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Review Article

# Targeted Neurotherapeutics: A Review of *Bacopa monnieri* Delivery Strategies for Neurodegeneration

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**ABSTRACT:**
Neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and Autism lead to Central Nervous System (CNS) degeneration, impairing both cognitive and motor functions. With the rising prevalence of these illnesses-closely linked to age and lifestyle factors-effective therapeutic strategies that can cross the Blood-Brain Barrier (BBB) is urgently needed. Conventional medications often fail due to the restrictive nature of the BBB, which has prompted growing interest in nanotechnology-based Novel Drug Delivery Systems (NDDS). Among herbal candidates, *Bacopa monnieri* (BM), an Ayurvedic herb, has demonstrated significant neuropharmacological potential. Its active constituents, primarily bacosides, exhibit antioxidant, anti-inflammatory, neuroprotective, and cognition-enhancing properties. These attributes make BM particularly promising for managing oxidative stress and neuronal damage associated with neurodegenerative conditions. However, BM suffers from limitations such as poor bioavailability, low solubility, and susceptibility to gastrointestinal degradation. To overcome these challenges, researchers have explored nanocarriers including liposomes, bilosomes, ethosomes, and solid lipid nanoparticles. These systems protect BM from degradation, enhance BBB permeability, and enable targeted, sustained drug release to the brain. In this thesis, BM is integrated with nanocarrier-based delivery approaches to improve therapeutic outcomes for neurological disorders. The discussion encompasses BM phytochemicals, neurodegenerative mechanisms, and the challenges of CNS drug delivery. Various nanocarriers are shown to enhance BM's pharmacokinetics, brain uptake, and clinical efficacy. Furthermore, advanced ligand-mediated and stimuli-responsive technologies offer precise targeting of phytochemicals. BM nanoformulations represent a convergence of herbal medicine and nanotechnology, paving the way for safer, more tailored treatments for neurodegenerative diseases. Ultimately, NDDS-based delivery of *Bacopa monnieri* holds the potential to transform CNS disease management by enabling effective, non-invasive, and long-term neuropharmacological interventions.

**Keywords:** *Bacopa monnieri*, Cognitive enhancement, Neuro-degenerative disorder, Novel drug delivery system, Oxidative stress.

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## INTRODUCTION

### General insight into neuro-degenerative disorder

Most brain diseases involve neurodegeneration as the main pathophysiological change. Modern science's efforts to produce a medical or surgical cure have failed (Abbott *et al.*, 2003). As the population ages, obesity, metabolic illnesses, and neurodegenerative disorders increase because they are connected. Parkinson's and Alzheimer's have a combined prevalence of 3% at 65 and 55% by 95. In neurodegenerative diseases, EC protein deposits, internalized cell aggregates, and cell shape abnormalities are produced (Allam *et al.*, 2004). Three brain lesions are diagnostic indicators. Extracellular proteins can form plaques, such as Amyloid beta (Ab) deposits in Alzheimer Disease (AD) and Down's syndrome and PrP deposits in CJD. Second, neurofibrillary tangles in AD, Lewy bodies in Parkinson's disease, dementia with Lewy bodies, pick bodies in Pick's disease, and tau-positive neurons or glial cells in corticobasal degeneration and MSA develop filamentous cellular inclusions. Third, enlarged swallow achromatic neurons (SN) in Parkinson's disease ('Pick cells') and CBD, as well as spindle-shaped 'torpedos' near cerebellar Purkinje cell axons in other diseases, may occur (Almeida *et al.*, 2002). Clinical diagnosis of neurodegenerative disease is challenging, however 80% of cases are verified after death. Brain tissue examination after death is often necessary for a definitive diagnosis. If the neurologic condition is not a major cause of death, gathering mortality data like death records is challenging since autopsies are rare. Most studies focus on lifelong symptoms, and many neurologic illness criteria are subjective, leading in disease misclassification. Since numerous neurologic diseases may coexist, differentiating them is challenging (Gan

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*et al.*, 2018). One study examined "Parkinson plus SD," PD and multiple system atrophy or progressive supranuclear palsy. Vascular diseases like stroke and heart disease often co-morbid. Diagnostic criteria have evolved over time, complicating things. Analysing neurologic symptoms separately and early before clinical diagnosis might help detect neurodegenerative diseases. Standardised neuropsychological tests give objective support (Behl *et al.*, 2021).

## SEARCH STRATEGY

The literature was sourced from PubMed, Scopus, and Google Scholar using combinations of keywords such as '*Moringa oleifera*,' 'anti-neurodegenerative', 'anti-aging,' and 'formulation.' Searches were limited to English-language publications between 1994 and 2025. Studies were included if they reported experimental or clinical data on herbal formulations with anti-aging potential. Reviews and studies full text were included. Titles and abstracts were screened, followed by full-text review, resulting in 47 articles that met the inclusion criteria.

## REVIEW OF LITERATURE

### Common factor that contributes neurological disorder

The predominant pathogenic characteristic is amyloid buildup. These aggregates contain misfolded proteins or peptides. Different neurodegenerative disorders have different amyloid-forming proteins. Although synthesized throughout the body, amyloidogenic protein only builds up in the central nervous system (Gibbons *et al.*, 2019). Protein aggregates start accumulating early in childhood, but clinical symptoms appear in mid to late adulthood. Genetic mutations that enhance protein misfolding and aggregation can cause hereditary forms, although most cases are rare.

### Blood Brain Barrier as an Obstacle in Delivering Drugs to the CNS

An active Blood-Brain Barrier (BBB) separates circulating blood from the brain's extracellular fluid in the central nervous system. It controls circulation molecules entering brain tissue to maintain brain stability. Brain microvascular endothelial cells form the BBB through tight connections that inhibit paracellular motion (Gitler *et al.*, 2017). Though it protects the brain from viruses, toxins, and plasma composition changes, the blood-brain barrier hinders the administration of therapeutic drugs, especially Big, hydrophilic molecules reach the CNS (Jellinger, 2010). Research on drug delivery methods that can cross the blood-brain barrier is important for treating brain tumors, neurodegenerative diseases, and mental health conditions (Jack *et al.*, 2014). Since they can be targeted, controlled, and bioavailable, nanoparticles are attractive central nervous system medication carriers. To enhance medication delivery, Receptor-Mediated Transcytosis (RMT) and Carrier-Mediated Transport (CMT) use blood-brain barrier receptors and transport proteins. Using targeted ultrasound, chemicals, or radiation to temporarily breach the blood-brain barrier can increase medication permeability (Cuervo, 2008).

### Challenges in Targeting Drug Delivery

As the population ages and competition rises, CNS problems are the second most common disease. The development success rate for CNS-targeted medications is 8%, compared to 20% for cardiovascular therapies. Since the blood-brain barrier blocks many big and small molecule medications, it affects CNS drug development (Craik, 1994). Pharmaceutical molecule distribution is most problematic due to the BBB's anatomy and selective permeability. Lipid-soluble drugs pass through the BBB more easily than water-soluble ones due to its lipid-based membrane formulation (Bozoki *et al.*, 2001). Transporter proteins' binding preferences and cargo limits limit medicinal compounds' CNS access. Insufficient molecular weights, polarities, and hydrophobicity's can prevent BBB penetration of several drugs, including Oxycodone (Deuschl *et al.*, 2020). Drug-targeted transportation is also hampered by biological modelling and assessment flaws. For example, *in vitro* and *in vivo* experimental models often fail to accurately represent the complex human blood-brain barrier, causing early-stage drug testing uncertainties (Alladi and Hachinski, 2018). Laboratory-based BBB models fail to recreate the complex blood-brain barrier environment and function *in vivo* systems (Taylor *et al.*, 2002). Key cell types are missing from many *in vitro* models. Drug processing, movement, and clearance routes may not be accurately simulated in *in vitro* models (Trojanowski and Hampel, 2011). Uncertainty rises in preclinical assessments. Health risks can result from blood-brain barrier permeability changes allowing hazardous chemicals, immunological components, and other medications to enter the CNS. Focused Ultrasound (FUS) and microbubble procedures to temporarily break the blood-brain barrier to improve medication delivery may damage the barrier permanently or temporarily, rendering it inappropriate for some candidates. In addition, age, sex, genetics, and physiological conditions like pregnancy might affect the barrier's function and medication penetration into the brain (Makkar *et al.*, 2020). Age alters the blood-brain barrier. The aged may have increased permeability and decreased efficiency, which can lead to neurological disorders.

