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RECENT ADVANCES OF HERBAL MEDICINES IN THE MANAGEMENT OF ALZHEIMER'S DISEASE: A REVIEW

Vandana Devi, Ankita Thakur, Jyoti Gupta, Panshul Sharma
IEC School of Pharmacy, IEC University, Baddi, Solan, Himachal Pradesh, India.

Email: tvandana940@gmail.com

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive cognitive decline and memory loss. Alzheimer's disease involves beta-amyloid plaques and tau protein tangles in the brain, leading to neuronal degeneration, with risk factors including genetics (like APOE ε4), age, family history, and certain lifestyle choices such as cardiovascular health. Recent interest in alternative therapies for Alzheimer's disease includes herbal interventions like ginkgo biloba, Withania somnifera, curcuma longa, bacopa monnieri, and convolvulus pluricaulis extract, which may offer neuroprotective effects and help mitigate AD symptoms.

INTRODUCTION

Alzheimer disease (AD) is a neurodegenerative disease that leads to memory loss and impaired cognitive function [1]. Alzheimer's disease (AD) is a major worldwide health concern and is currently the third leading cause of death in the United States. It's a progressive brain disorder that leads to memory loss and cognitive decline, often becoming a prominent cause of dementia in older adults. Individuals with Alzheimer's commonly experience difficulties in managing daily tasks and may also face cognitive and emotional challenges as the disease progresses [2].

Alzheimer's disease (AD) is a major worldwide health concern and is currently the third leading cause of death in the United States. It's a progressive brain disorder that leads to memory loss and cognitive decline, often becoming a prominent cause of dementia in older adults. Individuals with Alzheimer's commonly experience difficulties in managing daily tasks and may also face cognitive and emotional challenges as the disease progresses. Alzheimer's disease (AD) indeed poses a significant challenge to

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global healthcare systems and has become a pressing concern, particularly in aging populations. As you mentioned, it has risen to become the third leading cause of death in the United States. AD is a progressive neurodegenerative disorder primarily affecting the elderly population. Its hallmark features include cognitive decline, memory loss, and impairment in daily activities. The disease progressively worsens over time, leading to significant challenges in managing daily routines and responsibilities. Aside from cognitive impairment, AD often brings about emotional disturbances in affected individuals. This can manifest as mood swings, anxiety, depression, and behavioral changes, which further impact the quality of life for both patients and their caregivers. The exact cause of Alzheimer's disease remains elusive, but it is believed to involve a complex interplay of genetic, environmental, and lifestyle factors. As the population continues to age globally, the prevalence of AD is expected to rise, further highlighting the urgent need for effective treatments and interventions to alleviate its burden on individuals, families, and healthcare systems [3]. Alzheimer's disease (AD) indeed presents one of the most significant medical challenges of our time, particularly concerning the field of dementia. Dementia, of which AD is the most common cause, affects millions of people worldwide, posing substantial burdens on individuals, families, and healthcare systems. The statistics you provided underscore the magnitude of this issue. With an estimated 40 million people currently living with dementia globally, the numbers are expected to escalate dramatically in the coming decades. Projections suggest that this figure could double every 20 years, potentially reaching alarming levels by around 2050 [4]. Alzheimer's disease is a serious illness that gets worse over time and eventually leads to death. It happens because the brain cells start to break down, causing problems with memory, talking, making decisions, and thinking clearly. This decline in brain function is irreversible, meaning it can't be reversed or stopped once it starts. [5]. As people get older, their chances of developing Alzheimer's disease increase. About 3% of those aged 65 to 74 have it, while it affects around 17% of those aged 75 and older. For people aged 85 and above, the risk goes up even more, with around 32% experiencing Alzheimer's disease. So, the older you are, the higher the risk of getting Alzheimer's. [6]. Alzheimer's disease is very common among older adults and is the leading cause of dementia, which is a condition that affects memory and thinking. It's so serious that it's considered the sixth leading cause of death in the United States by the Centers for Disease Control and Prevention (CDC). For older adults, it's the third most common cause of death, just after heart disease and cancer [7].

In Alzheimer's disease, there are several factors that contribute to its development. One of these factors is the buildup of a substance called Aβ plaque outside of brain cells. This buildup is a key feature seen in the brains of people with Alzheimer's. Aβ plaque is normally made in the brain and helps with cell signaling and the ability of brain cells to change and adapt. However, in Alzheimer's disease, certain enzymes act on a protein called amyloid precursor protein (APP) in a way that leads to the production of too much Aβ. This excess Aβ then clumps together outside of brain cells, forming the plaque that is associated with the disease. As people age, changes in certain genes related to how proteins are

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processed can lead to too much of a substance called Aβ being produced in the brain. Additionally, there may be problems in clearing away this excess Aβ. This buildup of Aβ leads to the formation of clumps called plaques. These plaques can harm brain cells, causing them to dysfunction and eventually die.

