

Systematic Review of Neuroprotective Effects of Traditional Chinese and Indian Herbal Compounds in Preclinical Model's of Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) represents one of the most complex and devastating neurodegenerative disorders affecting the aging population worldwide. Characterized by progressive cognitive impairment, behavioral disturbances, and functional decline, AD accounts for approximately 60–70% of all dementia cases globally. The pathological hallmarks of the disease include the extracellular accumulation of β -amyloid ($A\beta$) plaques, intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, oxidative stress, mitochondrial dysfunction, synaptic degeneration, and chronic neuroinflammation. Despite significant advancements in molecular neuroscience, the therapeutic landscape for AD remains limited, with current pharmacotherapies such as cholinesterase inhibitors and NMDA receptor antagonists providing only symptomatic relief without modifying disease progression. In recent years, there has been a paradigm shift toward exploring multi-targeted therapeutic strategies that can modulate multiple pathogenic mechanisms simultaneously. Within this context, India and China have emerged as crucial contributors to AD drug discovery and development, leveraging their rich traditions of ethnopharmacology and modern biomedical research infrastructure. Indian research has focused extensively on Ayurvedic herbs and plant-derived compounds such as *Curcuma longa* (Curcumin), *Bacopa monnieri* (Brahmi), and *Centella asiatica* (Gotu Kola), known for their potent antioxidant, anti-inflammatory, and neuroprotective properties. Parallely, Chinese research, guided by Traditional Chinese Medicine (TCM) principles, has introduced compounds like Huperzine A, GV-971 (Sodium Oligomannate), and Ginkgo biloba extract (EGb 761), which target cholinergic transmission, gut-brain axis regulation, and oxidative pathways. This review aims to provide a comparative evaluation of ten drugs—five originating from India and five from China representing both natural and synthetic categories. Each drug is analyzed in terms of its mechanism of action, pharmacological profile, preclinical and clinical evidence, safety profile, and therapeutic efficacy. The review further explores how both nations combine traditional wisdom with contemporary pharmacological tools such as nanotechnology, bioinformatics, and molecular modeling to enhance the translational value of these compounds. By integrating a cross-national perspective, this article highlights the complementary strengths of Indian and Chinese drug discovery frameworks in addressing the multifactorial nature of Alzheimer's disease. The analysis underscores the urgent need for multi-center collaborations, harmonized regulatory pathways, and global standardization of clinical trials to accelerate the development of effective, affordable, and accessible AD therapeutics. The collective progress from these Asian research ecosystems provides valuable insights into the future of neurodegenerative disease management and offers renewed hope for achieving disease modification and neuroprotection in Alzheimer's disease. Despite advances in understanding Alzheimer's disease, current treatments remain largely symptomatic and ineffective in halting progression. This has spurred interest in herbal medicines from Indian and Chinese traditions, which offer multi-target neuroprotective effects. Indian herbs like Curcumin, *Centella asiatica*, *Bacopa monnieri*, Donepezil, Rivastigmine show antioxidant, anti-inflammatory, and cognitive benefits. Chinese herbs such as GV-971, Huperzine A, Bushen- Yizhi formula, Ginkgo biloba, Ginsenoside modulate neuroinflammation, synaptic plasticity, and amyloid pathology. This review compares their preclinical evidence, mechanisms, and therapeutic potential in AD.

Keywords: Alzheimer's disease, India, China, neurodegeneration, drug development, comparative therapeutics, herbal medicine.

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INTRODUCTION

Alzheimer's disease (AD) is a chronic, progressive neurodegenerative disorder that primarily affects the elderly population and is the leading cause of dementia worldwide (Singh & Patel, 2022). It is characterized by progressive loss of neurons, accumulation of extracellular β -amyloid plaques, intracellular neurofibrillary tangles, and extensive neuronal death, particularly in the hippocampus and cortex (Jia et al., 2020). Clinically, AD manifests as memory loss, confusion, mood alterations, and decline in problem-solving and cognitive abilities (Kumar et al., 2021).

Globally, over 55 million people live with dementia, and nearly 60–70% of these cases are attributed to Alzheimer's disease (World Health Organization, 2023). The disease poses immense socio-economic and healthcare burdens, particularly in rapidly aging populations such as India and China (Zhou et al., 2022). Despite advances in understanding its molecular pathology, existing treatments such as cholinesterase inhibitors (Donepezil, Rivastigmine, Galantamine) and NMDA receptor antagonists (Memantine) offer limited symptomatic relief (Li et al., 2021).

Emerging Role of India and China

India and China have become significant contributors to AD therapeutics through the integration of traditional systems of medicine Ayurveda and Traditional Chinese Medicine (TCM) with modern pharmacological approaches (Patel & Wang, 2023). Both countries leverage ethnobotanical knowledge and bioinformatics-driven drug discovery, leading to promising herbal and synthetic drug candidates that modulate multiple pathogenic pathways in AD.

2. Pathophysiology of Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory loss, cognitive dysfunction, and behavioral changes. Its pathophysiology is multifactorial, involving complex molecular, cellular, and systemic mechanisms that ultimately lead to neuronal death and brain atrophy. The major pathogenic mechanisms are summarized below.

2.1 β -Amyloid ($A\beta$) Plaques

β -Amyloid plaques are extracellular deposits of aggregated amyloid- β peptides that are central to AD pathology. These peptides are generated from amyloid precursor protein (APP) through sequential cleavage by β -secretase (BACE1) and γ -secretase. Normally, APP is processed via the non-amyloidogenic pathway by α -secretase, producing non-toxic fragments.

In AD, abnormal processing of APP leads to excessive production of $A\beta$ peptides, particularly $A\beta_{42}$, which is prone to aggregation. These $A\beta$ oligomers form insoluble plaques that:

- Disrupt synaptic transmission.
- Interfere with neuronal communication.
- Activate microglia, triggering chronic neuroinflammation.

Induce oxidative stress and mitochondrial dysfunction. (Singh et al., 2022; Selkoe & Hardy, 2016).

