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# ROLE OF MEDICINAL PLANTS IN MANAGEMENT OF ALZHEIMER'S AND NEURODEGENERATIVE DISEASE –REVIEW

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## ABSTRACT

Alzheimer's disease (AD) is a progressive, neurodegenerative disorder that primarily affects the elderly population and it is considered to be responsible for a 60% of all dementia in people aged 65 or older. Due to its unbearable nature, an enormous social and economic burden is placed on society. Currently there is no permanent heal for the disorder and much of the treatments available have been able to only delay the progression of the disease or provide symptomatic relief for a short period of time. Present are necessitating for an advance treatment of these diseases. Plants have been used since archeological find in the treatment of various diseases including cognitive disorders, such as AD. Phytochemical substances such as alkaloids (galathamine), curcuminoids, heperzine, ginkgolid, icariin, ginsenoside, carinatumins, esveratrol, berberine, rhapenticin, rhapontigenin, tenshinone, desitoindosi IX, salvianolic acid, diterpenes, triterpenoid (ursolicacids), stilbenes and withanolides were pharmacological activities relevant to treat AD. The medicinal plants have been act on multi functional molecular mechanism in AD (Senile plaque deposition, anti-amyloid, neurofibrillary tangle formation and tau hyperphosphorylation).

**KEYWORD**: amyloid plaques, neurofibrillary tangles, tau proteins, secretase inhibitors.

## INTRODUCTION

Alzheimer's disease (AD), an irretrievable neurodegenerative disorder primarily targeting elderly populations, affects approximately 36 million people worldwide according to the 2014 estimations. This infirmity is characterized by progressive neurodegenerative disorders, crumple of cognitive functions, formations of amyloid plaques and neurofibrillary tangles.

AD is the most frequent cause of dementia in mid- to late life and has an overwhelming impact on public health and society. The AD pathogenesis is complex and comprises genetic and environmental factors, thus AD is considered a multi factorial disease. Different hypotheses regarding the pathological routes of AD have been proposed and the main hypotheses are related to the cholinergic, amyloid-β (Aβ) and tau proteins. For this reason, drugs acting on acetylcholine (ACh) levels, mainly acetylcholinesterase inhibitors (AChE-I), or that reduce the formation of toxic Aβ peptides, mainly noncompetitive β-secretase (BACE-1) and secretase inhibitors, were studied for the development of anti-AD drugs. By its pharmacological nature, cholinesterase inhibitory therapy may be considered as a simple symptomatic intervention. However, therapy with AChE-I can be effective over a longer period, and it is believed that AChE also plays an important role in Aβ deposition. It seems likely that AChE interacts with Aβ and promotes the formation of amyloid fibril through a pool of amino acids located in proximity to the peripheral anionic-binding site of the enzyme. Furthermore cholinergic neurons are subject to control via the modulation of nicotinic receptors (nAChRs) and some AChE inhibitors, such as galantamine, bind at allosteric secondary binding sites, and potentiate the receptor response to the available ACh. Since AD is a multifactorial.

## SENILE PLAQUE DEPOSITION AND ANTI-AMYLOID

A major component of senile plaques is the Amyloid β (A β) peptide which is formed as a result of proteolytic cleavage of the amyloid precursor protein (APP) by secretes. According to the 'β -amyloid theory', it has been proposed that A β peptide deposits or even the partially aggregated soluble form are responsible for triggering a neurotoxic cascade of events which ultimately results in neuro degeneration.[1]

## α-SECRETASE ACTIVITY ENHANCERS

Secretes is a membrane bound enzyme that hydrolyses APP within the domain thereby there is no Aβ peptide formed as a result of proteolysis. This is the major pathway of APP processing and is referred to as the non-amyloidogenic pathway. Promoting this pathway by enhancing the activity of α -secretase can be considered as a line of therapy; however, the problem is information about α -secretase enzyme is limited.