The excess Aβ can also disrupt normal brain processes and lead to inflammation in the brain, further contributing to damage and loss of brain function [8]. In Alzheimer's disease, many different genes likely play a role in increasing the risk, but each gene only contributes a small part to the overall risk. Four genes specifically linked to Alzheimer's are APP, PSEN1, PSEN2, and APOE. Together, these genes are responsible for about half of the genetic risk for the disease. So, while genetics is important, there are likely many other genes involved in Alzheimer's risk that we haven't identified yet [9].

Alzheimer's disease can be classified into two main subcategories: Early-Onset Alzheimer's Disease (EOAD) and Late-Onset Alzheimer's Disease (LOAD).

- Early-Onset Alzheimer's Disease (EOAD) occurs when symptoms start before the age of 65.

It's the most common cause of dementia in younger individuals [10].

- Late-onset Alzheimer's Disease (LOAD) is a form of Alzheimer's where symptoms begin at age 65 or older. It's considered a complex genetic disorder, meaning it's influenced by multiple genes and other factors. Researchers estimate that between 60% to 80% of the risk for LateOnset Alzheimer's Disease is inherited or passed down through families. This suggests that genetics plays a significant role in determining who develops the condition [11].

Options from herbal and traditional remedies such as traditional Indian medicine (Ayurveda) and Traditional Chinese medicine (TCM) are being researched because of the natural approach with insignificant side effects as compared to conventional allopathy methods. Research into herbal and traditional remedies, such as those from Ayurveda and Traditional Chinese Medicine (TCM), is gaining attention due to their natural approach and minimal side effects compared to conventional treatments. These traditional systems have contributed valuable medicinal herbs, compounds, and unique management methods to the field of medicine. India, in particular, boasts a rich history of traditional systems recognized by the Ministry of AYUSH, Government of India. These include Ayurveda, Unani, Siddha, Homeopathy, Yoga, and Naturopathy. Among these, Ayurveda is the oldest, dating back to around 5000 years B.C. It is also widely accepted, practiced, and flourished as an indigenous system of medicine. Ayurveda is a holistic system of medicine that emphasizes personalized treatment and aims to promote harmony in various aspects of human life. It encompasses

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medicine, pharmacology, health, and biomedicine. The principles of Ayurveda are rooted in logic and philosophy, offering comprehensive approaches to maintaining and restoring health. Research and review of Ayurvedic practices, medicinal herbs, and treatment methods are ongoing, with the goal of integrating traditional knowledge with modern healthcare practices. This holistic approach to health and wellness offers promising avenues for the development of effective and sustainable healthcare solutions [12].

RISK FACTORS: There's growing evidence that certain things increase the risk of

Alzheimer's disease, like genetics, problems with blood vessels in the brain, and certain health conditions. But there are also social and psychological factors that can affect how the disease develops and shows up in a person. By addressing these factors early on, we might be able to reduce the risk of getting Alzheimer's or delay its symptoms from showing up. Based on studies looking at patterns in populations, brain imaging techniques, and research on brain tissue, scientists have come up with three main ideas about what causes Alzheimer's disease. These are strong or moderately supported by evidence:

- Age
- Genetics
- Family history
- Vascular [13]

Age: Most cases of Alzheimer's disease occur in older adults, typically after the age of 65. It's rare in younger people. As people get older, their chances of developing Alzheimer's increase. Age is the biggest factor in the risk of getting Alzheimer's. If we could find ways to delay when

Alzheimer's starts, it would be really beneficial, but we haven't succeeded in doing that yet. As people get even older, the chances of having Alzheimer's go up. For instance, about 19% of people between 75 and 84 years old may have Alzheimer's, and this number could go up to 3035%, or possibly even 50%, for those older than 85 [14].

Genetic: Genetics plays a big role in Alzheimer's disease, with about 70% of the risk being linked to genes. There are two main types of genetic factors involved in Alzheimer's: Earlyonset Alzheimer's: This type usually occurs before the age of 65 and is caused by mutations in genes like APP, PSEN1, and PSEN2. These genes are responsible for making proteins that play a role in the production of a substance called amyloid. Mutations in these genes can lead to an imbalance in the production of different forms of amyloid, favoring the buildup of a type called Aβ42, which is associated with

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Alzheimer's. Late-onset Alzheimer's: This form is mainly linked to a variation in a gene called APOE, especially a version known as the ε4 allele. This variation is associated with an increased risk of developing Alzheimer's, particularly as people get older. In early-onset Alzheimer's, mutations in APP, PSEN1, and PSEN2 genes are responsible for around 15% to 80% of cases. These mutations disrupt the balance between different forms of amyloid, leading to its buildup in the brain tissue. It's also believed that there may be other genes involved in early-onset Alzheimer's besides these three [15].

