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Review Article

"Brahmi" Herb of Grace: The Treatment of Alzheimer's Disease

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Abstract

A deterioration in cognitive function severe enough to impede with everyday tasks is referred to as dementia in general. Among individuals aged 65 and older, Alzheimer's disease (AD) accounts for at least two-thirds of dementia cases. AD is the most prevalent type of dementia. Alzheimer's disease is a neurological condition that gradually impairs behavioural and cognitive abilities such as memory, language, comprehension, attention, thinking, and judgement. It begins slowly and progresses over time. And ranks as the sixth leading cause of death in the US. The following are possible side effects of drugs for Alzheimer's disease: headaches, confusion, dizziness, vomiting, diarrhoea, allergic reactions, nausea, difficulty sleeping, Besides constipation, weight loss, twitching and cramping in the muscles, and vivid nightmares. Since ancient times, Brahmi, also known as Bacopa monnieri, has been used as a nootropic in Ayurvedic medicine to treat neurological conditions. Several strategies, including the use of synthetic and natural compounds, have been used to treat Alzheimer's disease. The two proteins amyloid-β and tau are key players in several neuronal dysfunctions associated with Alzheimer's disease.

Tau is a protein associated with microtubules that is known to have a role in Alzheimer's disease progression. The main physiological dysfunctions linked to Tau aggregates are increased neuro-inflammation, neurotoxicity, and reactive oxygen species production, contribute dementia and behavioural abnormalities, that can be treated by Bacosides A and Bacosides B which are the chemical components of Brahmi.

Keywords: Alzheimer's Treatment Strategies; Bacopa Monnieri; Behavioural; Cognitive Abilities; Dementia

Introduction

Alzheimer's disease (AD) is an irreversible progressive neurological ailment that is marked by memory loss, impaired thinking and reasoning, and changes in personality and behaviors. AD placing of physical and mental well-being of the elderly at grave risk [1]. Alois Alzheimer presented in his finding at the 37th convention of Southwest German Psychiatrists in 1906, highlighting the pathological features of the disease and discussed his initial notable case. Emil Kraepelin, a colleague of his, later named the illness in 1910 in recognition of his accomplishments. Researchers and medical professionals paid little attention to the disease for the next several years (1910) until Robert Terry and Michael Kidd's electron microscopy of neuropathological lesions in 1963 sparked renewed interest. Neurofibrillary tangles (NFTs) were detected in brain biopsies from two patients with severe AD, according to electron microscope research. Since then, research has been done for more than 50 years (from 1963 to the present) on the pathological characteristics, BBC processes, and medication therapies for AD [1].

Types of Alzheimer disease

Amyloid hypothesis, Mitochondrial dysfunction, Neuroinflammation and Insulin resistance are the types of Alzheimer's disease [2].

- Amyloid theory One of the fundamental theories that has been extensively explored in the pathophysiology of both Fa-

milial Alzheimer's Disease (FAD) and Sporadic Alzheimer's Disease (SAD) is amyloid pathology. The primary cause of amyloid disease is an imbalance between amyloid formation and clearance. A peptide is amyloid [2].

- Mitochondrial dysfunction: The mitochondrion, often known as the "powerhouse of the cell," is an essential cell organelle. Responsible for oxidative phosphorylation, it is constantly producing energy in the form of ATP [2].
- Inflammation of the nervous system inflammation is the body's defence mechanism against cellular invasion. If the same occurs in the brain, it is referred to as neuroinflammation. In addition to neurones, glial cells such as microglia and astrocytes are also widely distributed throughout the brain.
- Insulin sensitivity Brain insulin resistance is regarded one of the most striking symptoms of AD. Insulin receptors are widely distributed acrossthe various brain areas. The brain parts of the cerebral cortex and CA1 region of the hippocampus are often related to cognitive activities [2].

