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Review Article

Herbal help in Alzheimer's type of cognitive disorders: A Comprehensive Review

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ABSTRACT

Alzheimer's disease is the most frequent type of life threatening dementia which is characterized by oxidative stress and inflammation induced neuronal loss, impaired energy metabolism, and cholinergic deficits leading to severe cognitive impairments and other abnormal neuropsychiatric changes. Cure of cognitive disorders such as amnesia, attention deficit and Alzheimer's disease is still a nightmare in the field of medicine and several nootropic agents are being used to improve memory, mood and behavior, but the resulting side effects associated with these agents have made their use limited. Indian system of medicine emphasizes use of herbs, nutraceuticals and life style changes for age related neurodegenerative disorders like Alzheimer's disease. Current review sums up the plants that have shown the beneficial and encouraging results in treating ailments like Alzheimer's disease.

Keywords: Alzheimer's disease, memory, *Withania somnifera*

INTRODUCTION

Alzheimer's disease is a progressive neurodegenerative brain disorder that is slow in onset but leads to dementia, unusual behavior, personality changes and ultimately death (1). On average the duration of the disease is 6 to 10 years, although duration of survival decreases with increasing age (2).

In recent years, the incidence of Alzheimer's disease has been on the rise. At least 30-50% of all individuals above the age of 85 are affected in industrialized countries [3] Major correlates of Alzheimer type of dementia include cell loss, extracellular deposits of amyloid beta (A β) leading to formation of senile plaques (4) and intra-neuronal accumulations of hyperphosphorylated microtubule-associated proteins, such as Tau, resulting in the formation of neurofibrillary tangles (5).

Medication available today for the treatment of Alzheimer's disease include cholinesterase inhibitors and the NMDA-receptor antagonist i.e. memantine (6). Acetylcholinesterase inhibitors include Tacrine (Cognex), Donepezil (Aricept), Rivastigmine (Exelon), and Galantamine (Reminyl) (7). They have potentially troublesome cholinergic side effects, including nausea, anorexia, diarrhea, vomiting, and weight loss. Tacrine (Cognex) is used rarely because of potential liver toxicity and the need for frequent laboratory monitoring (8). NMDA antagonist, memantine is another drug approved in 2002 in Europe and in 2003 in the United States for the treatment of moderate to severe cases of Alzheimer's disease (9). These drugs produce modest improvement in approximately 30-40% of patients with mild to moderate AD (8).

Further, nootropic agents such as piracetam (Blazer), pramiracetam, aniracetam (10) are being primarily used to improve memory, mood and behavior. However, the resulting adverse effects associated with these agents have also limited their use (10,11). Therefore, it is worthwhile to explore the utility of traditional medicines for the treatment of various cognitive disorders including Alzheimer's disease (12).

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Ayurveda is the oldest medical science in the Indian subcontinent and has been practiced since the 12th Century BC. Its objective is to accomplish physical, mental, social and spiritual well-being by adopting preventive, health promoting and holistic approach towards life (13,14). Vata, pitta and kapha are the three psychobiological dimensions (energy) or biological rhythms regulating the entire functioning of the human body. Vata, is the energy that strengthens intellectual power, respiration and the activity of sensory organs. Sadhak Pitta regulates digestion of food and body temperature and is responsible for intelligence and memory. Tarpak kafa provides nutrition to the sense organs and is helpful in lubrications of the nervous tissue. According to ayurveda, Alzheimer's disease is an imbalance of vata, pitta and kapha (12, 15). Medhya herbs such as *Centella asiatica*, *Bacopa monnieri*, *Acorus calamus* and several others are beneficial in cognitive disorders including Alzheimer's disease and if their scientific evidences and proofs are taken into consideration they make themselves a reasonably good target in finding a cure for memory and intellectual disorders.

Withania somnifera

The Solanaceae family is comprised of 84 genera that include about 3,000 species, scattered throughout the world. Members of this family are generally annual shrubs. The genera *Withania* and *Physalis* play an important role in the indigenous medicine of South East Asia, e.g. in the Unani and Ayurvedic systems. The twenty-three known *Withania* species are widely distributed in the drier parts of tropical and subtropical zones, ranging from the Canary Islands, the Mediterranean region and northern Africa to Southwest Asia [16,17]. Among them, only two species, *W. somnifera* and *W. coagulans*, are economically and medicinally significant, being used and cultivated in several regions [18].