Family history: Having a close family member, like a parent or sibling, who has had dementia is known to increase the risk of developing Alzheimer's disease. However, we don't fully understand how this family history affects a person's thinking and memory abilities throughout their life [16]. If one of your parents or siblings has Alzheimer's disease, your risk of developing it yourself is somewhat higher. However, we don't fully understand how genes within families influence this risk, and it's likely that genetic factors involved are complex and not fully explained yet. One well-studied genetic factor related to Alzheimer's disease is a version of the apolipoprotein E (APOE) gene called APOE e4. Having this version of the gene increases the risk of developing Alzheimer's disease. However, it's important to note that not everyone who carries this gene variant will develop the disease. About 25% to 30% of the population carries the APOE e4 gene variant [17].

Vascular: Vascular risk factors, such as smoking, obesity, and high cholesterol levels, along with conditions like high blood pressure, diabetes, and silent strokes, are linked to a greater risk of developing dementia, including Alzheimer's disease [18].

High blood pressure: Keeping your blood pressure under control is important for both your heart and your brain. Eating a healthy diet and avoiding high blood pressure can lower your risk of developing Alzheimer's disease.

Obesity: Being overweight increases the risk of having a buildup of amyloid plaque in the brain as you get older, which is linked to Alzheimer's disease. However, maintaining a healthy weight can reduce your risk of developing Alzheimer's.

Smoking: Smoking is harmful because it raises your chances of developing vascular diseases and can cause inflammation. Both factors increase the risk of Alzheimer's and other types of dementia.

Social isolation and depression: Social isolation and depression are considered risk factors for Alzheimer's disease. Studies have shown that loneliness, social isolation, and depression can have negative effects on brain health and increase the risk of cognitive decline and Alzheimer's disease. Maintaining social connections and addressing mental health issues like depression may help reduce the risk of developing Alzheimer's.

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Poor sleep: Not getting enough good-quality sleep and feeling very sleepy during the day can harm your brain function and lead to more amyloid plaque buildup, which is linked to Alzheimer's. If you have untreated sleep apnea, it may also increase your chances of getting Alzheimer's.

Physical inactivity: Exercising regularly is great for your brain. It helps improve your blood flow, keeps your weight in check, helps you sleep better, and can lift your mood. These are all important for reducing the risk of Alzheimer's disease.

Alcohol use: Drinking a little bit of wine might be good for your brain, but drinking too much can raise your risk of getting Alzheimer's disease.

Diabetes: Having diabetes increases your risk of developing dementia, including Alzheimer's disease. The longer and more severe your diabetes is, the higher your risk becomes. It's important to manage your diabetes carefully to help reduce this risk [19].

PATHOGENESIS

So far, we still don't fully understand the exact cause of Alzheimer's disease (AD). It's believed that a combination of genetic factors and environmental influences contributes to the most common form of the disease, known as late-onset sporadic AD. Researchers have been working hard to figure out how AD develops and to find drugs that can modify the course of the disease.

Two main factors seem to play a key role in the development of AD: beta-amyloid protein and abnormal tau protein. Both are thought to be involved in the formation of plaques and tangles in the brain, which are characteristic features of Alzheimer's. Alzheimer's disease (AD) is marked by an excess of beta-amyloid proteins (Aβ) and hyperphosphorylated tau protein. These abnormalities can result in the loss of connections between brain cells (synapses) and the death of neurons, particularly in areas of the brain responsible for memory and thinking, such as the hippocampus and cerebral cortex. This leads to a decline in cognitive function and eventually dementia. Neuroimaging, such as MRI or CT scans, of individuals with AD or other types of dementia may show changes in the structure of the brain. These changes can include shrinkage of brain tissue, seen as enlarged ventricles (fluid-filled spaces) and grooves on the surface of the brain (sulci), as well as narrower folds of brain tissue (gyri). However, these structural changes are not always present or may vary in severity among individuals with AD [20].

Aβ and APP Hypothesis:

The Aβ peptide was initially recognized as the main component of amyloid found in blood vessels surrounding the brain (meningovascular amyloid) in 1984, as identified by Glenner and Wong. Later, it was discovered to be the primary component of amyloid plaques that form in the brain's nerve tissue

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(amyloid neuritic plaques) [21]. The amyloid precursor protein (APP) can be processed through two pathways: the amyloidogenic pathway and the nonamyloidogenic pathway. In the amyloidogenic pathway, APP is cleaved by enzymes called β- and γ-secretases, resulting in the release of the Aβ peptide into the cytosol. The functions of both APP and Aβ are not fully understood, but they are believed to be involved in signaling pathways important for the development, growth, and survival of neurons. In Early-Onset Alzheimer's Disease (EOAD), genetic mutations may explain the accumulation of Aβ, but it's still unclear how this buildup occurs in Late-Onset Alzheimer's Disease (LOAD). Aβ accumulation is thought to contribute to neuronal death through various mechanisms, including excitotoxicity, disruption of synaptic connections, oxidative stress, and dysfunction of mitochondria. Excitotoxicity can happen when certain receptors in the brain, like NMDA receptors, are overstimulated, either directly by Aβ or through downstream effects [22]. In Alzheimer's disease (AD) patients, the amyloid precursor protein (APP) is processed differently compared to healthy brains. In AD, the APP is digested by a series of enzymes, including beta and gamma-secretases. This process produces insoluble peptides called amyloid-beta (Aβ), which clump together to form plaques. These plaques are harmful and contribute to the degeneration of brain cells. In contrast, in healthy brains, the cleavage of Aβ is mainly carried out by beta-secretase enzymes. This results in the formation of soluble fragments of APP, and the remaining portion of the APP is further cleaved by gammasecretase. This process produces peptides that are released outside the cell and are quickly removed or degraded, preventing the accumulation of harmful plaques [23].