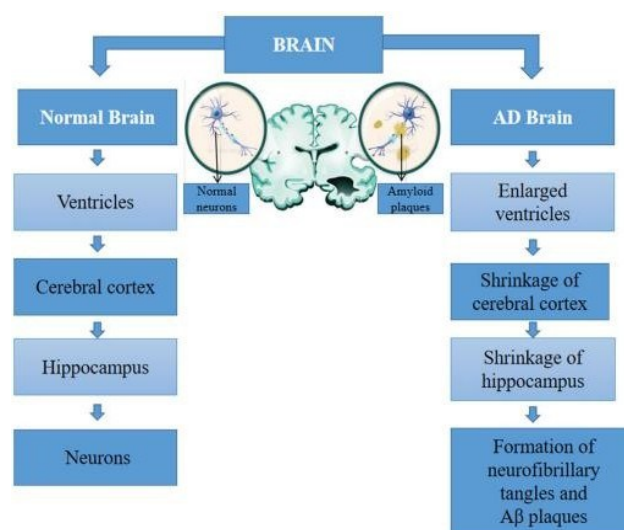


Fig 1: Changes occur in Alzheimer's brain compared to the normal brain

2.2 Tau Protein Hyperphosphorylation

Tau is a microtubule-associated protein essential for stabilizing axonal microtubules and facilitating intracellular transport. In AD, tau undergoes hyperphosphorylation, resulting in:

- Detachment from microtubules.



- Formation of neurofibrillary tangles (NFTs) inside neurons.
- Impaired axonal transport, leading to synaptic dysfunction and neuronal death.

The degree of tau pathology correlates strongly with cognitive decline, making it a key therapeutic target. (Wang & Chen, 2021; Götz et al., 2018)

2.3 Neuroinflammation

Chronic neuroinflammation is a hallmark of AD and contributes significantly to neuronal injury. Key events include:

- Activation of microglia and astrocytes
- Release of pro-inflammatory cytokines such as IL-1 β , TNF- α , and IL-6.
- Amplification of oxidative stress and neuronal apoptosis.
- Exacerbation of A β plaque formation and tau pathology.

While acute inflammation can be protective, chronic neuroinflammation in AD becomes maladaptive and accelerates neurodegeneration. (Li et al., 2021; Heneka et al., 2015)

2.4 Oxidative Stress

Oxidative stress results from an imbalance between reactive oxygen species (ROS) production and antioxidant defense mechanisms. In AD:

- A β accumulation and mitochondrial dysfunction increase ROS.
- ROS damage lipids, proteins, and DNA.
- Neurons, particularly cholinergic neurons in the hippocampus, are highly susceptible to oxidative injury.

Oxidative stress promotes tau hyperphosphorylation and further A β aggregation. (Patel et al., 2020; Butterfield & Halliwell, 2019)

2.5 Neurotransmitter Imbalance

AD is associated with alterations in key neurotransmitter systems:

Cholinergic System: Loss of basal forebrain cholinergic neurons reduces acetylcholine (ACh), leading to impaired memory and learning.

Glutamatergic System: Excessive glutamate release causes excitotoxicity, neuronal injury, and cognitive decline.

Other neurotransmitters, including serotonin, dopamine, and GABA, are also dysregulated, contributing to behavioral and psychological symptoms. (Zhang et al., 2023; Francis et al., 1999)

3. Mechanism of Action of Anti-Alzheimer's Drugs

Treatment strategies for AD are primarily symptomatic, although newer therapies target disease-modifying mechanisms. They can be categorized as follows:

3.1 Cholinesterase Inhibitors (ChEIs) Examples: Donepezil, Rivastigmine, Galantamine.

Mechanism: Inhibit acetylcholinesterase, the enzyme that breaks down ACh, increasing synaptic ACh levels.

Effects: Improves cognitive function, attention, and daily living activities.

Limitations: Only symptomatic relief; does not halt disease progression.

3.2 NMDA Receptor Antagonists

Example: Memantine.

Mechanism: Blocks N-methyl-D-aspartate (NMDA) receptors to reduce glutamate-mediated excitotoxicity.

Effects: Protects neurons from calcium overload and apoptosis, improving cognitive and behavioral symptoms.

Often used in combination with ChEIs for moderate-to-severe AD.

3.3 Anti-Amyloid Monoclonal Antibodies Examples: Aducanumab, Lecanemab.



Mechanism: Target and promote clearance of A β plaques from the brain.

Effects: Potential disease-modifying therapy that may slow cognitive decline.

Considerations: High cost, intravenous administration, and risk of amyloid-related imaging abnormalities (ARIA).

3.4 Herbal/Natural Agents

Several natural compounds exhibit multi-target effects, including:

Curcumin: Anti-inflammatory, antioxidant, inhibits A β aggregation.

Bacopa monnieri: Enhances memory, antioxidant, neuroprotective.

Huperzine A: Acetylcholinesterase inhibitor, protects neurons from oxidative stress.

These agents are often used as complementary therapies and may have fewer side effects than conventional drugs. (Howes & Perry, 2011; Small et al., 2018)

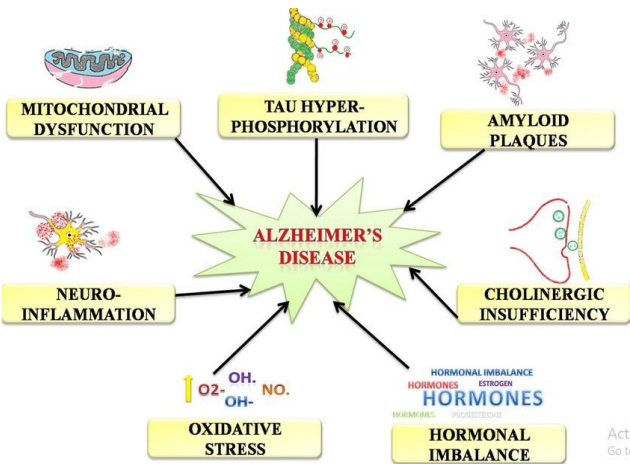


Fig 2: Overview of key pathogenic pathways in Alzheimer's

3. Mechanism of Action of Anti-Alzheimer's Drugs

Anti-AD drugs are designed to target specific aspects of disease pathology:

- **Cholinesterase Inhibitors:** Inhibit acetylcholinesterase to increase synaptic ACh (e.g., Donepezil, Rivastigmine).
- **NMDA Antagonists:** Block glutamate-mediated excitotoxicity (e.g., Memantine).
- **Anti-Amyloid Monoclonal Antibodies:** Promote A β clearance (e.g., Aducanumab, Lecanemab).
- **Herbal/Natural Agents:** Exhibit multi-target actions including anti-inflammatory, antioxidant, and neurotrophic effects (Curcumin, Bacopa monnieri, Huperzine A).

