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Current Trends in Pharmacy and Pharmaceutical Chemistry

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Review Article

Alzheimer'S disease and It's management: A review

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia, causing memory loss, thinking problems, and behavioral changes. Its primary features are amyloid-beta (Aβ) plaques, neurofibrillary tangles of hyperphosphorylated tau formation in the brain, and the degeneration of cholinergic neurons. Current available treatments which mainly target Aβ and cholinesterase pathways, have limited effectiveness and significant side effects. This has led to a growing interest in traditional medicinal plants as a potential alternative for managing AD. These plants contain various bioactive compounds like flavonoids, polyphenols, and alkaloids. These compounds are known for their anti-inflammatory, antioxidant, and anticholinesterase properties. While their exact mechanisms are still under investigation, these pharmacological properties suggest that medicinal plants could potentially slow down the disease's progression and support cognitive function. With many plant-derived products currently under investigation, these natural therapies could become valuable complementary strategies to existing conventional treatments.

Keywords: Acetylcholinesterase, Alzheimer's disease, Dementia, Neuroprotection.

Received: 11-07-2025; **Accepted:** 03-09-2025; **Available Online**:

1. Introduction

Alzheimer's disease (AD) is a prevalent form of dementia that impairs an individual's thinking, memory, and behaviour, often disrupting daily activities. The disease was first identified in 1901 by Dr. Alois Alzheimer, a German psychiatrist who observed cognitive issues in a patient. An autopsy studies revealed a shrunken brain with damaged nerve cells, leading to the diagnosis of Alzheimer's disease.[1]

AD is a progressive neurodegenerative condition characterized by the accumulation of amyloid plaques and congophilic amyloid angiopathy, as well as the presence of tau-containing neurofibrillary tangles (NFTs) in the brain. Both amyloid plaques and NFTs must be present for a neuropathological diagnosis of AD.[2] The most harmful forms of Aβ and tau are thought to be their soluble oligomeric forms. These oligomers can spread between cells, potentially through a mechanism similar to prion diseases.[3]

According to WHO, presently around 50 million people worldwide are suffering with AD, a number projected to increase to 152 million by 2050.[4] One of the biological pathways involved in AD is the acetylcholinesterase (AChE) pathway, which plays a significant role in the gradual loss of communication between neurons.[5] A key factor in AD is the reduction of acetylcholine levels, caused by damage and loss of cholinergic neurons.[6] This decrease in acetylcholine disrupts signal transmission between nerve cells, worsening memory and cognitive decline over time.[7]

The degeneration of cholinergic neurons, particularly in the hippocampus, is considered a major cause of memory loss in AD. The abnormal functioning of the AChE pathway is a hallmark of the disease. AChE is an enzyme that breaks down acetylcholine, and targeting this enzyme is a promising therapeutic approach.[8-9] Medications like Tacrine, Donepezil, Rivastigmine, and Galantamine have been approved to manage AD symptoms by boosting acetylcholine levels.

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https://doi.org/10.18231/j.ctppc.v.7.i.3.1

However, these drugs often have side effects such as fainting, nausea, vomiting, seizures, dizziness, and diarrhea.[10] Cognitive decline similar to that seen in AD can also result from other medical conditions, including substance intoxication, infections, respiratory or circulatory issues that limit oxygen to the brain, nutritional deficits (especially vitamin B12 deficiency), brain tumors, and other related health problems.[11-12]

Phytochemical research has identified several bioactive compounds in plants, including lignans, flavonoids, tannins, polyphenols, triterpenes, sterols, and alkaloids. These compounds have a wide range of medicinal properties, such as reducing inflammation, preventing amyloid plaque formation, inhibiting cholinesterase enzymes, lowering lipid levels, and providing antioxidant protection.[13,14]

2. Pathophysiology

AD is characterized by the build-up of abnormal protein structures in the brain, specifically neuritic plaques and neurofibrillary tangles. These structural abnormalities are accompanied by a significant degeneration of neurons, particularly cholinergic neurons, which are crucial for communication between the basal forebrain and neocortex (**Figure 1**).[15]

