ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed ( Group -I) Journal Volume 11, Iss 10, 2022

# A SYSTEMIC REVIEW ON USE OF HERBAL MEDICINES IN THE PREVENTION AND TREATMENT OF ALZHEIMER'S DISEASE

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**Abstract:**

Alzheimer's disease, also known as dementia (AD) is a multifaceted, progressive neurodegenerative illness marked by diminished memory, personality changes, and cognitive impairment. While the specific etiology of Alzheimer's disease is unknown, new research suggests that lifestyle, food, environmental, and hereditary variables all have a role in disease progression. To present, pharmaceutical therapies have had no effect on disease progression. Over the last decade, more than 200 potential drugs have failed clinical trials, indicating that the illness and its causes are likely to be complicated. Medicinal plants and herbal therapies are gaining popularity as complementary and alternative interventions, and they can be used to produce medication candidates for Alzheimer's disease.

Indeed, the use of numerous herbal remedies and their primary polyphenols in the management of AD has been detailed in a number of scientific investigations. Alzheimer's disorder is an inescapable neurological ailment in which memory loss, cognitive decline, and ultimately dementia are brought on by the demise of brain cells. For those 65 years of age and older, it is the most frequent cause of dementia. 10% of those over 65 and 50% of those over 85 are affected by it. In the United States of America (U.S.), there are about 4 million Alzheimer's sufferers, and yearly treatment expenditures are $100 billion. It is among the top four causes of mortality in the US and is spreading to many other nations. With Alzheimer's, the size of the entire brain decreases because the tissue contains gradually fewer neuronal

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cells and connections. As a result, dementia cannot be prevented from progressing or reversed when it comes to Alzheimer's disease. The objectives of the strategy include measures for contemporary therapies in addition to an aim to enhance research into protection and therapy. Increase public knowledge and engagement, as well as your support for those who suffer from dementia and their families, in order to alleviate suffering.

**Keywords:** Alzheimer's disease, Herbal, Memory loss, Ayurveda, Ashwagandha, Brahmi, Berberine.

## 1. Introduction:

Alzheimer's disease (AD) is a dementing sickness that can only be clinically detected in its latter stages. A reliable identification based on clinical observations is difficult and often erroneous. The initial symptom is an insignificant decline in ability to recall information while still aware. Psychological ratings subsequently deteriorate, and behavioural modifications appear, followed by an improvement in difficulty speaking and writing, a limitation of visual information operations, and, lastly, motor systems break down in the form of hypokinetic conduct, but it also which is typically accompanied with hypertension. Globally, approximately 50 million people suffer dementia-related disorders (1). Alzheimer's disease (AD) (2), an uncontrolled neurodegenerative condition characterised by a decline in memory and cognitive abilities as well as a change in personality traits, affects around 2% of the population. It was named after Alzheimer, also known as Alois, who discovered illnesses for the first time in 1908. Alzheimer's disease (AD) is a disorder marked by neuronal shrinkage and minimised synapse function in the cerebral cortex and memory region of the brain. Plaques of amyloid and neurofibrillary aggregates, generally known as tau (NFTs), build through the brain as a result of the creation of misfolded protein aggregates. Alzheimer's disorder is said to be triggered by both environmental and biological factors. While dominant genetic variations account for barely any percentage of cases (3-8), over forty percent of Alzheimer's disease cases are episodic and have no previously identified genetic origin. Diabetes, cerebrovascular illness, poor diet, brain traumas, and stress have all been associated with an increased risk of dementia. Despite ubiquitous acceptance, the amyloid the hypothesis, which explains how Alzheimer's illness develops and develops, raises certain concerns. "What is the most potential drug target?" remains a contentious topic. Aside from the standard inquiry of "what is the reason of an upsurge in amyloid-(A) in spontaneous cases?" We still have no understanding how Alzheimer's disease spreads, and there are no drugs to help patients combat the disease. Alzheimer's disease, which is more often known as dementia that looks is a long-term condition which leads to memory, language, cognition, and problem-solving abilities to decrease as well as behavioural irregularities that inevitably lead to death. While forgetfulness and executive dysfunction are the most common symptoms, alterations in vocabulary and vision are often the first to manifest. Furthermore, not all forms of memory are consistently affected. Despite the fact that some Alzheimer's disease patients have significantly diminished episodic, semantic, and operational memory, long-term memory, such as procedural memories, typically remains intact (9, 10). Alzheimer's disease is therapeutically categorised into seven stages. (Table 1)

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(11) Patients frequently die 3-10 years after the onset of symptoms as a result of immobility-related complications such as pneumonia or blood clots (12). Each year, around 50 million people are affected by schizophrenia. Alzheimer's disease affects more than two-thirds of the global population. (AD), an irreversible neurodegenerative condition characterised by memory and executive function abnormalities, as well as personality alterations (13). It was named after Alois Alzheimer, who discovered Alzheimer's disease in 1906 (14). Alzheimer's disease involves synapse loss and neuronal shrinkage in the hippocampus and cerebral cortex, particularly in the hippocampus. Throughout the brain, amyloid plaque deposits and neurofibrillary tau tangles (NFTs), which are misfolded protein particles, can be found. Alzheimer's disease is thought to be caused by a combination of genetic and environmental causes. While there are a few cases where inherited gene changes are to blame, the vast majority of Alzheimer's cases are unplanned and have no known genetic basis. Diabetes, cardiovascular disease, poor dietary habits, brain damage, and stress are all risk factors for dementia. The amyloid hypothesis, largely accepted as the main explanation for how Alzheimer's disease originates and progresses, faces a number of difficulties. It is noticeably ambiguous "what is the most viable drug target?" and "what is the stream of amyloid- (A) rise in unplanned cases." We still lack a fundamental knowledge of how Alzheimer's illness develops, as well as drugs to help people fight the condition. Alzheimer's disease is a lifelong neurological disorder that causes losses in memory, language, mental processes, and problem-solving abilities, as well as behavioural changes and rates of mortality. While difficulties with memory and executive functioning limitations are the most noticeable signs and symptoms, they are usually preceded by changes in language and vision (15). Furthermore, not all forms of recollection are affected equally. Even while Alzheimer's patients have significantly reduced episodic, semantic, and functional memory, long-term memory, such as procedural memories, is typically intact. (16). Patients frequently die 3-10 years after the onset of symptoms from immobility-related problems such as pneumonia or blood clots. Alzheimer's disease affects over 50 million people worldwide (17). Alzheimer's disease (AD), which affects around 2% of the population, is an incurable neurological ailment that causes memory and cognitive issues as well as personality conflicts. It was named after Alois Alzheimer, who defined Alzheimer's disease for the first time in 1906. Alzheimer's disease is characterised by hippocampus and cerebral cortex synapse loss and cellular atrophy. Through the brain, plaques of Amyloid and neurofibrillary tangles of tau (NFTs), which are clusters of misfolded proteins, can be detected. Alzheimer's disease is thought to be controlled by both environmental and hereditary factors. While dominant genetic variations are responsible for a limited percentage of cases , the great majority of AD cases are sporadic and lack a clear genetic basis. Diabetes, cerebrovascular illness, poor diet, brain injury, and stress are all environmental and metabolic factors that enhance the incidence of dementia. The amyloid hypothesis, which is widely recognised as to how Alzheimer's disease develops and progresses, has a variety of obstacles. The queries of "what is the best drug target?" and "What is cascade of the amyloid-(A) increase in spontaneous cases?" went responded. We still cannot comprehend how Alzheimer's disease expands, and there are no medication available to assist patients fight it. (18) Alzheimer's, also known as AD, is an

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incurable brain disorder that wreaks havoc on memory, language, mental processes, and problem-solving ability, as well as causing behavioural abnormalities and death. While memory loss and executive dysfunction are the most typical signs, they are generally preceded by changes in language. Additionally, not all forms of memory are affected differently. Patients who suffer from Alzheimer's condition have substantially decreased episodic, semantic, and working memory, although permanent memory, such as procedural memory, is preserved. Alzheimer's disease is classified into seven clinical stages. (Table 1). Patients often die three to ten years after the onset of symptoms from complications related to immobility, such as infections or blood thrombosis. (19)