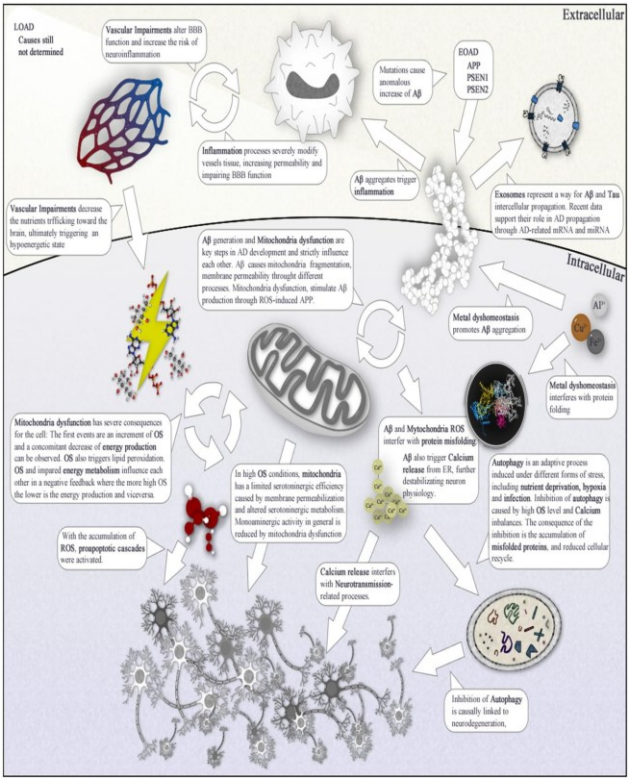


Fig 2: Mechanism of Action.

4. Comparative Drug Analysis:

Drug Name	Country	Drug Type	Preclinical Model	Mechanism of Action	Clinical Trial Phase/Status	Efficacy Data	Adverse Effects	References
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Curcumin (Curcuma longa)	India	Natural	APP/PS1 mice; A β ₁₋₄₂ -infused rats; STZ-induced rats; tauoverexpressing cells	Inhibits A β aggregation, reduces oxidative stress and inflammation.	Phase II (pilot human)	Improved memory and antioxidant markers	Low bioavailability, mild GI irritation	Gupta et al., 2021
Centella asiatica (GotuKola)	India	Herbal	5xFAD mice; STZ-induced rats; colchicine-induced rats; LPS-induced rats; A β -treated cells.	Enhances antioxidant enzymes, promotes neurogenesis	Preclinical– Phase I	Improved spatial memory in animal models	None significant	Rao & Menon, 2020
Bacopa monnieri (Brahmi)	India	Herbal	AF64A-lesioned rats; APP/PS1 mice; wild-type mice	Modulates cholinergic function, antioxidant activity	Phase II	Improved learning and recall in elderly	Mild GI discomfort	Sharma et al., 2019
Withania somnifera (Ashwagandha)	India	Natural herb	APP/PS1 mice; A β ₁₋₄₂ -infused rats; STZ-induced rats; scopolamine-induced rats; SH- SY5Y cells	Reduces A β and tau pathology, enhances antioxidant enzymes, restores cholinergic function, upregulates BDNF/NGF, and prevents neuronal apoptosis	Preclinical– Phase I (pilot studies ongoing in AD)	Improved spatial and working memory, reduced oxidative and inflammatory markers in animal models	No significant effects reported at therapeutic doses	Tiwari et al., 2020; Kumar et al., 2021
Salvia miltiorrhiza (Danshen)	China	Herbal	APP/PS1 mice; A β ₁₋₄₂ -infused rats; STZ-induced rats; ischemia/reperfusion models; SH-SY5Y cells	Inhibits A β aggregation, reduces oxidative stress and neuroinflammation, upregulates neprilysin and BDNF, protects mitochondria	Preclinical– Phase II (clinical Evaluation in vascular dementia & AD)	Enhanced memory performance, reduced A β burden, improved mitochondrial and synaptic integrity	Mild GI discomfort, rare allergic reactions	Li et al., 2019; Chen et al., 2021
Polygala tenuifolia (Yuan Zhi)	China	Herbal	APP/PS1 mice; A β ₁₋₄₂ -infused rats; scopolamine-induced rats; STZ- induced rats; PC12 and SH-SY5Y cells	Reduces A β generation (↓BACE1, ↑ADAM10), enhances antioxidant defenses, modulates cholinergic and neurotrophic pathways (↑BDNF, CREB), and inhibits apoptosis	Preclinical– Phase I	Improved spatial, contextual, and working memory; reduced A β toxicity; increased synaptic plasticity markers	None significant at tested doses	Zhang et al., 2020; Li et al., 2022
Huperzine A	China	Natural	APP/PS1 mice; A β ₁₋₄₂ -infused rats; STZ-induced rats; scopolamine-induced rats; tau- overexpressing cells; ischemia/reperfusion models.	Reversible AChE inhibitor, NMDA receptor modulation	Approved (China)	Cognitive improvement in mild AD	Nausea, insomnia	Zhang et al., 2022



