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Traditional Memory Tonic to Modern Neurotherapeutic*: Bacopa monnieri* in Alzheimer's Disease

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Abstract:

Alzheimer's disease (AD) is associated with cognitive decline and dementia, typically seen in the elderly due to ongoing neurodegeneration. It progressively deteriorates the patient's memory capabilities. The key diagnostic indicators include the presence of senile plaques and Neurofibrillary tangles (NFTs). A significant reduction in Acetylcholine (Ach), a neurotransmitter in the brain, occurs due to its breakdown by the enzyme Acetylcholine esterase before it can exert its effects, along with neural cell death, which are the main contributors to AD. Although there are various categories of Anti-Alzheimer's medications available for managing AD, successful outcomes have been limited due to poor patient adherence. Additionally, incorporating Nutraceuticals into daily diets, engaging in Aromatherapy, adjusting daily routines, and practicing yoga regularly can help alleviate stress, insomnia, improve blood circulation, detoxify organs through rhythmic breathing, and reduce headache frequency, as evidenced by surveys. Currently, herbal medicine has emerged as a preferred option for managing AD due to its accessibility, cost-effectiveness, high patient compliance, ease of preparation, and minimal adverse side effects. Innovative methods can be employed to enhance the development of herbal medicine. Bacopa monnieri is a native plant that grows across India. For centuries, it has been recognized in Ayurveda as a "Medhya Rasayan" (nootropic). Research has demonstrated several effects of Bacopa monnieri, including its ability to inhibit the enzyme cholinesterase. This inhibition can lead to a reduction in the breakdown of acetylcholine, a crucial neurotransmitter, the levels of which are diminished in Alzheimer's disease. key active ingredients in this plant include triterpene saponins known as bacosides, along with alkaloids like bramine and herpestine, as well as flavonoid and steroid compounds. Research conducted in vivo has demonstrated that an extract of B. monnieri containing 25% bacoside A produces an anxiolytic effect similar to that of lorazepam. While lorazepam is often associated with side effects such as amnesia, B. monnieri does not lead to these adverse effects and, in fact, offers memory-enhancing benefits.

Keywords: Alzheimer's disease (AD), Bacopa *monnieri*, Medhya Rasayan, Bacosides A, bramine and herpestine, Neurofibrillary tangles (NFTs), Acetylcholine (Ach).

1. Introduction:

Alzheimer's disease (AD) is a progressive neurodegenerative condition that impacts cognitive function. Symptoms usually start to appear around the age of 20 or later, with subtle brain changes that often go unnoticed by the individual. This disorder can lead to severe depression in older adults, particularly those over 65, and ultimately results in death. At this stage in life, individuals exhibit dementia symptoms linked to AD, commonly known as Alzheimer's dementia. Worldwide, more than 55 million people are affected by dementia, with nearly 60–70% of these cases being due to Alzheimer's disease [1,2,3]. The condition presents significant socio-economic and healthcare challenges, especially in rapidly aging countries like India and China. Despite progress in understanding its molecular mechanisms, current treatments, including cholinesterase inhibitors (Donepezil, Rivastigmine, Galantamine) and NMDA receptor antagonists, provide only limited symptomatic relief. The quest for alternative effective and safe treatments has sparked interest in herbs and extracts that have been anecdotally reported to help prevent and treat memory loss. Among the numerous herbs available, Bacopa monnieri (commonly referred to as Brahmi, bacopa, or water hyssop) has garnered significant attention. This herb has been recognized and widely utilized for centuries within Ayurveda, the traditional Indian system of complementary medicine, for enhancing cognitive function and preventing memory decline [2,3,4]. Numerous in vitro and animal studies have demonstrated the neuroprotective properties of this plant and its extracts [Figure 1]. Nevertheless, the application of this herb in human subjects has produced mixed outcomes, leaving its effectiveness in treating individuals with established Alzheimer's disease uncertain. Furthermore, the majority of research has focused on healthy adults. Many studies originating from the Ayurveda tradition are anecdotal, and several others suffer from methodological weaknesses. Systematic reviews concerning B. monnieri have primarily included research on healthy individuals and have overlooked studies conducted in the past five years [3,4,5,6,7,8].

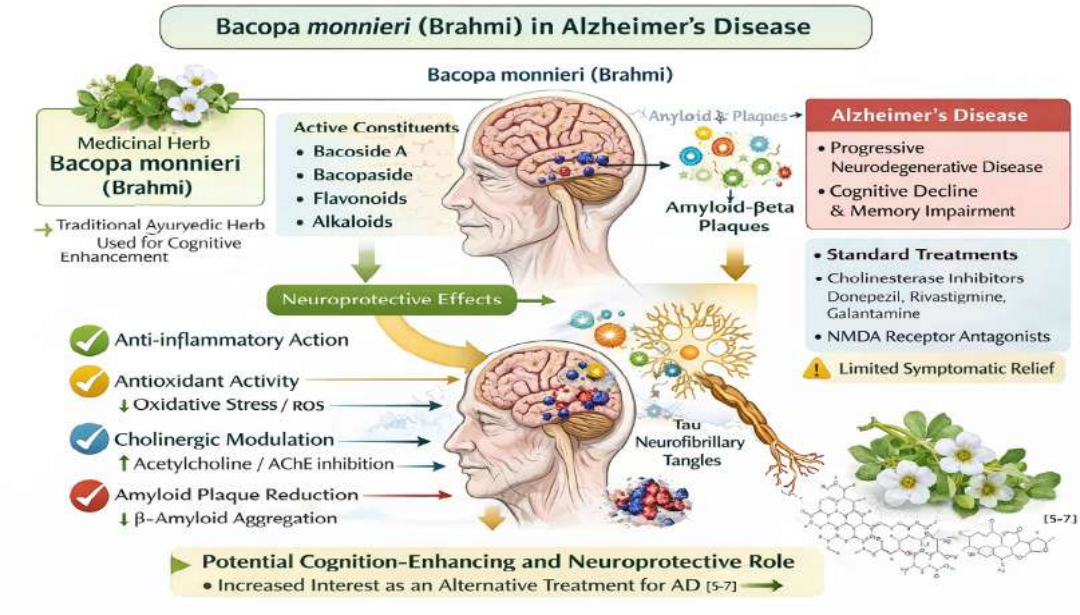

Figure 1: Pharmacological action *Bacopa monnieri* (L.) in Alzheimer's disease

1.1 Pathophysiology of Alzheimer's Disease:

There is a growing agreement that the production and accumulation of beta-amyloid (Ab) peptide play a crucial role in the development of Alzheimer's disease [Figure 2]. Evidence supporting the significant role of Ab includes several key points: mutations in the amyloid precursor protein are linked to early-onset Alzheimer's disease; all known mutations associated with Alzheimer's disease result in increased production of Ab.[5,7].individuals with trisomy (Down's syndrome) who possess three copies of the gene for amyloid precursor protein exhibit neuropathological features of Alzheimer's disease by midlife; Ab is neurotoxic in vitro and causes cell death; the over expression of human amyloid precursor protein in transgenic mouse models of Alzheimer's disease leads to the formation of neuritic plaques akin to those found in humans suffering from Alzheimer's disease; transgenic mice that over express the human

