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An Overview of Phytotherapeutic Approach in Prevention and Treatment of Alzheimer's Syndrome & Dementia

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ABSTRACT

Alzheimer disease (AD) is the most common form of the dementia which occurs among older people above the age of 60 years. The Alzheimer's disease once considered a rare disorder and it is now seen as a major public health problem that is seriously affecting millions of older people and their families world over. The incidence of AD ranges from 1 to 4 percent of the population per year rising 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. Alzheimer's is characterised by massive loss of neurons and disrupted signaling between cells in the brain. The disease can be diagnosed post mortem by observing tangles inside and senile plaques outside cells throughout the brain. The major component of the plaques is a small, 40- or 42-amino acid peptide: amyloid beta (Aβ,). Aβ, causative agent in Alzheimer's, was first suggested as the amyloid hypothesis about 15 years ago and is now widely accepted amongst scientific community.

The first neurotransmitter defect discovered in Alzheimer disease involved acetylcholine (ACh). As cholinergic function is required for short term memory, the cholinergic deficit in Alzheimer's disease is also believed to be responsible for much of the short term memory deficit. The studies related to clinical trials of drugs in patients with Alzheimer disease have focused on the development of drugs augmenting the level of neurotransmitter acetylcholine in the brain in order to compensate for the loss of cholinergic function. Amongst these drugs, acetylcholine precursors, muscarinic agonists, nicotinic agonists and choline esterase inhibitors have extensively been studied in patients with Alzheimer's disease and the successful approach to treat this disease have employed acetylcholineesterase (AChE) inhibition. The clinical response of few drugs namely donepezil (Aricept), rivastigmine (Exelon), galantamine (Reminyl) and Memantine (Nemenda) approved by Food and Drug Administration (FDA), USA for the treatment of Alzheimer's disease, available presently, have been often found to be unsatisfactory. The presently available drugs for the treatment of Alzheimer's disease are symptomatic only and do not alter the course or progression of the underlying disease and produce adverse reactions in patients thereby having limited scope for the treatment of patients of Alzheimer's syndrome. Thus, there is need to develop targeted effective therapeutics for the treatment of Alzheimer's disease which may alter the course or progression of the underlying disease by preventing the formation or clearing of plaques (beta-amyloid fragments), considered to be one hallmark of the disease, from the brain of the patients. There are several studies and alternative therapies which offer ways to slow the onset and progression of Alzheimer's disease in some patients. Various treatments can be used as preventive measures for people whose families have a history of the disease that indicate unique role of herbal medicine in the treatment of Alzheimer's disease. Herbal remedies for Alzheimer's disease have become more and more popular in the recent years and not without a reason that there is a possibility to slow down the brain's degeneration caused by Alzheimer's with natural treatments and it has drawn the attention of the scientific community. Many natural herbal treatments have been researched and the benefits derived from using herbal treatments for Alzheimer's and dementia have been very promising. This paper reviews the clinical effects of a number of commonly used herbal medicines for the treatment of Alzheimer's disease and dementia.

Keywords: Alzheimer's disease, *Ginkgo biloba*, *Galanthus caucasicus*, *Huperzia serrata*, *Catharanthus roseus*, *Melissa officinalis*, *Salvia officinalis*, *Rosmarinus officinalis*, *Euphorbia royleana* Boiss, *Withania somnifera*, *Centella asiatica*, *Bacopa monniera*, *Curcuma longa*, *Panax ginseng*, *Celastrus paniculatus*, *Glycyrrhiza glabra*.

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INTRODUCTION

Rapid industrialization, changes in life style, environmental degradation and excessive use of pesticides, herbicides and other toxic chemicals in production of food materials are

seriously threatening the life of human beings and posing health hazards. These toxic chemicals/xenobioticss produce neurotoxins that affect the transmission of chemical signals between neurons resulting into neurodegenerative disorders. Among different kind of neurodegenerative diseases, Alzheimer's disease (AD) is the most common form of the dementia which occurs among older people above the age of 60 years. The Alzheimer's disease once considered a rare disorder and it is now seen as a major public health problem that is seriously affecting millions of older people and their families world over.

