizes microtubule networks (Figure 3). The accumulation of free tau in the cytosol promotes the formation of NFTs, adversely affecting synaptic plasticity, neuronal growth, and cell survival.^{18,19}

3.3. Oxidative damage

Oxidative damage refers to cellular damage caused by the production of excess reactive oxygen species (ROS), including superoxide and hydrogen peroxide. ROS are natural byproducts of normal cellular metabolism, mainly formed inside mitochondria during oxidative

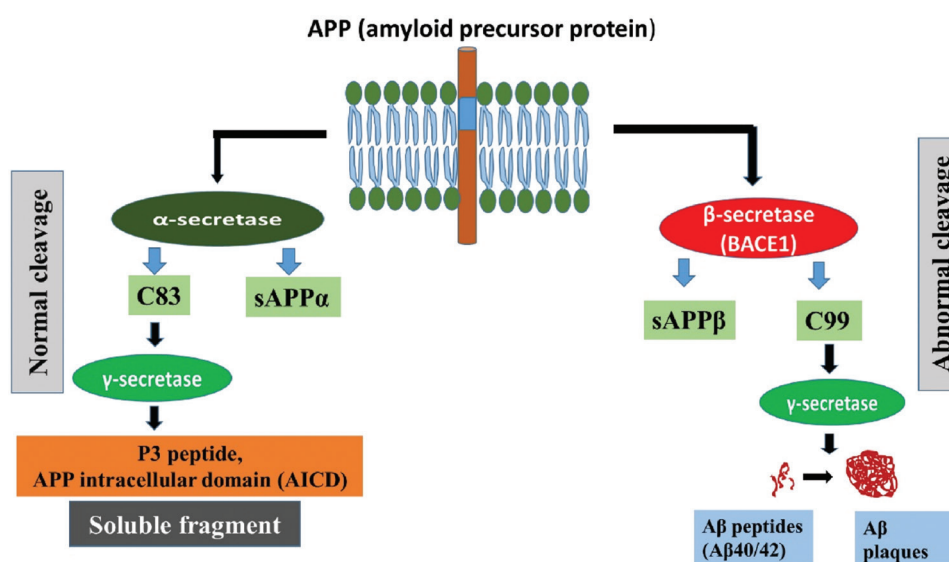


Figure 2. Formation process of amyloid- β ($A\beta$) plaques during Alzheimer's disease. Under normal cleavage (non-amyloidogenic pathway), amyloid precursor protein (APP) is cleaved by α -secretase, producing soluble APP α (sAPP α), and a C83 fragment, followed by γ -secretase cleavage, generating a harmless P3 peptide and APP intracellular domain. For abnormal cleavage (amyloidogenic pathway), APP is first cleaved by β -secretase, also known as beta-site amyloid precursor protein cleaving enzyme 1 (BACE1), producing soluble APP β (sAPP β) and a C99 fragment; then γ -secretase processes C99 to generate $A\beta$ peptides ($A\beta_{40/42}$), which aggregate into $A\beta$ plaques.