Symptoms of Alzheimer Disease

Early stage

The initial phase is frequently disregarded. It's considered "old age" by friends, family, and occasionally even experts; it's just a natural aspect of growing older. It is hard to pinpoint the precise start of the illness because it progresses gradually. Become disoriented, particularly with relation to items that just occurred Maybe have some trouble speaking, like trouble finding the right words. Get disoriented in locations you know well Ignore the passing of time, including the day, month, year, and season have trouble deciding what to do and managing their personal money. Mood and behaviour: may exhibit mood swings, such as depression or anxiety; may become less motivated and active; may lose interest in activities and hobbies; may occasionally react in an unusually hostile or violent manner.

Middle stage

As the illness progress, restrictions become more obvious and restrictive. Individuals may experience extreme forgetful, particularly regarding names and recent occurrences have trouble understanding time, place, and events; potentially leading to getting lost at both home and in the community; their communication (speaking and comprehension) deteriorates. Personal care assistance is needed (i.e., toileting, washing, clothing) unable to properly cook, clean, shop, or prepare food unable to securely live alone without a lot of assistance Changes in behaviour can include clutching, shouting out, wandering, incessant questioning, hallucinations (seeing or hearing things that are not there), and disrupted sleep. They may Behave inappropriately in the community or at home (e.g., aggressive or without inhibition).

Late stage

The final phase represents a state of near-total dependence. The physical aspect of the illness becomes more apparent, and memory problems are extremely acute. Usually oblivious to place and time have trouble comprehending what's going on around them unable to recognize friends, family, and familiar objects unable to eat on their own, might have a hard time swallowing Growing need for assisted self-care (toileting and bathing) may be incontinent in the bowel and bladder. Mobility deteriorates; possibly unable to move or confined to a bed or wheelchair A shift in behaviour, including hostility towards the carer and nonverbal agitation (kicking, striking, yelling, or moaning), may occur.

Diagnosis of Alzheimer disease

A study group known as NDICDS-ADRDA was established in 1984 by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) with the goal of developing clinical diagnostic standards for Alzheimer's disease.

These criteria include

- probable Alzheimer's disease, defined as dementia verified by neuropsychological testing, progressive memory loss, impaired day-to-day functioning, and additional symptoms such as aphasia (language impairment), apraxia (motor skill impairment), and agnosia (perception loss). Without the presence of any systemic or brain disorders, any of these symptoms can appear between the ages of 40 and 90.

- Potential Alzheimer's disease can also be diagnosed in the following situations:
  - No neurologic or psychiatric disorder;
  - Another illness, such as a systemic or brain disorder; however, these conditions do not constitute the primary cause of dementia; and
  - Alzheimer's disease that is positively identified by histopathologic confirmation obtained from a biopsy OR autopsy [3].

Causes and risk factors

Causative agents

In the past, the gene responsible for producing the substrate (APP), from which the Ab peptide is derived, was the first to be found to cause AD. The enzymes (presenilins) that generate Ab from APP are encoded by the two additional AD causal genes that have been found. A disruption of APP processing and an increase in the amount of Ab generated result from mutations in the presenilins or APP genes . Ab seems to be an early and initiating event that sets off a sequence of events, one of which is the misprocessing of the t protein. The clinical and pathologic characteristics of AD are finally brought on by this cascade, which also results in neuronal malfunction and death [10].

Risk factors

Alzheimer's illness as shown in figure (Figure 1.1), is a complex disease that is influenced by a number of risk factors, including ageing, genetics, head trauma, vascular disorders, infections, and environmental variables (such as heavy and trace metals). It is currently unknown what causes the pathogenic alterations (Aβ, NFTs, and synaptic loss) associated with Alzheimer's disease. A number of theories have been put forth to explain AD, but only two are thought to be primary: one holds that changes in the synthesis and processing of amyloid β-protein serve as the primary initiator of AD, while others contend that cholinergic dysfunction is a major risk factor. But as of right now, no recognised hypothesis exists to explain the pathophysiology of AD