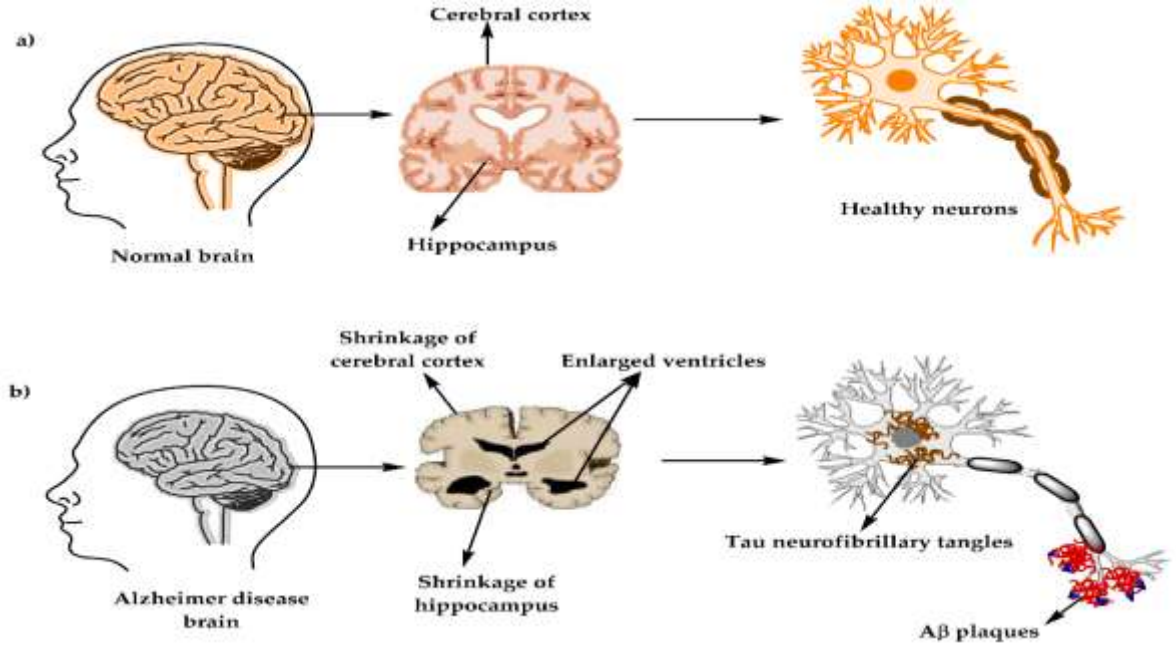


**Figure 1.1.**The physiological structure of the brain and neurons in (a) a healthy brain and (b) an Alzheimer's disease (AD) brain.

## 2. Pathophysiology of AD

Neuronal reduction and/or deviations can be seen in the area of the hippocampus, amygdala and entorhinal cortex in the brain, as well as cortical in nature in nature relationship regions of the forward, temporal, and The parietal cortices, as well as subcortical cells like the serotonergic dorsal raphe, noradrenergic sensory coeruleus, and the cholinergic nerve fundamental nucleus. Tangles form in a methodical manner, beginning in the trans-entorhinal the hemisphere and progressing to the entorhinal cortex, followed by the CA1 region of the hippocampus, and lastly the area of cerebral associative areas, where both parietal and frontal lobes are particularly severely harmed. The extent and orientation of tangle development, which is far greater than the amount of amyloid plaques, closely correlates with the severity of dementia. The buildup of protein known as tau has been correlated to mental decline and shrinking of the brain, particularly sector shortening. Axon loss and hyperplasia in the temporofrontal cerebral cortex produce inflammation and the creation of amyloid plaques, as well as an erroneous cluster of DNA disintegration and tangled strands of filaments.

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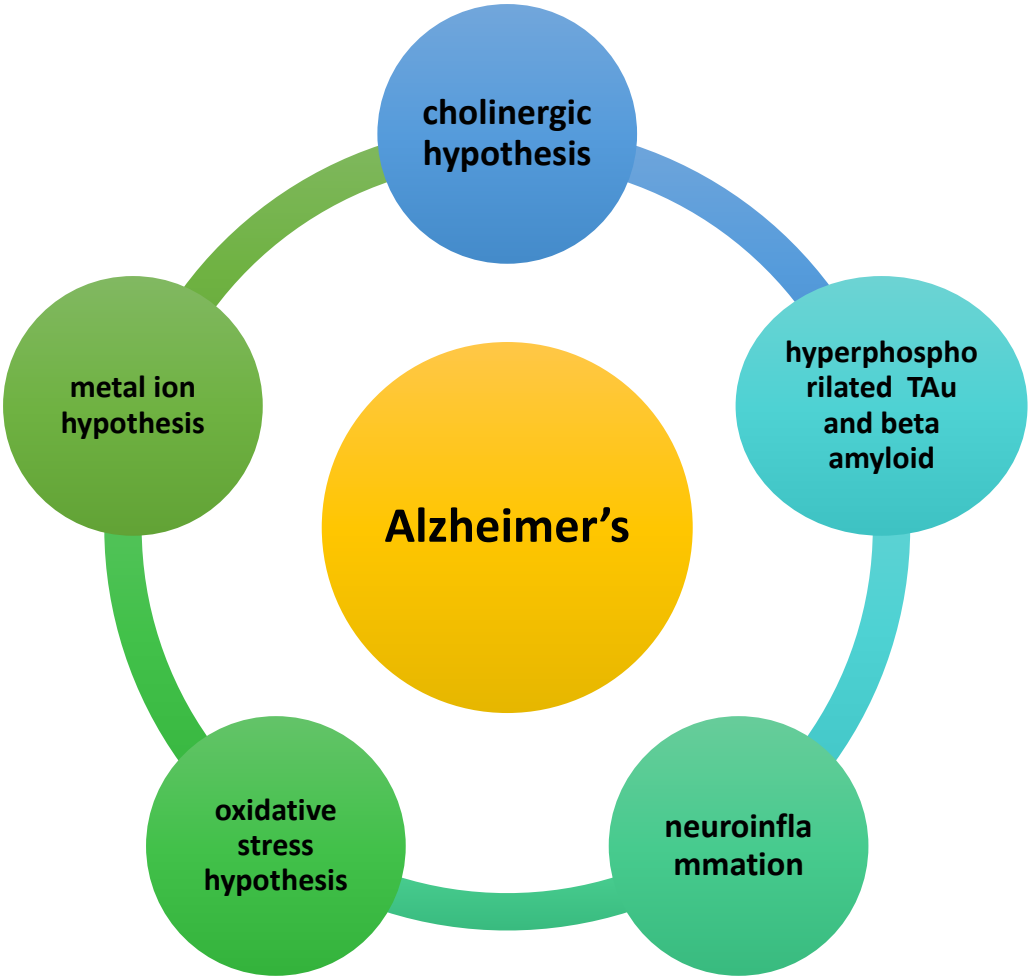


**Fig.1.2. Alzheimer's Pathophysiology Model**

**2.1.Cholinergic hypothesis:**

The that are generally regarded cholinergic hypothesis is based on the impairment of cholinergic functions in many different parts of the nervous system, such as the cortex and its hippocampus and a relationship with the advanced stage of Alzheimer's disease. Increased cholinergic mechanisms have been found in Alzheimer's disease consumers, including shifts in choline acetyltransferase and acetylcholinesterase hustle and bustle, increased acetylcholine levels, as well as fluctuations in neuropsychiatric and receptors for muscarinic substances concentrations throughout the brain. A particular type of cholinergic neurotransmitter binding capability increased in particular regions of the cerebellum of patients with mild to moderate Alzheimer's disease, a condition associated with schizophrenia symptoms. Live investigations revealed that cholinergic attachment to receptors has been associated to other necessary brain modification devices linked to withered and Alzheimer's disease. This connection could be a basic pharmaceutical target for Alzheimer's disease. Increased clinical manifestations of Alzheimer's disease are associated with a nationwide reduction in cholinergic synapses in the frontal lobe of the brain as well as an overall reduction in Ach-mediated neurological communication. Medication called as drugs that inhibit cholinesterase (ChEIs), such as donepezil, have

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been used to manage the signs and symptoms of Alzheimer's disease for nearly two decades.

**2.2.The hyperphosphorylated or tau and beta-amyloid hypothesis:**

The primary manifestations of the condition include a buildup of misfolded peptides including A and tau proteins that are phosphorylated in certain parts of the brain. Tau is a microtubule-associated polypeptide that maintains and controls neuronal microtubules; yet, in some sickness Under certain circumstances, phosphorylation of the corresponding protein can lead to the formation of insoluble forms that are harmful to axons. Poor transmission of synaptic signals and dysfunctional subcellular translocation are brought on by excessive tau expansion and aggregate. Dysfunctional tau influences the mitochondrial structure and causes brain damage by controlling biochemical fission/fusion amino acid pathways. Shorter hydrophobic peptides generated from amino acids, which include and-secretase-cleaving APP, are also observed. The buildup of plaque is one of the evidence of Alzheimer's disease, causing a vicious cycle of detrimental physiological abnormalities that leads to nervous system problems, memory that looks like dementia, and insanity. Peptide development causes cells to have problems and faulty connections among neurons in numerous parts of the neuronal system's system of neurons. It has been proposed that damage amplification can be triggered by a prion-like mechanism that involves oligomer spreading. Additionally, new data suggests a mutually beneficial relationship combining accumulating A and the protein tau, suggesting that exogenous A increases tau import inside cells.

**2.3. The inflammation of the brain hypothesis-** Interleukin is one of the most important components in the pathology of the condition known as Alzheimer's. Once activated, chronic inflammation and damaged nerves may produce additional molecules that conduct themselves as risk-associated pattern molecules (DAMPs), activating a sustained and continually defence mechanism in the nervous system.In the early phases of Alzheimer's disease progression, neuroinflammation plays an important role. This inflammation of the neurons might have been caused by the accumulation of amyloidosis and NFT aggregates. Genetics, obesity, a lack of activity, and diabetic all contribute to a longterm antibacterial profile in AD, which is further exacerbated by infection with viruses and the peripheral immunological system's responsiveness. The long-term inflammation affects microglia, driving them to release harmful cytokines that cause nerve damage and death. This is followed by symptoms of Alzheimer's disease and mental impairment. According to this viewpoint, continued use of anti-inflammatory drugs (NSAIDs) can postpone the onset of cognitive dysfunction (AD), but has little to no influence on medical management.

