THE USE OF HERBAL MEDICINE IN ALZHEIMER'S DISEASE – A SYSTEMATIC REVIEW

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ABSTRACT
Alzheimer’s disease (AD) is the progressive neurodegenerative disease and most common form of senile dementia which demolishes the vital brain cells, causing problems with memory, thinking and behavior. There is no cure for Alzheimer’s disease, but drugs designed to slow disease progression are available. Many of the current drugs taken to treat the disease have unpleasant side effects and poor compliances. Some herbs may help to improve brain function, but scientific evidence to prove that they can treat Alzheimer’s disease, is limited. At present herbal medicine has turn out to be best choice for the management of AD because of its availability, very economic, good patient compliance, ease of formulation and lower side effects. The objective of this review is to provide a systematic review of the ongoing evidence pertaining to the use of Anti-Alzheimer’s Disease medicinal herbs such as Curcuma longa, Centella asiatica, Gingko biloba, Juglans regia, Coffea Arabica, Vitis vinifera, Piper nigrum Withania somnifera, Glycyrrhiza glabra and Tinospera cordifolia in the treatment of Alzheimer’s disease (AD) and its associated symptoms.

KEYWORDS: Alzheimer’s Disease, Dementia.

INTRODUCTION
Alzheimer’s disease (AD) has become one of the common diseases in aged population. It is a neuro-degenerative disease and the most common cause of dementia.[¹] The main characteristics of this disease are difficulties in household handling routine and cognitive and emotional disturbance in the elderly.[²] The preponderance of this diseases increases with...
age,. Named after the German physician, Alois Alzheimer, who in 1906 first identified this disease.\cite{3} With an aging population, the incidence of AD increases each year. The incidence is 5\% among the population at the age over 65 and 20\% among the people at age over 85 in the United States of America.\cite{4} The World Health Organization estimated that in 2005, 0.379\% of people worldwide had dementia, and that the prevalence would increase to 0.441\% in 2015 and to 0.556\% in 2030. AD seriously infringes the physical and mental health of elderly people and their quality of life, and brings severe distress to the patients and heavy burden to their families and society.\cite{5} Researchers have found that genetic factors as well as environmental factors believed to play an important role in the development of AD. Genetic factors include age, family history and heredity whereas environmental factors include long-term exposure to silicon or aluminum, chronic exposure to other toxins, free radical damage and traumatic injury. It has been postulated that reduced survival is a consequence of the AD pathogenic process.\cite{6,7}

The treatment of AD is a clinical challenge. With the development of cholinesterase inhibitors and a N-methyl-d-aspartate antagonist (memantine), good perspectives have emerged in controlling the symptoms of AD.\cite{8} in the recent years, therapeutic potentials of complementary and alternative/herbal drugs/food supplements has gained popularity and attract researchers’ attention because of their market potential and currently assuming billion dollar worldwide market.\cite{9}

Overall consideration of the most recent collective evidence suggests that the optimal approach for Alzheimer's disease would seem to combine early, multicomponent nutritional approaches (a Mediterranean-style diet, multivitamins and key combinatorial supplements), along with a number of dietary factors such as antioxidants, vitamins, polyphenols, and fish have been reported to decrease the risk of AD, while saturated fatty acids, high-calorie intake, and excess alcohol consumption were identified as risk factors lifestyle modifications such as social activity and mental and physical exercise, with ultimate addition of pharmacological agents when warranted. The objective of this review is discusses different herbal drugs that have interesting pharmacological efficacy with special reference to anti-Alzheimer activity of food supplements and their extracts.\cite{10,11}

**METHODOLOGY**

A literature review was performed using research articles available from 1995 to 2020 regarding the use of herbal supplements and their relationship in managing clinical
manifestations of Alzheimer’s disease. The focus was mainly related to the use of food supplements as drug therapy for Alzheimer’s disease. Databases that were used to search for articles included Cumulative Index to Nursing and Allied Health Literature (CINAHL), Educational Resources Information Center (ERIC), Elton B. Stephens Co. Host (Ebsco Host), Medical Literature On-line (Medline), and Psychological Information Database (PsychINFO). Searches used a combination of the following terms: Alzheimer’s, dementia*, herbal supplement*, clinical manifestation*, symptom*, benefit*, and risk*. Inclusion criteria consisted of 1) published research in English, 2) Food supplements used at all stages of AD and as adjuvant therapy to prescriptive agents, and 3) Food supplements used in AD to control clinical manifestation of the condition. Articles that were excluded focused on AD therapy with only prescriptive agents and AD treatments that did not include the use of herbal supplements. The data was extracted to synthesize the relationship between the food supplements in controlling the clinical manifestations of AD. Subsequently, all the critiqued articles were synthesized by the researcher, and key findings were extracted along with consistent and inconsistent findings and gaps in the literature. Limitations of the study and recommendations for future research also were noted.