amyloid precursor protein show signs of learning and memory deficits, which coincide with the accumulation of amyloid; the apolipoprotein E e4 genotype, a significant risk factor for Alzheimer's disease, accelerates the deposition of amyloid; and the production of anti-amyloid antibodies in humans diagnosed with Alzheimer's disease appears to improve the disease process. The formation of neurofibrillary tangles, oxidation and lipid peroxidation, glutamatergic excitotoxicity, inflammation, and the activation of the apoptotic cell death cascade are viewed as secondary effects resulting from the generation and deposition of Ab. [5,6,8] This proposed amyloid cascade forms the basis for efforts to alter the onset and progression of Alzheimer's disease through the identification of anti-amyloid agents, antioxidants, anti-inflammatory medications, compounds that restrict the phosphorylation of tau protein, anti-apoptotic agents, and glutamatergic N-methyl-d-aspartate receptor antagonists. Dysfunction and death of cells in nuclear groups of neurons that are responsible for maintaining specific neurotransmitter systems lead to deficits in acetylcholine and norepinephrine. Alternative hypotheses concerning the pathophysiology of Alzheimer's disease highlight the significant potential impact of tau-protein irregularities, exposure to heavy metals, vascular issues, or viral infections [9].

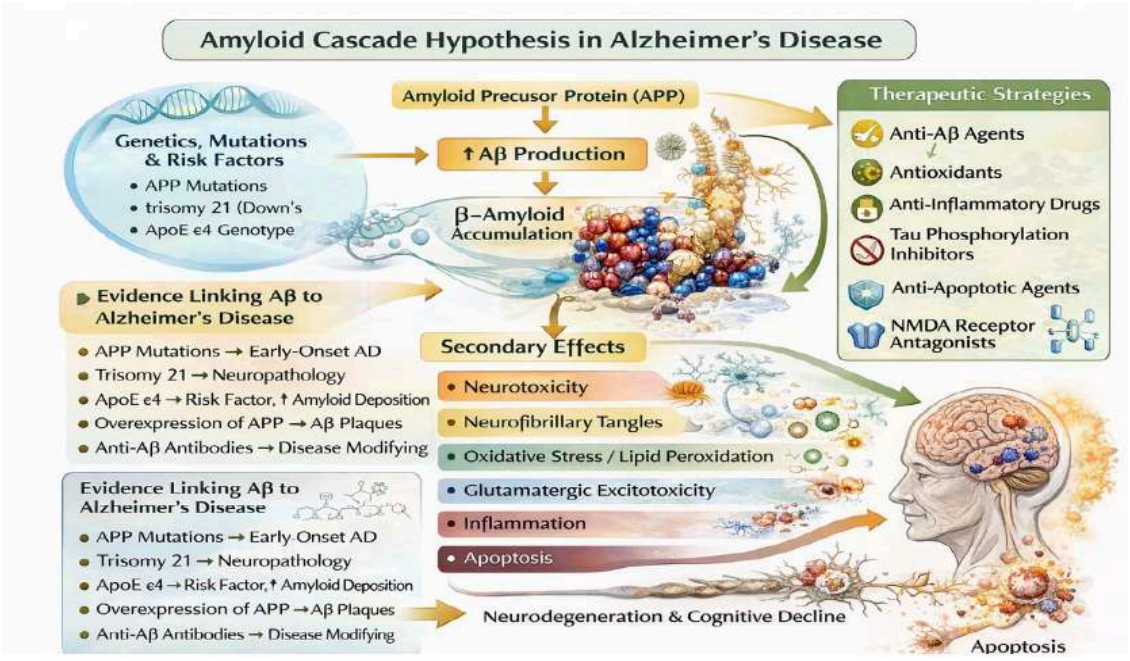

Figure 2: Pathophysiology of Alzheimer's disease

2. Bacopa monnieri:

Bacopa monnieri (L.) is a significant medicinal plant in traditional Indian Ayurvedic practices. It is a small, perennial herb commonly referred to as 'Brahmi', and it belongs to the Scrophulariaceae family [10]. This esteemed Indian medicinal herb has been utilized as a memory enhancer in the Ayurvedic system for over 3000 years. It is employed in traditional medicine to address various nervous disorders, aid digestion, enhance learning, memory, and concentration, and to alleviate anxiety and skin issues; specific applications include treating asthma, insanity, and epilepsy. The Bacopa herb, often termed a nootropic herb, facilitates the repair of damaged neurons, promotes neuronal synthesis, restores synaptic activity, and enhances brain function. B. monnieri is rich in alkaloids such as rahmine, nicotinine, herpestine, bacosides A and B, saponins A, B, and C, triterpenoid saponins, stigmastanol, β-sitosterol, betulinic acid, D-mannitol, stigmasterol, α-alanine, aspartic acid, glutamic acid, and serine, along with pseudo jujubogenin glycoside [10,11,12]. It plays a crucial role In Ayurvedic treatments aimed at addressing cognitive disorders associated with aging. Various mechanisms have been suggested to explain its cognitive benefits, such as the inhibition of acetylcholinesterase (AChE), providing antioxidant neuroprotection, reducing β-amyloid levels, modulating neurotransmitters (including acetylcholine [Ach], 5-hydroxytryptamine [5-HT], and dopamine [DA]), activating choline acetyltransferase, and enhancing cerebral blood flow [Table 1] [10,13].

Table 1: Pharmacological Profile and Cognitive Benefits of Bacopa monnieri (L.)