### Nanocarrier-Enabled Drug Delivery Systems for Brain Tumor Targeting

Nanomedicine has been greatly impacted by nanotechnology, especially in biological applications. It allows nanoscale material manufacturing and handling and the development of novel biotechnological diagnostic, therapeutic, monitoring, and regulatory techniques (Di *et al.*, 2013). Nanomaterials are nanoscale substances having internal or surface characteristics and exterior dimensions between 1 and 100 nm. Nanostructured

compounds can pass the blood-brain barrier and deliver therapeutic molecules to particular sites, making them promising. Polymeric micelles, dendrimers, liposomal carriers, quantum dots, and gold nanoparticles have been investigated for brain-targeted drug delivery (Gabathuler, 2010). Studies on nanocarriers and their usage have been published. Nanoparticles can cross the blood-brain barrier to carry medications to the brain (Nicolazzo and Katneni, 2009). Smaller amounts of active chemicals or therapeutic complexes can be directly transported into the brain, making therapy safer and more effective than unbound medicines. Nanocarriers have a large surface area, high drug loading, the ability to integrate hydrophilic and hydrophobic molecules, and exceptional stability. Shape and size affect NP qualities beyond composition. Monodispersed NPs that may be taken up by cells must be controlled in form, size, and aggregation. Their biological and chemical stability, capacity to load hydrophilic and hydrophobic medicinal chemicals, and diverse delivery paths make them suitable for medical usage (Stanimirovic *et al.*, 2015). Nanoparticles create covalent interactions with proteins and aptamers in particular tissues. High surface-area-to-volume ratio allows NPs to attach multiple copies of a ligand, increasing binding affinity via multifunctional function (Heymans *et al.*, 2018). Some NP applications have a larger surface mass ratio than conventional particles, allowing them to adhere, absorb, or convey substances. Additionally, two or more materials can be combined or designed to improve their qualities. Figures 1 depicts the most common nanocarriers, their mode of action, and their capacity to pass the blood-brain barrier for brain delivery (Figures 2-6) (Gandhi *et al.*, 2022).

## Traditional use of *Bacopa monnieri* in neuroprotective role

Cognitive improvement may be harmful and psychological. At regular dosages, *Bacopa monnieri* (BM) nootropic chemicals, notably the triterpenoid saponins termed bacosides, have little negative effects. BM is antioxidant, liver-, and neuroprotective. Recently, BM has been shown to inhibit acetylcholinesterase, activate choline acetyltransferase, reduce beta-amyloid plaques, increase cerebral blood flow, and potentiate monoamine neurotransmitters (Gatoo *et al.*, 2014). Brahmi, water hyssop,

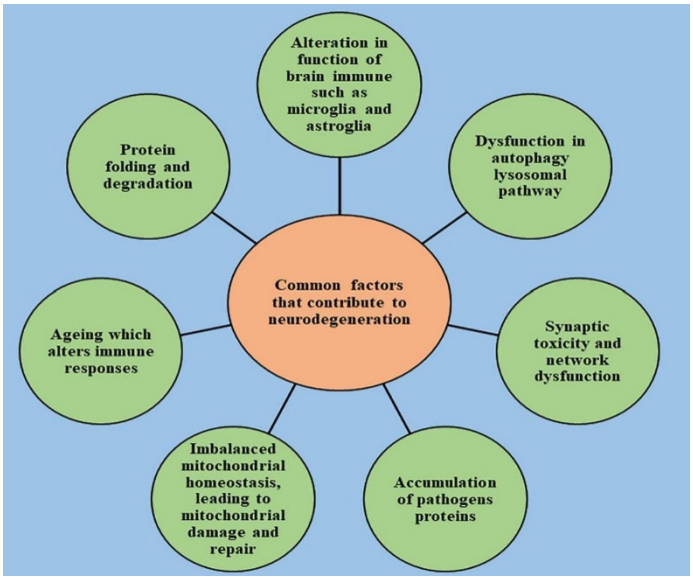



**Figure 1:** Shows some of the common components involved the development and advancement of neurological disorders.

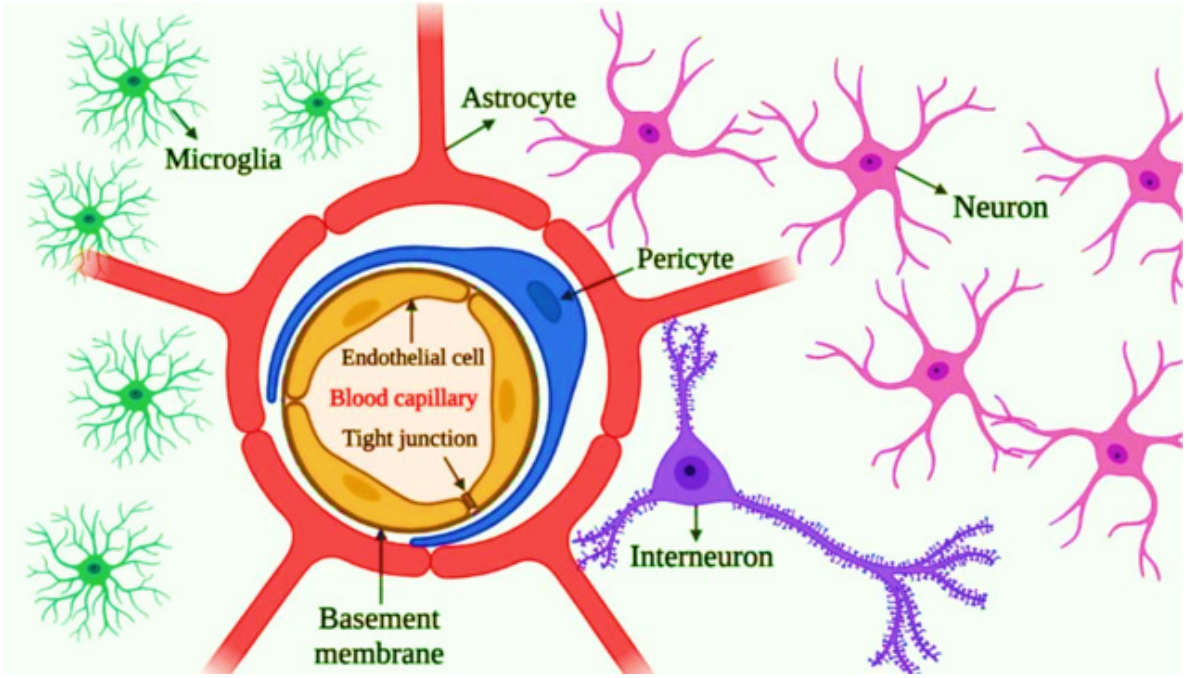



**Figure 2:** Depicts a diagrammatic representation of the blood-brain barrier, constructed by capillary endothelial cells and enclosed by the basal lamina along with astrocyte end-feet. The tight junctions between endothelial cells serve as both a structural and defensive barrier.