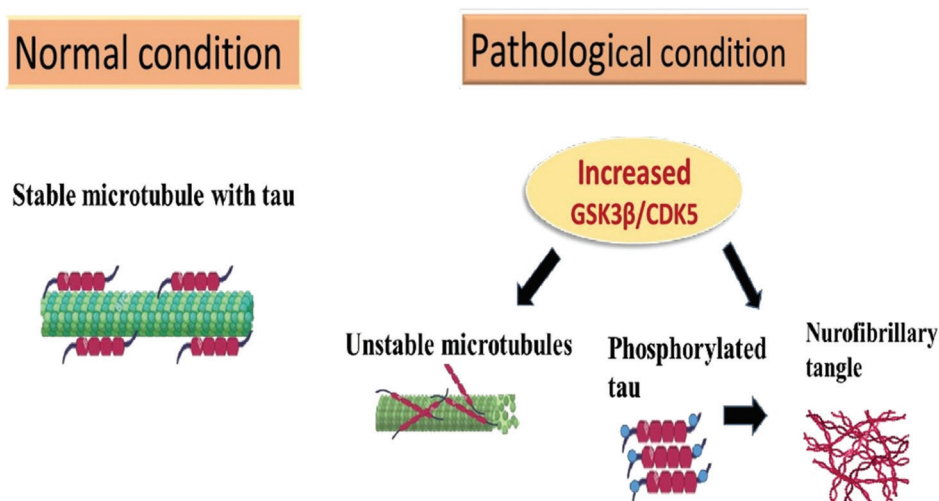


Figure 3. Tau hyperphosphorylation and neurofibrillary tangles (NFTs) formation. Under normal conditions, tau proteins are phosphorylated at controlled levels and stabilize microtubules, supporting axonal transport, synaptic function, and neuronal health. In pathological conditions, overactivation of glycogen synthase kinase-3 β (GSK3 β) and cyclin-dependent kinase-5 (CDK5), and reduced activity of protein phosphatase 2A cause excessive tau hyperphosphorylation, leading to tau detachment from microtubules, microtubule destabilization, formation of tau oligomers and paired helical filaments, and ultimately NFTs.

phosphorylation in the electron transport chain (ETC) by the Fenton reaction with metal ions and are neutralized by the body's antioxidant defense system, such as glutathione, superoxide dismutase, catalase, and Vitamin E.^{20,21} Excessive production of ROS leads to damage of cellular components, including oxidation of DNA bases (primarily mitochondrial DNA), lipid peroxidation, and protein oxidation. These oxidative markers are consistently observed in patients with AD.²² Mitochondrial dysfunction is closely associated with oxidative damage, as mitochondria are the primary source of ROS generated by the ETC during oxidative phosphorylation. In AD patients, mitochondria are structurally and functionally compromised, leading to reduced ATP production and increased ROS generation. This imbalance leads to excessive ROS accumulation, while antioxidant defenses become depleted and insufficient to neutralize the excessive oxidative stress.²³ Research using animal models has demonstrated that brain regions with higher concentrations of A β peptide in AD models exhibit increased oxidative damage, including oxidation of proteins and lipids; in contrast, regions with lower A β levels display significantly reduced oxidative stress. These findings suggest a strong correlation between A β accumulation and oxidative damage.^{24,25}

3.4. Neuronal death

Nerve cells rely primarily on oxidative phosphorylation for ATP production. Oxidative phosphorylation occurs at the inner mitochondrial membrane through the ETC.²⁶ In AD, mitochondrial dysfunction impairs this process; hence, nerve cells switch their energy source to glycolysis, which increases lactate production, reduces energy, and causes metabolic disturbances. This reduces neuronal survival and function, leading to both neuronal loss and cognitive decline.²⁷⁻²⁹ Furthermore, protein aggregation (A β and phosphorylated tau) impairs synaptic coordination and promotes neuroinflammation and neuronal death.²⁷

3.5. Neuro-inflammation

Neuro-inflammation plays a crucial role in driving the AD pathogenesis. This occurs through microglia and astrocytes, part of the brain's resident innate immune system, that are hyper-activated by toxic peroxidation byproducts and A β , tau deposition in AD brain, and release inflammatory cytokines, chemokines, ROS, and nitric oxide as immune mediators.^{30,31} Instead of providing protection, these substances worsen the neuronal injury and accelerate neurodegeneration and cognitive decline. Inflammatory mediators can induce neuronal apoptosis through caspase activation, dysregulate calcium homeostasis, and compromise the integrity of the blood-brain barrier (BBB),

thereby allowing peripheral immune cells to infiltrate the brain and exacerbate neuro-inflammation.^{32,33}

4. Medicinal plants as sources of anti-Alzheimer phytochemicals

For centuries, traditional medical systems, such as Ayurveda, traditional Chinese medicine, and Mediterranean herbal practices, have used plant-derived phytochemicals to enhance memory, cognition, and overall brain health. These systems, grounded in empirical knowledge and long-standing observations, have utilized a diverse range of plants to influence neurological well-being. In recent years, advances in modern technology and molecular studies have begun to validate these traditional claims, providing evidence for the neuroprotective effects of various phytochemicals. Studies have shown that numerous phytochemicals can target key pathological features associated with neurodegenerative disease (Table 1). Specifically, they have been found to inhibit A β aggregation, reduce tau protein hyperphosphorylation, increase antioxidant defense mechanisms, regulate mitochondrial function, and suppress neuro-inflammation, the critical processes involved in the onset and progression of AD (Figure 4). Unlike conventional drugs that often act on a single molecular target, phytochemicals exert their effects through a multi-target mechanism of action. This pleiotropic nature allows them to modulate multiple interconnected pathways simultaneously, offering a holistic therapeutic approach to complex neurological disorders. Hence, phytochemicals are a promising alternative for managing neurodegenerative diseases with complex underlying causes like AD.