Withania somnifera, commonly known as Ashwagandha, is an important medicinal plant that has been used in Ayurvedic and indigenous medicine for over 3,000 years. In view of its varied therapeutic potential, it has also been the subject of considerable modern scientific attention. It is an ingredient in many formulations prescribed for a variety of musculoskeletal conditions (e.g., arthritis, rheumatism), and as a general tonic to increase energy, improve overall health and longevity, and prevent disease in athletes, the elderly, and during pregnancy (19,20). Many pharmacological studies have been conducted to investigate the properties of ashwagandha in an attempt to authenticate its use as a multi-purpose medicinal agent.

Since many of ashwagandha's uses have not been scientifically validated, skepticism can naturally be expected when presented with an herb purportedly useful in so many ailments. The chemistry of WS has been extensively studied and over 35 chemical constituents have been identified, extracted, and isolated(21). The biologically active chemical constituents are alkaloids (isopelletierine anaferrine), steroidal lactones (withanolides, withaferins), saponins containing an additional acyl group (sitoindoside VII and VIII), and withanolides with a glucose at carbon 27 (sitoindoside IX and X). WS is also rich in iron(22).

Effects of sitoindosides VII-X and withaferin isolated from aqueous methanol extract of roots of cultivated varieties of WS were studied on brain cholinergic, glutamatergic and GABAergic receptors in male Wistar rats (23). The compounds slightly enhanced acetylcholinesterase (AChE) activity in the lateral septum and globus pallidus, and decreased AChE activity in the vertical diagonal band. These changes were accompanied by enhanced M1-muscarinic-cholinergic receptor-binding in lateral and medial septum as well as in frontal cortices, whereas the M2-muscarinic receptor-binding sites were increased in a number of cortical regions including amygdala, frontal, piriform, parietal, and retrosplenial cortex. The data suggest the compounds preferentially affect events in the cortical and basal forebrain cholinergic-signal transduction cascade. The drug-induced increase in cortical muscarinic acetylcholine receptor capacity might partly explain the cognition-enhancing and memory-improving effects of WS extracts in animals and in humans (22).

In patients with Alzheimer's disease, neuritic atrophy and synaptic loss are considered the major causes of cognitive impairment. Methanolic extracts of the plant have been reported to induce amygdal extension [24] and to contain withanolides such as withanolide A, withanoside IV and withanoside VI, which induce amygdal outgrowth in human neuroblastoma SHSY5Y [25].

In Aβ(25-35)-induced damaged cortical neurons, withanolide A, withanoside IV and withanoside VI showed neuritic regeneration and synaptic reconstruction. Dendritic atrophy was completely prevented by treatment with these withanolides, particularly withanoside IV and VI [26].

Withania somnifera extract (50, 100 and 200 mg/kg; orally) improved retention of a passive avoidance task in a step-down paradigm in mice. It also reversed the scopolamine-induced disruption of acquisition and retention and attenuated the amnesia produced by acute treatment with electro convulsive shock (ECS). The WS glycowithanolides was investigated in experimental model of Alzheimer's disease and was found to reverse both the cognitive deficits and perturbed central cholinergic markers induces as a result of neurodegeneration produced by the neurotoxins (27).

Ginkgo biloba

The *Ginkgo biloba* tree (ginkgo) is the oldest tree on earth: more than 200 million years old (28). Individual ginkgo trees sometimes live more than 1,000 years. There is a considerable amount of scientific research supporting the use of ginkgo as a treatment for age-related problems, as well as for other disorders. Medicinal use of ginkgo leaves was mentioned as early as 1505 in a Chinese herbal text. In modern Chinese medicine, ginkgo is recommended to improve brain function and to relieve asthma. (29).

The broad therapeutic spectrum of ginkgo may be explainable in part by the fact that it influences two fundamental aspects of human physiology: 1) it improves blood flow to the brain and other tissues and 2) it enhances cellular metabolism. Because these functions are essential for good health, it is not unreasonable to consider the possibility that ginkgo might have a broad spectrum of clinical applications. Most of the illnesses relieved by ginkgo are associated with old age, a time of life when both blood flow and cellular metabolism deteriorate.

Ginkgo increased the functional activity of the brain in both humans and animals, as determined by signal-analysis electroencephalographic tech-

niques. Administration of ginkgo increased cerebral glucose consumption in rats subjected to cerebral ischemia (30). Oral or intravenous administration of ginkgo normalized mitochondrial respiration, diminished cerebral edema, and preserved neurologic function in gerbils subjected to cerebral ischemia (31).