Parameter	Description	Reference No.
Botanical name	Bacopa *monnieri* (L.)	[10]
Common name	Brahmi	[10]
Family	Scrophulariaceae	[10]
Plant type	Small, perennial creeping herb	[10]
Traditional system	Ayurveda (used for >3000 years)	[10]
Traditional uses	Memory enhancement, learning and concentration improvement, digestion aid, treatment of anxiety, skin disorders, asthma, insanity, epilepsy, and nervous disorders	[10]
Nootropic activity	Repairs damaged neurons, promotes neuronal synthesis, restores synaptic activity, enhances brain function	[10, 11]
Major alkaloids	Brahmine, nicotinine, herpestine	[10, 11]
Saponins & glycosides	Bacosides A and B, saponins A, B, and C, triterpenoid saponins, pseudojujubogenin glycoside	[10,11,12]
Sterols & triterpenes	β-sitosterol, stigmastanol, stigmasterol, betulinic acid	[10,11,12]

Parameter	Description	Reference No.
Other constituents	D-mannitol, α-alanine, aspartic acid, glutamic acid, serine	[10,11,12]
Role in aging-related cognitive disorders	Used in Ayurvedic therapy to manage age-associated cognitive decline	[10, 13]
Acetylcholinesterase (AChE) inhibition	Enhances cholinergic neurotransmission by inhibiting AChE	[10, 13]
Neurotransmitter modulation	Modulates acetylcholine (ACh), serotonin (5-HT), and dopamine (DA)	[10, 13]
β-Amyloid regulation	Reduces β-amyloid accumulation linked to Alzheimer's disease	[10, 13]
Antioxidant neuroprotection	Protects neurons from oxidative stress–induced damage	[10, 13]
Choline acetyltransferase activation	Enhances acetylcholine synthesis	[10, 13]
Cerebral blood flow	Improves cerebral circulation, supporting cognitive function	[10, 13]

2.1. Phytochemicals: [Table 2]

Bacopa monnieri boasts a wealth of secondary metabolites, featuring various alkaloids such as herpestine and brahmine, along with saponins like bacosides, betulic acid, and hersaponin. Additionally, it contains alcohols, flavonoids, sterol glycosides, sugars, amino acids, and cucurbitacins [14].

2.1.1. Alkaloids:

The main alkaloids present in Bacopa monnieri include brahmine, which is thought to play a role in its neuroprotective properties. Brahmine was among the first alkaloids extracted from this plant. Another significant alkaloid in Bacopa monnieri is herpestine. This compound contains nitrogen atoms and features a complex molecular structure characteristic of alkaloids. Herpestine may affect neurotransmitter systems, including serotonin and dopamine, which are essential for regulating mood and cognitive functions. These compounds have been identified in ethanolic extracts and are integral to the plant's pharmacological profile. Herpestine is particularly noteworthy for its potential neuro modulatory effects, while monnierin is linked to cognitive-enhancing activities. Their identification highlights the chemical intricacy of Bacopa monnieri and reinforces its traditional applications in cognitive and neuroprotective therapies [15].

2.1.2. Saponins:

The primary chemical constituents of Bacopa monnieri are dammarane-type triterpenoid saponins, featuring jujubogenin or pseudo jujubogenin moieties as their aglycones. These compounds are distributed throughout the plant, notably in the leaves and stems. The saponins present in the plant include bacosides, Bacopasides, and betulinic acid, all of which are crucial for neuronal health and collectively account for up to 6% of the plant's dry weight. Among these, bacoside A is particularly significant, representing about 38% of the dry mass in standardized methanolic extracts. It

consists of four saponin glycosides: Bacopaside II, Bacopaside X, Bacoside A3, and Bacopasaponin C. Bacoside A has shown anti-tumor effects in both in vitro studies on cell lines and in vivo studies on mice. Additionally, Bacoside B, which includes Bacopaside IV, V, N1, and N2 and varies in optical rotation compared to bacoside A, can be isolated and is recognized as one of the bioactive marker compounds for this species. A yield of 0.65% (on a dry weight basis) has been documented for isolated bacoside B, affirming its status as a bioactive marker for this species. Bacogenins A1–A5 are the acid-hydrolyzed derivatives of bacosides, with bacogenin A4—ebelin lactone being the primary component. Bacopasides I-XII interact with sterols and contribute to membrane disruption. Among the bacopasaponins, Bacopasaponin C constitutes 0.3–0.6% of the ethanolic extracts of Bacopa monnieri. Bacopasaponin C is a glycoside of pseudo jujubogenin, incorporating glucose and rhamnose as sugar units, and it exhibits anti-dandruff properties. A study utilizing HPLC quantified the individual components of bacoside A in Bacopa monnieri, revealing that Bacoside A3 ranged from 0.14% to 0.85%, while Bacopaside II ranged from 0.12% to 0.69%. These figures indicate regional variations and confirm the presence of measurable quantities of bacoside A components within the plant [15,16,17].

2.1.2.1. Cucurbitacins:

Cucurbitacins are a group of highly oxygenated tetracyclic triterpenoids recognized for their bitter flavour and medicinal properties. These compounds feature a tetracyclic triterpenoid core made up of four interconnected rings that originate from cucurbitane. Bacopa includes cucurbitacin's like cucurbitacin B and cucurbitacin E, which play a role in its biological effects. Recent studies have shown that cucurbitacin E can inhibit the growth of various cancer cell lines, including those from human colon, breast, lung, and central nervous system cancers. Cucurbitacin B is known to cause cell cycle arrest and hinder angiogenesis and tumor cell migration, highlighting its potential as a valuable candidate for the development of anticancer drugs. However, it is crucial to understand that cucurbitacin B is not the main bioactive component of Bacopa monnieri, as its pharmacological benefits are primarily linked to bacosides [16,18,19,20].

3. Molecular Mechanisms:

Research has shown that B. monnieri effectively inhibits the release of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), from N9 microglial cells in system furthermore, it suppresses caspase-1 and -3, along with matrix metalloproteinase-3 (MMP-3), in a cell-free assay, highlighting its potential to mitigate inflammation within the central nervous system. Experts underscore the strong antioxidant properties of B. monnieri, which, via the nuclear factor kappa B (NF-κB) signalling pathway and MAPKs, play a crucial role in addressing neuroinflammation associated with neurodegenerative diseases. Additional studies have indicated that B. monnieri can inhibit tau aggregation in vitro. Moreover, cells treated with brahmi showed reduced levels of reactive oxygen species (ROS) and lower caspase-3 activity. Immunoblot and immunofluorescence analyses demonstrated that B. monnieri functions as an antioxidant and aids in restoring nuclear factor erythroid 2-related factor 2 (Nrf2) levels in Neuro2a cells. When Neuro2a cells were treated with B. monnieri, they exhibited a decrease in phospho-tau load compared to those subjected to formaldehyde. Additionally, this treatment led to a reduction in GSK-3β phosphorylation under formaldehyde stress. These findings suggest the promising potential of brahmi in the context of Alzheimer's disease (AD). [Figure 3] illustrates the potential mechanisms through which B. monnieri may operate in AD [21]. This activation, resulting in a diminished production of pro-inflammatory cytokines, including TNF-α and IL-6. By inhibiting NF-κB activation, it effectively reduces neuroinflammation through a decrease in the expression of inflammatory genes. Furthermore, this remarkable plant activates the PI3K/Akt pathway, which is essential for cell survival and neuroprotection. The activation of this pathway inhibits GSK-3β, a pivotal kinase implicated in tau hyperphosphorylation associated with Alzheimer's Disease.