## NEUROFIBRILLARY TANGLE FORMATION AND TAU INHIBITORS

One of the pathological hallmarks of AD is the formation of intracellular neurofibrillary tangles which consists of hyper-phosphorylated tau protein. Tau is an axonal protein which

binds to microtubules and by doing so promotes their assembly and stability. Phosphorylation of tau protein is regulated by the balance between multiple kinases (e.g. GSK-3and CDK5) and phosphatases (e.g. PP-1 and PP-2A). Hyperphosphorylation of tau protein starts in AD intra cellular and leads to sequestration of the protein and other microtubule associated proteins, thus preventing microtubule assembly and impairing axonal transport. These results in neuronal function being compromised which ultimately precipitates neuronal death.[3]

## PREVENTING TAU HYPERPHOSPHORYLATION

This approach address the imbalance in the kinase and phosphatase activities by inhibiting the action of protein kinases involved in phosphorylation of tau protein. There are several kinases implicated in tau phosphorylation such as glycogen synthetase kinase-3(GSK-3) and cyclin-dependent kinase 5 (CDK5).[3] which can be potential drug targets. The search for protein kinase inhibitors is an active one, however, to date, no kinase inhibitors have been launched as drug products. Among the compounds which have demonstrated GSK-3 inhibitory activity, lithium, bisindolylmaleimides I (1) and IX (2) and hiadiazolidinones derivatives can be mentioned. Hymenialdisine, indirubin and paullones and even bisindolylmaleimides I and IV have shown CDK5 inhibitory activity (Castro et al. 2002). One interesting development is that M1 muscarinic agonists AF102B (3), AF150(S) (4) and AF267B (5) are reported to have GSK-3 inhibitory activity.[4]

## OXIDATIVE STRESS AND ANTIOXIDANT ACTIVITY

The vulnerability of CNS to oxidative damage is due to a number of factors such as excessive oxygen uptake and high unsaturated lipid content. Under normal physiological conditions, damage by reactive oxygen species (ROS) is kept in check by antioxidant defense cascade consisting of enzymatic and non-enzymatic components.[5] However, during degenerative processes there is an imbalance between ROS and cellular antioxidant defenses, which leads to critical failure of biological functions. One of the sources of oxidative stress in AD is the disturbance in metal homeostasis such as iron, copper, zinc, aluminium and metals capable of catalyzing reactions that produce free radicals.[6] Mitochondrial dysfunction, as source of ROS generation, has been proposed to be associated with variety of degenerative pathways leading to AD progression.[7]

## INFLAMMATORY CASCADE AND ANTI-INFLAMMATORY ACTIVITY

Hallmarks of inflammation such as activated microglia cells and pro-inflammatory cytokines have been found in the post mortem brains of the AD patients. Clinical studies have also

pointed out an increase in the level of inflammatory markers.[8] Treatment of culture systems with fibrillier that has lead to microglia activation and the subsequent production of inflammatory cytokines. This is turn results in the production of ROS and RNS.[2] Hence, anti- inflammatory agents has been used to attenuate microglia associated cytokine and free radical formation.[12] In this context, non-steroidal anti-inflammatory drugs (NSAIDs) have exerted demonstrable beneficial effects in relation to AD therapy.[1] Several epidemiological studies pointed to an association between the use of NSAIDs and reduced risk of developing AD.[9] Some of these studies have suggested that they may affect the age and onset of the disease. Many mechanisms have been proposed for their activity ranging from COX inhibition to lowering of amyloidogenic 1-42 peptides.[12] Unfortunately, recent studies with NSAIDs such as celecoxib and rofecoxib were not benefit muscarinic agonist which has been tested for their cognitive enhancing function. Both the chemical are plant derived alkaloids. They have provided template for further drug development research.[13]

## CHOLINERGIC DEFICIT AND NEUROTRANSMITTER REPLACEMENT THERAPY

The degeneration of cholinergic neurons originate in the basal forebrain and projects to the cortex and hippocampus results in the loss of all known cholinergic markers, such as choline acetyltransferase (ChAT), acetylcholine (ACh) levels and acetyl cholinesterase (AChE). ACh is associated with cognition and it is the deficit of this neurotransmitter which contributes to cognitive dysfunction. The degeneration of these cholinergic neurons has been proposed to be a result of amyloid fibril-induced neuronal injury, tangle formation, ROS/RNS or astrocyte phagocytic activity.[13] On the other hand, ACh is known to promote non-amyloidogenic processing and reduce tau phosphorylation by reducing the activity of protein kinase which phosphorylates tau. Therefore, disruption of cholinergic signaling may lead to a feedback loop that increases production a through altered APP processing, increasing phosphorylation of tau protein, thereby contributing to the progression of AD pathology.[14] Based on what has been mentioned above, restoration of the central cholinergic function may significantly improve cognitive impairment and may inhibit AD progression in patients. There are 3 principal approaches by which the cholinergic deficit can be addressed: (i) nicotinic receptor stimulation, (ii) muscarinic receptor stimulation and (iii) cholinesterase inhibition.

