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Alzheimer's Disease: A Review

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ABSTRACT

Alzheimer's disease (AD) is an age-related, non-reversible neurodegenerative disease. AD is characterized by cognitive and behavioral problems. It is the most common cause of dementia among people aged 65yrs and older. It is the third leading cause of death in developed countries Alzheimer disease accounts for 60-70% cases of progressive cognitive impairment in elderly patients. The disease is more common among women than men by a ratio of 1.2 to 1.5. Two basic types of AD are familial and sporadic. While familial AD (FAD) is a rare form of AD, affecting less than 10 percent of AD patients, sporadic AD comprises the remaining 85-90%. However, no effective therapy exists till date. Because of the increased safety concerns about the synthetic drugs, cheaper and safer sources of drugs based on natural origin are the focus of current research. The traditional medicine all over the world is nowadays revalued by an extensive research activity on different plant species and their therapeutic applications. Since they have a relatively higher therapeutic index, lesser side effects and are economical, herbal drugs have gained a lot of acceptance and popularity in the recent years. These plants may show beneficial effects in animal models of AD.

INTRODUCTION

Alzheimer's disease (AD) is an age-related, non-reversible neurodegenerative disease. AD is characterized by cognitive and behavioral problems. It is the most common cause of dementia among people aged 65yrs and older. It is the third leading cause of death in developed countries (Ewbank, 1991). Alzheimer disease accounts for 60-70% cases of progressive cognitive impairment in an elderly patients. The total prevalence of AD in the United States is estimated at 2.3 million (range, 1.09 - 4.8 million) (Brookmeyer *et al*, 1998). The prevalence of AD doubles every 5 years after the age of 60yrs, increasing from a prevalence of 1% among those 60-64 years-old to up to 40% of those aged 85 years and older (Von Strauss et al, 1999). The disease is more common among women than men by a ratio of 1.2 to 1.5 (Gao *et al*, 1998). Two basic types of AD are familial and sporadic. While familial AD (FAD) is a rare form of AD, affecting less than 10 percent of AD patients, sporadic AD comprises the remaining 85-90 %. FAD is frequently observed in younger people while sporadic AD is related to advancing age and ultimately affects almost half of the population over the age 85 (Yaffe, 1998). It leads to death within an average of 8 years after diagnosis, the last 3 of which are typically spent in an institution. Besides memory loss, Alzheimer's patients show dramatic personality changes, disorientation, declining physical coordination, and an inability to care for themselves. In the final stages, victims are bedridden, lose urinary and bowel control, and suffer epileptic attacks. Death is usually due to pneumonia, bedsores or urinary tract infection. The diagnosis of AD can only be confirmed by the presence of amyloid plaque, neuro-fibrillary tangles, neuronal & synaptic loss and brain atrophy in specific brain areas. Dementia is diagnosed in a living patient (with at least 85% accuracy) on the basis of cognitive tests (especially delayed recall) and exclusion of other conditions such as stroke, hypothyroidism or nutritional deficiency.

However, no effective therapy exists till date. Because of the increased safety concerns about the synthetic drugs, cheaper and safer sources of drugs based on natural origin are the focus of current research. The traditional medicine all over the world is nowadays revalued by an extensive activity of research on different plant species and their therapeutic applications. Since they have a relatively higher therapeutic index, lesser side effects and are economical, herbal drugs have gained a lot of acceptance and popularity in the recent years. Curcumin has been shown to possess potent anti-amyloidogenic effects (Ono et al, 2004). Certain other plants like *Ginkgo biloba*, *St John's wort*, *Kava-kava*, Valerian, *Bacopa monniera* and

Convolvulus pluricaulis have shown beneficial effects in diseases of the nervous system (Kumar, 2006). These plants may show beneficial effects in animal models of AD.

Alzheimer's disease

Alzheimer's disease (AD) is the most frequent neurodegenerative disease and the most common cause of dementia in humans. Clinically, initial symptom of AD is impaired short-term memory that changes to profound memory failure. AD neuropathology exhibits two hallmark features:

- Senile plaques containing depositions of beta-amyloid protein
- Neurofibrillary tangles (NFT)

Quantitative neuropathological evaluation in early AD shows significant neuronal loss in brain memory regions. Genetic studies demonstrate that aberrant proteolytic processing of the amyloid precursor protein (APP) leads to 1–40 and 1–42 amyloid β peptide (Aβ) fragments capable of causing AD pathology. However, the mechanisms by which amyloid proteins lead to plaque deposition, NFT, and neuronal cell death is incompletely understood. AD is of two types:

- Familial AD (FAD)
- Sporadic AD

While familial AD (FAD) is a rare form of AD, affecting less than 10 percent of AD patients, sporadic AD comprises the remaining 85-90 %. FAD is frequently observed in younger people while sporadic AD is related to advancing age and ultimately affects almost half of the population over the age 85yrs (Yaffe, 1998).