Cholinergic Hypothesis:

The cholinergic hypothesis is a significant theory used to explain how Alzheimer's disease (AD) develops. According to this hypothesis, AD is caused by a decrease in the neurotransmitter acetylcholine (ACh) in the brain. Many drugs used to treat AD are based on this theory. The first neurotransmitter deficiency identified in AD was related to acetylcholine. Since acetylcholine is crucial for short-term memory function, researchers concluded that the deficit in cholinergic function in AD contributes significantly to the short-term memory problems experienced by individuals with the disease [24]. Markers for cholinergic neurons, like choline acetyltransferase and acetylcholinesterase, which are enzymes responsible for making and breaking down acetylcholine (ACh), are reduced in the cortex and hippocampus. These brain regions are crucial for memory and cognitive functions. In Alzheimer's disease, the earliest loss of neurons typically happens in the nucleus basalis and the entorhinal cortex. These areas are where cholinergic neurons are mostly affected. As the disease advances, up to 90 percent of cholinergic neurons in the nucleus basalis of Meynert may be lost. This loss of cholinergic neurons and decrease in acetylcholine contribute to the cognitive decline seen in Alzheimer's [25].

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Neurofibrillary tangles:

Neurofibrillary tangles (NFTs) are indeed another hallmark of Alzheimer's disease (AD), and they are primarily composed of a protein called tau. Tau is a microtubule-associated protein, meaning it plays a crucial role in stabilizing microtubules, which are structures essential for the transportation of nutrients and other substances within nerve cells, particularly in axons. In healthy neurons, tau proteins help maintain the structural integrity of microtubules, which are important for maintaining the shape of the cell and facilitating intracellular transport. However, in Alzheimer's disease, tau proteins become abnormally modified and accumulate within neurons, forming tangles. These tangles disrupt the normal functioning of the microtubules and are believed to contribute to neuronal dysfunction and ultimately cell death. In certain diseases, when tau proteins clump together, they can harm the axons of neurons, which are like the "wires" that transmit messages in the brain. This damage leads to the gradual breakdown of nerve cells, contributing to the decline of brain function, known as neurodegeneration. Despite many attempts to develop drugs targeting amyloid-beta (Aβ) for Alzheimer's disease (AD), these efforts have often ended in disappointment. As a result, there's growing interest in investigating therapies that target tau proteins instead. This interest has intensified because research suggests that tau pathology may be more closely associated with the advancement of AD, as indicated by studies on biomarkers. In essence, there's a shift in focus towards tau as a potential therapeutic target for AD treatment due to its apparent role in disease progression. Tau is a protein in the brain that plays a crucial role in maintaining the structure and function of nerve cells. It undergoes various changes, such as adding phosphate groups, attaching methyl groups to specific amino acids like arginine and lysine, adding acetyl groups to lysine, and removing methyl groups from lysine. These modifications can affect how tau behaves and interacts with other molecules, potentially influencing its function in nerve cell health and communication [26].

In simple terms, the progression of tau pathology in the human brain starts deep within the brain in areas like the locus coeruleus, which sends connections throughout the brain. Tau first appears in the axons of these cells before spreading to their main body. Then, it shows up in other deep brain areas with connections to the cortex. In the cortex, tau initially appears in certain types of brain cells involved in processing information. It starts in specific layers of the cortex before spreading to deeper layers and other regions involved in memory and learning. Finally, it reaches areas responsible for sensory and motor functions in the outer layers of the cortex [27,28].

Mitochondrial dysfunction and oxidative stress:

Mitochondrial dysfunction can indeed be associated with various neurodegenerative diseases, including Alzheimer's disease (AD). Mitochondria are essential organelles responsible for producing energy in the form of ATP through oxidative phosphorylation. They also play crucial roles in calcium signaling, apoptosis (programmed cell death), and cellular metabolism regulation. In Alzheimer's

