

REVIEW ARTICLE

An Overview of Etiology, Pathophysiology, and Promising Herbal Remedy for Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is a progressive brain disease that gradually reduces a person's ability to think clearly, remember things, and even carry out simple cognitive tasks. It is the most common cause of dementia among the elderly. Although the exact cause is still unknown, genetic factors account for 5 to 10% of instances having a family origin. The damage leads to significant degeneration of the afflicted areas, resulting in memory loss, impaired capacity to acquire new knowledge, fluctuations in mood, difficulties in cognitive functioning, and an inability to do basic everyday tasks. However, it is still commonly acknowledged as the primary reason of dementia worldwide. The two chief pathological landscapes of AD are the build-up of substances outside the cells and the formation of twisted fibers within the cells, known as neurofibrillary tangles. Accumulation of A β amyloid (A β) initiates neurodegeneration, leading to the development of clinical dementia, which is a defining feature of AD.

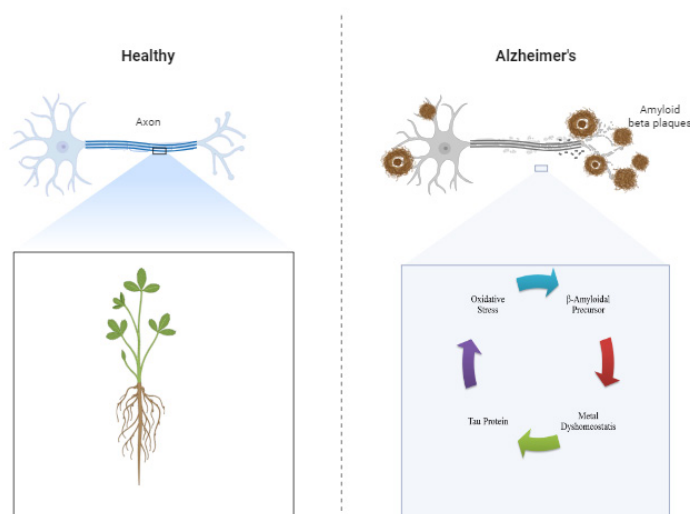
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Graphical Abstract

INTRODUCTION

Alzheimer's disease (AD) is a highly debilitating neurological condition that mainly affects geriatric residents.¹ This condition is not receiving enough treatment and is not being acknowledged, even though it is becoming a significant issue for public health.² He characterized this condition as a severe illness affecting the cerebral cortex.³ The worldwide occurrence of dementia among individuals aged 60 and above was assessed to be 3.9%.⁴ Dementia is a wide-ranging term that describes a noteworthy destruction in cognitive function that hampers one's capacity to carry out daily tasks.⁵ The stages in question diverge from the DSM-5 categorization of AD.⁶ This symptom may be identified in most patients, even if it is not the initial complaint. Deterioration of problem-solving, organizing, motivating, executive functioning, and judging skills follows short-term memory impairment. AD is universally acknowledged as a significant public health issue.⁸ Empirical evidence indicates that these days it might be considered a major global health concern. Hence, it is the need of hour to pay attention.⁹ Although there has been notable scientific and clinical progress in the diagnosis and treatment of AD. The current treatments primarily emphasize on improving symptoms slightly rather than addressing the fundamental causes.¹⁰

Etiology of AD

The two main neuropathological characteristics of AD are NFT and senile plaques. The senile plaques appear first in the regions of the brain that deal with cognition, and then gradually, they spread to the other cortical areas as the disease progresses.^{11,12} Senile plaques contain not only β -amyloid ($A\beta$) amyloids but also amyloid precursor protein (APP) and other components. The A peptide is made as an outcome of two sequential cleavage operations, with APP secretase catalyzing

proteolytic activity to produce the starting end of the A peptide. In addition, the γ -secretase also drinks up the proteolysis on the other side.¹³ There are two forms of A42: A42, which is lengthy, and A40, which is short. It is $A\beta_{42}$ that is first deposited and is generally responsible for starting the series of events that lead to amyloid deposition.¹⁴ There are still doubts about the part of senile plaques in AD, as whether they are the main cause or a secondary result remains uncertain. Nevertheless, there is presently the fact that interruption in handling of APP, resulting in accretion of insoluble $A\beta$, is the cause of AD.¹⁵ $A\beta$ is neurotoxic both directly, for instance, or indirectly via the induction of inflammation. The neurofibrillary tangles contain tau protein that has gone through different chemical alterations. Tau protein is a major part of microtubule production.¹⁶ The amount of tangle formation is directly related to how severe the disease is, with more tangles in the brain being associated with a later stage of the disease.¹⁷ However, neurofibrillary tangles are a feature of AD but have not been associated with changes in the gene located on chromosome in any patient. However, some families with this mutation have been discovered to have frontotemporal dementias with Parkinsonism. Recent research supports the observation that tau change occurs after $A\beta$ build-up in patients with AD.¹⁸