AD is an irreversible, progressive brain disease that slowly destroys memory and thinking skills and eventually even the ability to carry out the simplest tasks. According to the World Health Organization (WHO), 5% of men and 6% of woman of above the age of 60 years are affected with Alzheimer's type dementia worldwide. [1] World Health Organization (WHO) has estimated that 35.6 million people are currently living with dementia worldwide which will be further increased to 65.7 million by 2030 and 115.4 million by 2050. [2] It has been observed that there are seven stages found in Alzheimer's disease. Stage one is normal behavior. Stage two is minor memory lapse. In stage three, there is confusion and loss of names; this borderline condition which does not necessarily lead to Alzheimer's. Stage four or "mild" Alzheimer's is the inability to think rationally. In stage five, "moderate" Alzheimer's, the patient can't remember names of close relatives. In stage six, "moderately severe" Alzheimer's, there is inability to dress oneself and take care of personal needs. In stage seven, there is loss of speech and incontinence. The eighth stage of Alzheimer's disease is death. [3] Physically, Alzheimer's is characterised by massive loss of neurons and disrupted signaling between cells in the brain. The disease can be diagnosed post mortem by observing tangles inside and senile plaques outside cells throughout the brain. The major component of the plaques is a small, 40- or 42-amino acid peptide: amyloid beta (Aβ). Aβ, causative agent in Alzheimer's, was first suggested as the amyloid hypothesis about 15 years ago and is now widely accepted amongst scientific community. Uncovering the chemistry associated with Aβ is crucial to understanding Alzheimer's progression and may shed light on its cause or causes. Aβ is an elusive entity whose chemical and biological actions have been difficult to understand. It does not crystallize, is not very soluble, and has a highly changeable structure in solution. On incubation, it does form ordered fibrils that can be analyzed by nuclear magnetic resonance (NMR) analysis. Whilst the structure of the toxic species has not been established, the peptide is known to be as it's most damaging in aggregates of two or more. Therefore, the fibril structures can provide clues about the nature of the toxic aggregates. [4] The studies have indicated that as Alzheimer's disease progresses neuro-fibrillary tangles spread throughout the brain and plaques also spread throughout the brain, starting in the neocortex. By the final stage damage is wide spread and brain tissue has shrunk significantly. The neuro-chemical disturbances that arise in Alzheimer's disease have been studied intensively. [5] Studies have shown the involvement of neurotransmitter acetylcholine in Alzheimer's disease resulting into disproportionate deficiency of acetylcholine. It has been well documented that markers for cholinergic neurons namely acetylcholinetransferase and acetylcholinesterase responsible for acetylcholine synthesis and its degradation are decreased in the cortex and hyppocampus areas of the brain involved in cognition and memory. [6] The studies have demonstrated that the resultant decrease in acetylcholine dependent neurotransmission is associated with the functional deficit of AD in parallel with dopaminergic deficit in Parkinson disease and its clinical manifestation. [7-8] In light of cholinergic hypothesis for occurrence of Alzheimer's disease, experimental studies in animal models and clinical studies in patients suffering from Alzheimer's disease have been able to develop drugs with capacity to increase the level of acetylcholine in the brain in order to compensate for losses of cholinergic function in the brain. Amongst these drugs, acetylcholine precursors, muscarinic agonists, nicotinic agonists and choline esterase inhibitors are extensively studied in patients with Alzheimer's disease. [9-10] However, the use of cholinesterase inhibitors in the treatment of patients with Alzheimer's disease has been found to be better successful strategy. [11-12] The tacrine, the acridine derivative (COGNEX, 1, 2, 3, 4-tetrahydro-9-aminoacridine) was the first drug approved by the Food and Drug Administration (FDA), USA for general clinical use in Alzheimer's disease. The other four new cholinesterase inhibitors approved by Food and Drug Administration (FDA), USA to treat Alzheimer's are donepezil (Aricept), rivastigmine (Exelon), galantamine (Reminyl). [13-15] The above mentioned drugs are used to treat mild to moderately severe Alzheimer's. The newer drug Memantine (Nemenda) approved by Food and Drug Administration (FDA), USA in October 2003 is used for treatment of patients with Alzheimer's at the moderate to severe stages of disease. Other drugs such as selegiline, vitamin E, estrogen and anti-inflammatory drugs have also been studied for treatment of Alzheimer's but their clinical use has not been clearly demonstrated. [14, 16] Other agents including Ginkgo biloba have also been studied for treatment of Alzheimer's disease. [17-18] These drugs work by regulating neurotransmitters and may help maintain thinking memory and speaking skills and help with certain behavior problem. These drugs do not change the underlined diseased process and may help only for a few months to a few years. Furthermore, these allopathic drugs produce side effects. The drug tracine, cholinesterase inhibitor, produces significant side effects like abdominal cramping, nausea, vomiting, anorexia, diarrhea and hepato-toxicity thus it is rarely used. Other drugs namely donepezil, rivastigmine and galantamine have been found to produce low incidences of serious reactions but these drugs have cholinergic side effects such as nausea, anorexia, vomiting and diarrhea. [14, 16-20]