2.1. The cholinergic hypothesis

This theory suggests that a primary cause of AD is the loss of acetylcholine (ACh), a neurotransmitter vital for memory and learning. This decline is due to the degeneration of cholinergic neurons in the Nucleus Basalis of Meynert. Since these neurons are essential for cognitive function, their early loss underscores ACh's critical role in mental processing. Beta-amyloid is also believed to worsen this deficit by damaging synaptic connections and further reducing ACh availability. Clinical studies support this theory, showing that drugs that block ACh activity can negatively impact memory in older individuals.[16]

2.2. The amyloid hypothesis

This theory focuses on the role of amyloid-beta (Aβ) peptides, which are created from the cleavage of the amyloid precursor protein (APP). Normally, APP is processed into harmless fragments. However, when APP is sequentially cleaved by beta- and gamma-secretase, it produces a toxic fragment called Aβ42. This peptide, which consists of 42 amino acids, tends to aggregate and form amyloid plaques that are neurotoxic in nature. Compared to other APP breakdown products, Aβ42 has a much higher tendency to form these harmful accumulations.[17]

2.3. The oxidative stress hypothesis

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are by-products of normal cellular metabolism. While they are necessary for certain signaling pathways, their excessive production can damage cellular components like membranes, lipids, proteins, and DNA. The brain is particularly vulnerable to this oxidative stress due to its high oxygen consumption and reliance on mitochondrial energy. Neurons, which contain large amounts of polyunsaturated fatty acids, are especially susceptible to peroxidation by ROS, leading to cell damage and death. The naturally low concentration of glutathione, a major antioxidant in neurons, further increases their vulnerability to oxidative injury.[18]

2.4. The metal ion hypothesis

Disruptions in metal ion homeostasis have been linked to various chronic illnesses, including neurological disorders and cancer. In AD, imbalances in metals, especially redox-active elements like copper (Cu) and iron (Fe) have been observed, with abnormally high concentrations of these metals detected in the brains of AD patients. Other metals, such as manganese, aluminium, and zinc, are also implicated in the pathology of neurodegenerative conditions.[19]

Table 1: Medicinal plants with Anti-alzheimer's potential

Plant Name	Family	Part Used	Therapeutic Activities	Mechanism of Action	Reference
Acorus calamus	Acoraceae	Rhizome	Memory enhancer, antioxidant, anti-inflammatory, behavior modifier	Inhibits AChE; major bioactives: α- and β-asarone	[41]
Angelica archangelica	Apiaceae	Whole plant	Cognitive enhancer, improves cerebral blood flow	Inhibits AChE; contains phytochemicals similar to AD drugs without side effects	[42]
Bacopa monnieri	Plantaginaceae	Whole plant	Antioxidant, neuroprotective, memory enhancer, anti-inflammatory	Enhances kinase activity, supports synaptic function, upregulates SOD and GSH, reduces ROS and lipoxygenase activity	[43]