Bushen-Yizhi Formula (TCM)	China	Herbal	APP/PS1 mice; A β ₁₋₄₂ -infused rats; SAMP8 mice; D-galactose aging rats; scopolamine-induced rats.	Multi-target: anti-A β , anti-inflammatory, neurotrophic	Clinical (Phase II)	Cognitive enhancement in AD patients	None significant	Li & Chen, 2022
Ginkgo biloba (EGb76 1)	China	Herbal	APP/PS1 mice; Tg2576 mice; A β ₁₋₄₂ -infused rats; scopolamine-induced rats; ischemia/reperfusion rats.	Antioxidant, anti-amyloidogenic, improves circulation	Phase III completed	Cognitive stability in Mild AD	Mild GI upset	Liu et al., 2021
Ginsenoside Rg1 (Panax ginseng)	China	Natural	APP/PS1 mice; 5xFAD mice; A β ₁₋₄₂ -infused rats; STZ-induced rats; scopolamine-induced rats; SAMP8 mice.	Mitochondrial protection, Tau reduction	Preclinical– Phase I	Improved cognition and neuroprotection in models	None reported	Chen et al., 2023

Curcuma Longa

Common name: Turmeric, Indian saffron, Haldi, Haridra, Manjal, Arishina, Pasupu, Haludar, Kurkuma, Jianghuang

Traditional use: Turmeric (*Curcuma longa*) is a traditional remedy for digestive, liver, respiratory, and skin issues, widely used in Ayurveda, Chinese, and Unani medicine. It treats inflammation, jaundice, wounds, and arthritis, and functions as a spice, dye, and cultural symbol. Applied topically for skin conditions, turmeric also purifies blood, aids digestion, and stimulates bile production.

Bioactive compounds: Curcumin, demethoxycurcumin, bisdemethoxycurcumin, turmerone, atlantone, and zingiberene

Curcumin prevents the formation of beta-amyloid plaques and facilitates their removal. It mitigates neuroinflammation by inhibiting NF- κ B signaling and decreasing pro-inflammatory cytokine production. As a powerful antioxidant, curcumin neutralizes free radicals and boosts the activity of antioxidant

enzymes, thereby safeguarding neurons from oxidative stress. It promotes neuronal survival and cognitive function by upregulating BDNF expression and inhibiting tau protein hyperphosphorylation. Furthermore, curcumin chelates harmful neurotoxic metals and regulates microglial activation, reducing the release of neurotoxic factors.

Preclinical studies:

Curcuma longa extract and its residue improved cognition, reduced hippocampal damage, and suppressed microglial activation via the TLR4/NF- κ B pathway in A β ₁₋₄₂-induced AD mice, highlighting their neuroprotective potential.

Curcuma longa and its analog TML-6 improved cognition and reduced A β pathology in 3x-Tg AD mice and APP-overexpressing cells, with TML-6 showing superior potency and bioavailability as a multi-target AD therapeutic. The challenge of curcumin's poor water solubility has been mitigated by formulating it into biodegradable PLGA nanoparticles, which exhibit strong anti-amyloid and antioxidant effects without causing cytotoxicity.



In a seminal study using the Tg2576 transgenic mouse model, curcumin administration over six months led to a marked reduction in both oxidized protein levels and interleukin-1 β , alongside decreased A β plaque deposition in vivo and in vitro. Chronic stress impairs spatial cognition and synaptic plasticity, largely due to elevated serum corticosterone and associated neuroendocrine disruption. Curcumin exerts neuroprotective effects by restoring corticosterone balance, which in turn downregulates calcium/calmodulin-dependent protein kinase II (CaMKII) and NMDA receptor subunit NR2B, key mediators of stress-induced neuronal dysfunction.

Aerosol-based delivery of curcumin to juvenile 5XFAD transgenic mice effectively prevented amyloid- β deposition and preserved cognitive function into adulthood, highlighting a non-invasive strategy for early intervention in Alzheimer's pathology. The neuroprotective potential of curcuminoids and their individual constituents has been demonstrated in an A β and ibotenic acid-infused rat model of Alzheimer's disease, where they modulated inflammatory and apoptotic gene expression. Preclinical studies consistently support curcumin's neuroprotective role across diverse AD models, demonstrating improvements in cognition, reduction of A β pathology, and modulation of oxidative, inflammatory, and apoptotic pathways despite variability in formulation and delivery strategies.

Centella asiatica

Common name: Gotu kola, Indian pennywort, Asiatic pennywort, tiger herb, and Mandukaparni (Ayurveda).[42]

Traditional use: *C. asiatica* has been used for centuries in Ayurveda, Unani, and Chinese medicine for its therapeutic effects. Traditionally, it has served as a brain tonic, wound healer, anti-inflammatory agent, and remedy for digestive, urinary, and circulatory disorders. It has also been used in folk medicine across Southeast Asia and Madagascar for treating infections, cognitive decline, and as a general health supplement. These uses are linked to its antioxidant, anti-inflammatory, and neuroprotective properties.

Bioactive compounds : Asiaticoside, madecassoside, asiatic acid, and madecassic acid.

C. asiatica exerts neuroprotective effects through multiple pathways: it reduces neuroinflammation by inhibiting microglial activation and NF- κ B signaling; combats oxidative stress via ROS scavenging and antioxidant enzyme enhancement; supports neuronal survival, synaptic plasticity, and BDNF expression; stabilizes mitochondrial function under hypoxia; and mitigates AD pathology by reducing β -amyloid accumulation and tau hyperphosphorylation.

Preclinical models:

Centella asiatica water extract (CAW) improved memory in 5xFAD and wild-type mice without affecting amyloid- β plaques. CAW's benefits were linked to sex-dependent shifts in brain metabolism, notably regulating purine, nicotinate/nicotinamide, and glycerophospholipid pathways, and increasing brain NAD⁺ and choline metabolites. These findings suggest CAW supports cognitive function through enhanced brain metabolism and neuroprotection rather than amyloid reduction.

