



Role of indigenous medicinal plants in neurodegenerative diseases with special attention to treat alzheimer's disease and associated symptoms

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ABSTRACT-

Neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), are characterized by progressive loss (and even death) of structure and function of neurons, and have created great burden to the individual and the society. The actual cause of various neurodegenerative diseases still remains a mystery in healthcare. Some of the commonly studied showed that the causes for neurodegenerative diseases are protein degradation, oxidative stress, inflammation, environmental factor, mitochondrial defects, familial history, and abnormal protein accumulation in neuron. Medicinal plants like Withaniasomnifera (ashwagandha), Ginseng, curcumin, resveratrol, Baccopamonnieri, Ginkgo biloba, and Wolfberry have been applied to prevent or alleviate neurological diseases and relief of neurological symptoms reported in in vivo or in clinical trails. This review is a study to understand the role of herbal drugs and the pathophysiology of the disease along with this study indicated the presence of various bioactive compounds in herbs and discussed various mechanisms that have been implicated, including inflammation, anti-oxidant effects, anti-amyloidogenic, mitochondrial dysfunction and changes in protein clearance in treatment of Mild to Moderate Alzheimer's Disease.

KEYWORDS-Alzheimer's Disease , Withaniasomnifera, clinical trails, pathophysiology

INTRODUCTION-

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

Alzheimer's disease (AD) is a progressive, irreversible neurological disorder that occurs gradually and results in memory loss, unusual behavior, personality changes, and loss of the ability to thinking. ^[1]Alios Alzheimer in 1907, noticed abnormal changes in the brain tissue of a 51 year old woman Auguste Deter, who had died of an unusual mental illness^[2]. After she died, he inspected her brain and found some abnormal clumps called as "Amyloid Plaques" and tangled bundle called "neurofibrillary tangles" or "tau". It is estimated to affect 15 million people worldwide. AD is the cause of dementia in the elderly. AD is a progressive neurological disorder with duration of around 8.5 years between onset of clinical symptoms and death ^[3].

AD starts with loss of short term memory, forgetting names and addresses, as this condition progresses, the change become more marked and even individuals forget the home way. Unfortunately, AD has not any cure but can be prevented from progressing. Seventy percent of causes for AD is genetic and 21% is environmental. Most cases of Alzheimer's, approximately 95%, are the late-onset form, which develops after age 60. ^[4]

Brain areas associated with cognitive functions, particularly the neocortex and hippocampus, are the regions that mostly affected by the pathology which is characteristic of AD^[5].

The main cure for AD is pharmacological treatment. Pharmacological treatment strategies in AD include three categories of drug: 1) their mechanism is based on disease-modifying therapies such as vitamin E; 2) their mechanism is based on compensation of neurotransmitter such as a cholinesterase inhibitor; 3) psychotherapy factors that are prescribed for symptoms of conduct disorder^[6].

Although recently several synthetic drugs have been introduced to treat learning and memory disorder, but their therapeutic effects is low and most of them have undesirable side effects. Herbs and herbal remedies have a long history of traditional use and appear to be safe and effective, they have unfortunately received little scientific attention. Medicinal plants have great potential as part of an overall program in the prevention and treatment of cognitive decline associated with AD. This review provides the description of medicinal plants that possesses promising role in Alzheimers disease.

PREVALENCE-

It has been observed from different literatures worldwide 56.1 million people are affected Alzheimers disease. It is also estimated that 0.7% of the global population have suffered dementia^[7], with over 60% living in low and middle income countries. As the proportion of older people in the population is increasing in nearly every country, this number is expected to rise to 78 million in 2030 and 139 million in 2050. It is also studied that 6.2 million American population over age 65 are living with Alzheimer's In 2021. 72% people are of age 75 and above^[8]. The prevalence of Alzheimer's disease in Europe was estimated at 5.05%. The prevalence in men was 3.31% and in women 7.13% and increased with age^[9]. The prevalence in India According to the 2020 report is 5.3 million, above age 60 and this number is likely to exceed 14million by 2050^[10].

