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# Anti-Alzheimer, Neuroprotective & Anti-inflammatory Activity of *Bacopa moniera*: An Update

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## ABSTRACT

*Baccoside from Bacopa monniera is an versatile molecule with nootropic, neuroprotective and anti-inflammatory actions. The multifarious biological activities, low cost and easy availability of Baccosides directed scientists to explore the mechanism of action and novel clinical uses of the drug. This leads to the development of different extraction methods and clinical investigation of Baccosides in animals and human in the last decade. The authors attempted in this review to present the ongoing developmental investigation and versatile potency of Baccosides with reported mechanism of actions. This review will definitely serve as source for development of new derivatives of baccosides and be utilized for development of treatment of Alzheimer and other cognitive and behavioral disorders.*

**Keywords:** Alzheimer disease; Neuroprotective; Nootropic; Anti-inflammatory; Brahmi; *Bacopa Monnieri*

## INTRODUCTION

Alzheimer's disease is a CNS and ANS disorder which slowly affects memory and thinking skills and also the ability to carry out the routine tasks. In most people with the disease - those with the late-onset type - symptoms appear in old age of mid 60's. Alzheimer's disease is characterized by the loss of neurons and synapses in the cerebral cortex and certain subcortical regions. This loss results in gross atrophy of the affected regions, including degeneration in the temporal lobe and parietal lobe and parts of frontal cortex and cingulated gyrus. AD is classified into two types, one is genetic which is known as Familial Alzheimer's disease (FAD) and second is Sporadic Alzheimer's disease (SAD). SAD is not considered genetic as it is due to senility conditions. FAD represents only 4-8% cases of Alzheimer's while SAD represents most of the cases of Alzheimer's [1].

Functional MRI has shown changes in neuronal network activities in AD patients and people at risk of AD. It was observed that abnormal activity and connectivity in the AD patient was enough to distinguish from normal activity and connectivity in volunteers without AD [2].

Experiments suggests that AD is not only responsible for inactivation of neuronal networks but also causing abnormal activites in neuronal network which alters the learning, memory and other cognitive functions. As over activity in neuronal network was also found, this may be considered responsible for neurodegeneration and also for increased incidences of epileptic seizures [3,4].

### Brahmi

Medicinal Plants provide numerous pharmaceutically active compounds, which has been commonly used traditionally as worldwide for the treatment of various diseases. Increasing interest of plant based medicine worldwide has led to discoveries of many new natural components such as sapnonins, steroid, glycosides for the treatment of various disorders. Various literature survey and plant based study data revealed that the presence of various secondary metabolite such as alkaloids, steroidal lactones, triterpenoid, saponins, iridoids, glycosides, anthocyanins, flavonoids, ginsenosides, isoflavonoids, catechins, in plants responsible for their neuroprotective potential against PD. Various research related data stated that the medicinal plants may work as anti-parkinson by different mechanism.

Bacopa monniera, (Commonly known as bacopa, brahmi) belongs to the Scrophulariaceae family. This plant commonly found in wetlands and damp regions throughout India. In Ayurveda, clear reference was made to its action on the central nervous system (CNS) which is chronicled in several ancient texts including the Caraka Samhita (2500 B.C.) and the Susrata Samhita (2300 B.C.) (P.V., 2011; [5] Plant has long history as traditional medicine. Traditionally plant is used to provide relief to patients with anxiety; as a nervine tonic, also used in digestive complains, diuretic, for skin disorders, and as an antiepileptic, antipyretic, and analgesic. The plant has a vast number of active constituents; the main chemical entity of the plant responsible for reported activity is triterpenoid saponins called "bacosides." Bacosides are a complex mixture of glycosides of either jujubogenin or pseudojujubogenin as aglycon 11. Major bacopasaponins presented were bacosides A3, bacopaside II, bacopaside I, bacopaside X, bacopasaponin C, bacopaside N2 and the minor components were bacopasaponin F, bacopasaponin E, bacopaside N1 bacopaside III, bacopaside IV and bacon aside V. The alkaloids brahmine, nicotine, and herpestine have been recorded along with D-mannitol, apigenin, hersaponin, monnierasides I-III [6].