*Bacopa monniera*, or *Herpestis monniera* is a creeping perennial plant from warm marshland India and Australia. It is a prevalent weed in rice paddies in East Asia and the US. All of the plant is medicinal. According to over 1400 years of Ayurvedic wisdom, long-term, moderate usage of BM supports and nourishes neurons rather than exhausting them (Yasui *et al.*, 2013). In the 6th century A.D., the Charaka Samhita, Atharva Veda, and Sushrata Samhita classed BM as a Medhya rasayana, a drug that boosts intelligence and slows cognitive decline. Ancient Vedic academics employed BM to memorize holy chants and scriptures. Sometimes called Brahmi after the Hindu creator deity Brahma, *Bacopa monnieri* is used with other cognitive-enhancing herbs including *Centella asiatica* (Gotu Kola). Ayurvedic medicines for cognitive impairment sometimes contain it (Pillay *et al.*, 2014).

## Phytochemistry and Pharmacology of *Bacopa monnieri*

### *Active constitute of Bacopa monnieri*

Various pharmacological compounds, include alkaloids (brahmine, nicotine, herpestine), saponins (monnierin, hersaponin), and sterols (β-sitosterol, stigmasterol). Through biochemical studies, Bacopa ethanolic extracts included dmannitol, containing acid A and betulinic acid components. Bacopasaponins and dammarane-type bacosides make up B. monniera. Hindawi saponins' Evidence Based Complementary and Alternative Medicine publication reports that the only changes between jujubogenin and pseudojujubogenin are the glycosidic chain sugar units and the aglycone olefinic side chain. Bacopasaponins A-G and bacosides A1 and A3 represent a varied but related group of saponins. Bacopasaponins E and F, pseudojujubogenin glycosides, bacopasides I and II, two novel dammarane-type bisdesmosides based on jujubogenin, phenylethanoid glycosides from monnierasides I-III, and plantainoside B have also been found. Also isolated are bacopasides III, IV, and V. Bacoside A (64.28%) is key to *Bacopa monnieri's* neuropharmacological action, while bacoside B (27.11%) is chemically identical and varies mainly in optical rotation (Petkar *et al.*, 2011). Acid hydrolysis produces bacogenins A1-A4 from triterpenoid saponins pseudojujubogenin and jujubogenin. Bacopa's bacoside-enriched standardized extract has a high concentration of bacogenin A4.

## The neuroprotective function of *Bacopa monnieri*'s active constituent

*Bacopa monnieri* has shown potential in treating neurodegenerative diseases, anxiety, and epilepsy in *in vitro* and animal models. Free radical overproduction causes oxidative stress, which overwhelms the cell's defenses. Antioxidant enzymes include Glutathione Reductase (GR), Glutathione Peroxidase (GPx), superoxide dismutase (SOD), GST, and CAT neutralize radicals. Protective antioxidants include Vitamins A, C, E, and phenolic compounds (Montet *et al.*, 2006). Oxidative stress breaks molecular bonds, oxidizes lipids, impairs metabolic processes, fragments DNA, and denaturates proteins, causing many health problems, notably aging-related ones. The brain is especially susceptible to such damage due to its high metabolic activity, quantity of unsaturated fatty acids, and high prooxidant iron levels. In addition, the blood-brain barrier prevents many exogenous antioxidants from entering cerebral tissue, decreasing their ability to fight oxidative stress.

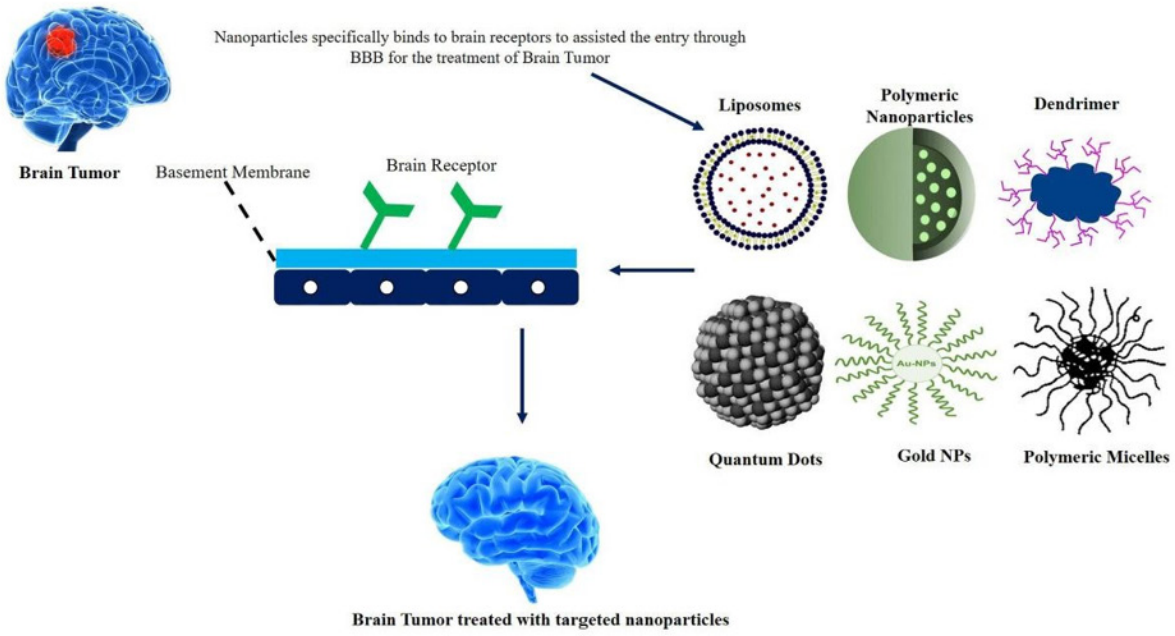



**Figure 3:** Shows emerging nanocarriers and their ability to traverse the blood-brain barrier for targeted brain delivery.




**Figure 4:** *Bacopa monnieri* plant: (A) Entire plant; (B) Stem close-up; (C) Flower close-up
*Bacopa monnieri* (Brahmi) is a widely recognized perennial creeping herb with bioactive compounds used extensively in the Indian Ayurvedic tradition to treat various health conditions.

Bacoside A is known to inhibit lipid peroxidation and preserve cell membranes. This adjusted blood and tissue enzyme levels and prevented CK from entering the circulation. Bacoside A treatment also reduced cigarette smoke-induced mitochondrial dysfunction in rats (Montet *et al*., 2006). Bacoside A stabilizes the mitochondrial membrane, boost mitochondrial enzymes, and lower lipid peroxides, cholesterol, and the Cholesterol/Phospholipid (C/P) ratio, protecting the brain. Bacosides also reduce lipofuscin, restrict lipid peroxidation, increase acetylcholine, and modify monoamines. The brain showed increased iNOS expression but lower levels of pro-inflammatory signaling molecules (IL-1β, TNF-α), total nitrite, and age-related pigment (lipofuscin). Ramasamy and colleagues evaluated the pharmacological characteristics of bacoside A, aglycones (jujubogenin, pseudojujubogenin), and derivates (ebelin lactone, bacogenin A1) using laboratory-based and computer-simulated screening methods Compare findings showed that Ebelin lactone had the highest binding affinity for M1 and 5-HT2A receptors and greater blood-brain barrier penetration. Bapaside, I protected rats from cerebral ischemia by reducing neurological deficits, cerebral infarct volume, and edema. Oral bacopasides I therapy dramatically increased brain ATP levels, antioxidant enzymes, and Ca (Mg) and Na(K) ATPases. Bacopasides I also lowered brain MDA (Kongkeaw *et al*., 2014).

