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Pharmacological Review on Various Antioxidant Ayurvedic Drugs in Alzheimer's Disease: an Overview

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ABSTRACT

Alzheimer disease (AD) is a progressive dementia affecting a large proportion of the aging population, which is characterized by memory impairment, cognitive dysfunction, behavioral disturbances, and deficits in activities of daily living. Multiple lines of evidence demonstrate that oxidative stress is an early event in Alzheimer's disease (AD), occurring prior to cytopathology, and therefore may play a key pathogenic role in AD. 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. In Ayurveda, *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. Current review sums up the plants that have shown the beneficial and encouraging results in treating ailments like Alzheimer's disease having antioxidant properties which play an important role in pathogenesis of Alzheimer's disease.

Keywords: Alzheimer disease, oxidative stress, *Medhya* herbs,

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INTRODUCTION

Free radical-induced oxidative stress is now believed to be a fundamental mechanism underlying number of cardiovascular, neurologic, and other disorders in humans.[1] Oxygen is an indispensable element for life. Its oxidative property plays a vital role in various biological phenomena. However, oxygen can also aggravate the damage within the cell by oxidative events. It is used by the cell to generate energy and as a consequence of ATP production by mitochondria free radicals are formed. Free radicals are mainly derived from oxygen (reactive oxygen species/ROS) and nitrogen (reactive nitrogen species/RNS), and are generated in our body by various endogenous systems, exposure to different physicochemical conditions or patho-physiological states.[2] Oxidative stress is defined as the imbalance between biochemical process leading to production of reactive oxygen species (ROS) and those responsible for the removal of ROS [3].

The brain, as a relatively small organ mass, has a disproportionately high level of oxygen consumption due to its high ATP demand. In fact, the brain accounts for approximately 20% of the body's total basal oxygen consumption and subsequently generates relatively high level of ROS. [4] So that Brain tissue has multiple potential sources of ROS and a large oxidative capacity, but its ability to combat oxidative stress is limited. [5,6] Under normal conditions, damage by oxygen radicals is controlled by an efficient array of antioxidant systems. These include antioxidant enzymes and free radical scavengers such as ascorbate, vitamin E and protein sulfhydryls. However, in neurodegenerative conditions, this control is altered favoring the accumulation of free radicals, mitochondrial dysfunction and neuronal injury.[7] Oxidative damage has been found in all classes of organic molecules (proteins, lipids, nucleic acids and sugars) that are critical for neuronal structural and functional integrity [8]. Excessive lipid peroxidation, protein oxidation, DNA and RNA oxidation and glycooxidation have all been documented in AD brains.[7]

Increasing evidence suggests that oxidative stress that is normally associated with aging is a prominent and early feature of Alzheimer disease (AD) and plays a role in its pathogenesis.[9] It is a progressive neurodegenerative brain disorder that is slow in onset but leads to dementia, unusual behavior, personality changes and ultimately death.[10] 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 [11]

Medication available today for the treatment of Alzheimer's disease include cholinesterase

inhibitors and the NMDA-receptor antagonist i.e. memantine.[12]Acetylcholinestrase inhibitors include Tacrine (Cognex), Donepezil (Aricept), Rivastigmine (Exelon), and Galantamine (Reminyl). [13] 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. [14] 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. [15] These drugs produce modest improvement in approximately 30-40% of patients with mild to moderate AD.[14] Further, nootropic agents such as piracetam (Blazer), pramiracetam, aniracetam[16] are being primarily used to improve memory, mood and behavior. However, the resulting adverse effects associated with these agents have also limited their use.[16,17] Therefore, it is worthwhile to explore the utility of traditional medicines for the treatment of various cognitive disorders including Alzheimer's disease. In Ayurveda, *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. [18]

If free radical injury is a key player in the initiation and/or progression of AD then antioxidant therapies envisaging the reduction of oxidative damage and the increase of endogenous antioxidant defenses should prevent, delay, or ameliorate the disease symptoms. Until now, only partial benefits have been documented in clinical trials where antioxidant therapies were used in AD patients. However, those results are encouraging and further studies should be performed to find "the antioxidant" capable of neutralizing free radicals and their dangerous actions in AD.[7] This present paper aims to review the ayurvedic drugs having antioxidant properties and proved to be effective in Alzheimer disease.