**2.4. The theory of oxidative stress:** The buildup of free radicals and respiratory metabolic processes are both playing key roles in the further development of Alzheimer's disease and act as the foundation for the AD-mediated oxidative stress idea. According to the study's the results, a situation known as oxidative stress (OS) causes a surge in biological markers (oxidation of naturally occurring biomolecules such as amino acids, lipids, DNA, and RNA) in the neurons of individuals with Alzheimer's disease. The

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effects of oxidative stress is an occurrence that causes a disparity between prooxidant and preventative elements, this is primarily caused by a buildup of reactive oxygen molecules (ROS) or an incorrectly functioning protective system. In the brain, this phenomenon becomes more pronounced with age. Oxidative stress is a condition that increases the development and progression of the disease known as Alzheimer's. When the brain demands 20% higher levels of oxygen than other parts of our bodies that respire via tiny mitochondria, the production of ROS grows. AD has been clinically linked to intracellular antioxidants and nitrosative strain, which causes oxidative damage to proteins, protein n glycol oxidation, and lipid oxidation, in addition to accumulation. The formation of ROS could also interfere with the function of linkages and transfer of signals in neurons, subsequently results in mental decline. In general, ROS can target calcium homeostasis, lipids, amino acids, nuclear and mitochondrial genomes, mitochondrial operate, cell architecture, the process known as end and energy regulation.

**2.5. Mechanism of metal ions:** Metal the equilibrium of ions in the brain and nervous system has been linked to a variety of mental system conditions. Ion balance in the nervous system's nerve cells, such as Cu2+, Zn2+, and Fe2+, is crucial for promising the maintenance of usual physiological function; thus, an imbalance of these ions may play a role in the onset and development of AD. The unbalanced distribution of these ions, on the other hand, creates changes in numerous cellular/subcellular circuits as well as injury prompted by A and tau, that leads to metal displacement/deposition or disturbances. Cu2+, Zn2+, and Fe2+ prioritise in the centres and margins of elderly people patches in cognitive decline patients, and when converted with A, their transit to other places is reduced in comparison to the normal physiologically circumstance. Serum Zn2+ levels in those with Alzheimer's disease, on the other hand, are lower but are higher in the brain's spinal fluid and neocortical tissue. Cu2+, Zn2+, and Fe2+ ion concentrations in neuropil sites have been shown to be higher among such people.

## 3. Role Of Herbal Medicine:

Numerous useful substances have been discovered through phytochemical studies, including lignans, flavonoids, tannins, polyphenols, triterpenes, sterols, and alkaloids. These chemicals exhibit anti-inflammatory, anti-amyloidogenic, anti-cholinesterase, hypolipidemic, and antioxidant properties. [5-3,6].

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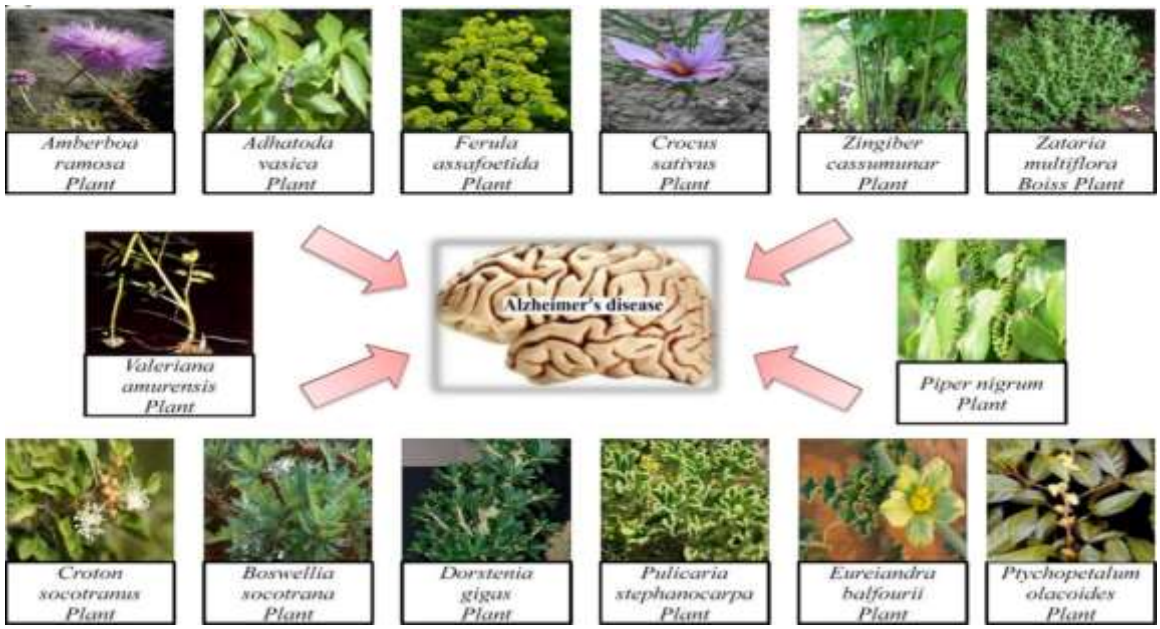


**Figure 1.** Herbs for Alzheimer's disease

**3.1. The multipronged approach of herbal medicines in Alzheimer's disease:** Herbs and medicinal products have been used for thousands of years and appear to be advantageous and safe, nevertheless they are getting little attention from scientists [7-8]. A variety of plants and their parts are used in traditional medicine to improve the brain's functioning and alleviate Alzheimer's illness symptoms and signs such as impeded cognition, deficits in memory, and anxiety. Only one herb or an amalgamation of herbs is normally utilised, in accordance with a number of events, particularly the level of seriousness of the ailment. The theory is that the herb's physiological active ingredients are not only able to synergistically function, but they could additionally impact the activity of other compounds from the precise same or different plant species[8-9]. In Ayurveda, traditional Chinese medicine (TCM), and Native American treatments, an individual herb or a blend of several plants are usually advised depending on the health concern. [7-10,11]. We analysed several kinds of Alzheimer's-related medication based on their unique characteristics, efficacy, and pharmacological effects (Table 1). The plants listed below were chosen for their (a) long and magnificent traditions of usage among traditional physicians for memory-related disorders such as Alzheimer's disease and dementia, and (b) longstanding and recognised tradition of use within traditional therapeutic practitioners. The detection of chemicals called phytochemicals from several of such botanical sources for their possible use in Alzheimer's disease therapy, (c) the potential long-term neuropharmacological function of these herbs, and (d) whether or not there was prior or current clinical study that confirmed their to consider human mental and anti-dementia consequences. The field of herbal medicine has increasingly aroused the fascination of doctors due to its superior therapeutic capacities and a lesser likelihood of side effects when when compared to artificial medications (12-13). Multidisciplinary effects have been successfully employed in the management of a variety of disorders. We investigated a number of plant medicines that have been demonstrated to be helpful in the treatment of

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Alzheimer's disease in this study.

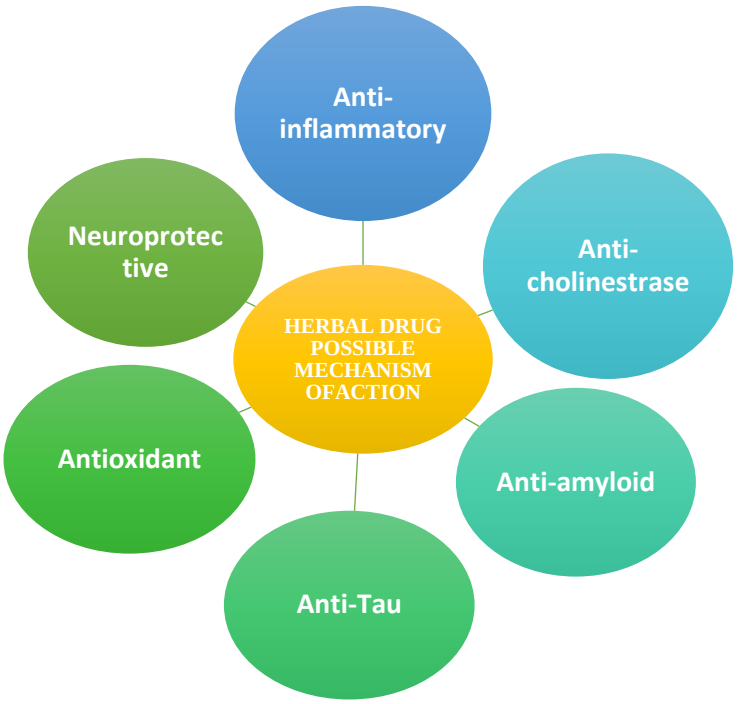


**Figure 1.2.** Herbal treatments' comprehensive approach in Alzheimer's illness.

**4. Clinical Features:** A logical arrangement should be subsequently followed for the clinical diagnosis of Alzheimer's disease: historical context should include appropriate information from an informant; the state of mind evaluation must include a demonstrated cognitive capacity test; and the examination of the body should concentrate on vascular and neurological signs of supplementation to the diet via examination. Dementia has been defined into two stages. To begin, dementia syndromes must be separated from other mental illnesses that can be misdiagnosed with them in their final days such as depressive symptoms, delirium, and mild cognitive impairment. Secondly, when a type of dementia syndrome has been recognised, establishing a subtype becomes essential since it can influence the sort of therapies available. Pre-dementia, small amounts of dementia, progressive dementia, and severe dementia are the four phases of Alzheimer's disease. Pre-dementia can be challenging to distinguish from ordinary ageing or stress-related disorders [40,41]. One of the first signs is a decrease in memory that is episodic. There is no loss in sensory or motor performance at this level, but additional traits such as executive, language-related, and cognitive processing are only mildly diminished. Schizophrenia with significant brain damage. Secondly, after a memory deficit diagnose can be verified, presenting a subtype is of the utmost importance as this may influence the type of medicines that are readily available. Pre-dementia, mild Alzheimer's illness, moderate to profound dementia that looks and significant neurotoxicity are the four main phases involved in dementia's progression. A individual experiencing Alzheimer's disorder retains his or her special characteristics but is no longer identifiable. [41] Extensive decline in memory has a significantly larger adverse effect on categorical simultaneous recollections in the initial stages of Alzheimer's disease than other grades such as short-term in nature declarative and unconscious remembers[42]. Because of their ability to generate distinct recollections during the mild phase of short-term memory impairment,