The phytochemicals listed in Table 1 represent either individual bioactive compounds (e.g., curcumin, resveratrol, lycopene, and asiaticoside) or groups/mixtures of related compounds naturally present in the plant extracts (e.g., withanolides, bacosides, ginsenosides, and ginkgolides). The reported biological functions are supported by experimental evidence obtained using isolated compounds or standardized plant extracts, as described in the cited references.

5. Phytochemicals

In this section, we provide an overview of important phytochemicals derived from the selection of well-documented medicinal plants, including *Withania somnifera* (ashwagandha), *Curcuma longa* (turmeric), *Bacopa monnieri* (brahmi), *Camellia sinensis* (green tea), *Vitis vinifera* (grapes), *Salvia rosmarinus* (rosemary), *Citrus limon* (lemon), *Coffea arabica* (coffee), and *Solanum lycopersicum* (tomato). These plants are known for their rich

Table 1. Phytochemicals with potential to treat Alzheimer's disease

Plants	Family	Part used	Phytochemicals	Functions	References
<i>Withania somnifera</i> (ashwagandha)	Solanaceae	Roots	Withanolides ^b	Directly binds to the hydrophobic core of A β , preventing plaque nucleation, and upregulates antioxidant genes	34-38
<i>Curcuma longa</i> (turmeric)	Zingiberaceae	Rhizome	Curcumin ^a	Disrupts A β fibrils and tau oligomers, has anti-inflammatory properties	39-43
<i>Bacopa monnieri</i> (brahmi)	Plantaginaceae	Leaf and stem	Bacosides ^b (Bacoside A and Bacoside B)	Enhance cholinergic function, reduce oxidative stress, and improve memory in AD models	44-47
<i>Camellia sinensis</i> (green tea)	Theaceae	Leaf	EGCG ^a	Convert toxic A β fibrils into a soluble non-toxic form and protect mitochondria	48-51
<i>Vitis vinifera</i> (grapes)	Vitaceae	Fruit	Resveratrol ^a	Enhance neuronal survival by activating the SIRT1-AMPK pathway, reducing inflammation	52-56
<i>Salvia rosmarinus</i> (rosemary)	Lamiaceae	Leaf	Rosmarinic acid ^a	Destabilizes preformed A β fibrils, reduces oxidative stress and inflammation	57-60
<i>Citrus limon</i> (lemon)	Rutaceae	Fruit	Limonene ^a	Has a powerful antioxidant property	61-63
<i>Coffea arabica</i> (coffee)	Rubiaceae	Leaf and beans	Caffeic acid ^a	Has anti-tau, antioxidant, and anti-inflammatory properties	64-66
<i>Solanum lycopersicum</i> (tomato)	Solanaceae	Fruit	Lycopene ^a	Crosses the blood-brain barrier effectively, and exhibits high bioavailability in brain tissue	67-70
<i>Ocimum sanctum</i> (tulsi)	Lamiaceae	Leaves	Eugenol ^a , rosmarinic acid ^a	Has acetylcholinesterase inhibitory, antioxidant, and anti-inflammatory properties	71-73
<i>Panax Ginseng</i> (ren-shen)	Araliaceae	Root	Ginsenosides ^b	Anti-amyloid, anti-tau, antioxidant, and anti-inflammatory properties	74-76
<i>Centella asiatica</i> (gotu kola)	Apiaceae	Leaves	Asiaticoside ^a	Has anti-amyloid, anti-inflammatory, and anti-apoptotic properties	77-79
<i>Cinnamon zeylanicum</i> (cinnamon)	Lauraceae	Bark	Cinnamaldehyde ^a	Has neuroprotective and cognitive benefits, improves memory and synaptic function	80,81
<i>Ginkgo biloba</i> (maidenhair tree)	Ginkgoaceae	Leaves	Ginkgolides ^b	Reduce lipid peroxidation, balance ion metabolism, and induce antioxidant defense systems	82,83
<i>Zingiber officinale</i> (ginger)	Zingiberaceae	Rhizome	Gingerol ^a	Modulate gut-brain microbiota to support cognitive health, protect neurons from A β -induced apoptosis	84-86
<i>Allium sativum</i> (garlic)	Liliaceae	Cloves	S-allyl-L-cysteine ^a	Has anti-glycation activity, prevents A β -induced toxicity and synaptic degeneration	87,88
<i>Azadirachta indica</i> (neem)	Meliaceae	Leaves and bark	Nimbin ^b , nimbidin ^b	Inhibits tau aggregation activity and has anti-inflammatory and antioxidant actions	89,90