## Antioxidant property of *Bacopa monniera*

### Effect of Oxidative Stress in CNS function

Even though oxygen is essential to life, the brain is susceptible to ROS-producing oxygen metabolic activities. Mitochondria produce 95%-98% ROS, such as $H_2O_2$, $OH_2$, $O_2^{-}\cdot$, and peroxynitrite, as byproducts of cellular respiration. Research on brain-isolated mitochondria showed ROS production from 2-5% of oxygen consumption. Unbalanced prooxidant and antioxidant responses result from oxidation-reduction equilibrium disruption. Due to this imbalance, macromolecule oxidative damage accumulates and worsens with age, limiting cellular

function and process efficiency. Free radicals severely damage DNA, proteins, membrane lipids, and mitochondrial components in the brain, affecting cellular function. The brain is especially susceptible to free radical damage due to its rapid metabolism, high concentration of unsaturated fatty acids, cytotoxic effects of glutamate, and diminished antioxidant systems with reduced GPx and CAT activity compared to other tissues (Saraf *et al.*, 2008). The brain gets less effective in neutralizing radicals with age. Free radicals severely damage DNA, proteins, membrane lipids, and mitochondrial components in the brain, affecting cellular function.

The brain is especially vulnerable to free radical damage due to its rapid metabolism, high concentration of unsaturated fatty acids, cytotoxic effects of glutamate, and diminished antioxidant systems with lower GPx and CAT activity than other organs. The brain's ability to scavenge free radicals decreases with age, reducing antioxidants, notably GSH, the most abundant endogenous antioxidant. The pros and cons of free radicals are subtle. Normal physiological ROS scavenging balances ROS production variability (Floyd and Hensley, 2002).

Oxidative stress occurs when ROS synthesis exceeds scavenging. Oxidative stress, induced by increased ROS generation, impaired redox state, and reduced ROS scavenging, is a significant part of aging. This imbalance in cellular redox pathways may cause age-related cognitive decline and neurodegenerative diseases. The very damaging effects of severe, extensive, or long-lasting oxidative damage accelerate aging.

## Pathophysiology and Role of *Bacopa monnieri* in Neurodegenerative Disorders

### *Alzheimer's Disease*

A chronic neurodegenerative disease, Alzheimer's disease permanently impairs the brain's neurological system. Cerebral dementia reduces speech, memory, and learning. As its source

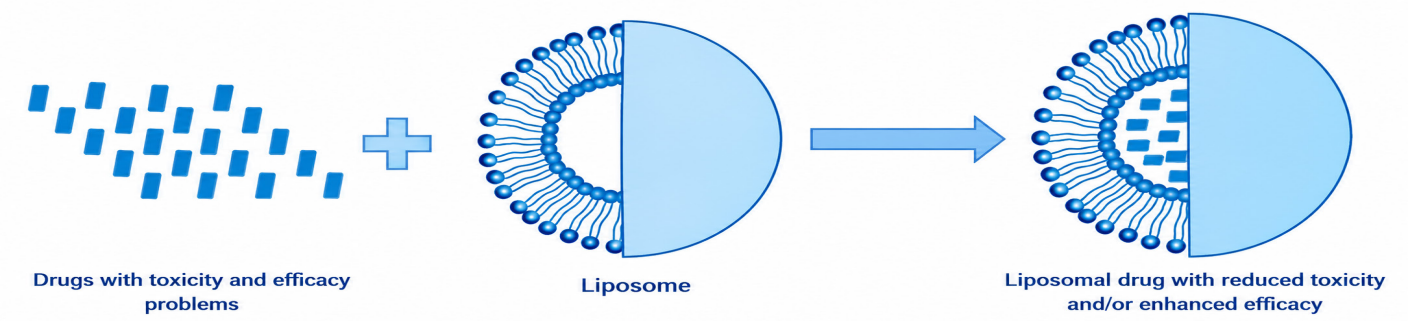



**Figure 5:** Schematic representation showing the advantages of formulating drugs in liposomes

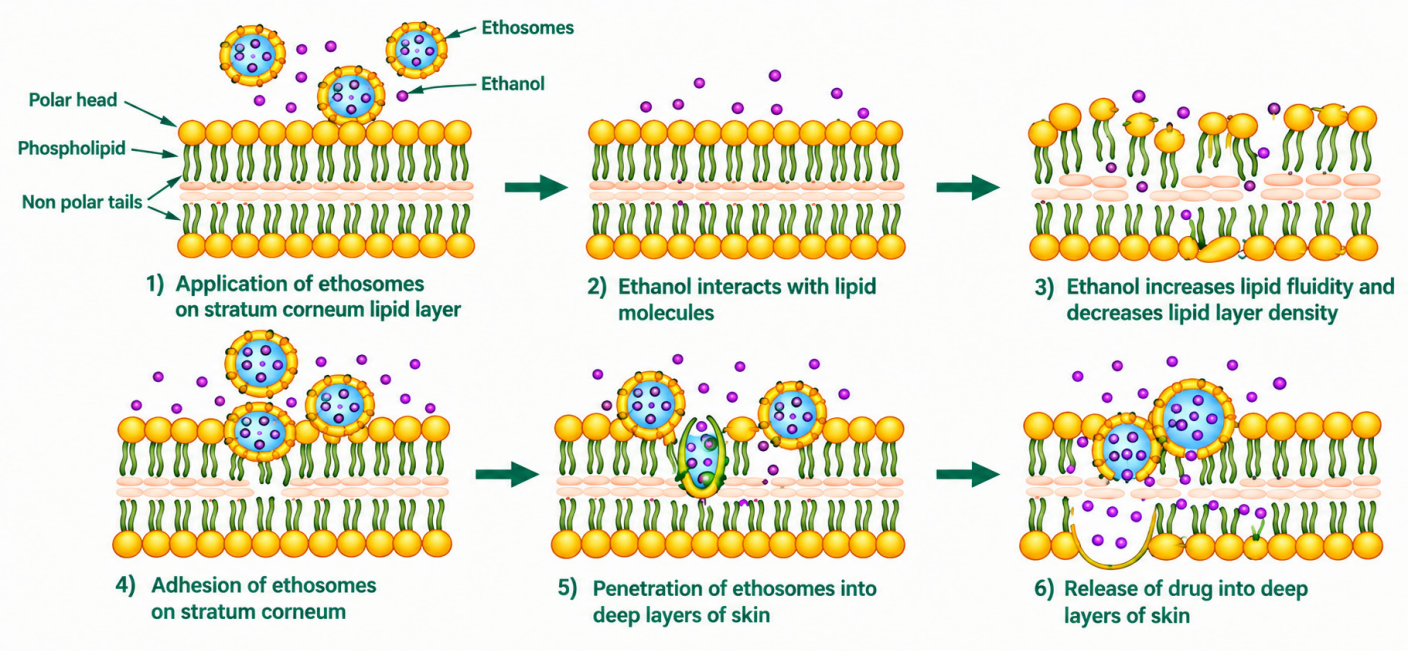



**Figure 6:** Mechanistic Insight into Ethosomal Drug Delivery Penetration.

is unclear, it is difficult to find effective therapies to slow its fast spread. Cholinesterase and glutamate antagonists are current therapy. Beta-amyloid plaques and Tau proteins accumulate in the brain abnormally. They create free radicals that block glucose passage in nerve cells, damaging and killing them. A reduction in cortical choline acetyltransferase, choline release, and acetylcholine synthesis results from neuronal death. Cholinergic transmission is increased to slow Alzheimer's disease development. Treatment for causation fails (Simpson *et al.*, 2015).