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Alzheimer's disease patients longed to live in the past [43]. A longitudinal study published in 1993 revealed that dementia, dementia, cognitive antagonism, depression as well, and cleanliness were all expected markers of nursing home placement at the time. [30]. Throughout this severe stage, even the earliest memories may be gone. At this moment, fundamental ADLs are being obstructed and degraded. Conversation is also restricted to single phrases or single words, and vocabulary has a significant impact [42,43]. Concerns about misbehaviour arise, bringing providers annoyance [42,44]. Particular types of inherited Alzheimer's disease emerge around the age of 65, often in the fifth cycle or earlier. They represent less than 1% of all individuals with Alzheimer's. Mutations such as these are frequently acquired, and they have been linked to changes in enzymes that affect beta-amyloid difficulties, polypeptide synthesis, or manufacture, such as presenilin-1 (PSEN1), amyloidogenic protein (APP), and presenilin-2 (PSEN2). In the aftermath of a methodical examination of independently collect information on around 1307 people suffering from considerably dominant Alzheimer's disease, an average age of onset of manifestations was 46 years, and it was found that was a substantial correlation between the age of the parents of onset and variations type [46,47].

**Table 1:** Clinical features that distinguish AD from other dementias –

| S.No | Clinical feature | Alzheimer's dementia | Vascular dementia | Parkinson's dementia | Dementia with Lewy bodies | Front temporal dementia |
|---|---|---|---|---|---|---|
| 1. | Patient profile | >65 years old | >40 years old Vascular risk factors | >65 years old | 75 years old (mean) | 50_70 years old 50% autosomal dominant |
| 2. | History | Gradual onset And deterioration | Acute onset, stepwise deterioration | Gradual onset and deterioration | Gradual onset and deterioration | Gradual onset and deterioration |
| 3. | Initial symptoms | Memory loss | Executive dysfunction | Visual hallucinations | Visual hallucinations Fluctuating attention | Memory intact Disinhibition, apathy, or aphasia |
| 4. | Physical findings | No motor impairment (until late stage) | Pyramidal (upper motor neuron) signs | Parkinsonism (precedes dementia by >1 year) | Parkinsonism (presents within 1 year of dementia) | Usually none (rarely associated with motor neuron disease) |

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**Notes:** Pyramidal (upper motor neuron) signs include hyperreflexia, spasticity, weakness, and extensor plantar responses (Babinski sign). Parkinsonism refers to the following features: bradykinesia, cogwheel rigidity, resting tremor, and postural instability[48, 49].

## 5. Risk Factors:

- **Age:** Age is the greatest major risk factor for Alzheimer's disease and the most prominent non-modifiable achievable confounder. The great majority of Alzheimer's disease cases occur in persons over the age of 65. Alzheimer's disease affects roughly 5% of those aged 65 to 74. Individuals above the age of 85 have a 50% greater risk. [15]. Many studies have shown that the old have an effect on the body's self-repair processes, including those in the brain. Furthermore, several risk factors for cardiovascular disease, such as high blood pressure, coronary artery disease, and high cholesterol, worsen with age.
- **Genetics:**

  Variations are found in Genomes 1, 14, and 21. A single diploid mutation increases a person's risk of Alzheimer's disease by 50% [52,53]. As indicated by the increasing incidence and prevalence of Alzheimer's disease, age is the most significant known risk factor in many scenarios. Alzheimer's disease is certainly getting more prevalent. There is no biological pattern of transmission identified in sporadic Alzheimer's disease. Alzheimer's disease has been connected to the ApoE chromosomes. This gene is thought to affect a protein component that transports lipoprotein through the coronary arteries. ApoE4 is one gene variant that has been associated to an increased risk of developing the disease. The ApoE2 variant, on the other hand, protects against the disease [50,51]. Infections that emerge before the age of 65 may be caused by a genetic defect. Familial Alzheimer's disease is a kind of Alzheimer's disease that affects less than 10% of the population. It has been suggested that it is caused by mutations that become more common with age, with Alzheimer's disease recurrence increasing from 2.8 per 1000 person-years in those aged 65 to 69 years to 56.1 per 1000 years in those aged 90 and beyond. Despite the fact that first-degree relatives of patients with delayed disease have nearly three times the expected lifetime risk of the disease, the observed pattern of transmission could be due to Mendelian genetic inheritance. Although hallucinations and delusional beliefs are not fully recognised as symptoms, they are believed to occur at any time during the illness. Convulsions, hypertonia, my bowel motions, and mutism are some symptoms of neurological illnesses that may appear during the course of the ailment. The primary causes of mortality, as exhaustively documented, include general inanition, haemorrhage, and pneumonia.
- **Late-onset Alzheimer's gene**

  Alzheimer's disease is becoming more prevalent beyond the age of 65, and apolipoprotein E (APOE) is the gene implicated. This APOE appears in three forms, with APOE e4 constituting especially dangerous. Alzheimer's disease has been

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associated with SORL1, CLU, PICALM, CR1, and other genes [54]. Polymorphisms in one of the homologous genes, those generating the precursor protein for amyloid (APP) and presenilins 1 and 2, develop the majority of those with autosomal dominant familial AD.

- **APP amyloid beta precursor protein**

This gene produces a receptor on the cell's surface and a transmembrane precursor protein, which is broken down by assets to form several peptides that, when secreted, connect to the acetyltransferase complex APBB1/TIP60 to promote transcription factor expression and form the alimentary basis of amyloid plaques found in Alzheimer's disease chemical effects treatments' brains. This gene is found on the 21st chromosomal region. Alzheimer's disease is characterised by a buildup of soluble -amyloids, which culminates in the formation of amyloid plaques. The monoclonal antibodies solanezumab, crenezumab, and gantenerumab, which target both insoluble and soluble A-aggregates, have been ineffective in improving the clinical result of AD due to limitations and side effects. [55,56].

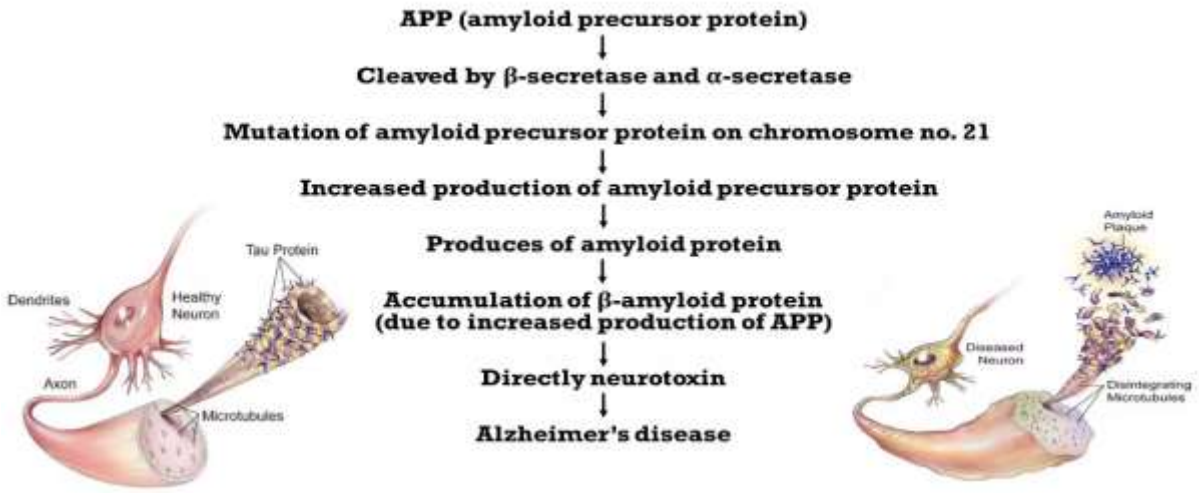


**Figure 1.4.** General pathogenesis of Alzheimer's disease (APP, amyloid precursor protein).

- **APOE Apolipoprotein E**

This gene encodes an enzyme that interacts with a particular receptor in order in the liver as well as the cells surrounding it and is required for proper digestion of triglyceride-rich transport components. This gene, along with C1 and C2 proteins, was found on chromosome 19. Type 3 hyperlipoproteinemia (HLP III) is marked by elevated plasma levels of cholesterol and triglycerides as a result of inefficient chylomicron and VLDL residue elimination induced by mutations in this gene. Alzheimer's disease occurs when all of these parts mix and aggregate in the brain as plaques filled with

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amyloid. As tau protein molecules reassemble and create tangles in the neurofibrillary system, brain cells die and the signs of Alzheimer's arise [52].