Notes: ^aan individual chemically defined compound; ^ba mixture of compounds.

Abbreviations: AMPK: Adenosine monophosphate-activated protein kinase; A β : Amyloid β ; EGCG: Epigallocatechin-3-gallate; SIRT1: Sirtuin 1 pathway.

profile of bioactive compounds, which have demonstrated promising anti-AD potential in preclinical and limited clinical studies (Table 1). This section aims to summarize the most relevant findings on these phytochemicals, emphasizing their therapeutic potential and mode of action in the prevention and management of AD.

5.1. Withanolide

Withanolides are steroidal lactones enriched in *W. somnifera* (ashwagandha) roots, also known as “Indian ginseng,” which has been traditionally used as a memory-boosting tonic.³⁴ After numerous pharmacological studies and animal testing, the underlying mechanism of withanolide's neuroprotective nature is becoming clearer.³⁵

In human neuroblastoma cell lines, bioactive compounds derived from *W. somnifera*, including Withanolide A, Withanolide B, Withanoside IV, and Withanoside V, have been shown to significantly inhibit A β aggregation. Molecular docking and molecular dynamics simulations suggest that these compounds directly interact with the hydrophobic core region (LVFFA) of A β , a region crucial for A β aggregation, thereby preventing A β plaque formation.³⁶ In *in vivo* studies, oral administration of the aqueous extract of ashwagandha root in 5xFAD mice, a mouse model exhibiting Alzheimer-like symptoms, such as memory loss, anxiety, and depression, as well as extensive amyloid plaque accumulation, showed improved memory, reduced anxiety, decreased amyloid plaques,

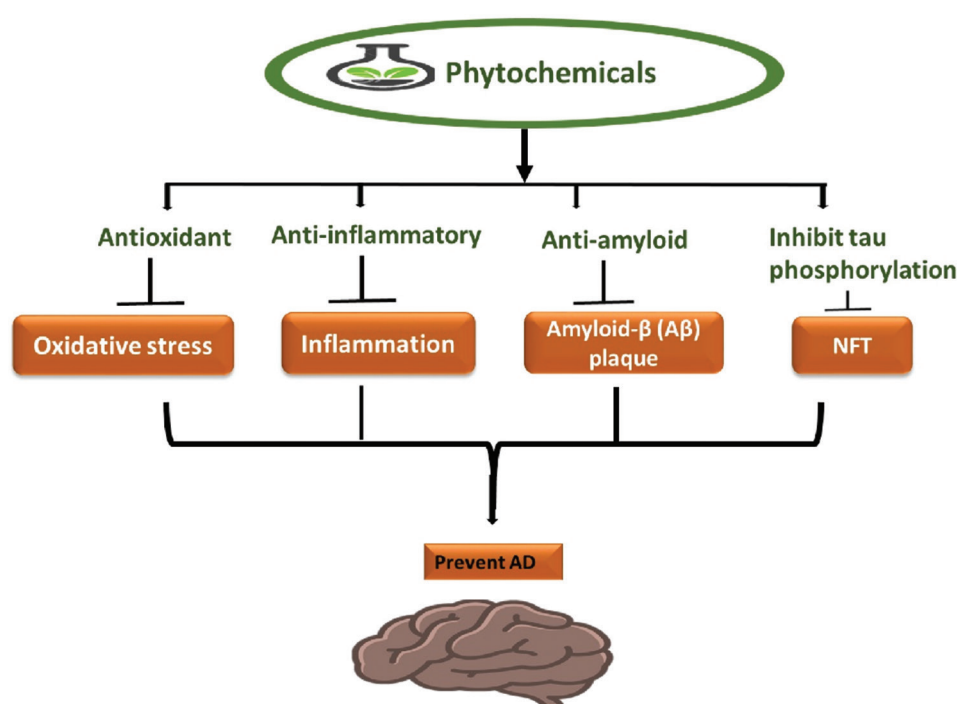


Figure 4. Protective role of phytochemicals in preventing Alzheimer's disease (AD). Multitargeted effects of plant-derived phytochemicals include mitigating oxidative stress, reducing neuro-inflammation, inhibiting amyloid β ($A\beta$) aggregation, and preventing the development of neurofibrillary tangles (NFTs).