**CHOLINESTERASE INHIBITORS**

Two types of cholinesterases, AChE and BuChE, are present in a wide variety of tissues. AChE, which is the prime cholinesterase in the brain, hydrolyzes ACh to choline and acetate, thereby terminating the effect of this neurotransmitter at cholinergic synapses (Mayeux 2005). AChE is target of cholinesterase inhibitors which are used for address the cholinergic deficit in AD patients. Over the last two decades, cholinesterase inhibition has become the most widely studied and effective clinical approach to treat the symptoms of AD.

Increasingly, research has indicated the possibility that cholinesterase inhibitors in addition to providing symptomatic relief are having modulator effects upon plaque deposition. Several recent studies using cell culture and animal models have shed light upon the effects of cholinesterase inhibitors at the level of a peptide. Specific cholinesterase inhibitors exert amyloid lowering effect as a consequence of both their cholinergic and non-cholinergic activities. Cholinesterase inhibition results in an increase in ACh which as mentioned before will promote non-amyloidogenic processing.[14] APP expression is suppressed with the result that the quantity of its proteolytic product, A peptide, will also decrease butyryl cholinesterase inhibitory agents may be especially critical in light of co-localization of BuChE and amyloid plaques, A peptide, NFTs and dystrophic neurons, all pathological hallmarks associated with AD pathology.[14,15]

The exposure of CNS to oxidative damage is due to a number of factors such as excessive oxygen uptake and high unsaturated lipid content. Under normal physiological conditions, damage by reactive oxygen species (ROS) is kept in check by antioxidant defense cascade consisting of enzymatic and non-enzymatic components. However, during degenerative processes there is an imbalance between ROS and cellular antioxidant defenses, which leads to critical failure of biological functions. One of the sources of oxidative stress in AD is the disturbance in metal homeostasis such as iron, copper, zinc, aluminum and metals capable of catalyzing reactions that produce free radicals mitochondrial dysfunction, as source of ROS generation, has been proposed to be associated with variety of degenerative pathways leading to AD progression. Peptides are another important source of oxidative damage, producing neuro toxic effects directly by inducing more ROS and indirectly by activating microglia. It has been proposed that peptides in the presence of transition metal ions produces ROS such as superoxide anion radical and hydrogen per-oxide which are known to be responsible for oxidative damage *in vivo*. Microglia activation leads to a massive production of inflammatory

cytokines, ROS and reactive nitrogen species (RNS), thereby contributing to oxidative damage.[16, 17]

**MEDICINAL PLANTS IN TREATMENT OF ALZHEIMER'S DISEASE.**

| S.NO. | PLANTS | ANIMAL | MOLECULAR MECHANISM |
|---|---|---|---|
| 1. | Angelica archangelica | Mice | Ethyl acetate extract inhibit the production of inflammatory mediators alleviate inflammatory hazards and protect mice from endotoxic shock.[33] |
| 2. | Aegle marmelos | Rat | Evaluated the effect of oral administration of A.marmelos on learning and spatial memory in diabetic rats used Morris water maze test.[34] |
| 3. | Azadirachta indica | Rat | A. indica is effective in reversing the neurobehavioral changes and decreasing the oxidative stress in experimental AD.[3] |
| 4. | Acorus gramineus | Mice | The pro-convulsant effect suggests a strong glutamatergic or cholinergic effect, or GABAergic inhibition the consequence of which would be to deplete the stock of neurotransmitter and result in lethargy after the seizer.[44] |
| 5. | Angelica dahurica | Mice | The methanolic extract from the root was found to inhibit the activities of GABA degradative enzymes.[44] |
| 6. | Atropa belladonna | | The plant causes a depressant action at the CNS and antagonist the muscarinic cholinergic receptors.[42] |
| 7. | Bertholettia excels | Mice | This building block the concentration of acetylcholine in AD patients.[43] |
| 8. | Berberine | Mice | Decrease of the secrection of amyloid beta protein.[67] |
| 9. | Butea monosperma | Mice | Preclinical studies have reported cognitive enhancing effects with various extract of butea monosperma.[20] |
| 10. | Centella asiatica | Mice | Centella asiatica extracts reversed the β amyloid pathology in the brains of PSAPP mice and modulated components of the oxidative stress response.[41] |
| 11. | Curcuma longa | Mice | It reduced oxidative damage and reversed the amyloid pathology in an AD transgenic mice.[41] |
| 12. | Convolvulus pluricaulis | Young adult rats | Increase acetylcholine content in the hippocampus may be the neuro chemical basis for their improved learning and memory.[36] |
| 13. | Curcuma longa | Mice | Protective and therapeutic effects against neurodegenerative disorders and AD induced by $AlCl_3$ on the pyramidal cells in cerebral cortex.[56] |
| 14. | Cassia Fistula | Rat | The present study provides use as a culinary spice foods as beneficial and scientific in combating stress induced disorders.[56] |
| 15. | Convolvulus pluricaulis | Mice | The whole plant in the form of a decoction is used with milk and cumin to treat fever, disability, memory loss, syphilis and scrofula.[36] |
| 16. | Curcuma comosa | Rat | Curcuma comosa hexane extract is beneficial to spatial learning and memory effect on rats.[36] |
| 17. | Cistanche tubulosa | Rat | That CT extract, containing enough echinacoside and acteoside, ameliorated the cognitive dysfunction caused by amyloid beta 1-42 via blocking amyloid deposition, reversing cholinergic and |

