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Review

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“Herbal Medicines and Their Neuroprotective Effects in Alzheimer's Disease and Associated Symptoms.”

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Abstract:

Alzheimer's disease (AD), a progressive neurodegenerative disorder, is the most common form of dementia which affects an estimated 10 million people worldwide. AD is characterized by a gradual decline in memory associated with shrinkage of brain tissue, localized loss of neurons mainly in the hippocampus and basal forebrain, and diminished level of central cholinergic neurotransmitter acetylcholine thereby causing trouble with memory, thinking, behaviour and social life. Many of the current drugs taken to treat the disease, such as donepezil, have unpleasant side effects and doctors are keen to find alternatives. Herbs and various naturally occurring compounds may play a promising role in the early treatment of AD and other conditions involving poor memory and dementia. One of the chief benefits is that they have low toxicity compared to pharmaceutical agents. This review will indicate the neuroprotective effect of various medicinal herbs in the treatment of Alzheimer's disease.

Keyword: Alzheimer's Disease, Medicinal Herbs, Neurodegenerative Disorder.

Introduction:

Alzheimer's disease (AD) is a progressive neurological disease of the brain named after German physician Aloes Alzheimer's, who first described it in 1906. It is the most common cause of severe mental deterioration (dementia) in the elderly^[1,2] and is estimated to account for 50%–60% of dementia cases in persons over 65 years of age^[3]. The main symptoms associated with AD involve cognitive dysfunction, primarily memory loss^[4-7]. Other features associated with the later stages of AD include language deficits, depression, behavioural problems including agitation, mood disturbances and psychosis^{[8-}

^{10]}. The pathological features that occur in the central nervous system (CNS) in AD are senile plaque and neurofibrillary tangle formation, oxidative and inflammatory processes and neurotransmitter disturbances. The key mechanism leading to AD pathogenesis is the abnormal metabolism of amyloid precursor protein (APP)^[11,12]. The AD brain is characterized by a variety of alterations in cellular and molecular mechanisms, including amyloid beta (A β) clearance capability, mitochondrial function, synaptic dysfunction, down-regulation of anti-oxidant, up-regulation of oxidative stress, and inflammatory response^[13-15]. Most therapeutic strategies for AD only provide symptomatic

treatment, including inhibition of generation or aggregation of A β , enhancement of the removal of A β from the neurons, interruption of tau hyper-phosphorylation, and the use of more efficacious antioxidant and anti-inflammatory drugs^[16-18]. However, no drug has yet been found to prevent the progressive loss of neurons in AD patients^[11,18].

A consistent neuropathological occurrence associated with memory loss is a cholinergic deficit, which has been correlated with the severity of AD^[19-25]. Therefore attempts to restore cholinergic function have been a rational target for drugs used to treat the symptoms of AD. Approaches to enhance cholinergic function in AD have included stimulation of cholinergic receptors (e.g. the stimulation of nicotinic receptors by nicotine), or by prolonging the availability of acetylcholine (ACh) released into the neuronal synaptic cleft. This may occur by inhibiting ACh hydrolysis by acetylcholinesterase (AChE), through the use of AChE inhibitors.

The first drug approved for general clinical use in AD was tacrine, followed a few years later by donepezil. Most recently, rivastigmine has been used in several countries around the world, and was launched in the US by June 2000. Another launched AChEI is galantamine, and metrifonate was being developed by Bayer Corp as an AChE inhibitor^[26,27]. All of these drugs have been tested primarily on patients with AD, with

most trials studying treatment in patients with mild to moderately severe illness.

Although a multitude of pharmaceutical agents are available for the treatment of mental disorders, physicians find that many patients cannot tolerate the side effects, do not respond adequately, or eventually lose their response. The cholinesterase inhibitor tacrine is used rarely because of potential liver toxicity and the need for frequent laboratory monitoring. Nevertheless, donepezil, rivastigmine, and galantamine have low incidences of serious reactions but they commonly have cholinergic side effects such as nausea, anorexia, vomiting, and diarrhea^[28-32].

In comparison, many therapeutic herbs have far fewer side effects. They can provide an alternative treatment or be used to enhance the effect of prescription medications. This review will indicate the quality of the evidence supporting the clinical effects of a number of commonly used types of herbal medicines for Alzheimer's Disease.

