INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Paper

Natural Neuroprotectants: Exploring Plant-Derived Compounds for the Prevention of Alzheimer's Disease

Anjali Kandekar*

SNJB Shriman Sureshdada Jain College Of Pharmacy, Chandwad, Nashik.

ARTICLE INFO

Published: 07 Aug 2026
Keywords:
Alzheimer's disease; Neuroprotection; Medicinal plants; Phytochemicals; Neuroinflammation; Oxidative stress; Nanotechnology; Blood-brain barrier
DOI:
10.5281/zenodo.21838085

ABSTRACT

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder and the leading cause of dementia worldwide. The progressive nature of the disease, together with increasing global life expectancy, has resulted in a substantial rise in the number of affected individuals, creating a major public health and socioeconomic challenge. Alzheimer's disease is characterized by progressive memory impairment, cognitive dysfunction, behavioral abnormalities, and irreversible neuronal degeneration. The principal pathological hallmarks include extracellular deposition of amyloid-beta (Aβ) plaques, intracellular accumulation of hyperphosphorylated tau protein as neurofibrillary tangles, oxidative stress, neuroinflammation, mitochondrial dysfunction, cholinergic neuronal loss, synaptic degeneration, and neuronal apoptosis.Current therapeutic approaches, including acetylcholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists, mainly provide symptomatic relief without effectively preventing disease progression. Consequently, increasing attention has been directed toward identifying naturally occurring neuroprotective compounds capable of modulating multiple pathological pathways involved in Alzheimer's disease. Plant-derived phytochemicals possess diverse pharmacological properties, including antioxidant, anti-inflammatory, anti-amyloidogenic, anti-tau, anti-apoptotic, cholinesterase inhibitory, and neurotrophic activities.Among the most extensively investigated phytochemicals are curcumin, resveratrol, quercetin, epigallocatechin-3-gallate, bacosides, ginsenosides, withanolides, berberine, rosmarinic acid, luteolin, apigenin, catechins, eugenol, and huperzine A. Experimental and clinical investigations have demonstrated that these bioactive compounds attenuate oxidative stress, inhibit amyloid-beta aggregation, reduce tau hyperphosphorylation, suppress neuroinflammation, improve mitochondrial function, and preserve neuronal survival..

***Corresponding Author:** Anjali Kandekar
Address: *SNJB Shriman Sureshdada Jain College Of Pharmacy, Chandwad, Nashik..*
Email ✉: anjalikandekar4@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

furthermore, recent advances in nanotechnology-based drug delivery systems have significantly improved the bioavailability, stability, and brain-targeting efficiency of plant-derived neuroprotective compoundsThis review comprehensively summarizes current evidence regarding medicinal plants and phytochemicals with neuroprotective potential against Alzheimer's disease. Particular emphasis is placed on molecular mechanisms, pharmacological evidence, nanotechnology-based delivery systems, clinical investigations, and future research directions. The integration of natural products with advanced pharmaceutical technologies may provide promising strategies for preventing or delaying Alzheimer's disease progression

INTRODUCTION

3.3 Tau Hyperphosphorylation and Neurofibrillary Tangles

Tau is a microtubule-associated protein that stabilizes neuronal microtubules and facilitates axonal transport. Under physiological conditions, tau undergoes reversible phosphorylation that regulates its interaction with microtubules. In AD, however, abnormal activation of kinases—including glycogen synthase kinase-3β (GSK-3β), cyclin-dependent kinase-5 (CDK5), mitogen-activated protein kinases (MAPKs), and c-Jun N-terminal kinase (JNK)—results in excessive tau phosphorylation, leading to microtubule destabilization and the formation of intracellular neurofibrillary tangles (NFTs) [21].

Hyperphosphorylated tau loses its affinity for microtubules, impairing axonal transport of mitochondria, synaptic vesicles, and essential proteins. This disruption compromises neuronal communication, synaptic plasticity, and cellular energy homeostasis. Aggregated tau also spreads trans-synaptically in a prion-like manner, contributing to the progressive anatomical distribution of AD pathology throughout the brain [22].

Several plant-derived polyphenols and flavonoids have demonstrated the capacity to inhibit tau phosphorylation through suppression of GSK-3β, activation of protein phosphatase-2A (PP2A), modulation of PI3K/Akt signaling, and attenuation of oxidative stress. These compounds also reduce tau aggregation and preserve microtubule integrity, suggesting an important disease-modifying role [23].

3.4 Oxidative Stress

Oxidative stress represents one of the earliest and most persistent pathological events in AD. The human brain is particularly susceptible to oxidative injury because of its high oxygen consumption, abundant polyunsaturated fatty acids, and relatively limited endogenous antioxidant defenses. Excessive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) damages lipids, proteins, nucleic acids, and cellular membranes, ultimately impairing neuronal viability [24].

Aβ accumulation, mitochondrial dysfunction, metal ion dysregulation, chronic inflammation, and impaired antioxidant enzyme activity collectively contribute to excessive oxidative stress. Elevated levels of malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), protein carbonyls, and oxidized DNA have consistently been observed in AD patients [25].

Phytochemicals exert antioxidant effects through multiple mechanisms:

- Direct scavenging of ROS and RNS
- Activation of the nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element pathway
- Upregulation of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx)
- Inhibition of lipid peroxidation
- Preservation of mitochondrial redox balance
- Chelation of redox-active transition metals [26]

Because oxidative stress contributes to virtually every stage of AD pathogenesis, antioxidant phytochemicals are considered among the most promising preventive interventions.

3.5 Neuroinflammation

Chronic neuroinflammation is increasingly recognized as a central driver rather than merely a consequence of AD progression. Persistent activation of microglia and astrocytes in response to Aβ plaques and damaged neurons leads to sustained release of pro-inflammatory cytokines, chemokines, nitric oxide, prostaglandins, and reactive oxygen intermediates [27].

Activated microglia secrete tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, interferon-γ, and inducible nitric oxide synthase (iNOS), creating a self-perpetuating inflammatory cycle that accelerates neuronal injury. Chronic activation of the nuclear factor-kappa B (NF-κB) pathway further amplifies inflammatory signaling and contributes to synaptic dysfunction [28].

Numerous phytochemicals suppress neuroinflammation by:

- Inhibiting NF-κB activation
- Reducing cyclooxygenase-2 (COX-2) expression
- Downregulating iNOS
- Decreasing inflammatory cytokine production
- Modulating NLRP3 inflammasome activation
- Promoting polarization of microglia toward anti-inflammatory phenotypes [29]

These anti-inflammatory properties complement their antioxidant and anti-amyloid activities, highlighting the multitarget potential of natural neuroprotectants.

3.6 Mitochondrial Dysfunction

Mitochondria play a pivotal role in neuronal energy metabolism, calcium regulation, and apoptosis. Mitochondrial abnormalities appear early in AD and contribute to ATP depletion, ROS overproduction, impaired calcium buffering, and activation of intrinsic apoptotic pathways [30].