The presently available drugs for the treatment of Alzheimer's disease are symptomatic only and do not alter the course or progression of the underlying disease and produce adverse reactions in patients thereby having limited scope for the treatment of patients of Alzheimer's syndrome. Thus, there is need to develop targeted effective therapeutics for the treatment of Alzheimer's disease which may alter the course or progression of the underlying disease by preventing the formation or clearing of plaques (beta-amyloid fragments), considered to be one hallmark of the disease, from the brain of the patients. Researchers also are looking at other treatments, including: cholesterol-lowering drugs called statins, anti-oxidants (vitamins) and folic acid, anti-inflammatory drugs, substances that prevent formation of beta-amyloid plaques, nerve growth factor to keep neurons

healthy. There are several studies and alternative therapies that offer ways to slow the onset and progression of Alzheimer's disease in some patients. Various treatments can be used as preventive measures for people whose families have a history of the disease that indicate unique role of Herbal medicine in the treatment of Alzheimer's disease.

Herbal remedies for Alzheimer's disease have become more and more popular in the recent years and not without a reason that there is a possibility to slow down the brain's degeneration caused by Alzheimer's with natural treatments and it has drawn the attention of the scientific community. Many natural herbal treatments have been researched and the benefits derived from using herbal treatments for Alzheimer's and Dementia have been very promising and the use of some medicinal herbs have been touted to extend beyond that of modern prescription drugs. With so many natural and healthy compounds, it's no wonder that these medicinal herbs may hold the key to the cure to this devastating disease. In addition, these herbs are inexpensive and can be easily obtained. Clinical research is being conducted world over to test the efficacy of herbal medicines vis-a-vis prescription medicines in treating Alzheimer's or dementia patients. The results are promising, as herbal products have been found to be not only as effective as prescription drugs but also with fewer side effects. Herbal supplements may be used as a substitute for pharmaceutical drugs or can be used in conjunction with the latter. In the present review, attempts have been made to present state of art of studies made on the role of few herbal medicines in the treatment and management of Alzheimer's disease.

GINKGO BILOBA

Kingdom	:	Plantae
Division	:	Ginkgophyta
Class	:	Ginkgoopsida
Order	:	Ginkgoales
Family	:	Ginkgoaceae
Genus	:	Ginkgo
Species	:	biloba

Fig. 1: Ginkgo biloba

Ginkgo biloba is an herbal medicine being used in traditional Chinese medicine for thousands of years to treat a variety of ailments. It has been shown to reduce memory loss, enhance the brain activity and to slow down the degenerative effects of Alzheimer's disease. [21] An extract of *Gingko biloba* has been found in several studies to improve the symptoms and slow the progression of Alzheimer's disease (AD). The clinical studies have demonstrated that extracts of *Ginkgo biloba* provide therapeutic benefits to Alzheimer's similar to prescription drugs such as Donepezil or Tactrin, with minimal undesirable side effects. The gingkolides present in *Ginkgo biloba* posses' activities pertinent to the disease mechanisms in Alzheimer's such as antioxidant, neuroprotective and cholinergic activities according to the studies conducted by Medical Research Council of New castle General Hospital. [22]

Various clinical studies have indicated that 3- to 6-month treatment with 120- 240 mg of *G. biloba* has produced significant effect in Alzheimer's patients and this herbal drug has shown no significant adverse effect except few case reports of bleeding complications, gastrointestinal discomfort, nausea, vomiting, diarrhoea, headache, dizziness, heart palpitations and restlessness. [23-28] *Gingko biloba* extract EGB761 which is commonly sold form of Gingko biloba in Europe, has been found very effective in the treatment of AD patients and it has been shown to prevent Beta Amyloid toxicity to brain cells, a key part of the development of the disease. [29-32]

***GALANTHUS CAUCASICUS* (Alkaloid –Galantamine)**

Kingdom	:	Plantae
Division	:	Magnoliophyta
Class	:	Liliopsida
Order	:	Liliales
Family	:	Liliaceae
Genus	:	Galanthus
Species	:	caucasicus