Additionally, B. monnieri alleviates oxidative stress and lowers the levels of MMP-3, caspase-1, and caspase-3, thereby contributing to a reduction in ROS production [21,22,23]

Table: 2 Major Phytochemicals Identified in Bacopa *monnieri* and Their Biological Significance

Phytochemical Class	Major Compounds	Key Characteristics / Description	Biological / Pharmacological Significance	Reference No.
Alkaloids	Brahmine, Herpestine, Monnierin	Nitrogen-containing secondary metabolites; brahmine was among the first alkaloids isolated from *B. monnieri*; herpestine exhibits complex molecular architecture typical of alkaloids	Neuroprotective and neuro modulatory effects; modulation of neurotransmitters such as serotonin and dopamine; associated with cognitive enhancement	[15]
Triterpenoid saponins (Dammarane-type)	Bacosides (A & B), Bacopasides (I–XII), Bacopasaponin C, Bacogenins A1–A5	Possess jujubogenin or pseudojujubogenin aglycones; constitute up to ~6% of plant dry weight; predominantly localized in leaves and stems	Primary contributors to nootropic activity; promote neuronal health, membrane interaction, synaptic repair, and antioxidant defence	[15,17]
Bacoside A (saponin mixture)	Bacoside A3, Bacopaside II, Bacopaside X, Bacopasaponin C	Represents ~38% of standardized methanolic extract; quantified via HPLC with regional variation	Memory enhancement, neuroprotection, antioxidant effects; demonstrated anti-tumour activity in vitro and in vivo	[15,16,17]
Bacoside B	Bacopaside IV, V, N1, N2	Differs from bacoside A in optical rotation; yield ~0.65% (dry weight basis)	Recognized bioactive marker compound for *B. monnieri*	[15,16]
Bacogenins (hydrolyzed derivatives)	Bacogenin A1–A5 (Ebelin lactone as major)	Acid-hydrolyzed forms of bacosides	Contribute to biological activity of bacoside metabolites	[15]
Sterols & riterpenes	Betulinic acid	Pentacyclic triterpene component	Supports neuronal health; anti-inflammatory and anticancer potential	[14, 15]

Phytochemical Class	Major Compounds	Key Characteristics / Description	Biological / Pharmacological Significance	Reference No.
Cucurbitacins	Cucurbitacin B, Cucurbitacin E	Highly oxygenated tetracyclic triterpenoids derived from cucurbitane	Anticancer activity; inhibit cell proliferation, angiogenesis, and tumor migration; not primary nootropic constituents	[18,19,20]
Flavonoids & phenolics	Not individually specified	Polyphenolic secondary metabolites	Antioxidant and neuroprotective roles	[14]
Other constituents	Alcohols, sterol glycosides, sugars, amino acids	Primary and secondary metabolites	Support metabolic and neurotransmitter-related functions	[14]

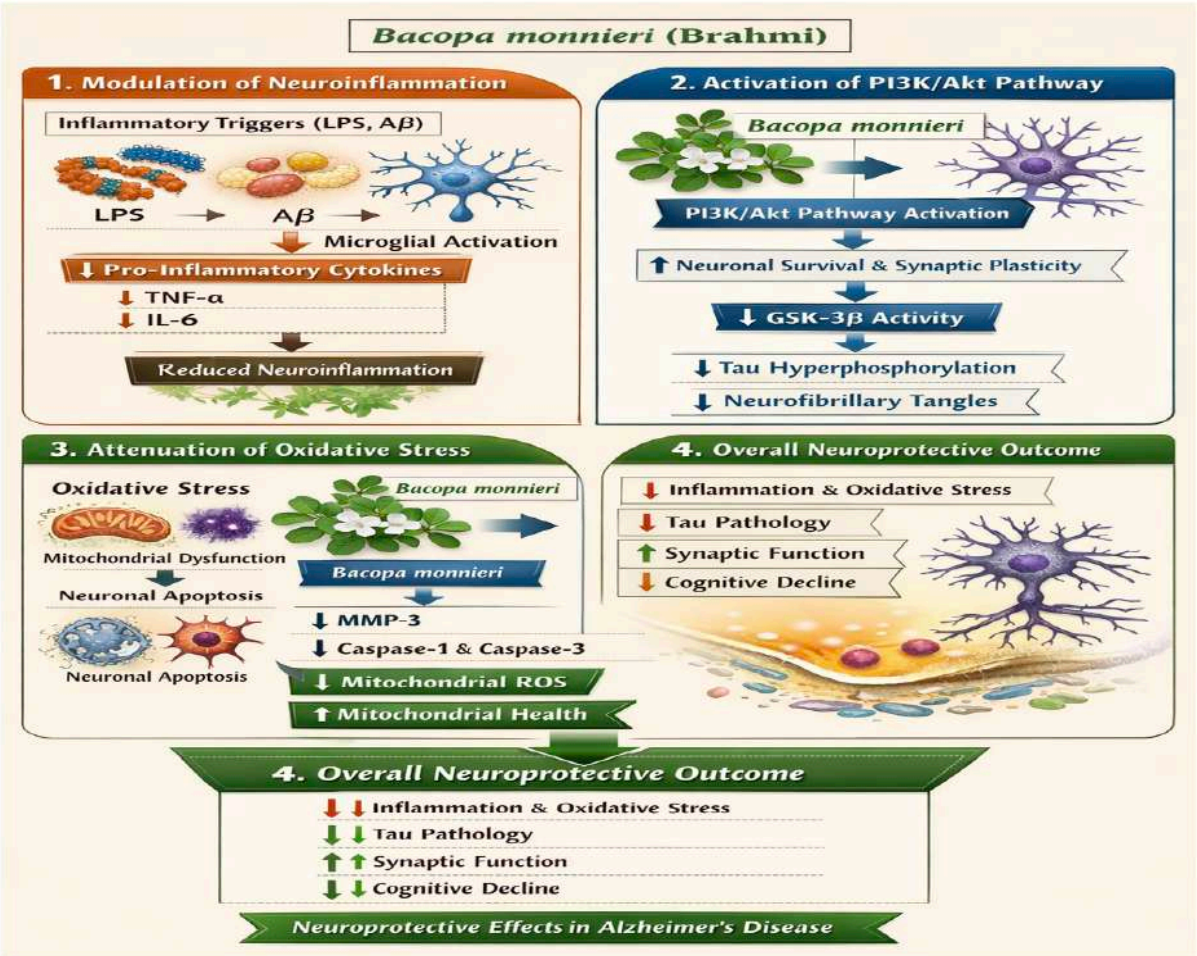

Figure 3: The potential mechanisms of B. monnieri in Alzheimer's Disease are noteworthy. Inflammatory triggers, such as LPS and Aβ, incite the activation of microglia. B. monnieri

