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Using herbs as a treatment for Alzheimer's Disease: A review

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ABSTRACT

Three components of mental talents are mentioned in Ayurveda: Dhi (acquisition/learning process), Dhuti (retention process), and Smriti (recall process) (Dua et al., 2009). Dementia is defined as a malfunction in the acquisition/learning, retention, or recall processes. An estimated 40 million senior people worldwide suffer from dementia (Liu et al., 2019 and Anonymous. 2020). According to Shahi et al. (2010), there are an estimated 3.7 million older persons in India who suffer from dementia. By 2030, the frequency is predicted to double, and by 2050, it is predicted to triple. Neurodegenerative conditions like epilepsy, Parkinson's disease, and Alzheimer's disease (AD) are linked to dementia. Just like coronary artery disease is a sort of heart disease, Alzheimer's disease is a type of brain disease. It is brought on by harm to the brain's neurons, which are nerve cells. Neurones in the brain are necessary for all human functions, including walking, talking, and thinking. With Alzheimer's disease responsible for between 60% and 80% of dementia cases, it is the most frequent cause of dementia. There are drug treatments and non-drug treatments for AD. The drug treatments may have side effects after prolonged consumption. Non-drug treatments include physical activity, memory and orientation exercises, and music- and art-based therapies. Reducing behavioural and psychological symptoms such sadness, apathy, wandering, sleep difficulties, agitation, and hostility may be the more targeted objective of non-drug therapy (Gregory et al., 2021). The experimental and clinical data on several Indian herbal remedies that have demonstrated promise in treating cognitive impairment have been examined in this article.

Keywords: Alzheimer's Disease; Herbal medicines; Antioxidants; Cognitive Decline

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INTRODUCTION

The most common type of dementia and a frequent neurodegenerative illness, Alzheimer's disease (AD) is defined by a progressive loss of memory and cognitive function (Hardy and Selkoe, 2002). AD is a neurological illness that progresses over time and is marked by a variety of symptoms, including personality changes, memory loss, and a deterioration in cognitive function. Although the precise etiology of AD remains unknown, current research indicates that genetic, environmental, dietary, and lifestyle factors all have a role in the disease's progression. Globally, particularly in India, dementia is becoming more prevalent in the elderly. Dementia's primary cause is Alzheimer's disease.

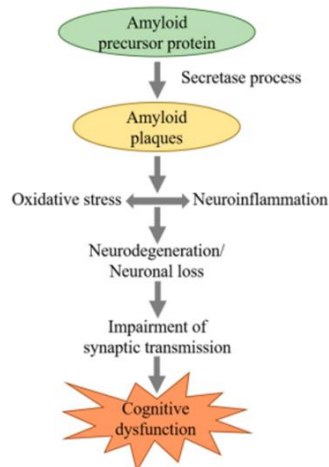


Figure 1. General pathogenesis of Alzheimer's disease (APP, amyloid precursor protein). Joginder Mala *et al.*, 2020

Alzheimer's Disease (AD) is a type of brain disease. In India, the estimated prevalence of dementia among persons 60 years of age and older is 7.4%. Approximately 8.8 million Indians who are older than 60 suffer from dementia. AD accounts for more than 75% of dementia cases and is the most prevalent kind of dementia. Alzheimer's disease (AD) is currently treated mostly with anticholinesterases, N-methyl-D-aspartate receptor antagonists, and disease-modifying medications. However, new discoveries in the field of Alzheimer's disease research have provided several new targets for treatment (www.knowledgeridge.com). Clinical features of AD include: a) Short-term memory loss or impairment; b) Language impairment/loss: difficulty finding words (Anomia); c) Apraxia: impaired motor coordination; d) Agnosia: inability to recognize familiar objects; e) Frontal executive function: impairment of organizing, planning, and sequencing; f) Parietal presentation: difficulties with orientation of space and visuospatial difficulties; g) Myoclonic jerks: abrupt, brief contractions of different muscles or the entire body. The variables that contribute to etiology are as follows: a) genetic (15%), including point mutations in the amyloid precursor protein (APP), presenilin 1 (PS1) and presenilin 2 (PS2), and inheritance of apolipoprotein-e4. b) environmental factors, such as age, gender, head trauma, and vascular risk factor. In the last ten years, more than two hundred intriguing medication options have failed clinical trials, raising the possibility that the illness and its causes are extremely complicated. As complementary and alternative therapies, medicinal plants and herbal medicines are currently gaining popularity. They are also a great place to find potential AD medications (Gregory *et al.* 2021).