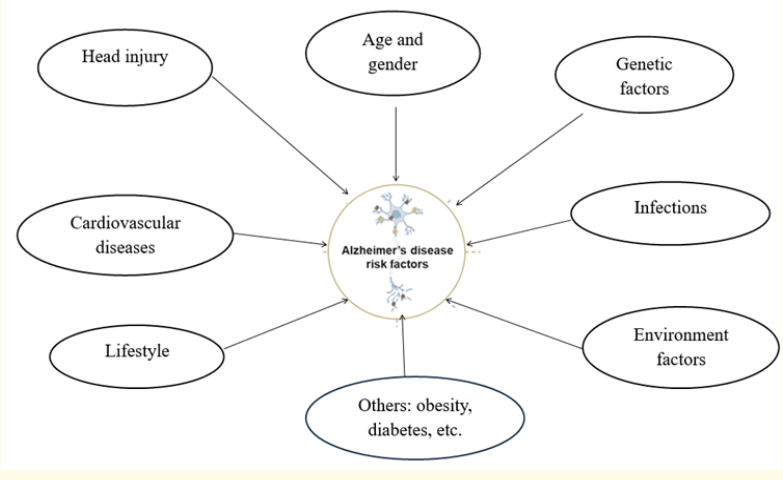

Figure 1.1: Risk factors of Alzheimer's Disease.

- **Significant genes' effects on Alzheimer's disease:** AD is a frequent kind of dementia, and various molecular lesions have been discovered in AD: Hyperphosphorylated tau protein and toxic beta amyloid (Aβ) aggregate to create extracellular amyloid plaques. Tangles in intracellular neural fibres.
- **Alzheimer's disease with sleep disorders:** Studies on the relationship between sleep and AD have revealed that sleep deprivation, particularly deep sleep deficit, raises the risk of AD. Numerous epidemiological investigations have confirmed this connection. Cerebrospinal fluid is a cleaner of brain trash since the brain lacks a lymphatic system for trash removal. Therefore, another mechanism is required to remove trash from the brain. The optimal time to clear brain waste is during deep sleep. The brain's glial cell volume decreases by 60% and the cerebrospinal fluid cleaning waste enters a high-speed operating mode during deep sleep.

- **Environmental Factors' Effect on Alzheimer's Disease:** Data on the global prevalence of dementia's geographic changes suggest that environmental risk factors are crucial to the aetiology of dementia. The risk of dementia has a dose-response relationship with elevated environmental levels of carbon monoxide and nitric oxide [4]. There are several significant risk factors for Alzheimer's disease that include: Extensive research indicates that AD is associated with a variety of risk factors. Several chronic illnesses are significant risk factors for AD among them. In the western world, a number of illnesses (such as diabetes, hypertension, obesity, and increased total cholesterol) are also risk factors for dementia and cognitive decline.
- **Physical Factors Like Overweight and Their Effects on Alzheimer's Disease:** Numerous epidemiological studies have connected middle-aged obesity to the elevated risk of dementia in later life. An American 27-year prospective study assessed the connection between middle-aged obesity, body mass index (BMI), and the chance of developing dementia later in life. Obesity in middle age raises the risk of AD. When comparing obese individuals (BMI ≥ 30) to those with normal weight (BMI = 18.6-24.9), the risk of dementia increased by 74%, while the risk for overweight individuals (BMI = 25-29.9) increased by 35% [4].
- **Effects of Psychological Stress on Alzheimer's Disease:** The impact of social psychological strain on cognitive decline is poorly understood, and the mechanism of influence is intricate. Most people agree that the early history of depression is somewhat linked to the later onset of dementia. Psychological suffering has been linked to an increased risk of memory loss, according to studies. An important mechanism for explanation could be the hypothalamus-pituitary-adrenal axis (also called the "pressure circuit"), which associates anxiety and depression with a cascade process involving the pituitary gland, the adrenal glands, and corticotropin-releasing hormone (CRH). Additional investigation has revealed that these hormones raise blood pressure, heart rate, and blood sugar levels [4].