3.1 Mechanisms of Action of Bacopa *monnieri*:

The biological foundations for therapeutic possibilities are as given-

3.1.1. Acetylcholinesterase Inhibition:

In a double-blind, randomized clinical trial, 60 healthy elderly participants who received 300 mg and 600 mg of Brahmi exhibited a decrease in acetylcholinesterase activity, leading to enhancements in attention and memory. Therefore, Bacopa monnieri could be beneficial in treating Alzheimer's disease and attention deficit disorder. Additionally, there were no observed side effects or toxicity. Bacopa monnieri has shown encouraging cognitive advantages in clinical trials; however, its effectiveness in Alzheimer's disease [Figure 4] needs to be assessed alongside current pharmacological therapies. The existing medications for Alzheimer's, like acetylcholinesterase inhibitors (AChEs), primarily focus on reducing cognitive decline by boosting cholinergic transmission or adjusting excitotoxicity. In a 52-week, randomized, double-blind trial, Brahmi exhibited effects similar to donepezil, a medication prescribed for Alzheimer's disease. The effectiveness and safety of Bacopa monnieri (300 mg) were compared with synthetic donepezil (10 mg) in a study involving 48 patients diagnosed with Alzheimer's disease and mild cognitive impairment. After one year of treatment, there was no significant difference observed between the two groups [24].

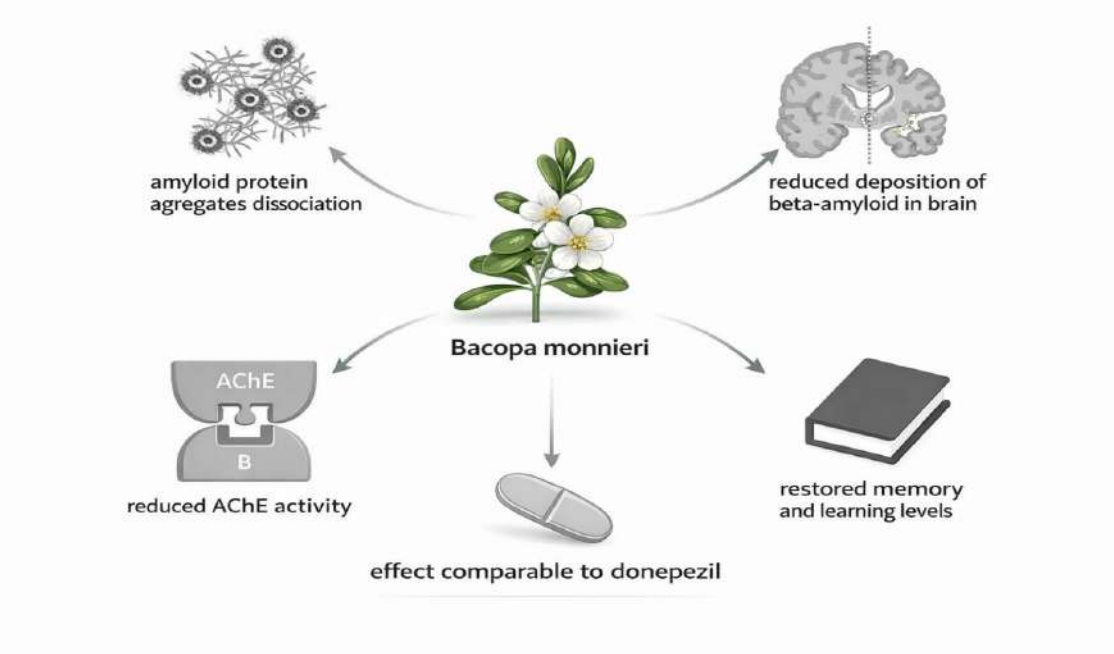

Figure 4: Illustrative depiction of the impact of Bacopa monnieri on individuals suffering from Alzheimer's disease.

3.1.2. Anti-amyloidogenic Effects:

A study demonstrated that bacoside-A showed a notable reduction in fibrillation, cytotoxicity, and Amyloid β (Aβ42). Bacoside-A is derived from Bacopa Monnieri. It has been shown to enhance cognitive functions and Boost memory performance. In a separate study, a combined Extract of Bacopa monnieri (30 mg/kg) was tested against

scopolamine-Induced impairment in mice over a period of 7 days. This extract resulted in a significant increase in transfer latency time and No transfer response. These extracts exhibited an anticholinesterase Antidementia effect

[Figure 5]. Carlo et al. highlighted the effectiveness of Bacopa monnieri in addressing anxiety, depression, and cognitive Impairment in older adults, leading to a significant improvement in their condition [25,26,27,28].

3.1.3. Anti-oxidant Effect:

B. Monnier's potent antioxidant effects, which, through the nuclear factor kappa B (NF-κB) signalling pathway and MAPKs, help combat neuroinflammation in neurodegenerative diseases, [29,30,31].