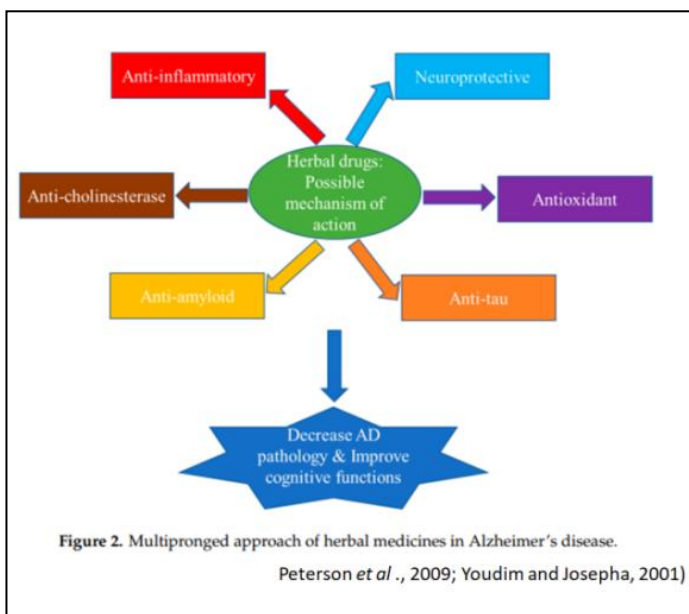
Galantamine and huperzine A are examples of traditional medications that have been used to treat Alzheimer's 6. The neuroprotective properties of plant medications including Brahmi, Shankhapushpi, Amla, Guduchi, Tulsi, Ashwagandha, and Haritaki are mentioned in the traditional Indian medical system, specifically in Ayurveda, and may enhance the therapeutic arsenal for Alzheimer's disease. The neurology of Alzheimer's disease is now well understood, and efforts to find more effective treatments are ongoing. This offers the chance to conduct additional study on an integrated approach that combines newer treatments, conventional and alternative medicines, and possible candidates for the management of Alzheimer's disease (www.knowldgeridge.com).

In fact, a number of academic studies have discussed the utilization of different medicinal plants and the primary phytochemicals found in them to treat AD. This article examines a selection of herbs for their ability to reduce inflammation, boost antioxidant levels, and improve cognitive function.

METHODOLOGY

This article provides a thorough analysis of recent research that looked into the potential significance of the Indian Knowledge System in relation to neuroprotective herbs and the bioactive substances they contain in treating dementia linked to Alzheimer's disease. Article abstracts from PubMed Central, Scopus, and Google Scholar databases were gathered, and their applicability to the topic was assessed.

Given that herbal remedies can target several locations of AD pathogenesis at both the cellular and molecular levels, they may be useful. These claims are backed by a plethora of traditional knowledge. Although the exact mechanisms by which herbal medicines protect against cognitive impairment remain unclear, it has been suggested that they do so by acting specifically on tau aggregation, AChE, β -amyloid fibril formation, and nonspecific antioxidant and anti-inflammatory activities. Study inclusion criteria: the studies that were carried out as clinical, in vivo, and in vitro investigations.