Aβ peptides accumulate within mitochondria, where they interact with mitochondrial proteins such as amyloid-binding alcohol dehydrogenase and cyclophilin D, disrupting oxidative phosphorylation and promoting permeability transition pore opening. These events trigger cytochrome c release, caspase activation, and neuronal apoptosis [31].

Several plant-derived compounds improve mitochondrial health by:

- Preserving mitochondrial membrane potential
- Enhancing ATP synthesis
- Promoting mitochondrial biogenesis through PGC-1α activation
- Improving electron transport chain efficiency
- Reducing mitochondrial ROS production
- Stimulating mitophagy and removal of dysfunctional mitochondria [32]

3.7 Cholinergic Dysfunction

Loss of cholinergic neurons within the basal forebrain contributes significantly to memory impairment in AD. Reduced acetylcholine synthesis, increased acetylcholinesterase (AChE) activity, and degeneration of cholinergic projections impair learning and cognitive performance [33].

Current FDA-approved symptomatic therapies primarily target this pathway through inhibition of AChE. Interestingly, numerous medicinal plants contain natural cholinesterase inhibitors capable of enhancing cholinergic neurotransmission while simultaneously providing antioxidant and anti-inflammatory benefits [34].

Natural cholinesterase inhibitors often exhibit lower toxicity and additional neuroprotective mechanisms compared with conventional synthetic inhibitors, making them attractive candidates for long-term preventive use.

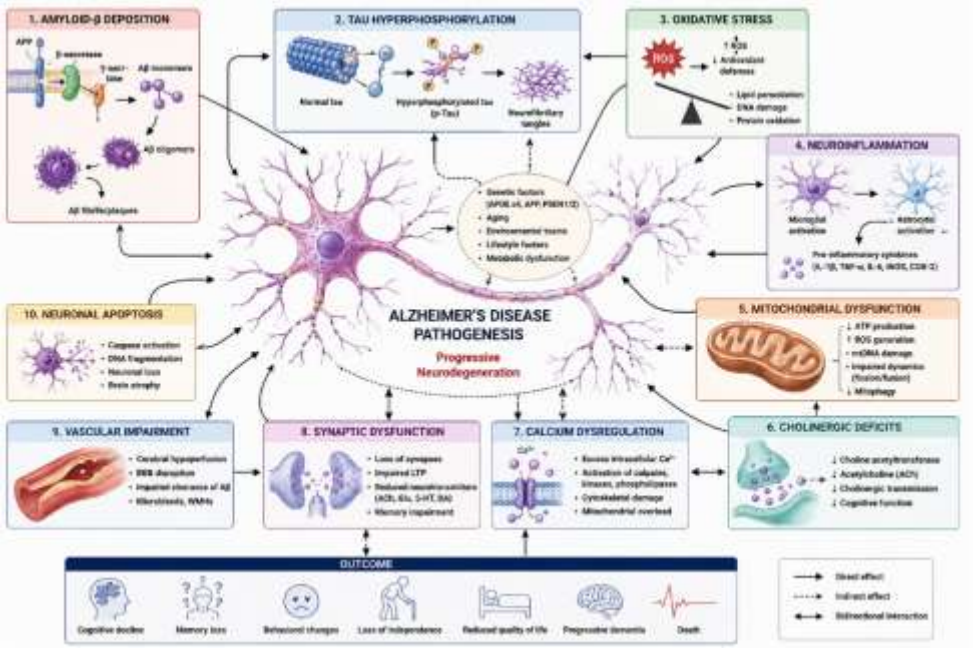

Fig.2 Multifactorial Pathogenesis of Alzheimer's Disease

4. Plant-Derived Neuroprotective Compounds

4.1 Classification of Neuroprotective Phytochemicals

Plants synthesize an enormous diversity of secondary metabolites that protect against environmental stressors and pathogens. Many of these compounds also interact with mammalian molecular targets implicated in neurodegeneration. The principal classes of neuroprotective phytochemicals include:

- Polyphenols
- Flavonoids
- Phenolic acids
- Stilbenes
- Alkaloids
- Terpenoids
- Carotenoids
- Lignans
- Coumarins
- Organosulfur compounds
- Saponins
- Glycosides [35]

Unlike conventional drugs that frequently target a single protein, phytochemicals often influence multiple signaling pathways simultaneously, producing synergistic neuroprotective effects.

4.2 Polyphenols

Polyphenols constitute one of the largest classes of naturally occurring antioxidants and have received considerable attention in AD research. They are abundant in fruits, vegetables, tea, cocoa, berries, grapes, nuts, herbs, and medicinal plants [36].

Major neuroprotective mechanisms include:

- Scavenging free radicals
- Inhibiting Aβ aggregation
- Suppressing tau phosphorylation
- Reducing neuroinflammation
- Improving mitochondrial function
- Enhancing synaptic plasticity
- Promoting autophagy
- Modulating gut microbiota composition [37]

Several epidemiological studies suggest that diets rich in polyphenols are associated with slower cognitive decline and reduced dementia risk.

4.3 Flavonoids

Flavonoids represent one of the most extensively studied groups of neuroprotective phytochemicals.

Structurally, they consist of two aromatic rings linked by a heterocyclic pyran ring and include flavones, flavonols, flavanones, flavanols, anthocyanins, and isoflavones [38].

Flavonoids readily modulate intracellular signaling pathways involved in neuronal survival, including:

- PI3K/Akt
- ERK/MAPK
- CREB
- Brain-derived neurotrophic factor (BDNF)
- Nrf2/HO-1
- NF-κB
- GSK-3β [39]

These compounds also improve cerebral blood flow, promote hippocampal neurogenesis, inhibit apoptosis, reduce excitotoxicity, and preserve synaptic proteins involved in learning and memory.

4.4 Curcumin

Curcumin, the principal polyphenolic constituent of *Curcuma longa*, is among the most extensively investigated phytochemicals for AD prevention. It exhibits remarkable antioxidant, anti-inflammatory, anti-amyloidogenic, metal-chelating, and neurogenic properties [40].

Experimental studies have demonstrated that curcumin:

- Inhibits Aβ fibril formation
- Destabilizes preformed amyloid plaques
- Suppresses tau hyperphosphorylation
- Reduces microglial activation
- Activates Nrf2-mediated antioxidant responses
- Inhibits NF-κB signaling
- Improves mitochondrial function
- Enhances hippocampal neurogenesis [41]

Despite these promising findings, clinical translation has been hindered by poor aqueous solubility, rapid metabolism, and limited blood-brain barrier penetration. Nanoparticle formulations, liposomes, phospholipid complexes, and polymeric delivery systems have significantly improved curcumin bioavailability and are currently under active investigation [42].

4.5 Resveratrol

Resveratrol, a naturally occurring stilbene found in grapes, berries, peanuts, and *Polygonum cuspidatum*, has attracted considerable interest because of its ability to activate sirtuin-1 (SIRT1), an important regulator of longevity and cellular stress resistance [43].