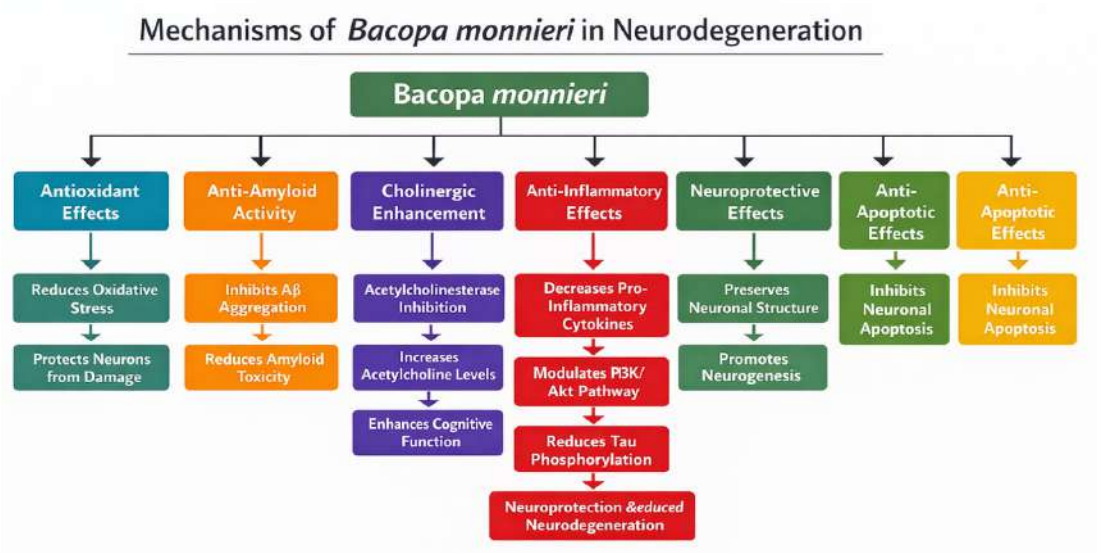

Figure: 5 Mechanism of Bacopa *Monnieri* effected of Neuroprotection

4. Pre-Clinical Evidence:

The aim of the pre-clinical study is to gather essential information regarding the safety of the herbal product prior to assessing its potential advantages in clinical trials. This study evaluates the chronic and acute toxicity of Bacopa monnieri extract in rats. In the acute toxicity assessment, female rats were split into two groups. Group I (control) received distilled water at a dosage of 1 mL/kg, while Group II (test) was given Bacopa monnieri extract at 5000 mg/kg. The rats underwent close monitoring for duration of 14 days. Body weight, along with haematological, biochemical, and histopathological parameters, was analysed. Consequently, no significant alterations were noted in the parameters mentioned above. Furthermore, the high dosage of 5000 mg/kg did not lead to any fatalities among the rats. Although there was a slight difference in body weights between the control and treatment groups at the beginning of the experiment, this difference was not statistically significant. Body weight exhibited minimal change, but it was significantly altered only after 14 days. This slight increase in body weight among the treated animals could be attributed to variations in food intake and may still be considered normal. The rats treated with B. monnieri did not display any significant histological changes in their internal organs, including the kidneys and liver. For chronic toxicity testing, doses of 30, 60, 300, and 1500 mg/kg/day of Bacopa monnieri extract were administered. The control group received distilled water, while the test group was given the appropriate doses of Bacopa monnieri extract over a period of 270 days. The study revealed no significant changes that would suggest toxicity of the extract [32,33,34].

4.1. Morris Water Maze Studies:

The water maze was composed of a metallic pool measuring 170 cm in diameter and 58 cm in height, filled with tap water maintained at a temperature of 25 ◦C and a depth of 40 cm. This pool was divided into four quadrants (northeast, northwest, southeast, and southwest) by two

imaginary lines intersecting at the centre. At the centre of the first quadrant, there was a removable escape platform situated below the water surface and concealed with a nontoxic milk powder. For each rat, the location of the invisible platform was consistently positioned at the centre of one quadrant throughout the training sessions. The rats were required to memorize the platform's location in relation to various environmental cues, as there were no direct indicators of the escape platform's position either in or outside the pool. Consequently, the arrangement of the water tank and platform remained unchanged across all acquisition trials. Each rat was carefully placed in the water facing the wall of the pool from one of the four designated starting points (north, east, south, or west) along the pool's perimeter, and the animal was permitted to swim until it discovered and ascended onto the platform. During the training session, if the rat was unable to reach the platform within 60 seconds, the experimenter would gently place the rat on the platform. In either scenario, the subject was allowed to remain on the platform for 15 seconds before being removed from the pool. The duration taken for the animals to ascend onto the concealed platform was recorded as escape latency, while the time spent in the area that previously housed the platform was noted as retention time. In each trial, the animal was promptly dried with a towel prior to being returned to its cage. All tests were conducted within 45 minutes following the administration of the vehicle, plant extract, or aricept, a cholinesterase inhibitor that served as a positive control [Figure 5] [35].

5. Clinical Evidence (Human Study):

The clinical trial, which included 23 participants, revealed no alarming alterations that would imply toxicity from the formulation containing Bacopa monnieri. Each volunteer received a 300 mg tablet and a 450 mg tablet over a period of 30 days, with each dosage administered for 15 days. Investigations carried out prior to and following the use of the product indicated no significant adverse effects. [36,37,38,39,40,41] An expanding collection of clinical research substantiates the cognitive and neuropsychological benefits of Bacopa monnieri. To date, over 50 peer-reviewed clinical trials, carried out in 18 different countries over a span of approximately 25 years, have examined its effects on memory, cognitive abilities, stress levels, and overall brain health, involving a total of 3,247 participants. n a randomized, double-blind, placebo-controlled study published in the Journal of Ethnopharmacology (2022), 144 healthy individuals were administered 300 mg/day of standardized Bacopa monnieri extract for a duration of 12 weeks. This intervention led to a 28% enhancement in verbal learning and memory recall, with notable improvements recorded in Rey Auditory Verbal Learning Test scores, memory consolidation, and working memory capacity. Likewise, a 16-week randomized controlled trial involving middle-aged adults (ages 40–65), published in Psychopharmacology (2021), revealed advancements in attention, executive function, and cognitive processing speed, including a 23% rise in sustained attention and an 18% boost in processing speed. In addition to cognitive benefits, Bacopa monnieri has demonstrated effects on stress modulation. A double-blind, placebo-controlled trial published in the Journal of Alternative and Complementary Medicine (2020), which included 120 adults experiencing chronic stress, found a 23% decrease in morning cortisol levels, restoration of circadian cortisol patterns, a 27% reduction in perceived stress scores, and improvements in anxiety metrics after 12 weeks of supplementation. Taken together, these results indicate that Bacopa monnieri has significant effects on memory, attention, cognitive processing, and stress management, although the variability in study designs and participant demographics necessitates careful interpretation [42, 43].

6. Comparison with Standard Anti-Alzheimer's Drugs (donepezil):

The ethics committee of the Institute (Postgraduate Institute of Medical Education and Research, Chandigarh, reference number PGI/IEC/2012/1171) granted approval for the trial protocol and consent forms. Informed consent was obtained from all participants. The study took place from February 2013 to December 2016.