1. Ashwagandha (*Withania somnifera*)

Common name: Indian ginseng or winter cherry



Function/Outcome Measure

Antioxidant, anti-inflammatory, prevents the synthesis of A β , inhibits the death of neural cells, dendrite extension, neurite outgrowth, and restores synaptic function. It also reverses mitochondrial dysfunction and helps patients with their executive function, processing speed, social cognition, and auditory-verbal working memory. (Yarnell, 2004; Howes, 2003, Pratte et al. 2014; Pingali, 2014; Namdeo et al, 2020; Chengappa et al., 2013; Zahiruddin et al., 2020 and Kuboyama et al., 2002).

A total of 50 participants with mild cognitive impairment participated in a prospective, randomized, double-blind, placebo-controlled pilot trial. For eight weeks, the participants received either ashwagandha root extract (300 mg twice a day) or a placebo. In comparison to the placebo group, the ashwagandha treatment group showed statistically significant gains in both immediate and general memory tests after eight weeks of study. The group receiving treatment showed noteworthy enhancements in executive function, sustained attention, and information-processing speed (Choudhari et al. 2017)

2. Brahmi (*Bacopa monnieri*)



Function/Outcome Measure

Antioxidant, anti-inflammatory, enhances memory, focus, and executive functioning; prevents the generation of A β ; hinders the death of neural cells; postpones the ageing of the brain; and strengthens the heart (Stough et al . 2001; Benson et al. 2014; Sadhu et al. 2014; Farooqui et al .2018; Aguiar and Borowski, 2013; Uabundit et al. 2010; Kumar , 2006, Raghav et al . 2006)

The majority of research on Bm's ability to improve cognition in humans has been conducted on older, healthy subjects. Thirty-five people over the age of fifty-five participated in a double-blind, randomized, placebo-controlled experiment in which they were given 125 mg of Bm extract or a placebo twice a day for twelve weeks, with an additional four weeks of placebo. A series of memory tests were administered to the subjects, covering general knowledge, digit forward and backward, orientation, mental control, logical memory, visual reproduction, and paired association learning. Each subtest yielded a score for the subjects, and the sum of the subtest scores determined the overall memory score. At 8 and 12 weeks following the start of the trial, patients receiving Bm

showed a substantial increase in mental control, logical memory, and paired association learning when compared to the placebo group. (Raghav et al . 2006)

3. Cat's claw (*Uncaria tomentosa*)



Function/Outcome Measure

Anti-inflammatory, antioxidant, lessens gliosis, prevents plaque buildup and tangles, and enhances memory (Stough et al . 2001; Benson et al. 2014; Sadhu et al. 2014; Farooqui et al .2018; Aguiar and Borowski, 2013; Uabundit et al. 2010; Kumar , 2006, Raghav et al . 2006)

Using a transgenic mouse model of Alzheimer's disease, the CC extract treatment for 14 days resulted in a considerable reduction in the A β burden (by 59%) and plaque number (by 78%) in the hippocampus and cortex of the mice (Snow et al. 2019).

4. Ginkgo biloba



Function/Outcome Measure

Antioxidant that enhances mitochondrial performance, increases cerebral blood flow, prevent the death of brain cells, and promote neurogenesis (Yasuno et al. 2012; Osman et al. 2016; Smith and Luo, 2004; Ramassamy et al. 2007 and Mahadevan and Park, 2008)

Gb is often used to treat vascular dementia and early-stage AD. In vitro, β -amyloid and NO-induced toxicity are reversed by Gb extract, which also lowers apoptosis in both in vivo and vitro settings (Bastianetto et al.,2000; Schindowski et al., 2001 and Yao et al., 2001). Treatment with Gb extract improved mice's short-term memory and increased memory retention in both young and aged rats (Ramassamy et al. 2007 and Gong et al.,2006]. According to a number of studies, ginkgo is just as efficient as cholinesterase inhibitors in treating AD by delaying the disease's progression. Several randomized, double-blind, placebo-controlled trials (Hashiguchi et al., 2015; Janssen et al., 2010 and Wochenschr, 2017) showed a slight improvement in cognitive function in AD individuals. Because of its few side effects, GB extract is favored over other AD drugs and helps AD patients perform their ADLs better.