PUBMED, MEDLINE database were searched for studies published from January 1990 to june 2012. The key words used for the search was Alzheimer diseases, Ayurveda, Herbal medicinal plant, antioxidant etc. In-vitro analysis, as well as experimental trails was included in the review. Only search articles in English language were considered. Other languages were approved when there was an English abstract containing data essential for extraction.

Hemidesmus indicus:

Shete R V *et al.*, (2010) investigated the potential of an Ayurvedic *rasayana* (rejuvenator) drug *Hemidesmus indicus* roots as a memory enhancer. Elevated plus maze and passive avoidance paradigm were used to evaluate learning and memory parameters. The chloroform and *n-butanol*

fractions of ethanolic extract of *Hemidesmus indicus root* (3, 10 and 30 mg/kg, p.o.) were screened for claimed potential in mice. The *n-butanol* fraction of *H. indicus* ethanolic extract significantly improved learning and memory at all doses in mice. Hence, *H. indicus* might prove to be a used as memory restorative agent in the treatment of dementia seen in the Alzheimer's disease.[19] *HI* is reported to possess antioxidant activity which might protect the susceptible brain cells from oxidative stress resulting in reduced brain damage and improved neuronal function.[20] The preliminary phytochemical evaluation and HPTLC analysis showed prominent presence of saponins and triterpenoids in HIBF indicating role of these phytochemicals in the observed effect. Hence, H. indicus might prove to be a useful memory restorative agent in the treatment of dementia seen in the Alzheimer's disease. [19] ***Ficus Hispida:***

An animal experiment was designed to determine the ameliorating effect of ethanolic leaf extract of Ficus hispida Linn. (EEFH) on (amyloid beta) Aβ 25-35- induced cognitive deficits and oxidative stress in mice, in which animal were treated with EEFH for periods of 4 weeks dose-dependently (200 and 400 mg kg^{-1}) then received a single intracerbroventricular (i.c.v.) injection of Aβ 25-35 (µg $mouce^{-1}$). Behavioral changes in the mice were evaluated using passive avoidance, Y-maze, Hole board and water-maze test. Anti-oxidant enzymes and neurotransmitter levels were also been estimated. EEFH at the dose of 400 mg kg^{-1} significantly ameliorated the cognitive and memory deficits caused by i.c.v. injection of Aβ 25-35. EEFH attenuated the Aβ-induced increase in brain levels of thiobarbituric acid reactive substances. There was an increase in glutathion peroxidase, glutathion reductase and super oxide dismutase activity in EEFH treated groups. the acetyl cholinesterase activity in the brain was lower in EEFH supplemented groups than the Aβ-injected group. The acetyl cholinesterse activity in the brain was lower in EEFH supplemented groups than Aβ-injected group. EEFH treated group showed a significant alteration in behaviour when compare to negative control in Y maze, plus-maze and also in water maze test. These findings suggest EEFH exerts a protective effect against cognitive deficits induced by Aβ 25-35 accumulation in Alzhemirs diseases, because its potential antioxidant property.[21]

Decalepis hamiltonii:

