EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 9
334-343
Year: 2020

HERBAL DRUGS IN TREATMENT OF ALZHEIMER'S DISEASE

Megha S. Shah[1]*, Aher Pallavi[2], Durekar Tanuja[3] and Dr. Rajesh J. Oswal[4]

*[1]Assistant Professor Department of Pharmacognosy, Genba Sopanrao Moze College of Pharmacy, Wagholi, Pune.
[2,3]UG Student, Genba Sopanrao Moze College of Pharmacy, Wagholi, Pune.
[4]Principal, Genba Sopanrao Moze College of Pharmacy, Wagholi, Pune.

***Corresponding Author: Megha S. Shah**
Assistant Professor Department of Pharmacognosy, Genba Sopanrao Moze College of Pharmacy, Wagholi, Pune.

Article Received on 13/07/2020 **Article Revised on 03/08/2020** **Article Accepted on 23/08/2020**

ABSTRACT
Alzheimer s disease (AD) is characterized by profound memory loss sufficient to interfere with social and occupational functioning. It is the most common form of dementia, affecting more than 20 million people worldwide. AD is characterized by an insidious loss of memory, associated functional decline and behavioral disturbances. Patients may live for more than a decade after they are diagnosed with AD, making it the leading cause of disability in the elderly. The incidence of AD ranges from 1 to 4% of the population per year, increasing from its lowest level at ages 65 to 70 years to rates that may approach 6 percent for those over the age of 85 years. The first neurotransmitter defect discovered in AD involved acetylcholine (ACh). As cholinergic function is required for short-term memory, the cholinergic deficit in AD was also believed to be responsible for much of the short-term memory deficit. Clinical drug trials in patients with AD have focused on drugs that augment levels of Ach in the brain to compensate for the loss of cholinergic function. These drugs have included ACh precursors, muscarinic agonists, nicotinic agonists and acetylcholinesterase inhibitors. The most highly developed and successful approaches to date have employed acetylcholinestrase inhibition. Although some Food and Drug Administration approved drugs are available for the treatment of Alzheimer's disease, the outcomes are often unsatisfactory, and there is a place for alternative medicine, in particular, herbal medicine. This paper reviews the clinical effects of a number of commonly used types of herbal medicines for the treatment of AD.

KEYWORDS: Alzheimer disease, *Ginkgo biloba*, herbal medicine, *Panax ginseng*, Brahmi.

INTRODUCTION
Alzheimer's disease (AD) is a brain disorder named after German physician Aloes Alzheimer, who first described it in 1906. Alzheimer's disease is a progressive and neurodegenerative disease that primarily affects the elderly population of over 65 years of age, and is estimated to account for 50 - 60% of the dementia cases.[1] The prevalence has been found to rise exponentially with age, ranging from 3.0% in patients aged 65 to 74 years to as much as 47.2% in those aged 85 years.[2,3] This condition is characterized by a progressive loss of memory, deterioration of virtually all intellectual functions, increased apathy, decreased speech function, disorientation, and gait irregularities.

Electronic databases like MEDLINE, LILACS, Cochrane Library, dissertation Abstract (USA), National Research Register, Current Controlled trials, Center watch Trials Database and Psych INFO Journal Articles bases were used to search for information related to studies done on plants in the past years. The search combined the terms Alzheimer disease, dementia, cognition disorders, Herbal and Phytotherapy.

The brain has 100 billion nerve cells (neurons). Each nerve cell connects with many others to form communication networks. Groups of nerve cells have special jobs. Some are involved in thinking, learning and remembering. Others help us see, hear and smell. To do their work, brain cells operate like tiny factories. They receive supplies, generate energy, construct equipment and get rid of waste. Cells also process and store information and communicate with other cells. Keeping everything running requires coordination as well as large amounts of fuel and oxygen.

The beta-amyloid peptide, with 39 - 42 amino acid residues (BAP), plays a significant role in the development of AD. Although there is no cure for AD, it can be managed with the available drugs, to some degree. Several studies have revealed that natural antioxidants, such as vitamin E, vitamin C, and beta-carotene, may help in scavenging free radicals generated during the initiation and progression of this disease. The loss of memory is considered to be the result of a shortage of the nerve transmitter acetylcholine. It is possible to increase the level of this transmitter in the

brain by inhibiting the activity of the enzyme acetylcholinesterase, which splits or breaks down the transmitter substance. Drugs that inhibit the breakdown of the messenger or transmitter acetylcholine delay the development of the disease.[4] Alzheimer's is the most common form of dementia.

Pathophysiology of AD

Neuronal loss and/or pathology may be seen particularly in the hippocampus, amygdala, entorhinal cortex and the cortical association areas of the frontal, temporal and parietal cortices, but also with subcortical nuclei such as the serotonergic dorsal raphe, noradrenergic locus coeruleus, and the cholinergic basal nucleus. The deposition of tangles follows a defined pattern, starting from the trans-entorhinal cortex; consequently the entorhinal cortex, the CA1 region of the hippocampus and then the cortical association areas, where frontal, parietal and temporal lobes are particularly affected. The extent and placement of tangle formation correlates well with the severity of dementia, much more so than numbers of amyloid plaques.[5]

The accretion of tau proteins correlates very closely with cognitive decline and brain atrophy, including hippocampal atrophy. In the neuropathology of Alzheimer's disease there is a loss of neurons and atrophy in temporofrontal cortex, which causes inflammation and deposit the amyloid plaques and an abnormal cluster of protein fragments and tangled bundles of fibers due to this there is an increase in the presence of monocytes and macrophages in cerebral cortex and it also activates the microglial cells in the parenchyma.[6] Summary of pathophysiology of AD is shown in Figure 1.