In a clinical study, 216 patients with mild-to-moderate dementia of the Alzheimer's type or multi-infarct dementia were randomly assigned to receive ginkgo (120 mg twice daily) or a placebo for 24 weeks, in a double-blind trial. Of the 156 patients who completed the trial, significantly more patients receiving ginkgo (28%) showed an improvement in psychological tests, compared to patients receiving placebo (10%). Beneficial effects were slightly greater in the patients with Alzheimer's disease than in those with multi-infarct dementia (32).

Ginkgo leaf extract contains terpenoids (bilobalides and ginkgolides) and flavonoid glycosides. Flavones can reduce the fragility of capillaries, and protect the body from blood loss through damaged capillaries, particularly in the brain. The Ginkgolides, particularly ginkgolide B, inhibit the platelet-activating factor and so increase the fluidity of the blood that improves circulation, again particularly in the micro-capillaries of the brain. This is also why it is believed to reduce the incidence of cerebral thrombosis and resultant strokes(33).

The terpenoid fraction increases cerebral blood flow (CBF) and ginkgolide A and B act as platelet activating factor (PAF) antagonists. Extract of ginkgo biloba reduces iNOS and mRNA protein expression and thus NO release, although eNOS mediated NO production is increased by GB resulting in vasodilatation and increased CBF. The constituents responsible for NO production are not known (31). It has a positive effect on cholinergic transmission; the extract delays the decrease in acetylcholine receptor density in older rats (34). Bilobalide increases GABA and prevents neuronal over excitation. It decreases neurofibrillary tangles by a seven-fold up-regulation of neuronal tyrosine/threonine phosphatase 1, an enzyme involved in formation/breakdown of neurofibrillary tangles, in the cortex of mice administered 36 mg/kg Egb 761 p.o. for four weeks. Significant memory and behavioural improvement was seen in mild to moderate AD patients in placebo controlled trials with GB extract (120 mg/day, p.o.).

Bacopa monniera

Bacopa monniera, also referred to as *Bacopa monnieri*, *Herpestis monniera*, water hyssop, and "Brahmi," has been used in the Ayurvedic system of medicine for centuries. Traditionally, it was used as a brain tonic to enhance memory development, learning, and concentration, (35) and to provide relief to patients with anxiety or epileptic disorders. (36). The plant has also been used in India and Pakistan as a cardiac tonic, Digestive aid, and to improve respiratory function in cases of bronchoconstriction (37). Recent research has focused primarily on Bacopa's cognitive-enhancing effects, specifically memory, learning, and concentration and results support the traditional Ayurvedic claims. Research on anxiety, epilepsy, bronchitis and asthma, irritable bowel syndrome, and gastric ulcers also supports the Ayurvedic uses of Bacopa. Compounds responsible for the pharmacological effects of Bacopa include alkaloids, saponins, and sterols. Many active constituents—the alkaloids Brahmine and herpestine, saponins d-mannitol and hersaponin, acid A, and monnierin—were isolated in India over 40 years ago. Other active constituents have since been identified, including betulinic acid, stigmastanol, beta-sitosterol, as well as numerous bacosides and bacopasaponins. The constituents responsible for Bacopa's cognitive effects are bacosides A and B (38).

The triterpenoid saponins and their bacosides are responsible for Bacopa's ability to enhance nerve impulse transmission. The bacosides aid in repair of damaged neurons by enhancing kinase activity, neuronal synthesis, and restoration of synaptic activity, and ultimately nerve impulse transmission. Loss of cholinergic neuronal activity in the hippocampus is the primary feature of Alzheimer's disease. Based on animal study results, bacosides appear to have antioxidant activity in the hippocampus, frontal cortex, and striatum.

Animal research has shown Bacopa extracts modulate the expression of certain enzymes involved in generation and scavenging of reactive oxygen species in the brain.

Eclipta alba

(syn. *Eclipta prostrata* L.), commonly known as False Daisy, yerba de tago, and bhringraj, is a plant belonging to the family Asteraceae. It is widely distributed throughout India, China, Thailand, and Brazil. In ayurvedic medicine, the leaf extract is considered a powerful liver tonic, rejuvenative, and especially good for the hair. The herb *Eclipta alba* contains mainly coumestans i.e. wedelolactone (I) and demethylwedelolactone (II), polypeptides, polyacetylenes, thiophene-derivatives, steroids, triterpenes and flavonoids.

