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Review Article

Effect of plant extracts on Alzheimer's disease: An insight into therapeutic avenues

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ABSTRACT

Alzheimer's disease (AD) is a devastative neurodegenerative disorder which needs adequate studies on effective treatment options. The extracts of plants and their effect on the amelioration of AD symptoms have been extensively studied. This paper summarizes the mechanisms like acetylcholinesterase (AChE) inhibition, modification of monoamines, antiamyloid aggregation effect, and antioxidant activity which are actively entailed in the process of amelioration of AD symptoms. These effects are induced by extracts of a few plants of different origin like *Yizhi Jiannao*, *Moringa oleifera* (Drumstick tree), *Ginkgo Biloba* (Ginkgo/Maidenhair tree), *Cassia obtisufolia* (Sicklepod), *Desmodium gangeticum* (Sal Leaved Desmodium), *Melissa officinalis* (Lemon Balm), and *Salvia officinalis* (Garden sage, common sage).

Key words: Alzheimer's disease, antiamyloid aggregation, antioxidants, acetyl choline esterase inhibitors, plant extracts.

Introduction

Alzheimer's association estimated that one in eight Americans above age of 65 years and half of the Americans above age of 85 years have been presently suffering from this devastative neurodegenerative disorder.[1] According to this estimation, the number of patients may reach 16 million by 2050[1-4] thus augmenting the economic cost of Alzheimer's disease (AD) health care system, which is 80–100 billion dollars presently.[1] Loss of cholinergic synapses in hippocampus and neocortex has been a consistent finding in AD, thus accentuating the need to employ a substantial strategy that regulates the AChE function to combat this defect.[1] Tacrine, donepezil, and rivastigmine are a few AChE inhibitors approved by U.S. Food and Drug Administration for the amelioration of AD symptoms.[1,5,6] Although advent of such inhibitors has been effective in function yet there has been augmenting need to quest for new drugs.[1] In the light of this fact, polyphenolic compounds from fruits and vegetables have been exploited because of their potential antioxidative properties.[1,7-12] There has been growing focus on traditional herbal medicines presently since the failure of existing treatments.[13] The first neurotransmitter found to be involved in AD is acetylcholine.[14] Therefore, there have been manifold studies to employ AChE inhibitors.

Plants provide wealth of bioactive compounds, which exert a substantial strategy for the treatment of neurological disorders such as Alzheimer's disease.[15] It has been recently shown that a Chinese herb, Yizhi Jiannao Granules is effective in improving AD symptoms, and it also aggravates such amelioration when combined with acupuncture.[16] Zeatin has been found to have a protective role against Aβ-induced neurotoxicity in PC12 cells and ameliorate scopolamine-induced amnesia in ICR mice.[17]

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Cholinesterase Inhibition

Growing lines of evidence suggests that among 73 native and naturalized plants collected from the central region of Argentina, organic fractions obtained from extracts of *Achyrocline tomentosa* (Marcela) *(Asteraceae), Eupatorium viscidum* (Common boneset) *(Asteraceae), Ruprechtia apetala* (manzano del campo) *(Polygonaceae), Trichocline reptans* (arnica) *(Asteraceae), and Zanthoxylum*

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coco (cochucho, coco) *(Rutaceae)* demonstrated substantial inhibition of AChE (higher than 80%)[Table 1].[15] *Poncirus trifoliate* (Trifoliate Orange) extract has been shown to inhibit AchE considerably.[1] Methoxsalen isolated from medicinal herbs *Treculia obovoidea* (Catterall) and *Angelica archangelica* (Garden Angelica), shows antimicrobial and anti-AchE activities *in vitro*.[1,18,19,20]

Studies on the seeds of *Cassia obtisufolia* proved their neuroprotective role in mice via attenuation of secondary Ca^{2+} dysregulation and mitochondrial toxin 3-NP.[13] Moreover, they can improve memory impairment via AChE inhibition.[13,21] Flavonoids, a group of phenolic compounds which demonstrate antimutagenic, anticarcinogenic, and antiageing properties[22,23,24,25] may be responsible for neuroprotective role of *Cassia obtusifolia* extracts.[13] Dried ginger has been shown to induce Ca^{2+} antagonistic activity and butylcholinesterase inhibitory activity which are effective in AD treatment.[26]