Fig. 2: Galanthus caucasicus

Clinical studies on the efficacy of Galantamine have demonstrated its use in the treatment of mild to moderate Alzheimer's disease and other memory impairments. Galantamine is an alkaloid derived from the bulbs and flowers of *Galanthus caucasicus* (Caucasian snowdrop, Voronov's snowdrop), *Galanthus woronowii* (Amaryllidaceae) and related genara like *Narcissus* (Europian daffodil). [33] This drug has been found to be a competitive and selective acetylcholinesterase (AChE) inhibitor. It is hypothesized that this action might relieve some of the symptoms of Alzheimer's. This drug has also been shown to modulate allosterically nicotinic Ach receptors on cholinergic neurons to increase acetylcholine release. [34] Galantamine has a half life of 5-6 hours and in vitro studies have shown that Hepatic CYP-450 enzymes (CYP2D6 and CYP3A4) are involved in galantamine metabolism. Galantamine has not been associated with hepatotoxicity in clinical trials. Pooled data from four randomized trials of this drug on patients with mild AD have shown that patients who received galantamine 24 mg/d for

six months had improved cognition more often than those who received placebo, and that a higher proportion receiving galantamine were globally improved. This study suggests that patients with mild AD may benefit from galantamine treatment. [16, 35]

***HUPERZIA SERRATA* (Alkaloid –Huperzine A)**

Kingdom	:	Plantae
Division	:	Lycopodiophyta
Class	:	Lycopodiopsida
Order	:	Lycopodiales
Family	:	Lycopodiaceae
Genus	:	Huperzia
Species	:	serrata

Fig. 3: Huperzia serrata

Huperzine A is a natural cholinesterase inhibitor derived from the Chinese herb *Huperzia serrata***.** Huperzine A is a medicinally active plant derived chemical that belongs to the class known as alkaloids. This substance is really more a drug than an herb, but it is sold as a dietary supplement for memory loss and mental impairment. This drug has been shown to posses' antioxidant and neuroprotective properties suggesting thereby its potential in the treatment of Alzheimer's disease. [36-37] This drug has been shown to inhibit acetylcholinesterase (such as tacrine and donepezil) and to improve memory and mental functioning in patients with Alzheimer's and other severe conditions. [38-40] Three Chinese double blind clinical trials of huperzine A on more than 450 patients, suggest that the use of huperzine-A may significantly improve the symptoms of Alzheimer's disease and other form of dementia. [37, 41-42]

***CATHARANTHUS ROSEUS* (Alkaloid – Vinpocetine)**

Kingdom	:	Plantae
Division	:	Magnoliophyta
Class	:	Magnoliopsida
Order	:	Gentianales
Family	:	Apocynaceae
Genus	:	Catharanthus
Species	:	roseus

Vinpocetine is a chemical derived from vincamine, a constituent found in the leaves of *Catharanthus roseus***,** common name periwinkle (Vinca minor) as well as the seed of various African plants. [43] It is used as a treatment for memory loss and mental impairments. Studies have demonstrated that Vinpocetine posse's potential to enhance cerebral blood flow [44] and neuroprotective effects. [45] It is used as a drug in Eastern Europe for the treatment of cerebrovascular disorders and age-related memory impairment. [46] Several double-blind studies have evaluated vinpocetine for the treatment of AD and related conditions. [47-53] The clinical trials of Vinpocetine on 728 patients with AD have produced significant result in the improvement of Alzheimer's disease. Further, a 16-week double-blind placebo-controlled trial of Vinpocetine on 203 patients with mild to moderate dementia produced significant benefit in the treated group. Several clinical studies have also been conducted to prove the beneficial effects of this drug in the treatment of Alzheimer's and severe conditions., even this trial had several technical limitations, and the authors of the review concluded that vinpocetine cannot yet be regarded as a proven treatment. Currently, several better-quality trials are underway. [47]

Fig. 4: Catharanthus roseus

MELISSA OFFICINALIS, SALVIA OFFCINALIS & ROSMARINUS OFFICINALIS

MELISSA OFFICINALIS

Kingdom	:	Plantae
Division	:	Magnoliophyta
Class	:	Magnoliopsida
Order	:	Lamiales
Family	:	Lamiaceae
Genus	:	Melissa
Species	:	officinalis

Fig. 5: Melissa officinalis

Melissa officinalis (Lemon Balm) has been shown to improve cognitive function and to reduce agitation in patients with mild to moderate Alzheimer's disease. Studies have demonstrated that *M. officinalis* posses Ach receptor activity in central nervous system with both nicotinic and muscarinic binding properties. [22, 54] This plant has also been reported to

modulate mood and cognitive performance when administered to young, healthy volunteer. [55] In addition, a parallel, randomized, placebo-controlled study assessed the efficacy and safety of *M. officinalis* in 42 patients with mild to moderate AD. The results of this study indicated that patients receiving *M. officinalis* extract experienced significant improvements in cognition after 16 weeks of treatment and no significant difference in the frequency of side effect between the placebo group and those receiving the herbs extract could be noticed. The above clinical study also revealed that the frequency of agitation was higher in the placebo group compared to those receiving active treatment. [56]