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disease, changes happen in how mitochondria look, how many there are, and how they move around in cells. Also, the activity of a key enzyme called cytochrome oxidase decreases, which affects how mitochondria produce energy. There are not enough important proteins for metabolism, and the membrane of mitochondria changes. This all leads to more oxidative stress in cells. Neurons, the cells in our brains that help us think and feel, need a lot of energy to do their job. They get this energy from tiny structures called mitochondria, which act like power stations. These mitochondria gather around the connections between neurons, called synapses, to provide the energy needed there. But when these synapses are busy, they produce a lot of waste in the form of reactive oxygen species (ROS) [29]. In Alzheimer's disease, reactive oxygen species (ROS) and reactive nitrogen species (RNS) are produced during normal processes in the brain but can also increase due to the disease. While these substances have some helpful roles in signaling within brain cells, they can also cause damage to important structures like the cell membrane, fats, proteins, and DNA. This damage contributes to the progression of Alzheimer's disease by harming brain cells and disrupting their function. So, controlling these reactive species could be important in managing the disease. The brain's high demand for oxygen makes it more prone to oxidative stress, where harmful molecules called reactive oxygen species can damage brain cells. Neurons, the building blocks of the brain, are particularly vulnerable because they contain many delicate polyunsaturated fatty acids. When these fatty acids are attacked by reactive oxygen species, it can lead to further damage and contribute to the progression of Alzheimer's disease. So, protecting neurons from oxidative stress could be crucial in managing Alzheimer's. There is a process called lipid peroxidation, where reactive oxygen species (ROS) can mess with the fats in brain cells. This can lead to a chain reaction causing cell death, known as apoptosis. Moreover, neurons in Alzheimer's disease often have lower levels of a protective substance called glutathione, which makes them more vulnerable to oxidative stress. So, when there's not enough glutathione and ROS messes with the fats, it can cause serious damage to brain cells, contributing to the progression of Alzheimer's disease [30].

Diagnosis:

There is no single test for the diagnosis of AD; currently in clinical practice, AD is typically diagnosed by a multi-disciplinary workup based on patient history; clinical symptoms; a variety of neuropsychiatric, physical, and functional assessments [31]. Currently, available diagnosis for AD includes mini-mental state examination (MMSE) evaluations, cerebrospinal fluid

(CSF) assay for Aβ, magnetic resonance imaging (MRI) for brain volume, and positron emission tomography (PET) scan for Aβ plaques and alterations in glucose metabolism [32].

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MMSE (Mini-mental state examination)

The Mini-Mental State Examination (MMSE) is a test commonly used to check for memory and thinking problems in older adults. It works best when it's done regularly, carefully, and in a structured way. If someone's scores on the test go down over time, it could mean they're having trouble with their memory or thinking skills. However, how well the MMSE works as a test for dementia depends on how much education the person being tested has had [33].

CSF (Cerebrospinal fluid Assay)

Doctors can test the fluid around the brain and spine, called cerebrospinal fluid (CSF), to help diagnose Alzheimer's disease. They look for specific markers like Aβ42, tau, and ptau. By analyzing these markers together, doctors can tell if someone has Alzheimer's or not. In Finland, these CSF Alzheimer's biomarker tests have been available since 2004 and have been used in the country's guidelines for diagnosing and treating memory problems since 2010 [34].

MRI (Magnetic resonance imaging)

Magnetic resonance imaging (MRI) is a useful and safe way to take detailed pictures of the brain without surgery. It can show both the structure and function of the brain. Doctors use MRI to look for signs of Alzheimer's disease by examining things like the thickness of the brain's outer layer (cortex) and changes in brain tissue over time. For example, when neurons die, the brain can shrink, so MRI can help spot these changes. It can also show blood flow and activity in different parts of the brain, which can be important for understanding Alzheimer's disease [35].

PET (Positron emission tomography)

Positron emission tomography (PET) is a type of imaging technology that helps doctors detect certain proteins associated with Alzheimer's disease. Recent advancements in PET scanning allow doctors to see these proteins, specifically amyloid-beta (Aβ) and tau, in the brain. Amyloid PET is currently recommended by the Alzheimer’s Association and the Amyloid Imaging Task Force to help diagnose Alzheimer's disease. During an amyloid PET scan, special tracers bind to Aβ plaques in the brain, which can confirm their presence. This helps doctors better understand the extent of amyloid buildup in the brain, aiding in the diagnosis of Alzheimer's disease [36].

Treatment

Right now, there are about 24 million people worldwide with Alzheimer’s disease. By 2050, it's estimated that this number will quadruple. This means Alzheimer's is becoming a big public health concern. However, there are only two types of drugs approved to treat Alzheimer's. One type works

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by blocking an enzyme called cholinesterase, and the other type blocks a receptor called NMDA. These drugs help manage symptoms, but they don't cure the disease [37].

Currently, the drugs available for Alzheimer's disease only help with symptoms and don't cure the disease. These drugs focus on improving communication between brain cells or protecting them from damage. The main ones work by either boosting a chemical called acetylcholine or blocking another chemical called glutamate. These drugs include donepezil, rivastigmine, galantamine, and memantine. They can improve memory and thinking skills, which helps patients, and their families cope better with the challenges of Alzheimer's. However, they don't stop the disease from getting worse. Researchers are working on developing new drugs that target the specific proteins involved in Alzheimer's, like amyloid and tau, with the hope of finding a cure. A review of studies where people with moderate to severe Alzheimer's disease took memantine showed that it helped improve their memory, ability to do daily tasks, and behavior after using it for 6 months. This means that memantine can make a positive difference in the lives of people with advanced Alzheimer's disease [38].