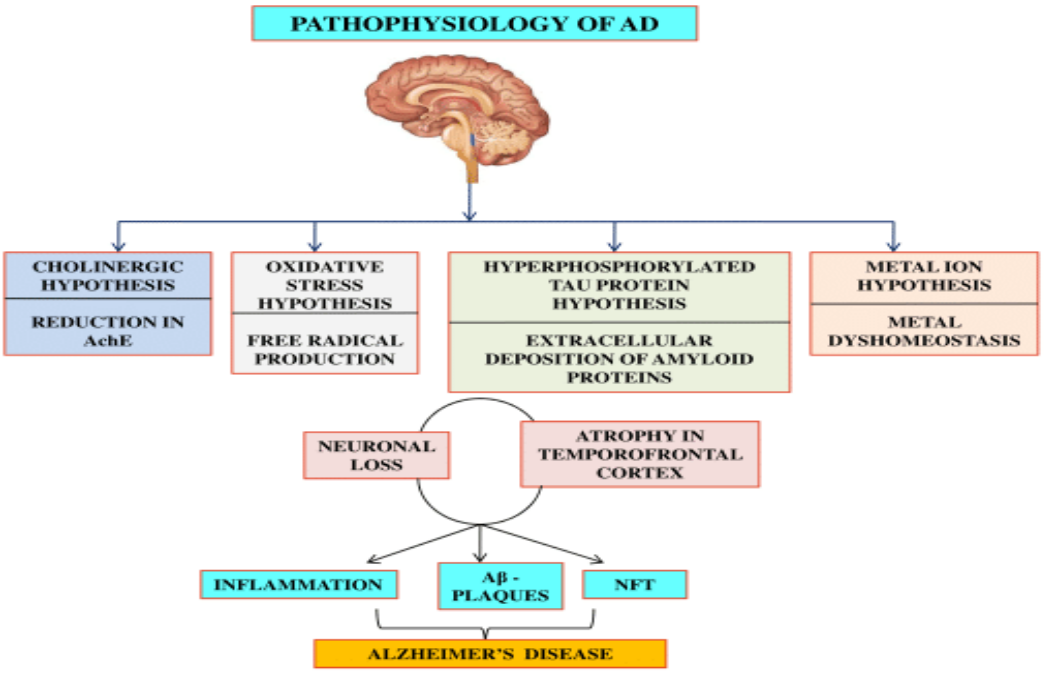

Fig. 1 Hypothesis for pathophysiology of alzheimer's disease.

Hyperphosphorylated tau protein and amyloid β hypothesis

One of the main pathological features of AD is the formation of senile plaques (SP), which is caused by amyloid beta (Aβ) deposition. Normally, Aβ are soluble small peptides, which are produced by the splitting of the precursor protein of amyloid (APP) by the action of α-secretase, β-secretase and γ-secretase. The imbalance between β-amyloid (Aβ) production and clearance leads to various types of toxic oligomeric, namely protofibrils, fibrils and plaques depending upon the extent of oligomerization. The reason of the formation of Aβ is still unclear, but the sequence, concentration and conditions of stability of Aβ are important factors.[7] The pathophysiology of Alzheimer's disease is credited to a number of factors such as the cholinergic dysfunction, amyloid/tau toxicity and oxidative stress/ mitochondrial dysfunctions.[8]

Oxidative stress hypothesis

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are produced in many normal and abnormal processes in humans, they play dual role as both have beneficial functions in cellular signaling pathways and venomous processes that can lead to damage of cellular structures (including cell membrane, lipid, protein and DNA). The high oxygen consumption of the brain, which utilizes 20% more oxygen than other mitochondrial respiratory tissues, means that the brain is more vulnerable to oxidative stress. The neuron is the basic functional unit of the brain, which contains a large number of polyunsaturated fatty acids. It can interact with ROS, leading to the lipid peroxidation reaction and

molecular apoptosis, in addition, less glutathione in neurons is also one of the causes of oxidative stress injury.[7]

Metal ion hypothesis

Metal dyshomeostasis is involved in the progression and pathogenesis of diseases, including neurodegerative diseases and cancer. Ionosphere and metal chelators are well known modulators of transition metal homeostasis, and a number of these molecules are used in clinical trials. Metal-binding compounds are not the only drugs capable of targeting transition metal homeostasis.[9] Current evidence indicates changes in the equilibrium of redox transition metals; mainly copper (Cu), iron (Fe) and other trace metals. Their levels in the brain are found to be high in AD. In other neurodegenerative disorders, Cu, manganese, aluminum and zinc are involved.[10]

Cholinergic hypothesis

The effects of apo-lipo-protein E (APOE) genotype on the useful effect of acetyl-cholinesterase inhibitors (AChEIs) in patients with Alzheimer's disease. AchEI medications are the core of the treatment of AD, and APOE genotype is the most important factor associated with AD. This lack of major effect of APOE is analyzed with respect to the "Cholinergic Hypothesis" of AD, dating from 1976, through the recognition that cholinergic neurons are not the main target of AD.

Cholinergic receptor binding is reduced in specific brain regions with mild to moderate AD and is related to neuropsychiatric symptoms. Among healthy older adults, lower receptor binding may be associated with slower processing speed. Cholinergic receptor binding in vivo may reveal links to other key brain changes associated with aging and AD and may provide a potential molecular treatment target.[11] Clinical decrease is related to an extensive loss of cholinergic neurons formed in the forebrain nuclei (medial) and a related decline in acetylcholine-mediated neurotransmission, drugs tending to regularize acetylcholine transmitter level, such as cholinesterase inhibitors (ChEIs) and donepezil, have for over 20 years served as the foundation of symptomatic therapy for AD.[12]

PHARMACOLOGICAL TREATMENT WITH MEDICINAL HERBS

While no drug has been shown to completely protect neurons, agents that inhibit the degradation of ACh within the synapse are the mainstay of treatment for AD. Acetylcholinesterase/cholinesterase inhibitors and memantine are the only agents approved by the Food and Drug Administration for the treatment of AD. Other drugs, such as selegiline, vitamin E, estrogen and anti-inflammatory drugs have been studied, but their use remains controversial.[13,14] Various other agents have been used in an attempt to modify the course or improve the symptoms of AD, including *Ginkgo biloba*.[15-17] 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.[13-17] Many of today's synthetic drugs originated from the plant kingdom and only about two centuries ago the major pharmacopoeias were dominated by herbal drugs.