RESULTS AND DISCUSSION
Many nutrients, such as antioxidants, vitamins, fat, and can affect the risk of AD. Although the mechanisms of these nutrients on AD are not clear, reducing the oxidative stress and amyloid beta-peptide (Aβ) accumulation is considered to play a role in the process of AD.\textsuperscript{[12]}

Walnut (\textit{Juglans regia})

Fig. 1: \textit{Juglans regia}. 
Findings of this study suggest that long-term supplementation of a diet with 6% or 9% walnuts in Alzheimer's disease transgenic mice significantly reduced or prevented deficits in memory and learning compared to Alzheimer's disease transgenic mice on a diet without walnuts, and there was no statistically significant difference in the performance of these mice compared to wild-type control mice. This study proposes that early intervention with a diet with walnuts may help in reducing the risk of developing Alzheimer's disease or delaying its onset because of the cumulative antioxidant and anti-inflammatory effects of components in walnuts.\[13\]

In this study, from 4 months of age, experimental Alzheimer's disease transgenic mice were fed diets containing 6% or 9% walnuts (equivalent to 1 or 1.5 oz, of walnuts per day in humans) for 5, 10, or 15 months. The control groups, i.e., Alzheimer's disease transgenic mice and wild-type mice, were fed diets without walnuts. This study suggests that long-term supplementation with walnuts for 10 or 15 months was more effective in reducing oxidative stress in Alzheimer's disease transgenic mice. The findings indicate that walnuts can reduce oxidative stress, not only by scavenging free radicals, but also by protecting antioxidant status, thus leading to reduced oxidative damage to lipids and proteins in Alzheimer's disease. Therefore, by reducing oxidative stress, a walnut-enriched diet may help reduce the risk or delay the onset and progression of Alzheimer's disease.\[14\]

**Curcumin (Curcuma longa)**

![Curcuma longa](image)

Fig. 2: Curcuma longa.

Aß plaque accumulation noted on advanced scanning techniques, such as magnetic resonance imaging (MRI) of the brain, is one of the main signs of AD. In a research study involving the
effects of curcumin intake in people with AD, curcumin blocked the aggregation of Aβ1–40 and the formation of Aβ1–42 fibrils and oligomers. These substances accumulate in the brain as individual’s age and are associated with the onset of AD. In the same research, the accumulation of Aβ plaques was found to be reduced in aging mice (Anekonda & Reddy, 2005).\[15\]

A study evaluating the effects of curcumin on mice found that the mice receiving curcumin were able to perform better in memory task related activities, and showed improvement in spontaneous behavior, compared to mice in the control group not receiving curcumin (Mi Hye, Sung-Hoon, & Woong Mo, 2014). Further research in human participants could possibly provide insight into the beneficial effects of curcumin in slowing the progression of plaque formation in the brain.\[16\]

The molecular underpinnings of these effects have been found to involve the regulation of diverse molecular targets, including transcription factors (such as nuclear factor-κB), growth factors (such as vascular endothelial cell growth factor), inflammatory cytokines (such as tumor necrosis factor, interleukin 1 and interleukin 6), protein kinases (such as mammalian target of rapamycin, mitogen-activated protein kinases, and Akt) and other enzymes (such as cyclooxygenase 2 and 5 lipoxygenase). Its ability to regulate multiple targets and its safety for human use, made curcumin an amenable therapeutic agent for the prevention and/or treatment of various malignant diseases, arthritis, allergies, AD, and other inflammatory illnesses.\[17\]

**Black pepper (Piper nigrum)**

![Fig. 3: Piper nigrum.](image-url)
The effect of piperine (alkaloid0 from fruit of *Piper nigrum* was investigated for memory performance and neurodegeneration in the Alzheimer’s disease rat model. Piperine at the dose of 5,10 and 20mg/kgBW) was given orally to Alzheimer’s disease rat for the period of 2 weeks before and 1 week after the intracerebroventricular administration of ethylcholine aziridinium ion bilaterally. This study concluded that significantly improved memory impairment and neurodegeneration in hippocampus of AD rat model.[18]