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| | | | hippocampal dopaminergic neuronal function.[21] |
| 18. | Cressa cretica | Mice | Those ethanolic extract of plant of cressa cretica at a dose of 400 mg/kg possess nootropic activity.[59] |
| 19. | Cistanche tubulosa | Rat | CT is a potential anti-amnesic and anti-dementia activity.[21] |
| 20. | Celastrus paniculatus | Mice | Celastrus paniculatus have been used in Ayurvedic medicine for ‘’stimulating intellect and sharpening the memory’’.[20] |
| 21. | Cistanche tubulosa | Rat | CT is a potential anti-amnesic and ant-dementia property.[21] |
| 22. | Ficus carica | Mice | The hexane extract of ficus carica afforded mild memory enhancing effects. The higher dose evoking pronounced alteration of behavior and better learning assessments.[56] |
| 23. | Ficus religiosa | Rat | From the results of the present study it is concluded that the leaf extract of ficus religiosa might posses anti amnesic as well as notropic properties.[57] |
| 24. | Ginkgo biloba | Mice | Improves protection against Aβ protein induced oxidative damages.[55] |
| 25. | Ginseng | Mice | Increase in the uptake of choline in central nervous system.[33] |
| 26. | Galanthus nivalis | Rats | A potential source of Ach inhibitors is certainly provided by the abundance of plants in nature.[61] |
| 27. | Hippophae rhamnoides L. | Rat | It is concluded that SBT leaf extract a showed potential cognitive enhancing activity by regulating cholinergic marker enzyme activity and promoting the antioxidant system.[64] |
| 28. | Herba epimedii | Rat | Icariin represent an important an important active component in herba epimedii. Icariin administration may effectively prevent or delay the onset of age –related cognitive degeneration.[33] |
| 29. | Indirubins | Mice | Inhibition of abnormal tau phosphorylation by inhibiting glycogen synthase kinase-3 beta and CDK5/P25.[65] |
| 30. | Komatsuna extract | Albino mice | KSE reduces the toxicity of Aβ modifying the Aβ KSE improves the inhibition of Aβ uptake therefore modifying Aβ.[66] |
| 31. | Lavandula angustifolia ssp | Rat | That antioxidant and anti apoptotic activities of the lavender essential oils are the major mechanism for their potent neuro protective effect against scopolamine-induced oxidative stress in the rat brain.[33] |
| 32. | Lavandula angustifolia Mill | Rat | That antioxidant and anti apoptotic activities of the lavender essential oils are the major mechanism for their potent neuro protective effect against scopolamine-induced oxidative stress in the rat brain.[33] |
| 33. | Lavandula hybrid | Rat | That antioxidant and anti apoptotic activities of the lavender essential oils are the major mechanism for their potent neuro protective effect against scopolamine-induced oxidative stress in the rat brain.[33] |
| 34. | Magnolia officinalis | Rats | This review concentrates on the toxicity of Aβ and the mechanism of accumulation of this toxic protein in the brain of individuals with Alzheimer’s disease cognitive impairment.[45] |
| 35. | Melissa officinalis | Rat | It is European traditional system of medicine as a remedy for improving memory.[36] |
| 36. | Magnolia officinalis rehd | Rat | Hydro alcoholic leaf extract was effective in improving function in mild to moderate AD patients.[36] |
| 37. | Morinda citrifolia L. | Mice | The beneficial effect of the morinda citrifolia fruit on |