Bertholettia excelsa	Lecythidaceae	Seed (nut)	Cholinergic support	High lecithin content, enhances acetylcholine concentration	[44]
Centella asiatica	Apiaceae	Leaves	Antioxidant, cognitive enhancer, stress-relieving	Inhibits Aβ aggregation, improves memory, reduces oxidative stress, improves learning and recall in Wistar rats	[45]
Collinsonia canadensis	Lamiaceae	Aerial parts	Cholinergic support, neuroprotective	Prevents acetylcholine breakdown; active components carvacrol and thymol cross blood-brain barrier	[46]
Convolvulus pluricaulis	Convolvulaceae	Root	Nootropic, memory enhancer, anxiolytic, neuroprotective	Enhances AChE activity in hippocampus, regulates stress hormone synthesis, reverses Aβ pathology, modulates serotonergic pathways	[47]
Curcuma longa	Zingiberaceae	Rhizome	Antioxidant, anti-amyloidogenic, anti-inflammatory, lipid lowering	Binds Aβ, reduces plaque formation, inhibits pro-inflammatory cytokines, lowers serum peroxides and cholesterol, improves cognition at low dose	[48]
Galanthus nivalis	Amaryllidaceae	Bulb	AChE inhibitor, anti-inflammatory, cognitive enhancer	Inhibits AChE, activates nicotinic receptors, reduces Aβ-induced cytotoxicity, improves passive avoidance and spatial memory in models	[49]
Ginkgo biloba	Ginkgoaceae	Leaves	Antioxidant, anti-apoptotic, cognition enhancer, anti-amyloidogenic	Inhibits Aβ-induced neurotoxicity, enhances SOD and GPx activity, improves oxygen delivery, scavenges free radicals, modulates ERK/JNK pathways	[50]
Glycyrrhiza glabra	Fabaceae	Root	Antioxidant, anti-inflammatory, memory-enhancing, neuroprotective	Inhibits Aβ-induced toxicity, enhances cognition, reduces oxidative stress and inflammation, protects neurons in ischemia and neuropathic pain models	[51]
Huperzia serrata	Lycopodiaceae	Aerial part	Anticholinesterase, neuroprotective, anti-inflammatory	Inhibits AChE, protects neurons from glutamate toxicity, enhances cognition in scopolamine-induced impairment, protects neuronal networks	[52]
Lepidium meyenii	Brassicaceae	Hypocotyl part	Antioxidant, neuroprotective, memory-enhancing	Reduces oxidative stress, modulates CB1 receptors, protects neuronal cells from MnCl2-induced neurotoxicity	[53]
Magnolia officinalis	Magnoliaceae	Bark	Memory enhancer, anti-anxiety, neuroprotective	Inhibits AChE; active components (magnolol, honokiol) possess antioxidant activity	[54]
Melissa officinalis	Lamiaceae	Leaves	Anxiolytic, antioxidant, anti-inflammatory, neuroprotective	Inhibits AChE, modulates cholinergic receptors, reduces agitation, interferes with β-amyloid aggregation	[55]

Panax ginseng	Araliaceae	Root	Memory enhancer, cognition enhancer, anti-fatigue	Enhances brain cholinergic function, reduces AD pathology, repairs neuronal networks	[56]
Rosmarinus officinalis	Lamiaceae	Leaves	Antioxidant, anti-inflammatory, anti-AChE, neuroprotective	Inhibits COX-2, AChE, BChE, induces NGF production, reduces NF-κB and TNF-α, counters β-amyloid-induced toxicity	[57]
Salvia officinalis	Lamiaceae	Leaves	Antioxidant, cholinesterase inhibition, anti-inflammatory, anxiolytic, antidepressant	Inhibits oxidative stress, activates muscarinic/nicotinic receptors, modulates cholinergic pathway, reduces Aβ toxicity	[58]
Tinospora cordifolia	Menispermaceae	Stem & Leaves	Memory enhancer, neuroprotective, immunostimulant	Enhances cognitive function via choline synthesis and immunostimulation	[59]
Urtica dioica	Urticaceae	Stem & Leaves	Anti-inflammatory, mood enhancer, memory support	Contains boron that boosts estrogen levels, improves short-term memory and mood	[60]
Withania somnifera	Solanaceae	Root	Antioxidant, rejuvenator, nervine tonic	Inhibits AChE, boosts SOD, catalase, GPx activities, enhances cellular energy and function	