Herbal medicine went into rapid decline when basic and clinical pharmacology established themselves as leading branches of medicine. Nevertheless, herbal medicine is still of interest in many diseases, in particular, psychiatric and neurological disorders. There are some reasons for this issue: 1) patients are dissatisfied with conventional treatment, 2) patients want to have control over their healthcare decision, and 3) patients see that herbal medicine is congruent with their philosophical values and beliefs.[13] There are several studies and documents that indicate a unique role of herbal medicines in the treatment of AD.

***Panax ginseng* (Araliaceae)**

Studies demonstrated that *Panax* ginseng extract improves AD symptoms in patients with AD, and the two main components of ginseng might contribute to AD amelioration. Ginsenosides show various AD-related neuroprotective effects. **Gintonin** is a newly identified ginseng constituent that contains lysophosphatidic acids and attenuates AD-related brain neuropathies. Ginsenosides decrease amyloid β-protein (Aβ) formation by inhibiting β- and γ-secretase activity or by activating the nonamyloidogenic pathway, inhibit acetylcholinesterase activity and Aβ-induced neurotoxicity, and decrease Aβ-induced production of reactive oxygen species and neuroinflammatory reactions. Oral administration of ginsenosides increases the expression levels of enzymes involved in acetylcholine synthesis in the brain and alleviates Aβ-induced cholinergic deficits in AD models. Similarly, gintonin inhibits Aβ-induced neurotoxicity and activates the nonamyloidogenic pathway to reduce Aβ formation and to increase acetylcholine and choline acetyltransferase expression in the brain through lysophosphatidic acid receptors. Oral administration of gintonin attenuates brain amyloid plaque deposits, boosting hippocampal cholinergic systems and neurogenesis, thereby ameliorating learning and memory impairments. It also improves cognitive functions in patients with AD. Ginsenosides and gintonin attenuate AD-related neuropathology through multiple routes.[18]

The effects of ginseng on the cognitive function with underlying mechanisms have been proposed. Ginsenoside is known to improve learning and memory in hippocampus-dependent tasks and increased cell survival in the dentate gyrus and hippocampal subregion CA3. Ginsenoside attenuated $A\beta_{1-42}$-induced neurotoxicity and tau hyperphosphorylation at multiple AD-related sites in a dose-dependent manner. In addition, it has been suggested that

ginsenoside potentiated the cholinergic pathways in the central nervous system. Thus, enhanced choline acetyltransferase activity and inhibited acetylcholine esterase activity, thereby enhancing the function of cholinergic system. Administration ginsesenoside increased the cortex thickness and density of synapses in the hippocampal CA3 region, which is suggested to modulate synaptic plasticity, regarded as one of the most essential mechanism in learning and memory.[19]

***Ginkgo biloba* l. (ginkgoaceae)**

Ginkgo biloba (Gb) is currently the most investigated and adopted herbal remedy for cognitive disorders and Alzheimer's disease (AD). Nevertheless, its efficacy in the prevention and treatment of dementia still remains controversial. Specifically, the added effects of Gb in subjects already receiving "conventional" anti-dementia treatments have been to date very scarcely investigated. The use of Gb is associated with additional cognitive and functional benefit in AD patients already in treatment with cholinesterase inhibitors (ChEIs). Data are from mild to moderate AD patients under ChEI treatment recruited in the Impact of Cholinergic Treatment USe (ICTUS) study. Mixed model analyses were performed to measure six-monthly modifications in the Mini Mental State Examination (MMSE), the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) subscale score, and the Activities of Daily Living (ADL) scale over a follow-up of 1 year according to the additional Gb supplementation. Findings suggest that Gb may provide some added cognitive benefits in AD patients already under ChEIs treatment. The clinical meaningfulness of such effects remains to be confirmed and clarified.[20]

GBE appears to be most effective in the early stages of AD. This could potentially mean that patients with early AD may be able to maintain a reasonably normal life. GBE has been shown to have the ability to normalize the ACh receptors in the hippocampus area of the brain (the area most affected by the disease) in aged animals.[21] GBE has also demonstrated the ability to increase cholinergic activity and to provide improvements in other aspects of the disease.[22]

Gotu kola (*centella asiatica*) (apiaceae)

In the Ayurvedic system of medicine, **leaves of gotu kola** is one of the important rejuvenating herbs for nerve and brain cells and is believed to be capable of increasing intelligence, longevity, and memory.[23,24] **Asiaticoside** derivatives, including **asiatic acid** and asiaticoside, were shown to reduce hydrogen peroxide-induced cell death, decrease free radical concentrations, and inhibit beta-amyloid cell death *in vitro*, suggesting a possible role for gotu kola in the treatment and prevention of AD and beta-amyloid toxicity.[25] Gotu kola extracts reversed the beta-amyloid pathology in the brains of mice and modulated the components of the oxidative stress response.[24-28]

Ashwagandha (*withinia somnifera*)

Ashwagandha contains steroidal compounds of great interest to researchers, such as the ergostane-type steroidal lactones, including withanolides A to Y, dehydrowithanolide R, withasomniferin A, withasomidienone, withasomniferols A to C, withaferin A and withanone. Other constituents include the phytosterols sitoindosides VII to X and beta-sitosterol as well as alkaloids (for example, ashwagandhine, cuscohygrine, tropine, pseudotropine, isopelletierine, and anaferine), a variety of amino acids (including tryptophan), and high amounts of iron.[29,30] A subset of these components (**withanamides**) has been shown to scavenge free radicals generated during the initiation and progression of AD. Neuronal cell death triggered by amyloid plaques was also blocked by withanamides.[31-35] Molecular modeling studies showed that withanamides A and C uniquely bind to the active motif of beta-amyloid (Aβ 25-35) and prevent fibril formation.[33,35] In the CNS, Ashwagandha has been reported to increase memory and learning.[36] **Aqueous extracts** of this herb have been found to increase cholinergic activity, including increases in the acetylcholine content and cholineacetyl transferase activity in rats and this might partly explain the cognition-enhancing and memory-improving effects.[37,38] In addition, recent reports have provided exciting information on the ability of this herb to stimulate neurite outgrowth.[39] Treatment with the **methanol extract** of Ashwagandha caused neurite outgrowth in a dose- and time-dependent manner in human neuroblastoma cells.[37,40] The levels of two dendritic markers, MAP2 and PSD-95, were found to be markedly increased in cells treated with Ashwagandha, suggesting that it stimulates dendrite formation.[37,40] In an extension of the above study, the same research group treated cultured rat cortical neurons with amyloid peptide that induced axonal and dendritic atrophy and loss of pre- and postsynaptic stimuli. Subsequent treatment with a methanol extract of Ashwagandha induced significant regeneration of both axons and dendrites. In addition to the reconstruction of pre- and postsynapses in the neurons, methanol extracts of Ashwagandha reversed amyloid peptide-induced memory deficit in mice.[40] These *in vivo* effects of Ashwagandha were maintained even after the discontinuance of the drug administration.

