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Nutraceuticals in the management of alzheimer's disease

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Abstract

The aim of this review is attempts to enlist and display the role of some nutraceuticals being used as in the prevention and management of Alzheimer's disease. Various cognitive enhancer are widely used traditionally as medicine to prevent Alzheimer's disease. Nutraceuticals are food or part of a food including naturals (like plants, animals, minerals, or microbial sources) or chemical groups (like vitamins, antioxidants, amino acids and fatty acids) that promote wellness or health benefits including the prevention and/or treatment of a disease. One of the best benefits of nutraceuticals is that they provide a better therapeutic hope with lesser side effects compared to pharmaceutical agents or other conventional approach. Some of the herbal nutraceuticals like Gingko Biloba, Huperzine Alpha are used in clinical practice to target the pathogenesis of Alzheimer's disease.

Keywords: Nutraceuticals, Alzheimer's disease, Herbal Drugs, Gingko Biloba, Huperzine Alpha, Vitamins.

Introduction

Alzheimer's disease (AD), was first described by German psychiatrist Alois Alzheimer in 1906. Alzheimer's disease (AD) is a progressive neurodegenerative disorder, characterized by deposition of beta amyloid protein, neurofibrillary tangles, astrogliosis and microgliosis, leading to neuronal dysfunction and loss of memory function.

Alzheimer's disease is the most common cause of dementia and a group of brain disorders where brain cells degenerate and die, causing a steady decline in memory and mental function that cause the loss of intellectual and social skills.[1]

Dementia is a syndrome associated with progressive impairments in memory and learning ability, cognitive skills, behaviour, activities of daily living and quality of life. There are more than 47.5million people with dementia world wide and 7.7 million new cases are added to the dementia pool each year.[2]

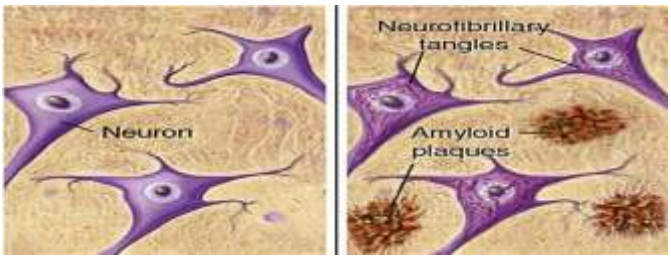
Pathophysiology of alzheimer's disease

Cognitive impairment is the primary symptom of AD, which causes a disturbance in mood, behaviour and reduces the quality of life. The main risk factors associated with AD include hypertension, hyperlipidemia, diabetes, genetic disposition, cardiac diseases, physical inactivity, and obesity.[3]

The pathophysiology of AD is complex. It may developed due to interactions between vascular aetiologies (cerebrovascular disorders and vascular factors), changes in the brain (infarcts, white matter lesions, and atrophy).[4] Other pathogenic factors of AD such as deposition of beta amyloid protein, atherosclerosis, ischemic damage in various areas of the brain and ageing, also contribute via inflammation and oxidative stress Figure 1[3].

Table 1 Pathogenesis of Alzheimer's Disease

Amyloid hypothesis:-	Neurofibrilary tangles:-	Cholinergic regulation:-
Altered amyloid protein precursor may cause excess production of Beta amyloid protein(BAP), having tendency to clump each other and form plaque ↓ Plaque cause neurodegeneration & disturb impulse transmission. ↓ Finally neuron cell loss and block cell to cell signal & result in Alzheimer [5]	Abnormal Hyper phosphorylation Leads twist formation of Tau protein (which provide structural support to microtubules & transportation of (neutrients). ↓ Microtubules get collapse, which stop neutrient supply & may cell death. ↓ Neuronal loss result in Alzheimer [5-6]	The first neurotransmitter defect discovered in AD involved acetylcholine (ACh). Abnormal release of Ach from cholinergic neuron to brain at Hippocampus and cortex, which inhibit the regulation of learning and memory result in Alzheimer [6-7]



Normal neurons Abnormal neurons

Figure 1 Neuronal changes in AD

Nutraceuticals approach for Alzheimer's disease

The term nutraceuticals derived from "nutrition" and "pharmaceutical" was coined by Stephen Defelice MD, founder and chairman of the foundation for innovation in medicine (FIM) Cranford, New Jersy, in 1989. According to Defelice "nutracetuicals are food or part of a food that promote health wellness including the prevention and/or treatment of a disease"[8].