These treatments, while they can help with some symptoms of Alzheimer's disease, don't address the root cause of the disease itself. They only provide temporary relief and don't stop the disease from progressing. So, while they can improve quality of life for some time, they don't offer a permanent solution or cure for Alzheimer's [39]. The medications known as acetylcholinesterase inhibitors (AChEI), used to treat Alzheimer's disease, can sometimes cause problems in the heart because they increase the level of acetylcholine not just in the brain but also in the rest of the body. Some of the reported cardiovascular side effects include slowing of the heart rate (bradycardia) and lengthening of the QT interval on an electrocardiogram (QTc prolongation). In severe cases, this can lead to a dangerous heart rhythm disorder called Torsade de Pointes (TdP) [40]. Thirteen case reports in total (10 for donepezil, 2 for galantamine, and 1 for rivastigmine) from the period of time up until October 2019 were included. QTc prolongation resulted in TdP in 5 out of the 10. Memantine may cause various gastrointestinal side effects including constipation, diarrhoea, vomiting, and abdominal pain. The increased risk of gastrointestinal side effects for dual therapy with memantine [41].

In recent years, there has been growing interest among researchers and doctors in using herbalbased medicines to treat neurodegenerative diseases (ND). These herbal remedies, which have their roots in ancient practices and principles, have become popular because they often have fewer side effects compared to conventional medications. They are also effective in treating a wide range of health issues, they tend to be less expensive, and they are easier to find and access [42].

Herbs used in treatment of Alzheimer's disease Withania somnifera (Ashwagandha):

Withania somnifera, commonly known as Ashwagandha, belongs to the Plantae kingdom, Magnoliophyta division, and Magnoliopsida class. It is further classified under the Solanales order and

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Solanaceae family. Within the Solanaceae family, Ashwagandha is placed in the genus Withania [43]. This remarkable substance exerts a multifaceted impact on neurological health by functioning as both an antioxidant and anti-inflammatory agent, effectively addressing oxidative stress and inflammation—integral factors in neurodegenerative processes.

It plays a crucial role in inhibiting the production of Aβ, a protein linked to Alzheimer's disease, while also preventing neural cell death [44].

In the study by Sharma et al. 2023 studied the effect of the aqueous extract of the roots of *W. somnifera* in the cell-based assays and in the experimental animal models of (Lipopolysaccharide) LPS-induced inflammation. In addition, *W. somnifera* extract also showed potent anti-inflammatory activity in the lung tissues of mice challenged intranasally with LPS. Results obtained thus suggest the potential utility of *W. somnifera* extract in reducing airway inflammation and recommend the clinical evaluation of *W. somnifera* extract in COVID-19 patients with a high propensity for lung inflammation [45].

In another study by Omar, F et al 2021 prepared aqueous chloroform extract of Withania somnifera roots. They subjected the extract on rat and observed that the extract reduced cholinergic marker activity. Their result shows the Anti cholinergic activity and used in the treatment of Alzheimer's disease [46]. Further study Uddin et al 2019 prepared the aqueous methanol extract of Withania somnifera root. The extract was administered on mice, they observed effect centred around the reversal of anti-acetylcholinesterase (anti-AChE) activity. Their study suggested that Withania somnifera extract may play a role in augmenting cholinergic function, potentially offered therapeutic implications for conditions related to cholinergic neurotransmission dysfunction [47].

Curcuma longa (Turmeric):

Curcuma longa (C. longa) Linn is a perennial herb belonging to the family Zingiberaceae. It is grown for commercial use in South and Southeast Asia. Curcumin, also known as turmeric, is obtained from the rhizome of the plant. Several preparations of the plant have been used for centuries in the Ayurvedic system of medicine [48]. Curcumin has powerful antioxidant and anti-inflammatory properties; according to the scientists, these properties believe help ease Alzheimer's symptoms caused by oxidation and inflammation. The process through which AD degrades the nerve cells is believed to involve certain properties: inflammation, oxidative damage and most notably, the formation of beta-amyloid plaques, metal toxicity [49]. In a randomized controlled trial conducted by Thota et al., 29 individuals received a placebo, while 14 participants were administered a daily dose of 180 mg of curcumin for a duration of 12 weeks. The study focused on assessing the impact of curcumin supplementation on plasma levels of glycogen synthase kinase-3 (GSK-3) and islet amyloid polypeptide (IAPP). The results indicated a significant decrease in both GSK-3β levels with dietary supplementation of curcumin. These findings suggest a potential modulatory effect of curcumin on

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GSK-3 and IAPP, emphasizing its role as a candidate for further exploration in the context of glycemic control and associated metabolic processes [50].In another study by HV S et al 2020 investigated the cholinesterase inhibitory effects of a first-of-its-kind turmeric extract (REVERC3) having enriched content of bisdemethoxycurcumin as major active curcuminoid.