Incidence and Prevalence

AD affects more than four million people in the United States. Currently the number of deaths caused by AD is similar to the number of deaths caused by stroke. AD and stroke together rank as the third most common cause of death (Ewbank, 1991). In developed countries; AD appears to be more common in women. Prevalence of dementia according to the Diagnostic and Statistical Manual of Mental Disorders (4th edition) varied widely, from less than 1% in the least developed countries, such as India and rural Peru, to 6·4% in Cuba.

Compared with developed countries, relatively lower annual incidence estimates of 1–2% are reported in certain countries, such as Brazil, Nigeria, India, and Taiwan (Liu et al., 1998; Chandra et al., 1998; Hendrie et al., 2001; Nitrini et al., 2004). In a study in India the median survival time after onset of dementia symptoms was determined to be 3.3 years for patients with dementia and 2.7 years for patients with AD compared with 5.0–9.3 years in developed countries (Chandra et al., 1998).

Molecular changes / neurotransmitter changes in Alzheimer's Disease

The molecular pathogenesis of AD is depends on the Aβ production and its clearance. Aβ is primarily generated in the neurons by the cleavaging of APP by β and ϒ-processing enzymes, and cleared from brain by its diffusion, export to vascular system, phagocytosis, or degradation. APP is the first gene to be identified as a causative gene of familial AD (FAD) and has been a key molecule in the study of the molecular mechanism of AD. Endogenous APOE-4 in mouse brain enhances Aβ deposition in APP animal models (Bales et al., 1999; Sadowski et al., 2004). Presence of neuro fibrillary tangles (NFT) is one of the neuropathological hallmarks of AD. NFT are fibrous tangles composed of insoluble, conformationally abnormal, hyperphosphorylated tau protein deposited in neuronal cell bodies. Hyperphosphorylated tau can form a specific insoluble structure known as a paired helical filament (PHF) (Buee et al., 2004; Lee et al., 2001). Six tau protein isoforms are generated by alternative mRNA splicing of the *tau* gene. The primary function of tau is to bind to and stabilize microtubules, thereby promoting microtubule polymerization. Hyperphosphorylation of tau appears to cause tau to dissociate from microtubules and form tau protein aggregates, which becomes PHF (Biernat et al; 1993; Bramblett et al; 1993).

Oxidative stress & Alzheimer's disease

The brain has a high lipid content and poor antioxidant defences. In addition, a high metabolic rate and an abundant supply of the necessary transition metals, make the brain an ideal target for free radical attack. The direct evidence supporting increased oxidative stress in AD is: (1) increased brain Fe, Al, and Hg in AD, capable of stimulating free radical generation; (2) increased lipid peroxidation and decreased polyunsaturated fatty acids in the AD brain, and increased 4-hydroxynonenal, an aldehyde product of lipid peroxidation in AD ventricular fluid; (3) increased protein and DNA oxidation in the AD brain; (4) diminished energy metabolism and decreased cytochrome c oxidase in the brain in AD; (5) advanced

glycation end products (AGE), malondialdehyde, carbonyls, peroxynitrite, heme oxygenase-1 and SOD-1 in neurofibrillary tangles and AGE, heme oxygenase-1, SOD-1 in senile plaques; and (6) studies showing that amyloid beta peptide is capable of generating free radicals. One of the results of oxidative stress is increased damage to biological macromolecules majorly focused on malonyldialdehyde and lipofuscin formation (Dowson et al., 1998). Studies suggested that oxidative damage primarily involved the lesions, possibly due to low protein turnover (Mattson et al., 1995). The lipid peroxidation adduction productions of hydroxynonenal (Montine et al., 1996) and acrolein (Calingasan et al., 1999) were found in the lesions of AD. However, the dominant site of damage was not the lesions, but rather the neuronal cytoplasm of neurons vulnerable to death in AD. Since the products of lipid peroxidation and glycation can yield cross linked molecules, oxidative modification by these pathways can make molecules more resistant to breakdown. Cross link formation not only makes proteins resistant to removal by the proteosome but also inhibits proteosome activity (Friguet et al., 1994). Protein-based reactive carbonyl and nitro tyrosine formation were essentially confined to the cytoplasm of vulnerable neurons, with less evidence of their formation in amyloid β or τ deposits. These findings point to the cytoplasm, not the lesions, as the source of ROS. 8-Hydroxyguanosine (8-OHG), a nucleic acid modification predominantly derived from hydroxyl free radical attack of guanidine, is greatly increased in cytoplasmic RNA in vulnerable neuronal populations (Nunomura et al., 1999a). Ultrastructural analysis shows that most 8-OHG immune decoration is in the endoplasmic reticulum, with the majority of mitochondria showing little 8-OHG.