NUTRITION (Required for Health) **PHARMACEUTICALS** (Required for remedy for sickness/injury)

↓

NUTRACEUTICALS
(Preventive Medical Approach for disease)

Figure 2 Concept of Nutraceuticals

From an ancient era herbal medicine are traditionally used to boost memory, cognitive functions and manage behavioral as well as psychological symptoms associated with dementia/AD. Some of the most commonly used herbs are Ginkgo biloba, Huperzia serrata, Salvia miltiorrhiza, Bacopa monnieri, Curcuma longa, Panax ginseng, Panax notoginseng, Crocus sativus, and Camellia sinensis.

Gingko biloba

Ginkgo biloba containing flavonoidal glycosides is one of the best known medicinal herbs for prevention and management of Alzheimer's disease and its associated symptoms. In controlled clinical trials, using a placebo and control group, *Ginkgo biloba* extracts showed therapeutic benefits in Alzheimer's, similar to prescription drugs such as Tactrin or Donepezil, with little undesirable side effects [9-10].

The principal constituents of Ginkgo include flavonol glycosides (e.g. quercetin and kaempferol) and terpenoids (e.g. ginkgolide and bilobalide). Ginkgolide having antioxidant property with neuroprotective and cholinergic activities that help in the management of AD. Ginkgo biloba provide protection against amyloid β protein-induced oxidative damages (degrading hydrogen peroxide, preventing lipids from oxidation, and trapping the reactive oxygen species).[9,11]

Maurer *et al.* [12] conducted a large-scale double blind, multicenter randomized controlled trial(RCT), for determining the clinical efficacy of G. biloba extract EGb 761 in AD. The RCT were conducted on twenty AD patients aged 50–80 with mild to moderate dementia. After recruiting two patients were excluded, the remaining 18 patients were randomly divided into the two groups as treatment and control groups. Over a 3-month period, the treatment group received a normal daily dose of 240mg EGb 761, where as the control group received a placebo.

The primary outcome measure was short cognitive performance test for assessing memory and attention by using SKT (Syndrom-Kurz Test). Secondary measures such as Alzheimer's Disease Assessment Scale (ADAS) and EEG were analyzed qualitatively. The study confirmed the efficacy of EGb761 as measured by SKT, for the treatment of mildly to moderately severe AD. In addition, EEG showed some improvement in brain activity. However, the results based on the ADAS were not statistically significant, possibly due to the small sample size. The quality of this study is fair. No sufficient details were reported with respect to the procedures of randomization and blinding as well as the tracking of dropouts in the process.

Mazza *et al.* [13] conducted a double blind, randomized controlled trial to compare *G. biloba* extract EGb 761 and a second generation cholinesterase inhibitor, donepezil, for their efficacy in the treatment of AD. Patients aged 50–80 years with a mild to moderate degree of AD were recruited but patients with dementia of other etiologies were excluded. Medications with cognitive effects were prohibited. In the study, 76 patients were randomized into three groups. Over a 24-week period, 25 patients received daily an oral dose of 160mg EGb 761; 25 patients received daily an oral dose of donepezil 5mg; and remaining 26 patients took a placebo. The primary outcome measures were MMSE (mini-mental state examination), SKT and Clinical Global Impression (CGI). The study found that both G. biloba and donepezil were more effective than the placebo for improving the cognitive function in patients with mild to moderate AD according to the measures of SKT and CGI (but not of MMSE), and the differences were statistically significant, however, there was no statistical difference between G. biloba and donepezil based on all three measures. In addition, there were no major side effects reported. Thus, this study concluded that G. biloba could be a valuable alternative to cholinesterase inhibitors for the treatment of AD.