➢ **Down's syndrome:**

- People with Down syndrome are more prone to get Alzheimer's disease. This is because the genetic defect that causes Down's syndrome can cause amyloid plaques to collect in the brain over time, leading to Alzheimer's disease in certain people.

**Table 1.2:** Factors that modify the risk of Alzheimer's Disease.

| Antecedent | Direction | Basic Effect |
|---|---|---|
| Cardiovascular disease | Increased | Parenchymal destruction Strategic region beta (symbol) deposition |
| Smoking | Increased | Cerebrovascular repercussions Damage resulted from oxidation |
| Hypertension | Increased and decreased | Cerebral vasculitis |
| Type II diabetes | Increased | Insulin and A beta (symbol) battle for elimination |
| Obesity | Increased | proinflammatory type II diabetes risk |
| Traumatic head injury | Increased | Deposition of A beta (symbol) and amyloid precursor proteins |
| Education | Decreased | Provides cognitive reserve |
| Leisure activity | Decreased | Improves lipid metabolism and cognitive stimulation |
| Mediterranean diet | Decreased | Antioxidant, anti-inflammatory |
| Physical activity | Decreased | Brain plasticity is stimulated and brain vascularization is promoted. |

**Source:** Epidemiology of Alzheimer's Disease [57]

➢ **Coexisting Health Problems:** Alzheimer's patients' cardiovascular and brain health are inextricably intertwined. A heart issue, high blood pressure, or high cholesterol levels can all dramatically increase your risk of developing Alzheimer's disease. Damage to the capillaries that supply blood to the brain results in decreased blood flow and the likelihood of significant brain tissue loss. Diabetes type 2 may increase the risk of acquiring Alzheimer's disease. Diabetes' failure to convert glucose levels to energy may result in elevated sugar levels in the brain, causing severe harm to the entire body. Disorientation and cognitive impairment are minor in the early stages of the illness, which can be diagnosed in almost every case, but they gradually improve as the infection clears and neurological impairment becomes more acute and visible. (58) Some Alzheimer's patients suffer from major depression and are concerned how they will cope with the loss of cognitive and essential skills. Among the symptoms of depression are:

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- Insomnia
- Mood swings
- Less contact with the people around
- Difficulty in concentrating

Depression symptoms can frequently be similar to those of Alzheimer's disease. This might render distinguishing both sadness and normal signs of Alzheimer's disease more difficult. Attending community events and relating with a licenced counsellor to help him appreciate what's happening are two essential approaches for limiting melancholy in people with dementia who have Alzheimer's. It can also be tempting to connect with individuals experiencing Alzheimer's disease. Constant physical movement and involvement in artistic endeavours may also help to enhance their emotional attitude. In rare circumstances, a doctor may prescribe pharmaceuticals to treat unhappiness. the condition known as Alzheimer's can also cause issues with physical balance and coordination. As the dementia progresses, the likelihood of collapse increases.

## 6. Detection Methods:

Neuroimaging is a significant and fast expanding field that is being studied in identifying signs of Alzheimer's disease. PET, MRI, and CT (computed tomography) are all regarded as preliminary testing for detecting illnesses and can assist with the identification of neurological issues. Each scan utilises an innovative method for assessing specific characteristics and irregularities in the neural network and its neighbouring areas. Although mental imaging is no longer an everyday component of Alzheimer's disease testing, possibly recent clinical studies discovered significant advancements that they could influence the methods for evaluation used by healthcare professionals to identify the ailment. No successful treatments for Alzheimer's disease, which is the most frequently type of cognitive decline, have been discovered despite a long period of challenging and scientific investigation. It has grown increasingly clear that when it comes to for a medical condition to be effectively treated, it must be recognised as soon as achievable, frequently before its symptoms develop. As a result, there exists an enormous demand for dependable healthcare diagnostics so that therapy aimed at limiting or avoiding the progression of the diseases can begin immediately as possible. Alzheimer's illness, as well as various other forms of dementia.

**6.1. PET** (positron emission tomography) provides a holographic colour image of a human body by utilising illumination signals [60]. A radiotracer, a radioactive therapy that is associated with a substance that naturally occurs, is put into the patient. The component typically involves glucose, and it has been widely used in Alzheimer's disease research. The radioactive element gets delivered to the organs that utilise a specific chemical to generate energy. Positron particles are particles that are released as a result of molecules digestion. The radiation surrounding these places was successfully recognised by the PET scan and interpreted as something apparent on the serial displayed. The horizontal line with dots illustrates how much of the radioactive component has been broken away in the recipient's

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body. The entire amount of electrical energy distributed produces an assortment of colours and intensities that symbolises the level of activity within the brain. A magnetic resonance imaging (MRI) scan can detect variations in metabolism, distribution, and cellular communication mechanisms in the brain's cortex, as well as other mental functions [60]. A 1996 study which appeared in the Journal of Clinical Mental Health established how to use a PET scan for recognising variations in the level of carbohydrates in an Alzheimer's disease the individual's brain. The occipital, transverse, and anterior cortices have extremely low glucose metabolism. People who had a significant disease that damaged more areas of their brain cortex [61]. Small and company investigated if a PET scan was capable of identifying alterations in glucose equilibrium before symptoms emerged clinically. A PET envision could be used for two purposes: to assess the successful outcome of Alzheimer's disease medications and to characterise the disease [62].

**6.2. CT:**

A computed tomography (CT) scan of the body generates a sequence of cross-sectional images [63]. Individual scans are evaluated and integrated into a comprehensive, detailed image using a computer. The CT scan only displays the doctor the density of tissues in the body and certain brain areas. To improve comprehension, a contrast dye may be administered to differentiate between homologous tissues. [64].

**6.3. MRI**

MRI (magnetic resonance imaging) techniques, which were initially available in 1977, create two- or three-dimensional visualisations of the body that the can be exploited for determining irregularities and illness. The ultrafast magnet, which creates an immense and stable field of magnetism, is an important component of the MRI system [65]. Smaller gradient magnets produce weaker electromagnetic fields. The same magnetic can be used to image other regions of the body as well. The magnetism has an effect on hydrogen molecules. A single atoms of hydrogen moves haphazardly down an axis, but the atoms of molecules that live underneath the MRI's electromagnetic field have orientations in the same orientation as the field. Half of the atoms represent the head of a human being, while the other half symbolise the patient's feet. Few particles in a million are able to cancel each other out. The device then generates a radio frequency pulse tailored specifically for the element hydrogen, prompting these protons to rotate in the other manner. When this uprising is over, the neutrons emit energy, which the entire system detects. When a contrast dye is put into use, each type of tissue behaves differently and can be seen in the photographic representation as a separate grey colour [60]. If investigators can figure out how the mechanism works, they can determine if an MRI can identify mutations in DNA and cell division in an Alzheimer's disease patient's brain. In Alzheimer's patients, PHY of the hippocampus is prevalent. [51]. PHY of the hippocampus is common among Alzheimer's patients. [51]. The Nun Memorial Research gathered post-mortem MRI scans from 56 individuals suffering from varying degrees of cognitive decline in 2002. An MRI was used for calculating the volume of the hippocampus in order to ascertain its value as a manifestation of neuropathology linked with Alzheimer's disease [66]. Apparently to the academics, the scans might identify non-demented older individuals with Alzheimer's disease-associated brain symptoms who might

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have yet to experience remembering loss. Specialists may be able to reduce the progression of Alzheimer's condition in these patients through surveillance of the disease's susceptibility well before symptoms emerge. Another study, performed in 2009 by the Colleges of Radiology and Medicine at the University of Pennsylvania, studied into the use of plasma from magnetic resonance imaging in the identification of Alzheimer's disease. The same procedure as described in earlier sections is used in the above imaging method. This method recognises sodium atoms rather than the more prevalent hydrogen atoms that are found in nature. Because sodium in the central nervous system has the ability to determine cancer and detect cell death, it was chosen [67]. The participants were five healthy old persons and five with Alzheimer's disease. The intracellular space of neurons diminishes when they die.As a result, the extracellular salt concentration rises, resulting in increased MRI signal intensity in Alzheimer's disease patients. While the effectiveness of this strategy has yet to be verified, research is being conducted to identify whether the improved digital signal is the result of a change in percentage or an increase or decrease in volume. [62].

## 7. Diagnosis method

Alzheimer's disease has been characterised in clinical settings mainly on medical history, physical and cognitive examination, and comprehensive findings, including the ruling out of possible aetiologies with specific auxiliary testing. The clinical recognition of Alzheimer's disease has an accuracy range from 70-90 percentile when compared to pathological diagnosis, with higher accuracies found in dedicated settings such as remembering disorder clinics. [58] The National Institute on Ageing Alzheimer's Association (NIA AA) workgroup revised an established set of consensus criteria that were initially released in 1984 [44] and was most recently updated in 2011. [59].