Its neuroprotective activities include:

- Promotion of mitochondrial biogenesis
- Reduction of oxidative stress
- Enhancement of autophagy
- Inhibition of Aβ accumulation
- Suppression of tau pathology
- Improvement of cerebral blood flow
- Reduction of neuroinflammation
- Enhancement of synaptic plasticity [44]

Clinical studies suggest that resveratrol is generally well tolerated; however, optimization of dosing strategies and formulation technologies remains necessary to maximize therapeutic efficacy.

4.6 Epigallocatechin-3-Gallate (EGCG)

Epigallocatechin-3-gallate (EGCG), the principal catechin found in green tea (*Camellia sinensis*), is one of the most extensively studied natural neuroprotective compounds. Owing to its potent antioxidant and anti-inflammatory properties, EGCG has demonstrated significant efficacy in experimental models of AD. It readily interacts with multiple molecular targets involved in neurodegeneration, making it a representative example of a multitarget phytochemical [45].

EGCG reduces amyloid pathology by inhibiting β-secretase (BACE1) activity, preventing Aβ oligomerization, remodeling mature amyloid fibrils into less toxic conformations, and

enhancing amyloid clearance through autophagy. Additionally, EGCG suppresses tau hyperphosphorylation by modulating GSK-3β and MAPK signaling pathways [46].

Beyond its anti-amyloid effects, EGCG attenuates oxidative stress by activating the Nrf2/HO-1 antioxidant pathway and increasing endogenous antioxidant enzyme activity. It also suppresses neuroinflammation through inhibition of NF-κB signaling, reduction of pro-inflammatory cytokine production, and modulation of microglial activation. Experimental studies have further shown improvements in mitochondrial function, synaptic plasticity, and cognitive performance following EGCG administration [45,46].

4.7 Quercetin

Quercetin is a naturally occurring flavonol widely distributed in onions, apples, berries, grapes, broccoli, citrus fruits, and numerous medicinal plants. It exhibits diverse pharmacological activities, including antioxidant, anti-inflammatory, antiviral, anticancer, cardioprotective, and neuroprotective effects [47].

The neuroprotective activity of quercetin involves:

- Scavenging reactive oxygen and nitrogen species
- Inhibiting lipid peroxidation
- Suppressing Aβ aggregation
- Modulating tau phosphorylation
- Enhancing mitochondrial biogenesis
- Preserving blood-brain barrier integrity
- Reducing neuronal apoptosis
- Improving synaptic plasticity [47]

Quercetin also activates AMP-activated protein kinase (AMPK) and SIRT1 signaling, thereby promoting cellular energy homeostasis and autophagy. However, its relatively poor oral bioavailability has stimulated the development of nanoformulations, liposomal carriers, and polymeric nanoparticles to improve brain delivery [48].

4.8 Ginkgo biloba Extract

Standardized extracts of *Ginkgo biloba* leaves, particularly EGb 761, have been widely investigated for cognitive enhancement and dementia management. The extract contains flavonoid glycosides, terpene lactones (ginkgolides and bilobalide), and other bioactive constituents with antioxidant and vasoprotective properties [49].

The principal mechanisms of *Ginkgo biloba* include:

- Reduction of oxidative stress
- Improvement of cerebral blood flow
- Inhibition of platelet-activating factor
- Stabilization of mitochondrial function
- Enhancement of cholinergic neurotransmission
- Suppression of inflammatory mediators
- Protection against glutamate-induced excitotoxicity [49]

Several randomized clinical trials have reported modest improvements in cognition, memory, and activities of daily living among patients with mild-to-moderate dementia. Nevertheless, variability in extract composition, study design, treatment duration, and patient populations has contributed to inconsistent clinical findings [50].

4.9 Bacopa monnieri

Bacopa monnieri (Brahmi) is a traditional medicinal herb extensively used in Ayurvedic medicine as a cognitive enhancer. Its major bioactive constituents, bacosides A and B, exert neuroprotective effects through multiple molecular pathways [51].

Experimental evidence indicates that *Bacopa monnieri*:

- Enhances cholinergic neurotransmission
- Increases antioxidant enzyme activity
- Reduces lipid peroxidation
- Protects hippocampal neurons
- Improves synaptic communication

- Promotes dendritic branching
- Attenuates neuroinflammation
- Enhances learning and memory [51]

Clinical studies have demonstrated improvements in attention, memory acquisition, information processing, and cognitive performance in healthy individuals and elderly populations, supporting its potential role in AD prevention [52].

4.10 Ashwagandha (*Withania somnifera*)

Withania somnifera (Ashwagandha) is another important medicinal plant in Ayurvedic medicine with substantial neuroprotective potential. Its principal constituents, withanolides, exhibit antioxidant, anti-inflammatory, immunomodulatory, and neuroregenerative properties [53].

Mechanistic studies suggest that Ashwagandha:

- Promotes neurite outgrowth
- Facilitates synaptic regeneration
- Reduces Aβ accumulation
- Enhances clearance of amyloid deposits
- Modulates cholinergic signaling
- Reduces oxidative stress
- Suppresses inflammatory cytokines
- Improves mitochondrial integrity [53]

Animal studies consistently demonstrate improvements in cognitive function and reductions in neurodegenerative pathology following treatment with Ashwagandha extracts. Early clinical evidence is encouraging, although larger randomized controlled trials are required to confirm efficacy in AD patients [54].

4.11 Huperzine A

Huperzine A is a sesquiterpene alkaloid isolated from *Huperzia serrata*. Unlike many phytochemicals that primarily function as antioxidants, Huperzine A is a potent, reversible, and selective acetylcholinesterase inhibitor with additional disease-modifying properties [55].

Its pharmacological activities include:

- Potent inhibition of acetylcholinesterase
- Reduction of glutamate excitotoxicity
- Protection against oxidative stress
- Suppression of apoptosis
- Improvement of mitochondrial function
- Enhancement of synaptic plasticity
- Reduction of Aβ neurotoxicity [55]

Several clinical studies have demonstrated cognitive benefits comparable to currently approved cholinesterase inhibitors, although broader international studies are needed before widespread clinical adoption [56].

Table 2. Major Plant-Derived Neuroprotective Compounds and Their Principal Mechanisms of Action

Plant/Compound	Major Bioactive Constituent(s)	Principal Mechanisms	Potential Role in AD
Curcuma longa	Curcumin	Anti-amyloid, antioxidant, anti-inflammatory, anti-tau	Prevention of amyloid deposition and neuronal loss
Camellia sinensis	EGCG	Antioxidant, BACE1 inhibition, autophagy induction	Reduction of Aβ toxicity
Ginkgo biloba	EGb 761	Cerebral blood flow improvement, antioxidant	Cognitive enhancement
Bacopa monnieri	Bacosides	Cholinergic enhancement, antioxidant	Memory improvement
Withania somnifera	Withanolides	Neurogenesis, anti-inflammatory, anti-amyloid	Neuroregeneration

Huperzia serrata	Huperzine A	Acetylcholinesterase inhibition	Symptomatic cognitive improvement
Grapes/*Polygonum cuspidatum*	Resveratrol	SIRT1 activation, mitochondrial protection	Neuroprotection
Fruits and vegetables	Quercetin	Antioxidant, anti-inflammatory, autophagy	Synaptic protection

5. Molecular Mechanisms Underlying Plant-Derived Neuroprotection

Plant-derived neuroprotectants exert therapeutic effects through simultaneous modulation of multiple signaling pathways rather than acting on a single molecular target. This multitarget pharmacological profile is particularly advantageous for complex neurodegenerative disorders such as AD.