and lowered inflammation levels. The extract is shown to upregulate antioxidant-producing genes, such as *Nrf2*, and to inhibit the activation of neuro-inflammatory cells, such as microglia and astrocytes.³⁷ In a clinical study involving 13 healthy adults, a single 400 mg dose of an ashwagandha capsule improved memory, reduced response times, enhanced focus, and improved overall cognition, with no side effects.³⁸ Overall, evidence for the mechanisms underlying the effects of withanolides in AD remains limited, and robust clinical trials are needed to confirm their therapeutic potential.

5.2. Curcumin

Curcumin, a hydrophobic polyphenolic compound derived from *C. longa*, is responsible for its vibrant golden-yellow color and has been extensively studied for its neuroprotective roles. An *in silico* study on the interaction of curcumin and $A\beta$ peptide using molecular docking and molecular dynamics simulations shows that curcumin binds more strongly with the short $A\beta$ fragment containing KLVFFA (the main aggregation core) than a full-length $A\beta$ fibril, suggesting that curcumin targets the key region of $A\beta$ that is responsible for the toxic $A\beta$ plaque formation.³⁹ Further investigation using curcumin and rosmarinic acid on *in vitro* synthetic $A\beta$ fibrils has shown that they effectively suppress fibril formation and destroy preformed

fibrils.⁴⁰ In *in vivo* studies, mice administered $A\beta$ and treated with curcumin for 10 days showed improved memory, reduced brain cell death, and decreased $A\beta$ aggregation. Furthermore, it targets the toxic nuclear factor kappa-light-chain-enhancer of activated B-cells (NF- κ B) pathways that drive inflammation, thereby reducing brain inflammation.⁴¹ Curcumin was also reported to suppress soluble phosphorylated tau dimers and monomers effectively when transgenic aged mice expressing human tau are fed with a curcumin-rich diet.⁴² A new curcumin derivative, Derivative 27, when administered to APP/PS1 (presenilin-1) transgenic mice (an animal model of AD), showed enhanced efficacy in reducing memory loss, inflammation, and other forms of brain damage.⁴³ Due to poor bioavailability and rapid metabolism, the clinical translation of curcumin is hindered. Moreover, robust clinical evidence supporting its efficacy in AD is limited, underscoring the need for well-designed human studies to confirm its therapeutic potential.

5.3. Bacosides

Bacoside is the main phytochemical extracted from leaves and stems of *B. monnieri* (brahmi). *B. monnieri* extracts are frequently used in traditional medicine as a nerve tonic. Preclinical studies have demonstrated their neuroprotective potential in AD. In studies on male

Wistar rats, Alzheimer's-like symptoms were induced by intracerebroventricular administration of ethylcholine mustard aziridinium ion (Aminofluoropyridine derivative 64A), a selective cholinergic neurotoxin that irreversibly damages cholinergic neurons by inhibiting choline uptake, leading to cognitive impairment. Subsequent treatment with an alcoholic extract of *B. monnieri* over several weeks resulted in improved memory and cognitive function, along with enhanced neural health.⁴⁴ Similarly, in an *in vitro* experiment, pre-treatment with Bacoside-A, a major neuroprotective saponin from *B. monnieri*, in the presence of the A β (1–42) peptide reduced toxic fibril formation, minimized neuronal cell damage, and inhibited the peptide's interaction with membranes, thereby preventing membrane disruption. Bacopaside I, another key saponin from *B. monnieri*, was administered to APP/PS1 mice for 2 months, resulting in a reduction in A β plaque deposition and memory enhancement. Although it does not directly clear A β , it activates the brain's immune cells, such as microglia and astrocytes, to engulf this protein. In a small clinical trial involving 34 patients, bacopa extract showed no significant difference in cognitive improvement compared to the standard drug, donepezil. However, due to the limited sample size, the findings remain inconclusive.⁴⁷ Overall, most evidence remains preclinical, and the clinical data are insufficient to support therapeutic efficacy, underscoring the need for larger controlled human trials.