Lack of neural plasticity can generate pertinent cognitive deficits which indeed can affect the quality of life. In order to circumvent this problem, memory elevators are being constantly explored, of which herbs play a vital role. Luteolins being an active constituent in the extract of *Eclipta alba* may be responsible for minimizing cognitive deficits due to cholinergic dysfunctioning. Their profound free radical scavenging action could insulate neuronal tissues from degeneration probably by preserving these areas from stress perturbations. Protection of neuronal tissues may be possibly due to the immunomodulatory action of *Eclipta alba*. Therefore, *Eclipta alba* can serve as a potential memory modulator (39)

Eclipta alba has been found to activate Na⁺K⁺ATPase which could produce an elevation in the intracellular concentration of Ca²⁺. Stimulation of the Ca²⁺ receptor could induce the release of 5-hydroxytryptamine. The enhanced turnover of 5-HT can cause blunting of aggression and could be a plausible reason for the antiaggressive property of *Eclipta alba*. In conclusion, the total aqueous extract of *Eclipta alba* was found to be efficacious in producing serenity and masking the constellation of behavioral changes encountered during aggressive bouts making it a promising naturally derived product (40).

Ginseng

The English word ginseng derives from the Chinese term rénshēn (simplified: 人蔘; traditional: 人蔘), literally “man root” (referring to the root’s characteristic forked shape, resembling the legs of a man). The herbal remedies referred to as “ginseng” are derived from the roots of several plants. One of the most commonly used and researched of the ginsengs is Panax ginseng, also called Asian or Korean ginseng. The main active components of Panax ginseng are ginsenosides, which have been shown to have a variety of beneficial effects, including anti-inflammatory, antioxidant, and anticancer effects. Results of clinical research studies demonstrate that Panax ginseng may improve psychological function, immune function, and conditions associated with diabetes.

In Asian countries, ginseng has been used as a dietary supplement to enhance cognitive performance and reduce mental fatigue for thousands of years (41). Reports of its various therapeutic actions, including beneficial effect on cognition and mood date back as far as 101 B.C. claiming that it can “...support the five visceral organs, calm the nerves, tranquilize the mind, stop convulsion, expunge evil spirits, clear the eyes, and improve memory...” (“The Herbal Classic of the Divine Plowman”, published around 101 B.C(41).

Ginseng contains multiple active chemical constituents including ginsenosides, polysaccharides, peptides, polyacetylenic alcohols, and fatty acids. However, the majority of its pharmacological actions are being attributed to the ginsenosides (41). To date more than twenty such ginsenosides have been isolated (42) and some of these appear to have important mechanisms of action in the central nervous system, including interactions with neurotransmitter systems involved in the neural mediation of memory and cognition (43).

The Ginseng root (Panax Ginseng) is a common constituent of a large number of traditional oriental medicines. Among its diverse effects on the central nervous system, Ginseng is known to improve learning and memory.

Panax Ginseng is a commonly used galenic known to have an enhancing effect on learning. Neurogenesis, defined as the creation of new nerve cells, consists of a series of distinct developmental steps, two of which can be examined separately; proliferation and survival/differentiation (44). Neurogenesis in the hippocampus has been shown to be necessary for hippocampus/mygdale-dependent learning tasks. An increase in CFC-related neurogenesis may be one mechanism of Ginseng’s properties to enhance learning ability.

The molecular mechanisms underlying the regulation of hippocampal neurogenesis by Ginseng may be its two major constituents: crude Ginseng saponin and crude Ginseng non-saponin fractions. To date, more than 20 saponins have been isolated from Ginseng root and identified chemically (45). Ginsenosides (the saponin constituents of Ginseng root) have been reported to have a number of actions on the CNS. These include CNS stimulation or depression (46), anticonvulsant activity (47), antipsychotic activity and improvement of performance in various memory paradigms (48). The beneficial effects of Ginseng on learning and memory have often been attributed to ginsenoside Rb1 and Rg1. Ginsenoside Rg1 increases cAMP level and c-fos gene expression in the rat hippocampus. The elevation of intracellular cAMP level induces c-fos expression (49). The cAMP-CREB cascade could contribute to the actions of neurotransmitters and neurotrophic factors on adult neurogenesis (Nakagawa et al., 2002). In recent reports, CREB was shown to be necessary for both steps of neurogenesis: proliferation and cell survival (50). Activation of the cAMP/CREB cascade by Ginseng and ginsenosides Rb1 and Rg1 (51) are also thought to enhance learning and memory by facilitation of cholinergic function, which is apparently essential for the functional integration of learning processes. For example, Rb1 facilitated acetylcholine (ACh) release and improved passive avoidance learning. Rb1 and Rg1 increased the number of ACh receptors and improved passive avoidance learning in anisodine-treated mice, Rg1 improved the performance of scopolamine-injected rats in an eight-arm radial maze task. Consistent with these results, Rb1 facilitated choline uptake and increased choline acetyltransferase. ACh is also shown to increase neurogenesis (52). Thus, the increase of neurogenesis by Ginseng may be mediated via an increase in ACh release and ACh receptor and that may be the probable mechanism of beneficial effects of panax ginseng in Alzheimer’s disease.

