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REVIEW ARTICLE

Herbal Neurotherapeutics in Alzheimer's Disease: A Comprehensive Review of Traditional Cognitive-Enhancing Medicinal Plants

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ABSTRACT

Alzheimer disease (AD) is a progressive neurodegenerative disease that involves the deterioration of cognition, loss of memory and behavioral abnormalities and it is a serious health problem in the world with no clear-cut cure. Existing pharmacological treatments are mainly symptomatic remedies that are associated with low effectiveness and undesirable outcomes, which conditions the increased attention given to the application of plant-based neurotherapeutics as additional treatment options. Medicinal systems have traditionally used a number of botanicals to stimulate memory and neuroprotection and some of these plants are currently under scientific review as to their applicability in Alzheimer disease. This is a review paper which focuses on the detailed evaluation of the traditional medicinal plants that are used in enhancing cognition, namely Clitoria ternatea, Bacopa monnieri, Withania somnifera, Ginkgo biloba and Centella asiatica. Phytochemical constituents, pharmacologic mechanism and reported neuroprotective effects of these plants are discussed as per preclinical and existing clinical evidence. Bacosides, withanolides, ginkgolides, flavonoids, and triterpenoid saponins are bioactive compounds which have proven to target oxidative stress, aggregation of β-amyloid, pathology of tau, cholinergic dysfunction and synaptic impairment, and are used in the treatment of AD which is characterized by multiple pathological hallmarkers. Although these results demonstrate the multi-target therapeutic potential of herbal compounds, much of the available evidence are preclinical with not many extensive randomized clinical trials. Safety evaluation, drug interaction with herb, standard of dosage, and phytochemical variability remain problematic to clinical translation. More researched studies are needed to determine the effectiveness, safety and protracted therapeutic applicability of these medicinal plants in the management of Alzheimer disease.

Keywords: Alzheimer's disease, Neuroprotection, Cognitive enhancement, Plant-based therapeutics, Flavonoids, Alkaloids, Anti-amyloidogenic, Cholinesterase inhibition

INTRODUCTION

Historical Background of Alzheimer's Disease (AD)

Alzheimer's disease (AD) was first clinically and neuropathologically described in 1906 by Dr. Alois Alzheimer, a German psychiatrist and neuropathologist. He observed the case of Auguste Deter, a 51-year-old woman suffering from progressive memory loss, disorientation, hallucinations, and unpredictable behavior. Following her death, Dr. Alzheimer examined her brain and reported the presence of two hallmark features: extracellular amyloid plaques and intracellular neurofibrillary tangles, which are now considered the pathological hallmarks of AD[1].

His findings were first presented at the 37th Meeting of South-West German Psychiatrists in Tübingen and later published in 1907. The term "Alzheimer's disease" was formally coined by Dr. Emil Kraepelin in 1910 in the 8th

edition of his Handbuch der Psychiatrie (Handbook of Psychiatry), in honor of Alois Alzheimer's work.

For several decades, AD was considered a rare disease, primarily affecting middle-aged individuals with early-onset symptoms. However, during the latter half of the 20th century, advancements in medical science and increasing life expectancy revealed that AD was, in fact, the leading cause of dementia among the elderly. Epidemiological studies demonstrated that its prevalence significantly increases with age, particularly after 65 years[2].

Today, AD is recognized as a major public health concern. According to the World Health Organization (WHO) and Alzheimer's Disease International (ADI), over 55 million people world wide are currently living with dementia, with AD accounting for 60–70% of these cases. This number is projected to rise to 78 million by 2030and 139 million by 2050, driven by aging populations, especially in low- and middle- income countries[10].

The increasing global burden of AD has led to the declaration of dementia as a public health priority by the WHO, sparking international efforts in early detection, treatment development, and caregiver support. Despite more than a century of research, no definitive cure exists for AD, underscoring the ongoing need for novel therapeutic strategies, including multi-targeted plant-based interventions explored in this review[3].

TYPES OF ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a heterogeneous condition that can be broadly classified based on the age of onset, genetic involvement, and clinical progression. Understanding these subtypes is essential for improving diagnosis, treatment strategies, and the development of personalized interventions[4].

Early-Onset Alzheimer's Disease (EOAD)

Early-onset AD occurs in individuals younger than 65 years of age and accounts for approximately 5–10% of all AD cases. It is often more aggressive in progression and may present with atypical symptoms, such as language impairment, visuospatial deficits, or executive dysfunction, rather than just memory loss[20].