SALVIA OFFICINALIS

Kingdom	:	Plantae
Division	:	Magnoliophyta
Class	:	Magnoliopsida
Order	:	Lamiales
Family	:	Lamiaceae
Genus	:	Salvia
Species	:	officinalis

Fig. 6: Salvia officinalis

The extract of *Salvia officinalis* (sage) has been found to produce significant benefits in cognition to the patients with mild to moderate AD after 16 weeks of treatment with S. officinalis. [57] The studies have demonstrated that the side effect associated with *S. officinalis* where similar to those observed with cholinesterase inhibitor. [58] However, frequency of agitation appeared to be higher in placebo group which may indicate an additional advantage in the management of patient with Alzheimer's disease.

ROSMARINUS OFFICINALIS

Kingdom	:	Plantae
Division	:	Magnoliophyta
Class	:	Magnoliopsida
Order	:	Lamiales
Family	:	Lamiaceae
Genus	:	Rosmarinus
Species	:	officinalis

The essencial oil of *Rosmarinus officinalis* has been shown to produce a significant decrement in performance of working memory, and impaired reaction times for both memory and attention based tasks. The findings of the study indicate that the olfactory properties of this essential oil can produce objective effects on cognitive performance, as well as subjective effects on mood. [59] The above three herbal plants, *Melissa officinalis*, *Salvia officinalis* & *Rosmarinus officinalis* have been evaluated using different *in vitro* and *in vivo* models to prove their efficacy in the management of patients with AD and the studies have demonstrated that extracts from plants of the Lamiaceae family are active not only in inhibition of AChE or β-amyloid deposits inhibition *in-vitro* but also may have anti-BuChE (butyrylcholinesterase) activity. In addition, the antioxidant, cytoprotective, anti-apoptotic and anti-inflammatory activities have also been found in Lamiaceae plant extracts. [60]

Fig. 7: Rosmarinus officinalis

***EUPHORBIA ROYLEANA* BOISS (Source of Shilajit)**

Kingdom	:	Plantae
Division	:	Magnoliophyta
Class	:	Magnoliopsida
Order	:	Euphorbiales
Family	:	Euphorbiaceae
Genus	:	Euphorbia
Species	:	royleana boiss

Fig. 8: Euphorbia royleana Boiss.

Shilajit is a dark, thick, viscous, sticky, unctuous, complex substance having a number of organic and inorganic compounds [61-66] flowing out from the rocks occurring in the north western belt of lower Himalayan hills from Nepal to Kashmir and is known as bitumen or mineral resin. The bituminous nature is due to a colloidal asphaltic substance mixed oils and resin and varies greatly in consistency from a free flowing liquid to a hard brittle solid. Latex of *Euphorbia royleana* Boiss is the source of Shilajit. *E. royleana* bioss is

large deciduous fleshy shrub up to 1.5 m girth and 6 m in hight with copious milky juice in all it parts. The plant is abundant between 600-1800 m above sea level [67] in close association with the weeping rocks and slopes shedding the dark coloured substance which is called shilajit. [68] The name Shilajit refers to one which has won the rocks in Ayurveda i.e. it penetrates through rocks dissolving in the stones and come out from the cracks of the stones. [66] Shilajit is used in the Ayurveda, the traditional Indian system of medicine. , Shilajit is a rasayana material which has adaptogenic / anti-stress and immunomodulatory activities. [69] Studies have demonstrated the potential of Shilajit in the treatment of Alzheimer's disease. [70] The studies to assess its effectiveness in the management of Alzheimer's disease demonstrate that shilajit affects some events in cortical and basal forebrain cholinergic singnal transduction cascade in rat brain. Studies have been conducted on drugs that enhance cholinergic activity as potential therapeutic agents in the treatment of Alzheimer's disease. Further, it has also been seen that systemic administration of defined extracts from *Withania somnifera* (Indian Ginseng) in combination with Shilajit differentially affects preferentially events in the cortical and basal forebrain cholinergic signal transduction cascade. [71] The experimental studies in mouse animal model have revealed that the side effects of Shilajit may be utilized safely in clinical practice as shilajit has been found to be quite safe up to a dose of 3 g/kg in mice (24 h mortality). [72]

WITHANIA SOMNIFERA

Kingdom	:	Plantae
Division	:	Magnoliophyta
Class	:	Magnoliopsida
Order	:	Solanales
Family	:	Solanaceae
Genus	:	Withania
Species	:	somnifera