They used a method called Ellman's colorimetric assay to study how well REVERC3 could inhibit acetylcholinesterase and butyrylcholinesterase, which are enzymes involved in breaking down certain chemicals in the brain. To understand how REVERC3 interacts with these enzymes, they looked at their kinetics using a technique called Lineweaver–Burk double reciprocal plots. Additionally, they used a computer program called Auto Dock tools to predict how well a compound called bisdemethoxycurcumin could bind to the active sites of cholinesterases, providing insight into its potential effectiveness as a treatment. The findings suggested that turmeric extract with a high amount of bisdemethoxycurcumin could enhance brain functions related to memory and thinking by blocking two key enzymes, cholinesterases [51].

Ginkgo biloba:

Ginkgo biloba, belonging to the family Ginkgoaceae, is a unique and ancient species with no close living relatives. Native to China, this deciduous tree is renowned for its distinctive fanshaped leaves and resilience, as it is often referred to as a "living fossil." The biological source of medicinal interest lies in the leaves, which contain various bioactive compounds, including flavonoids and terpenoids. Ginkgo biloba has been extensively utilized in traditional medicine for its potential health benefits. Widely recognized for its neuroprotective properties, it is often employed to enhance cognitive function and memory. As a herbal supplement, its medicinal uses extend to its antioxidant properties, suggesting a role in mitigating oxidative stress [52]. Remarkably, the extract of G. biloba leaves (EGb) attenuates the neuronal damage in animals and in vitro. The chemical constituents of EGb are evaluated as follows: 22%–27% of flavone glycosides, 2.8%–3.4% of Ginkgolide A, B, and C, 2.6%–3.2% of bilobalide, and less than 5 ppm of ginkgolic acid [53].

Singh et al 2023 outlined the research employing EGB761 as a dual target for AD. This study explored different methods to stop Alzheimer's disease by using computer-based methods like molecular docking, network pharmacology, ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity), and predicting how effective certain compounds. In this study, researchers looked at the effects of different plant compounds found in EGB761 on Alzheimer's disease. They found that four specific compounds—kaempferol, isorhamnetin, quercetin, and ginkgotoxin—were very effective at blocking enzymes associated with Alzheimer's disease, like acetylcholinesterase (AChE) and GSK3β. Among these compounds, quercetin, kaempferol, and isorhamnetin showed the highest activity against these enzymes, even more than some synthetic drugs used for Alzheimer's. The study suggested that these plant compounds might work on multiple targets involved in Alzheimer's disease and that

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blocking AChE could be a key factor in the effectiveness of EGB761 in treating Alzheimer's [54].

In another study by Batawi A H et al 2022 used natural products such as G*inkgo biloba* (*G. biloba*) extract that has the potential to reduce Aβ formation and increase AchE inhibition with its ability to save neuronal DNA from damage. In the study, sixty male rats were used to create an Alzheimer's disease model by exposing them to aluminum chloride (AlCl3). These rats were then divided into six groups and treated with Ginkgo biloba (G. biloba) extract. The researchers collected brain tissues from the rats to study various factors related to Alzheimer's disease, including apoptosis rate (cell death), generation of reactive oxygen species (ROS), activity of acetylcholinesterase (AChE), changes in the expression of genes associated with Alzheimer's (ApoE4 and Clu), DNA fragmentation, and activity of an enzyme called glutathione peroxidase (GPx). The study showed that rats exposed to aluminum chloride (AlCl3) had higher levels of cell death (apoptosis), increased production of reactive oxygen species (ROS), DNA damage (fragmentation), higher expression of genes linked to Alzheimer's (ApoE4 and Clu), and reduced activity of acetylcholinesterase (AChE) and glutathione peroxidase (GPx) compared to rats not exposed to AlCl3. However, when the AlCl3-exposed rats were treated with Ginkgo biloba (G. biloba) extract, these negative effects were reduced. In simpler terms, the G. biloba extract helped improve the harmful effects caused by exposure to AlCl3 in the rats' brains, which are like changes seen in Alzheimer's disease [55].

Bacopa Monnieri (Brahmi):

Brahmi, or Bacopa monnieri (Bm), is a perennial creeper medicinal plant found in the damp and marshy wetlands of Southern and Eastern India, Australia, Europe, Africa, Asia, and North and South America. In the Ayurvedic system of medicine, Bm is recommended for mental stress, memory loss, epilepsy, insomnia, and asthma. The bioactive phytochemicals present in this plant include saponins, bacopasides III, IV, V, bacosides A and B, bacosaponins A, B, C, D, E, and F, alkaloids, sterols, betulic acid, polyphenols, and sulfhydryl compounds, which may be responsible for the neuroprotective roles of the plant.

Bacopa monnieri, or Brahmi, has an antioxidant and anti-inflammatory effect that enhances memory, attention, and executive function. It also prevents the generation of Aβ, slows the aging process of the brain and improves heart function [56].