Genetic basis: EOAD is frequently associated with autosomal dominant mutations in the following genes:

- APP (Amyloid precursor protein)
- PSEN1 (Presenilin-1)
- PSEN2 (Presenilin-2)

These mutations lead to abnormal processing of the amyloid precursor protein, resulting in excessive formation of amyloid-beta (Aβ42) peptides, which aggregate into neurotoxic plaques.

Familial Alzheimer's Disease (FAD): A subset of EOAD with a strong hereditary pattern. Inheritance is typically autosomal dominant, and affected individuals often have a family history of similar cases across generations.

EOAD poses significant challenges as it affects individuals during their most productive years, leading to early loss of employment, independence, and increased caregiver burden.

Late-Onset Alzheimer's Disease (LOAD)

Late-onset AD, also known as sporadic AD, occurs after the age of 65 and represents 90–95% of AD cases. It is a multifactorial disorder influenced by complex interactions between genetic, environmental, lifestyle, and aging-related factors.

- **Apolipoprotein E (ApoE ε4) allele** is the most significant genetic risk factor associated with LOAD. Individuals carrying one or two ε4 alleles have an increased risk of developing AD and may experience earlier symptom onset.
- **Pathogenesis:** Although not directly caused by mutations, LOAD shares common pathological features with EOAD, including amyloid-beta plaque accumulation, tau protein hyperphosphorylation, neuroinflammation, oxidative stress, and synaptic degeneration[5].
- **Environmental & lifestyle factors:** Hypertension, diabetes, obesity, physical inactivity, smoking, and low education levels are known contributors to the development of sporadic AD.

Other Subtypes and Clinical Variants

While EOAD and LOAD are the major types, there are atypical clinical presentations or subtypes of AD that deviate from the typical amnestic profile:

- **Posterior Cortical Atrophy (PCA):** Affects visual processing regions of the brain, leading to difficulties in reading, depth perception, and coordination.
- **Logopenic Variant Primary Progressive Aphasia (lvPPA):** Language impairment is predominant, with difficulty in word retrieval and sentence repetition.
- **Frontal Variant AD:** Behavioral and executive dysfunction are more prominent than memory loss.

These variants may be misdiagnosed as other forms of dementia (e.g., frontotemporal dementia) and require careful differential diagnosis using neuroimaging and biomarker analysis[6].

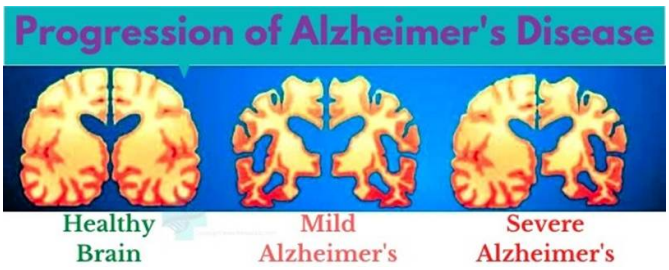


Fig. 1

DIAGNOSIS OF ALZHEIMER'S DISEASE

Sr. No.	Diagnostic Method	Description
1	**Clinical Assessment**	Involves patient history, observation of memory loss, behavioral changes, and daily life challenges.
2	**Cognitive Testing**	Tests like MMSE and MoCA evaluate memory, language, attention, and visuospatial skills.
3	**Neurological Examination**	Assesses motor function, reflexes, coordination, and helps rule out non-AD neurological conditions.
4	**Neuroimaging**	MRI and CT scans detect brain atrophy, while PET scans assess amyloid plaques and glucose metabolism.
5	**Biomarker Analysis (CSF)**	Measurement of amyloid-β42, total tau, and phosphorylated tau proteins in cerebrospinal fluid.
6	**Genetic Testing**	Detects mutations in APP, PSEN1, PSEN2 genes (in EOAD) and presence of ApoE ε4 allele (in LOAD).
7	**Differential Diagnosis**	Rules out other forms of dementia (e.g., vascular, Lewy body) and psychiatric disorders.

PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is characterized by progressive neurodegeneration that leads to cognitive decline, memory loss, and behavioral dysfunction. The underlying pathophysiology involves several interconnected processes:

Amyloid-β Plaque Formation

- The hallmark of AD is the accumulation of extracellular amyloid-β (Aβ) peptides.
- These are formed by the abnormal cleavage of amyloid precursor protein (APP) via β-secretase and γ-secretase enzymes.
- Aβ peptides aggregate to form insoluble plaques, which disrupt synaptic communication and induce inflammation[7].

Neurofibrillary Tangles (NFTs)

- Inside neurons, hyperphosphorylation of the tau protein leads to the formation of neurofibrillary tangles.
- These tangles destabilize microtubules, impair intracellular transport, and ultimately lead to neuronal death.