Nearly 60% of dementia cases in persons over 65 are caused by Alzheimer's disease. Cases are anticipated to quadruple or treble by 2050, showing little progress. In Alzheimer's disease, long-term pharmaceutical treatment is often impossible due to gastrointestinal side effects that damage the stomach mucosa and cause peptic ulcers. Alzheimer's disease accounts for 60% of dementia cases in adults over 65. No progress is shown, with instances predicted to increase or treble by 2050. Long-term pharmacological treatment for Alzheimer's is often prevented by gastrointestinal responses that damage stomach mucosa and produce peptic ulcers.

*Bacopa monnieri* may have protected neurons via inhibiting acetylcholinesterase, not glutamate. By decreasing reactive oxygen species, the extract lowered intracellular oxidative stress and improved neuronal longevity. Antioxidant and lipid peroxidation-reducing extract. *Bacopa monnieri* (100 mg/kg for 180 days) enhanced 72 mice's cognition. Healthy mice improved memory, focus, and learning, whereas Alzheimer's mice recovered. The Morris water maze test showed significant differences across groups ($p<0.01$). A randomised, double-blind clinical research of 60 healthy, aged volunteers taking 300 mg and 600 mg Brahmi improved memory and focus by lowering acetylcholinesterase activity. Alzheimer's and ADHD may be treated with bacopa. No side effects or toxicity were detected. *Bacopa monnieri* improves cognition in clinical tests, although its efficacy in Alzheimer's disease must be studied alongside pharmaceutical treatments. Acetylcholinesterase inhibitors (AChEIs) improve cholinergic signaling or reduce excitotoxicity to prevent cognitive deterioration. Brahmi responded comparable to Alzheimer's disease medication donepezil in a 52-week, randomized, double-blind trial. *Bacopa monnieri* (300 mg) and synthetic donepezil 10 mg were tested in 48 mildly cognitively impaired Alzheimer's patients. They were comparable after a year of treatment (Meena and Maurya, 2025).

## Parkinson's Disease

Parkinson's disease is a neurodegenerative disorder characterized by nigral dopaminergic neuron loss and α-synuclein-containing Lewy bodies. Tremors, muscular rigidity, and cognitive impairment arise from these causes. Age, genetics, brain traumas, and chemical exposure all affect the syndrome. *Bacopa monnieri* may support Parkinson's disease neuroprotection. *In silico* molecular docking showed Bacoside-A's affinity for Parkinson's disease protein 7 active site and Bacopasides-XII's KEP1 inhibition. Inhibiting DJ-1 and KEAP1 may reduce Lewy body formation caused by oxidative stress.

Invertebrate experiments also demonstrated success. A *B. monnieri* tincture (100 g DW/650 mL 96% ethanol) was diluted ten times in OP50 liquid culture for 48 hr in transgenic Caenorhabditis worms expressing α-synuclein and *C. elegans* subjected to 25 mM 6-hydroxydo The *Bacopa monnieri*-treated transgenic *C. elegans* showed considerably reduced α-synuclein accumulation and lipid peroxidation compared to the control group Dopaminergic neuron loss in the 6-hydroxydopamine group was decreased by *Bacopa monnieri*. Research examined transgenic Parkinson's *Drosophila melanogaster* exposing them to *Bacopa monnieri* extracts at 0.25, 0.5, and 1.0 μL/mL for 24 days. Oxidative damage and motor impairments were delayed in extract-treated flies. Singh and colleagues gave male albino mice 40 mg/kg oral *Bacopa monnieri* extract for 30 days. Intraperitoneal MPTP (15 mg/kg) simulated Parkinson's-like degeneration from days 15 to 30. Co-treatment with *Bacopa monnieri* improved motor performance and reduced dopaminergic neuronal loss in MPTP-only mice. Neuroanatomy showed decreased oxidative stress indicators, pro-apoptotic proteins, antioxidant levels, and Bcl-2 overexpression. After three weeks of 40 mg/kg *Bacopa monnieri* extract and 30 mg/kg MPTP injections, another group of mice had similar results. This suggests *Bacopa monnieri* protects and restores. Shomol *et al.* gave rats 180 mg/kg *Bacopa monnieri* extract orally for 80 days and 2.5 mg/kg rotenone from 20 to 80. Brain noradrenaline, adrenaline, dopamine, and serotonin rose while MAO activity decreased. *B. monnieri* supplementation (225 or 400 mg/day for 90 days) improved cognitive and emotional well-being and quality of life in 20 Parkinson's disease patients in a randomized, placebo-controlled, double-blind experiment in one research study (Paun *et al.*, 2021; Rainka *et al.*, 2023).

## Autism Spectrum Disorder

Modern autism is a major neurodevelopmental condition. Over the previous two decades, its incidence (1 in 150) has increased. During sensitive brain development, especially in genetically vulnerable children, exposure to hazardous exogenous substances such thalidomide, ethanol, valproic acid, and methyl mercury or stress may accelerate this surge. Symptoms include social challenges, verbal and nonverbal communication issues, restricted interests, and repetitive or stereotyped activities. Self-harm and hyperactivity may occur. Worldwide, one in 100 children has ASD, a rising trend. ASD's genesis and pathophysiology are unknown, and there is no cure. Novel therapies targeting the disorder's pathophysiological mechanisms are needed. *Bacopa monnieri* (Brahmi) has been studied for its potential to alleviate oxidative stress, inflammation, and neuroprotection, which could help treat ASD (Shoukat *et al.*, 2023).

## Novel Drug Delivery System for Brain Targeting

Innovation in Natural Drug Delivery Systems (NDDS) has been a focus for decades. Two requirements are ideal for contemporary delivery trucks. During therapy, it should release medicine in accordance with the body's therapeutic requirement. Second, the herbal drug's active ingredient should reach its target. These cannot be met by conventional dose forms, including delayed release. in phyto-formulation studies, developing nano formulations (polymeric nanoparticles and nano capsules, liposomes, solid lipid nanoparticles, phytosomes and nanoemulsion, etc.) can improve herbal drug solubility, bioavailability, pharmacological action, stability, targeting to macrophage-rich tissues, sustained delivery, and resistance to physical and chemical degradation. New nanoscale drug delivery technologies for herbal therapies may boost activity and solve herbal medicine difficulties. Liposomes, ethosomes, niosomes, solid lipid nanoparticles, and coated nanoparticles can deliver herbal medications. Biologically compatible and non-toxic liposomes can include hydrophilic and hydrophobic substances. Liposome-based drug delivery systems can improve anti-cancer drug sensitivity by increasing drug concentration in tumor cells and/or decreasing exposure in normal tissues, using the EPR effect, and targeting. Unique formulation tactics can boost herbal cosmetics' health benefits. In addition, nanoemulsions, ethosomes, and transferosomes are excellent delivery architectures that provide several benefits (Peth *et al.*, 2012). *Ginkgo biloba*, grape seed, hawthorn, milk thistle, green tea, and ginseng have already been treated with phytosomes. Flavonoids and terpenoid elements of these plant extracts interact well with phosphatidylcholine. The binding of herbal extract components to phosphatidylcholine creates phytosomes, which have superior intestinal absorption and effects than typical herbal extracts. Compared to typical milk thistle extracts, silybin phytosomes absorb silybin sevenfold more. Drugs can dissolve, attach, or embed in nanoparticles. Nanoparticle-encapsulated drugs improve solubility and absorption, allowing new chemical entities with poor pharmacokinetics to be used therapeutically. Engineered degradable synthetic macromolecular polymers and biological macromolecules carry nanoparticles. Polyvinyl alcohol, polylactide, polylactide-co-glycolide, and poly (alkyl cyanoacrylate) esters are common. Albumin, gelatine, and plant-derived proteins are protein-based compounds, while cellulose, modified starches, alginate, chitin, and chitosan are polysaccharides.