**Grape (*Vitis vinifera* L.) and red wine**

![Fig. 4: Vitis vinifera.](image)

As recently reviewed, many prospective, population-based cohort and case control studies have provided the substantial evidence that a regular (daily or possibly 3-4 times weekly) intake of moderate amounts (2 glasses/days) of red wine, at meals and in the context of a Mediterranean dietary style, is associated with a lower risk of developing dementia and AD.19 Recently, a grape seed polyphenolic extract significantly prevented Aβ protein oligomerization, by inhibiting the Aβ protein aggregation into high-molecular-weight oligomeric Aβ species, both in vitro and in Tg2576 mice. Besides, when orally administered to these animals, the extract attenuated the cognitive deterioration typical of AD.[20]
Penny wort (*Centella asiatica*)

*Fig. 5: Centella asiatica.*

*Centella asiatica* is a psychoactive medicinal plant used for centuries in Ayurvedic and Unani system of medicine. It has been shown to decrease the oxidative stress on the brain. Major bioactive compounds of this plant contain highly variable triterpenoid saponins, and related sapogenins. It also contains triterpenoid acids. However, the exact mechanism of action of triterpenoid acids in the treatment and management of neurological disorders has not been fully elucidated. [21]

A study shows that aggregated Aβ1(amyloid β1)-40 treatment resulted in reduced cell viability, which can be reversed by cotreatment with 25, 50, and 100 μg/mL *C. asiatica* ethanol extract. Moreover, *C. asiatica* ethanol extract eliminated the Aβ1–40-mediated increase in reactive oxygen species production. Thus, *C. asiatica* ethanol extract-mediated protection against aggregated Aβ1–40-induced neurotoxicity is attributable to modulation of the antioxidative defense system in cells, including the activities of superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and levels of glutathione and glutathione disulfide by *C. asiatica* ethanol extract. This study emphasizes the potential therapeutic and preventive value of *C. asiatica* ethanol extract in the treatment of Alzheimer’s disease. [22]

Another study investigated the effect of *Centella asiatica* (CA) extract in the prevention of sporadic dementia of Alzheimer’s type using intracerebroventricular colchicines-induced rats. This study suggests that chronic administration of CA prevents colchicine-induced cognitive
impairment and associated oxidative stress. Thus, the use of CA is promising for the treatment of AD and other neurodegenerative disorders.[23]

**Coffee (Coffea arabica L.)**

Fig. 6: *Coffea arabica.*

Two studies had combined coffee and tea drinking and indicated some positive effects on cognitive functioning. For tea drinking, protective effects against cognitive decline/dementia are still less evident. In the CAIDE study, coffee drinking of 3–5 cups per day at midlife was associated with a decreased risk of dementia/AD by about 65% at late-life.[24]

**Indian Ginseng (Withania somnifera)**

Fig. 7: *Withania somnifera.*

Withania somnifera is an important medicinal herb and widely used in traditional systems of medicine as an adaptogen, nerve tonic, anti-stress, memory enhancer and against cognitive deficits, insomnia, anxiety, infectious diseases, infertility, rheumatoid arthritis and gout over
thousands of years. Its formulations are mainly used in Unani and Ayurvedic system of medicine.[25]

**Brahmi (Ginkgo biloba)**

The extract of Ginkgo biloba leaves contain chemical constituents such as 24% flavonoid glycosides (containing quercetin, kaempferol, isorhamnetin ect.), 6% terpenoids (in which 3.1% are ginkgolides A, B, C, and J and 2.9% is bilobalide), and 5–10% organic acids. Various in vivo and in vitro preclinical studies suggest *Ginkgo biloba* extract may be effective in the treatment and prevention of AD and other age-related, neurodegenerative disorders. Anti-oxidation, anti-apoptosis, anti-inflammatory, protection against mitochondrial dysfunction, amyloidogenesis and Aβ aggregation, ion homeostasis, modulation of phosphorylation of tau protein and even induction of growth factors are possible mechanisms of action.[26]

**Liquorice (Glycyrrhiza glabra)**

![Fig. 8: Ginkgo biloba.](image)