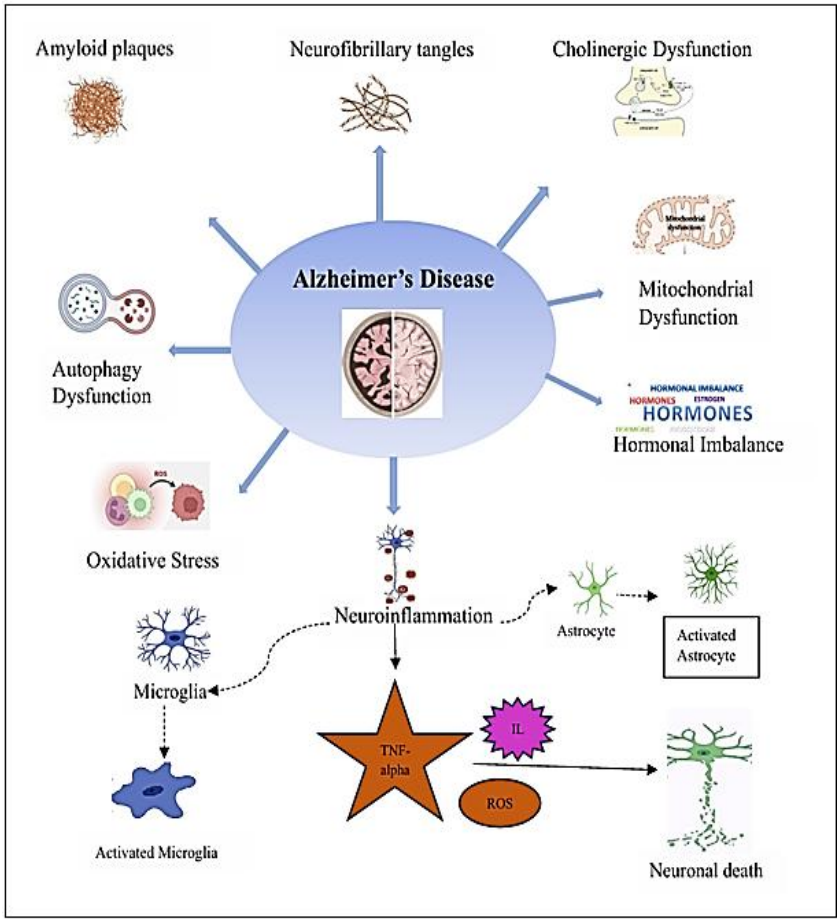

Figure 1: Pathophysiology of Alzheimer's disease

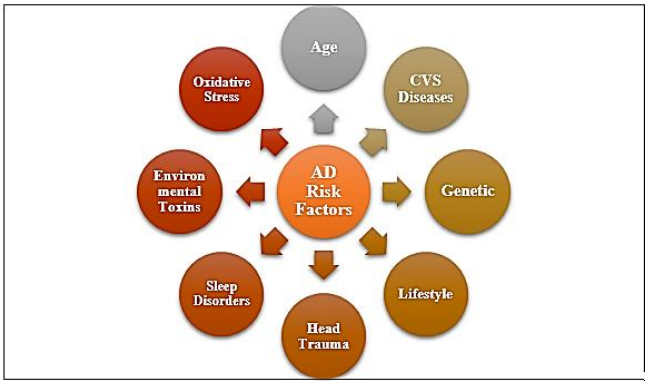

Figure 2: Risk factors of Alzheimer's disease

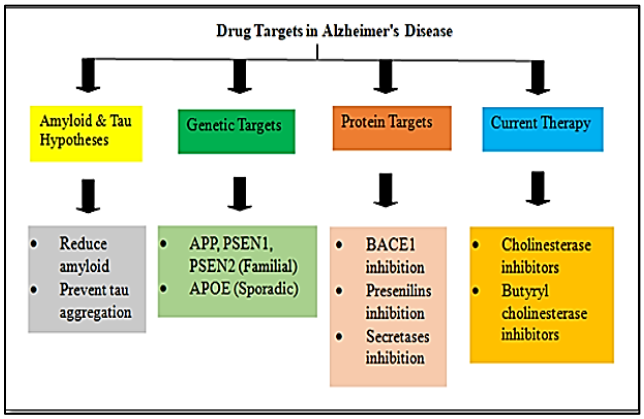

Figure 3: Drug targets in Alzhemier's disease

3. Alzheimer's Disease Diagnosis

AD is classified as a clinicopathological disorder, meaning that a definitive diagnosis requires both observable clinical symptoms and specific pathological changes in the brain. The first diagnostic criterion involves clinical manifestations, such as memory loss particularly affecting episodic memory or other cognitive, behavioral, or neuropsychiatric impairments. The second criterion is the presence of hallmark neuropathological features, specifically amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFTs) within brain tissue.