Inflammation and Alzheimer's disease

The pathophysiology of Alzheimer's disease (AD) involves the deposition of amyloid in the brain and the extensive loss of neurons. Extracellular senile plaques result from the accumulation of several proteins and an inflammatory reaction around deposits of amyloid. Neurofibrillary tangles result from intracellular deposition of hyperphosphorylated degenerate filaments, which result from aggregations of the microtubular protein tau. As these cellular changes progress, neurons are lost in the hippocampus, entorhinal cortex and associated areas of the neocortex. The mechanisms involving neuronal death in the disease remain unclear, although it has been postulated that this is due to apoptosis. There is evidence that inflammatory processes play a role in disease progression and pathology. Amyloid plaque deposition is accompanied by the association of microglia with

the senile plaque, and this interaction stimulates these cells to undergo phenotypic activation and the subsequent elaboration of proinflammatory and neurotoxic products (Maria, 2002).

Chronically activated microglia and astrocytes can kill adjacent neurons by the release of highly toxic products such as reactive oxygen intermediates, nitric oxide, proteolytic enzymes, complement factors or excitatory amino acids. Proinflammatory cytokines enhance Aβ40 and Aβ42 peptide production and slow down the soluble fraction of APP with neuronal protective effect. The APP modification begins two to three decades ahead of disease onset. During this period, the microglia and astrocyte cells become active. The microglia cell activation in AD can be due to the binding of Aβ to the CD14 receptor and its co-receptor, TLR4. After activation, the microglia cells modify their morphology and become tissue macrophages producing inflammatory molecules.

So, in the present study, anti-inflammatory effect of selected extracts of plants will be evaluated *in-vitro*.

Enzyme involved in Alzheimer's disease

Acetylcholinesterase (AChE) & Butrylcholinesterase (BuChE): Acetylcholine (ACh) is a neurotransmitter responsible for the cholinergic transmission both in the central and peripheral nervous system. Acetylcholinesterase (AChE) catalyzes the hydrolysis of ACh. Furthermore, butyrylcholinesterase (BuChE) is also present in selected areas of central and peripheral nervous system. The cognitive impairment in AD is associated with loss of cholinergic functions, accumulation of neurofibrillary tangles, constituting of hyper-phosphorylated Tau protein. Acetylcholinesterase and butyrylcholinesterase activities emerge in association with plaques and tangles in Alzheimer's disease (Mariam et al. 2005). Acetylcholinesterase and butyrylcholinesterase are present in various regions of the brain and are increased in the brains of patients with Alzheimer's disease. Thus, higher the activity of acetylcholinesterase and butyrylcholinesterase, more severe the manifestations of Alzheimer's disease and increasing number of cortical and neocortical amyloid-rich neuritic plaques and neurofibrillary tangles (Greig et al, 2005). The loss of cholinergic neurons is also associated with apoptotic cell death induced cortical shrinkage in AD brains, which express more AChE than other neuron. Acetylcholinesterase (AChE) inhibitors serve to ameliorate symptoms by prolonging acetylcholine (ACh) availability in the neurons (Mesulam, 2004). Recent studies suggest that inhibition of both BuChE and AChE might enhance the

