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Review Article

Medicinal plants effective against Alzheimer's disease: An update

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ABSTRACT

Alzheimer's disease (AD) is a memory-related neurodegenerative disease that affects individuals as they grow older. AD is highly devastating; beginning with memory problems and progressing to total dependency and failure to perform daily activities. Several trials have been conducted in order to discover therapeutic approaches for AD, however, the proper cure is still unavailable. Late initiation of AD drugs is argued to decrease their efficacy. While AD has no cure, symptomatic therapy can help with memory and other dementia-related issues. Due to the complexities of the underlying pathologies, the lack of disease-modifying medications necessitates the production of newer medicinal agents and various target-based techniques. Many herbs and herbal formulations have been used for memory and cognitive enhancement in the past, and many of them have been researched thoroughly in the last few years for therapeutic efficacy in AD. The effectiveness of most herbs and plants has been confirmed in clinical trials and has been chemically tested. This study will concentrate on recent scientific results on the effectiveness of different plants in the management of AD based on their memory boosting, neuroprotective, antioxidant, and anti-inflammatory effects.

1. Introduction

The word 'herb' refers to each and every part of the plant. The use of plants for medicinal purposes dates back to as early as 4000 years ago. Due to their minimal side effects, treatment with medicinal plants is considered safe. The contribution of plant drugs is as high as 80% from India and China. Medicinal herbs are now essential sources for pharmaceutical production. More than 75% of the global population depends mainly on plants/plant extracts for their health care needs.[1] With the introduction of AYUSH (Department of Ayurveda, Yoga, and Naturopathy, Unani, Siddha, and Homeopathy) as early as 2003, not only equal importance was given to the natural way of treating various diseases but also the research and development was geared up in the above fields. One of the main objectives is to improve the current research institutions and to ensure a time-bound research program on diseases. In India's AYUSH programs, over 8,000 herbal remedies have been codified.[2] Out of the several diseases targeted by these medicinal herbs, we are concentrating this review on Alzheimer's disease.

Chronic neurodegeneration leading to Alzheimer's disease (AD) has become a major health challenge affecting over 50 million people globally with a prediction to reach 152 million by 2050.[3] Multiple factors are responsible for neuronal damage including oxidative stress and accumulation of the amyloid β (Aβ) protein in the brain. However, the biggest challenge here is in its treatment. Currently, the two classes of drugs approved to treat AD, include inhibitors to cholinesterase enzyme and antagonists to N-methyl d-aspartate (NMDA). These regimens are mainly targeted towards alleviating the symptoms and palliative effects only; not in preventing

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the neurodegeneration or initiating neuronal repairing.[4–6] Thus, the urge for novel research for treating this disease is imperative. And here comes the medicinal plants which are the important leads for drug development against AD. Though their mechanism of action is yet to be elucidated, phytochemical studies have revealed that they have a wide spectrum of pharmacological activities like antioxidants, anti-inflammatory, anti-cholinesterase, anti-amyloidogenic and hypolipidemic effects.[7] Traditionally, several herbal preparations are used to enhance the cognitive activity of the elderly. Researchers have turned to phytotherapy due to a lack of new treatment approaches and strategies for AD.[8] Several clinical and in vivo experiments have been performed to assess the magnitude and true potentials of certain medicinal plants that are thought to enhance memory, identify biologically active constituents, and reveal the underlying pathways. This study will focus on the most current scientific results on the potential of a variety of medicinal plants in the treatment of AD.

2. Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disease that mostly affects the elderly. Alois Alzheimer, a German neuropathologist and psychiatrist, discovered AD in 1906. AD is characterized by memory loss, decreased speech function, performance impairment, disorientation, behavior deterioration, gait irregularities, and thought slowness.[9] Extreme depression is a condition that resembles the condition. The accumulation of oxidative damage to nucleic acid, protein, and mitochondria in the brain causes cognitive and neurological impairment. Patients aged 65 to 74 years old had a prevalence of 3.0 percent, while people aged 85 years old had a prevalence of 47.2 percent.[10] Due to duplication or mutation of β -amyloid precursor proteins (APP) and a presenilin-encoding gene for proteolytic enzymes, AD is characterized by elevated neurofibrillary tangles and β-amyloid levels. Brain neurodegeneration and β-amyloid (Aβ) deposition are used as biomarkers to identify people at risk of AD. Neurodegenerative diseases are caused by a combination of environmental and genetic causes, as well as aging. AD begins with changes in normal brain functions, first with an inability to produce new memory due to the difficulties of consolidating new memory, which contributes to rapid forgetting.[11] Plaques develop, which are then accompanied by inflammation, a loss of cholinergic function, and stress. Some changes in the microglia induce inflammation in the central nervous system (CNS), which raises the risk of neurological aging and AD. Antioxidant enzymes normally counteract oxidative stress in a natural physiological state, but in AD, these enzymes fail to fulfill their normal function in the brain. Pathology of AD progresses from the perirhinal zone to the hippocampus complex, then to the temporal lobes with the basal forebrain.[12] AD is predominantly concerned with emotions, and it has an impact on both patients' and caregivers' quality of life. Good or detrimental improvements in behavior are important criteria for determining the quality of life in Alzheimer's patients. Aging, genetics, education, ethnicity, and the apolipoprotein E ε4 allele, all play a role in the development of AD.[13] AD and dementia are exacerbated by cardiovascular disease, diabetes, and smoking. Current approaches focus on helping people manage behavioral symptoms, maintain mental function, and slow or delay the symptoms of the disease. Researchers hope to develop therapies targeting specific genetic, molecular, and cellular mechanisms so that the actual underlying cause of the disease can be stopped or prevented. Targeting neuritic plaques (NPs) and neurofibrillary tangles (NFTs), which have the ability to prolong neurodegeneration, is the future of AD care.[14]

2.1. Causes

Two major hypotheses have been proposed as a cause of AD viz. Cholinergic & Amyloid hypothesis.

2.1.1. Cholinergic hypothesis

Acetylcholine (Ach) synthesized from acetyl coenzyme A and choline catalyzed by the enzyme acetylcholinesterase, in the cytoplasm of cholinergic neurons and transported to the synaptic vesicles. Ach serves vital roles in the brain like sensory information, memory, attention, and learning. Degeneration of these cholinergic neurons leads to cholinergic synaptic loss and amyloid fibril formation leading to derangement in memory and cognitive function.[15,16]

2.1.2. Amyloid hypothesis

A strong correlation exists between dementia and the deposition of amyloid β (Aβ) protein in the central nervous system. The degradation of this protein by the enzyme secretase is diminished either by age or pathologically leading to the formation of amyloid fibrils which leads to neuronal cell death and neurodegeneration.[17–19]

2.2. Pathogenesis

Patients with AD have two distinct characteristics in their brains.

1. Extracellular deposits of amyloid-beta (Aβ), a peptide formed by the breakdown of Aβ precursors (genetic locus 21q21–22), can be found in senile plaques. Abnormal deposit of Aβ has also been found in blood vessels.[20]
2. People with AD have neurofibrillary tangles, which are thick clusters of irregular fibers in the cytoplasm of neurons made up of an altered version of the microtubular-associated protein.[21]

2.3. Stages of AD

1. Pre-symptomatic: mild memory loss with no functional impairment of routine activities
2. Early: the appearance of several symptoms with loss of concentration and memory.
3. Moderate: increased memory loss and difficulty in reading, speaking, writing, and recognizing the family members, with the disease spreading in the cerebral cortex
4. Severe: complete cognitive impairment due to accumulation of neuritic plaques proving fatal[22–25].