5. Gotu Kola (*Centella asiatica*)

Function/Outcome Measure

Enhances mood and memory; lowers oxidative stress, A β levels, and apoptosis; fosters dendritic development and mitochondrial health; and is neuroceutical and cogniceutical.



(Puttarak et al. 2017; Wattanathorn, 2008; Soumyanath et al. 2012, Mehla et al. 2020, Cervenka and Jahodar , 2006; Shinomol et al 2011, Orhan, 2012; Da Rocha *et al*, 2011)

A total of 28 healthy individuals received one daily doses of 250, 500, and 750 mg for two months. Prior to the trial, following the first administration, and one and two months following therapy, mood and cognitive function were evaluated. The high dosage of the plant extract improved working memory, according to the results. Following the Gk treatment, improvements in self-rated mood were also observed, indicating the potential of Gk to mitigate age-associated declines in cognitive function and mood swings in healthy elderly individuals (Wattanathorn, 2008).

6. Lion's Mane (*Hericium erinaceus*)



Function/Outcome Measure

Enhances mood and memory; lowers oxidative stress, A β levels, and apoptosis; fosters dendritic development and mitochondrial health; and is neuroceutical and cognitive. (Puttarak et al. 2017; Wattanathorn, 2008; Soumyanath et al. 2012, Mehla et al. 2020, Cervenka and Jahodar , 2006; Shinomol et al 2011, Orhan, 2012; Da Rocha *et al*, 2011)

A 16-week therapy with 3000 mg of Lm extract produced higher scores on the cognitive function scale in the experimental group compared to the placebo group in a double-blind, parallel-group, placebo-controlled study included 30 patients with MCI (Li et al. 2020). Lm extract increased scores on activities of daily living (e.g., personal hygiene, clothing, food preparation, etc.) over 49 weeks in another small, randomized study involving individuals with moderate AD (Akhondzadeh et al. 2010). As a result, the pre-clinical and clinical data presented above imply that lion's mane is a safe, well-tolerated herb for the treatment of AD.

7. Saffron (*Crocus sativus*)

Function/Outcome Measure

Antioxidant, neuroprotective, immunomodulatory, anti-inflammatory, anti-amyloidogenic, and depressive (Adalier *et al*. 2016; Khazdair *et al*., 2015 and Gohari *et al*., 2013)



In order to evaluate the effectiveness of saffron in the management of mild to moderate AD, 46 individuals were recruited and randomly randomized to receive either a placebo or 30 mg/day of saffron. Following sixteen weeks, saffron outperformed placebo in terms of cognitive performance as measured by ADAS-cog and CDR scores. According to the double-blind, placebo-controlled trial, saffron was both safe and beneficial for mild to moderate AD patients. 54 participants were randomly assigned to receive either a 10 mg/day dose of donepezil or a 30 mg/day capsule of saffron in 22 double-blind, randomized, controlled trials.

At the conclusion of the trial, saffron improved cognitive function in AD patients in a manner comparable to that of donepezil, but with fewer adverse effects. The saffron extract was similar to memantine in lowering cognitive loss in patients with moderate to severe AD, and it also shown a low rate of side effects. As a result, saffron has been identified in all of the aforementioned research as a herbal spice that may help people with AD and MCI with their ADLs and cognitive performance. Although saffron can cure AD patients just as well as traditional medicine, it is a safer option due to its natural ingredients and lower risk of side effects.

8. Shankpushpi (Convolvulus pluricaulis)



Function/Outcome Measure

Enhances mental performance, reduces brain aging, and has anti-inflammatory and antioxidant properties (Farooqui, 2018; Kumar, 2006; Mukherjee et al., 2008, Malik et al., 2011; Sethiya et al., 2009; Balakrishna et al., 2020).