![Fig. 9: Glycyrrhiza glabra.](image)
A study was carried out to investigate the effects of Glycyrrhiza glabra root extract on learning and memory in three months old male Wistar albino rats. The aqueous extract of root of Glycyrrhiza glabra was administered orally in three doses (75, 150 and 300 mg/kg) for 4 weeks. Elevated plus-maze and Morris water maze tests were conducted to evaluate the learning and memory parameters and served as the exteroceptive behavioral models. Diazepam induced amnesia served as the interoceptive behavioral model. The aqueous extract of root of Glycyrrhiza glabra showed improvement in learning and memory in a dose dependent manner. Finding of the study suggests that Glycyrrhiza glabra appears to be a promising drug for improving memory and it would be worthwhile to explore the potential of this plant in the management of impaired learning, dementia, Alzheimer’s disease and other neurodegenerative disorders.\cite{27}

**Gilo (Tinospora cordifolia)**

![Fig. 10: Tinospora cordifolia.](image)

A study was carried out on albino mice, divided into 4 groups of 6 animals each (either sex, 3-4 months of age, weight 25-30g). Amnesia was induced by administering alprazolam (2 mg/kg body weight for 14 days) in all 4 groups for 14 days from 1st to 14th day. Group 1 was given alprazolam (2 mg/kg/p.o) alone for 14 days. In addition, group 2 was given piracetam (400 mg/kg p.o) from 8th to 15th day. Group 3 was given alcoholic extract of Tinospora cordifolia 140 mg/kg, p.o. from 1st to 15th day. Group 4 was given alcoholic extract of Tinospora cordifolia 280 mg/kg, p.o. from 1st to 15th day. The learning and memory of the animals was assessed by employing elevated plus maze (EPM) and step-down type passive avoidance model (SDA). Tinospora cordifolia at 140 mg/kg (p<0.02) and 280 mg/kg was significant in both models (p<0.02) and in EPM model, Tinospora cordifolia at 280 mg/kg showed highly significant result (P<0.01). This study concludes Tinospora cordifolia can
useful for treatment of various ailments and also be a useful alternative for treating dementia and associated diseases like alzheimer’s disease.\textsuperscript{[28]}

**Sage (Salvia officinalis)**

![Salvia officinalis](image)

**Fig. 11: Salvia officinalis.**

It is a perennial flowering subherb native to meditarian region and also in many places throughout the world, grows in all types of soil; this herb was reported to be a multipurpose herb with medicinal, traditional, ornamental and culinary use. The Phytochemicals in the plant makes it more special in treating various problems related to infertility, diuretics, and local anaesthetic for skin, styptic, anti-oxidant. These constituents include 1,8cineole camphor, α and β-thujone, vridiflorol, α-pinene. To the patients in mild to moderate stage of AD a fixed dose of 60 drops/kg extract is administered for a period of 4 months results from the study stated that patients are free from agitation through out there life time. This extract also protects brain from oxidative damage to presences of Rosmarinic and carhosic acid in it.\textsuperscript{[29]}

**Black oil plant (Celastress panicultus)**

![Celastress panicultus](image)

**Fig. 12: Celastress panicultus.**
It is a climbing shrub grows throughout India used as traditional medicine in Unani and Ayurveda. This plant sharpens the memory and its seed possess’s cholinergic activity. It improves medhya-guna which means improved memory power to serve this purpose almond, Cardamom, Jatamanasi, Shankhpushpi are used along with it. Phytochemicals in the stem portion are alkaloids they include Winfornine F, Paniculatine A and B, where as the seed portion contains Celastrine, Celapagine, Celpangine, Celapanine. These extracts protect neuronal cells against hydrogen peroxide induced cell death in part by virtue of their antioxidant enzymes; aqueous extracts have dose dependent cholinergic activity thereby improving memory performance (according to P.L.Rajagopal.et al.). Organic methanolic fraction of seed extract exhibited Anticholinesterase activity and cholinesterase inhibitory effect this was found to be significant with respect to IC50 values (according to Shashank. D et. al.).[30-32]

CONCLUSION
The use of herbal medicines in the treatment of AD should be compared with the pharmacological treatment currently in use. Due to poor patient compliance towards drugs and their lethal side effects upon chonic usage, at present there was a paradigm shift of patient choice of medication towards herbal which made a revolution this due to many advantages over the medications it has less adverse effects and they target the site easily upon slight modification its physicochemical properties, in spite of all these herbal therapy is economical to all classes of population. Such studies should include the 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.

REFERENCES