Synaptic Dysfunction and Neurodegeneration

- Aβ plaques and tau tangles interfere with synaptic function and plasticity.
- Progressive synapse loss contributes to memory and learning deficits.

Neuroinflammation

- Chronic activation of microglia and astrocytes occurs in response to Aβ deposits.
- These immune cells release pro-inflammatory cytokines and reactive oxygen species, worsening neuronal damage.

Oxidative Stress

- Imbalance between reactive oxygen species (ROS) and antioxidant defenses leads to oxidative damage of lipids, proteins, and DNA.
- Mitochondrial dysfunction further exacerbates energy failure and neuronal apoptosis.

Cholinergic Hypothesis

- AD is associated with a significant reduction in acetylcholine (ACh) levels due to degeneration of cholinergic neurons in the basal forebrain.
- This deficit contributes to cognitive impairments and forms the basis for current symptomatic therapies.

Glutamatergic Excitotoxicity

- Excess glutamate activates NMDA receptors excessively, leading to calcium overload and neuronal death.
- This mechanism also contributes to synaptic loss and memory dysfunction.

Vascular Dysfunction

- Impaired cerebral blood flow and blood-brain barrier dysfunction contribute to the accumulation of toxic proteins and reduced nutrient delivery to brain tissue.

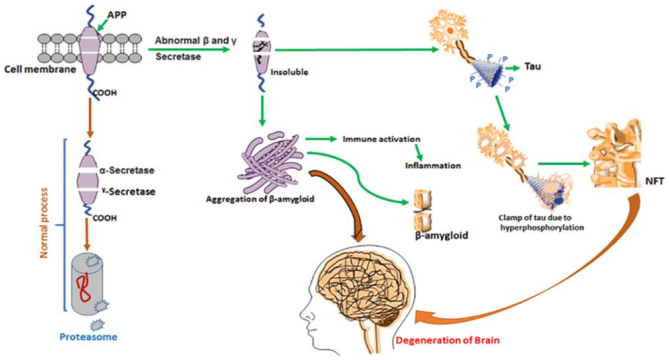


Fig. 2

PLANTS USED FOR ALZHEIMER'S DISEASE

Given the complexity of AD pathophysiology and the limited efficacy of monotherapeutic drugs, the role of phytotherapy is gaining momentum. Medicinal plants contain diverse bioactive compounds capable of targeting multiple disease pathways simultaneously, often with fewer side effects. Traditional systems like Ayurveda, Siddha, and Traditional Chinese Medicine have long recognized the neuroprotective potential of various herbs[8].

Butterfly Pea (*Clitoria ternatea*)

Fig. 3: *Clitoria ternatea*

Botanical Classification

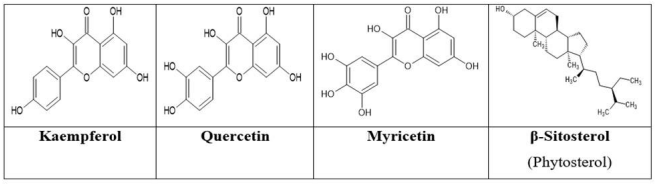
- **Botanical Name:** *Clitoria ternatea*
- **Common Name:** Butterfly Pea, Blue Pea, Aparajita (in Hindi), Asian Pigeonwings
- **Geographical Source:** Native to tropical Asia, especially India, Sri Lanka, and Southeast Asia. Also found in Africa, Australia, and Central & South America.
- **Kingdom:** Plantae
- **Family:** Fabaceae (Leguminosae)
- **Tribe:** Phaseoleae
- **Genus:** *Clitoria*
- **Species:** *Clitoria ternatea*

Botanical characteristics

The Butterfly Pea Flower (*Clitoria ternatea*) is a perennial climbing vine with pinnate leaves and vibrant blue, purple, or white flowers. It produces oblong pods containing 6–10 seeds and has a deep taproot with nitrogen-fixing properties. Thriving in tropical climates, it prefers well-drained soils and full sunlight. Propagated by seeds or cuttings, it is valued for its ornamental appeal, soil enrichment, and natural dye properties[9].