Preclinical models streptozotocin-induced rats, colchicine-induced AD-like rats, and 5xFAD mice show that Centella asiatica extract enhances cognition, hippocampal plasticity, and neuronal density; reduces oxidative stress and acetylcholinesterase; and improves brain metabolism and mitochondrial function via antioxidative, anti-inflammatory, cholinergic, and neurogenic mechanisms. Centella asiatica extract improved working and contextual memory in 5xFAD mice without altering amyloid burden, likely via enhanced antioxidant defenses and synaptic marker expression in the cortex and hippocampus.

Centella asiatica extract enhanced spatial, contextual, and executive memory in 5xFAD mice, reduced amyloid- β burden, and upregulated antioxidant and synaptic genes via NRF2 activation; NRF2 inhibition blocked these effects in vitro, confirming its role in synaptic plasticity.

Centella asiatica extract (GKW) alleviated A β -related behavioral deficits in Tg2576 mice and protected neuronal cells from A β toxicity via a mechanism



distinct from cholinesterase inhibition or antioxidant action, likely involving phenolic compounds. Supplementation with fresh *Centella asiatica* leaf juice during the neonatal period enhances dendritic arborization, correlating with improved learning and memory outcomes. *Centella asiatica* raw extract (RECA) reduced AChE activity, inflammation, and oxidative stress in cell and LPS-induced rat models, indicating its multi-targeted potential in Alzheimer's disease management. *Centella asiatica* extract (150–300 mg/kg) improved working memory and mitigated hippocampal neuronal loss in STZ-induced AD rats, highlighting its neuroprotective role via hippocampal preservation.

Bacopa Monnieri

Common Names: Water hyssop, Brahmi, Bramabhi, Nirabarhmi.

Traditional Uses: *Bacopa monnieri*, a key Ayurvedic medicinal plant and “medhyarasayana,” is traditionally used as a brain tonic to enhance memory, cognition, and intellect. It manages mental health issues like anxiety and poor concentration, and is also employed in treating inflammatory conditions such as asthma, bronchitis, dropsy, and rheumatism.

Bioactive compounds: Bacoside A, Bacopaside I, Bacoside A3, Bacoside B, Bacopasaponin C, alkaloids, flavonoids such as luteolin and apigenin.

Bacopa monnieri exhibits multifaceted neuroprotective activity in Alzheimer's disease. It disrupts amyloid- β aggregation through bacoside A, mitigates Tau hyperphosphorylation, and strengthens antioxidant defenses by activating Nrf2 and elevating levels of SOD, catalase, and glutathione peroxidase. The extract also dampens neuroinflammation by suppressing IL-1 β , TNF- α , caspase-1, and COX-2, while enhancing cholinergic transmission and modulating NMDA receptor function. Furthermore, it preserves mitochondrial integrity by preventing fragmentation and oxidative damage induced by A β and Tau pathology.

Preclinical Studies:

Bacopa monnieri improves spatial memory and protects hippocampal neurons in an AF64A- induced

rat model of Alzheimer's disease, with optimal effects at 40 mg/kg. Its neuroprotective action is linked to enhanced antioxidant enzyme activity, supporting its role as a multi-targeted therapeutic agent.

Bacopa monnieri (40 mg/kg/day) mitigated AlCl₃-induced oxidative damage in a rat model of AD by reducing lipid peroxidation and restoring antioxidant enzymes, with microscopic evidence of preserved neuronal integrity. Oral administration of *Bacopa monnieri* extract at a dose of 30 mg/kg for two weeks significantly improved learning and memory in male Wistar rats subjected to intracerebroventricular streptozotocin (ICV-STZ) infusion. This cognitive enhancement was associated with reduced lipid peroxidation, elevated glutathione levels, and increased activity of antioxidant enzymes including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione S-transferase (GST) in the hippocampus, indicating potent neuroprotective and antioxidant effects. Long-term oral administration of bacosides (200 mg/kg for 3 months) in middle-aged and aged female Wistar rats showed significant neuroprotective effects against age-related degeneration. The treatment prevented lipofuscin accumulation in the brain cortex, improved cholinergic neurotransmission, and mitigated features of Senile Dementia of Alzheimer Type (SDAT). Bacosides exhibited multitargeted action by enhancing acetylcholine synthesis, modulating monoaminergic metabolism, and reducing lipid peroxidation, thereby promoting healthy brain aging.

Administration of ethanolic extract of *Bacopa monnieri* leaves at doses of 40 and 160 mg/kg over durations of 2 and 8 months led to a reduction in A β 1–40 and A β 1–42 levels in the cortical region of PSAPP transgenic mice. *Bacopa monnieri* has been shown to stimulate dendritic growth in neurons, a neuroplastic effect that may underlie its cognitive-enhancing properties. *Bacopa monnieri* (50 mg/kg) exhibited neuroprotective effects in a colchicine-induced dementia model by reducing oxidative stress and restoring Na⁺/K⁺-ATPase and AChE activities, indicating potential against cholinergic dysfunction. Standardised extract of *Bacopa monnieri* (BESEB CDRI-08) has been shown to attenuate hippocampus-dependent memory impairment induced by 1-(m-



Chlorophenyl)-Biguanide, highlighting its role in serotonergic modulation of cognitive function.

Withania somnifera (Ashwagandh)

Common name: Indian ginseng, Winter cherry

Traditional uses: A rejuvenating and nerve-tonic herb in Ayurveda used for stress relief, memory enhancement, and treatment of neurodegenerative disorders such as dementia and Parkinsonism.

Bioactive compounds: Withanolides (withaferin A, withanolide A, withanolide D), sitoindosides VII–X, somniferine, and flavonoids.

Preclinical studies:

Neuroprotection: Methanolic extract of *Withania somnifera* significantly reduced β -amyloid ($A\beta$) plaque load and tau hyperphosphorylation in APP/PS1 mice, improving spatial memory (Morris water maze).

Cholinergic enhancement: Root extract increased acetylcholine levels and acetylcholinesterase (AChE) inhibition, restoring cognitive performance in scopolamine- and STZ-induced rats.