Modification of Monoamines

Moringa oleifera (MO) which belongs to the family *Moringaceae,* is prevalent almost all over the Asian and African countries. Its fruit and leaves which show anti-inflammatory and hypotensive effect are consumed as food by the people.[27-29] It has been found recently that *Moringa oleifera* leaf extract which is not toxic even at higher concentration levels, enhances memory via nootropics activity and provides substantial antioxidants like vitamin C and E to combat oxidative stress in AD.[27,30-32] Wealth of studies substantiated that monoamines entailed in the memory loss are altered by *Moringa oleifera* leaf extracts [Table 1].[27,33] Several lines of evidence also suggest that colchicines-induced AD can be ameliorated by ethanolic extract of *Moringa oleifera* by modifying the brain monoamines (norepinephrine, dopamine, and serotonin) and electrical activity in a rat model.[27]

Antiamyloid Aggregation Effect

Ginkgo biloba being a potential store house of antioxidants offers ample of health benefits to AD patients like antiamyloid aggregation effect [Table 1].[34-36] Extensive studies on *Ginkgo biloba* revealed that 240 mg of *Ginkgo biloba* per day can decrease the incidence of AD.[34] Although there are a few substantial studies on *Ginkgo biloba* to ameliorate AD symptoms and worldwide sales of it exceed $249 million annually in the United States,[34] yet there has been augmenting need to initiate more promising clinical trials in this direction.[34] It has been found that the *Ginkgo biloba* extracts ameliorate cognitive defects in a mouse model of AD (Tg2576).[37,38] Manifold clinical trials proved amelioration of AD symptoms[39,40] and the clinical evaluation of EGb 761 that is widely used for dementia in many countries and an extensively used dietary supplement in the United States for memory enhancement,[41-44] is presently in progress.[45] Although *in vivo* mechanism for EGb 761 is elusive yet it has been found to ameliorate AD symptoms both *in vivo* (AD mice Tg 2576) [46] and *in vitro*.[36,37,47-51] Upregulation of a small APP release, a nontoxic, nonamyloidogenic metabolite of APP, via a PKC-independent manner in hippocampi and cortices of EGb761-treated rats has been studied.[37,52]

Antioxidants

Desmodium gangeticum generally known as Salparni, is prevalent in India and has significant medicinal use as a bitter tonic, febrifuge, digestive, anticatarrhal, antiemetic,[53,54] and anti-inflammatory conditions.[53,55] Moreover, it has been extensively used in ayurveda for the amelioration of neurological symptoms.[53] Its extracts employed in mice to evaluate the efficacy in amelioration of AD symptoms via nootropic activity and deterioration of AChE activity yielded considerable outcome.[53] It also possesses antioxidative property [Table 1].[53,56]

Rosmarinic acid isolated from *Salvia officinalis,* attenuates a number of events provoked by Aβ-like reactive oxygen species formation, lipid peroxidation, DNA fragmentation, caspase-3 activation, and tau protein hyperphosphorylation.[57,58] Despite a few pharmacological activities of sage attributed[59] to AD include antioxidant activity,[60] anti-inflammatory effects[61] and cholinesterase inhibition,[62] yet the mode

Table 1: Neuroprotective mechanisms exerted by various plant extracts

Mechanism	Plant extracts
Cholinesterase inhibition	*Achyrocline tomentosa, Eupatorium viscidum, Ruprechtia apetala, Trichocline reptans, Zanthoxylum coco, Poncirus trifoliate, Treculia obovoidea and Angelica archangelica, Cassia obtisufolia, Desmodium gangeticum, Salvia officinalis*
Modification of monoamines	*Moringa oleifera*
Antiamyloid aggregation effect	*Ginkgo biloba*
Antioxidant activity	*Desmodium gangeticum, Ginkgo biloba, Moringa oleifera, Salvia officinalis*

of sage-protective action is unclear.[57] Rosmarinic acid has been known to initiate antioxidant, anti-inflammatory, antimutagen, antibacterial, and antiviral properties.[63] Rosmarinic acid effectively inhibits hall mark events of AD-like formation of fibrils from Aβ, destabilization preformed Aβ fibrils *in vitro* and tau hyperphosphorylation.[57,64]

Neuroprotective Effect of Traditional Japanese-Chinese, Korean, and European Plant Extracts

Kihi-to, a traditional Japanese-Chinese traditional medicine, shows significant amelioration of Aβ(25–35)-induced impairments in memory acquisition, memory retention, and object recognition memory in mice. It also attenuates neuritic, synaptic, and myelin losses in the cerebral cortex, hippocampus and striatum. Kihi-to also effectively attenuates the calpain augmentation in the cerebral cortex and hippocampus.[65] Abundance of research revealed that among several traditional Chinese medicines, Ginseng Radix[66,67] Astragali Radix[68] and Polygalae Radix[69] demonstrated potential axonal extension activity against amyloid β (Aβ) (25–35)-induced axonal atrophy.[65]