5.4. Epigallocatechin-3-gallate (EGCG)

EGCG, a dominant catechin found in *C. sinensis*, exhibits potent antioxidant neuroprotective properties, particularly mitigating mitochondrial-associated oxidative stress. In an *in vitro* study using a transgenic mouse neuronal cell line carrying an *App* mutation, treatment with EGCG altered APP processing, leading to increased production of sAPP α and a C-terminal fragment, likely through upregulation of the γ -secretase gene. This suggests that EGCG reduces A β by altering the toxic processing of APP, promoting the non-amyloid pathway, and *in vivo*, mice treated with EGCG contain low levels (40–60%) of A β and few plaques.⁴⁸ EGCG was administered to lab-grown human neuron-like cells (*in vitro*) and a transgenic Alzheimer's mouse model (*in vivo*) and has been shown to attenuate A β -induced apoptosis, potentially by reducing endoplasmic reticulum stress responses (e.g., lowering endoplasmic reticulum-stress markers). In transgenic mice, EGCG exerts a similar suppressive effect on endoplasmic reticulum stress protein, hence protecting nerve cells in both cases.⁴⁹ Rats treated with EGCG showed better performance in memory and cognitive tests, and this was achieved by lowering β -secretase 1, the enzyme that cleaves APP, thereby reducing toxic A β plaques, decreasing hyperphosphorylation of tau

protein, and boosting antioxidant defense.⁵⁰ EGCG and ascorbic acid, when packed into transferosomes (tiny, flexible lipid vesicles), showed increased bioavailability, improved memory and cognition, reduced oxidative stress, and enhanced antioxidant defense when tested *in vitro* in lab-grown cells and *in vivo* transgenic mice.⁵¹ Despite the promising results, EGCG remains largely experimental, and some issues, such as poor bioavailability and the absence of convincing clinical data, limit its therapeutic value in AD.

5.5. Resveratrol

Resveratrol is a highly studied polyphenolic phytochemical derived primarily from the skin of red grapes, *V. vinifera*. Studies investigating the effects of resveratrol on senescence-accelerated mouse prone strain 8, a model for age-related AD, showed an increase in life span and cognition by activating key survival pathways, such as the sirtuin 1 pathway and adenosine monophosphate-activated protein kinase pathway (SIRT1). In addition, resveratrol-treated mice exhibited reduced accumulation of A β peptides and decreased tau protein hyperphosphorylation, the two important hallmarks of AD.⁵² A 52-week clinical trial in patients with mild-to-moderate AD showed that resveratrol and its active metabolites can cross the BBB effectively. It is also concluded that resveratrol is safe and well-tolerated for Alzheimer's patients.⁵³ In an *in vivo* *Caenorhabditis elegans* model of AD expressing human A β (1–42), resveratrol treatment significantly reduced A β toxicity by enhancing proteasomal degradation and autophagy of misfolded A β .⁵⁴ Similarly, in another *in vivo* transgenic mouse model of AD characterized by a high level of A β toxicity, 60 consecutive days of resveratrol treatment resulted in a significant decrease in amyloid plaque formation and a reduction in β -secretase 1 levels.⁵⁵ Resveratrol has also been shown to reduce neural inflammation in a transgenic mouse model of AD by inhibiting the NF- κ B pathway. Overall, it demonstrates dual action, preventing both A β accumulation and neuro-inflammation.⁵⁶ Together, these findings highlight resveratrol's strong therapeutic promise, with early clinical data supporting its safety and BBB permeability and encourage further trials to determine its full potential in AD.