2.4. Risk Factors

A recent review has identified more than 50 environmental risk factors.[26] Armstrong RA in his review has grouped the various risk factors under broad categories as in the tabular column below.[27]

The genetic and environmental factors increase the release of oxygen free radicals thereby aggravating normal aging.[28]

S. No.	Grouping	Risk factors
01	Demographic	Age, Education, Gender Race, Social class
02	Genetics	Amyloid precursor protein (APP), Presenilin 1 and 2 (PSEN1/2), Apolipoprotein E (APOE), ATP-binding cassette transporter A1, (ABCA1), Adaptor protein evolutionarily conserved signaling intermediate in Toll pathway (ECSIT), Clusterin gene (CLU), Estrogen receptor gene (ESR), Fermitin family homolog 2 gene (FERMT2), Glyceraldehyde-3-phosphate dehydrogenase (GAPDH), Histocompatibility locus antigen (HLA class III), mtDNA haplotype Transferrin gene (Tf), Triggering receptor expressed on myeloid cells 2 (TREM 2), Vascular protein sorting-10 domain (VpS10) genes, Vitamin D receptor gene (VDR), Epigenetic factors
03	Lifestyle	Alcohol, Lack of exercise, Lack of cognitive activity, Malnutrition, Poor diet, Smoking
04	Medical	Cancer, Cardiovascular disease, Congestive heart failure, Immune system dysfunction, Micro-infarcts, Obesity, Poor cholesterol homeostasis, Poorly controlled type-2 diabetes, Stroke, Traumatic brain injury
05	Psychiatric	Depression, Early stress
06	Environmental	Air pollution, Calcium deficiency, Geographic location, Metals (especially aluminium, copper, zinc), Military service, Organic solvents, Occupation, Vitamin deficiency
07	Infections	Bacteria, e.g. Chlamydophila pneumonia, Treponema, Dental infections, Fungi, Viruses

2.5. Diagnosis

It is important to get an early and correct diagnosis of AD so that treatment can begin as soon as possible. To increase the chances of living a normal and stable life, these herbal therapies should begin as soon as possible after diagnosis (along with daily brain exercises).[29]

A Comprehensive analysis that contains the following examinations will correctly detect AD:[30]

1. A detailed medical and mental history is needed
2. A neurological examination
3. Anemia, vitamin deficiency, and other disorders may all be ruled out of laboratory testing
4. A mental status assessment is used to assess a person's ability to think and remember
5. Having a conversation with family members or caregivers

3. Herbal Treatment

In recent years, interest in herbal medicine has grown, resulting in expanded research interest in the therapeutic use of plants to cure illness and improve health, often without causing major side effects. Herbal medications and herbal ingredients are among the world's oldest treatments. Medicinal plants have been used by all cultures throughout history. In the current situation, the market for herbal products is increasing exponentially all over the world.[6]

Herbs with anti-inflammatory and antioxidant properties can be useful in the treatment of AD. Acetylcholine deficiency is common in Alzheimer's patients. German chamomile, licorice, turmeric, and white willow bark are anti-inflammatory herbs that can help to reduce inflammation of the brain tissue in AD. Acetylcholine is a neurotransmitter that is essential for cognitive function and reasoning. Mild-to-moderate AD, a chronic form of dementia, has abnormally low acetylcholine concentrations in the brain. This suggests that any substance that improves the cholinergic pathway in the brain may be beneficial in the treatment of AD and other brain disorders. The herbs that inhibit Acetylcholinesterase (AchE) contain natural COX-2 inhibitors, also reported as medicinal herbs, for AD indication.[31]

Due to the lack of a sufficient number of treatment options, the management of AD has remained a major concern for medical research over the years; only a few drugs have been developed and accepted by the US FDA as of today. Natural ingredients may be the ideal choice