Because these structural abnormalities can only be confirmed through post-mortem examination, clinicians must rely on symptom-based assessments during a patient's lifetime, while systematically excluding other potential causes of the symptoms.[20,21] In 2012, the National Institute on Aging and the Alzheimer's Association introduced standardized protocols for post-mortem evaluation of brain tissue to confirm an AD diagnosis.[22]

Currently, neurological assessments play a critical role in the clinical evaluation of AD. Cognitive screening tools such as the Montreal Cognitive Assessment (MoCA)[23] and the Mini-Mental State Examination (MMSE)[24] are frequently used to evaluate cognitive impairment and memory decline. However, a definitive diagnosis can only be made posthumously, when the presence of Aβ plaques and tau tangles is confirmed in brain tissue.[25]

4. The stages of Alzheimer's disease

Alzheimer's disease typically progresses through four main stages:

4.1. Preclinical stage (Asymptomatic Phase)

This early phase can persist for many years and is characterized by subtle brain changes, including early damage to the cortex and hippocampus, and mild memory difficulties. However, individuals in this stage do not exhibit noticeable symptoms or impairments in daily functioning.[26,27]

4.2. Mild or early stage

Symptoms begin to emerge during this stage. Individuals may experience memory lapses, difficulty concentrating, and challenges with everyday tasks. Disorientation in time and place, mood swings, and early signs of depression are also common.[27]

4.3. Moderate stage

As the disease advances, it affects broader areas of the brain, particularly the cerebral cortex. This results in significant memory loss, trouble recognizing familiar faces, reduced self-control, and increasing difficulty with basic activities such as reading, writing, and speaking.[28]

4.4. Severe or late stage

In the final stage, widespread damage across the brain occurs due to extensive accumulation of plaques and tangles. Patients experience profound cognitive and functional decline, often losing the ability to recognize loved ones or perform basic tasks. Many become bedridden, face difficulties with swallowing, and suffer complications such as incontinence. These complications frequently lead to death.[29]

5. Risk Factors of Alzheimer's disease

Risk factors for Alzheimer's disease includes age, cardiovascular disease, genetics, unhealthy lifestyle, head trauma, sleep disorders, toxins, and oxidative stress (**Figure 2**).

6. Genetics of Alzheimer's disease

Although the majority of AD cases are sporadic, certain genetic mutations and variants significantly increase disease risk. The development of AD is influenced by a complex interplay of genetic, lifestyle, and environmental factors, with age being the most prominent risk factor. Approximately 82% of cases are diagnosed after the age of 65 and are classified as late-onset Alzheimer's disease (LOAD). In contrast, early-onset Alzheimer's disease (EOAD), which manifests before age 65 and accounts for roughly 10% of

cases, typically has a stronger genetic basis. Among EOAD patients, 35–60% report having a first-degree relative with dementia. The most well-established genetic mutations linked to EOAD are found in the APP gene on chromosome 21, PSEN1 on chromosome 14, and PSEN2 on chromosome 1.[30]

6.1. β-Amyloid precursor protein (APP)

APP is a membrane-associated protein cleaved by α-, β-, and γ-secretases. In about 90% of cases, cleavage by α-secretase precludes the formation of amyloid-beta (Aβ). However, in approximately 10% of cases, sequential cleavage by β- and γ-secretases leads to the production of Aβ40 (less toxic) and Aβ42, a more neurotoxic and aggregation-prone form. Mutations in the APP gene can increase the production of Aβ42, contributing directly to AD pathogenesis. Supporting the amyloid hypothesis, individuals with Down syndrome who carry an extra copy of chromosome 21, where APP is located frequently develop AD-like neuropathology by the age of,[40,31]