The primary chemical constituents of Cp that are responsible for its nootropic and memory-improving effects include triterpenoids, flavonol glycosides, anthocyanins, and steroids. A class of nutritional supplements known as racetams has the ability to improve glutamatergic and cholinergic transmission. Racetams and Cp have some effects that are comparable. Adrenaline and cortisol production in the body are regulated by Cp. Additionally, CP is advised for mental exhaustion and stress, anxiety, and insomnia. When neonatal rat pups were given an aqueous root extract of Cp, their performance in spatial learning and retention increased. Furthermore, a notable rise in ACh activity and content was noted, which might be the reason for their enhanced memory and learning. When compared to age-matched saline controls, rats fed with Cp extract showed a significant increase in dendritic branching points and processes. This finding suggests that Cp enhances learning and memory by promoting dendritic arborization.

9. Turmeric (*Curcuma longa*)



Function/Outcome Measure

Antioxidant, anti-inflammatory, and antibacterial, prevents the synthesis of A β and delays the death of brain cells (Begum et al., 2008; Lim et al., 2001; Sharif Rad, 2003; Chainani-Wu, 2003; Aggarwas et al., 1995; Parachikova et al., 2010; Voulgaropoulou et al., 2019)

Plaque burden was significantly reduced in aged rats with advanced plaque deposits when curcumin was administered orally. In mouse models of AD, curcumin also decreased oxidative damage, inflammation, and amyloid pathology. Injecting curcumin directly into the brains decreased the amount of plaque and prevented it from developing further. Unlike research on animals, curcumin's impact on human cognitive functioning has only been the subject of a small number of clinical investigations, and the findings are not very clear. The general consensus among researchers is that curcumin has a synergistic impact and amplifies its neuroprotective properties when combined with other dietary supplements such as piperine, α -lipoic acid, N-acetylcysteine, B vitamins, vitamin C, and folate [83–85]. Therefore, enhancements are required, and future studies ought to concentrate on methods of boosting curcumin's BBB permeability and systemic bioavailability.

10. Triphala (*Embllica officinalis*, *Terminalia bellerica*, and *Terminalia chebula*)



Function/Outcome Measure

Antioxidant, anti-inflammatory, immunomodulatory, antibacterial, antiparasitic, and capable of reversing metabolic abnormalities. It also protects dental cavities.

(Peterson et al. 2017; Baliga, 2010; Chouhan et al., 2013; Sabu and Kuttan, 2002; Baratakke et al., 2017; Peterson et al., 2018)

In addition to being high in vitamin C, amalaki also has anti-cancer qualities due to its phenolic, tannin, and other components. Additionally, amalaki shows broad therapeutic potential by suppressing neurodegeneration in fly models of Alzheimer's and Huntington's disease. Tannins, ellagic acid, gallic acid, lignans, and flavones—all of which have anti-inflammatory and antidiabetic qualities—are present in bibhitaki. Haritaki is said to have anti-inflammatory, anti-bacterial, antiviral, and antioxidant qualities in addition to reducing digestive disturbances. It includes terpenes, polyphenols, anthocyanins, and

flavonoids. In a double-blind, controlled study, 62 obese participants were randomized to receive five grams of triphala (n = 31) or a placebo twice a day for a period of 12 weeks. Neither group experienced any negative effects, nor were there any notable alterations in the tests for liver and kidney function. When comparing the triphala group to the placebo group, there was a substantial drop in body weight, mean fasting blood sugar, and fasting serum insulin. Mouthwash formulations were tested in larger, double-blind, randomized controlled studies on patients with periodontal disorders. With no negative side effects, triphala extract mouthwash proved useful in lowering gingival irritation and plaque buildup.

CONCLUSION

In an all-encompassing approach for the prevention and treatment of cognitive loss linked to Alzheimer's disease, medicinal plants have a lot of promise. It is envisaged that these medicinal plants may help find safe and effective small molecules for AD through drug discovery efforts.

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