Chemical Constituents and Bioactive Components of *Clitoria ternatea*

- **Flavonoids** (Kaempferol, Quercetin, Myricetin) – Strong antioxidants
- **Anthocyanins** (Clitorin, Delphinidin, Ternatin) – Responsible for blue pigmentation and cardiovascular benefits
- **Tannins & Saponins** – Anti-inflammatory and lipid-lowering properties
- **Alkaloids** – Neuroprotective and vasodilatory effects
- **Peptides & Proteins** – Enzyme inhibitors that help regulate blood pressure



Pharmacological Activity

- **Cardio protective** – Lowers cholesterol and prevents oxidative damage
- **Neuroprotective** – Enhances cognitive function and reduces neuroinflammation
- **Anti-inflammatory** – Suppresses pro-inflammatory markers like TNF-α, IL-6
- **Antioxidant** – Neutralizes free radicals, reducing oxidative stress in arteries
- **Anti-thrombotic** – Prevents platelet aggregation and reduces clot formation
- **Hypolipidemic** – Lowers LDL cholesterol and increases HDL cholesterol

Mechanism of Action in Treating Alzheimer's disease

Clitoria ternatea, commonly known as Aparajita or Butterfly Pea, has been traditionally used in Ayurvedic medicine as a brain tonic. Recent pharmacological studies highlight its multimodal neuroprotective mechanisms that

make it a promising candidate in Alzheimer's disease (AD) therapy[10].

1. Acetylcholinesterase (AChE) Inhibition

The ethanolic and aqueous extracts of *Clitoria ternatea* exhibit significant AChE inhibitory activity, helping to increase acetylcholine levels in the brain. This compensates for the cholinergic deficit observed in AD, thereby improving memory and cognition.

2. Antioxidant Activity

Rich in anthocyanins, flavonoids, and other polyphenolic compounds, the plant effectively scavenges free radicals. This combats oxidative stress, a key contributor to neuronal damage and progression of AD.

3. Anti-inflammatory Effects

The bioactive components of C. ternatea suppress the release of pro-inflammatory cytokines (e.g., TNF-α, IL-1β) and inhibit microglial activation, thus reducing neuroinflammation, a major pathological feature of Alzheimer's disease.

4. Neurogenesis and Synaptic Plasticity

Studies indicate that the extract enhances expression of brain-derived neurotrophic factor (BDNF) and other synaptogenic proteins, which promote neuronal survival, neurogenesis, and synaptic remodeling, essential for learning and memory.

5. Anti-amyloidogenic Effect

Preliminary studies suggest *C. ternatea* may also inhibit the aggregation of β-amyloid peptides, which are central to the formation of amyloid plaques in AD brains. Though more research is needed, this suggests potential disease-modifying effects.

6. Modulation of MAO Enzymes

Some extracts have demonstrated monoamine oxidase (MAO) inhibitory activity, which could improve neurotransmitter balance and mood-related symptoms commonly associated with Alzheimer's.

Preclinical Evidence

- AChE inhibition in animal studies
- Memory enhancement in rodent models
- Strong antioxidant and anti-inflammatory effects
- Increased BDNF expression in some experimental studies

Clinical Evidence

- There are still inadequate clinical data on diagnosed patients of Alzheimer.

Toxicity & Side Effects

- Low toxicity is observed with animals.
- Human safety data limited
- None of the significant side effects associated with the conventional use.

Standardized Dose

- There is no standardized dosage of AD.
- One of the limitations is extract variability.

Evidence Gaps

- Absence of pharmacokinetic information.
- No standardization procedures.

Bacopa monnieri

Fig. 4: *Bacopa monnieri*

Botanical Classification

- **Botanical Name:** *Bacopa monnieri* (L.) Wettst
- **Common Name:** Brahmi (a name also used for Gotu kola), Andri, Water Hyssop, Indian Pennywort.
- **Geographical Source:** Mainly found in marshy wetlands of an altitude 1500 m of Indian subcontinent, Southeast Asia, Australia, subtropical United States, and tropical Africa.
- **Kingdom:** Plantae
- **Family:** Plantaginaceae
- **Tribe:** Gratioleae
- **Genus:** *Bacopa*
- **Species:** *Bacopa monnieri*
- **Binomial Name:** *Bacopa monnieri* (L.) Wettst.

Botanical characteristics

The plant *Bacopa monnieri* (L.) is semisucculent and creeping. Usually rectangular or spatulate, *Bacopa* leaves are thick and sessile, and the flowers are either light purple or white. Traditional medical practitioners have been using *bacopa* for thousands of years. The effects of *bacopa* on the central nervous system are mentioned explicitly in a number of ancient Ayurvedic writings, such as the Charaka Samhita (2500 B.C.) and the Sushruta Samhita (2300 B.C.)[11].

Chemical constituents of *Bacopa monnieri* and bioactive components

- **Triterpenoid Saponins (Bacosides)**: Major active components include bacoside A (A3, bacopaside II, bacoside X, bacosaponin C) and bacoside B, known for enhancing cognitive function.
- **Alkaloids**: Brahmine, herpestine, and hydrocotyline contribute to neuroactive effects.
- **Flavonoids**: Apigenin and luteolin offer antioxidant and anti-inflammatory properties[12].
- **Other Constituents**: Includes glycosides (asiaticoside), sterols (β-sitosterol, stigmastarol), and acids (brahmic, betulic, isobrahmic acid).