## Synthesized Copper Oxide Nanoparticles of *Bacopa monnieri*

In the present investigation, Copper Oxide Nanoparticles (CuO-NPs) were synthesized using *Bacopa monnieri* seed extract, which functioned as both a reducing and stabilizing agent. This plant, classified under the Plantaginaceae family, is rich in various bioactive compounds, notably dammarane-type triterpenoid saponins referred to as bacosides, in which pseudojujubogenin acts as the aglycone component. So far, twelve structurally related bacoside variants have been identified within this Bacopasides I-XII are recently identified saponins. D-mannitol, apigenin, and herpestine B are among the five known alkaloids (herpestine, nicotine, brahmine, monnierasides I-III, and plantainoside B). Aside from bacoside A, which is composed of bacoside A3, bacopasides II, Bacopasaponins C, and a jujubogenin variant of Baco saponin C, the most frequently studied constituents of this plant include bacoside A3, bacopasides II, bacopasaponin C, and jujubogenin. *B. monnieri* offers a variety of scientific applications, including the treatment of seizures, depression, pain, inflammation, ulcers, and liver health. The morphological and physicochemical features of produced CuO-NPs were investigated using Fourier Transform Infrared (FTIR), Ultraviolet (UV), X-ray Diffraction (XRD), Scanning Electron Microscopy (SEM), and Transmission Electron Microscopy (TEM). Finally, anti-arthritis, antidiabetic, Chapter-4 analgesic, leukocyte migration assay, and antibacterial assays were used to better examine the therapeutic effects of green CuO-NPs in pharmaceutical application. These studies demonstrated the eco-friendly green synthesis of CuO-NPs using *B. monnieri* leaf extract. A variety of analytical techniques were employed to analyze the CuO-NPs, including UV, XRD, FTIR, SEM, TEM, and EDX. *In vitro* and *in vivo* evaluations confirmed that the synthesized CuO-NPs exhibit potent antibacterial, antidiabetic, and development anti-inflammatory activities. The CuO-NPs displayed significant antimicrobial and antidiabetic effects, indicating their potential in the of innovative drugs for these purposes. Nevertheless, this research emphasized the biochemical mechanisms and functional properties of CuO NPs; additional investigations are necessary to establish how these processes relate to the clinical outcomes observed in animal models (Schütz *et al.*, 2006). The discovery of active plant-derived compounds with enhanced attributes has broadened the scope of CuO-NPs in biomedical applications.

## Liposomal formulation of *Bacopa monnieri*

Liposomes given orally would be partially dissolved by gastric acid, resulting in the release of the therapeutic payload. Those that remain intact then move to the small intestine, where they are subjected to enzymatic degradation. If some vesicles remain intact, they traverse the mucus barrier and interact with the epithelial lining of the intestine. Even at this point, liposomes can be destroyed. Only a few liposomes that withstand the digestive environment are taken up by M cells and transported into the lymphatic circulation in vesicular form. Various strategies are employed to enhance the structural integrity of liposomes. Bile salts can improve the flexibility of lipid membranes, helping them endure the disruptive influence of bile acids present in the gastrointestinal tract. Imaging investigations have revealed that bilosomes that survive the GI environment can be ingested as whole vesicles. These are vesicular systems that offer partial protection to protein and peptide molecules from degradation

in to the Gastrointestinal Tract (GIT). The vesicular structure is formed by incorporating bile salts into the lipid bilayer, enhancing their resistance disruption in the digestive environment. As a result, the vesicle shields the contained chemicals from the hostile gastrointestinal environment. In this modern drug delivery design, agents such as deoxycholic acid are integrated into liposomal membranes. Bile salts aid the absorption of lipophilic drugs by facilitating their transport across cellular membranes, thereby improving oral bioavailability. Due to low absorption or first-pass hepatic metabolism, many phytochemicals fail to deliver sufficient therapeutic benefit. Advancements in drug delivery technologies can overcome these issues, ensuring efficient delivery of plant-based actives to the target site. An advanced vesicular delivery system helps guide the drug to the intended site at a rate matching physiological demand during treatment. Several studies on cancer and Central Nervous System (CNS) disorders, such as Alzheimer's disease, have explored nano-vesicular formulations. These delivery methods have been shown to improve drug properties such as therapeutic efficacy, solubility, and protection from degradation They attempted to boost the nootropic action of BM through bilosomal administration, hence adding value to the ancient Ayurvedic knowledge system. BME-loaded liposomes and bilosomes were synthesized in accordance with the methods section. To dissolve the lipophilic active constituents in BME, ethanol was used, enhancing entrapment efficiency. Since solvent evaporation resulted in larger vesicles, the final formulations of liposomes and bilosomes were developed using the thin-film hydration technique. The incorporation of bile salt into bilosomes during the hydration process distinguished them from liposomes. Adding cholesterol alters membrane permeability and flexibility, resulting in smaller vesicles. These studies demonstrate that the bilosomal formulation of BM is an effective delivery strategy (Udupa *et al.*, 1993).

### Ethosomal formulation of *Bacopa monnieri*

Nano cream comprising Canola (*Brassica napus* L.) Oil was tested for skin aging activities, and nano creams showed a higher percentage recovery than other conventional creams. These have promising applications, and when incorporated into novel nano-vesicular carriers, their penetration into deeper skin layers improves, offering enhanced therapeutic outcomes. This investigation demonstrated that ethosomes containing *B. monnieri* (BM) extract serve as a reliable system for transporting the extract into lower layers of the epidermis, thus increasing its therapeutic effects. BM extract is composed of antioxidants and polyphenols, both of which are recognized for their anti-photoaging activities. Using ethosomal technology enables the extract to reach deeper dermal regions, skincare with observed penetration up to 30-40 µm in goat skin. BM-loaded ethosomes may be utilized in anti-aging formulations for effective age-related skin management. Further validation through clinical trials may support the broader use of herbal-based formulations (Sarker *et al.*, 2015).

### Solid-lipid nanoparticles of *Baccopa monnieri*

In this investigation, SLNs were made from lipid glyceryl monostearate and filled with a bacoside-A rich extract. SLNs were created utilizing a hot homogenization process followed by sonication. The generated SLNs were analysed, and based on initial results of particle size and zeta potential, the optimum formulation was chosen for further characterisation to evaluate its in-vitro performance. Bacoside-A rich concentration was isolated from the aerial section of the nootropic/cognitive enhancer medicine *Bacopa monnieri* (Scrophulariaceae) and put into solid lipid nanoparticles made of glyceryl monostearate. The extract was confirmed to comply with the reported criteria. The FTIR research demonstrated that the bacoside-A rich extract had comparable characteristic bands to the marker. A total of four formulations were created using glyceryl monostearate using heat homogenization and sonication. The formulation has a zeta potential of -10.4 mV at 0.350 PDI. The drug entrapment efficiency was discovered to be 81.9% for glyceryl monostearate nanoparticles (Morel *et al.*, 1998). TEM pictures of solid lipid nanoparticles revealed nearly spherical shapes with uneven surfaces. The solid lipid nanoparticle formulation was able to prolong medication release for up to 24 hr (90% drug release) while adhering to the Hixson Crowell model. Furthermore, the formulation was proven to be stable at refrigerated temperatures for three months. The *in vitro* performance of created solid lipid nanoparticles was satisfactory, and it is necessary to evaluate their *in vivo* performance to determine the potential of the established delivery system in terms of CNS targeting and sustained nootropic impact (Olbrich *et al.*, 2002; Peter Speiser, 1990).