Bacopa monnieri

Bacopa Monnieri (Brahmi) is an indigenous plant distributed mostly in India and other Asian countries and is used as a nootropic agent. Its main chemical constituents include alkaloids such as brehmine, herpestine, nicotine and saponin. Its antioxidant property is postulated to be responsible for its antistress, immunomodulatory, cognition facilitatory, anti-inflammatory and anti-aging

effects. Its anti-lipid peroxidation property has been credited with memory enhancing and sedative actions. *B. monniera* extract is reported to facilitate learning and acquisition and showed anti-oxidant effects in rat frontal cortex, striatum and hippocampus; bacosides A and B are reported to inhibit the amnesic effects of scopolamine in rodents^[33]. *B. monniera* also improved acquisition and memory in mice treated with the anti-convulsant phenytoin^[34] and improved the performance of rats in various learning situations^[35]. *B. monniera* may also improve cognitive processes in humans^[36]. Oral administration of Bacopa to AD patients for 6 months showed an improvement in cognitive and memory. An AChE inhibitory activity was also reported^[37].

Celastrus paniculatus

C. paniculatus seeds and seed oil have been used in Ayurvedic medicine for stimulating intellect and sharpening the memory^[38,39]. Most of the studies undertaken to establish any pharmacological basis for the reputed effects have focused on the seeds and seed oil. *Celastrus* oil, extracted from the seeds of *C. paniculatus*, when administered orally to the albino rats decreased the levels of noradrenaline, dopamine and 5-hydroxytryptamine (5-HT) in the brain, which was correlated with an improvement in learning and memory processes; in addition, the oil was not shown to be neurotoxic^[40]. Administration of the seed oil to rats also

reversed a scopolamine-induced task deficit, but this effect was not associated with anti-ChE activity^[41]. An antioxidant effect in the CNS, observed with an aqueous seed extract, may also explain the reputed benefits on memory, since this extract enhanced cognition *in vivo*^[42]. The studies conducted to date regarding this plant have not identified the active constituents, nor any therapeutic potential has been established for use in AD patients. Thus, further investigation is required.

Curcumin

Preparations of the plant *Curcuma longa* Linn have been used to treat various ailments for centuries in Ayurvedic medicine, a traditional Indian system of healing^[43]. This plant, also known as turmeric, is a member of the Zingiberaceae, or ginger family. It has been demonstrated in various experimental preparations to have anti-oxidant, anti-inflammatory (see below), which are felt to be key processes involved in the pathogenesis of AD. Curcumin exerts potent anti-oxidant activity. Using a rat liver microsome preparation, Reddy and Lokesh^[44] demonstrated that curcumin inhibited lipid peroxidation and Sreejayan and Rao^[45] replicated this in a distinct *in vitro* model, demonstrating that curcumin, demethoxy-curcumin, and desmethoxy-curcumin were more antioxidants than alpha-tocopherol. Shih and Lin^[46] showed that curcumin prevented oxidative damage of DNA in mouse

fibroblasts. Investigators have demonstrated that curcumin inhibits lipoxygenase and cyclooxygenase 2, enzymes that are responsible for the synthesis of the pro-inflammatory leukotrienes, prostaglandins and thromboxanes^[47]. It also inhibits AP-1 mediated transcription related to cytokine regulation *in vitro*^[48] and suppresses inducible nitric oxide synthase (iNOS) in activated macrophages^[49], processes that promote inflammation. As lipid peroxides also promote inflammation, curcumin's antioxidant effects also serve to decrease inflammation. Rats treated with A β , after incorporating with curcumin showed a reduction in oxidative stress, inflammation and cognitive deficits^[50]. *In vivo* and *in vitro* studies substantiated the ability of curcumin to prevent A β aggregation and fibril formation. Interestingly, curcumin showed neuroprotective effect against quinolinic acid induced neurotoxicity in primary neuronal cell culture. Pre-treatment of curcumin resulted in a significant reduction in neuronal nitric oxide synthase level. Curcumin can potentially regulate the signalling pathways involved in NOS mediated neurotoxicity such as Jun-N-terminal kinase pathway, protein kinase C, and nuclear kappa B^[51-63].

Galantamine

Galantamine was used traditionally in Bulgaria and Turkey for neurological conditions^[64]. Galantamine is an Amaryllidaceae alkaloid obtained from

Galanthus nivalis L. (and also *Narcissus* spp. and the Chinese herb *Lycorus radiata*)^[65]. Galantamine is reported to be more selective for AChE than BuChE, and provides complete oral bioavailability^[66-68]. Galantamine is licensed in Europe for AD treatment and was well tolerated and significantly improved cognitive function when administered to AD patients, in multi-centre randomized controlled trials^[69,70]. Galantamine is also reported to stimulate nicotinic receptors^[71,72], which may also enhance cholinergic function and memory. This additional activity suggests that galantamine may have therapeutic advantages over other AChE inhibitors.