5.1 Antioxidant Mechanisms

Most neuroprotective phytochemicals directly neutralize reactive oxygen species while simultaneously stimulating endogenous antioxidant defense systems. Activation of the Nrf2 signaling pathway increases transcription of antioxidant genes encoding SOD, CAT, GPx, heme oxygenase-1 (HO-1), and glutathione biosynthetic enzymes [57].

Reduction of oxidative stress prevents lipid peroxidation, protein oxidation, mitochondrial injury, and DNA damage, thereby preserving neuronal viability.

5.2 Inhibition of Amyloidogenesis

Many phytochemicals interfere with multiple stages of Aβ formation and aggregation.

Reported mechanisms include:

- Inhibition of BACE1 activity
- Modulation of γ-secretase
- Promotion of non-amyloidogenic APP processing
- Prevention of oligomer formation
- Destabilization of amyloid fibrils
- Enhancement of autophagic clearance
- Stimulation of microglial phagocytosis [58]

Collectively, these effects reduce amyloid burden and preserve synaptic function.

5.3 Suppression of Tau Pathology

Natural compounds reduce tau pathology through inhibition of GSK-3β, CDK5, and MAPKs while enhancing phosphatase-mediated dephosphorylation of tau proteins. Several flavonoids also inhibit tau aggregation directly, thereby reducing neurofibrillary tangle formation [59].

5.4 Anti-inflammatory Mechanisms

Phytochemicals attenuate neuroinflammation by inhibiting NF-κB activation, suppressing NLRP3 inflammasome assembly, reducing inflammatory cytokine release, decreasing cyclooxygenase expression, and promoting anti-inflammatory microglial phenotypes [60].

Reduction of chronic inflammation interrupts the vicious cycle linking oxidative stress, amyloid deposition, and neuronal injury.

5.5 Mitochondrial Protection

Maintenance of mitochondrial function represents another major mechanism through which plant-derived compounds preserve neuronal survival.

These compounds:

- Improve ATP production
- Stabilize mitochondrial membranes
- Reduce mitochondrial ROS generation
- Stimulate mitochondrial biogenesis
- Promote mitophagy
- Prevent cytochrome c release
- Suppress caspase-mediated apoptosis [61]

5.6 Enhancement of Neurogenesis and Synaptic Plasticity

Several phytochemicals stimulate neurogenesis through activation of BDNF, CREB, PI3K/Akt, and ERK signaling pathways. Increased expression of synaptic proteins such as synaptophysin and PSD-95 contributes to improved learning, memory consolidation, and cognitive resilience [62].

Table 3. Molecular Targets of Plant-Derived Neuroprotectants in Alzheimer's Disease

Molecular Target	Pathological Role	Representative Phytochemicals	Therapeutic Effect
Aβ aggregation	Plaque formation	Curcumin, EGCG, Resveratrol	Reduced amyloid burden
Tau hyperphosphorylation	Neurofibrillary tangles	Curcumin, Quercetin	Reduced tau pathology
Oxidative stress	ROS-mediated injury	Polyphenols, Flavonoids	Enhanced antioxidant defense
Neuroinflammation	Cytokine release	Curcumin, EGCG, Ashwagandha	Reduced inflammatory signaling
Mitochondrial dysfunction	Energy deficit	Resveratrol, Quercetin	Improved ATP production
Cholinergic dysfunction	Memory impairment	Huperzine A, Bacopa	Improved neurotransmission

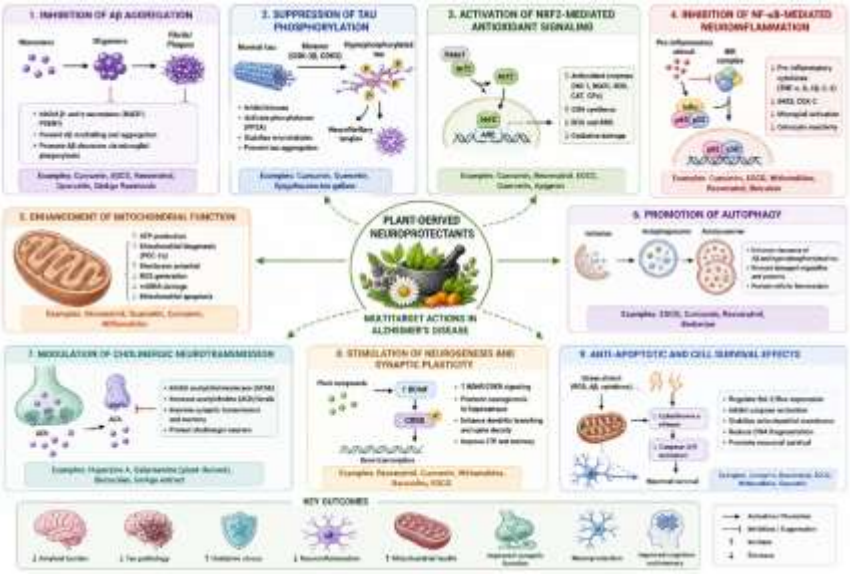

Figure 3 Molecular Mechanisms of Plant-Derived Neuroprotectants

6. Recent Advances in Plant-Based Neuroprotective Research

Recent years have witnessed remarkable advances in the development of plant-derived therapeutics for AD. Integration of modern technologies has substantially accelerated phytochemical discovery and optimization.

Major developments include:

- Artificial intelligence-assisted screening of phytochemicals
- Network pharmacology approaches
- Multi-omics analyses
- Molecular docking and molecular dynamics simulations
- High-throughput metabolomics

- CRISPR-assisted target validation
- Systems pharmacology
- Machine learning-based drug discovery [63]

Nanotechnology has further enhanced phytochemical delivery by improving solubility, stability, blood-brain barrier penetration, and sustained drug release. Liposomes, polymeric nanoparticles, solid lipid nanoparticles, dendrimers, exosomes, and nanoemulsions have significantly improved the pharmacokinetic profiles of several plant-derived compounds, including curcumin, quercetin, and resveratrol [64].

These technological innovations are expected to facilitate the translation of promising phytochemicals from laboratory research to clinical application.