Huperzine Alpha (A)

Huperzine A, a novel Lycopodium alkaloid, extracted from the Chinese herb Huperzia serrata, is well known as a reversible, potent, and selective acetyl cholinesterase, which activity is even stronger than galantamine. It is also known as 'Qian Ceng Ta' in China. Huperzine A is an FDA-approved drug for the treatment of mild to moderate AD and other memory disorders.[14-15]

Zhang *et al.* [16] conducted a large-scale double blind, multicenter randomized controlled trial, for determining the clinical efficacy of huperzine A in AD. The RCT were conducted on 202 AD patients aged 50–80 with mild to moderate dementia from 15 centers. Over a 12-week period, the treatment group received a normal daily dose of 400mg of huperzine, where as the control group received a placebo. Results showed remarkable improvements on several scales, including the ADAS cognitive scale, the MMSE scale, the CIBIC-Plus (Clinician Interview Based Impression of Change-Plus) scale, and the

activities of daily living (ADL) scale. Huperzine A was found to significantly improve cognition, behavior, activity of daily life and mood in AD patients.

Xu *et al.* [17] conducted a double-blind placebo-controlled multi-centered trial, was aimed to comparing the effect of huperzine A in capsules to huperzine A in tablets. The study were conducted on 60 patients comparing the effect of 200 mg of huperzine A in capsules, to 200 mg of huperzine A in tablets, just to observed a difference in absorption and bioavailability. Results based on numerous mental and quality of life scales revealed that patients treated with both huperzine A tablets and capsules significantly and remarkably improved. In addition, free radicals in erythrocytes and plasma reduced in both groups. There was no change at all in the placebo group.

Melissa officinalis

It has been reported that *Melissa officinalis* (lemon balm) belongs to Lamiaceae family, which improves cognitive function and reduces agitation in patients with mild to moderate AD. *M. officinalis* is known to ACh receptor activity in the central nervous system with both nicotinic and muscarinic binding properties [18]. A recent study has shown that this plant modulates mood and cognitive performance when administered to young, healthy volunteers [19].

Akhondzadeh *et al.* [20] conducted a parallel, randomized, placebo-controlled study to measure the efficacy and safety of *M. officinalis* in 42 patients with mild to moderate AD over four months period. The study measures the main efficacy as the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Clinical Dementia Rating-Sum of the Boxes (CDR-SB) scores. The CDR-SB provides a consensus-based global clinical measure by summing the ratings from six domains: memory, orientation, judgment, problem solving, community affairs, home and hobbies, and personal care. The results revealed that patients receiving *M. officinalis* extract experienced significant improvements in cognition after 16 weeks of treatment.

Salvia officinalis

It has been reported that *Saliva officinalis* (sage) belongs to Lamiaceae family, which improves cognitive function and reduces agitation in patients with mild to moderate AD [21].

Akhondzadeh *et al.* [22] reported that patients with mild to moderate AD receiving *Salvia officinalis* extract experienced statistically significant benefits in cognition after 16 weeks of treatment. The clinical relevance of these findings was emphasized by the improvements seen in both the ADAS-cog and CDR-SB measures in the *S. officinalis* extract group on both observed case and intention-to-treat analyses. The changes at the endpoint compared to baseline for Salvia extract and placebo respectively on the CDR-SB scores. The side effects associated with Salvia in this study were generally those expected from cholinergic stimulation and were similar to those reported with cholinesterase inhibitors. This

study may indicate an additional advantage for M. officinalis in the management of patients with AD.