Bhrami (*bacopa monnieri*) (*scrophulariaceae*)

The principal constituents of *Bacopa monnieri* (BM) are saponins and triterpenoid bacosaponins that include bacopasides III to V, bacosides A and B, and bacosaponins A, B, and C. Other saponin glycosides include the jujubogenin bisdesmosides bacopasaponins D, E, and F. Other constituents include alkaloids, plant sterols, betulic acid, polyphenols, and sulfhydryl compounds that confer antioxidant activity.[41,42,43] Thus, BM could act by reducing divalent metals, scavenging reactive oxygen species, decreasing the formation of lipid peroxides and inhibiting lipoxygenase activity.[44]

Traditionally, BM was used to improve memory and cognitive function.[45] The BM extracts have been investigated extensively for their neuropharmacological effects and their nootropic actions.[42,45-47] In the hippocampus, BM enhances protein kinase activity that may contribute to its nootropic action.[48] BM also inhibited cholinergic degeneration and displayed a cognition-enhancing effect in a rat model of AD.[49] A team of researchers also reported that a standardized extract of BM reversed the cognitive deficits induced by intracerebroventricularly administered colchicines and ibotenic acid into the nucleus basalis magnocellularis.[50] In the same study, BM also reversed the (a) depletion of acetylcholine, (b) reduction in choline acetyltransferase activity, and (c) decrease in muscarinic cholinergic receptor binding in the frontal cortex and hippocampus.[50] BM extracts protected neurons from beta-amyloid-induced cell death by suppressing cellular acetylcholinesterase activity. In addition, BM extract-treated neurons expressed a lower level of reactive oxygen species, suggesting that Brahmi restrained intracellular oxidative stress.[51]

Turmeric (*curcuma longa*) zinziberaceae

Curcumin (Turmeric) has been used in various types of treatments for dementia and traumatic brain injury. Curcumin also has a potential role in the prevention and treatment of AD. Curcumin as an antioxidant, anti-inflammatory and lipophilic action improves the cognitive functions in patients with AD. A growing body of evidence indicates that oxidative stress, free radicals, beta amyloid, cerebral deregulation caused by bio-metal toxicity and abnormal inflammatory reactions contribute to the key event in Alzheimer's disease pathology. Due to various effects of curcumin, such as decreased Beta-amyloid plaques, delayed degradation of neurons, metal-chelation, anti-inflammatory, antioxidant and decreased microglia formation, the overall memory in patients with AD has improved. This paper reviews the various mechanisms of actions of curcumin in AD and pathology.[52]

Liquorice (*glycyrrhiza glabra*) (fabaceae)

The effect of liquorice components in specific neurotoxic processes in AD. Amyloid-β peptide (25-35) (Aβ(25-35))-induced neurotoxicity is major pathway which is known to play role in pathogenesis of AD. ISL **(isoliquiritigenin** constituent of liquorice) was found to significantly reduce the effects of neurotoxicity induced by exposure of cortical neural cells to Aβ(25-35) *in vitro*. Downstream mediators of Aβ (25-35) neurotoxicity including Bax and caspase-3 were decreased as well as inflammatory indicators such as Ca^{2+} and ROS levels. **Water extract** of licorice was shown to significantly decrease neurotoxic effects of Aβ(25-35) protein. A side from inhibition of molecular pathways involved in pathogenesis of AD, licorice has been shown to improve memory and learning in animal models. After 7 days of treatment with water extract of licorice, studied mice had increased learning and memory functions assessed by elevated plus maze and passive avoidance paradigm. Licorice was also found to reverse amnesia induced by scopolamine and diazepam in that study, indicating that liquorice may have anticholinesterase activity. Anticholinesterase medications are one of the key treatments offered for patients with AD. A similar study design was applied to purified **glabridin from licorice root** to investigate its effect on functional memory and learning as well as acetylcholinesterase activity. The results revealed enhancement of memory and learning in mice which received glabridin orally for 3 days. Cholinesterase activity was found to be significantly decreased in glabridin-treated group compared to controls.[53]

Following are some useful plants with their constituents and possible mechanism of action for AD.

Table 1: Other Useful Plants with effect on AD.

Name of Plant	Parts of plants used	C.C	Possible Mechanism of Action	Helpful in AD
Huperzia serrate, **[54-57] (Lycopodiaceae)**	club moss	Huperzine A (Alkaloidal nature)	Potent, reversible and selective inhibitor of acetylcholinesterase, which activity is even stronger than galantamine	As a dietary supplement for memory loss and mental impairment. Modification of APP processing, protection against A*β*-induced oxidative injury and neuronal apoptosis, regulation of nerve growth factor and reduction in glutamate-induced toxicity
Vinca minor, **[58]**	leaves	Vinpocetine is a chemical derived from vincamine		As a treatment for memory loss and mental impairment.
Melissa officinalis, **[59 60] (lemon balm)**			ACh receptor activity in the central nervous system with both nicotinic and muscarinic binding Properties	modulates mood and cognitive performance