Complications

Nearly 120,000 people die from AD each year, ranking it as the sixth leading cause, according to the National Centre for Health Statistics 2023. People over 65 are primarily affected by AD, which increases their chance of developing problems that could seriously harm their health and well-being. Physical and mental/behavioral issues are the two main categories of AD complications. The following is a list of them: Patients with AD often have mental/behavioral depression as a comorbidity, which makes treating their illness more difficult. Individuals with AD who suffer from depression frequently experience mood fluctuations, sleep disturbances, social withdrawal, and concentration challenges and difficulties focusing. In the later stages of AD, agitation and delirium-including sun-downing-are frequent occurrences and present difficulties for both patients and carers. Taking care of these symptoms is crucial to guaranteeing the security and well-being of AD patients. Nevertheless, there has been evidence linking the use of anti-psychotic drugs to treat these conditions to higher mortality rates and other side effects. Straying Infections, especially respiratory and urinary infections, and physical fever are common in older AD patients. Aspiration pneumonia might result from swallowing issues, which exacerbates their medical condition. Falls in malnutrition and dehydration Bowel and bladder issues [5].

Pathophysiology of the diseases

The primary theories about the path-physiology of AD include Aβ toxicity, tau protein, gene mutation, synapse destruction, anomalies in intermediate neurons and networks, alterations in mitochondrial function, chemo-kines, etc.

Neuro pathophysiology

Neuron-pathological alterations in AD are classified into two categories

- Positive lesions (due to accumulation), which are defined by the build-up of neuro-fibrillary tangles, amyloid plaques, dystrophy neuritis, neuronal threads, and other deposits in the brains of AD patients.
- Negative lesions (caused by losses) that exhibit significant atrophy as a result of a loss of neurons, neurosis, and synapses [8].

Stages

The Alzheimer's Disease Stages The clinical phases of Alzheimer's disease can be categorize into

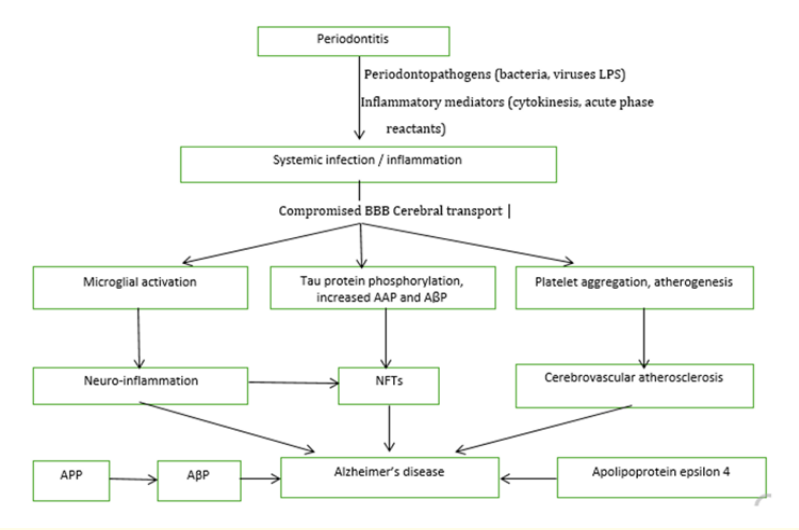

Figure 2

- Pre- clinical or the per-symptomatic stage , there is no functional impairment in day-to-day activities, minor memory loss, and no clinical signs or symptoms of AD [8].
- The moderate or early stage of AD, during which a number of symptoms first manifest in patients. These symptoms include difficulties adjusting to daily life due to memory loss and attention problems, confusion [8].
- Moderate AD stage: As the disease progresses to parts of the cerebral cortex, it causes memory loss that is more severe and impairs the ability to recognize friends and relatives [8].
- Severe AD, or late-stage, is characterized by a severe build-up of neuritic plaques and neuron-fibrillary tangles throughout the cortex, resulting in a progressive loss of function and cognition [8].