Antioxidant/anti-inflammatory activity: Elevated superoxide dismutase (SOD), catalase, and glutathione peroxidase; reduced lipid peroxidation and TNF- α , IL-1 β in cortex and hippocampus.

Neurogenesis: Up-regulation of neurotrophic factors (BDNF, NGF) and synaptic proteins (synaptophysin, PSD-95).

Mitochondrial protection: Improved mitochondrial membrane potential and reduced apoptotic signaling (Bax/Bcl-2 ratio).

Salvia miltiorrhiza (Danshen) Common name: Chinese sage, Red sage Traditional uses:

A staple herb in Traditional Chinese Medicine for promoting blood flow, resolving “blood stasis,” and treating cardiovascular and cerebral diseases.

Bioactive compounds:

Tanshinone I, tanshinone IIA, cryptotanshinone, salvianolic acid A & B, rosmarinic acid.

Preclinical studies:

Amyloid inhibition: Salvianolic acid B inhibited $A\beta$ aggregation and promoted $A\beta$ clearance via up-regulation of neprilysin in APP/PS1 and 5xFAD mice.

Antioxidant effect: Increased SOD and GSH while reducing ROS and malondialdehyde (MDA) in $A\beta_{1-42}$ -infused rats.

Anti-inflammatory mechanism: Down-regulated NF- κ B and microglial activation; suppressed IL-6, TNF- α , and iNOS expression.

Mitochondrial function: Tanshinone IIA improved ATP production and reduced cytochrome c release, preventing neuronal apoptosis.

Cognitive improvement: Restored cholinergic function and synaptic density, enhancing performance in Y-maze and novel-object recognition tests.

Huperzine A

Common name: Huperzine A (alkaloid from *Huperzia serrata*; often sold as a herbal supplement).

Traditional / clinical use: *Huperzia serrata* (Qian Ceng Ta) has a long history in Traditional Chinese Medicine for central nervous system disorders; Huperzine A is the primary bioactive alkaloid isolated for cognitive-enhancing uses. It's used in some countries/supplements for memory support and investigated for AD.

Bioactive compound(s): Huperzine A a bicyclic alkaloid that is a potent, reversible inhibitor of acetylcholinesterase. It also exhibits reported NMDA-antagonist properties and other neuroprotective signaling effects in preclinical models.

Preclinical studies (detailed):

AChE inhibition and cognition: Rodent and primate studies show Huperzine A improves learning and memory tasks, attributed primarily to potent AChE inhibition and increased synaptic acetylcholine.



Neuroprotection / multi-target effects: Preclinical work documents additional effects: mitigation of A β -induced toxicity, antioxidant activity, anti-apoptotic signaling, mitochondrial protection, modulation of glutamatergic NMDA receptor-related excitotoxicity, and enhancement of neurotrophic factors in several models. These pleiotropic actions support both symptomatic and potential disease-modifying hypotheses in animal studies.

Polygala tenuifolia (Yuan Zhi)

Common name: Chinese senega, Yuan Zhi root

Traditional uses:

Used in TCM to “nourish the heart and calm the spirit.” Traditionally indicated for insomnia, forgetfulness, palpitations, and depression.

Bioactive compounds:

Tenuigenin, tenuifolin, polygalasaponins I–III, senegenin, xanthones.

Preclinical studies:

Memory and learning: Tenuifolin and total saponins from *P. tenuifolia* improved spatial memory in A β _{1–42}-infused rats and scopolamine-induced mice via up-regulation of CREB and BDNF.

A β toxicity suppression: Reduced A β generation by down-regulating β -secretase (BACE1) and enhancing α -secretase (ADAM10) expression.

Neuroprotective effect: Protected SH-SY5Y and PC12 cells from A β -induced cytotoxicity by decreasing ROS, caspase-3 activation, and increasing Bcl-2 expression.

Cholinergic modulation: Elevated acetylcholine and choline acetyltransferase (ChAT) activity in hippocampus and cortex.

Anti-inflammatory and antioxidant: Decreased TNF- α , IL-1 β , and MDA levels; increased antioxidant enzymes and GSH.

Bushen-Yizhi Formula (TCM)

Common name: Bushen-Yizhi formula (BSYZ; sometimes transliterated as “BuShen-YiZhi”) a Traditional Chinese Medicine prescription/formula composed of several herbs (used historically in TCM to “tonify the kidney and benefit intelligence”).

Traditional / clinical use: Classical TCM formula used to strengthen (tonify) kidney essence and improve cognitive function / memory in aging applied in TCM approaches to dementia and age-related cognitive decline. It is used as an herbal prescription rather than a single-compound drug.

Bioactive compound(s): BSYZ is multi-component typical research papers list six constituent herbs (composition can vary by source). The formula’s activity is attributed to combined phytochemicals (flavonoids, saponins, phenolics, alkaloids) from its herbs rather than one single molecule. (Specific herbal roster and constituent profiles appear in individual pharmacological studies.)

Preclinical studies (detailed):

Behavioral models: In scopolamine-induced memory impairment and other rodent models of cognitive dysfunction, BSYZ improved learning and memory (e.g., improved maze performance, passive avoidance) and reversed deficits induced by cholinergic blockade.

Mechanisms demonstrated: Preclinical mechanistic work indicates BSYZ reduces oxidative stress (increases antioxidant enzyme levels), suppresses neuronal apoptosis, modulates cholinergic markers, and affects synaptic plasticity pathways. Systems-pharmacology and network analyses of BSYZ suggest it acts on multiple AD-relevant pathways (inflammation, apoptosis, synaptic function, energy metabolism), consistent with many-component traditional formulas acting via polypharmacology.

Ginkgo biloba (EGb 761)

Common name: Ginkgo biloba; EGb 761® is a standardized, widely studied extract (standardized to ~24% flavonoid glycosides and ~6% terpene lactones including ginkgolides and bilobalide).