Huperzia serrata

Huperzia serrata is a source of Huperzine A, a naturally occurring sesquiterpene alkaloid compound. Huperzine A is an Acetylcholinesterase inhibitor similar to other compounds donepezil, rivastigmine, and galantamine. In the US Huperzine A is sold as a dietary supplement for memory support. The botanical has been used in China for centuries for the treatment of swelling, fever and blood disorders. Clinical trials in China have shown it to be effective in the treatment of Alzheimer’s disease, and has been shown to enhance memory in healthy young students in one study.

It is currently being investigated as a possible treatment for diseases characterized by neurodegeneration – particularly Alzheimer’s disease. It has been found to be an inhibitor of the enzyme acetylcholinesterase. This is the same mechanism of action of pharmaceutical drugs such as galantamine and donepezil used to treat Alzheimer’s disease. Huperzine A is also a NMDA receptor antagonist which protects the brain against glutamate induced damage, and it increases nerve growth factor levels.

Clinical trials in China have shown that huperzine A is comparably effective to the drugs currently on the market, and may even be a bit safer in terms of side effects. Currently, the National Institute on Aging is conducting a Phase II clinical trial to evaluate the safety and efficiency of huperzine A in the treatment of Alzheimer’s disease in a randomized controlled trial of its effect on cognitive function. Recently, it has been investigated for its effectiveness against epilepsy in an initial 20-person clinical study by Harvard University neuroscientists examining its worth and side effects in those who are not satisfactorily

treated by existing pharmaceuticals.

Most adverse events were cholinergic in nature and no serious adverse events occurred. Huperzine A is a well-tolerated drug. The retrograde loss of the cholinergic system from the basal forebrain is the most common and the most severe neurochemical consequence of the disease. The cholinergic neuron clusters of the basal forebrain innervate the hippocampus and areas of association in the cortex involved in higher processes such as long-term memory, working memory, and attention. In these structures, the concentration of choline acetyltransferase (ChAT) decreased, accompanied by the impaired ability of high-affinity choline transport and synthesis of acetylcholine (ACh). The severity of memory impairments seen in AD is consistent with dysfunction of the cholinergic system (53).

Vinpocetine

Vinpocetine (Cavinton) is an acid derivative of the alkaloid vincamine. Vinpocetine is described as a specific inhibitor of basal and calmodulin-activated phosphodiesterase 1 (PDE1). This effect leads to an increase of cAMP over cGMP. It is mainly used as a pharmacological tool to implicate PDE1. Vinpocetine has been shown to facilitate long-term potentiation (55), enhance the structural dynamics of dendritic spines improve memory retrieval (56), and enhance performance on cognitive tests in humans (57). Vinpocetine is found to dilate the cerebral vasculature, promote the redistribution of blood flow and favor the aerobic glycolysis towards damaged areas (58).

It increases levels of neurotransmitters like cholinergic, noradrenaline and dopamine associated with spatial working memory tasks (59) and enhances cognition and memory (56). Vinpocetine decreases the disrupting effect of scopolamine on acquisition and prevent the memory loss. Recently same author has reported that vinpocetine improve memory and reduce oxidative stress and cholinergic deficits in experimental model of Alzheimer's disease (59)

CONCLUSION

Memory improving activity of all these plants may be attributed to their antioxidant, anti-inflammatory, neuroprotective, pro-cholinergic and anti-acetylcholinesterase properties of several active constituents present in them. Several of these plants may be of enormous use in delaying the onset and reducing the severity of Alzheimer's disease but lot more is required to be done to bring these preparations to the market.

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