## FUTURE DIRECTIONS

#### *Neuropharmacological action*

Several studies have shown that the plant, plant extracts, and isolated bacosides have nootropic effects. Early research found that the herb and its alcoholic extract improved rat learning. B, two saponins, bacosides A, in the alcohol-based extract improve memory. In healthy rats, these chemicals improved memory and learning and prevented memory loss following scopolamine, electroshock, and immobilization stress. Bacosides may dephosphorylate membranes, increasing protein and RNA turnover in certain brain areas. In the hippocampus, BM increases protein kinase activity, which may explain its cognitive effects (Taylor *et al.*, 2002). For two weeks (Bhattacharya *et al.*, 1999) gave rats a standardized BM extract rich in bacosides to correct memory impairments produced by intracerebroventricular colchicine and biogenic acid into the nucleus basalis magnocellular is. Neurotransmitters like the central cholinergic circuit control cognitive function. An anticholinesterase medication is the mainstay of AD-type senile dementia, which is caused by

hippocampal cholinergic neuronal loss. Colchicine-induced acetylcholine depletion, choline acetylase activity reduction, and muscarinic cholinergic binding to receptors in the frontal cortex and hippocampus were restored by BM over two weeks. Decreased noradrenergic function may diminish cholinergic degeneration's behavioural consequences. BM decreases norepinephrine and increases 5-hydroxytryptamine in the hippocampus, hypothalamus, and cerebral cortex. Thus, BM may indirectly affect Ach concentrations via other neurotransmitter systems. Standardized BM and *Ginkgo biloba* extracts were tested for antidementic and anticholinesterase properties in adult male Swiss mice. BM and GB substantially boosted TLT and NTR, lowering dementia. All of the extracts dose-dependently reduced acetylcholinesterase/AChE activity *in vitro*, but none of the BM extracts inhibited more than 50%, suggesting that the GB and BM extracts increase cognition through different processes.

### Anxiolytic effect

BM extract increases cognition, unlike benzodiazepine anxiolytics, that makes its anxiolytic properties interesting. Standards BM extract and benzodiazepine were compared in experimentally verified rat models of clinical anxiety. Rats were given BM extract at 5, 10, and 20 mg/kg orally and Lorazepam (LZP) at 0.5 mg/kg intraperitoneally. Higher dosages of BM extract had much more anxiolytic action than LZP (Bendas and Tadros, 2007).

### Potential Antidepressant Effects of *Bacopa monnieri*

Recent studies have explored the antidepressant potential of a standardized methanolic extract of *Bacopa monnieri* (BM) using established depression models in mice. Its efficacy was compared to that of imipramine, a commonly prescribed antidepressant (15 mg/kg, intraperitoneally). Oral administration of the BM extract at doses of 20 and 40 mg/kg for five consecutive days resulted in notable antidepressant-like activity in both the forced swim test and the conditioned helplessness paradigm, producing effects on par with imipramine (Limpeanchob *et al.*, 2008).

### Seizure-Preventing Effects of *Bacopa monnieri*

Several experimental investigations have shown that *Bacopa monnieri* (BM) can prevent seizures. A crude BM aqueous extract decreased lab mouse seizure episodes, according to (Shanmugasundaram *et al.*, 1991). BM was given orally to mice and rats at levels from 1 to 30 g/kg to examine its central nervous system effects. Pentobarbitone-induced sleep, motor abilities, tail-flick delay, electroshock reaction, chemically generated seizures, haloperidol-induced catalepsy, and conditioned avoidance behaviour were affected. The extract sedated and prolonged pentobarbitone-induced hypnosis. It also suppressed conditioned avoidance variable. BM's antinociceptive properties, protection against electroshock and chemically triggered convulsions, and reduction of haloperidol-induced catalepsy suggest GABAergic pathway involvement in its CNS-related pharmacological effects. Most GABA-enhancing compounds are anticonvulsant, analgesic, and sedative. To investigate this, BM was tested alone and with Phenytoin (PHT), a common antiepileptic medicine that impairs cognition. We studied their effects on mice's Passive Avoidance (PA), maximum electroshock seizures, and movement patterns. BM attenuated PHT-induced PA task cognitive impairment. It Chapter-5 improved learning and memory retention without reducing PHT's seizure-prevention. More studies of BM alone or with additional anticonvulsants are needed to determine its potential to treat epilepsy and avoid cognitive negative effects from traditional antiepileptic treatment (Kunte *et al.*, 2013).

### Antioxidant Activity

Numerous studies suggest bacosides' antioxidant properties may boost BM's memory. One study examined how alcohol and hexane BM extracts affected ferrous sulphate and cumene hydroperoxide-induced lipid oxidation in rat liver homogenate. The alcohol extract protected against both oxidizers. Comparing the results to hydroxyl radical scavenger tris (2-amino-2-hydroxymethyl-1,3-propanediol), metal-binding agent EDTA, and natural antioxidant vitamin E. For ferrous sulphate-induced lipid peroxidation, EDTA and Vitamin E demonstrated concentration-dependent protection. Metal ion chelation at the start phase of the free radical chain reaction or free radical neutralization during propagation may explain why BM offered modest protection against reduced glutathione oxidation. Recently, BM extract was tested on rats' frontal cortex, striatum, and hippocampus for its effects on SOD, CAT, and GPX enzyme activities. This was compared to deprenyl, a well-known nervous system antioxidant, throughout the same duration. After 14 or 21 days, BM dramatically increased SOD, CAT, and GPX in all brain areas. But after 12 or 21 days, deprenyl increased these enzymes' activity in the frontal cortex and striatum but not the hippocampus. The hydroalcoholic extract of the whole BM plant inhibited superoxide generation from polymorphonuclear cells in the nitro blue tetrazolium test, according to (Pawar *et al.*, 2001). Bacoside A3 caused this result. Oral BM alcohol extracts protected rats against enzyme inhibition and glutathione depletion in morphine-treated rats, according to (Sumathy *et al.*, 2001). BM can also protect the liver from morphine-induced damage by inhibiting lipid peroxide production. BM extract prevented mitochondrial enzyme activity declines in morphine-treated brains, according to the same group (Heymans *et al.*, 2018).