ETIOLOGY-

The pathogenic process that causes Alzheimer's has not been fully described, however, it clearly leads to neuropathology specified by amyloid plaques, neurofibrillary tangles, and loss of cholinergic neurons. It has also been observed that both Genetic and Environmental factors played a vital role in the manifestation of AD^[11]. Early onset Alzheimer's caused by mutations in amyloid precursor protein, presenilin-1 and presenilin-2 genes^[12]. The majority of Alzheimer's cases are sporadic in terms of risk factor profile^[13]. Genetic factors, including mutations in the amyloid precursor protein and the both presenilin genes, appear important in the development of early-onset Alzheimer's, whereas the apolipoprotein E influences after age 65. Genetic factors may accelerate deposition of beta-amyloid protein to form plaques, as well as abnormal phosphorylation of tau protein to form neurofibrillary tangles. Several biochemical factors, such as inflammation, oxidative stress, and hormonal deficiency such as estrogen, and other risk factors, primarily aging, also play a vital role in the pathogenic process. The loss of neurons and synaptic connection causes deficiencies in cholinergic and other neurotransmitter systems, leading to cognitive dysfunction, psychiatric and behavioral disturbances, and eventual loss of ability to understand. The etiology of AD are highly complex and more effective therapeutic approaches than those currently available will be needed to address these underlying factors more specifically.

PATHOPHYSIOLOGY-

Hippocampus plays a critical role in learning and memory, which is a complex biological process including the acquisition, consolidation and retrieval of information.^[14] Neurogenesis in the hippocampus, defined as the generation of new nerve cells, is involved in memory formation. Increased neurogenesis is improved spatial memory while impaired neurogenesis indicates poor cognitive function.^[15] Changes in brain's structures, visible differences in brain tissue in form of misfold protein called "plaques", and neurofibrillary tangles. Those plaques and tangles work together to breakdown the brain's structure. Plaques arise when another protein in the fatty membrane surrounding nerve cells gets sliced up by a particular enzyme resulting beta-amyloid proteins, which are sticky and have a tendency to clump together, that clumping is what forms the plaque^[16]. The clumps blocks signalling and therefore communication between cells disrupted and also seem to trigger immune reactions that cause the destruction and also triggers immune reactions that cause the destruction of disabled nerve cells. Neurofibrillary tangles are built from a protein known as "tau protein". The brain's nerve cells contain a network of tubes that act like a highway for food molecules, tau protein ensures that these tubes are straight, allowing molecules to pass through freely. But in Alzheimer's disease the protein collapse into twisted strands or tangles making the tube disintegrate, obstructing nutrients from reaching the nerve cell and leading to cell death.

Signs and Symptoms-

Memory impairment is the hallmark symptom of Alzheimer's disease and usually involves behaviors such as forgotten appointments, away from home, misplaced items, and repetitive questions. Along with memory problems, AD can be recognized by insomnia, anxiety, depression, disruptive behavior, and hallucinations. Several studies have found evidence that Alzheimer's disease is a disease that is caused by or is a result of decreased metabolic activity in the brain. Alzheimer's disease has been classified into three different stages and each stage has its specific symptoms. Stage One usually lasts two to four years. It involves confusion, forgetfulness, disorientation, recent memory loss, and mood changes. Stage Two often lasts two to ten years. It is typically characterized by decreased memory reduced attention span, hallucinations, restlessness, muscle spasms, reduced to perform logic, increased irritability, and increased inability to organize thoughts where as in stage three, it generally lasts one to three years with risk factors that include age, head injury, and most often involve incontinence, swallowing difficulty, the development of skin infections, and seizures^[17].

Diagnosis –

It is very important to get an early and accurate diagnosis of Alzheimer's disease in order to effectively treat it as early as possible. Alzheimer's disease can be reliably diagnosed with following tests.^[17,18]

- 1) Mental status examination to evaluate the person's thinking and memory
- 2) Laboratory tests to rule out anemia, vitamin deficiencies, and other conditions
- 3) A neurological examination
- 4) The Mini Mental State Examination (MMSE) is most commonly used to test for memory problems and contributes to a possible diagnosis of dementia.
- 5) The electroencephalogram (EEG) is a useful tool in the diagnosis of Alzheimer's. Those with the disease have a diffuse and symmetrical slowing of the brain waves that register on the EEG

Drugs used for the treatment of Alzheimers disease-

The beta-amyloid peptide, with 39 – 42 amino acid residues (BAP), plays a significant role in the development of AD. Although there is no cure for AD, it can be managed with the available drugs, to some degree. Several studies have revealed that natural antioxidants, such as vitamin E, vitamin C, and beta-carotene, may help in scavenging free radicals generated during the initiation and progression of this disease. The loss of memory is considered to be the result of a shortage of the nerve transmitter acetylcholine. It is possible to increase the level of this transmitter in the brain by inhibiting the activity of the enzyme acetylcholinesterase, which splits or breaks down the transmitter substance. Drugs that inhibit the breakdown of the messenger or transmitter acetylcholine delay the development of the disease.^[18]