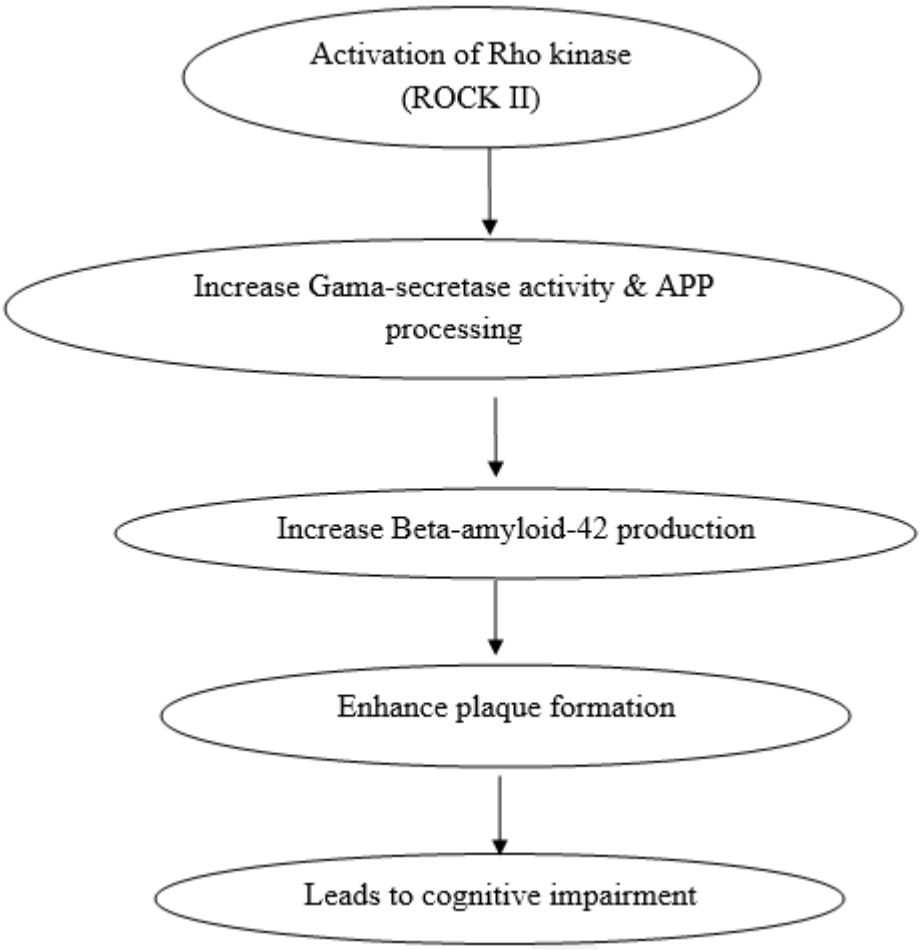
cholinergic transmission in AD. Therefore the current treatment of AD employs inhibition of AChE and BuChE using small molecule drugs such as donepezil, galanthamine and rivastigmine.

So, in the proposed study the AChE and BuChE inhibitory effect of extract of selected plants will be evaluated *in-vitro* and *in-vivo* studies.

Rho kinase (ROCK II): Rho kinase, is serine/threonine kinase that is activated by binding to the active GTP-bound form RhO. It exists as two isoform i.e. ROCK II (ROK α/Rho kinase α) and ROCK I (Rho Kinase β/ROK β) which are known to phosphorylate various substrates, including myosin-binding subunit (MBS) of myosin phosphatase, myosin light chain (MCL). ROCK1 is abundantly expressed in non-neuronal tissues such as the liver, stomach, and kidney, whilst ROCK2 is preferentially expressed in the brain and muscle tissues. Several functions have been attributed to Rho/Rho-kinase signaling within central nervous system including central regulation of axonal growth (Borisoff et al, 2003), neurotransmitter release (Narita et al, 2003), formation of branched dendrites (Leemhuis et al, 2004), regulation of the level of amylodogenic A β_{42} (Zhou et al, 2003) and long-term spatial memory (Dash et al, 2004). Morphological changes in neurons (dendritic length, and the size, shape and number of synapses) are the hallmarks of long – term memory in both vertebrates and invertebrates. Actin filaments are involved in neuronal morphology and their regulation can influence memory. The Rho-ROCK pathway becomes an attractive target for the development of drugs for treating central nervous system (CNS) disorders, since it has been recently revealed that this pathway is closely related to the pathogenesis of several CNS disorders such as spinal cord injuries, stroke, and Alzheimer's disease (AD). In the adult CNS, injured axons regenerate poorly due to the presence of myelin-associated axonal growth inhibitors such as myelin-associated glycoprotein (MAG), Nogo, oligodendrocyte-myelin glycoprotein (OMgp), and repulsive guidance molecule (RGM). The effects of these inhibitors are reversed by blockade of the Rho-ROCK pathway *in vitro*, and the inhibition of this pathway promotes axonal regeneration and functional recovery in the injured CNS *in vivo*. The Rho-ROCK pathway is also an important regulator of cell growth, migration, and apoptosis via regulation of actin cytoskeleton assembly.