Galanthus nivalis L. [61] **(Amaryllidaceae)**	European daffodils or common snowdrops,	Galantamine Isoquinoline alkaloid	A competitive and selective acetylcholinesterase inhibitor.	Galantamine also allosterically modifies nicotinic ACh receptors, potentiating the presynaptic response to ACh. Used to delay the process of degeneration of neurons in Alzheimer's disease.
Salvia officinalis, [62] **(Lamiaceae)**		Carnosic acid and Rosmarinic acid	Antioxidants	Protect the brain from oxidative damage.
Rosmarinus officinalis [63] **(Lamiaceae) Rosemary (Satapatrika)**		Carnosic acid and ferulic acid		greater reported antioxidant activity than the widely common synthetic antioxidants butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA)
Commiphora whighitti, [64] **(Burseraceae)**		Guggulipid guggulsterone resin	Acts on impairment in learning and memory and decreased choline acetyl transferase levels in hippocampus.	A potential cognitive enhancer for improvement of memory
Lipidium Meyenii **Walp (maca),** [65] **(Brassicaceae)**	Macamides structurally similar to endocannabinoids		Its antioxidant and AChE inhibitory activities.	reduce LPO (Lipid peroxidation)
Acorus Calamus **(Sweetflag),** [66] **(Araceae)**	Rhizomes	α-and β-asarone.	Inhibits the acetylcholinesterase (AChE)	for the treatment of memory loss A*β*-induced JNK activation, Bcl-w and Bcl-xL levels, cytochrome c release, and caspase-3 activation
Angelica archangelica L. [67] **Dudhachoraa (*Laghu Coraka*) (umbelliferae)**	Seed ethanolic extract	imperatorin and xanthotoxin	Methanol extract inhibit AChE *in-vitro*.	Increase blood flow in the brain.
Tinospora cordifolia **(Guduchi),** [68] **(Menispermaceae)**	Whole plant, alcoholic extract		Mechanism for cognitive enhancement is by immunostimulation and synthesis of acetylcholine,	
Magnolia officinalis **(*talauma*),** [69] **(Magnoliaceae)**	Ethanolic extract of bark	Magnolol and honokiol,	Inhibits the memory impairment induced by scopolamine through the inhibition of AChE	Neuroprotective on beta amyloid induced toxicity on PC 12 cells
Collinsoni Canadensis, [70] **(Lamiaceae) Horsebalm(*Monarda*)**		carvacol and thymol	To prevent the breakdown of acetylcholine.	
Bertholettia excelsa **(Lecythidaceae),** [71]	Seed, brazil nuts	Lecithin, choline	high concentration of lecithin, which contains choline. Choline is a building block for acethycholine. These building blocks enhance the concentration of acethylcholine in AD patients.	
Uncaria rhynchophylla [72]			potent inhibitory effects on fibril formation of A*β* and can also destabilize preformed A*β* fibrils	
Polygala tenuifolta [73]		Tenuigenin	inhibit the secretion of A*β* in cultured cells, which may explain its ability to improve	

			cholinergic function degraded through Aβ in rat models	
Coptidis[74]	Rhizome	Berberine	reduce Aβ secretion by altering APP processing in a way to shift from the amyloidogenic to non-amyloidogenic pathway	
Satis tinctoria, Polygonum tinctorium, Strobilanthes cusia[75]	Leaves	Indirubin	inhibiting two protein kinases involved in abnormal tau phosphorylation in AD	
Jyotishmati Celastrus paniculatus[76,77]	Aqueous extract of seeds		dose-dependent cholinergic activity, antioxidant activity by free radical scavenging	sharpening the memory and improving concentration and cognitive function
Jatamansi (nardostachys jatamansi)[78]	Rhizomes and roots			Alcoholic extract significantly improved learning and memory
Shankhpushpi ***Convolvulus pluricaulis***[79]	Aqueous root extract		Hippocampal regions associated with the learning and memory functions showed a dose-dependent increase in acetylcholine esterase activity in the CA1 and CA3 area with CP treatment	Increase in acetylcholine content in the hippocampus may be the neurochemical basis for their improved learning and memory

CONCLUSION

The pharmaceutical industry is facing serious challenges as the drug discovery process for neurodegenerative diseases is becoming extremely expensive, riskier, and critically inefficient. A significant shift from a single-target to a multi-target drug approach, especially for chronic and complex disease syndromes, is being witnessed. Approaches based on reverse pharmacology (from the clinic to the bedside) also offer efficient development platforms for herbal formulations. The Ayurvedic system of medicine has garnered increasing recognition in recent years with regard to diet and treatment options. Early development of Ayurvedic herbal supplements required only anecdotal or epidemiologic information (or both) without an understanding of the mode of action. The Ayurvedic medicine industry has come a long way from when it was considered unnecessary to test Ayurvedic formulations prior to use, to several randomized, double-blind, controlled studies and to the introduction of good manufacturing practice guidelines for the industry. It has taken a more rigorous scientific and quality-enhanced approach to provide 'proof of concept' and a 'mode of action'. It might be worth pointing out that, while Ayurvedic therapeutics has been prescribed for centuries for neurodegenerative diseases (including dementias), only recently have there been Western, mechanistic studies on AD; however, these mechanistic studies point to the same mechanisms addressed by the Ayurvedic therapeutics (for example, increase in nerve growth factors and neurotrophic factors and reduction in inflammation and oxidative damage), providing strong support for herbal therapy for AD.[80] It is hoped that the strong knowledge base of Ayurveda coupled with combinatorial sciences and high-throughput screening techniques will improve the ease with which Ayurvedic products and formulations can be used in drug discovery campaigns and development process, thereby providing new functional leads for AD and other age-associated neurodegenerative diseases.