6.2. Presenilin 1 and 2 (PSEN1 and PSEN2)

PSEN1 and PSEN2 encode essential components of the γ-secretase complex responsible for cleaving APP into Aβ peptides.[34] Mutations in these genes are associated with increased production of Aβ42. Among them, PSEN1 mutations are the most common cause of familial EOAD, often leading to disease onset 8.4-14.2 years earlier than mutations in APP or PSEN2, and accounting for around 6% of EOAD cases. In contrast, PSEN2 mutations are rare (<1%) and often exhibit incomplete penetration. Other genes with low pentration have also been implicated in familial forms of AD.[32,33]

6.3. Apolipoprotein E (APOE)

The APOE gene, located on chromosome 19q13, is the most significant genetic risk factor for familial LOAD. It encodes apolipoprotein E, which plays a key role in lipid metabolism. There are three major isoforms: ε2, ε3, and ε4. The ε3 allele is the most common and is considered neutral. The ε4 allele is associated with a markedly increased risk of AD and an earlier age of onset in a dose-dependent manner. In contrast, the rare ε2 allele may offer protective effects, particularly when co-inherited with ε3. Beyond AD, APOE variants are also linked to cardiovascular and cerebrovascular diseases, age-related macular degeneration, and longevity-related traits.[34]

6.4. Inheritance patterns of AD

In autosomal dominant inheritance, a single mutated gene copy confers a 50% chance of transmission to offspring. Autosomal recessive inheritance requires two mutated copies, typically inherited from asymptomatic carrier parents. While most EOAD cases are associated with dominant mutations exhibiting high penetration, around 10% deviate from this pattern and 90% lack an identifiable mutation. Avramopoulos D. suggested that a subset of EOAD may follow a recessive inheritance model. In contrast, LOAD generally results from a multifactorial interaction of genetic susceptibility and environmental factors.[35]

7. Drug Targets

The amyloid and tau hypotheses have been central in guiding therapeutic research for AD, focusing on strategies to reduce amyloid levels, inhibit amyloid aggregation and toxicity, and prevent tau hyperphosphorylation and aggregation.[36] While familial early-onset AD is associated with mutations in the APP, PSEN1, and PSEN2 genes, the majority of AD cases are sporadic and have an unclear etiology. Among known genetic risk factors for sporadic AD, the APOE gene plays a prominent role. Proteins such as APP, APOE, BACE1, presenilins, secretases, and tau are central to AD pathogenesis,[37,38] and thus represent key targets for therapeutic intervention. Current strategies include the inhibition of BACE1, PSEN1, and various secretases. Additionally, cholinesterase inhibitors remain widely used in clinical management of AD, and research is ongoing into newer generations of acetylcholinesterase and butyrylcholinesterase inhibitors.[39] Other therapeutic approaches under investigation include hormone therapies, antioxidants, cholesterol-lowering agents, anti-inflammatory drugs, and vaccines (**Figure 3**).[40]

8. Medicinal Plants in the Treatment of Alzheimer's disease

Medicinal plants offer significant therapeutic potential in the treatment of AD due to their antioxidant, anti-inflammatory, and neuroprotective properties. As illustrated in Table 1, various herbal plants have demonstrated the ability to enhance memory, reduce amyloid-beta accumulation, and protect neuronal integrity. These plant-based compounds not only address critical pathological aspects of AD but also hold promise as complementary therapies to conventional treatments, providing safer, more accessible, and cost-effective options for the management and prevention of neurodegeneration.

8. Conclusion

Traditional medicinal plants offer a promising complementary approach to Alzheimer's disease treatment, owing to their rich content of bioactive compounds with neuroprotective properties. Although further clinical research is necessary to fully understand their mechanisms and efficacy, these natural therapies hold potential to address current treatment limitations, potentially slowing disease progression and improving quality of life for AD patients.

9. Source of Funding

None.

10. Conflict of Interest

None.

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Cite this article: Manke MB, Kalshetti MP, Giram PS, Bhusnure OG. Alzheimer'S disease and It's management: A review. *Curr Trends Pharm Pharm Chem*. 2025;7(3):79-86.