The inhibition of Aβ production by statins is mediated by both the cholesterol lowering-dependent and independent mechanisms. Although the precise molecular mechanisms remain to be determined, the reduction of Aβ by statins is at least partly associated with the

enhancement of α-secretase activity. Independent of the depletion of cellular cholesterol levels, statins inhibits small GTPases including Rho by lowering protein isoprenylation via the reduction of mevalonate synthesis (Cole and Vassar 2006). It has been suggested that the inhibition of Rho-ROCK by statins results in the activation of α-secretase cleavage (Pedrini et al 2005) or the enhancement of APP lysosomal degradation (Ostrowski et al 2007), both of which lead to the inhibition of Aβ production. In addition, it was recently reported that Aβ inhibits neurite outgrowth through the activation of the Rho-ROCK pathway in SH-SY5Y neuroblastoma cells (Petratos et al, 2008). It was suggested that the inhibitory effect of Aβ is at least partly mediated by the induction of an alternatively spliced form of CRMP-2, ie, CRMP-2A, and the upregulated phosphorylation of CRMP-2 by ROCK. These studies suggest that the Rho-ROCK pathway is involved not only in Aβ production but also in Aβ-induced neurite outgrowth inhibition, suggesting that Rho-ROCK blockers would be beneficial in the treatment of AD



Prolyl endopeptidase (PEP): PEP is a serine protease, which is known to cleave peptide substrates in the C-terminal side of proline residues. It involved in the metabolism of proline containing neuropeptide such as substance P, arginine vasopressin and thyrotropin-releasing hormone which are involved in learning and memory process (Taylor & Dixon, 1980; Toide et al, 1995; Shishido et al, 1998). PEP is widely distributed in various organs, particularly in the brains of amnestic patients. Evaluation of PEP levels in postmortem brains of Alzheimer's disease patients revealed significant increases in PEP activity, suggesting that a specific PEP inhibitor can be a good candidate for an antiamnestic drug. Recent studies have suggested that prolyl endopeptidase could be involved in the processing of the C-terminal portion of the APP in AD. It was found that the PEP activity of AD patients is significantly higher than that of the normal person (Portevin et al., 1996). It has been suggested that specific PEP inhibitors could prevent memory loss and increase attention span in patients suffering from senile dementia. It is also reported that PEP inhibitors improves memory and learning in scopolamine-treated rats and dorsal hippocampal-lesioned rats (Toide et al, 1997). The memory-enhancing effect of JTP-4819 (PEP inhibitor) may result from prevention of the metabolic degradation of brain neuro-peptides by PEP as well as from the enhancement of acetylcholine release. It increased acetylcholine release from the frontal cortex and hippocampus, regions closely associated with memory, in both young and aged rats.

So, in the present study the PEP inhibitory activity of extracts of selected plants will be evaluated *in-vitro*.

Monoglycerol lipase (MGL): MGL is a serine hydrolase that converts monoglycerides to fatty acid and glycerol, participates in 2-AG inactivation. Endocanabinoids system has also been postulated as a relevant target for various pathological conditions such as neuro-inflammation, pain modulation and neuro-protection. The cannabinoid CB1 and CB2 receptors, the endogenous endocannabinoid (EC) ligands anandamide (AEA) and 2-arachidonylethanolamide, and the degradative enzymes fatty acid amide hydrolase (FAAH) and monoglyceride lipase (MGL) are key elements of the EC system implicated in different physiological functions including cognition, motor activity and immune responses. Thus, both the possible neuro-protective role of ECs and their modulating action on neurotransmitter systems affected in several neurodegenerative diseases such as Alzheimer's disease (AD), Huntington's disease (HD) and multiple sclerosis (MS) are currently under investigation. The data from various studies show an unbalance in the EC system (i.e.

decrease of neuronal cannabinoid CB1 receptors, increase of glial cannabinoid CB2 receptors and over-expression of FAAH in astrocytes) in experimental models of AD as well as in post-mortem brain tissue of AD patients, suggesting its possible role in inflammatory processes and in neuro-protection (Micale et al, 2007). So, in the present study the PEP inhibitory activity of extracts of selected plants will be evaluated *in-vitro*.