## CONCLUSION

The rise of neurodegenerative diseases and the limits of pharmacological therapies necessitate alternate and improved remedies. Neurotransmitter abnormalities, oxidative stress, neuroinflammation, and mitochondrial dysfunction characterize Alzheimer D, Parkinson D, and Autism. To effectively manage

these illnesses, therapeutic medicines must be able to not only target these complicated pathways but also traverse the strong Blood-Brain Barrier (BBB). This thesis examined the medicinal potential of Ayurvedic herb *Bacopa monnieri* (BM) in treating neurological diseases. Bacosides and other phytoconstituents exhibit antioxidant, anti-inflammatory, anxiolytic, depressive, anticonvulsive, and neuroprotective actions in BM. BM have been proven to retain neuronal integrity, enhance neurotransmitter regulation, and stimulate neurogenesis in *in vitro* and *in vivo* experiments. BM cuts acetylcholinesterase, lowers amyloid plaque, and improves cognition in Alzheimer's disease. BMA decreases oxidative stress, preserves dopaminergic neurons, and improves motor and behavioural outcomes in Parkinson's disease. In ASD models, BM improves redox balance, neuroinflammation, and behaviour. Though medicinal, BM's weak water solubility, low gastrointestinal absorption, quick metabolism, and restricted BBB permeability have limited its clinical application. Oral BM formulations require high doses to be effective, which often yields inconsistent results. Innovative Drug Delivery Systems (NDDS) using nanotechnology to enhance BM's pharmacokinetic and pharmacodynamic characteristics exist to overcome these challenges. For BM delivery, liposomes, ethosomes, bilosomes, Solid Lipid Nanoparticles (SLNs), and polymeric nanoparticles provide benefits. These include better solubility, stability, drug release, circulation time, and, most importantly, BBB penetration for brain targeting. Distribution systems have different benefits. Hydrophilic and lipophilic drugs can be in biocompatible liposomes. Bilosomes transform bile salts into liposomes, improving oral bioavailability and gastrointestinal stability. Ethanol-loaded ethosomes easily cross epidermal and mucosal barriers, but SLNs are stable and lasting. Many tests showed BM-loaded nanocarriers' value in the thesis. Ethomal formulations increase skin penetration and anti-aging, whereas BME-loaded bilosomes boost brain absorption and cognition in animal models. These findings suggest transdermal uses for BM. The therapeutic and biocompatible properties of BM extract green nanoparticles seem promising. BM nano formulations promote patient adherence, reduce dose frequency, and reduce adverse effects. Many synthetic drugs cause gastrointestinal distress and hepatotoxicity, while BM formulations are well tolerated. The tranquil and amnesic effects of standard anxiolytics and antidepressants are absent in BM. Instead, it improves cognitive function, making it particularly useful in cognitive decline and neurodegeneration associated with aging Research on BM nano formulation is promising and varied. Brain tissues may selectively absorb ligand-conjugated nanocarriers. Another intriguing approach is to use stimulus-responsive delivery devices that release the medicine in reaction to pH, enzymes, or oxidative stress levels in sick brain areas. Furthermore, hybrid systems combining polymers, lipids, and functional biomolecules might balance biocompatibility, drug loading, and controlled release. Intranasal or microneedle-based transdermal patches may change BM administration. Unlike oral or parenteral delivery, these methods avoid hepatic metabolism and are patient-friendly. Personalizing BM formulations based on pharmacogenomics and disease profiles may be possible using 3D printing and tailored medication delivery systems. Progress has been made, yet problems persist. Standardization of BM extracts is critical for consistent therapeutic outcomes because variations in active ingredient concentrations can affect efficacy. Herbal nano formulation regulatory criteria must be precisely established to assist clinical translation. For long-term safety, especially with repeated dosing and sensitive populations, thorough toxicological investigations are needed. To summarize, the integration of *Bacopa monnieri* with nanotechnology-based drug delivery methods offers a substantial leap in the treatment of neurodegenerative illnesses. This collaboration bridging the divide between traditional herbal wisdom and modern medical research, *Bacopa monnieri* (BM) nano formulations offer promising potential by overcoming the limitations of conventional herbal preparations and enabling precise delivery to brain tissues. These technologies might change Alzheimer's, Parkinson's, and autism therapy. Millions of people with chronic and severe neurological diseases may find safer, more effective, and tailored medicines as science advances.

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## ABBREVIATIONS

**BM:** *Bacopa monnieri*; **BBB:** Blood Brain Barrier; **Ab:** Amyloid beta; **AD:** Alzheimer disease; **SN:** swallow achromatic neurons; **CNS:** Central nervous system; **ROS:** Reactive oxygen species; **AChEIs:** Acetylcholinesterase inhibitors; Intraperitoneal **MPTP:** Intraperitoneal 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; **NDDS:** Novel drug delivery system; **CJD:** Creutzfeldt-Jakob disease; **MSA:** Multiple system atrophy; **CBD:** Corticobasal degeneration; **PD:** Parkinson's disease; **RMT:** Receptor-mediated transcytosis; **CMT:** Carrier-mediated transport; **FUS:** Focused ultrasound; **NP:** Nanoparticles; **NPs:** Nanoparticles; **GR:** Glutathione reductase; **GPx:** Glutathione peroxidase; **SOD:** Superoxide dismutase; **GST:** Glutathione S-transferase; **CAT:** Catalase; **CK:** Creatine kinase; **C/P:** Cholesterol/phospholipid; **iNOS:** Inducible nitric oxide synthase; **IL:** Interleukin; **TNF:** Tumor Necrosis Factor; **MDA:** Malondialdehyde; **ATP:** Adenosine triphosphate; **GSH:** Reduced glutathione; **DW:** Dry weight; **MPTP:** 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; **MAO:** Monoamine oxidase; **ASD:** Autism Spectrum Disorder; **EPR:** Enhanced permeability and retention; **CuO-NPs:** Copper oxide nanoparticles; **FTIR:** Fourier transform infrared; **UV:** Ultraviolet; **XRD:** X-ray diffraction; **SEM:** Scanning electron microscopy; **TEM:** Transmission electron microscopy; **EDX:**

Energy-dispersive X-ray spectroscopy; **GI:** Gastrointestinal; **GIT:** Gastrointestinal tract; **BME:** *Bacopa monnieri* extract; **SLNs:** Solid lipid nanoparticles; **PDI:** Polydispersity index; **Ach:** Acetylcholine; **TLT:** Transfer latency time; **NTR:** Neurotransmitter receptor; **LZP:** Lorazepam; **PHT:** Phenytoin; **PA:** Passive avoidance; **EDTA:** Ethylenediaminetetraacetic acid.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHORS CONTRIBUTION

Conceptualized of the study by Suzain Garasiya. Suzain Garasiya also performed the literature search and data collection. Divya Kanojiya analysed and interpreted the data. Ghanshyam Parmar contributed to manuscript drafting and critical revision. All authors approved the final version of the manuscript.

## SUMMARY

Due to the blood-brain barrier and adverse consequences, neurodegenerative diseases including Alzheimer's, Parkinson's, and autism are challenging to treat with traditional medications because of oxidative stress, neuroinflammation, mitochondrial malfunction, and neurotransmitter abnormalities. With bacosides and other phytoconstituents providing antioxidant, anti-inflammatory, neuroprotective, anxiolytic, and antidepressant properties, the Ayurvedic herb *Bacopa monnieri* (BM) exhibits outstanding therapeutic potential. Research shows that BM can preserve dopaminergic neurons in Parkinson's disease, lower amyloid plaques and enhance cognition in Alzheimer's disease, and restore redox balance and behaviour in models of autism. However, BM's low absorption, poor solubility, and restricted brain penetration limit its therapeutic use. By improving solubility, stability, controlled release, and brain targeting, drug delivery technologies based on nanotechnology-such as liposomes, bilosomes, ethosomes, solid lipid nanoparticles, and polymeric carriers-help get beyond these obstacles. Transdermal patches, intranasal administration, and customized nanocarriers are examples of cutting-edge methods that enhance patient compliance and reduce adverse effects. BM nano-formulations provide safer, more effective, and tailored treatments for neurodegenerative illnesses despite difficulties with standardization, regulation, and long-term safety. They are a potent fusion of ancient herbal wisdom and contemporary science.

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