### 7.1.Diagnosis Criteria:

The medical diagnosis of Alzheimer's disease follows a logical sequence: the history should include information from an informant, i.e. a person related to the patient; the mental state assessment should include a reviewed cognitive function test; and the physical evaluation should focus on current and neurological signs, supplemented by examinations and patient history. A normal cognitive assessment is divided into two sections. To begin, dementia syndromes must be recognised from other ailments that can mimic them, and such as grief, sleepiness, and intermediate cognitive dysfunction, which affects a large percentage of patients; these medical conditions then need to be recognised. Second, after Alzheimer's disease demands are identified, defining a variant is of the utmost importance since it could influence the type of treatment provided. The clock test is a widely accepted method of performing psychological evaluations since it is non-confrontational and eliminates the possibility of major cognitive impairment. The test grading techniques, on the other end of the spectrum, are very challenging and employing a single intellectual exam to screen for the development of a dementia syndrome fails to adequately reflect the enormous array of symptoms and discoveries that comprise the clinical diagnosis of dementia. Even though the inspection instruments used are not uniform, everyday functions such as cognition are included [41].

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- **Establishing the Diagnosis of Alzheimer's Disease:**
  Clinical-neuropathologic evaluation is used to make the diagnosis of Alzheimer's disease. The gold standard for diagnosing Alzheimer's disease is still neuropathologic findings on autopsy. The clinical diagnosis of Alzheimer's disease (before autopsy confirmation) is correct roughly 80%-90% of the time.

**8. Causes**

In the beginning, the only apparent symptoms of Alzheimer's disease involve elevated irresponsibility or extreme bewilderment. On the other conjunction, the sickness gradually depletes you of more intimate memories, specifically recent ones. The onset of indications varies depending upon temperament and age. If you have the disease known as Alzheimer's, you may be the first to discover that you're having trouble remembering things and organising what you are thinking. Apparently you won't notice anything incorrect if your family, close friends, fellow employees, and colleagues incorporate changes. Three hypotheses can be used to explain the causes of Alzheimer's disease. Alzheimer's disease is responsible for 60%-70% of dementia cases. It is a chronic neurological disorder that normally begins gradually and worsens with time. Plaques, one theory holds, prevent brain nerve cells from connecting properly. Tangles may make it difficult for cells to access the nutrients they require. It is understandable that as Alzheimer's disease progresses, damaged nerve cells die. As the disease progresses, an enormous number of sensory neurons, also known as neurons, are lost.

- **Cholinergic Hypothesis:** It is understandable that wounded nerve cells die as the condition known as Alzheimer's progresses. A great deal of sensors, also known as the neurons, are lost as the disease proceeds. The Cholinergic Inference had been suggested in the 1970s. Mechanism of Cholinergic Action: In the 1970s, it was considered that neocortical and synaptic cholinergic complications had been triggered by the enzyme choline acetyltransferase (ChAT), which is in charge of the manufacture of acetylcholine, which is additionally known as ACh. Considering ACh is involved in memory retention, a cholinergic hypothesis concerning the illness was postulated. The ChAT nucleotide integrates ACh from acetylcholine and acetyl-coenzyme A in the cytoplasm of neurons with cholinergic activity and transports it to synaptic vesicles via the cylindrical acetylcholine exporter (VAChT). ACh participates in a range of pharmacological actions in the brain, includes sensory information storage and memory, learning, and other preventative functions. Alzheimer's disease is caused by cholinergic neuron loss, which produces mental health issues and problems with recall. B-amyloid is considered to influence neurotransmission via cholinergic neurons by minimising choline intake and enhancing ACh release. Pursuant to the study, A oligomer neurodegeneration and interactions amongst AChE and A peptides have been connected to cholinergic synaptic loss and amyloid fibril formation. A decrease in nicotinic and muscarinic (M2) Ach receptors, which are found on presynaptic cholinergic nerve terminals, as well as a deficit of particular amino acids that are essential (EAA) neurological dialogue, with glutamate concentration in order and D-aspartate acceptance drastically

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reduced in many brain regions of the AD cerebral cortex, are all variables which contribute to Alzheimer's disease progression. Similarly, cholinergic the receptor antagonism, such as scopolamine as has been scientifically associated to recollection. This chemical procedure can be avoided by using pharmaceuticals which enhance acetylcholine the manufacturing process.

[68–69].

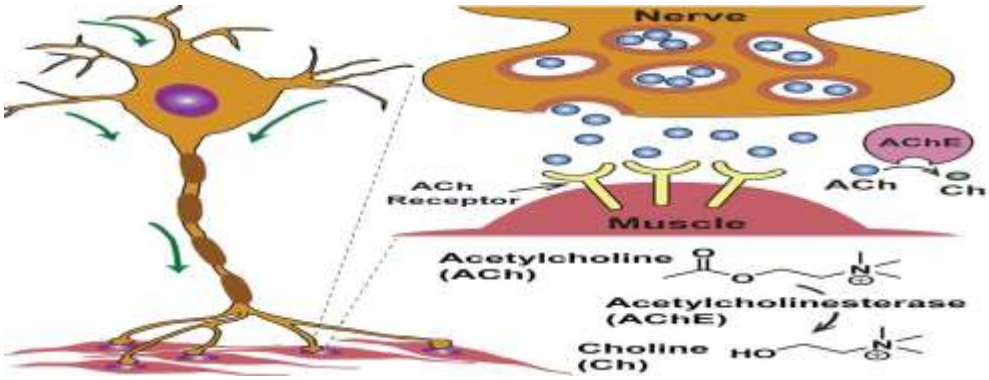


**Figure 1.5.**The pathway for the synthesis and transportation of acetylcholine between presynaptic and postsynaptic nerve terminals.

As a result, three concepts underpin the cholinergic hypothesis: significantly reduced presynaptic cholinergic markers in the cerebral cortex, extreme neurodegeneration of the nucleus basalis of Meynert (NBM) in the basal forebrain, which serves as the source of cortical cholinergic innervation, and the role of dopaminergic antagonists in memory impairment, particularly when compared to agonists, which have the opposite effect. [70-71]

- **Amyloid hypothesis:**

For decades, the amyloid hypothesis held that aberrant -sheet deposition in the central nervous system was linked to dementia. However, amyloid plaques (AP) have been seen to build in totally healthy synapses with age, raising the question of whether or not AP deposition is responsible for the development of Alzheimer's disease. As a result, despite the fact that various explanations for the non-inherited form of Alzheimer's disease (NIAID) have been developed in recent years, the amyloid hypothesis remains the most widely accepted pathogenic mechanism for transmitted Alzheimer's disease. According to the amyloid hypothesis, being older or sustaining clinical symptoms interferes with the breakdown of A, which originates from APP via and -secretase, which causes an accumulation of A peptides A40 and A42). Increasing A42/A40 ratio promoted the emergence of A amyloid fibrils, which leads to neurotoxicity and tau pathology, ultimately leading to the death of neurons and neurodegeneration. Alzheimer's disease and abnormalities in certain genes, including as APP, PSEN1, and PSEN2, have been revealed to cause disruptions in A degradation and anabolism, resulting in rapid buildup of and neurodegeneration economic growth [72-73]. Aß is produced from APP by the breakdown of proteins in the amyloidogenic pathway, and which is mediated by ß secretase (BACE1) and secretase in outside of the cell and intracellular regions, respectively. ß-secretase cleavage conduces to the development of APPsß and C99. C99 is afterwards cleaved by secretase resulting in either Aß1-40 or the more hydrophobic in nature aggregation-prone Aß1-42 [74].

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Aß40 is more frequently found in the cerebral endothelium [15]. Because APP can be cleaved by secretase and yield Appam in the non-amyloid genic route, it has been speculated that the polymerization of Aß1-42 plays a more important function. Aß1-42 oligomerization brings about soluble Aß oligomers, which have been described as Aß-derived diffusible ligands (ADDLs). Experiments demonstrated that these ADDLs may be more dangerous than Aß fibrils because they target synaptic spines and impede synaptic plasticity, impairing cognitive function. Toxin receptors on cell surfaces and Fyn, a tyrosine kinase receptor overexpressed in Alzheimer's disease, are responsible for their toxicity [76,77].

- **Tau hypothesis:**

The Tau hypothesis concerning Alzheimer's disease depends on the emergence of neurofibrillary tangled complexes (NFTs). Enhanced Tau phosphorylation (formerly connected to microtubules) resulted in greater amounts of unbound tau and fewer operable microtubules [39]. Phosphorylated Tau can be identified in hexagonal filaments with pairs (PHFs) of NFTs. Protein transport between neurons can be hindered by metabolic malfunction, resulting in dementia [78].