Bacopa monnieri

Bacopa monnieri (Brahmi) belong to Scrophulariaceae family has been traditionally used in Ayurvedic medicine to treat conditions including pain, asthma, fever, inflammation, and memory decline [23]. Various mechanisms may be involved in the neuroprotective and memory enhancing effects of Brahmi such as increasing antioxidant activity [24], free radical scavenging, modifying levels of acetylcholine [25], and increasing cerebral blood flow via vasodilation [26].

Steroidal saponins and bacosides A and B are responsible for improving learning and memory [27]. Bacosides enhance kinase activity and neuronal synthesis, which is linked with the restoration of synaptic activity, ultimately improving nerve impulse transmission [28].

Goswami *et al.* [29] evaluate the effect of *Bacopa monnieri*, associated with the Ayurveda system of medicine, on the cognitive functions in Alzheimer's disease patients, and conclude that it could be beneficial in these patients, but more study is needed.

The hope for future drugs [30-31]

Current drugs in research that targets beta-amyloid Protein

Two anti-amyloid compounds such as **CAD106**, an active immunotherapy, and **CNP520** are being studied to determine if they can prevent or delay the emergence of symptoms of Alzheimer's among higher-risk cognitively healthy older adults who have two copies of the e4 type of the APOE gene, one from each parent. The two studies, will determine whether the drugs can combat the accumulation of the protein fragment beta-amyloid into the amyloid plaques that are a hallmark of Alzheimer's. Plaques form between nerve cells (neurons) in the brain and interfere with neuron-to-neuron communication that enables the brain to store new information. The studies are expected to conclude in 2025.

Current drug in research that targets beta-secretase

JNJ-54861911 inhibits the ability of the beta-secretase enzyme to make beta-amyloid. It is currently in a Phase 3 study to determine if it slows cognitive decline in people who do not have Alzheimer's symptoms but have elevated levels of beta-amyloid in the brain. The study is expected to be completed in 2024. JNJ-54861911 is administered in pill form. (Drug is still in research; not available to the public.)

Current drug in research that targets tau protein

AADvac1 is a vaccine that stimulates the body's immune system to attack an abnormal form of tau protein that destabilizes the structure of neurons. If successful, it has the potential to help stop the progression of Alzheimer's disease. A Phase 2 clinical trial, called ADAMANT, enrolled 208 volunteers living with mild Alzheimer's disease began in March 2016 and was completed in June 2019. Initial results

were announced in September 2019 and showed that 98.2% of participants who were given the vaccine generated antibodies to the tau protein. The results also showed no difference in adverse events between the treatment and control groups, meaning that the treatment was well tolerated. The change in several biomarkers for Alzheimer's disease showed trends that suggest AADvac1 may slow the progression of the disease. The slowing of the progression was also supported by positive changes in several cognitive endpoints. Based on the results, the vaccine will continue to be studied in the next level of clinical trials (Drug is still in research; not available to the public).

Conclusion

Herbal medicine as nutraceuticals may play a major role in the early treatment either as single preparations or as complex herbal formulations for the treatment of Alzheimer's and improving other conditions involving poor memory and dementia. One of the best benefits is that they provide a better therapeutic hope with lesser side effects compared to pharmaceutical agents. The use of herbal medicines in the treatment of AD should be compared with the pharmacological treatment currently in use.

Currently FDA-approved medications for AD such as acetyl cholinesterase inhibitors and glutamate receptor antagonists improve cognitive function but do not treat the cause of the disease characterized by the deposition of amyloid plaques and formation of neurofibrillary tangles. While cholinesterase inhibitors and glutamate receptor antagonists such as Gingko Biloba, Salvia officinalis and Huperzine A are the most effective pharmaceutical options for the treatment of AD. Such studies should include identification of the active principle in order to improve the validation of the clinical trial. Further large-scale, multicenter studies are necessary to determine the effectiveness of these substances in the cognitive deterioration of AD. Until then, this review provides some evidence of the benefit of a wide range of herbs (included in the Indian Medicine System, Chinese Medicine System, European Medicine System, etc.) in the treatment of AD.

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