Table 4. Emerging Technologies Enhancing Phytochemical-Based Therapy

Technology	Application	Advantages	Technology
Liposomes	Encapsulation of hydrophobic phytochemicals	Improved BBB penetration	Liposomes
Polymeric nanoparticles	Controlled drug delivery	Sustained release and higher bioavailability	Polymeric nanoparticles
Solid lipid nanoparticles	Brain-targeted delivery	Enhanced stability	Solid lipid nanoparticles
Nanoemulsions	Improved solubility	Better oral absorption	Nanoemulsions
Molecular docking	Target identification	Accelerated drug discovery	Molecular docking
Artificial intelligence	Virtual screening	Faster lead optimization	Artificial intelligence
Multi-omics	Mechanistic investigation	Personalized medicine	Multi-omics

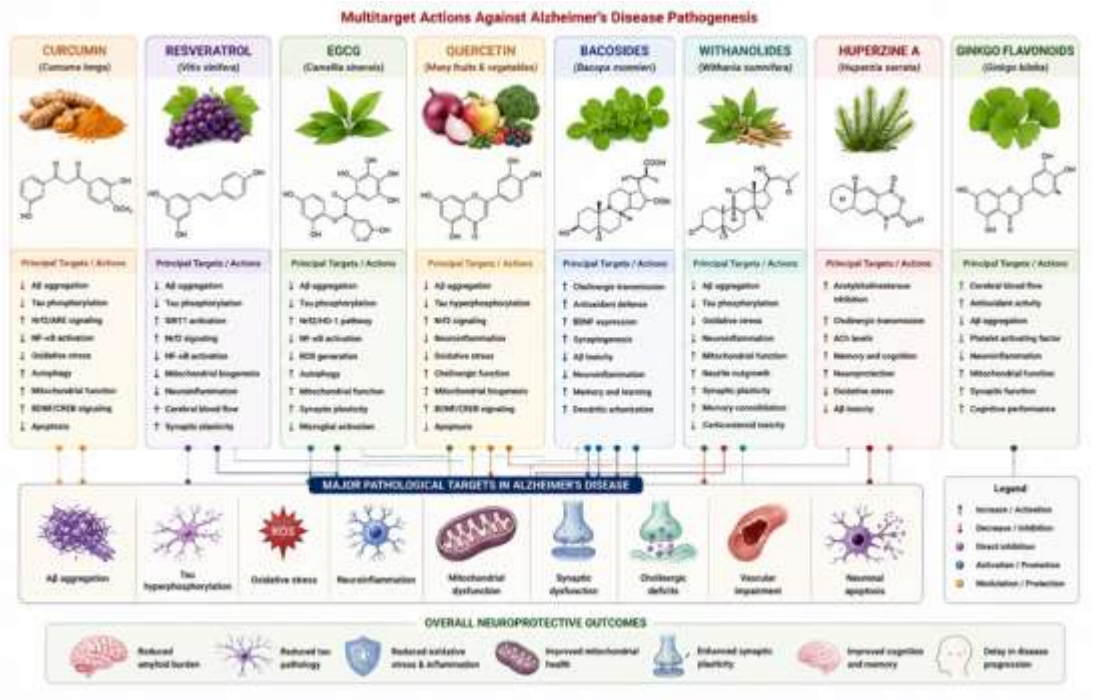

Fig.4 Representative Neuroprotective Phytochemicals and Their Therapeutic Targets

7. Challenges and Limitations in the Clinical Translation of Plant-Derived Neuroprotectants

Despite encouraging preclinical evidence, relatively few plant-derived neuroprotective

compounds have progressed to routine clinical use for the prevention or treatment of Alzheimer's disease (AD). Several scientific, pharmacological, manufacturing, and regulatory challenges continue to hinder their successful translation into evidence-based therapeutics [65].

7.1 Poor Bioavailability

One of the major limitations of many phytochemicals is their poor oral bioavailability. Compounds such as curcumin, quercetin, resveratrol, and EGCG exhibit limited aqueous solubility, low intestinal absorption, rapid metabolism, and extensive first-pass hepatic elimination, resulting in low systemic exposure and insufficient concentrations within the central nervous system [66].

Current approaches to overcome these limitations include:

- Liposomal formulations
- Polymeric nanoparticles
- Solid lipid nanoparticles
- Nanoemulsions
- Cyclodextrin inclusion complexes
- Phospholipid complexes (phytosomes)
- Intranasal drug delivery
- Polymeric micelles

These advanced delivery systems improve stability, prolong circulation time, enhance blood-brain barrier (BBB) penetration, and increase therapeutic efficacy.

7.2 Blood-Brain Barrier Penetration

The BBB is a highly selective physiological barrier that restricts the entry of many therapeutic agents into brain tissue. Although some low-molecular-weight phytochemicals can cross the BBB, their transport is often limited by efflux transporters such as P-glycoprotein and multidrug resistance-associated proteins [67].

Recent advances in receptor-mediated transport systems, ligand-targeted nanoparticles, exosome-based carriers, and intranasal delivery strategies offer promising alternatives for enhancing brain-specific delivery of plant-derived compounds while minimizing systemic toxicity.

7.3 Standardization of Herbal Preparations

The phytochemical composition of medicinal plants varies considerably depending on species, cultivar, geographical origin, harvesting season, environmental conditions, extraction methods, and storage conditions [68].

Consequently, differences in phytochemical content may lead to inconsistent pharmacological activity and variable clinical outcomes. Standardization requires:

- Botanical authentication
- Good Agricultural and Collection Practices (GACP)
- Good Manufacturing Practices (GMP)
- Quantitative phytochemical fingerprinting
- Batch-to-batch quality control
- Stability testing
- Standardized extraction procedures

Implementation of these measures is essential for ensuring reproducibility and regulatory approval.

7.4 Limited Clinical Evidence

Although hundreds of in vitro and animal studies have demonstrated neuroprotective effects of phytochemicals, comparatively few large-scale randomized controlled clinical trials have been completed [69].

Common limitations include:

- Small sample sizes
- Short treatment duration
- Heterogeneous patient populations
- Variable dosing regimens
- Different cognitive assessment tools
- Lack of biomarker-based endpoints
- Inadequate long-term follow-up

Future multicenter clinical trials incorporating neuroimaging, cerebrospinal fluid biomarkers,

plasma biomarkers, and digital cognitive assessments are necessary to establish clinical efficacy.

7.5 Safety Considerations and Herb–Drug Interactions

Most medicinal plants possess favorable safety profiles when consumed at dietary levels; however, concentrated extracts or long-term supplementation may produce adverse effects or interact with conventional medications [70].

Potential concerns include:

- Altered cytochrome P450 enzyme activity
- Drug transporter interactions
- Anticoagulant effects
- Hepatotoxicity (rare)
- Gastrointestinal disturbances
- Allergic reactions

Careful pharmacovigilance and evaluation of herb–drug interactions are particularly important in elderly patients receiving multiple medications.