REFERENCES

1. Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer's disease: A review of progress. Journal of Neurology and NeuroPsychiatry, 1999; 66: 137-47.
2. Wernicke TF, Reischies FM. Prevalence of dementia in old age: Clinical diagnoses in subjects aged 95 years and older. Neurology, 1994; 44: 250-3.
3. Williams BR, Nazarians A, Gill MA. A review of rivastigmine: A reversible cholinesterase inhibitor. Clinical Therapeutics, 2003; 25: 1634-53.
4. Jayaprakasam B, Padmanabhan K, Nair MG. Withanamides in *Withania somnifera* fruit protect PC-12 cells from beta-amyloid responsible for Alzheimer's disease. Phytotherapy Research, 2010; 24: 859-63.
5. Kumar A, Singh A, Ekavali. A review on Alzheimer's disease pathophysiology and its management: an update. Pharmacological Reports, 2015; 67(2): 195–203.
6. Mishra S, Palanivelu K. The effect of curcumin (turmeric) on Alzheimer's disease: An overview. Annals of Indian Academy of Neurology, 2008; 11(1): 13–19.
7. Liu Z, Zhang A, Sun H, et al. Two decades of new drug discovery and development for Alzheimer's disease. Royal Society of Chemistry Advances, 2017; 7(10): 6046– 6058.
8. Mohamed T, Shakeri A, Rao PPN. Amyloid cascade in Alzheimer's disease: Recent advances in

medicinal chemistry. European journal of Medicinal Chemistry, 2016; 113: 258–272.
9. Weekley CM, He C. Developing drugs targeting transition metal homeostasis. Current Opinion in Chemical Biology, 2017; 37: 26–32.
10. Prakash A, Dhaliwal GK, Kumar P, et al. Brain biometals and Alzheimer's disease – boon or bane? Interational Journal of Neuroscience, 2017; 127(2): 99–108.
11. Sultzer DL, Marder SR. Older Brains are Different: Brain–Behavior Studies and Their Clinical Utility. The American Journal of Geriatric Psychiatry, 2017; 25(1): 11–12.
12. Chase TN, Farlow MR, Clarence–Smith K. Donepezil Plus Solifenacin (CPC–201) Treatment for Alzheimer's Disease. Neurotherapeutics, 2017; 14(2): 405–416.
13. Akhondzadeh S, Noroozian M: Alzheimer's disease: Pathophysiology and pharmacotherapy. Drugs, 2002; 4: 1167-1172.
14. Bullock R: New drugs for Alzheimer's disease and other dementias. British Journal of Psychiatry, 2002; 180: 135-139.
15. Shadlen MF, Larson EB: What's new in Alzheimer's disease treatment? Reasons for optimism about future pharmacologic options. Postgraduate Medical journal, 1999; 105: 109-118.
16. Mayeux R, Sano M: Treatment ofAlzheimer's disease. New England Journal of Medicine, 1999; 34: 1670-1679.
17. Bush Al: Therapeutic targets in the biology of Alzheimer's disease. Current Opinion in Psychiatry, 2001; 14: 341-348.
18. Hyeon-Joong Kim , Seok-Won Jung , Seog-Young Kim, Ik-Hyun Cho, Hyoung-Chun Kim , Hyewhon Rhim , Manho Kim, Seung-Yeol Nah. ·*Panax ginseng* as an adjuvant treatment for Alzheimer's disease. Journal of Ginseng research, 2018, 42(4):401-411
19. Jae-Hyeok Heo, Soon-Tae Lee, Min Jung Oh, Hyun-Jung Park, Ji-Young Shim, Kon Chu, and Manho Kim. Improvement of Cognitive Deficit in Alzheimer's disease Patients by Long Term Treatment with Korean Red Ginseng. Journal of Ginseng research, 2011; 35(4): 457–46.
20. Marco Canevelli, NawalAdali, Eirini Kelaiditi, Christelle Cantet, Pierre-Jean Ousset, Matteo Cesari. Effects of *Gingko biloba* supplementation in Alzheimer's disease patients receiving cholinesterase inhibitors: Data from the ICTUS study**.** Phytomedicine, 2014; 21(6): 888-892.
21. De Feudis FV: *Ginkgo biloba* Extract EGb761. Pharmacological Activities and Clinical Applications. Paris: Elsevier, 1991.
22. Kleijnen J: *Ginkgo biloba.* Lancet, 1992; 340: 1136-1139.
23. Shinomol GK, Bharath MM. Exploring the role of 'Brahmi' (*Bocopa monnieri* and *Centella asiatica*) in brain function and therapy. Recent Patents on Endocrine Metabolic and Immune Drug Discovery, 2011; 5: 33–49.
24. Cervenka F, Jahodar L. Plant metabolites as nootropics and cognitive. Ceska Slov Farm, 2006; 55: 219–229.
25. Dhanasekaran M, Holcomb LA, Hitt AR, Tharakan B, Porter JW, Young KA, Manyam BV. *Centella asiatica* extract selectively decreases amyloid beta levels in hippocampus of Alzheimer's disease animal model. Phytothery Research, 2009; 23: 14–19.
26. Rocha MD, Viegas FP, Campos HC, Nicastro PC, Fossaluzza PC, Fraga CA, Barreiro EJ, Viegas C Jr. The role of natural products in the discovery of new drug candidates for the treatment of neurodegenerative disorders II: Alzheimer's disease. CNS Neurological Disorder Drug Targets, 2011; 10: 251–270.
27. Veerendra Kumar MH, Gupta YK. Effect of *Centella asiatica* on cognition and oxidative stress in an intracerebroventricular streptozotocin model of Alzheimer's disease in rats. Clinical and Experimental Pharmacology and Physiology, 2003; 30: 336–342.
28. Xu Y, Cao Z, Khan I, Luo Y. Gotu Kola (*Centella asiatica*) extract enhances phosphorylation of cyclic AMP response element binding protein in neuroblastoma cells expressing amyloid beta peptide. Journal of Alzheimer's Disease, 2008; 13: 341–349.
29. Mishra LC, Singh BB, Dagenais S. Scientific basis for the therapeutic use of *Withania somnifera* (ashwagandha): a review. Altern Med Rev, 2000; 5: 334–346.
30. Matsuda H, Murakami T, Kishi A, Yoshikawa M. Structures of withanosides I, II, III, IV, V, VI, and VII, new withanolide glycosides, from the roots of Indian *Withania somnifera* DUNAL. and inhibitory activity for tachyphylaxis to clonidine in isolated guinea-pig ileum. Bioorganic and Medicinal Chemistry, 2001; 9: 1499–1507.
31. Monograph. *Withania somnifera*. Alternative Medicine Review, 2004; 9: 211–214.
32. Dhuley JN. Effect of ashwagandha on lipid peroxidation in stress-induced animals. Journal of Ethnopharmacology, 1998; 60: 173–178.
33. Jayaprakasam B, Padmanabhan K, Nair MG. Withanamides in *Withania somnifera* fruit protect PC-12 cells from beta-amyloid responsible for Alzheimer's disease. Phytotherapy Research, 2010; 24: 859–863.
34. Parihar MS, Hemnani T. Phenolic antioxidants attenuate hippocampal neuronal cell damage against kainic acid induced excitotoxicity. Journal of Bioscience, 2003; 28: 121–128.
35. Kumar S, Harris RJ, Seal CJ, Okello EJ. An aqueous extract of *Withania somnifera* root inhibits amyloid beta fibril formation *in vitro*. Phytotherapy Research, 2012; 26: 113–117.