The neuroprotective potential of the aqueous extract of the roots of *Decalepis hamiltonii* (*D. hamiltonii* root aqueous extract-DHRAE) was studied against ethanol-induced oxidative stress in the rat brain. Ethanol, single dose (5 g/kg body weight), induced oxidative stress in the rat brain which was evident from the increased lipid peroxidation and protein carbonylation, reduced glutathione, and suppressed activities of antioxidant enzymes such as superoxide dismutase,

catalase, glutathione peroxidase, glutathione reductase, and glutathione-S-transferase. Pretreatment of rats with multiple doses of DHRAE, 50 and 100 mg/kg b.w., for 7 consecutive days significantly prevented the ethanol-induced oxidative stress. DHRAE, as such, boosted the antioxidant status of the rat brain. The neuroprotective potential of DHRAE can be attributed to the known antioxidant constituents or its interaction with antioxidant response elements (AREs) which needs to be ascertained and can be useful memory restorative agent in the treatment of dementia seen in the Alzheimer's disease.[22] Similarly, by the same author the effect of multiple-dose (7, 15, and 30 days) treatment of *Decalepis hamiltonii* aqueous root extract (DHA) (50 and 100 mg kg^{-1} body weight) on the antioxidant profile of rat liver and brain were screened. Activities of the antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), and glutathione-*S*-transferase (GST) were increased and glutathione content was elevated in both liver and brain, apart from reduction in the basal level of lipid peroxidation. DHA induced stronger antioxidant boost in brain by increasing the activities of SOD, CAT, and GPx compared to liver. This further justifies the antioxidant property of DHRAE which can be useful in treatment of Alzheimer disease. [23]

Centella asciatica:

The effect of *Centella asiatica* extract and powder in reducing oxidative stress in rats was evaluated in study. Lipid peroxidation was monitored by measuring malonaldehyde (MDA) level in blood. Activities of free radical-scavenging enzymes (superoxide dismutase and catalase) were determined using H_2O_2 decomposition and nitrobluetetrazolium reduction, respectively. Results revealed that *C. asiatica* extract and powder may ameliorate H_2O_2-induced oxidative stress by decreasing lipid peroxidation via alteration of the antioxidant defense system of the rats. [24]It has also been reported that *Centella asiatica* supplementation is effective in reducing brain regional lipid peroxidation (LPO) and protein carbonyl (PCO) levels and in increasing anti oxidant status. [25] Cognitive -enhancing effects were observed in rats following oral administration of an aqueous extract of *Centella asiatica* and this effect was associated with an antioxidant mechanism in the CNS.[26] Intracerebroventricular streptozotocin in rat has been likened to sporadic Alzheimer's disease in humans and cognitive impairment is associated with free radical generation in this model. Aqueous extract of *Centella asiatica* is reported to be effective in preventing the cognitive deficits as well as oxidative stress caused by intra cerebro ventricular streptozotocin in rats. [27] Beneficial effect of *Centella asiatica* has been reported on cognitive functions and oxidative stress in rats.[28] In another study, only the aqueous extract of whole plant (200mg/kg for 14 days) showed an improvement in learning and memory in both shutte box and step through

paradigams.[29] Frederico Pittella *et al.*, **(***2009)* investigated the antioxidant [2, 2-diphenyl-2-picrylhydrazyl hydrate (DPPH) assay] and cytotoxic activities of an aqueous extract (AE) of *Centella asiatica* leaves by isolating the phenolic (Folin-Dennis) and flavonoid (colorimetric assay) constituents. The aqueous extract (50 g/L) was obtained by cold maceration for 24 h and the phenolic and flavonoid compounds were isolated as 2.86g/100g and 0.361g/100g, respectively. The AE of *C. asiatica* showed elevated DPPH scavenging activity, with an IC50 value of 31.25 µg/mL.[30] All the findings indicated that the aqueous extract of *Centella asiatica* has cognitive enhancing effect and an antioxidant mechanism which is helpful in Alzheimer disease.