CONCLUSION

Alzheimer's disease (AD) remains one of the most challenging neurodegenerative disorders worldwide because of its complex etiology, progressive clinical course, and the limited disease-modifying efficacy of currently available pharmacological therapies. Accumulating evidence indicates that AD results from the interaction of numerous pathological mechanisms, including amyloid-β (Aβ) aggregation, tau hyperphosphorylation, oxidative stress, chronic neuroinflammation, mitochondrial dysfunction, cholinergic deficits, impaired autophagy, calcium dyshomeostasis, vascular abnormalities, and synaptic degeneration. The multifactorial nature of AD highlights the limitations of conventional single-target therapeutic approaches and emphasizes the need for multitarget interventions capable of simultaneously modulating multiple disease pathways [18–20].

Plant-derived bioactive compounds have emerged as promising neuroprotective agents because of their broad spectrum of pharmacological activities and long history of medicinal use. Polyphenols, flavonoids, alkaloids, terpenoids, stilbenes, carotenoids, lignans, and other phytochemicals possess antioxidant, anti-inflammatory, anti-amyloidogenic, anti-tau, mitochondrial protective, metal-chelating, anti-apoptotic, and cholinesterase inhibitory properties. Their ability to influence several interconnected molecular pathways simultaneously distinguishes them from many conventional synthetic drugs and supports their potential role as preventive or adjunctive therapeutic agents for AD [35–40].

Among the numerous phytochemicals investigated, curcumin, resveratrol, epigallocatechin-3-gallate (EGCG), quercetin, *Ginkgo biloba* extract, *Bacopa monnieri*, *Withania somnifera*, and Huperzine A have demonstrated particularly encouraging results in experimental models. These compounds improve neuronal survival, reduce oxidative damage, suppress inflammatory signaling, inhibit amyloid and tau pathology, preserve mitochondrial function, enhance synaptic plasticity, and improve cognitive performance through diverse yet complementary mechanisms [40–56].

Despite extensive preclinical evidence, successful clinical translation remains limited. Poor oral bioavailability, restricted blood-brain barrier penetration, variability in phytochemical composition, lack of standardized herbal preparations, insufficient long-term randomized clinical trials, and regulatory challenges continue to impede widespread therapeutic application. Nevertheless, substantial progress has been achieved through nanotechnology-based drug delivery systems, systems pharmacology, computational drug discovery, metabolomics, and precision medicine approaches, which collectively

offer realistic solutions to many of these limitations [63–70].

Overall, plant-derived neuroprotectants represent an important and rapidly expanding area of neuropharmacological research. Their multitarget pharmacological profile, relatively favorable safety characteristics, and potential compatibility with existing therapeutic strategies make them attractive candidates for preventing or delaying Alzheimer's disease progression. Continued interdisciplinary collaboration among pharmacologists, neuroscientists, medicinal chemists, clinicians, botanists, and pharmaceutical scientists will be essential for translating these promising natural compounds into clinically effective interventions.

9. Future Perspectives

Future research on plant-derived neuroprotectants should move beyond traditional phytochemical screening toward integrated multidisciplinary strategies capable of accelerating drug discovery and clinical translation. Several emerging technologies and research directions are expected to reshape the development of botanical therapeutics for AD.

9.1 Precision and Personalized Phytotherapy

Increasing understanding of genetic susceptibility, epigenetic regulation, metabolomics, gut microbiota composition, and disease biomarkers may enable personalized phytotherapeutic interventions tailored to individual patients. Integration of APOE genotype, plasma biomarkers, neuroimaging, and multi-omics analyses could facilitate precision medicine approaches that optimize phytochemical selection and dosing while improving therapeutic outcomes [63,69].

9.2 Artificial Intelligence-Assisted Drug Discovery

Artificial intelligence (AI), machine learning, deep learning, and network pharmacology are expected to play increasingly important roles in identifying novel neuroprotective phytochemicals, predicting molecular targets, optimizing lead compounds, and designing multitarget therapeutic combinations. These computational approaches can substantially reduce the time and cost associated with conventional drug discovery pipelines [63].

9.3 Nanotechnology-Based Drug Delivery

Advanced drug delivery systems remain one of the most promising strategies for overcoming poor bioavailability and limited blood-brain barrier permeability. Liposomes, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, dendrimers, nanoemulsions, exosomes, and intranasal formulations are expected to improve brain targeting, controlled drug release, pharmacokinetic profiles, and therapeutic efficacy of phytochemicals such as curcumin, quercetin, resveratrol, and EGCG [64,66].

9.4 Combination Therapy

Given the multifactorial nature of AD, combination therapies involving multiple phytochemicals or phytochemicals combined with approved anti-dementia medications may produce synergistic neuroprotective effects. Rational combinations targeting oxidative stress, inflammation, amyloid pathology, tau aggregation, mitochondrial dysfunction, and cholinergic deficits simultaneously may prove more effective than monotherapy.

9.5 Standardization and Regulatory Harmonization

Future commercialization of botanical neuroprotectants will require internationally accepted standards for botanical authentication, phytochemical characterization, quality control,

manufacturing practices, and clinical evaluation. Adoption of standardized extraction procedures and validated analytical techniques will improve reproducibility and facilitate regulatory approval across different countries [68].

9.6 Biomarker-Guided Clinical Trials

Future randomized controlled trials should incorporate validated biomarkers such as plasma phosphorylated tau, amyloid PET imaging, cerebrospinal fluid biomarkers, structural and functional MRI, and digital cognitive assessments to provide objective evidence of disease modification. Long-term multicenter studies involving diverse populations are essential for establishing the preventive efficacy and safety of plant-derived neuroprotectants [69,70].

9.7 Exploration of Understudied Medicinal Plants

Although several phytochemicals have been extensively investigated, thousands of medicinal plant species remain pharmacologically unexplored. Ethnopharmacological knowledge, biodiversity conservation, metabolomic profiling, and high-throughput screening may identify novel compounds with unique mechanisms of action against AD. Exploration of traditional medicinal systems such as Ayurveda, Traditional Chinese Medicine, Kampo, and African herbal medicine may further expand the repertoire of neuroprotective agents.