36. Tohda C, Kuboyama T, Komatsu K. Search for natural products related to regeneration of the neuronal network. Neurosignals, 2005; 14: 34–45.
37. Kuboyama T, Tohda C, Zhao J, Nakamura N, Hattori M, Komatsu K. Axon- or dendrite-predominant outgrowth induced by constituents from. Ashwagandha Neuroreport, 2002; 13: 1715–1720.
38. Schliebs R, Liebmann A, Bhattacharya SK, Kumar A, Ghosal S, Bigl V. Systemic administration of defined extracts from *Withania somnifera* (Indian Ginseng) and Shilajit differentially affects cholinergic but not glutamatergic and GABAergic markers in rat brain. Neurochem Int, 1997; 30: 181–190.
39. Tohda C, Kuboyama T, Komatsu K. Dendrite extension by methanol extract of Ashwagandha (roots of *Withania somnifera*) in SK-N-SH cells. Neuroreport, 2000; 11: 1981–1985.
40. Kuboyama T, Tohda C, Komatsu K. Neuritic regeneration and synaptic reconstruction induced by withanolide A. British Journal of Pharmacology, 2005; 144: 961–971.
41. Kumar V. Potential medicinal plants for CNS disorders: an overview. Phytotherapy Research, 2006; 20:1023–1035.
42. *Bacopa monniera*. Monograph. Alternative Medicine Review, 2004; 9: 79–85.
43. Russo A, Borrelli F. *Bacopa monniera*, a reputed nootropic plant: an overview. Phytomedicine, 2005; 12: 305–317.
44. Dhanasekaran M, Tharakan B, Holcomb LA, Hitt AR, Young KA, Manyam BV. Neuroprotective mechanisms of ayurvedic antidementia botanical *Bacopa monniera*. Phytotherapy Research, 2007; 21: 965–969.
45. Stough C, Downey LA, Lloyd J, Silber B, Redman S, Hutchison C, Wesnes K, Nathan PJ. Examining the nootropic effects of a special extract of *Bacopa monniera* on human cognitive functioning: 90 day double-blind placebo-controlled randomized trial. Phytotherapy Research, 2008; 22: 1629–1634.
46. Singh RH, Narsimhamurthy K, Singh G. Neuronutrient impact of Ayurvedic Rasayana therapy in brain aging. Biogerontology, 2008; 9: 369–374.
47. Shinomol GK, Bharath MM. Exploring the role of 'Brahmi' (*Bocopa monnieri* and *Centella asiatica*) in brain function and therapy. Recent Patent in Endocrinology, Metabolite and Immune Drug Discovery, 2011; 5: 33–49.
48. Singh HK, Dhawan BN. Effect of *Bacopa monniera* Linn. (brahmi) extract on avoidance responses in rat. Journal of Ethnopharmacololgy, 1982; 5: 205–214.
49. Uabundit N, Wattanathorn J, Mucimapura S, Ingkaninan K. Cognitive enhancement and neuroprotective effects of *Bacopa monnieri* in Alzheimer's disease model. Journal of Ethnopharmacology, 2010; 127: 26–31.
50. Bhattacharya SK, Bhattacharya A, Kumar A, Ghosal S. Antioxidant activity of *Bacopa monniera* in rat frontal cortex, striatum and hippocampus. Phytotherapy Research, 2000; 14: 174–179.
51. Limpeanchob N, Jaipan S, Rattanakaruna S, Phrompittayarat W, Ingkaninan K. Neuroprotective effect of *Bacopa monnieri* on beta-amyloid-induced cell death in primary cortical culture. Journal of Ethnopharmacol, 2008; 120: 112–117
52. Shrikant Mishra and Kalpana Palanivelu. The effect of curcumin (turmeric) on Alzheimer's disease: An overview. Annals of Indian Academy of Neurology, 2008; 11(1): 13–19.
53. Parsa Ravanfar, Golnaz Namazi, Afshin Borhani-Haghighi, Shaghayegh Zafarmand. Neurologic Effects of Licorice: A Review. Pharmacognosy Reviews, 2018; 12(23): 115-119.
54. Xu SS, Gao ZX, Weng Z: Efficacy of tablet huperzine-A on memory, cognition, and behavior in Alzheimer's disease. Zhongguo Yao Li XueBao, 1995; 16: 391-395.
55. Zhang RW, Tang XC, Han YY: Drug evaluation of huperzine A in the treatment of senile memory disorders. Zhongguo Yao LiXue Bao, 1991; 12: 250-252.
56. Zhang Z, Wang X, Chen Q: Clinical efficacy and safety of huperzine alpha in treatment of mild to moderate Alzheimer disease: A placebo-controlled, double-blind, randomized trial. Zhonghua Yi XueZaZhi, 2002; 82: 941-944.
57. Xu SS, Cai ZY, Qu ZW: Huperzine-A in capsules and tablets for treating patients with Alzheimer disease. Zhongguo Yao Li Xue Bao,1999; 20: 486-490.
58. Szatmari SZ, Whitehouse PJ: Vinpocetine for cognitive impairment and dementia;. Cochrane Database Systematic Review, 2003; 003 119.
59. Kennedy DO, Scholey AB, Tildesley NTJ, et al.: Modulation of mood and cognitive performance following acute administration of *Melissa officinalis* lemon balm. Pharmacology and Biochemical Behaviour, 2002; 72: 953-964.
60. Akhondzadeh S, Noroozian M, Mohammadi M, et al.: *Melissa officinalis* extract in the treatment of patients with mild to moderate Alzheimer's disease: A double blind, randomised, placebo controlled trial. The Journal of Neurology, Neurosurgry and Psychiatry, 2003; 74: 863-866.
61. Raskind MA, Peskind ER, Wessel T: Galantamine in AD: A six month randomized placebo-controlled trial with a six month extension. Neurology, 2000; 54: 2261-2268.
62. Akhondzadeh S , Noroozian M, Mohammadi M, Ohadinia S, Jamshidi AH, Khani M. *Salvia officinalis* extract in the treatment of patients with mild to moderate Alzheimer's disease: a double blind, randomized and placebo-controlled trial. Journal of Clinical Pharmcy and Therapeutics, 2003; 28(1): 53-9.