Curcuma longa:

Ataie A *et al.*, (2010) investigated the antioxidant and neuroprotective properties of *Curcuma longa* Linn, were curcumin (5, 15, 45 mg/kg) was injected intraperitonealy once daily for a period of 10 days beginning 5 days prior to homocysteine (Hcy) intracerebroventricular injection in rats. Biochemical and behavioral studies, including passive avoidance learning and locomotor activity tests were studied 24 hrs after the last curcumin or its vehicle injection. Hcy could induce lipid peroxidation and increase Malondialdehyde (MDA) and Super Oxide Anion (SOA) levels in rat's brain. Additionally, Hcy impaired memory retention in passive avoidance learning test. Results indicated that treatment of curcumin improves the memory in rats that was inducted by Hcy.[31] In another study, Curcuminoids (a mixture of curcumin, bisdemethoxycurcumin and demethoxycurcumin) possess acetylcholinesterase (AChE) inhibitory and memory enhancing activities. For screening the effect of Curcuminoids on memory in rats, the in-vitro and ex-vivo models of AChE inhibitory activity were used along with Morris water maze test. It was observed that, Curcuminoids inhibited AChE in the in-vitro assay with IC_{50} value of 19.67, bisdemethoxycurcumin 16.84, demethoxycurcumin 33.14 and curcumin 67.69 µM. In the ex-vivo AChE assay, curcuminoids and its individual components except curcumin showed dose-dependent (3–10 mg/kg) inhibition in frontal cortex and hippocampus. When studied for their effect on memory at a fixed dose (10 mg/kg), all compounds showed significant ($p < 0.001$) and comparable effect in scopolamine-induced amnesia. These data indicate that curcuminoids and all individual components except curcumin possess pronounced AChE inhibitory activity. Curcumin was relatively weak in the in-vitro assay and without effect in the ex-vivo AChE model, while equally effective in memory enhancing effect, suggestive of additional mechanism(s) involved. Thus curcuminoids mixture might possess better therapeutic profile than curcumin for its medicinal use in AD. [32]

Convolvulus pluricaulis:

Bihaqi S.W. et al (2011) investigated cognitive-enhancing property (neuroprotective effect) of aqueous extract (AE) of *Convolvulus pluricaulis* against scopolamine (1 mg/kg body weight (bwt))-induced neurotoxicity in the cerebral cortex of male Wistar rats using Elevated plus maze (EPM) (transfer latency [TL]) and Morris water maze (MWM). Besides evaluating the effect of extract on neurochemical enzymes, *in vivo* antioxidant and free radical scavenging activities were also screened. All the measured parameters were compared with rivastigmine tartrate (1 mg/kg bwt) which was taken as standard. Pretreatment of rats with AE (150 mg/kg bwt) significantly reduced scopolamine-induced increase in the TL in EPM, whereas in MWM, administration of extract improved the impairment of spatial memory induced by scopolamine. The activity of acetylcholinesterase (AChE) was significantly inhibited by extract within the cortex and hippocampus. Reduced activities or contents of glutathione reductase, superoxide dismutase, and reduced glutathione within the cortex and hippocampus induced by scopolamine were elevated by the extract. So AE of *convolvulus pluricaulis* exert its potent-enhancing activity through both anti-AChE and antioxidant action, which can be used in Alzheimer disease. [33]

Asparagus racemosus:

Asparagus Racemosus (AR) is an Ayurvedic rasayana possessing multiple neuropharmacological activities. Study was undertaken by Rakesh ojha et al (2010) to assess nootropic and anti-amnesic activities of MAR in rats. The Morris water maze (MWM) and elevated plus maze (EPM) models were employed to evaluate learning and memory activity. Subsequently, the anti-amnestic activity was evaluated in scopolamine and sodium nitrite ($NaNO_2$)-induced amnestic models in rats. Rats pre-treated with MAR (50, 100 and 200 mg/kg, p.o) for 7 days showed significant decrease in escape latency in the MWM test indicating nootropic activity. MAR also significantly reversed scopolamine and sodium nitrite-induced increase in transfer latency on EPM indicating anti-amnesic activity. Further, MAR dose-dependently inhibited acetylcholinesterase enzyme in specific brain regions (prefrontal cortex, hippocampus and hypothalamus). Thus, MAR showed nootropic and anti-amnesic activities in the models tested and these effects may probably be mediated through augmentation of cholinergic system due to its anti-cholinesterase activity.[34]

