ROLE OF HERBAL MEDICINE IN THE TREATMENT OF ALZHEIMER'S DISEASE

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Abstract: Cognitive impairment, associated with ageing, stress, hypertension and various neurodegenerative disorders including Parkinson's disease and epilepsy, is a major health issue. The present review focuses on Alzheimer's disease (AD), since it is the most important cause of cognitive impairment. It is characterized by progressive memory loss, language deficits, depression, agitation, mood disturbances and psychosis. Although the hallmarks of AD are cholinergic dysfunction, β-amyloid plaques and neurofibrillary tangle formation, it is also associated with derangement of other neurotransmitters, elevated levels of advanced glycation end products, oxidative damage, neuroinflammation, genetic and environmental factors. On one hand, this complex etiopathology makes a response to commonly used drugs such as donepezil, rivastigmine, galantamine and memantine less predictable and often unsatisfactory. On the other hand, it supports the use of herbal medicines due to their nonspecific antioxidant and anti-inflammatory activity and specific cholinesterase inhibitory activity. The popularity of herbal medicines is also increasing due to their perceived effectiveness, safety and affordability. In the present article, the experimental and clinical evidence have been reviewed for various Indian herbal medicines such as *Centella asiatica*, *Bacopa monnieri*, *Curcuma longa*, *Clitoria ternatea*, *Withania somnifera*, *Celastrus paniculatus*, *Evolvulus alsinoides*, *Desmodium gangeticum*, *Eclipta alba*, *Moringa oleifera* and *Convolvulus pluricaulis*, which have shown potential in cognitive impairment. Some commonly available herbal formulations for memory impairment in India have also been reviewed.

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Introduction:

Ayurveda mentions three aspects of mental abilities, i.e., Dhi (process of acquisition/learning), Dhuti (process of retention) and Smriti (process of recall) [**1**]. A dysfunction in the process of acquisition/learning, retention or recall is known as dementia. Worldwide, about 40 million elderly are living with dementia [**2**,**3**]. In India, an estimated 3.7 million elderly people have dementia, and the prevalence is expected to increase two-fold by 2030 and three-fold by 2050 [**4**]. Dementia is associated with neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease and epilepsy. This review is focused on the potential of herbal medicine in AD since it is responsible for more than two-thirds of all dementia cases [**5**,**6**].

Cognitive functions that are mainly affected in AD patients include memory, executive functioning, language, visuospatial functioning and attention. Several hypotheses have been proposed for establishing the cause of AD. Cholinergic hypothesis, which is the oldest theory, describes acetylcholine (ACh) deficiency as the causative factor [**7**]. Currently available therapies for AD management are based on this hypothesis [**8**]. The β-amyloid hypothesis, most cogent hypothesis [**9**,**10**,**11**,**12**] provides the basis for development of new therapeutic strategies for AD treatment [**13**]. The histopathological hallmarks of AD are neuritic plaque and neurofibrillary tangle (NFT) formation in the brain [**14**]. Other associated factors that may also contribute to neurodegeneration in AD are elevated levels of advanced glycation end products, oxidative damage and neuroinflammation (**Figure 1**). The involvement of free radicals and inflammation in pathogenesis of AD hint towards the possible role of antioxidant and anti-inflammatory agents as therapeutic tools [**15**]. Studies have also reported that antioxidants protect against Aβ induced neuronal toxicity [**16**,**17**]. Fuzhisan (FZS), a herbal drug, demonstrated a neuroprotective effect by inhibiting Aβ (25–35)-induced activation of cyclin-dependent kinase 5, calcium influx, calpain activation and tau hyperphosphorylation [**18**]. Inhibitory effect of an aqueous extract of *Ceylon cinnamon (C.*

zeylanicum) on tau aggregation and filament formation has also been reported [**19**].

Review of Literature:

Gut microbiota dysbiosis refers to quantitative and qualitative changes of microbiota in the gut, like the reduction in beneficial microbiota, such as anti-inflammatory bacteria, and increase in detrimental microbiota, such as pro-inflammatory bacteria (**Yang et al., 2020**).