Ginkgo biloba

Ginkgo biloba is an herbal medicine that has been used to treat a variety of ailments for thousands of years in China. An extract of *G. biloba* has been found in several studies to improve the symptoms and slow the progression of AD. There is some evidence (electroencephalographic data) to suggest that *G. biloba* extract EGb 761 has a local effect in the CNS^[73]; in addition, this extract has shown various biological activities relevant to the treatment of cognitive dysfunction. Favourable effects have been observed on cerebral circulation and neuronal cell metabolism^[74-76], on the muscarinic cholinergic system^[77], and the extract showed antioxidant activity^[78-80]. EGb 761 was also

neuroprotective against β -amyloid- and nitric oxide (NO)-induced toxicity in vitro^[81,82] and could reduce apoptosis both in vitro and in vivo^[83,84]. *G. biloba* extracts have also been evaluated for their influence on cognitive function. Treatment with *G. biloba* extracts attenuated scopolamine-induced amnesia in rats^[85], enhanced memory retention in both young and old rats^[86] and improved short-term memory in mice^[87]. Further studies have demonstrated the clinical efficacy of *G. biloba*. Extracts, including EGb 761, have been associated with modest improvements in cognitive function following administration to both AD and non-AD patients in various studies, including randomised, double-blind, placebo-controlled, multicentre trials^[88-95]. A study compared the effectiveness of the most common AD drugs, such as donepezil and rivastigmine, to that of a *G. biloba* extract called EGb761^[96]. The researchers determined that EGb761 was as effective as any of these commonly prescribed drugs in treating the symptoms of AD patients. With reference to the numerous studies conducted, it is apparent that *G. biloba* may be useful in the treatment of AD symptoms, but further research is necessary to identify appropriate dosing regimens, potential effects of long-term use, interactions with other medicines, and standardisation of extracts must also be a consideration.

Huperzine A

Huperzine A is a lycopodium alkaloid derived from a particular type of club moss (*Huperzia serrata*). Huperzine A improved memory retention processes in cognitively impaired aged and adult rats^[97]. In a multi-centre, double blind trial, huperzine A significantly improved memory and behaviour in AD patients, and was reported to be more selective for AChE than BuChE and less toxic than the synthetic AChE inhibitors donepezil and tacrine^[98,99]. Huperzine A is also reported to decrease neuronal cell death induced by glutamate toxicity^[100], it may favourably affect other neurotransmitter systems to improve memory^[101], and it protected cortical neurons against β -amyloid induced apoptosis *in vitro*^[102]. Huperzine A may also have potential in the attenuation of memory deficits and neuronal damage that occur after ischaemia, so may therefore be beneficial in the treatment of cerebrovascular type dementia^[103]. According to three Chinese double-blind trials enrolling a total of more than 450 people, use of huperzine A can significantly improve symptoms of AD and other forms of dementia^[104-106].

Melissa officinalis

It has been reported that *Melissa officinalis* (lemon balm) improves cognitive function and reduces agitation in patients with mild to moderate Alzheimer's disease. *M. officinalis* is known to have acetylcholine receptor

activity in the central nervous system with both nicotinic and muscarinic binding properties^[107,108]. A recent study has shown that this plant modulates mood and cognitive performance when administered to young healthy volunteers^[109]. In addition, a parallel, randomized, placebo-controlled study assessed the efficacy and safety of *M. officinalis* in 42 patients with mild to moderate AD^[110]. Subjects were treated for four months. The main efficacy measures were the cognitive subscale of 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. Improvements were seen on both the ADAS-cog and CDR-SB scores.

Salvia officinalis

Salvia officinalis is used as a herbal medicine for neuronal dysfunction. Its ability to act as AChE inhibitor made it as a natural remedy for the prevention of AD. S. Akhondzadeh et al. conducted a four month double-blind, randomized and placebo-controlled trial to test the efficacy and safety of *S. officinalis*

using a fixed dose, in patients with mild to moderate Alzheimer's disease. The results of this study showed that the patients experienced improved cognitive performance after 16 weeks treatment thereby indicating the efficacy of the *S. officinalis* extract in the management of mild to moderate Alzheimer's disease^[111]. Although further studies are needed to explore the full potential of *S. officinalis* in AD