6.1. Study design:

The research was designed as a randomized, double-blind, parallel-group, phase-2 single-centre clinical trial that assessed the efficacy and safety of Bacopa monnieri (brahmi) 300 mg OD versus donepezil 10 mg OD over a period of 52 weeks for each participant, involving 48 patients diagnosed with Alzheimer's Disease (AD) and Mild Cognitive Impairment due to Alzheimer's Disease (MCI-AD), focusing on cognitive and quality of life outcomes. The trial adhered to the Declaration of Helsinki and the principles of good clinical practice. An independent data and safety monitoring board oversaw all adverse events. During the screening process, eligible participants were those over 50 years of age, diagnosed with MCI-AD or AD according to Dubois criteria, possessing a modified Hachinski ischemic scale score of less than 5 points, a mini-mental status examination (MMSE) score greater than 10, having a study informant available, and demonstrating sufficient vision and hearing for neuropsychological assessments. The diagnosis of AD/MCI-AD was validated through magnetic resonance imaging (MRI) of the brain, fluorodeoxyglucose-positron emission tomography (FDG PET) of the brain, and cerebrospinal fluid (CSF) analysis for amyloid beta and total tau. Patients already receiving a cholinesterase inhibitor were excluded from the study. Additional exclusion criteria encompassed young onset dementia, vascular dementia, frontotemporal dementia, and other secondary causes of dementia.

6.2. Safety Analysis:

In a comparative evaluation, Bacopa monnieri (Brahmi) showed cognitive and functional results that were mostly similar to donepezil across various assessment scales; however, neither treatment led to strong or consistent improvements in all areas. Donepezil had a statistically significant edge only on the MMSE at one follow-up point, while Bacopa monnieri did not show lasting or specific superiority in memory, functional ability (ADCS-ADL), language, or executive function tests. Analysing the PGI memory scale by domain also showed slight and varying changes in remote memory, attention, recall, and visual retention in both groups, with no clinically significant or statistically meaningful differences. These results indicate that while donepezil has a slight advantage in overall cognitive scoring, Bacopa monnieri offers a similar stabilizing effect instead of real cognitive improvement, suggesting it could be useful as an additional or alternative option for patients with mild cognitive impairment or those who cannot tolerate cholinesterase inhibitors, rather than as a complete replacement for standard medication [44].

7. Dose Optimization and Long-Term Safety:

Assessing the safety of plant-based raw materials is crucial for several reasons. It enables the evaluation of their effects on both human health and the environment. Bacopa monnieri, a well-known herb in Ayurvedic medicine, has garnered scientific attention for its influence on the nervous system. Nevertheless, there remains a significant gap in research regarding the safe application of these raw materials in pregnant and breastfeeding women, which is vital for fetal and early childhood development [45].

7.1. Dose:

Bacopa monnieri is typically a non-toxic plant. The ethanol extract was the most frequently used in the Studies. Doses generally range from 300 to 600 mg daily. A clinical study showed that doses of 320 mg and 640 mg had a positive impact on human cognitive function (like memorization and eye tracking). Those who took the 640 mg dose experienced slightly Stronger effects. Clinical studies have shown that daily doses of 300 to 600 mg of Bacopa monnieri extract, standardized for the amount of Bacosides, which is equivalent to 5 to 10 g of the dried herb, can improve cognitive function and reduce symptoms of anxiety and depression. These benefits are usually seen after 12 weeks of regular supplementation. However, more research is necessary to fine-tune these dosage guidelines and to evaluate the long-term safety and effectiveness of Bacopa monnieri in various populations [45, 46].

7.2. Side Effects:

Currently, there are no indications of significant adverse effects. The most frequently reported

side effects include gastrointestinal issues. Research indicates that Bacopa monnieri may impact the memory of older adults, with nausea, severe abdominal cramps, and frequent bowel movements noted after extended use. Additionally, a study

evaluating the effects of Bacopa monnieri extract on mouse fertility revealed that it can lead to reversible suppression of spermatogenesis and fertility in mice. Importantly, it does not influence libido or produce toxic effects. When administered a dose of 500 mg/kg, rats exhibited reduced appetite and elevated levels of albumin, urea, nitrogen, and aspartate aminotransferase, among other changes. However, no significant alterations in organ weights were recorded at the conclusion of the 90-day study.

8. Bioavailability:

Bacoside A is a primary active ingredient present in Bacopa monnieri. Nevertheless, its insolubility in water leads to reduced bioavailability when taken orally. The main active ingredient in Bacopa monnieri is delivered through two cutting-edge formulation techniques: Cyclodextrin inclusion complexes and Phospholipid complexes.

8.1. Cyclodextrin (β-CD) Inclusion Complex:

To tackle the issues of Bacoside A's low water solubility and its undesirable bitter flavor, researchers employed the co-precipitation technique to form inclusion complexes with B2-cyclodextrin (B2-CD).

8.1.1. Optimal Ratio: Out of the different molar ratios examined (ranging from 1:1 to 1:5), the 1:4 ratio was found to be the most effective.

8.1.2. Outcome: This formulation enhanced solubility by three times and effectively concealed the bitter taste, thereby improving patient adherence to oral formulations.

8.2. Phospholipid Complex (Phytosomes):

A distinct study employed L-b1-phosphatidylcholine to form a complex with Bacopa extract, aiming to enhance intestinal absorption and penetration through the blood-brain barrier (BBB).

8.2.1. Improved Bioavailability: The phospholipid layers physically integrate the bacosides, resembling cell membranes. This resulted in a 170% increase in maximum serum concentration (C_{max}) when compared to traditional extracts.

8.2.2. Pharmacokinetics: The complex exhibited an extended half-life ($t_{1/2}$) and a slower rate of elimination, sustaining effective therapeutic levels in the bloodstream [47].

9. Novel Drug Delivery Approaches:

Contemporary drug delivery techniques are gaining significant traction within the realm of phytotherapy. Bacopa monnieri, due to its multifaceted effects, can be provided to patients through various administration routes, thereby enhancing its efficacy and bioavailability. Furthermore, scientific reports provide information

regarding alternative methods for administering active ingredients, including bilosomes, ethosomes, and poly merosomes. Through these advancements, Bacopa monnieri is becoming increasingly significant within the framework of a holistic approach to health and well-being.