Mechanism of AD

AD Mechanisms encompasses two main forms: familial (which make up 1-5% of cases) and sporadic (which make up over 95% of cases). Familial AD (FAD) is largely defined by autosomal dominant genetic mutations in amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin 2 (PS2) genes, often presenting between 30-65 years and developing fast. On the other hand, sporadic AD (SAD), sometimes referred to as late-onset AD, typically appears after the age of 65 and is impacted by a number of comorbidity, environmental variables, and genetic risks [9].

Treatment

There are currently no disease-modifying therapies on the market that have been shown to change the underlying pathophysiology or course of the condition. A multidisciplinary approach involving doctors, nurses, social workers, and charitable organizations and support agencies is essential to manage condition effectively. The cornerstone of symptomatic therapy is acetyl-cholinesterase inhibitors (AChEIS), which include galantamine, rivastigmine, and donepezil. By preventing acetylcholine from being broken down in the synapse, AChEIS increase acetylcholine availability. Leg cramps and stomach discomfort are typical peripheral cholinergic side effects, but they are typically well tolerated, particularly if the medication is started at a low dosage and increased gradually. It's vital to exercise caution when administering AChEIs to individuals with heart conduction abnormalities, as these medications can heighten the risk of bradyarrhythmias. Therefore, in such cases, avoidance or careful utilization of AChEIs is recommended to ensure patient safety [12].

Allopathic remedies [13]

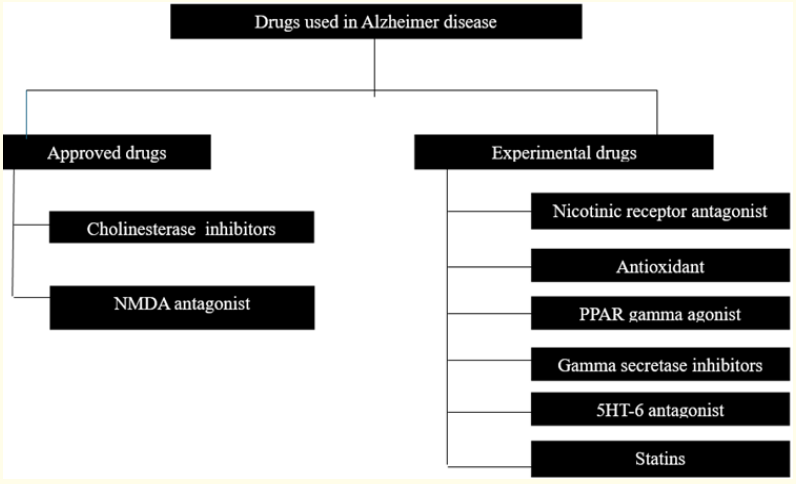

Figure 3

Plants used for treatment

Brahmi

Role of "Brahmi (Bacopa Monnieri): The Ayurvedic Herb in Enhancing Memory and Cognitive Function in Alzheimer's Disease".

For many decades, Ayurveda practitioners of traditional Indian medicine have utilised brahmi, a natural herbal plant. Several medical issues can be resolved with the help of this plant. The herb can be used to cure dyspepsia, neutral allergic reactions, increase memory, and lessen worry and tension, among other things. "Brahmi has shown potential in aiding Alzheimer's Disease (AD) due to its ability to enhance and improve memory. Research indicates that consistent and early consumption of this plant can either prevent or reduce the incidence of AD. Brahmi has been shown to considerably improve the cognitive functioning of AD patients. Its mechanism of action involves enhancing memory and increasing the learning rate of the patient.