Galantamine (Razadyne):

This drug is used to prevent or slow the symptoms of mild to moderate AD. It is a cholinesterase inhibitor^[19]. It was extracted from botanical sources *Galanthus nivalis*^[20]. It blocks the breakdown of acetylcholine in the synaptic cleft, therefore increasing acetylcholine neurotransmission^[21]. Galantamine blocks the enzyme responsible for the breakdown of acetylcholine, thereby enhancing cholinergic neurofunctions. The therapeutic effects of galantamine may decrease as the disease progresses and some neurons remain functionally intact.

Donepezil (Aricept):

This drug is used to delay or slow the symptoms of mild, moderate, and severe AD. Donepezil is a piperidine derivative acetylcholinesterase inhibitor used in the management of the dementia of Alzheimer's Disease. It selectively and reversibly inhibits the acetylcholinesterase enzyme, which normally breaks down acetylcholine^[22,23,24,25].

Rivastigmine (Exelon):

This drug is used to prevent or slow the symptoms of mild to moderate AD. Rivastigmine is a parasympathomimetic and a reversible cholinesterase inhibitor. An early pathophysiological feature of Alzheimer's disease that is associated with memory loss and cognitive deficits is a deficiency of acetylcholine as a result of selective loss of cholinergic neurons in the cerebral cortex, nucleus basalis, and hippocampus.

Memantine:

Memantine is an NMDA (N-methyl-D-aspartate) receptor antagonist used to treat moderate to severe dementia in Alzheimer's Disease. It is normally employed in the management of Alzheimer's disease. Memantine blocks the effects of glutamate, a neurotransmitter in the brain that leads to neuronal excitability and excessive stimulation in Alzheimer's Disease^[26,27].

Medicinal indigenous herbs to treat Alzheimer's disease

Ashwagandha (Withaniasomnifera): Ashwagandha, commonly called as winter cherry, is one of the well known herbs prescribed as a brain restorer for AD. It is found in Native to dry regions of India, Northern Africa and the Middle East. It is prescribed to increase energy, improve health and longevity, and as a nerve tonic^[28, 29, 30]. Ashwagandha contains several bioactive compounds such as withanolides A-Y, dehydrowithanolide-R, withasomniferin-A, Withanone, Withaferin-A, withasomniferone, withasomniferols

A-Cand others. Other constituents include the phytosterolssitoinosides VII-X and beta-sitosterol and alkaloids [31, 32] the medicinal properties are like antioxidant, anti-inflammatory, blocks A β production, inhibits neural cell death, dendrite extension, neurite outgrowth and restores synaptic function, neural regeneration, reverses mitochondrial Dysfunction, improves auditory–verbal working memory, executive function, processing speed, and social cognition in patients [31].

Brahmi (Bacopamonnieri):

Brahmi, or Bacopamonnieri is a perennial creeper medicinal plant found in the damp and marshy wetlands of Southern and Eastern India. In the Ayurvedic system of medicine, Brahmi is recommended for mental stress, memory loss, insomnia, and asthma. The bioactive phytochemicals present in this plant include saponins, bacopasides III, IV, V, bacosides A and B, bacosaponins A, B, C, D, E, and F, alkaloids, sterols, betulinic acid, polyphenols, and sulfhydryl compounds, which may be responsible for the neuroprotective roles of the plant [32, 33, 34]. The neuroprotective actions and positive effects of bacoside A on memory, mental, and intellectual functions can be largely attributed to its ability to reduce beta amyloid aggregation and toxicity. Promising indications for use in humans include improving cognition in the elderly and in patients with neurodegenerative disorders. Bacopa is considered by some authors as a kind of “bulletproof vest” against Alzheimer’s disease [35]. It causes antioxidant, anti-inflammatory, improves memory, attention, executive function, blocks A β production, inhibits neural cell death, delays brain aging, improves cardiac function [36, 37].