So, in the present study the MGL inhibitory activity of extracts of selected plants will be evaluated *in-vitro*.

Catechol-*O*-methyl transferase (COMT): COMT degrades catacholamines such as dopamine, epinephrine, and norepinephrine. The link between impairments in these sorts of cognitive tasks and the COMT gene is thought to be mediated by an effect on dopamine signaling in the frontal lobes. The gene encoding catechol-O-methyltransferase (COMT) has been suggested as a candidate for Alzheimer-related psychosis (AD-P) susceptibility, and an association between AD-P and a functional valine to methionine polymorphism has been reported (Sweet et al, 2005).

Neurotrophic factors, like e.g. nerve growth factor (NGF), neurotrophin 3 (NT-3) or brain-derived neurotrophic factor (BDNF) promote the survival and function of neurones in the peripheral and central nervous system. Dopamine or other biogenic amines induce the biosynthesis of neurotrophic factors in glial and neuronal cells. Therefore inhibition of enzymes, like the extraneuronal and neuronal located Mono Amine Oxidase (MAO) or the predominantly glial situated COMT, which both metabolize catecholamines, may induce an increased biosynthesis of neurotrophic factors. Due to clinical studies especially MAO-B-inhibitors appear to slow the progression of neurological deficits in Parkinson's disease and the cognitive decline in Alzheimer's disease. On the one hand inhibition of COMT alone may also slow the metabolisation of biogenic amines in glial cells and may consequently induce synthesis of neurotrophic factors in glial cells (Muller et al, 1993).

So, in the present study the COMT inhibitory activity of extracts of selected plants will be evaluated *in-vitro*.

Present treatment and their side effects

Several drugs are available to slow the progression of AD and possibly improve the person's mental capabilities. Memantine is currently the only drug approved for the treatment of

moderate-to-severe Alzheimer's disease. It interferes with glutamatergic excitotoxicity and provides symptomatic improvement through effects on the function of hippocampal neurons (Parsons et al., 1999). Negative outcomes have been reported from the trials of anti-inflammatory drugs i.e prednisone (isen et al., 2000), diclofenac (Scharf et al.,1999), rofecoxib (a selective cyclooxygenase-2 inhibitor), and naproxen (a mixed cyclooxygenase-1 and cyclooxygenase-2 inhibitor)(Aisen et al., 2003). Other medicines include donepezil**,** rivastigmine, galantamine, and tacrine. These drugs affect the level of acetylcholine in the brain as they are anticholinestrase inhibitors. Major drawbacks of the present therapy are their side effects. They may cause nausea and vomiting. Tacrine also causes an elevation in liver enzymes leads to hepatotoxicity. It is now rarely used. Donepezil is taken once a day and may stabilize or even improve the person's mental capabilities. It is generally well tolerated. Rivastigmine seems to work in a similar way. It is taken twice a day.

Alzheimer's Disease & Herbal drugs

Traditional medicines have significant role in the treatment of Alzheimer's disease. Extensive activity of research is going on different plants all around the world. Since they have a relatively higher therapeutic window, lesser side effects and are economical, herbal drugs have gained a lot of acceptance and popularity in the recent years. Plants like *Ginkgo biloba, St John's wort, Kava-kava, Valerian, Bacopa monniera* and *Convolvulus pluricaulis* have been investigated and well established for their effectiveness in diseases of the nervous system (Kumar, 2006). Various plants are studied for their anticholinestrase activities like *Withania somnifera, Semecarpus anacardium, Embelia ribes, Tinospora cordifolia, Ficus religiosa* and *Nardostachys jatamansi* (Vinutha et al, 2007). *Ginkgo biloba* extract (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 (selkoe et al., 1996). Galantamine is a competitive and selective acetylcholinesterase inhibitor. According to three Chinese double-blind trials, use of huperzine A has shown significant improvement in symptoms of AD and other forms of dementia (Xu et al., 1995; Zhang et al., 2002). It has been reported that *Melissa officinalis* (lemon balm) improves cognitive function and reduces agitation in patients with mild to moderate AD. *M. officinalis* is known to have ACh receptor

activity in the central nervous system with both nicotinic and muscarinic binding properties (Perry et al., 1998; Perry et al., 1999).

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