Epidemiology

AD is a predominant neurological ailment that significantly impacts global health. Numerous facets of AD, such as its incidence, risk factors, and effects on people globally, have been clarified by epidemiological studies. Up to 75% of cases worldwide are caused by AD, making it the most prevalent dementia cause. AD is more common as people age, especially beyond the age of 65. Between the ages of 60 and 85, there is a notable increase in the disease's prevalence. The worldwide prevalence of AD is predicted to increase due to demographic

Table 1: Incidence of dementia in developed and developing countries²⁰

<i>Region</i>	<i>Consensus dementia prevalence at age \geq 60 years (%)</i>	<i>Estimated annual incidence of dementia (per 1,000 individuals)</i>	<i>People with dementia aged \geq years in 2001 (millions)</i>	<i>Estimated increase in proportion of people with dementia from 2001 to 2040 (%)</i>
Western Europe	5.4	8.8	4.9	102
Eastern Europe (regions with low adultmortality)	3.8	7.7	1.0	169
Eastern Europe (regions with high adultmortality)	3.9	8.1	1.8	54
North America	6.4	10.5	3.4	172
Latin America	4.6	9.2	1.8	393
North Africa and Middle Eastern crescent	3.6	7.6	1.0	385
Developed western pacific	4.3	7.0	1.5	189
China and developing western Pacific	4.0	8.0	6.0	336
Indonesia, Thailand, and Srilanka	2.7	5.9	0.6	325
India and south Asia	1.9	4.3	1.8	314
Africa	1.6	3.5	0.5	235
Combined values	3.9	7.5	24.3	234

trends and aging populations, particularly in emerging nations. This will provide serious challenges to public health and systems for caring for the aged. The frequency and occurrence of dementia in advanced and evolving countries is shown in Table 1. Alzheimer's disease causes significant mental stress and emotional difficulties for caregivers as well as for patients.¹⁹

Pathophysiology of AD

AD is a complicated brain disease that affects various brain functions. Furthermore, it should be noted that subcortical nuclei, which is associated with the serotonergic activity; the locus coeruleus, which is responsible for noradrenergic function; and the basal nucleus, which is involved in cholinergic processes, also demonstrate a reduction in neuronal population. The strength of the relation between the harshness of dementia and the size and location of tangle formation surpasses the correlation seen with the number of amyloid plaques. A robust correlation has been shown between the aggregation of tau proteins, the weakening in mental abilities, and the decrease in brain volume, namely in the hippocampus. The neuropathological features of AD include neuronal demise and shrinkage in the temporofrontal cortex, which subsequently triggers the emergence of inflammatory responses and the accretion of amyloid plaques. The plaques comprise an anomalous accumulation of protein fragments,

followed by the development of intertwined bundles of fibers, consequently, around the significant rise in the population of macrophages and monocytes inside the cortex. Furthermore, this particular procedure elicits microglial cells' activation inside the parenchyma.²¹⁻²³

Furthermore, it should be noted that subcortical nuclei, such as the dorsal raphe, which is associated with serotonergic activity; the locus coeruleus, which is responsible for noradrenergic function; and the basal nucleus, which is involved in cholinergic processes, also demonstrate a reduction in neuronal population. The strength of the link between the harshness of dementia and the size and location of tangle formation surpasses the correlation seen with the number of amyloid plaques. A robust correlation has been shown between the aggregation of tau proteins, the decline in cognitive abilities, and the reduction in brain volume, namely in the hippocampus. The neuropathological features of AD include neuronal demise and shrinkage in the temporofrontal cortex, which subsequently triggers the emergence of inflammatory responses and the accumulation of amyloid plaques. The plaques comprise an anomalous accumulation of protein fragments, followed by the development of intertwined bundles of fibers. Furthermore, this particular procedure elicits microglial cells' activation inside the parenchyma.²⁴⁻²⁶

The growth of senile plaques (SP) is a prominent extreme characteristic of AD, subsequent from the deposition of amyloid beta ($A\beta$). The etiology behind the creation of $A\beta$ remains uncertain; nonetheless, the order, concentration, and constancy situations of $A\beta$ are recognized as significant contributing factors. The etiology of AD is believed to be triggered by

several mechanisms, counting failure in the cholinergic system, toxicity resulting from amyloid and tau proteins, and dysfunctions in oxidative stress and mitochondrial processes.²⁷