Trichilia catigua:

Preparations have been popularly used in Brazil as a tonic for the treatment of fatigue, stress, impotence, and deficiency of memory. Janaine M. Chassot et al (2011) investigated the possible antidepressant, anxiolytic, motor and cognitive effects of the crude extract (CE) or ethyl-acetate

fraction (EAF) of *Trichilia catigua* and analyses of the total phenolics and total tannins content, as well as the *in vitro* antioxidant activity of CE and EAF. CE (200–800 mg/kg) and EAF (100–400 mg/kg) were orally administered to mice and 1 h later the behavioral tests were performed. The free radical scavenging activity was measured by using 2,2-diphenyl-1-picryl-hydrazyl (DPPH) method. After Single administration of CE (200–400 mg/kg) or EAF (100–400 mg/kg) did not change the behavior of the animals submitted to the elevated plus maze or their locomotor activity in the open field test. An antidepressant-like effect was detected with EAF (400 mg/kg) after acute administration. Both CE (800 mg/kg) and EAF (200 and 400 mg/kg), improve memory in mice as measured by an increased latency in the step-down inhibitory avoidance test. The EAF presented higher total phenolics and total tannins as compared to CE as well as it exhibited the best antioxidant activity. The present results showed an *in vitro* antioxidant activity for EAF and suggested that it may be useful for cognitive improvement and Alzheimer disease. [35]

Celastrus paniculata:

Mrinmoy Chakrabarty et al (2012) investigated the effects of *Celastrus paniculatus* seed oil in preventing the onset of chronic aluminum induced cortico-hippocampal neurodegeneration and oxidative stress. In which an animal model of senile dementia of Alzheimer's type was produced by administering aluminum as aluminum chloride (4.2 mg/kg) intraperitoneally to male Wistar rats for 60 days and results compared to untreated control. Neurobehavioral investigations of Morris water maze tests, passive avoidance test, rotarod test and biochemical estimations of acetylcholineterase, malondialdehyde, glucose-6-phosphate dehydrogenase, superoxide dismutase, and hemoglobin in blood were performed fortnightly which gauged the extent of global oxidative stress and progressive neural damage. Findings were fortified by the above enzyme assays and histology of brain at necropsy. Prophylactic oral *C. paniculatus* in two doses 0.5 ml and 1 ml, were given to animals and the results were analyzed in comparison to a similar rodent model with standard drug donepezil (0.5 mg/kg) intraperitoneally. *C. paniculatus* showed a significant prevention in onset of aluminum induced neural insult and overall systemic oxidative stress which was corroborated by the enlisted neurobehavioral, biochemical, and histological evidence. From above result it can be concluded that *C. paniculatus* is a putative decelerator of Al-mediated Alzheimer's like pathobiology. [36]

***Caesalpinia crista*:**

Amyloid beta (Aβ) is the major etiological factor implicated in Alzheimer's disease (AD). Aβ(42) self-assembles to form oligomers and fibrils via multiple aggregation process. B.N.

Ramesh et al 2010 has performed one study focused on ability of *C. crista* leaf aqueous extract on the prevention of (i) the formation of oligomers and aggregates from monomers (Phase I: Aβ(42) + extract co-incubation); (ii) the formation of fibrils from oligomers (Phase II: extract added after oligomers formation); and (iii) dis-aggregation of pre-formed fibrils (Phase III: aqueous extract added to matured fibrils and incubated for 9 days). The aggregation kinetics was monitored using thioflavin-T assay and transmission electron microscopy (TEM). The results showed that *C. crista* aqueous extract could able to inhibit the Aβ(42) aggregation from monomers and oligomers and also able to dis-aggregate the pre-formed fibrils. Thus leaf aqueous extract of *Caesalpinia crista* has Anti-amyloidogenic property which is to be good therapeutic agents in Alzheimer's disease. [37]