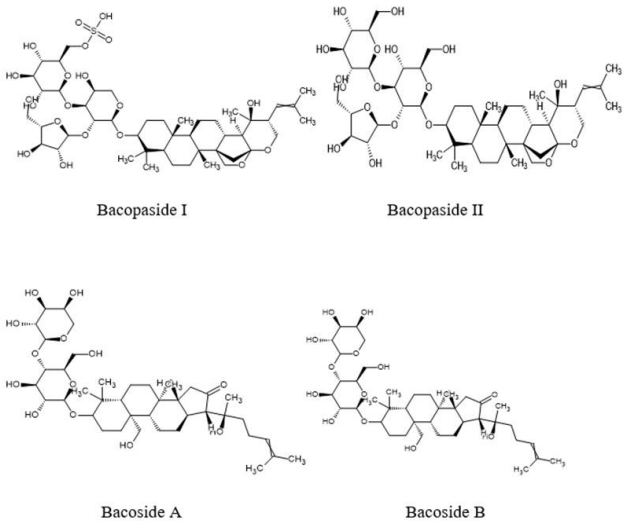


Fig. 5: Chemical constituents of *Bacopa monnieri*

Mechanism of Action in Treating Alzheimer's disease

Bacopa monnieri (Brahmi) exerts neuroprotective effects through multiple pathways:

- **Enhancement of Cholinergic Transmission**:
  Bacosides improve acetylcholine levels by inhibiting acetylcholinesterase, leading to better memory and learning.
- **Amyloid-Beta Inhibition**:
  Prevents formation and accumulation of β-amyloid plaques, one of the hallmarks of Alzheimer's pathology.
- **Antioxidant Activity**:
  Neutralizes free radicals and reduces oxidative stress in neuronal cells through flavonoids and saponins.
- **Anti-inflammatory Action**:
  Reduces neuroinflammation by downregulating pro-inflammatory mediators like TNF-α and IL-6.
- **Neurogenesis and Synaptic Repair**:
  Promotes dendritic growth and enhances synaptic plasticity, aiding in cognitive regeneration.
- **Metal Chelation**:
  Binds toxic metal ions (like iron and copper), reducing metal-induced neuronal damage.

Preclinical Evidence

- In vitro activities indicate acetylcholinesterase (AChE) inhibition.
- Animal models demonstrate –
  -Reduction of β amyloid aggregation.
  -Reduced oxidative stress indicators.
  -Better spatial memory (water maze models Morris water mazes)
  -Bacosides increase the dendritic branching and synaptic plasticity.

Clinical Evidence

- **Calabrese *et al.*, 2008 -** Randomized controlled trial in the elderly subjects.
  Normalized extract of 300 mg/day.
  Great enhancement in acquisition and retention of memory.
- **Kongkeaw *et al.*, 2014 - Meta analysis**
  Demonstrated low but meaningful cognitive growth.

Toxicity & Side Effects

- Generally well tolerated
- Mild
- Nausea
- Abdominal cramps
- Increased bowel movement
- Fatigue

Drug - Herb Interactions

- May interact with: Sedatives (additive CNS depression)
- Thyroid medications - Cholinergic medication (potentiation possibility)

Standardized Dose

- 300-450 mg/day
- Normalized to 20-55 % bacosides.
- Duration: 8 to12 weeks in the majority of trials.

Evidence Gaps

- Safety > 6 months open-ended.
- Inadequate extensive clinical trials.
- No comparison with donepezil or memantine.

***Withania somnifera* (Ashwagandha)**

Fig. 6: *Withania somnifera*

Botanical Classification

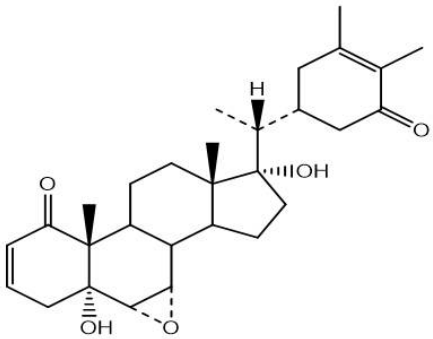
- **Botanical Name**- *Withania somnifera*
- **Common Name**- Ashwagandha, Indian ginseng, Winter cherry
- **Geographical source**- Ashwagandha is grown in the dry regions of India, Pakistan, Afghanistan, Sri Lanka, the Democratic Republic of Congo, South Africa, and Egypt. In India, it is cultivated widely in Madhya Pradesh, Uttar Pradesh, Punjab, Gujarat, and Haryana.
- **Kingdom**- Plantae
- **Order**- Solanales
- **Family**- Solanaceae
- **Genus**- *Withania*
- **Species**- *W. somnifera*
- **Binomial Name**- *Withania somnifera*

Botanical Characteristics

Short, erect shrub with greyish hairy shrub, Oval dull green leaves, Greenish yellow bisexual flowers Orange red berries in a papery covering, disc-shaped Fleshy medicinal roots[13].