The creation of neurofibrillary tangled structures (NFTs) is central to the Tau theory of Alzheimer's disease. Increased Tau phosphorylation (which has previously been linked to microtubules) leads in more free tau and fewer operational microtubules [39]. The phosphorylation of Tau protein changes cytoskeleton interaction and assembly [79]. Large filament clumps occur when conventional tau protein is combined with hyperphosphorylated tau protein [80]. When the tau protein becomes hyperphosphorylated in Alzheimer's disease, it forms paired helical tangles in the brain. Neurodegeneration occurs when tangles of neurofibrillary fibres lose their ability to adhere to micro tubules Tau phosphorylated in A-activated embryonic brain cells requires an abundance of astrocytes [81]. The explanations for variances in tau protein activation are unknown.is one part of, whereas several stages in this process should be expected based on experiences. The abnormal adherence of a hyperphosphorylated form of tau protein to microtubules in Alzheimer's disease patients causes polymerization destabilisation, and this causes issues with synaptic transmission of information that depends on microtubules. Molecular drivers transport A and hepatocytes via tiny tubules. When neuronal transit is hampered, APP congregates in the cell body. It has been demonstrated that decreased synapse expansion within organelles such as mitochondria could end up resulting in increased oxidative stress [82].There has been no genetic changes in the tau chromosome that were linked to Alzheimer's disease. The H1c subhaplotype of the MAPT chromosome was found to be correlated with a greater risk of Alzheimer's disease in 360 pathologist-identified symptoms and 252 controls. [83]. The MAPT expression rs242557 polymorphism, which is part of the H1c subhaplotype, has been shown to have resulted in lower MAPT gene transcription [84]. The H1/H2 MAPT haplotype additionally collaborates with functional SNPs in the GSK3B gene and increases the risk of dementia and Alzheimer's, according to the study.The relationship between tau protein and mitochondria was recently discovered. Tau protein was discovered on the mitochondrial membrane. It is becoming obvious that hepatocyte movements and density in microscopic areas with energy and Ca2+-buffering specifications, such as synapses, play an essential role for successful

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communication between neurons [85]. The presence of mitochondria in axons and dendrites is directly related to their projected power consumption. On a regular basis, both dendrites and axons transfer mitochondria. Synaptic activity alters mitochondrial motility, shape, dispersion of mitochondria in dendrites, and mobilisation at dendritic spine bases. [86]. In a study of neurons transfected with tau protein, mitochondria migrated from neurites to the cell body [87]. As tau protein levels grew, kinesin mechanical motors hindered plus-end-directed trafficking of mitochondrial and other compartments (beyond the cell centre). Then, minus-end-directed transportation (within the cell centre) takes over via a dynein-like motor. [87].

**9. Treatments**

To treat Alzheimer's disease, amyloid peptide aggregation inhibitors, -secretase inhibitors, immunomodulatory, anti-amyloid immunotherapeutic, tau hyperphosphorylation inhibiting agents (inhibitors of JNK3, CDK5, GSK3, and Fyn kinase), tau accumulation inhibitors, microtubule maintenance, anti-Tau immunotherapy, and AChE inhibitors have recently been used. Notwithstanding the fact that present technology has made very little advancement in completely managing Alzheimer's disease [88], current Alzheimer's disease pharmaceutical medications focus on treatment symptoms rather than targeting the underlying causes of the circumstance. Tacrine (COGNEX, 1,2,3,4-tetrahydro-9-aminoacridine) was the first acridine derivative to receive FDA approval. However, the FDA has approved AChE inhibitors donepezil (Aricept), rivastigmine (Exelon), and galantamine (Reminyl) for the treatment of Alzheimer's disease. Several drugs can raise acetylcholine levels in the brain while reducing AChE [89-90]. Donepezil is the only medicine approved to treat all stages of Alzheimer's disease [91]. The remaining drugs are used to treat mild to moderate Alzheimer's disease. In 2003, the FDA approved memantine (Namenda) as a treatment for moderate to severe Alzheimer's disease. Despite the fact that researchers have researched several drugs, they are not administered. Selegiline, vitamin E, oestrogen, and anti-inflammatory medicines are among the treatments available. [92,93]. These medications work by changing neurotransmitters, which can aid in the improvement of memory, speaking ability, and behavioural issues linked with Alzheimer's disease. Tracing is an AChE inhibitor that can cause appetite suppression, diarrhoea, stomach discomfort, vomiting, nausea, and hepatotoxicity. Other antidepressants, such as donepezil, rivastigmine, and galantamine, produce nausea, vomiting, and diarrhoea. [92,93-94] These medications' effectiveness in Alzheimer's disease intervention is limited because they only treat the symptoms of the disease rather than monitoring its progression. Herbal, complementary, and alternative treatments are being investigated as potential Alzheimer's disease prevention, promotion, and therapy options.

**10. Herbal medicines used in Alzheimer's disease-**

**Table 1.3.** Neuroprotective herbs for the management of AD have a wide gamut of physiological actions. Listed below are the neurotherapeutic properties of these herbs that ultimately enhance memory and restore normal cognitive functions.

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| Herb | Study Type | Function/Outcome Measure | Reference |
|---|---|---|---|
| Ashwagandha (Withania somnifera) | in vitro, in vivo, clinical studies | antioxidant, anti-inflammatory, blocks A production diminishes neurons cell death, dendritic extension, and neurite development while additionally restoring the function of synaptic and brain regenerating treating the mitochondrial malfunction, and strengthening auditory-verbal transmission. Memory, working memory, executive function, rate of processing, and thinking about others in patients | [95,96–97] |
| Brahmi (Bacopa monnieri) | in vitro, in vivo, clinical studies | antioxidant, anti-inflammatory, improves memory, attention, and executive function blocks Aβ production, inhibits neural cell death, delays brain aging, improves cardiac function | [98–99] |
| Cat's claw (Uncaria tomentosa) | in vitro, in vivo, pre-clinical studies | Anti-inflammatory and antioxidant; diminishes gliosis, improvements memory | [100–101] |
| Ginkgo biloba | in vitro, pre-clinical, and clinical studies | antioxidant, improves mitochondrial function raises cerebral blood flow, reduces neuronal cell death, and enhances neurogenesis | [102–103] |
| Gotu Kola (Centella Asiatica) | in vitro, in vivo, clinical studies | reduces a state of oxidative stress, levels of antioxidants, and apoptosis; stimulates development of dendritic cells and metabolic health; and promotes mood and memory | [104–105] |
| Lion's mane (Hericium Erinaceus) | in vitro, in vivo, pre-clinical and clinical studies | neuroprotective, improves cognition, anti-inflammatory, suppresses A emergence, stimulates neuronal communication, and promotes neurite expansion | [106–107] |
| Saffron (Crocus sativus) | in vitro, in vivo, clinical studies | an antioxidant, anti-amyloidogenic, anti-inflammatory, antidepressant, immune system regulation, protective effects on neurons | [108–109] |
| Shankhpushpi (Convolvulus pluricaulis) | in vitro, in vivo, pre-clinical studies | improvements cognitive function, declines brain advancing age, anti-inflammatory, antioxidant | [110,111,112–113] |

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| | | | |
|---|---|---|---|
| Triphala (Emblica Officinalis, Terminalia bellerica, and Terminalia schedule) | in vitro, in vivo, pre-clinical and clinical studies | antioxidant, anti-inflammatory, immune system modulation, interferes with cavity formation, antiseptic in nature antiparasitic, reversed and metabolic disturbances | [114–115] |
| Turmeric (Curcuma longa) | in vitro, in vivo, pre-clinical and clinical studies | antioxidant, anti-inflammatory, antiseptic in nature blocks neural cells from dying by preventing A production | [116–117] |

**Notes:**It is hoped that the historical knowledge base of traditional systems of medicine, coupled with combinatorial sciences and high-throughput screening techniques, will improve the ease with which herbal products and formulations can be used in the drug development process to provide new functional leads for AD.

**10.1. Ashwagandha (Withania somnifera):**

Ashwagandha, commonly referred to as Indian ginseng or winter cherry, is a herb that is one of the most successful Alzheimer's disease treatments. It was previously used to raise energy, general well-being, and longevity as well as as a neuron tonic [118]. It has been shown in the past that ashwagandha exhibits antioxidant activity, the ability to eradicate free radicals, and the ability to maintain an effective immune system [119]. Withanolides A-Y, dehydrowithanolide-R, withasomniferin-A, withasomidienone, somniferous A-C, withaferin A, withanyone, along with others are among among the most notable biologically active substances discovered in ashwagandha. Aside from alkaline compounds, phytosterols such as sitoindosides VII-X and beta-sitosterol are found [118,120]. The curative effects of ashwagandha have been controlled by the liver's low-density lipoprotein receptor-related polypeptide [122]. In a Drosophila melanogaster, or Drosophila me AD model, ashwagandha pharmaceuticals reduced A toxicity while increasing lifespan [123]. Despite a significant study on ashwagandha's pharmacological properties, there is limited knowledge concerning its clinical applicability for cognitive impairment. [124]. In a prospective customers, randomised, double-blind study placebo-controlled pilot research, 50 participants with minor mental challenges have been provided either ashwagandha root extract (300 mg twice daily) or a placebo as their treatment for eight weeks. After eight weeks of testing, the ash group getting therapy outperformed the placebo control group in both short-term and long-term memory assessments. Furthermore, the therapy group showed significant improvements in cognitive function, sustained attention, and information processing speed [125]. The use of ashwagandha to improve memory and executive function in persons with SCI or MCI was supported by these researches.

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**10.2.Ginkgo Biloba:**

Ginkgo biloba (Gb) has gotten a lot of attention recently because of its possible applications in Alzheimer's disease treatment. Gb appears to be equipped with the ability to treat a wide range of chronic and acute ailments. Flavonoids and terpenoids are two of the most effective chemical combination. Gb extract, which contains quercetin glycosides, as terpene lactones, and ginkgolic acids, has been used in the majority of therapeutic trials [103]. Gb extracted has been shown to be effective for human beings suffering from Alzheimer's disease, cancer, coronary artery disease, and other age-related disorders [126,103]. Gb extract's antioxidant action, anti-platelet activating factor activity for vascular illnesses, a decrease in -amyloid peptide aggregation in Alzheimer's disease, and lower expression of regional benzodiazepine transmitter for stress reduction are all proposed techniques [127-103]. Gb is often used to treat the early stages of Alzheimer's disease, as well as dementia caused by vascular disease. Gb extract protects against Amyloid and NO-induced toxic interactions in vitro, and it improves morbidity both in the lab and in vivo [128-129]. Gb extract enhanced knowledge retention in both young and aged rats, as well as mice with short-term memory deficits. [126,130].