Fig. 9: Withania somnifera

Withania somnifera (Ashwagandha) has been described as a nervine tonic [73-74] in Ayurveda and that is why it is a common ingredient of Ayurvedic tonic. Tonics, rejuvenators and vitalizers of Ayurveda appear to allay disease and induce immunity and longevity in the users. [75-77] *Withania somnifera* (Ashwagandha) has been shown to slow, stop reverse and remove neuritic atrophy and synaptic loss, the main cause for neurodegenerative disorders including Alzheimer's and dementia as confirmed by several clinical studies. Therefore, this medicinal herb can be used for the treatment and management of patients with AD. It improved growth of new dendrites of neurons. Glycowithanolides withaferin- A and sitoindosides VII-X isolated from the roots of *Withania somnifera* have been shown to significantly reverse the ibotenic acid induced cognitive defects in Alzheimer's disease model. [78]

In other study, it has been shown that chronic oral administration of withanoside IV attenuated the axonal, dendritic and synaptic losses and memory deficits induced by amyloid peptide Aβ (25-35) in mice. [79] The experimental studies have revealed that after oral administration in mice, withanoside IV is metabolized into sominone, which induces marked recovery in neurites and synapses and also enhance axonal and dendritic outgrowth and synaptogenesis. These effects maintain for at least 7 days after discontinuing withanoside IV administration which reflects the clinical usefulness of withanoside IV, and its metabolite, sominone in the treatment and management of Alzheimer's and dementia.

***BACOPA MONNIERA* (Neer Bramhi) and *CENTELLA ASIATICA* (Mandookparni/ Bramhi)**

Both Centella and Bacopa are called Brahmi because they have overlapping properties, but they are not the same plant. Main difference between these herbal plants is that Centella is cooling, making it better for pitta, whereas Bacopa is warming, indicated in kapha/vata. Although both plants are 'mental rejuvenatives', Centella is also indicated in skin issues and for wound-healing, whereas Bacopa has additional properties for helping throat and lung issues.

***BACOPA MONNIERA* (Neer Bramhi)**

Kingdom	:	Plantae
Division	:	Angiospermae
Class	:	Dicotyledonae
Order	:	Lamiales
Family	:	Scrophulariaceae
Genus	:	Bacopa
Species	:	monniera

Fig. 10: Bacopa monniera

Various studies have shown that patients suffering from age related cognitive decline gain significant benefit from *Bacopa monniera*, both in terms of memory and life quality. Neer Bramhi has been reported as a major component which has capability to prevent the process of early aging and related disorders. It has been found to be useful in improvement of memory and intelligence, life prolongvity and maintaining good health. In ancient Indian literature, Bacopa has been described as one of most popular medhya drug (Noo-tropic agent). Several studies have revealed that this medicinal herb is advocated as a nervine and mental tonic and may be used for the treatment of neurological and mental disorders. [76, 80-83] Studies conducted in animal models

have revealed that Bacopa has potential to influence the learning and memory process. [84-88] In another recent study conducted in animal model, Bacopa has been shown to decrease whole brain AChE activity which reflects that Bacopa might prove to be a useful memory restorative agent in the treatment of Alzheimer's and dementia. [89] A clinical study on human subjects has demonstrated the potential of *Bacopa monniera* in the treatment of Neuritis. [90]

***CENTELLA ASIATICA* (Mandookparni/ Bramhi)**

Kingdom	:	Plantae
Division	:	Angiospermae
Class	:	Dicotyledonae
Order	:	Umbelliferae
Family	:	Apiaceae
Genus	:	Centella
Species	:	asiatica

Fig. 11: Centella asiatica

Centella asiatica has been demonstrated to possess neuro protective property. [91] The studies have revealed that *Centella asiatica* has ability to prevent cognitive deficits that occur following treatment with Streptozotocin and to protect cholinergic neurons from the toxic effects of aluminium indicating its role in reducing the Alzheimer's disease neuropathy. [92-93] Recent study conducted on transgenic animal model to evaluate the efficacy of *Centella asiatica* extract (CaE) in the management of A.D. has shown that CaE can impact the amyloid cascade altering amyloid β pathology in the brains of PSAPP (presenilin 'Swedish' amyloid precursor protein) mice and modulating components of the oxidative stress response that has been implicated in the neurodegenerative changes occurring in Alzheimer's disease. [94]

***CURCUMA LONGA* (Haldi)**

Kingdom	:	Plantae
Division	:	Magnoliophyta
Class	:	Liliopsida
Order	:	Zingiberales
Family	:	Zingiberaceae
Genus	:	Curcuma
Species	:	longa