Chemical constituents of *Withania somnifera* and bioactive components

W. somnifera contains chemical compounds that include alkaloids (isopelletierine, anaferine, cuseohygrine, anahygrine, etc.), steroidal lactones (withanolides, withaferins), saponins, sitoindosides and acylsterylglucosides. Major bioactive ingredients of W. somnifera consists of withanolides, withaferin A, withanolide A, withanolide D and Anaferin[14].



Withanone

Fig. 7: Phytochemical constituent Present in *Withania somnifera*

Mechanism of Action in Treating Alzheimer's disease

Withania somnifera (Ashwagandha) supports brain health and counters Alzheimer's disease through multiple pathways:

- **Anti-Amyloid Activity**: Reduces amyloid-β (Aβ) plaque accumulation by promoting its clearance and inhibiting aggregation.
- **Antioxidant Effects**: Neutralizes reactive oxygen species (ROS) and reduces oxidative damage in neurons.
- **Neuroregeneration**: Promotes axonal and dendritic growth, and restores synaptic function.
- **Anti-inflammatory Action**: Suppresses neuroinflammation by downregulating pro-inflammatory cytokines (e.g., TNF-α, IL-6).
- **Modulation of HPA Axis**: Lowers stress hormones like cortisol, which are linked to cognitive decline.
- **Acetylcholinesterase Inhibition**: Enhances cholinergic transmission and memory function.
- **Neuroprotective Steroidal Lactones**: Withanolides (e.g., withaferin A) protect against neuronal toxicity.

These mechanisms make *Withania somnifera* a potent herbal candidate for the prevention and management of Alzheimer's disease.

Preclinical Evidence

- Mouse models show:
  -Reduced Aβ plaque burden
  -Higher amyloid clearance.

-Scholarly reversal of synaptic degeneration.

- Withinolides enhance regeneration of axons.
- Anti-inflammatory and anti-oxidant properties were determined

Clinical Evidence

- Small scale human cognitive experiments.
- More evidence of stress and mild cognitive impairment.
- None of the large RCT in confirmed AD population.
- Majority of the evidence is preclinical.

Toxicity & Side Effects

- Mild: GI upset & Drowsiness
- Rare cases of hepatotoxicity.
- Avoid in pregnancy

Drug–Herb Interactions

- Possible interaction with: Sedatives, Thyroid medication, Immunosuppressants

Standardized Dose

- The standardized root extract (300-600 mg/ day)
- Normalized to withanolide concentration.

Evidence Gaps

- Neurocognitive trials that do not involve the long term.
- Lack of clarity of dose-response relationship.

Ginkgo biloba

Fig. 8: *Ginkgo biloba*

Botanical Classification

- **Botanical Name:** *Ginkgo biloba*
- **Common Name:** Ginkgo, Maidenhair Tree
- **Geographical Source:** Native to China; cultivated worldwide
- **Kingdom:** Plantae
- **Family:** Ginkgoaceae
- **Tribe:** Not applicable (Ginkgoaceae is a monotypic family)
- **Genus:** *Ginkgo*
- **Species:** *biloba*

Botanical characteristics

Ginkgo biloba is a deciduous tree with distinctive fan-shaped leaves that turn golden yellow in autumn. It has a tall, upright growth habit, reaching heights of up to 30–40 meters. The tree produces separate male and female reproductive structures, with female trees bearing fleshy, foul-smelling seeds. Ginkgo is highly resistant to pollution, pests, and diseases, making it a long-living and resilient species. It thrives in well-drained soils and temperate climates.