In a study by Sushma et al. 2023 looked into how a natural herb called Bacopa monnieri (BM) could help in Alzheimer's disease (AD). They used rats with conditions similar to AD by injecting them with amyloid-β42 (Aβ42) fibrils in their hippocampus. The rats were given BM extract orally for four weeks. The study found that BM treatment improved the rats' cognitive abilities and exploration behaviour, which were impaired due to Aβ42. BM also lowered oxidative stress, reduced inflammation, and decreased cholinesterase activity in the AD rats. Additionally, BM helped balance

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the levels of proteins related to cell survival (Bcl-2) and cell death, increased the expression of growth factors for nerves, and protected against nerve cell damage in the hippocampus. Remarkably, BM treatment even reduced the buildup of amyloid plaques in the hippocampus and normalized the increased levels of certain proteins associated with AD, like phospho-tau and total tau. Scientists discovered that BM interacts with a protein called glycogen synthase kinase (GSK-3β) and restores a signaling pathway important for cell communication. Overall, the study showed that BM could potentially be a helpful treatment for Alzheimer's disease by targeting various aspects of its progression [57].

In another study by Dubey, T et al 2023 examined whether an extract from Bacopa monnieri, a type of herb, could help in Alzheimer's disease. They tested it to see if it could stop Tau, a protein that builds up in Alzheimer's, from clumping together and damaging brain cells. They found that the Bacopa monnieri extract did indeed prevent Tau from clumping in lab tests. When they tested the extract on cells stressed by Tau, they saw that it reduced the levels of harmful substances like ROS and caspase-3, which can harm brain cells. The extract also acted as an antioxidant, helping to protect the cells from damage, and restored the levels of a protein called Nrf2, which is important for cell health. The Bacopa monnieri treatment also reduced the amount of phosphorylated Tau, another harmful form of the protein, in stressed cells.

Additionally, it lowered the activity of a protein called GSK-3β, which is involved in Taurelated damage. The study also looked at how Bacopa monnieri affected the transport of proteins in cells. They found that when cells were stressed by a substance called formaldehyde, a protein called NUP358, which helps with protein transport, was disrupted. However, treatment with Bacopa monnieri restored the normal arrangement of NUP358, suggesting it could help with protein transport in stressed cells. Overall, the results suggested that Bacopa monnieri could be a powerful tool against the harmful effects of Tau in Alzheimer's disease, making it a promising treatment option [58].

Convolvulus pluricaulis (Shankhpushpi):

Convolvulus pluricaulis (synonym, Convolvulus prostratus Forssk) belongs to family Convolvulaceae is a perennial herb native to the Indian subcontinent. Commonly termed as Shankhpushpi in Ayurveda, C. pluricaulis (Cp) has been indicated for various human ailments, including those affecting the central nervous system, namely, anxiety, depression, epilepsy, and dementia [59]. Shankhpushpi, or Convolvulus pluricaulis (Cp), is used for nerve regeneration and for improvement of memory.

In a study by Deore, S.L. et al 2023 compared the neuroprotective effects of Convolvulus pluricaulis (C. pleuricaulis) and Convolvulus ternatea (C. ternatea), both herbs were extracted using ethanol. Through various laboratory tests, including in vitro assays for free radical scavenging and enzyme inhibition, it was found that both extracts exhibited neuroprotective properties. However, in vivo

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experiments using rats with Alzheimer's disease-like symptoms induced by scopolamine showed that C. pleuricaulis significantly improved spatial and working memory compared to C. ternatea. This suggests that C. pleuricaulis may be more effective in reducing oxidative stress, inflammation, and memory impairment associated with Alzheimer's disease. As a result, it is recommended that C. pleuricaulis be prioritized as the primary source of Shankhpushpi in neuroprotective formulations over C. ternatea [60]. In another study by Nath, R. et al 2022 evaluated the effect of C. pluricaulis alone and in combination with Omega-3 fatty acids to address Alzheimer's disease. The study conducted on Wistar rats administered C. pluricaulis whole plant powder at doses of 100 mg/kg and 400 mg/kg body weight, along with Omega-3 fatty acids at a dose of 500 mg/kg body weight. Using a scopolamine-induced amnesia model, behavioral analysis was conducted to assess memory enhancement. Additionally, acetylcholinesterase (AchE) estimation in rat brain tissue was performed using spectrophotometry. Results indicated that C. pluricaulis significantly enhanced memory in a dose-dependent manner, both when administered alone and in combination with Omega-3 fatty acids at the higher dose of C. pluricaulis (400 mg/kg body weight). These findings suggest the potential of C. pluricaulis, particularly in combination with Omega-3 fatty acids, for memory enhancement in Alzheimer's disease [61].

Conclusion

Herbal medicine shows potential as an alternative or complementary treatment for Alzheimer's disease. Some herbal remedies have demonstrated promising effects in improving cognitive function and reducing symptoms in patients. However, the evidence is still limited, and more rigorous studies are needed to confirm the safety and effectiveness of these treatments. Standardized dosages, quality control, and clear guidelines for use are essential to ensure the safe application of herbal medicine for Alzheimer's. Collaboration between researchers, healthcare providers, and regulatory bodies can help integrate herbal treatments into Alzheimer's care, offering patients more options for managing their condition.

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