Ginkgo Biloba : Ginkgo biloba also known as Maidenhair tree, whose origins date back to 250 million years ago to the Permian period. Ginkgo Biloba extract, derived from the leaves of the Ginkgo biloba tree, is often used as a memory aid or memory enhancer. But it appears unlikely that Ginkgo biloba extract can slow or prevent age-related memory problems linked with mild cognitive impairment or Alzheimer's disease. The extracts of Gb leaves have been used since antiquity in traditional Chinese medicine to treat various diseases. All clinical studies use Ginkgo biloba extract that contains a combination of flavonoid glycosides, terpene lactones, and ginkgolonic acids [38]. Ginkgo biloba extract has shown beneficial effects in treating Alzheimer’s, cardiovascular diseases, premenstrual syndrome, cancer, asthma, tinnitus, and other age-related disease [39, 40]. Nowadays, extracts of this plant are used in Europe, especially in Germany and France, for the treatment of memory and concentration problems, depressive anxiety disorder, dizziness, headache, and many other issues [41]. It produces antioxidant, improves mitochondrial function, stimulates cerebral blood flow, blocks neural cell death, stimulates neurogenesis [42].

Curcuma Longa:

Curcuma longa of the ginger family belongs to Zingiberaceae and has anti-inflammatory activity which is associated with reduced Alzheimer’s risk [43]. It is most likely to reduce deposition of Amyloid plaques in the brain. It decreases oxidative stress. The active constituents of turmeric are turmerone oil and water-soluble curcuminoids. Curcuminoids include curcumin, demethoxycurcumin (DMC), bisdemethoxycurcumin (BDMC), and cyclocurcumin [65]. Curcumin is the principal. Recent studies showed that in Southeast Asian countries where turmeric is frequently utilized in diet there are 4.4-fold lower cases of Alzheimer. A study reported that low doses of Curcumin reduced A β (Amyloid-Beta) level up to 40% in mice with Alzheimer’s disease as compared to control drug. Another study indicates that anti-inflammatory property of turmeric is correlated with a decrease in Alzheimer risk [44]. It produces antioxidant, anti-inflammatory, antimicrobial, blocks A β production, inhibits neural cell death [45].

Centella asiatica (gotu kola):

Centella asiatica belongs to the Apiaceae family and is found throughout India, also in Sri Lanka and Bangladesh. It contains various bioactive compounds such as triterpenes, asiatic acid, asiaticoside, adenoside, saponins, glycosides, madecassic acid, and centelloside. Asiatic acid and asiaticoside showed to reduce

hydrogen peroxide-induced cell death, decline concentration of free radicals, and β -amyloid cell death inhibition in vitro which suggested possible role in Alzheimer's disease treatment and β -amyloid toxicity prevention. Extracts of *Centella asiatica* reversed the β -amyloid pathology in mice brains and modulated oxidative stress response components. It is an important plant for nerve and brain cells and is considered being capable of enhancing intellect, memory and longevity [70]. It causes neuroprotective, cognitive, reduces oxidative stress, $A\beta$ levels, and apoptosis, promotes dendritic growth and mitochondrial health, improves mood and memory [46,47].

***Convolvulus pluricaulis* (shankhpushpi):**

Convolvulus pluricaulis known as shankhpushpi is an herb found in India and Burma. It belongs to the convolvulaceae family and is used for treatment of hypertension, neurodegenerative diseases, ulcers, blood pressure, epilepsy, diabetes, sun stroke [48]. A study has shown that aqueous extract and ethyl acetate of *Convolvulus pluricaulis* increases memory functions and learning abilities. [49, 50] This plant has been reported to calm nerves by regulating stress hormone synthesis like cortisol and adrenaline in the body. Ethanol extract of this plant also significantly improved learning abilities and memory retention in rats. The plant promotes cognitive function, slows brain aging, antioxidant, anti-inflammatory [51,52].

***Glycyrrhizaglabra*:** commonly known as Licorice, is a flowering plant of the Fabaceae family. This plant is a perennial legume native to Western Asia, North Africa, and Southern Europe. [53] It contains various bioactive compounds which include linalool oxide, geraniol, benzoic acid, terpinen, tetramethylpyrazine, propionic acid, ethyl linolenate, butanediol, ferulaldehyde, methyl ethyl ketone, furfurylformate, trimethylpyrazine, glycyrrhizin, tannin, and glycyrrhizic acid. Memory enhancing activity of this plant was found in scopolamine induced dementia [54, 55, 56]. *Glycyrrhizaglabra* appears to be a promising drug for improving memory in the management of impaired learning, Alzheimer's disease, and other neurodegenerative disorders [57]. It boosts memory.