Chronic inflammation of nerve cells has been implicated as one of the important pathogenesis in Alzheimer's disease. Since Curcumin has been found to produce remarkable anti-inflammatory effects therefore it may have clinical use in the cure of Alzheimer's disease. It has been shown that this medicinal herb has ability to inhibit Aβ-induced expression of Egr-1 protein and Egr-1 DNA-binding activity in THP-1 monocytic cells. Further, the studies have demonstrated the role of Egr-1 in amyloid peptide-induced cytochemokine gene expression in monocytes. The anti-inflammatory action of Curcumin may be hypothesized due to inhibition of Egr-1 DNA-binding activity by curcumin. [95-96]

Fig. 12: Centella asiatica

Curcumin has been found to improve neurological deficit, decrease in mortality and reduce the water content in the brain. [97] The studies conducted on Alzheimer's disease mice model have shown that the levels of beta amyloid in AD mice that were given low doses of curcumin are significantly decreased as compared to those not treated with curcumin. Curcumin at low doses has also been found to decrease the "plaque burden" that these beta-amyloid have on the brains of AD mice. These experimental studies have also revealed that the low doses of curcumin for longer period is more effective rather than high doses in combating the neurodegenerative process of Alzheimer's disease. [98] It has been shown that the antioxidant and anti-inflammatory property of curcumin may be useful to ease Alzheimer's symptoms caused by oxidation and inflammation. [99] Curcumin has been found to reduce the level of lipid peroxidation and lipofuscin accumulation that is normally increased with aging. Further, the studies have also revealed that curcumin is found to increase the activity of super oxide dismutase (SOD) and sodium-potassium ATPase that normally decreased with aging. [100] It has been observed that Curcumin given to APPswe/PS1dE9 mice for 7 days crosses the blood-brain barrier as demonstrated by muliti-photon microscopy and reduces the existing senile plaques. [101] In addition, the results of another study have demonstrated that curcumin increases phagocytosis of amyloid-beta, effectively clearing them from the brains of patients with AD. [102]

PANAX GINSENG

Kingdom	:	Plantae
Division	:	Eudicots
Class	:	Asterids
Order	:	Apiales
Family	:	Araliaceae
Genus	:	Panax
Species	:	ginseng

Ginseng has been shown to exhibit protective and trophic effects in the memory function of Alzheimer's disease. Clinical study conducted on group of AD patients has

demonstrated that Panax ginseng is clinically effective in the cognitive performance of AD patients. [103]

Fig. 13: Panax ginseng

In addition, the studies conducted to evaluate the efficacy of Panax ginseng in the treatment of Alzheimer's disease patients have demonstrated significant effect in favour of ginseng on the Mini-Mental Status Examination, and on the Alzheimer 's Disease Assessment Scale (ADAS) - cognitive. These results suggest that Panax ginseng has potential role in the treatment of Alzheimer's disease but it requires extensive clinical trials. [104] Studies have revealed that Panax ginseng in combination with Ginko biloba can be very effective to the patients with memory loss. [105] Studies conducted to investigate the effects of Panax ginseng ginsenoside Rg_2 on cerebral ischemia-reperfusion induced impairment of neurological responses, memory and caudate-putamen neuronal apoptosis in a vascular dementia (VD) rat model indicate that ginsenoside Rg_2 has ability to improve neurological performance and memory ability of Vascular Dementia (VD) rats through mechanisms related to anti-apoptosis. Thus, the ginsenoside Rg_2 may represent a potential treatment strategy for vascular dementia or other ischemic conditions.

***CELASTRUS PANICULATUS* (Malkangni)**

Kingdom	:	Plantae
Division	:	Magnoliophyta
Class	:	Mangniopsida
Order	:	Celastrales
Family	:	Celastraceae
Genus	:	Celastrus
Species	:	paniculatus

Fig. 14: Celastrus paniculatus

Jothismati oil from seeds of *Celastrus paniculatus* (CP) is used in indigenous system of medicine for the treatment of brain related disease. It has been described to promote memory and to posses various pharmacological activities. [106-107] Research studies have shown that CP oil causes an overall decrease in the turnover of all three central monoamines norepinephrine (NE), dopamine (DA) and serotonin (5-HT) and implicate the involvement of these aminergic systems in the learning and memory process. [108] Experimental studies with Jyothismati oil from seeds of *Celastrus paniculatus* (CP) on the the adult male Wistar rats have revealed that there is enhancement in radial arm maze acquisition with chronic administration of CP oil and a decrease in AChE activity in treated animals leading to increased cholinergic activity in the brain. Further, the study has also indicated that there is significant decrease in the AChE activity in hypothalamus, frontal cortex and hippocampus of the rat brain treated with 400 mg/kg body weight. [109] The studies have shown that seed oil of CP, when administered chronically, may reverse the impairment in spatial memory product produced by acute central muscarinic receptor blockade, supporting the possibility that one or more constituents of the oil may offer cognitive enhancing properties. [110] The studies have also revealed that aqueous extract of CP has property to prevent the cognitive deficits as well as the oxidative stress caused by ICV Streptozotocin in rat model of Alzheimer's disease. [111] Another study has indicated that Celastrus paniculatus preferentially affects learning and recall of memory and also regulate the serum biochemistry. [112]