**10.3.Turmeric (Curcuma longa):**

Turmeric is a flowering plant in the Zingiberaceae family that is native to the Indian subcontinent and Southeast Asia. The yellow-orange colour of this rhizome plant is primarily attributable to polyphenolic compounds known as curcuminoids. Turmeric has long been used to cure a range of ailments, including liver detoxification, disease and injury prevention, cholesterol adjustment, allergy therapy, digestive acceleration, and immune system stimulation [80].

**Table 1.4.**Plant-derived alkaloids are effective in AD.

| Class of alkaloids | Alkaloids | Plants source | Targets | References |
|---|---|---|---|---|
| Isoquinoline alkaloids | Berberine | Hydrastis canadensis, coptis Chinensis, Berberis plant aquifolium, Berberis vulgaris, the Berberis plant aristate | A blockade of BACE-1 activity is reduced, its hippocampus apoptosis is prevented, and MAO and AChE are blocked. | [132–133] |
| | Morphine | Papaver somniferum | Binding to the -opioid receptor (MOR) in the CNS improvements the amounts of -aminobutyric acid (-ABA) in the brain the synaptic junction shields against iA venomousness, reverses iA-induced electrochemical alterations such as resistivity and passive membrane potential, and lowers the A-tempted | [134] |

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| | | | | |
|---|---|---|---|---|
| | Gasoline | Salsola oppositifolia | Inhibits AChE enzyme | [135] |
| | Galantamine | Narcissus tazetta, Galanthus nivalis, Leucojum aestivum | The neuroprotective role, Inhibits AChE enzyme, Aβ accumulation, cytotoxicity, ROS scavenging activity | [136] |
| Indole alkaloids | Geissospermine | Geissospermum vellosii | Inhibits AChE | [137] |
| Pyrroloindole alkaloids | Physostigmine | Physostigma venosum | Inhibits AChE | [138] |
| Piperidine alkaloids | Piperine | Piper nigrum and Piper longum | Neuroprotective, inhibits AChE and β-secretase enzymes, attenuates oxidative stress and cognitive deficits | [139] |
| Pyridine alkaloids | Nicotine | Nicotiana tobacco | Prevents the Aβ peptides accumulation and neuroprotective action | [137] |
| Methylxanthine derivative | Caffeine | Coffea Arabica | Neuroprotective action reduces the Aβ deposition in the cortex and hippocampus and suppresses the level of PS1, β-secretase. It reduces tau phosphorylation in the hippocampus and the corresponding proteolytic tau fragments | [137] |
| Lycopodium alkaloid | Huperzine A | Huperzia serrata | The neuroprotective role, mitochondrial protection from Aβ aggregation-induced toxicity, an inhibitor of Aβ, also promotes the production of BDNF | [140] |
| Indole β-carboline | Harmine | Peganum harmala | Inhibits AChE and DYRK1A catalyzed phosphorylation of tau | [137] |
| Tetracyclic oxindole alkaloids | Rhynchophylline and isorhynchophylline | Uncaria rhynchophylla | Neuroprotective, antioxidant, inhibits tau protein hyperphosphorylation, reverses the Aβ-attenuated phosphorylation of Akt, cAMP response element-binding protein, and GSK-3β-signaling proteins | [141,142] |
| Capsaicin | Capsaicin | Hot chili peppers of the | Ameliorates synaptic damage | |

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| | | | | |
|---|---|---|---|---|
| oid | | plant genus Capsicum | and tau hyperphosphorylation | [143] |
| Indirubin | Indirubin-3′-monoxime | indigo naturalis | Kinase inhibitor, GSK-3β inhibitor, prevents abnormal tau phosphorylation | [144] |

## 11. Mode of action of herbal medicines used in Alzheimer's-

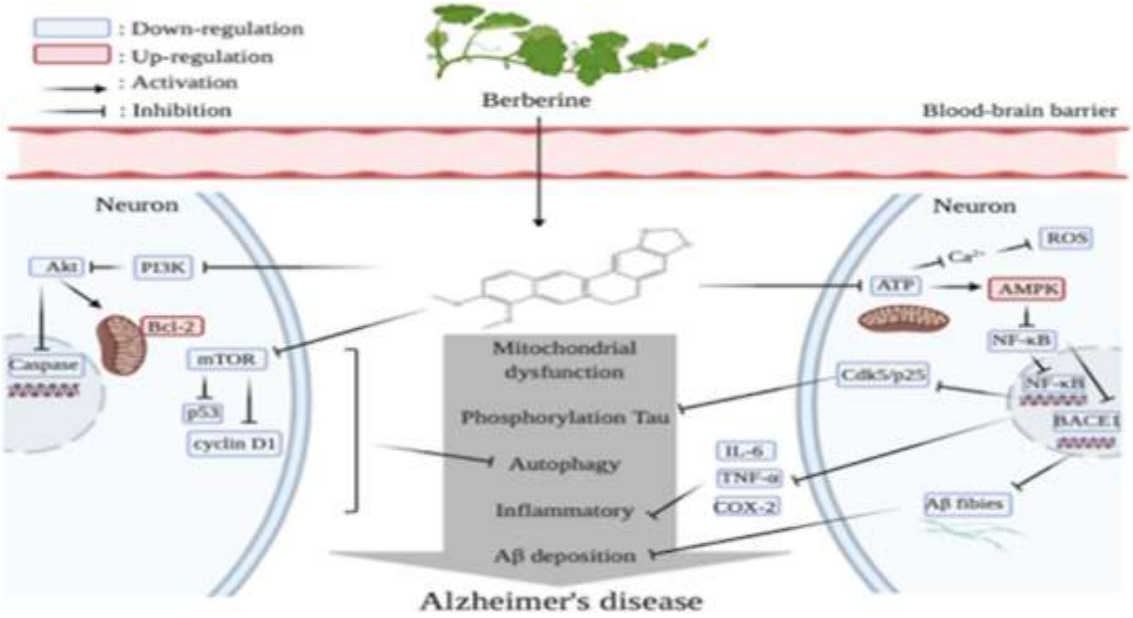


**Figure 1.6.** Mode of action of Berberine in Alzheimer's

**Table 1.5.** FDA-approved plant-derived compounds against AD.

| Phyto Compound | Product name | Plant source | FDA approved | Clinical trials | Targets | Reference |
|---|---|---|---|---|---|---|
| Rivastigmine | Exelon | Physostigma venenosum (Leguminosae) | 2000 | – | Inhibits AChE in the cortex and hippocampal region | [145] |
| Galantamine | Razadyne | Lycoris radiata (Amaryllidaceae) | 2001 | – | Reversible inhibition of AChE and allosteric potentiation of nicotinic ACh receptors | [146,147] |
| Resveratrol | – | Vitis vinifera (Vitaceae) | – | Phase III | Prevents cognitive impairments and associated oxidative stress by reducing plaque formation | [148,149] |
| Huperzine A | – | Huperzia serrata (Lycopodiaceae) | – | Phase III | Restores cognitive deficits by reversibly inhibiting AChE | [150] |

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| | | | | | | |
|---|---|---|---|---|---|---|
| Curcumin | Longvida ® | Curcuma longa (Zingiberaceae ) | – | Phase II | Anti-amyloidogenic, anti-inflammatory, anti-ChE, anti-β-secretase | [151] |

## 12. Conclusion:

Alzheimer's disease develops because genetic, lifestyle, and environmental factors all converge to beginning the disease process. AD is a progressive neurodegenerative disease, without an effective treatment at present and, currently approved drug treatments have been based solely on controlling symptoms and slowing the development of the disease. In order to fully cure Alzheimer's disease, it is vital to identify the reason and make healthy behaviors in addition to herbal formulations. Since herbal pharmaceuticals have less or no adverse effects as compared to chemical-based drugs, they only play a minimal role in the treatment of Alzheimer's. Among the reasons for the failure of available therapies are obstacles to understanding the pathogenesis of the disease, the development of drugs that pursue a specific therapeutic target, and subsequent design of clinical trials. Interestingly, the most important findings of these clinical trials are that different compounds have different functions against AD. Nevertheless, various options can be offered from natural products to reduce symptoms and disease progression. Natural products have been rediscovered as a source of novel medicines thanks to the popularity of secondary metabolites as an important and unique compound. Natural products are a new therapeutic approach to AD treatment. Treating AD with these compounds is probably an approach to seriously consider for the disease and for their great therapeutic potential without side effects. These compounds have also been shown to be effective in treating other disorders and certain diseases that accompany aging and AD (such as Parkinson's Disease). This review shows that natural products have therapeutic potential in neurodegenerative disorders such as AD and, in the future, these products should be considered as possible drug candidates. Studies represented here displayed that natural products can act through different ways against AD. Some of them include inhibiting Aβ-peptide production (by modulating secretase enzymes), inhibiting the formation of neurofibrillary tangles, promoting Aβ degradation, inhibiting AChE, reducing oxidative stress, and reducing neuroinflammation. Many valuable herbs can be used to decrease dementia and treat AD. Therefore, to find the active compounds of medicinal plants effective against AD it is necessary to develop additional studies to study them in depth..

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