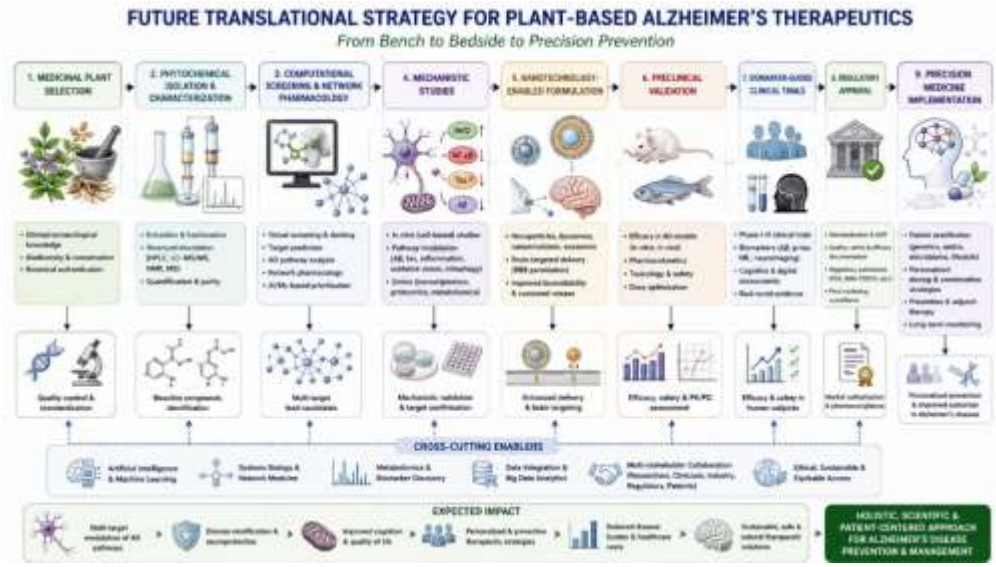

Fig.5 Future Translational Strategy for Plant-Based Alzheimer's Therapeutics

9.8 Overall Perspective

Future success in preventing or delaying Alzheimer's disease is likely to depend on the integration of natural products with advanced pharmaceutical technologies, biomarker-guided precision medicine, computational drug discovery, and well-designed clinical trials. Rather than replacing conventional therapies, plant-derived neuroprotectants are expected to complement existing therapeutic strategies by targeting multiple pathological mechanisms simultaneously. Continued investment in multidisciplinary research will be crucial for translating these promising compounds into safe, standardized, and clinically effective interventions for the global population at risk of Alzheimer's disease.

REFERENCES

1. Prince M, Wimo A, Guerchet M, Ali GC, Wu YT, Prina M. *World Alzheimer Report 2015: The Global Impact of Dementia*. London: Alzheimer's Disease International; 2015.
2. Nichols E, Steinmetz JD, Vollset SE, et al. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. **Lancet Public Health**. 2022;7(2)–e125.
3. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. **Lancet**. 2020;396(10248):413–446.
4. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. **EMBO Mol Med**. 2016;8(6):595–608.
5. De Strooper B, Karran E. The cellular phase of Alzheimer's disease. **Cell**. 2016;164(4):603–615.
6. Long JM, Holtzman DM. Alzheimer disease: an update on pathobiology and treatment strategies. **Cell**. 2019;179(2):312–339.
7. Cummings J, Lee G, Zhong K, Fonseca J, Taghva K. Alzheimer's disease drug development pipeline. **Alzheimers Dement (N Y)**. 2021;7(1).
8. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. **N Engl J Med**. 2023;388:9–21.
9. Howes MJR, Perry NSL, Houghton PJ. Plants with traditional uses and activities relevant to Alzheimer's disease. **Pharmacol Biochem Behav**. 2003;75(3):513–527.
10. Singh M, Kaur M, Kukreja H, Chugh R, Silakari O, Singh D. Acetylcholinesterase inhibitors as Alzheimer's therapeutics. **Eur J Med Chem**. 2013;70:165–188.
11. Mandel SA, Amit T, Weinreb O, Reznichenko L, Youdim MBH. Simultaneous manipulation of multiple brain targets by green tea catechins. **J Nutr Biochem**. 2008;19(4):229–234.
12. Vauzour D. Dietary polyphenols as modulators of brain functions. **Proc Nutr Soc**. 2012;71(1):104–111.
13. Kumar A, Singh A, Ekavali. A review on Alzheimer's disease pathophysiology and its management. **Pharmacol Rep**. 2015;67(2):195–203.
14. Lane CA, Hardy J, Schott JM. Alzheimer's disease. **Eur J Neurol**. 2018;25(1):59–70.
15. Scheltens P, De Strooper B, Kivipelto M, et al. Alzheimer's disease. **Lancet**. 2021;397(10284):1577–1590.
16. Wimo A, Guerchet M, Ali GC, et al. The worldwide costs of dementia 2015. **Alzheimers Dement**. 2017;13(1):1–7.
17. Kivipelto M, Mangialasche F, Ngandu T. Lifestyle interventions to prevent cognitive impairment and dementia. **Lancet Neurol**. 2018;17(5):391–392.
18. Querfurth HW, LaFerla FM. Alzheimer's disease. **N Engl J Med**. 2010;362(4):329–344.
19. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease. **Science**. 2002;297(5580):353–356.
20. Busche MA, Hyman BT. Synergy between amyloid-β and tau. **Nat Neurosci**. 2020;23(10):1183–1193.
21. Wang Y, Mandelkow E. Tau in physiology and pathology. **Nat Rev Neurosci**. 2016;17(1):5–21.
22. Congdon EE, Sigurdsson EM. Tau-targeting therapies for Alzheimer's disease. **Nat Rev Neurol**. 2018;14(7):399–415.
23. Cummings JL, Tong G, Ballard C. Treatment combinations for Alzheimer's disease. **Alzheimers Dement**. 2019;5:271–282.

24. Butterfield DA, Halliwell B. Oxidative stress in Alzheimer's disease. **Nat Rev Neurosci**. 2019;20(3):148–160.
25. Sultana R, Perluigi M, Butterfield DA. Oxidatively modified proteins in Alzheimer's disease. **Free Radic Biol Med**. 2009;47(10):1487–1494.
26. Uttara B, Singh AV, Zamboni P, Mahajan RT. Oxidative stress and neurodegenerative diseases: a review of upstream and downstream antioxidant therapeutic options. **Curr Neuropharmacol**. 2009;7(1):65–74.
27. Heneka MT, Carson MJ, El Khoury J, et al. Neuroinflammation in Alzheimer's disease. **Lancet Neurol**. 2015;14(4):388–405.
28. Leng F, Edison P. Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? **Nat Rev Neurol**. 2021;17(3):157–172.
29. Heppner FL, Ransohoff RM, Becher B. Immune attack: the role of inflammation in Alzheimer disease. **Nat Rev Neurosci**. 2015;16(6):358–372.
30. Swerdlow RH. Mitochondria and mitochondrial cascades in Alzheimer's disease. **J Alzheimers Dis**. 2018;62(3):1403–1416.
31. Wang X, Wang W, Li L, Perry G, Lee HG, Zhu X. Oxidative stress and mitochondrial dysfunction in Alzheimer's disease. **Biochim Biophys Acta**. 2014;1842(8):1240–1247.
32. Reddy PH, Oliver DM. Amyloid beta and phosphorylated tau-induced defective autophagy and mitophagy in Alzheimer's disease. **Cells**. 2019;8(5):488.
33. Hampel H, Mesulam MM, Cuello AC, et al. The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. **Brain**. 2018;141(7):1917–1933.
34. Colović MB, Krstić DZ, Lazarević-Pašti TD, Bondžić AM, Vasić VM. Acetylcholinesterase inhibitors: pharmacology and toxicology. **Curr Neuropharmacol**. 2013;11(3):315–335.

Vauzour D, Rodriguez-Mateos A, Corona G, Oruna-Concha MJ, Spencer JPE. Polyphenols and human health: prevention of disease and mechanisms of action. **Nutrients**. 2010;2(11):1106–1131.