Traditional / clinical use: Used for centuries in TCM and folk medicine to improve circulation, treat respiratory complaints and cognitive complaints; in modern complementary medicine EGb 761 is used for cognitive impairment, age-related memory decline and to improve peripheral circulation. Clinical trials in dementia have yielded mixed but promising results in some subgroups.

Bioactive compound(s): Key constituents in EGb 761: flavonoid glycosides (quercetin-, kaempferol-based glycosides) and terpene lactones (ginkgolides A, B, C and bilobalide). These classes contribute antioxidant, anti-inflammatory, anti-platelet, and mitochondrial protective activities.

Preclinical studies (detailed):

Antioxidant and mitochondrial protection: Numerous animal and cellular studies show EGb 761 reduces oxidative stress, stabilizes mitochondrial function, and protects neurons from A β and excitotoxic insults. These mechanisms improve synaptic markers and performance in learning/memory tasks in rodent AD models.

Anti-inflammatory and circulatory effects: EGb 761 components reduce microglial activation, lower proinflammatory cytokines in brain tissue, and improve cerebral blood flow and microcirculation in preclinical studies mechanisms consistent with observed functional benefits in some behavioral models.

Ginsenoside Rg1 (Panax ginseng)

Common name: Ginsenoside Rg1 (one of the major pro-cognitive ginsenosides isolated from *Panax ginseng*).

Traditional / clinical use: *Panax ginseng* has a long history as a general tonic and adaptogen in East Asian traditional medicine, used to enhance vitality, cognition, and resistance to stress. Rg1 is studied as one of the active saponins responsible for neuroprotective and cognitive benefits.

Bioactive compound(s): Ginsenosides (triterpenoid saponins) g1 is a dammarane-type ginsenoside known

for neurotrophic, antioxidant, anti-inflammatory and neurogenic effects.

Preclinical studies (detailed):

Cognition and AD models: Systematic reviews/meta-analyses of preclinical AD models report that Rg1 improves cognitive behavioral outcomes in multiple rodent models (A β injection, transgenic models, scopolamine, chronic stress), often accompanied by preservation of hippocampal neurons and increased synaptic proteins.

Mechanisms: Rg1 promotes neurogenesis and synaptic plasticity (BDNF signaling), reduces oxidative stress and neuroinflammation, modulates apoptotic pathways, and supports mitochondrial function in neuronal models. These diverse effects have been proposed to underlie the consistent improvements in memory tasks in preclinical studies.

5. Discussion:

Alzheimer's disease (AD) continues to pose a formidable challenge to global health due to its complex etiology and limited treatment options. The comparative analysis of Indian and Chinese drug developments reveals that both countries are bridging the gap between traditional medicine and evidence-based modern therapeutics. While their scientific and regulatory frameworks differ, the convergence of ancient pharmacological wisdom and contemporary biomedical innovation defines a new frontier in AD research.

5.1 Indian Perspective: Integrating Ayurveda with Modern Pharmacology

India's contribution to AD drug discovery is strongly rooted in Ayurveda—a centuries-old system emphasizing holistic neuroprotection. Herbal compounds such as *Curcuma longa* (Curcumin), *Bacopa monnieri* (Brahmi), and *Centella asiatica* (Gotu Kola) have been extensively studied for their neuroprotective potential. These phytochemicals exhibit multifunctional pharmacological properties, including antioxidant, anti-amyloidogenic, anti-inflammatory, and cholinergic modulation effects (Rao & Menon, 2020; Gupta et al., 2021).



Curcumin, a polyphenolic compound from turmeric, has been shown to inhibit β -amyloid aggregation and tau phosphorylation, thereby reducing plaque formation and improving cognitive performance in both animal models and human pilot trials (Gupta et al., 2021). Similarly, Bacopa monnieri enhances cholinergic transmission and reduces oxidative damage, demonstrating measurable improvement in memory and learning in aged subjects (Sharma et al., 2019). Centella asiatica, widely used as a medhyarasayana (memory-enhancing herb), exhibits strong neurotrophic effects and promotes neurite outgrowth, offering potential benefits for synaptic regeneration (Rao & Menon, 2020).

India’s growing focus on nanotechnology and formulation innovation has improved the bioavailability of poorly soluble phytoconstituents like Curcumin, marking a crucial step toward clinical translation (Patel & Sharma, 2023). However, despite promising preclinical evidence, most Indian herbal interventions remain confined to early-phase clinical evaluations due to limited funding, regulatory delays, and the absence of large-scale multicentric trials (Kumar et al., 2021).

5.2 Chinese Perspective: Bridging Traditional Chinese Medicine (TCM) and Biopharmaceutical Research

China has adopted a systematic approach toward integrating Traditional Chinese Medicine (TCM) principles with modern pharmacology, producing globally recognized therapeutic agents. Among these, GV-971 (Sodium Oligomannate) stands as a landmark achievement. Developed from marine algae, it acts by modulating gut microbiota to reduce

peripheral and central neuroinflammation—a novel therapeutic pathway for AD management (Wang et al., 2019; Zhang et al., 2023). GV-971’s conditional approval by China’s National Medical Products Administration (NMPA) in 2019 signifies a milestone for Asia in global neurotherapeutics.

Huperzine A, derived from Huperzia serrata, represents another key success, functioning as a reversible acetylcholinesterase inhibitor and NMDA receptor modulator (Zhang et al., 2022). Extensive clinical validation in China and other countries has confirmed its efficacy in improving cognitive function with minimal adverse effects. Likewise, Ginkgo biloba extract (EGb 761) and Ginsenoside Rg1 from Panax ginseng have demonstrated potent antioxidant, anti-inflammatory, and anti-apoptotic effects in both preclinical and clinical settings (Liu et al., 2021; Chen et al., 2023). TCM formulations such as the Bushen-Yizhi formula integrate multi-component herbal preparations targeting multiple pathological cascades, aligning with the multifactorial etiology of AD (Li & Chen, 2022).