Changes in the composition of the gut microbiota in AD patients have been observed in different studies and their results varied from distinctly enriched Enterobacteriacea, *Bacteroides*, Actinobacteria, Ruminococcus, Lachnospiraceae, and Selenomonadales to decrease of *Bacteroides*, and increase of Prevotella. While other analysis revealed that AD patients showed a decreased abundance of Firmicutes and Bifidobacterium, along with increased abundance of Bacteroidetes (**Vogt et al., 2017**). Gut dysbiosis exacerbated AD pathologies and cognitive deficits by activating the Ccaat/Enhancer binding proteinβ(C/EBPβ)/AEP signaling pathway in mouse models (**Chen et al., 2022**), which was documented to mediate neuroinflammation in AD pathologies (**Wang et al., 2018**). Data from Aβ precursor protein (APP) transgenic mouse model supported the essential role of gut microbiota in AD development as a remarkable shift in the gut microbiota was accompanied with an obvious reduction in cerebral Aβ amyloid pathology (**Harach et al., 2017**). In conditions of dysbiosis, compounds produced by gut bacteria activated TREMs on macrophages, resulting in pro-inflammatory responses which not only damaged the gut barrier, but also promoted a systemic inflammatory response via the microbiota-gut-brain axis, leading to impairment of the blood-brain barrier and neuroinflammation (**Natale et al., 2019**). Gut dysbiosis is directly and closely related to a "leaky gut," manifested by gut barrier dysfunction and impaired gut permeability, which subsequently leads to an increased risk of AD (**Spielman et al., 2018**). In a state of dysbiosis, the level of benificial products like SCFAs decreases while deleterious substances like LPS increases, the integrity of the epithelial barrier is broken, leading to increased intestinal permeability and subsequent systemic inflammation (**Al et al., 2020**; **El-Sayed et al., 2021**). Ultimately, this results in neuroinflammation and the formation of amyloid plaques. In the meantime, the microbial-derived amyloids can translocate through the impaired epithelial barrier, and cross-seed with endogenous amyloids, leading to aggravation of neuroinflammation, amyloid deposition, amyloidosis and AD progression (**Leblhuber et al., 2020**; **Bairamian et al., 2022**).

Chronic neuroinflammation, along with systemic inflammation is closely associated with amyloidosis and AD progression (**Mou et al., 2022**). Growing evidence shows that gut microbiota dysbiosis has important influence on AD pathogenesis (**Leblhuber et al., 2020**) by increasing the secretion of LPS and amyloids (**Lin et al., 2019**), permeability of the intestinal membrane and the blood-brain barrier, promoting oxidative stress, neuroinflammation, Aβ formation, and ultimately neuronal death (**Bonfili et al., 2021**; **Janeiro et al., 2022**). Overall, gut dysbiosis can influence both central and peripheral pathological processes, thereafter contributing to the pathogenesis and progression of AD (**Ma et al., 2019**; **Liu et al., 2020**; **Sun et al., 2020**; **Weber et al., 2023**). Therefore, maintaining a balanced or healthy state of gut microbiota composition is crucial for ameliorating peripheral low-grade inflammation, suppressing neuroinflammatory stimuli and exerting beneficial effects on AD (**Bonfili et al., 2021**; **El-Sayed et al., 2021**; **Shabbir et al., 2021**).

The composition of gut microbiota undergoes dynamic changes due to endogenous or exogenous factors, such as dietary pattern, environmental factors, lifestyle, diseases, and medications (**El-Sayed et al., 2021**). An increased intake of a high-energy or low-fiber diet, obesity (**Grigor Eva, 2021**), a sedentary lifestyle (**O'Toole and Shiels, 2020**), and antibiotic treatment can contribute to gut dysbiosis (**Lee et al., 2022**). Current evidence has shown that diet and dietary components can exert modulatory effects on the composition of the gut microbiota. Specific dietary components like fat or sugar abundant in the Western diet affect microbial composition in a negative manner and are related to chronic low-grade inflammation, while other dietary components like fiber or resistant starch rich in plant-based and Mediterranean diet are capable of shifting the microbial composition in a positive manner (**Beam et al., 2021**).