35. Scalbert A, Johnson IT, Saltmarsh M. Polyphenols: antioxidants and beyond. **Am J Clin Nutr**. 2005;81(1 Suppl):215S–217S.
36. Spencer JPE. The impact of flavonoids on memory and cognition. **Br J Nutr**. 2010;104(S3)–S47.
37. Kumar S, Pandey AK. Chemistry and biological activities of flavonoids: an overview. **ScientificWorldJournal**. 2013;2013:162750.
38. Nabavi SF, Sureda A, Daglia M, et al. Curcumin and neurological diseases: focus on Alzheimer's disease. **Phytother Res**. 2019;33(2):318–329.
39. Ringman JM, Frautschy SA, Teng E, Begum AN, Bardens J, Cole GM. Oral curcumin for Alzheimer's disease: tolerability and efficacy. **Alzheimers Res Ther**. 2012;4(5):43.
40. Pasinetti GM. Novel role of red wine-derived polyphenols in the prevention of Alzheimer's disease dementia and brain pathology. **J Alzheimers Dis**. 2012;28(1):1–14.
41. Bastianetto S, Quirion R. Natural extracts as possible protective agents of brain aging. **Neurobiol Aging**. 2002;23(5):891–897.
42. Weinreb O, Amit T, Mandel S, Youdim MBH. Neuroprotective molecular mechanisms of green tea polyphenols. **J Nutr Biochem**. 2009;20(12):946–954.
43. Singh HK, Dhawan BN. Neuropsychopharmacological effects of the Ayurvedic nootropic *Bacopa monnieri*. **Indian J Pharmacol**. 1997;29–S365.
44. Kuboyama T, Tohda C, Komatsu K. Neuritic regeneration and synaptic reconstruction

induced by *Withania somnifera*. **Br J Pharmacol**. 2005;144(7):961–971.

45. Wang BS, Wang H, Wei ZH, Song YY, Zhang L, Chen HZ. Efficacy and safety of Huperzine A in Alzheimer's disease and vascular dementia: a meta-analysis. **J Neural Transm (Vienna)**. 2009;116(4):457–465.
46. Anand R, Gill KD, Mahdi AA. Therapeutics of Alzheimer's disease: past, present and future. **Neuropharmacology**. 2014;76(Pt A):27–50.
47. Teleanu DM, Chircov C, Grumezescu AM, Teleanu RI. Neurotoxicity of nanomaterials: an up-to-date overview. **Nanomaterials (Basel)**. 2019;9(1):96.
48. Chen XQ, Mobley WC. Alzheimer disease pathogenesis: insights from molecular and cellular biology studies. **Clin Neurosci Res**. 2019;17:1–18.
49. Cummings J, Aisen PS, DuBois B, et al. Drug development in Alzheimer's disease: the path to 2025. **Alzheimers Res Ther**. 2016;8:39. **References (51–70)**
50. Reitz C, Brayne C, Mayeux R. Epidemiology of Alzheimer disease. **Nat Rev Neurol**. 2011;7(3):137–152.
51. Cummings J, Lee G, Ritter A, Sabbagh M, Zhong K. Alzheimer's disease drug development pipeline: 2020. **Alzheimers Dement (N Y)**. 2020;6(1):e12050.
52. Howes MJR, Perry E. The role of phytochemicals in the treatment and prevention of dementia. **Drugs Aging**. 2011;28(6):439–468.
53. Ahmed T, Gilani AH. Therapeutic potential of *Turmeric (Curcuma longa)* in Alzheimer's disease: curcumin or curcuminoids? **Phytother Res**. 2014;28(4):517–525.
54. Williams RJ, Spencer JPE. Flavonoids, cognition, and dementia: actions, mechanisms and potential therapeutic utility for Alzheimer disease. **Free Radic Biol Med**. 2012;52(1):35–45.
55. Spencer JPE. Food for thought: the role of dietary flavonoids in enhancing human memory, learning and neuro-cognitive performance. **Proc Nutr Soc**. 2008;67(2):238–252.
56. Mandel SA, Amit T, Kalfon L, Reznichenko L, Weinreb O, Youdim MBH. Cell signaling pathways in the neuroprotective actions of green tea polyphenols: implications for neurodegenerative diseases. **J Neurochem**. 2008;106(2):458–470.
57. Joseph JA, Shukitt-Hale B, Willis LM. Grape juice, berries, and walnuts affect brain aging and behavior. **J Nutr**. 2009;139(9):1813S–1817S.
58. Vafeiadou K, Vauzour D, Rodriguez-Mateos A, et al. The neuroprotective potential of flavonoids: mechanisms and clinical implications. **Nutr Healthy Aging**. 2007;1(2):95–111.
59. Bhullar KS, Rupasinghe HPV. Polyphenols: multifunctional agents for the prevention of neurodegenerative diseases. **Oxid Med Cell Longev**. 2013;2013:891748.
60. Amor S, Puentes F, Baker D, van der Valk P. Inflammation in neurodegenerative diseases. **Immunology**. 2010;129(2):154–169.
61. Mattson MP. Pathways towards and away from Alzheimer's disease. **Nature**. 2004;430(7000):631–639.
62. DeTure MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. **Mol Neurodegener**. 2019;14:32.
63. Sweeney MD, Kisler K, Montagne A, Toga AW, Zlokovic BV. The role of brain vasculature in neurodegenerative disorders. **Nat Neurosci**. 2018;21(10):1318–1331.
64. Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. **Science**. 1992;256(5054):184–185.

65. Bhat AH, Dar KB, Anees S, et al. Oxidative stress, mitochondrial dysfunction and neurodegenerative diseases: a mechanistic insight. **Biomed Pharmacother**. 2015;74:101–110.
66. Tarozzi A, Morroni F, Merlicco A, et al. Neuroprotective effects of anthocyanins and their metabolites in neurodegenerative diseases. **Curr Med Chem**. 2020;27(10):1585–1607.
67. Dinda B, Dinda M, Kulsi G, Chakraborty A, Dinda S. Therapeutic potentials of plant iridoids in Alzheimer's disease and other neurological disorders. **Eur J Med Chem**. 2019;166:185–199.
68. Ayaz M, Sadiq A, Junaid M, Ullah F, Ovais M, Ahmed J. Neuroprotective and anti-aging potentials of essential oils from aromatic and medicinal plants. **Front Aging Neurosci**. 2017;9:168.
69. Khan H, Ullah H, Aschner M, Cheang WS, Akkol EK. Neuroprotective effects of phytochemicals in Alzheimer's disease: mechanistic insights and therapeutic opportunities. **Phytomedicine**. 2022;100:154074.

,

HOW TO CITE: Anjali Kandekar, Natural Neuroprotectants: Exploring Plant-Derived Compounds for the Prevention of Alzheimer's Disease, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 8, 1304-1321, https://doi.org/10.5281/zenodo.21838085