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| | | | scopolamine induced memory impairment is due to its antioxidant property and inhibition of AChE activity.[36] |
| 38. | Nardostchys jatamansi | Mice | The ethanolic extract of plant significant improved learning and memory in young mice.[20] |
| 39. | Ocimum sanctum | Rat | The standardized extract of Ocimum sanctum drastically improved learning and memory deficits with IB.[48] |
| 40. | Polygala tenuifolia | Rat | Rhizome has been used as a sedative, tranquilizer and for the treatment of amnesia and insomnia.[33] |
| 41. | Salvia lavandulaefolia | Rats | Ethanol extract of the plant showed, while the essential oil resulted in mood elevation and improvement of memory in clinical studies.[44] |
| 42. | Salvia officinalis | Mice | ADAS-cognitive and CDS in patients with mild to moderate.[36] |
| 43. | Salvia miltiorrhizia bung | Rat | The ethanol extract improved cognitive dysfunction in rate.[36] |
| 44. | Soybean | Mice | Inhibiting acetyl cholinesterase enzyme activity in the brain.[36] |
| 45. | Sesbania grandiflora | Rat | The pods are considered useful for promoting memory power and for resolving glandular tumors or enlargement.[20] |
| 46. | Typha angustata | Mice | Methanolic extract of Typha angustata was shown significant nootropic activity.[55] |
| 47. | Terminalia chebula | Mice | Mehyl gallate induced significant increase of leukocyte counts in mouse, indicating its immune modulator activity.[56] |
| 48. | Typha angustata | Mice | Typha angustata has shown momentous nootropic activity in mice.[42] |
| 49. | Tenuigenin | Mice | Decrease of the secrection of amyloid beta protein via BACE1 Inhibition.[43] |
| 50. | Terminalia chebula | Rat | The ripe fruit of terminalia chebula is considered to possess the ability to promote memory intellect.[20] |
| 51. | Uncaria rhynchophylla | Mice | Inhibition of aggregation of amyloid beta protein.[64] |
| 52. | Vinca minor | Mice | Improves memory in animal models of AD.[65] |
| 53. | Vigna Mungo Linn | Mice | Ethanolic extract of Vigna Mungo Linn., producing antioxidant activity and also decreased brain acetylcholinesterase concentration in brain and ultimately improved memory in scopolamine induce mice.[69] |
| 54. | Withania sonnifera | Rats | Treated cultured rat cortical neurons with amyloid peptide the induced axonal and dendritic atrophy and loss of pre- and postsynaptic stimuli.[36] |
| 55. | Ziziphus mucronata | Rats | Used to nourish heart and calm the sprit. It is often used to aid sleep or calm mind.[69] |
| 56. | Zingiber officinale | Rat | Ginger has a protective and therapeutic effect on AD.[70] |

## DISCUSSION

The review focuses on several memory enhancing medicinal plants acting on dementia. AD is the most frequent form of dementia and it is delineate by memory loss, mental and physical behavioral changes, and alleviate quality of life for patients with an important impact on public health. The pathology is progressive and causes β-amyloid plaque Formation and deficiency in the neurotransmitter acetylcholine in the brain. Now a Day the available drugs have limited effect on this pathology and in fact are only able to control symptoms to

desiccate cognitive function and slow down the progression of the illness. AD is a multi factorial disease and several pathogenic events are involved in this disease including primary events such as genetics, neuronal death and brain dysfunction.

Furthermore, secondary (β-amyloid deposition, tau protein hyperphosphorylation), tertiary (neurotransmission deficiency, neuroinflammation), and quaternary (neuronal death, free radical formation, cerebrovascular dysfunction) events also play a complex role in this pathology.

Despite the new findings, AChE-I still represent an important symptomatic Therapy and research of new drugs acting on this enzyme is essential. The plant kingdom, an important source of several drugs or "lead compounds" for medicinal chemistry, is still largely unexplored despite the relatively large amount of tested plant extracts for anti-AChE-I.

In recent years, many botanical species have been studied as potential sources of AChE-I alkaloids, but relatively few isolated compounds were considered as potential new "leads" for the development of drugs for AD treatment. Different compounds belonging to various alkaloids classes were identified as enzyme inhibitors, in some cases not only from plants, but also from other natural organisms.

Tenuigenin were decrease the amyloid beta protein and lavendula hybrid were antioxidant and apoptotic activities of the lavender essential oils are the major mechanism for their potent neuroprotective effect against scopolamine induce oxidative stress in the rat brain.

No human or animal studies have been performed in much medicinal plant therefore studies of their safety, efficacy and toxicity are needed. Many approved drugs in the market for AD treatment are natural alkaloids and galantamine is an example.

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