Etiopathogenesis

In the progression of AD, synaptic loss or dysfunction, reduced neuronal metabolism, and the loss of numerous neurotransmitter systems are all seen [21]. Senile plaques made up of Amyloid-Beta (Aβ) deposits and Neurofibrillary Tangles (NFT) made up of aggregated tau proteins are the two neuropathological hallmarks of Alzheimer's disease. These plaques form as a result of abnormal processing of amyloid precursor protein, resulting in

an overproduction of β-amyloid protein. The neuronal degeneration seen in Alzheimer's disease is caused by the formation of neurofibrillary tangles and amyloid plaques. Furthermore, oxidative stress, metal ion dyshomeostasis, mitochondrial dysfunction, neuroinflammation, autophagy, Endoplasmic Reticulum (ER) dysfunction, cell cycle dysregulation, and decreased levels of the neurotransmitter acetylcholine are thought to play a role in Alzheimer's disease progression which have been implicated in the aetiology of Alzheimer's disease [22,23,24]. Some recent research has revealed that epigenetic control may play a role in the progression and progression of Alzheimer's disease [25]. Although the pathophysiology of Alzheimer's disease is still unknown, it is clear that multiple factors are involved.

Herbal medicine has gained significant attention in the management of Alzheimer's Disease (AD) due to the complex, multi-factorial nature of the condition. While conventional treatments often focus on symptom management, many herbal compounds are being studied for their potential to target the underlying mechanisms of neurodegeneration.

Here is an overview of the primary roles herbal medicines play in the treatment and support of Alzheimer's patients.

Herb	Primary Active Compound	Role in Alzheimer's Treatment
Ginkgo Biloba	Flavonoids & Terpenoids	Improves cerebral blood flow and protects mitochondrial function.
Turmeric	Curcumin	Powerful anti-inflammatory; helps clear amyloid plaques in laboratory models.
Ashwagandha	Withanolides	Acts as an adaptogen to reduce stress and may help regenerate neurites (nerve cell extensions).
Brahmi	Bacosides	Enhances memory performance and reduces oxidative stress in the hippocampus.
Sage	Essential oils	Acts as a natural AChE inhibitor, improving alertness and cognitive function.
Lemon Balm	Rosmarinic acid	Often used to manage the agitation and anxiety associated with moderate AD.

3. Integrated Roles in Patient Care

Beyond direct neuroprotection, herbal medicine serves several supportive roles:

- **Management of Behavioral and Psychological Symptoms (BPSD):** Herbs like Valerian and Chamomile are often used to address the sleep disturbances and irritability that frequently accompany AD.

Biological Mechanisms

Herbal treatments often contain bioactive compounds (such as polyphenols, alkaloids, and terpenoids) that target specific AD pathways:

- **Acetylcholinesterase (AChE) Inhibition:** Many herbs work similarly to pharmaceutical drugs (like Donepezil) by preventing the breakdown of acetylcholine, a neurotransmitter essential for memory and learning.
- **Anti-Amyloid Aggregation:** Certain herbs help inhibit the formation of amyloid-beta plaques, which are toxic protein fragments that build up between neurons.
- **Antioxidant Support:** Since the brain is highly susceptible to oxidative stress, herbs high in antioxidants help neutralize free radicals that damage brain cells.
- **Anti-Inflammatory Action:** Chronic neuroinflammation is a hallmark of AD. Herbal compounds can reduce the production of pro-inflammatory cytokines in the brain.

2. Prominent Herbal Candidates

Research has highlighted several plants with promising neuroprotective properties:

- **Neurogenesis:** Some studies suggest that certain herbs can stimulate the production of Nerve Growth Factor (NGF), potentially aiding the brain's ability to repair itself.
- **Synergistic Effects:** Herbal medicine is frequently explored as a "complementary" therapy, used alongside standard medications to potentially enhance efficacy or reduce side effects.

4. Important Considerations

While the potential is vast, there are critical caveats to keep in mind:

- **Bioavailability:** Many potent compounds, such as curcumin, are difficult for the body to absorb in high enough concentrations to cross the blood-brain barrier effectively.
- **Standardization:** The concentration of active ingredients can vary wildly between different herbal supplements.
- **Drug Interactions:** Herbal medicines can interact with prescription blood thinners or diabetes medications.

Clinical Note: While laboratory and animal studies are highly promising, many herbal treatments are still undergoing rigorous large-scale human clinical trials to definitively prove their efficacy in reversing or stopping Alzheimer's progression.

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