***Magnolia officinalis*:** *Magnolia officinalis* commonly known as Giloy, it is a species of *Magnolia* native to the mountains and valleys of China. It belongs to the family magnoliaceae and improves scopolamine induced memory deficits. It is used for the treatment of anxiety, asthma, depression, gastrointestinal disorders, headache, and more [61]. It inhibits acetyl cholinesterase activity. Magnolol and honokiol derived from *Magnolia officinalis*, have the ability to enhance choline acetyltransferase effects. [58] also inhibits the acetylcholine cleavage and has been seen to release acetylcholine from hippocampus. Honokiol exhibits anti-inflammatory activity by reactive oxygen species synthesis inhibition. Anti-inflammatory and antioxidant activity of *Magnolia officinalis* plays a significant role in the Alzheimer treatment [59]. It produces anti-inflammatory, antioxidant, treats anxiety.

***Triphala*:** *Triphala* is an Ayurvedic herbal rasayana formula in combination of three fruits or three myrobalans, namely *amalaki* (*Emblica officinalis*; *Phyllanthusemblica*), *bibhitaki* (*Terminalia bellerica*), and *haritaki* (*Terminalia chebula*). They are usually mixed at a 1:1:1 ratio. *Triphala* is the therapeutic herb of choice for the treatment of several metabolic diseases, dental issues, skin conditions, eye diseases, fat loss, heart conditions, hypercholesterolemia, colon issues. *Triphala* contains powerful anti-inflammatory compounds that may help protect against certain cancers and other chronic diseases. *Triphala* is a rich source of vitamin C and contains phenols, tannins, and other compounds that have anti-cancer properties. Furthermore, it suppresses neurodegeneration in fly models of Huntington's and Alzheimer's diseases, thereby revealing its broad therapeutic potential [60]. It is having antioxidant, anti-inflammatory, immunomodulation, prevents dental caries, antibacterial, antiparasitic, reverses metabolic disturbances.

Saffron (Crocussativus):

Saffron is a spice derived from *crocus sativus*. It is crimson-colored and is widely cultivated in Iran, India, and Greece. In addition to its usage in the textile and cosmetic industries, saffron is also recommended for its medicinal properties.^[61] The major component of saffron is safranal, a carboxaldehyde. In vitro and in vivo studies show that the phytochemicals present in saffron possess antioxidant, anti-inflammatory, and anti-amyloidogenic properties. Several analyses revealed that saffron significantly improves cognitive function measured by the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and Clinical Dementia Rating Scale-Sums of Boxes (CDR-SB), compared to placebo groups^[62]. It produces antioxidant, anti-amyloidogenic, anti-inflammatory, antidepressant, immunomodulation action^[63].

Genes/Enzymes/Proteins Responsible for the disease:

Alzheimer Disease (AD) Genes:

Loci	Gene Symbol	Gene Name	Chromosome	Inheritance
AD1	APP	Amyloid precursor protein	21q21	Autosomal Dominant
AD2	APOE	Apolipoprotein E	19q13.32	Sporadic
AD3	PSEN1	Presenilin 1	14q24.2	Autosomal Dominant
AD4	PSEN2	Presenilin 2	1q42.13	Autosomal Dominant

Genes has been identified as possibly contributing to an increased risk of Alzheimer's disease is the e4 allele of Apolipoprotein E gene or APOE-e4. Apolipoprotein E helps breakdown beta-amyloid but the e4 allele seems to be less effective than the other alleles, like the APOE-e2 allele, the patients are more likely to develop beta-amyloid plaques.

Familial Alzheimer's disease accounts between 5 and 10% of cases and can be caused by several gene mutations. First mutation is the Presenilin-1 or Presenilin-2 genes on chromosome 14 or chromosome 1 respectively, have been linked to early-onset Alzheimer's disease. These genes encode for Presenilin-1 or Presenilin-2, Both protein subunits of gamma-secretase.

Mutations in these Presenilin-1 or Presenilin-2 genes can change the location where Gamma secretase chops Amyloid precursor Protein, producing different length Beta amyloid molecules, which seem to be better at clumping up and forming plaques.

Conclusion

Important neuropathological features of AD include deposition of amyloid plaques in brain tissue and meningeal blood vessels as well as presence of neurofibrillary tangles in the hippocampus and the cerebral cortex of the brain. Herbs may play a promising role in the early treatment of Alzheimer's and other conditions involving poor memory and dementia. One of the chief benefits is that they have a low toxicity compared to pharmaceutical agents. It has been observed from the herbs and pathophysiology that a comparison study is required as per the use of herbal medicines along with current available drugs in the treatment of AD. Further large-scale, research studies are required to determine the effectiveness of some indigenous herbs in the cognitive deterioration of AD.

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