Among the 90 traditional Korean tea plants, methanolic extracts of *Pueraria thunbergiana* (Kudzu) rich in Daidzein (4,7 dihydroxy isoflavone), are actively entailed in the amelioration of scopolamine induced amnesia in mice.[70] Abundance of research unraveled the neuroprotective effect of Gossypium Herbaceam extracts against ibotenic acid induced learning and memory impairment in rats.[71]

Melissa officinalis extract has been proven to ameliorate mild to moderate AD.[14] Among the European herbs *M. officinalis* and another herb in the labiatae family, *S. officinalis*, might present a natural treatment for AD by amelioration of cognition.[14,58,72] This herb actively amends mood and cognitive ability during acute administration in healthy young volunteers and has no side effects or symptoms of toxicity.[14,73,74,75] *S. triloba* (Greek Sage) and *Teucrium polium* (Cat Thyme) are also effective in amelioration of AD symptoms.[76]

Ayurvedic Plants and AD

Formulation of some Indian medicinal plants classified in Ayurveda, the classic Indian system of medicine, as Medhyarasayanas or drugs considerably ameliorates memory and intellect.[77,78] Studies on rats demonstrated that the oral administration of Trasina, a herbal formulation, once daily for 21 days can effectively ameliorate colchicine induced effects like reduced frontal, cortical and hippocampal acetylcholine (Ach) concentrations, choline acetyltransferase (ChAT) activity, and muscarinic cholinergic receptor (MCR) binding.[77] It has been reported recently that alcoholic extract of *Bacopa monnieri* (Water Hyssop) significantly improves escape latency time in Morris water maze test and ameliorates reduction of neurons and cholinergic neuron densities in Wistar rats which are employed as AD animal models.[79] Anwala churna (*Emblica officinalis* Gaertn.), an Ayurvedic preparation showed an exemplary improvement in memory and brain cholinesterase activity, thus ameliorating the scopolamine induced amnesia in young and aged mice.[80]

Curcumin

Curcuma longa (Turmeric) has been the source of Curcumin (diferuloylmethane), an orange–yellow component of turmeric or curry powder. This being a potential polyphenol natural product has been predominantly used in some medicinal preparation or used as a food-coloring agent. Wealth of studies *in vitro* and *in vivo* substantiated that curcumin has anticancer, antiviral, antiarthritic, anti-amyloid, antioxidant, and anti-inflammatory properties. The molecular underpinnings of these effects have been found to involve the regulation of diverse molecular targets, including transcription factors (such as nuclear factor-κB), growth factors (such as vascular endothelial cell growth factor), inflammatory cytokines (such as tumor necrosis factor, interleukin 1 and interleukin 6), protein kinases (such as mammalian target of rapamycin, mitogen-activated protein kinases, and Akt) and other enzymes (such as cyclooxygenase 2 and 5 lipoxygenase). Its ability to regulate multiple targets and its safety for human use, made curcumin an amenable therapeutic agent for the prevention and/or treatment of various malignant diseases, arthritis, allergies, AD, and other inflammatory illnesses.[81]

Recent studies on cultured astrocytes obtained from pregnant Sprague-Dawley (SD) rat and neonatal 0–2-day-old SD rats showed improved neuronal survival by curcumin treatment in NMDA toxicity through the activation of PI3K/MAPK signaling pathways.[82] Studies employing surface plasmon resonance experiments, unraveled that the liposomes exposing the curcumin derivative (maintaining the planarity) demonstrate considerable affinity for Aβ1-42 fibrils (1–5 nM), through the exhibition of multivalent interactions, thus opening an amenable therapeutic avenue unlike the nonplanar curcumin.[83]

Conclusion

There have been manifold studies to combat this dreadful neurodegenerative disorder for a few decades. Although a few drugs are available today for the management of AD and many plants and their extracts are extensively employed in animal studies and AD patients, yet no substantial drug or plant extract is able to reverse the AD symptoms adequately. The intervention of phytotherapy, which entails the use of herbal medicines may be a potential corner stone based on which treatment strategies can be streamlined.[14,84-86] It is tangible that there has been augmenting need for such therapeutic intervention.

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