5.6. Rosmarinic acid

Rosmarinic acid is a polyphenolic compound obtained from medicinal herbs of the Lamiaceae family, such as rosemary, sage, basil, and mint. Studies using purified tau fibrils have demonstrated that treatment with rosmarinic acid notably reduces fibril formation. Molecular docking study of tau hexa-peptide VQIVYK (the region responsible for aggregation) further revealed that rosmarinic acid

attaches to this seed sequence of tau as an inhibitor, thereby preventing fibril formation.⁵⁷ In neuronal cells with oxidative stress and lipid peroxidation induced by A β , rosmarinic acid treatment resulted in a reduction in oxidative damage by promoting the *Nrf2* gene, which is responsible for promoting antioxidant defense.⁵⁸ In an *in vivo* transgenic mouse model, when treated with rosmarinic acid, a reduction in A β formation was shown by increasing the secretion of several neurotransmitters (dopamine and norepinephrine). Moreover, in a behavioral study, rosmarinic acid-treated mice showed improvement in memory and cognition.⁵⁹ Furthermore, *in vivo* studies on transgenic AD mouse models, when fed with a rosmarinic acid-rich diet, observed a reduction in tau hyperphosphorylation. The researchers found that rosmarinic acid reduces inflammation in the brain and downregulates the c-Jun N-terminal kinase signaling pathway, the major kinase pathway behind tau phosphorylation.⁶⁰ Collectively, these findings highlight rosmarinic acid as a promising multi-target phytochemical with beneficial effects on tau aggregation, oxidative stress, neurotransmitter balance, and neuro-inflammation.

5.7. Limonene

Limonene, the main phytochemical of the citrus genus, has recently attracted attention in neurological research due to its potent antioxidant properties. When tested in the AD *Drosophila* model expressing human A β 42, limonene does not directly clear A β peptide or prevent its accumulation, but it mitigates oxidative stress caused by A β aggregation by reducing extracellular signal-regulated kinase (ERK) phosphorylation.⁶¹ Another study on cortical neuronal cells showed that the limonene treatment effectively protects the cells from A β toxicity.⁶² On a behavioral test on anxiety-induced mice, when treated with limonene, they showed improved memory and decreased anxiety and stress through its antioxidant and neuro-modulatory effects.⁶³ Overall, current findings suggest that limonene primarily modulates oxidative and stress-related pathways, though evidence remains limited to experimental models.

5.8. Caffeic acid

Caffeic acid is a predominant polyphenolic compound obtained primarily from coffee beans. An *in vitro* study on rat primary cortical neurons treated with caffeic acid showed reduced tau phosphorylation and calcium dysregulation, thereby mitigating neurotoxicity caused by A β plaques and promoting neural cell survival.⁶⁴ Similarly, in an *in vivo* study using an AD mouse model injected with A β peptide, oral administration of caffeic acid significantly improved cognitive health, memory, and reduced oxidative stress.⁶⁵ Recently, nanotechnology-

based approaches have enhanced the therapeutic potential of caffeic acid. Researchers developed nano-vesicles encapsulating caffeic acid-coupled carbon quantum dots to increase bioavailability. The results show reductions in A β aggregation, oxidative stress, and neuro-inflammation in the mouse model.⁶⁶ These findings are currently confined to experimental studies, and further investigations are needed to determine their relevance in clinical settings.

5.9. Lycopene

Lycopene is a carotenoid pigment responsible for the vibrant red color of tomatoes. It has powerful antioxidant properties, which have drawn attention in neurological research. Transgenic mice expressing tau that received dietary lycopene supplementation showed improved memory and cognition in a behavioral study. Biochemical analysis has further revealed that lycopene decreases tau hyperphosphorylation and reduces oxidative stress.⁶⁷ In addition, *in vivo* studies in AD rat models have demonstrated that lycopene significantly reduces A β -induced inflammation by suppressing NF- κ B signaling, the key pathway involved in neuro-inflammation.⁶⁸ A recent nanotechnology-based *in vivo* investigation demonstrated that lycopene-loaded micro-emulsion, when administered to A β -induced AD mice, led to improved cognitive function, reduced oxidative stress, and decreased neuronal apoptosis.⁶⁹ In an *in vitro* study, lycopene was shown to reduce A β -induced oxidative damage, mitochondrial dysfunction, and apoptosis.⁷⁰ Further studies are necessary to evaluate its therapeutic potential in clinical contexts.