Chemical Constituents and Bioactive Components of *Ginkgo Biloba*

- **Flavonoids (Flavonol Glycosides):** Quercetin, Kaempferol, Isorhamnetin, Rutin
- **Terpenoids (Ginkgolides & Bilobalide):** Ginkgolide A, B, C, J, and M (Diterpenes), Bilobalide[15]
- **Organic Acids & Polyphenols:** Proanthocyanidins, Vanillic acid, Gallic acid, Shikimic acid

Pharmacological Activities of *Ginkgo Biloba*

- Anti-inflammatory (reduces cytokine production)
- Antioxidant (neutralizes free radicals)
- Cardioprotective (improves blood circulation and reduces atherosclerosis risk)
- Anti-thrombotic (prevents blood clot formation)
- Hypolipidemic (reduces LDL cholesterol and triglycerides)
- Anti-hypertensive (lowers blood pressure)

Mechanism of Action in Treating Alzheimer's disease

Ginkgo biloba, a traditional herbal remedy, exerts multiple neuroprotective effects through its rich phytochemical constituents such as flavonoids (e.g., quercetin, kaempferol) and terpenoids (e.g., ginkgolides, bilobalide). Its mechanism in Alzheimer's disease (AD) therapy is multifactorial and involves the following key pathways[16].

1. **Antioxidant Activity**
   Ginkgo flavonoids neutralize reactive oxygen species (ROS) and lipid peroxides, thereby protecting neuronal membranes from oxidative stress—a major contributor to Alzheimer's pathogenesis.

2. **Anti-inflammatory Effects**
   Ginkgolides modulate the activity of pro-inflammatory cytokines (e.g., IL-1β, TNF-α) and reduce microglial activation in the CNS, which helps limit neuroinflammation associated with plaque formation and neuronal injury.

3. **Inhibition of Amyloid-β Aggregation**
   Ginkgo biloba extracts interfere with the aggregation and deposition of Aβ peptides, potentially by downregulating β-secretase activity, which limits plaque formation and neurotoxicity.

4. **Improved Cerebral Blood Flow**
   Ginkgolides enhance microcirculation by decreasing blood viscosity and promoting vasodilation, leading to improved oxygen and glucose delivery to brain tissues—essential for cognitive performance in AD patients.

5. **Neurotransmitter Modulation**
   Ginkgo biloba may exert mild cholinergic effects by inhibiting acetylcholinesterase (AChE), thereby increasing acetylcholine levels, which are typically deficient in Alzheimer's patients.

6. **Mitochondrial Protection**
   Bilobalide supports mitochondrial function by preserving membrane potential and ATP synthesis, preventing energy failure in neurons affected by Alzheimer's pathology.

7. **Anti-apoptotic Action**
   Ginkgo extracts modulate apoptotic pathways by upregulating Bcl-2 and inhibiting caspase-3 activation, thus preventing neuronal cell death.

Preclinical Evidence

- Antioxidant activity, anti-inflammatory activity.
- Inhibits Aβ aggregation
- Enhances the blood flow to the brain.
- Protects mitochondria

Clinical Evidence

- Several RCTs conducted
- Weinmann *et al*., 2010 meta-analysis:
  -Mild to moderate cognitive improvement MSI.
  -Moderate non-significant evidence.

Toxicity & Side Effects

- Risks of bleeding (antiplatelet effect)
- Headache
- GI upset
- Dizziness

Drug Herb Interactions

Intrinsic risk of strong interaction with:

- Warfarin
- Aspirin
- Clopidogrel
- NSAIDs

Standardized Dose

- 120 to 240 mg/day

Evidence Gaps

- Conflicting trial outcomes
- Benefit mainly in mild cases

Centella asiatica (Gotu Kola)

Fig. 9: *Centella asiatica (Gotu Kola)*

Botanical Classification

- **Botanical Name**: *Centella asiatica* (L.) Urban
- **Common Name**: Gotu Kola, Mandukaparni (in Ayurveda), Indian Pennywort
- **Geographical Source**: Native to India, Sri Lanka, China, Southeast Asia, and parts of Africa; cultivated worldwide in tropical and subtropical regions
- **Kingdom**: Plantae
- **Family**: Apiaceae (Umbelliferae)
- **Tribe**: Mackinlayeae
- **Genus**: Centella
- **Species**: *asiatica*

Botanical Characteristics

Centella asiatica is a small, herbaceous plant with fan-shaped green leaves and small, pink or white flowers. It commonly grows in moist, swampy areas and spreads horizontally via stolons. The plant is prized for its adaptogenic and neuroregenerative properties in traditional Ayurvedic and Chinese medicine[17].