Brahmi is known to lower the amount of beta amyloid in mice with AD brains, according to a study conducted by the National Brain Research Centre (NBRC). Notably, an increase in beta amyloid increases the death of brain cells, therefore leading in memory loss. Moreover, Brahmi modifies the oxidative stress cascade and lowers the patient's blood cell concentration of divalent metals. Among the compounds found in brahmi are polyphenol and sulfhydryl, which are in charge of getting rid of divalent materials and reactive oxygen particles. By means of these mechanisms, Brahmi aids in enhancing the patient's cognitive function and stopping the degeneration of the patient's brain cells [14]. Bacopa monnieri also known as water hyssop, brahmi, thyme-leafed gratiola, herb of grace, and Indian pennywort, is a perennial creeping herb that has long been valued in traditional Ayurvedic medicine. This herb of the wetlands is difficult to identify exactly, but most scientists agree that it has been growing in wetlands for hundreds of thousands of years across southern and eastern India, Australia, Europe, Africa, Asia, and North and South America. Ayurvedic practitioners of bacopa (Dhanasekaran., *et al*., 2007) refer to the plant as "Brahmi" in honour of Brahma, the Hindu pantheon's creator god. Texts including the Charaka Samhita, Atharva-Veda, and Susrut Samhita first mention bacopa monnieri in the sixth century A.D. as a medhya rasayana-class plant used to hone intelligence and lessen mental impairments. Ancient Vedic academics are said to have used the herb to help them memorise lengthy holy chants and writings [15].

Botanical discription

The herb lacks fragrant. This plant has oblong, succulent leaves that are 4-6 mm (0.16-0.24 in) thick. On the stem, the oblanceolate leaves are arranged oppositely, or opposite deccusate pattern. The tiny, actinomorphic, white flowers have four to five petals. Being able to thrive in water, it's a common aquarium plant.It flourishes even in slightly brackish conditions. Cuttings are frequently used

to achieve propagation in conditions like dementia and Alzheimer's disease. It has been demonstrated via research to be a successful strategy for promoting the development of new neural connections and reducing oxidative stress in the brain, keeping cognitive abilities sharp well into old age [15].

- **Synonyms:** Indian Pennywort, Mangosteen.
- **Biological Source**: Brahmi is the fresh or dried herb of Centella asiatica (L.) (syn. Hydrocotylasiatica Linn.)
- **Family**: Umbelliferae.
- **Geographical Source**: The plant is found in swampy areas of India, often considered a weed in crop fields and other neglected areas throughout India up to an altitude of 600 M and also found in Pakistan and Sri Lanka [16].

Chemical constituents

The main chemical constituents responsible for the memory-enhancing effect of BM, includes Bacoside A, assigned as 3-((alpha)-L-arabinopyranosyl)-O-(beta)-D-glucopyranoside-10, and 20-dihydroxy-16-Keto-dammar-24-ene [17].

Function

Learning and Memory-Boosting Exercise: Numerous research laboratories have responsible extensively studied the neuropharmacological effects of plant extracts and isolated Bacosides, and a number of publications have provided evidence of their nootropic properties. Preliminary research indicated that the Rats' ability to learn improved by treatment with plant or an alcoholic extract of BM plant . Further research revealed that the presence of Bacosides A and B in the ethanol extract was responsible for the impact that helped with cognition. In addition to improving learning and memory in healthy rats, these active compounds also demonstrated a protective effect against the amnesic impact of scopolamine, electroshock, and immobilization stress.

It is yet unclear how these pharmaceutical activities work. It has been proposed that in certain brain regions, bacosides cause membrane dephosphorylation, which increases protein and RNA turnover concurrently [18].

Mechanism of action

It repairs damaged neurones by increasing kinase activity, restoring synaptic activity, and ultimately improving neuronal transmission in the brain. Its nootropic properties are believed to be mediated via the glutamatergic mechanism through which its constituent saponins, bacosides A and B, work. Reduction of positive symptoms and overall psychopathology in schizophrenia may influenced by the dopaminergic system and its ability to enhance neurotransmission.

Conclusion

Allopathic drugs, such as AChEIS, boost acetylcholine levels. Common peripheral cholinergic side effects include leg cramps and stomach discomfort. Due to the increased risk of bradyarrhythmias in patients with heart conduction disorders, caution is advised when using AChEIs. Brahmi (Bacopa monnieri L) is an Ayurvedic herb used to treat neurological and psychiatric conditions. It is a cost-effective and safe complementary therapy for various disorders. Brahmi has significant potential for managing Alzheimer's disease if treated early. Clinical research indicate that herbal remedies can improve memory and cognitive capacity in mice with Alzheimer's.

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