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are formed due to numerous physiological and pathological mechanisms inside the human body. These species have a dichotomous characteristic, as they fulfill crucial roles in intracellular signaling cascades while presenting a plausible peril to cellular constituents such as the DNA, proteins, lipids and cell membrane, resulting in detrimental effects. The brain has a notably higher oxygen consumption rate than other tissues that undergo mitochondrial respiration. This heightened metabolic demand concentrates the brain's additional liability towards the detrimental properties of oxidative stress. The neuron, the brain's fundamental operational component, comprises a substantial quantity of polyunsaturated fatty acids.²⁸

The dysregulation of metal homeostasis plays a significant role in advancing and developing several illnesses, including neurodegenerative disorders and tumors. Several of these compounds have been used in clinical studies to investigate their therapeutic potential. Metal chelators are not the only pharmaceutical agents able to modulate transition metal equilibrium.²⁹

The binding of cholinergic receptors in some brain areas is diminished in entities with slight to severe AD, and this reduction is associated with the manifestation of neuropsychiatric symptoms. A potential correlation between reduced receptor binding and decreased processing speed has been seen in the elderly in good health. Furthermore, it may provide a viable biological target for therapeutic interventions. This drop in cholinergic neurons is accompanied by a corresponding fall in neurotransmission mediated by acetylcholine. Key pathophysiological factors that are responsible for AD are depicted in Figure 1.³⁰

Natural Herbs Recommended in AD

Withania somnifera

Indian Ayurvedic herb *W. somnifera*, popularly called ashwagandha, is used in various neurological disorders like AD.³¹ It has been demonstrated that the active component of

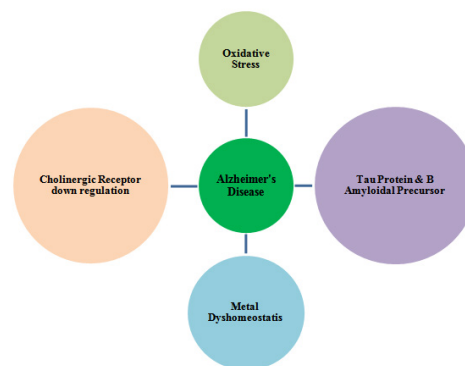


Figure 1: Key pathophysiological factors responsible for AD

ashwagandha, which raises the liver's synthesis of a protein connected to low-density lipoprotein receptors, effectively treats a variety of neurodegenerative diseases, including AD.³² This improvement is supposed to be critical in reversing the pathophysiology of AD. When *W. somnifera* root extracts were given orally to Alzheimer's transgenic mice, the accumulation of A β and behavioral abnormalities were reduced.³³⁻³⁴ This was due to an increase in liver-associated protein that is linked to low-density lipoprotein receptors considerably and dose-dependently lower stress and memory loss.³⁵ Additional research on ashwagandha has revealed that it possesses antioxidant and anti-inflammatory qualities, which may support its neuroprotective benefits.³⁶

Bacopa monnieri

B. monnieri is the ancient Indian herb *B. monnieri*, also referred to as Brahmi, has been utilized in millennia in traditional medicine for a variety of conditions, including epilepsy, anxiety reduction, and memory improvement.^{37,38} Strong antioxidants found in *B. monnieri* may help guard against cell damage brought on by free radicals, which have been related to a number of chronic illnesses, including neurological diseases like AD. The herb's possible therapeutic benefits in AD may be attributed to its antioxidant properties.³⁹ The ancient Indian herb *B. monnieri* has demonstrated encouraging

neuroprotective and cognitive effects in experiments conducted on animals and *in-vitro*, indicating that it may be useful as a treatment for AD.⁴⁰⁻⁴² The herb's antioxidant qualities and neuroprotective effects make it an intriguing subject of study for the treatment of AD, even if human investigations have yielded conflicting results. To completely comprehend the impact of *B. monnieri* on neurodegenerative disease, more research is required.⁴³⁻⁴⁴

Ginkgo biloba

G. biloba has garnered attention primarily due to its possible efficacy in dealing with AD. *G. biloba* has the potential as a beneficial agent for several long-lasting and acute disorders.^{45,46} The primary classes of pharmacologically active compounds present in plants are flavonoids and terpenoids.⁴⁷ The administration of *G. biloba* extract has demonstrated advantageous outcomes in the treatment of AD, cardiovascular disorders, cancer, tinnitus, and other problems related to aging.⁴⁸ The planned mechanisms of action for *G. biloba* extract include its antioxidant properties.⁴⁹ The *G. biloba* extract counteracts the harmful effects of β amyloid and NO in laboratory settings and reduces cell death in laboratory settings and living organisms.^{50,51}