Panax ginseng

Panax ginseng is used as a traditional medicine for various ailments across the world. Recent evidence has shown the effectiveness of *P. ginseng* extract and powder and various ginsenosides on AD using *in vitro* and *in vivo* models^[112-115]. Patients receiving Korean red ginseng powder (9.0g/d) or Korean white ginseng powder (4.5 g/d) showed significant improvement on the AD assessment scale, the mini-mental state examination scores, and the clinical dementia rating after 12 week of ginseng therapy when compared with those in the control group^[112,113]. Longterm (for 7 months) consumption of ginseng total saponins (100 and 200 mg/kg/day) demonstrated significant prevention of the memory loss in aged senescence-accelerated mouse prone 8 (SAMP8) mice by decreasing oxidative stress and up-regulating plasticity-related proteins that include postsynaptic density protein 95, p-N-methyl-Daspartic acid receptor 1 (p-

NMDAR1), p-Ca²⁺/calmodulin- dependent protein kinases II, p-protein kinase A (p-PKA) catalytic β subunit, p-protein kinase C γ subunit, p-cyclic adenosine monophosphate (p-cAMP), p-cAMP response element-binding (p-CREB), and brain derived neurotrophic factor (BDNF) in the hippocampus^[114]. It also has been suggested that *P. ginseng* extracts bestow neuroprotection by regulating the phosphatase activity of purified calcineurin and tau phosphorylation in SY5Y human neuroblastoma cells^[115]. Calcineurin, a Ca²⁺/calmodulin-dependent protein phosphatase, plays an important role in tau hyperphosphorylation, which is one of the neuropathologic features in the brains of AD patients^[115]. In an open label study *P. ginseng* powder was administered to AD patients for a period of 12 weeks. Cognitive performances were monitored using the mini-mental state examination (MMSE) and Alzheimer disease assessment scale (ADAS). It was observed that *P. ginseng* powder supplementation improved cognitive performance in AD subjects^[116].

Withania somnifera

Withania somnifera also known as Ashwagandha has been used for thousands of years as a popular remedy for many conditions. *W. somnifera* is one of the best known and most researched Ayurvedic herbs and holds a place in the Ayurvedic traditions similar to Ginseng in Chinese therapies. For

that reason, *W. somnifera* has been often referred to as the “Indian Ginseng”. *W. somnifera* is used in several indigenous drug preparations for maintaining health as well as treatment of several disease conditions. There have been numerous studies regarding the cognitive enhancing activities of *W. somnifera*. Steroidal derivatives, sitoindosides IX and X, isolated from *W. somnifera* root augmented learning acquisition and memory in both young and old rats^[117]. The extract containing the sitoindosides VII–X and withaferin A also reversed the ibotenic acid-induced cognitive deficit and reversed the reduction in cholinergic markers (e.g. ACh, ChAT) in rats^[118]. The root extract of *W. somnifera* also reversed scopolamine-induced disruption of acquisition and attention, and attenuated amnesia following electroconvulsive shock in mice, effects that are possibly attributed to the root extract having nootropic activity^[119]. *W. somnifera* administration to mice treated with a carcinogen reduced IL-1 and TNF- α levels^[120], which may also be relevant in AD, considering the possible involvement of these inflammatory mediators in senile plaque formation and neurodegeneration. *W. somnifera* leaves are also reported to have anti-inflammatory activity^[121]. Withanoside IV, a chemical compound of *W. somnifera*, on oral administration attenuated axonal, dendritic and synaptic loss, and memory deficits in A β (25-35) induced rats. In an *in*

vitro study, rat cortical neurons were cultured with A β (25-35) for 4 days after which sominone and withanoside were introduced into the medium. It was observed that there was a significant increase in axons and dendrites. Sominone is a hydrophobic compound which can readily cross the blood brain barrier^[122]. The molecular mechanism behind the neuroprotective action needs to be explored in detail.

Conclusion

The rising health care costs of western allopathic medicine and its inability to effectively improve the health of the world's population signal the need for a more holistic system of health care to come to the forefront. The use of herbal drugs is increasing worldwide as they have fewer or no side effects as compared with synthetic drugs. Herbs may play a promising role in the early treatment of Alzheimer's Disease and other conditions involving poor memory and dementia. The neuroprotective effects of various herbs and natural compounds needs to be addressed due to the limited studies available which assess their neuroprotective activities. Most of these natural products act against A β formation and/or tau hyper phosphorylation. AChE inhibitory activity of herbs and other natural products can also play important role in the prevention of AD. Even though evidence supporting the neuroprotective effect of certain natural

products is currently available, further studies regarding the compounds responsible for activity are necessary to identify which compounds are responsible for the pharmacological activities observed, or if compounds act synergistically to enhance activity. For many of the plants and compounds that have shown activities relevant to AD therapy, clinical data are very limited. Clinical efficacy and potential toxicity of active plants and compounds in larger trials require further assessment before recommendations regarding their use can be established.

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