Withania somnifera:

The active principles of WS, sitoindosides VII-X and withaferin A (glycowithanolides), have been tested for antioxidant activity using the major free-radical scavenging enzymes, superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) levels in the rat brain frontal cortex and striatum. Decreased activity of these enzymes leads to accumulation of toxic oxidative free radicals and resulting degenerative effects. An increase in these enzymes would represent increased antioxidant activity and a protective effect on neuronal tissue. Active glycowithanolides of WS (10 or 20 mg/kg intraperitoneally) were given once daily for 21 days to groups of six rats. Dose-related increases in all enzymes were observed; the increases comparable to those seen with deprenyl (a known antioxidant) administration (2 g/kg/day intraperitoneally). This implies that WS does have an antioxidant effect in the brain which may be responsible for its diverse pharmacological properties and useful in Alzheimer disease. [37]

The β-amyloid peptide, with 39–42 amino acid residues (BAP), plays a significant role in the development of AD. *Withania somnifera* fruit afforded lipid peroxidation inhibitory withanamides that are more potent than the commercial antioxidants. In this study, we have tested two major withanamides A (WA) and C (WC) for their ability to protect the PC-12 cells, rat neuronal cells, from β-amyloid induced cell damage. The cell death caused by β-amyloid was negated by withanamide treatment. Molecular modeling studies showed that withanamides A and C uniquely bind to the active motif of β-amyloid (25–35) and suggest that withanamides have the ability to prevent the fibril formation. Further understanding of the mechanism of action and *in vivo* efficacy of these withanamides may facilitate its development as a prophylaxis. [38]

DISCUSSION

Popularity of herbal remedies is increasing globally and at least one quarter of patients with brain disorders use ethnobotanicals. More efforts need to be directed towards methodological scientific evaluation for their safety and efficacy by subjecting to vigorous preclinical studies followed by clinical trials to unravel the mysteries hidden in the plants. This approach will help exploring the real therapeutic value of these natural pharmaco therapeutic agents and standardized the dosage regimen on evidence-based findings to become more than a fashionable trend. Many herbals are on the market to support health, relieve symptoms and cure diseases. However, most of these products lack scientific pharmacological validation. In experimental neurotoxicity models in laboratory or higher animals, several herbals exerted neuroprotective/curative effects that warrants their clinical testing. Due to lack of scientific based pharmacological data, most of the herbal formulations cannot be recommended as nootropics. In spite of the availability of more than 300 preparations for the treatment of brain disorders in Indian Systems of Medicine (using more than 76 Indian medicinal plants,) only four terrestrial plants have been scientifically elucidated while adhering to the internationally acceptable scientific protocols.

In depth studies have proved *Bacopa monniera* and *Ginkgo biloba* to be antioxidative, free radical scavenger and neuro regenerative. *Centella asiatica* has been proved as excellent treatment as neuroprotective and capable of memory enhancer. Various species of Shankhpushpi were reported to be having antiinflammatory, nootropics and treat neuropsychopharmacological disorders.

CONCLUTION

Alzheimer's diseases stand as one of the foremost health troubles observed in old peoples, with oxidative stress and drug induced neurodegeneration roming worldwide. Therapies developed along the principles of western medicine are often limited in efficacy, carry the risk of adverse effects, and are often too costly, especially for the developing world. Therefore, treating AD with plant derived compounds which are accessible and do not require laborious pharmaceutical synthesis seems highly attractive. In this review article, an attempt has been made to give the information about the Alzheimerogenic agents (or) neurotoxin agents and also compile the reported neuroprotective plants from India and abroad which may be useful to the health professionals, scientists and scholars working the field of pharmacology and therapeutics to develop evidence based alternative medicine to cure different kinds of neuronal diseases in man and animals.

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