***GLYCYRRHIZA GLABRA* (The Licorice Root)**

Kingdom	:	Plantae
Division	:	Magnoliophyta
Class	:	Asterids
Order	:	Fabales
Family	:	Asteraceae
Genus	:	Glycyrrhiza
Species	:	glabra

Fig. 15: Glycyrrhiza glabra

The roots and rhizomes of *Glycyrrhiza glabra* have been used for centaury for their anti-inflammatory, antiulcer, expectorant, antimicrobial and anxiolytic activities in traditional system of medicine. Recent studies have shown that the dose of 150 mg/kg of the aqueous extract of Liquorice significantly improved learning and memory of mice. [113] The studies conducted on animal model have revealed that 9 mg/kg/day of natural product 2, 2′, 4′-Trihydroxychalcone (TDC) from Glycyrrhiza glabra has been found to decrease β Amyloid production and β Amyloid plaque formation, and to improve the memory impairment. The results of above study suggest that the natural product TDC as new BACE 1 inhibitor could ameliorate memory impairment in mice, and is expected to be potentially used as a lead compound for further anti-AD reagent development. It is discovered that treatment of 9 mg/kg/day of TDC could obviously decrease Aβ production and Aβ plaque formation, while efficiently improve the memory impairment based on

Morris water maze test. The findings thus demonstrated that the natural product TDC as a new beta-site amyloid precursor protein (APP)-cleaving enzyme 1 (BACE1) inhibitor could ameliorate memory impairment in mice, and is expected to be potentially used as a lead compound for further anti-AD reagent development. [114]

At our institute (International Institute of Herbal Medicine, Lucknow, U.P. India), we have developed a herbal formulation "Neurocare" with combination of medicinal herbs namely Malkangni (*Celastrus paniculata*), Ashwagandha (*Withania somnifera*), Bramhi (*Cenella asiatica*), Bala (*Sida cardifolia*) and *Tinospora cordifolia* (Guruchi). This herbal formulation improves the functions of nervous system, nourishes the neuronal cells, increases nervous resistance against stress and provides mild tranquilizing effects. [115] Besides, long term use of Ashwagandha (*Withania somnifera*) and Bramhi/ Mandookparni (*Cenella asiatica*) together produced benefits in cases of schizophrenia, memory deficit, pan epileptics, improved memory and concentration in school children and even produced gradual benefits in brain damage in post encephalitis cases. This was also effective in Parkinson's disease. These studies are in progress in our institute since 15 years. [116] The clinical trial of this herbal formulation on elderly patients above the age of 65 years suffering from dementia and related disorders has shown improvement in the memory which could be a potential drug for the treatment and prevention of Alzheimer's Syndrome.

FUTURE PROSPECTIVE

The above mentioned studies suggest that the treatment strategies for the management of patients with Alzheimer's disease will have to include a variety of interventions directed at multiple targets. The presently available allopathic drugs approved by Food and Drug Administration (FDA), USA have not offered satisfactory solution for the treatment and complete cure of the disease and they produce various side effects. Moreover, these drugs are symptomatic and do not alter the course or progression of the underlying disease. This warrants for the exploration of better therapeutics with least side effects for the treatment and management of this disease. Medicinal herbs abundantly available throughout the world can help in the development of effective therapeutics for the disease. This review is aimed at highlighting the possible role of many herbs, which have shown the possibility of their effectiveness in Alzheimer's or memory related disorders in experimental models and human studies. This gives a sum up of all details of herbs from which scientists can get lead to work extensively to find out the technique which will further establish the authenticity of the reported matter as well as will carry out advance research work in this field to find out the "SOFT" drugs of future in prevention and treatment of Alzheimer's and memory deficient CNS disorders. Thus, multidisciplinary investigations on medicinal herbs described above as well as new medicinal herbs using modern biological tools and animal models followed by extensive clinical trials are needed in order to develop effective therapeutic protocols for the management of the Alzheimer's disease.

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