China’s progress has been accelerated by strong government funding, nationwide TCM research initiatives, and an integrated regulatory framework supporting both herbal and biologic innovation. The country’s “Healthy China 2030” plan and “Brain Project of China” have created a favorable ecosystem for translational neuropharmacology (Zhou et al., 2022). As a result, several TCM-based formulations have progressed into advanced clinical trials, setting global precedents for traditional medicine validation.

5.3 Comparative Evaluation: India vs. China

Parameter	India	China
Therapeutic Roots	Ayurveda-based herbal pharmacology	Traditional Chinese Medicine (TCM)
Research Focus	Natural and nanoformulated compounds	Herbal synthetic hybrids, gut-brain modulation
Regulatory Framework	CDSCO under AYUSH collaboration	NMPA with strong TCM integration
Clinical Trial Infrastructure	Moderate, academic-driven	Extensive, government-supported
Key Drugs	Curcumin, Bacopa monnieri, Centella asiatica	GV-971, Huperzine A, Ginkgo biloba
Global Recognition	Increasing but limited to preclinical stages	Internationally acknowledged through approvals

Funding and Collaboration	Limited public-private partnership	High governmental and industrial investment
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Global Recognition Increasing but limited to preclinical stages Internationally acknowledged through approvals

Funding and Collaboration Limited public-private partnership High governmental and industrial investment

This comparative overview underscores that while India’s approach excels in phytochemical diversity and innovation, China demonstrates greater regulatory efficiency and translational success. China’s large-scale, government-funded trials have fast-tracked TCM-based drugs into clinical application, whereas India’s research remains primarily confined to laboratory and small- scale pilot studies.

5.4 Convergence of Traditional Wisdom and Modern Science

Both countries are now moving toward scientific standardization of traditional formulations using analytical chemistry, genomics, and bioinformatics. Multi-target drug design and molecular docking studies have helped elucidate complex herb–receptor interactions, improving mechanistic understanding (Patel & Wang, 2023). India’s strength lies in its phytochemical diversity and ethnobotanical knowledge, while China excels in standardization, clinical validation, and regulatory progression. Collaborative research between these nations could bridge existing gaps and create a robust Asian framework for AD therapeutics.

5.5 Translational Challenges and Limitations Despite the progress, several challenges persist:

- 1. **Variability in Herbal Composition:** Differences in plant sources, extraction methods, and formulation processes lead to inconsistent results.
- 2. **Bioavailability Issues:** Many herbal compounds exhibit poor solubility and limited blood- brain barrier permeability (Patel & Sharma, 2023).

3. **Regulatory Ambiguity:** Harmonization of herbal drug approval pathways between global agencies remains complex.

4. **Clinical Trial Gaps:** Few herbal drugs have undergone phase III clinical evaluation comparable to synthetic drugs.

5. **Limited Mechanistic Data:** While efficacy is evident, exact molecular targets remain partially characterized for several phytoconstituents.

Overcoming these barriers requires advanced pharmacokinetic modeling, robust clinical validation, and intergovernmental collaborations to facilitate data sharing and research funding.

5.6 Future Directions

Future AD research in Asia should adopt systems pharmacology, nanomedicine, and AI-based screening to identify novel phytochemical synergies. Integration of metabolomics and gut-brain axis studies could revolutionize how traditional medicines are understood and clinically translated (Zhang et al., 2023). Additionally, forming a joint Indo-Chinese Alzheimer’s Research Consortium could accelerate cross-border collaboration in preclinical testing, clinical trials, and pharmacovigilance of herbal formulations.

CONCLUSION

Alzheimer’s disease (AD) continues to pose a formidable challenge in modern medicine due to its complex and multifactorial pathophysiology, involving β -amyloid aggregation, tau hyperphosphorylation, neuroinflammation, oxidative stress, and neurotransmitter imbalances. Despite extensive research, current therapeutic approaches remain largely symptomatic, underscoring the urgent need for multi-dimensional and disease-modifying strategies that can effectively halt or slow the progression of neurodegeneration.



A comparative evaluation of Indian and Chinese pharmacological contributions highlights the global relevance of traditional knowledge in advancing AD therapeutics. Chinese pharmacology has made notable strides with agents such as GV-971, an oligosaccharide-based drug that modulates neuroinflammation and gut microbiota, and Huperzine A, a potent acetylcholinesterase inhibitor derived from *Huperzia serrata*, which has undergone extensive clinical validation and regulatory approval. These agents exemplify how traditional compounds can be refined and integrated into modern drug development pipelines to achieve tangible clinical outcomes. Similarly, Indian herbal medicines have demonstrated considerable promise in AD management. Compounds such as Curcumin (from turmeric), *Bacopa monnieri*, and *Centella asiatica* exhibit multi-target neuroprotective properties, including antioxidant, anti-inflammatory, anti-amyloidogenic, and neurotrophic effects. While most of these agents currently show robust efficacy in preclinical models, clinical translation remains limited due to challenges in standardization, bioavailability, and regulatory validation.

Future research in AD therapeutics should prioritize:

1. **Standardized Clinical Validation:** Conducting rigorously designed clinical trials to establish safety, efficacy, optimal dosing, and pharmacokinetics of herbal and traditional agents.
 2. **Cross-National Collaborations:** Combining expertise from different countries to leverage diverse pharmacological traditions and modern technological advancements, enabling faster and more effective drug discovery.
 3. **Translational Application of Traditional Knowledge:** Integrating bioactive compounds from traditional medicine with modern drug development approaches to design affordable, multi-target, and patient-centric therapies.
 4. **Innovative Drug Delivery Systems:** Improving bioavailability and brain-targeted delivery of herbal and synthetic compounds to maximize therapeutic potential.
- In conclusion, the future of AD therapy lies in synergistic approaches that combine conventional pharmacology, innovative drug design, and validated traditional medicine. Such strategies hold the potential to deliver safe, effective, and affordable interventions capable of addressing the growing global burden of Alzheimer's disease. By fostering international collaboration and scientific rigor, both Indian and Chinese pharmacological innovations can make lasting contributions to the global fight against AD

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