5.10. Others

Several additional medicinal plants exhibit promising neuroprotective potential against AD through multi-target mechanisms. *Ocimum sanctum* (tulsi) contains eugenol and rosmarinic acid that enhance cholinergic activity, reduce oxidative stress, and prevent A β -induced neuronal apoptosis.⁷¹⁻⁷³ *Panax ginseng* (ginseng) ginsenosides, such as Rg1 and Rh4, promote A β peptide degradation, inhibit tau hyperphosphorylation, and regulate neuro-inflammation through ERK/peroxisome proliferator-activated receptor gamma (PPAR γ) and GSK3 β pathways.⁷⁴⁻⁷⁶ *Centella asiatica* (gotu kola) asiaticoside improves memory, inhibits A β aggregation, and prevents mitochondrial apoptosis.⁷⁷⁻⁷⁹ *Cinnamomum zeylanicum* (cinnamon) cinnamaldehyde alleviates amyloid pathogenesis and enhances mitochondrial and synaptic function through SIRT1-PPAR γ coactivator-1 alpha-PPAR γ signaling.^{80,81} *Ginkgo biloba* ginkgolides mitigate oxidative stress and inflammation by suppressing the NOD-like receptor protein 3/caspase-1 pathway.^{82,83} The 6-gingerol from *Zingiber officinale* (ginger) modulates

the gut-brain axis, prevents A β -induced apoptosis, and regulates multiple neuroprotective targets.⁸⁴⁻⁸⁶ *Allium sativum* (garlic) S-allyl-L-cysteine detoxifies reactive carbonyls, prevents synaptic degeneration, and reduces oxidative stress.^{87,88} *Azadirachta indica* (neem) compounds, such as nimbin and nimbidin, inhibit tau aggregation and NF- κ B-mediated inflammation.^{89,90} Collectively, these phytochemicals demonstrate synergistic antioxidant, anti-amyloid, anti-tau, and anti-inflammatory properties, highlighting their therapeutic potential in preventing or slowing the AD progression.

6. Challenges of phytochemical-mediated treatment

Although significant progress is being made in understanding the pathophysiology of AD and an increasing number of clinical trials support phytochemicals as potential candidates to address this complex neurodegenerative disorder, a substantial research gap remains in translating these findings into clinical therapies. Most current research relies on *in vitro* or *in vivo* studies that cannot fully emulate the complexity of human brain pathology. Clinical trials investigating these phytochemicals are limited, often small-scale, and yield inconsistent results, making it difficult to draw definitive conclusions. Although phytochemicals such as curcumin and resveratrol have shown excellent neuroprotective effects and have been extensively studied, their therapeutic efficacy is limited by poor bioavailability, rapid metabolism, and limited ability to cross the BBB. Similarly, while EGCG demonstrates strong antioxidant effects, its oral bioavailability under physiological conditions remains low. In addition, at higher doses, it may act as a pro-oxidant, inducing gastrointestinal discomfort, which further restricts its clinical use. Furthermore, the mechanisms of action of numerous phytochemicals remain poorly understood, underscoring the need for more detailed mechanistic research. Addressing these challenges is crucial for transitioning from experimental promise to effective clinical treatments for AD.

7. Conclusion

Due to its multifactorial nature, AD remains the most challenging neurological disorder, and conventional pharmacological therapy only provides some symptomatic relief without clearing the root cause of the disease. Phytochemicals, such as withanolides, curcumin, bacosides, EGCG, resveratrol, rosmarinic acid, limonene, caffeic acid, and lycopene, due to their pleiotropic nature, target multiple pathways, thereby inhibiting A β aggregation, suppressing tau hyperphosphorylation, decreasing oxidative stress, enhancing antioxidant

defenses, and regulating neuro-inflammatory responses simultaneously. Therefore, these compounds are emerging as promising candidates.

While preclinical studies have strongly supported the neurotherapeutic potential of phytochemicals, translating their efficacy into clinical trials remains severely limited by inconsistent outcomes in human trials and by their poor bioavailability. Advanced nanotechnology-based delivery systems, such as transferosomes, carbon quantum dots, and micro-emulsions, offer promising strategies to overcome major limitations in bioavailability and BBB permeability. Future research should prioritize conducting large-scale, well-controlled clinical trials to enable robust clinical validation. Another important direction is optimizing nanotechnology-based delivery systems to enhance bioavailability and BBB penetration. In addition, studies on the synergistic effect should be conducted to maximize their therapeutic potential. By bridging the gap between traditional medicine and modern nanotechnology-based delivery systems, phytochemicals hold the potential to redefine therapeutic strategies for AD in the coming decades.

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Conflict of interest

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