Centella asiatica

C. asiatica is a fundamental component in Chinese, Indonesian, and Ayurveda medicine. Research has indicated that extended administration of *C. asiatica* can augment cognitive performance, lower amyloid- β levels, and boost memory and executive function in models of Alzheimer's disease.^{52,53} Moreover, it has been found that *C. asiatica* prevents Alzheimer's disease symptoms by triggering

specific brain communication channels.^{54,55} The constituents madeassic acid, asiatic acid, asiaticoside, and made cassoside are responsible for its anti-inflammatory, wound-healing, and antioxidant properties.⁵⁶ Because of its supposed benefits for skin, *C. asiatica* is frequently used in skin care products as moisturizers, anti-aging lotions, and wound treatments.^{57,58} Based on the study in AD models, it has been demonstrated that *C. asiatica* reduces the build-up of amyloid- β and the development of plaque.^{59,60}

Hericium erinaceus

H. erinaceus a consumable fungus, is prevalent in North America, Europe, and Asia.⁶¹ Traditional Chinese medicine commonly employs it due to its neuroprotective, anti-cancer, and anti-inflammatory qualities.⁶² The advantages can be linked to the two main components of *H. erinaceus*, specifically hericenones and erinacines.⁶³ Through the use of many cell lines, it was noted that the administration of *H. erinaceus* extract resulted in an augmentation in NGF expression.⁶⁴ The extract of *H. erinaceus* demonstrated the ability to enhance the length of neuritis in both cell lines and cultured neurons when NGF was present (Li IC *et al.* 2018). *H. erinaceus* also increased hippocampal neurogenesis and enhanced cognitive performance in aged rodents fed an extract of *H. erinaceus* for two months.⁶⁵⁻⁶⁸

Convolvulus pluricaulis

C. pluricaulis is utilized for nerve regeneration and enhancing memory.⁶⁹ These compounds are accountable for the cognitive-enhancing and memory-improving effects of the plant.⁷⁰⁻⁷² The herb is also suggested for alleviating mental stress, weariness, anxiety, and sleeplessness. *C. pluricaulis* extract dissolved in ethanol exhibited notable antioxidant properties during *in-vitro* testing and substantially enhanced learning and memory in rats.⁷³ Neonatal rat pups that were given an aqueous root extract of *C. pluricaulis* showed enhanced retention and spatial learning abilities. Furthermore, a notable augmentation in acetylcholine (ACh) levels and functioning was detected, potentially serving as the foundation for their enhanced cognitive abilities and retention.⁷⁴⁻⁷⁶

Curcuma longa

C. longa is a flowering plant belonging to the Zingiberaceae family, part of the ginger family. *C. longa* possesses anti-inflammatory, antiseptic, and antibacterial properties. It has a longstanding history of treating many ailments, such as liver purification, infection and inflammation prevention, cholesterol level regulation, allergy management, digestive stimulation, and immune system enhancement.⁷⁷ The primary components of *C. longa* are turmerone oil and curcuminoids that are soluble in water. The findings indicate a notable enhancement in cognitive function in both dosage groups compared to the untreated group. Moreover, the group receiving a larger dose of curcumin exhibited a more pronounced cognitive improvement. Furthermore, curcumin decreased the accumulation of A β deposits may be enhanced by autophagy.⁷⁸

CONCLUSION

Approximately 5.8 million individuals in the US are afflicted with AD. By 2050, the anticipated number of individuals suffering from AD or other forms of dementia is expected to reach 13.8 million. The US alone incurred healthcare expenditures and missed income up to an estimated USD 290 billion in 2019 for individuals with AD and their caretakers. It is predicted that by 2050, the US will spend USD 1.1 trillion on AD. Hence, it is imperative to discover novel medications to prevent and treat AD. Although several novel strategies for treating symptoms and regulating the progression of AD are presently being developed, the ultimate success of these endeavors in reaching the market remains unknown. A successful strategy for chronic and complicated disorders like AD may involve transitioning from a single treatment method to a complete, personalized, and multi-therapeutic approach. One intervention we employ to regulate metabolic parameters is using medicinal herbs. These herbs possess diverse physiological activities that eventually improve memory and restore cognitive processes to their natural state. Medicinal plants are the most fruitful source of potential candidates for medication development. Resulting in the creation of more than one hundred new pharmaceuticals that are currently undergoing clinical trials. Herbs are typically recommended individually, as a combination of many herbs, such as triphala, or as an herbal extract. Administering either a single herb or a combination of herbs offers increased effectiveness, reduces non-specific toxicity, and, most significantly, prevents the development of drug resistance. The safety and effectiveness of herbs can be attributed to their diverse components and interactions with many physiological targets in the body, resulting in a lengthy history of positive outcomes. Further investigation of a more rigorous kind is required to address the methodological constraints.

AUTHORS' CONTRIBUTIONS

R.V.J.: Conceptualization, Data curation, Formal analysis, Investigation, P.K.: Project administration, Supervision, A.P.K.: Editing and Grammar, S.K.: Review, Editing, Funding acquisition.

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