63. Duke JA. Rosemary, the herb of remembrance for Alzheimer's disease. Alternative and Complementary Therapy, 2007: 287-90.
64. Ajaikumar B. Kunnumakkara, Kishore Banik, Devivasha Bordoloi, Choudhary Harsha, Bethsebie L. Sailo, Ganesan Padmavathi, Nand K. Roy, Subash C. Gupta, and Bharat B. Aggarwal. Googling the Guggul (Commiphora and Boswellia) for Prevention of Chronic Diseases. Frontiers in Pharmacology, 2018; 9: 686.
65. Julio Rubio, Wang Qiong, Xinmin Liu, Zhen Jiang, Haixia Dang, Shi-Lin Chen and Gustavo F. Gonzales. Aqueous Extract of Black Maca (*Lepidium meyenii*) on Memory Impairment Induced by Ovariectomy in Mice. Evidance Based Complementary and Alternative Medicine, 2011; 2011: 253958.
66. Vineet Sharma, Rohit Sharma, DevNath Singh Gautam, Kamil Kuca, Eugenie Nepovimova and Natália Martins. Role of Vacha (*Acorus calamus* Linn.) in Neurological and Metabolic Disorders: Evidence from Ethnopharmacology, Phytochemistry, Pharmacology and Clinical Study. Journal of Clinical Medicine, 2020; 9(4): 1176.
67. Steinthor Sigurdsson, Sigmundur Gudbjarnason. Inhibition of Acetylcholinesterase by Extracts and Constituents from *Angelica archangelica* and *Geranium sylvaticum*, 62(9-10): 689-93.
68. Jyothi CH, Shashikala G, Vidya HK, Shashikala GH. Evaluation of effect of alcoholic extract of *Tinospora cordifolia* on learning and memory in alprazolam induced amnesia in albino mice. International journal of Basic and clinical pharmacology, 2016; 5(5): 2159-2163.
69. Chu Peng Hoi, Yee Ping Ho, Larry Baum, Albert H. L. Chow. Neuroprotective effect of honokiol and magnolol, compounds from *Magnolia officinalis*, on beta-amyloid-induced toxicity in PC12 cells. Phytotherapy research, 2010; 24(10); 1538-1542.
70. Rajagopal PL, Ashly James, Premaletha K, Sajith Kumar PN. Herbal Options In Alzheimer's Disease - A Review. Journal Of International Academic Research For Multidisciplinary, 2013; 1(9): 178-189.
71. Katiuchia Pereira Takeuchi, Mariana Buranelo Egea. Bioactive Compounds of the Brazil Nut (*Bertholletia excelsa* Bonpl.): Nutritional and Health Aspects. Bioactive Compounds in Underutilized Fruits and Nuts, 2020: 207-221.
72. Fujiwara H, Iwasaki K, Furukawa K, et al. *Uncaria rhynchophylla*, a Chinese medicinal herb, has potent antiaggregation effects on Alzheimer's *β*-amyloid proteins. *Journal of Neuroscience Research*, 2006; 84(2): 427–433.
73. Jia H, Jiang Y, Ruan Y, et al. Tenuigenin treatment decreases secretion of the Alzheimer's disease amyloid *β*-protein in cultured cells. Neuroscience Letters, 2004; 367(1): 123–128.
74. Asai M, Iwata N, Yoshikawa A, et al. Berberine alters the processing of Alzheimer's amyloid precursor protein to decrease A*β* secretion. Biochemical and Biophysical Research Communications, 2007; 352(2): 498–502.
75. Leclerc S, Garnier M, Hoessel R, et al. Indirubins inhibit glycogen synthase kinase-3*β* and CDK5/P25, two protein kinases involved in abnormal tau phosphorylation in Alzheimer's disease. A property common to most cyclin-dependent kinase inhibitors? Journal of Biological Chemistry, 2001; 276(1): 251–260.
76. Bhanumathy M, Harish MS, Shivaprasad HN, Sushma G. Nootropic activity of *Celastrus paniculatus* seed. Pharmceutical Biology, 2010; 48: 324–327.
77. Kumar MH, Gupta YK. Antioxidant property of *Celastrus paniculatus* willd.: a possible mechanism in enhancing cognition. Phytomedicine, 2002; 9: 302–311.
78. Joshi H, Parle M. *Nardostachys jatamansi* improves learning and memory in mice. Journal of Medicinal Food, 2006; 9: 113–118.
79. Nahata A, Patil UK, Dixit VK. Effect of *Convulvulus pluricaulis* Choisy. on learning behaviour and memory enhancement activity in rodents. Natural Product Research, 2008; 22: 1472–1482
80. Wollen KA. Alzheimer's disease: the pros and cons of pharmaceutical, nutritional, botanical, and stimulatory therapies, with a discussion of treatment strategies from the perspective of patients and practitioners. Alternative Medicine Review, 2010; 15: 223–244.