Chemical Constituents and Bioactive Components

- **Triterpenoids**: Asiaticoside, Madecassoside, Asiatic acid, Madecassic acid
- **Flavonoids**: Quercetin, Kaempferol
- **Sterols**: β-sitosterol
- **Other**: Amino acids, sugars, essential oils

Pharmacological Activities

- **Neuroprotective** – Enhances cognitive function and memory
- **Anti-inflammatory** – Inhibits neuroinflammation by downregulating pro-inflammatory mediators
- **Antioxidant** – Scavenges free radicals and protects against oxidative damage
- **Anxiolytic and Adaptogenic** – Reduces anxiety and enhances stress resilience

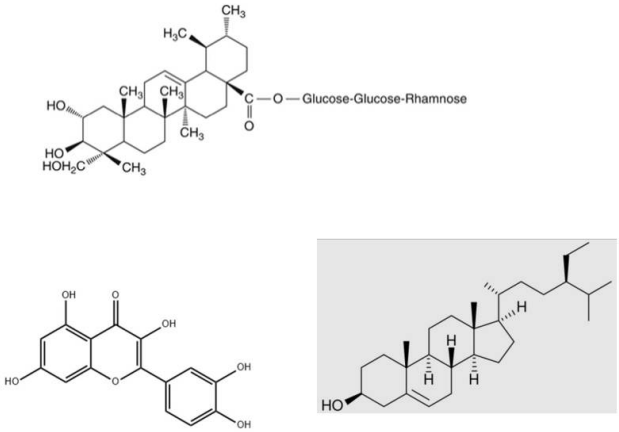


Fig. 10: Asiaticoside, Madecassoside, Asiatic acid

Mechanism of Action in Treating Alzheimer's Disease

1. **Enhancement of Cognitive Function**
   Centella asiatica has been shown to improve learning and memory by modulating BDNF (Brain-Derived Neurotrophic Factor) and enhancing synaptic plasticity[18].

2. **Antioxidant and Free Radical Scavenging**
   The triterpenoid saponins (asiaticoside and madecassoside) and flavonoids reduce oxidative stress in the brain, which is a major factor in AD progression.

3. **Anti-inflammatory Effects**
   Gotu Kola inhibits the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, reducing neuroinflammation associated with AD.

4. **Amyloid Plaque Reduction**
   Some studies suggest that *Centella asiatica* may decrease β-amyloid deposition and reduce plaque load in the brain.

5. **Neurogenesis and Synaptic Repair**
   It promotes the growth of dendrites and axons and restores damaged neurons, thereby aiding in neural regeneration.

6. **Acetylcholinesterase Inhibition**
   Mild inhibition of AChE enzyme enhances cholinergic transmission and improves memory in Alzheimer's disease models.

Preclinical Evidence

- Decreases oxidative stress on AD models.
- Reduces Aβ deposition in animals.
- Improves the quality of work of mitochondria.
- Promotes dendritic growth

Clinical Evidence

- Extremely small AD specific human trials.
- More evidence in: Memory enhancement and Anxiety reduction
- In confirmed AD patients, evidence is still preliminary.

Toxicity & Side Effects

- Generally safe
- In case of High doses: Headache and Dizziness

Drug - Herb Interactions

- Possible interaction with: Sedatives and Hepatotoxic drugs

Standardized Dose

- 500 to 750 mg per day extract

Evidence Gaps

- Lack of large RCTs
- None of the therapeutic-window established.

CONCLUSION

Alzheimer disease is one of the most intricate and problematic neurodegenerative disorders on a worldwide scale, which is progressive, marked by impaired cognitive functions and multi-factorial pathological processes, such as oxidative stress, aggregation of amyloid-β, hyperphosphorylation of tau, neuroinflammatory processes, mitochondrial dysfunction, and cholinergic disabilities. Although there has been a great leap in the biology of

various diseases, the available pharmacological treatment options are associated with minimal efficacy and may have side effects due to inadequate understanding and characteristics of symptoms.

The reviewed study is an overview of the neuroprotective effect of the chosen traditional medicinal plants: *Clitoria ternatea, Bacopa monnieri, Withania somnifera, Ginkgo biloba*, and *Centella asiatica*, which are multi-target proteins in the pathogenesis of Alzheimer disease. They are reported to have acetylcholinesterase, antioxidant and anti-inflammatory, amyloid-2 pathway modulation, synaptic relying plasticity, and neurotrophic support. These pharmacological actions are provided by bioactive compounds that include bacosides, withanolides, ginkgolides, flavonoids, and triterpenoid saponins.

It should however be noted that much of existing evidence is still preclinical and large burdens of randomized controlled trials in clinically diagnosed Alzheimer patients have not been done on a large scale and over extended period of time. Further, differences in extract formulations, absence of overall standardization, inadequate pharmacokinetic and evaluation of safety profiles and drug-herb interactions are major clinical translation problems.

Further studies must be done on rigorously designed clinical trials, standardized phytochemical characterization, dose-optimization, long-term safety assessment and mechanistic validation. As much as herbal neurotherapeutics have a promising future as complementary approaches, the evidence-based analysis of development on this disease has to define their role in daily clinical practices.

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