Table 1: Medicinal plants used for the treatment of Alzheimer's disease

S. No.	Medicinal plants (Family)	Parts of the plant used	Bioactive constituents	Properties	Ref
01	Curcuma longa (Zingiberaceae)	Rhizome extracts	Curcumins, flavonoids, phenols	Neuroprotective, anti-inflammatory, protein hyperphosphorylation inhibitor	32
02	Ginkgo biloba (Ginkgoaceae)	Leaf extracts	Antioxidant, AChE inhibitor	Terpenes, bilobalide, ginkgolide	33
03	Bacopa monniera (Plantaginaceae)	Leaf extracts	Brahmine, herpestine	Antioxidant, antilipoxygenase	34
04	Withania somnifera (Solanaceae)	Root extracts	Sitoindosides, withaferin	Antioxidant, adaptogenic, leukotriene signaling inhibitor	35
05	Panax ginseng (Araliaceae)	Root extracts	Ginsenosides, gintonin	Neuroprotective	36,37
06	Sargassum sagamianum (Sargassaceae)	Seaweed extracts	Plastoquinon, sargachrome, sargaquinoic acid	AChE inhibitor	38
07	Crocus sativus (Iridaceae)	Dry stigma powder	Crocin, crocetin, picrocrocin, and safranin	Antioxidant, neuroprotective	39
08	Convolvulus pluricaulis (Convolvulaceae)	Leaf extracts	Ascorbic acid, flavonoids, rivastigmine, terpenoids, steroids	Antioxidant, muscarinic receptor stabilizer	40
09	Ficus carica (Moraceae)	Mesocarp extract	C-Sitosterol	Antioxidant	41
10	Psidium guajava (Myrtaceae)	Leaf and fruit extract	Linoleic acid	Antioxidant, antidiabetic	42
11	Lawsonia inermis (Lythraceae)	Leaf extract	Phytol, pseudoephedrine, aspidofractinine-3-methanol, phenol, 2,6-bis (1,1-dimethyl ethyl)-4-methyl, methylcarbamate	Antioxidant, nootropic potential	43
12	Clitoria ternatea (Fabaceae)	Leaf and root extracts	Quercetin and myricetin glycosides	Brain tonic antioxidant, muscarinic receptor stabilizer	44
13	Lavandula angustifolia (Lamiaceae)	Arial part extract	Linalool, tannins, linalyl acetate, camphor, coumarins, triterpenes, flavonoids	Antioxidant, neurotransmitter, antianxiety, hypnotic, anticonvulsant	45
14	Coriandrum sativum (Apiaceae)	Leaf extract, volatile oil	Petroselinic acid, linalool, fatty acids	Antioxidant, antidepressant, and anxiolytic	46
15	Mangifera indica (Anacardiaceae)	Leaf extract	Flavonoids, phenols	Antipyretic, antioxidant	47
16	Ferula asafetida (Apiaceae)	Whole plant extract, resins	Ferulic acid, umbelliferone, coumarins, and other terpenoids	AChE inhibitor, antioxidant activity	48
17	Saururus chinensis (Saururaceae)	Whole plant extract	Flavonoids, alkaloids, α-pinene, cinnamic acid, camphene, safrole, β-caryophyllene, linalool, and humulene	Antioxidant, anti-inflammatory	49
18	Syagrus romanzoffiana (Arecaceae)	Leaf and fruit extract	Stilbenoids, flavonoids, lignans, phenols, and fatty acids	AChE inhibitor	50
19	Hancornia speciosa (Apocynaceae)	Fruit extracts	Flavonoids, phenols, tannins	Antioxidant, AChE inhibitor	51
20	Andrographis paniculata (Acanthaceae)	Active compound	Grandifloric acid, phenolic acids	AChE, BChE, and BACE-1 inhibitor	52

for producing an anti-AD drug due to their diversity of structures and functions. Secondary metabolites derived from medicinal plants have the ability to be converted into a lead molecule effective against AD, according to research. Various medicinal plants have been recapitulated in tabular form (Table 1) in this review based on their therapeutic potential to treat AD.

4. Conclusion

AD is the most common neurodegenerative disease in the world, and there are no effective medications or therapies to cure it. It encourages the discovery of new chemical entities, with medicinal plants playing a vital role as a rich source of pharmacological principles and variability. Herbs may play a promising role in the early management of AD and other conditions involving poor memory and dementia. One of the chief benefits is that they have low toxicity compared to pharmaceutical agents. The secondary metabolites of plants with flavonoids, alkaloids, and phenolic acids play a crucial role in improving regeneration and/or inhibiting neurodegeneration. These drugs may help to enhance memory in patients. Thus, the knowledge of medicinal plants helps to develop drugs in the modern medicine system.

5. Conflicts of Interest

All contributing authors declare no conflicts of interest.

6. Source of Funding

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