9.1. Bilosomes:

Bacopa monnieri extracts must traverse the blood–brain barrier to exert their effects within the central nervous system. To achieve this, efforts were made to encapsulate the extract within nanovesicles, specifically forming liposomes and bilosomes. Two techniques were employed to create these formulations: solvent evaporation and thin-film hydration utilizing phosphatidylcholine. A thorough analysis was conducted on bilosomes and liposomes, which were characterized by uniform particle size and suitable zeta potential. In a study involving Swiss mice exhibiting memory impairment, Bacopa extract was administered at a dosage of 200 mg/kg. The findings indicated that the application of bilosomes led to a more significant enhancement in memory compared to liposomes. This improvement can be attributed to superior bioavailability and enhanced stability under conditions mimicking gastric and intestinal juices. It is important to highlight that only one-tenth of the dosage evaluated for acute

toxicity was utilized in this study. This reduction is a result of the markedly improved bioavailability, which still necessitates further advanced investigations, including radio-labelling [48,49].

8.2. Nanoparticles:

Bacoside II, a bioactive compound found in Bacopa monnieri, demonstrates in vitro cytotoxic effects against a variety of cancer cell lines. It has been observed to induce cell cycle arrest and apoptosis specifically in colorectal cancer cell lines, while also inhibiting the migration and tubule genesis of endothelial cell lines, thus showcasing anti-angiogenic properties. Research examined the impact of PLGA-PEG-encapsulated Bacopaside II nanoparticles (BM1NPs), which are characterized by an extended retention time in systemic circulation, on C6 glioma cells has indicated that BM1NP enhances the internalization of particles within these cells. This finding implies its potential anti-tumor activity through the elevation of ROS levels, suppression of cell proliferation, and the induction of apoptosis in C6 glioma cells [50].

9.3. Ethosomes:

Regarding skin aging, Brahmi is essential for preserving a youthful and healthy look due to its antioxidant properties, which shield the skin from free radicals—key factors in premature aging. Additionally, Brahmi contains compounds that promote collagen synthesis and enhance skin elasticity, thereby diminishing the visibility of wrinkles. This phenomenon is linked to the plant's chemical makeup, especially the presence of bacosides and alkaloids. Research has been conducted where Bacopa monnieri extract was integrated into nano lipoidal vesicles, such as ethosomes, to improve its absorption into the deeper layers of goat skin, with the goal of boosting collagen production and minimizing elastin breakdown in the dermal layer. Ethosomes are characterized by their flexibility and deformability, enabling them to traverse the disordered stratum corneum and access deeper skin layers. Utilizing ethosomes, Bacopa monnieri extract was able to penetrate to a depth of 30–40 μm in goat skin. Permeation studies indicated that systems exhibiting zero-order kinetics facilitate a sustained release of substances over a prolonged duration, thereby enhancing therapeutic outcomes. Consequently, ethosomes are well-suited for the transdermal delivery of herbal extracts [51, 52].

10. Regulatory Aspects:

In the European Union (EU), Bacopa monnieri is recognized as a pharmacopeial plant, and a monograph is currently being developed by the European Medicines Agency (EMA) for this species. Bacopa monnieri is legally permitted as an ingredient in dietary supplements; however, it does not fall under the classification of a novel food, as it was utilized in dietary supplements within the EU prior to 15 May 1997, thus exempting it from Regulation (EU) 2015/2283. Nevertheless, uses beyond dietary supplements—such as the incorporation of Bacopa monnieri in food products—may necessitate authorization in accordance with the Novel Food Regulation (EU) 2015/2283 prior to its introduction to the EU market. Furthermore, it is essential to consider general food safety regulations, including Regulation (EC) No 178/2002, which outlines the fundamental principles and requirements of food law, along with other regulations that may impose restrictions or govern the use of the product in specific EU member states. The U.S. Food and Drug Administration (FDA) has not established specific regulations pertaining to Bacopa monnieri dietary supplements and has not sanctioned this plant as a pharmaceutical drug. Consequently, the FDA has not released any formal statements regarding its safety or efficacy. The FDA has, however, promulgated several general regulations concerning dietary supplements, including the Dietary Supplement Health and Education Act (DSHEA) and the Current Good Manufacturing Practice (CGMP). DSHEA delineates dietary supplements and sets forth guidelines for their labeling and marketing, while CGMP establishes quality standards for the manufacturing processes of dietary supplements. The FDA intervenes only when a supplement is deemed unsafe or is marketed in violation of regulations. Therefore, it is advisable to consult a healthcare professional prior to the consumption of any dietary

supplement containing Bacopa monnieri. Products containing Bacopa monnieri are regulated in Canada as Natural Health Products (NHPs). They are consequently subject to the applicable regulations set forth by Health Canada, including the Natural Health Products Regulations and the Natural Health Products Ingredients Database. Bacopa monnieri is utilized in dietary supplements; however, there are limitations on the maximum dosage, which vary based on factors such as age and health condition. Furthermore, manufacturers and importers are required to secure the necessary license to engage in these activities and adhere to quality manufacturing standards [53,54,55,56].

Conclusion:

Bacopa monnieri has evolved from a traditional Ayurvedic cognitive enhancer to a scientifically credible candidate in neurotherapeutic research, fuelled by an increasing interest in multi-target strategies for neurodegenerative diseases. Experimental studies consistently show that Bacopa provides antioxidant, anti-amyloid, cholinergic-modulating, and anti-inflammatory benefits—mechanisms that directly relate to the fundamental pathological processes of Alzheimer's disease and dementia. These results establish a coherent mechanistic framework that underlines its neuroprotective capabilities. Preclinical research presents the strongest evidence for Bacopa's effectiveness, indicating enhancements in memory, synaptic integrity, and neuronal survival across various animal and cellular models of cognitive decline. Bacopa's capacity to target multiple pathological pathways at once offers a theoretical edge over single-target pharmacotherapies, which have predominantly failed to alter the course of Alzheimer's disease. Nevertheless, biological plausibility does not automatically translate to clinical effectiveness. Clinical data, although promising, are still limited and methodologically restricted. Trials carried out in healthy adults and older populations consistently show modest yet significant enhancements in memory, attention, and cognitive processing speed. Conversely, the evidence available for Alzheimer's disease and dementia populations is limited, underpowered, and varied, lacking sufficient duration and consistent outcome measures. Crucially, there is currently no high-quality evidence that supports Bacopa monnieri as a disease-modifying treatment for established neurodegenerative diseases. From a safety perspective, Bacopa monnieri shows good tolerability, which enhances its appropriateness for long-term use and further research. However, inconsistencies in extract standardization, dosing, and study design continue to hinder reproducibility and clinical application without rigorous phase III trials that include validated cognitive endpoints and biological biomarkers, its therapeutic role remains uncertain.

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