Bacopamonnieri (Brahmi) is commonly used in Indian traditional medicine as a nerve tonic and thought to improve memory. A large number of literatures is available on Brahmi with extensive research on neuroprotective functions in Alzheimer's and other inflammatory neuronal disorders improving cognitive and behavioural improvements. Bacopamonnieri has been shown the up regulation of the AMPA receptor GluR2 subunit gene expression in the hippocampus. Various studies have proved that different baccosides are responsible to activation of AMPA and NMDA receptors in brain. AMPA and NMDA are the glutamate ionic receptors and their activation enhances cognitive skills [7,8] (Figure 1).

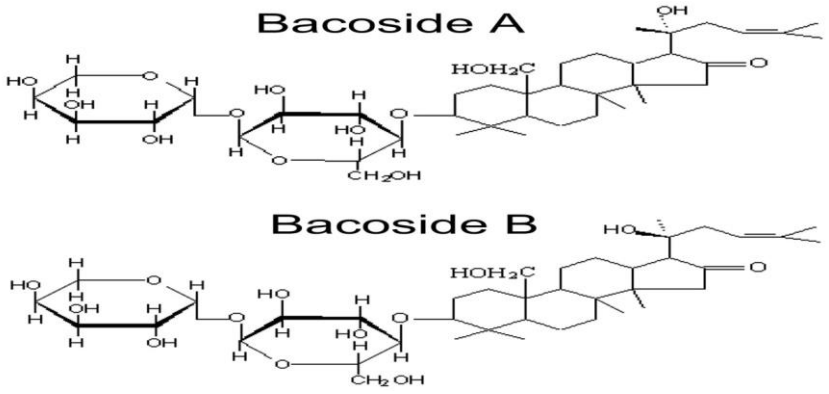


**Figure 1:** Bacoside A and B

Various docking studies have proved that memory enhancement actions of *Bacopa monnieri* are due to binding of Bacosides to AMDA and NMDA receptors.

Bacopa traditionally also has been used to treat various inflammation related problems such as a bronchitis, rheumatism, and asthma. (channa). Bacopa inhibits the release of IL-6 and TNF-α from monocytes.

This review highlighted the neuropharmacological mechanisms of the herb based on clinical and non-clinical studies. Plant exhibit anti-parkinsonsactivity by inhibitingaggregation of alpha-synuclein, turns away dopaminergic neurodegeneration, and recovers the lipid content [9].

**Etiology of AD**

Mainly accumulation of two proteins is responsible for AD that Amyloid Beta protein extracellularly and Tau protein intracellularly in grey matter of nervous system. The main pathological hallmarks of Alzheimer's disease includes: extracellular deposition of ß-amyloid (Aß) plaques, intraneuronal neurofibrillary tangles comprising of filaments of phosphorylated tau proteins. Loss of cortical cholinergic neurons in AD probably accounts for memory impairment [10,11].

**Literature Review**

KastureS. B, et al; (2007) evaluated the nootropic potency of extract of *Bacopa monnieri* in mice which are treated with elevated plus maze, massive shock avoidance test and object recognition test. BME was administered for 7 days at the dose of 40, 60 and 80 mg/kg to mice in elevated plus maze and passive shock avoidance test and 27, 40 and 54 mg/kg to rats in object recognition test. Scopolamine was used for the induction of amnesia and piracetam (100 mg/kg) used as reference standard. BME showed significant results in reducing anxiety in passive shock avoidance test and increasing memory in recognition test [12].

Sulaimankutty R, et al; (2008) investigated the significant effect of bacopamannieri on glutamate receptors and gene expression of NMDA R1 in hippocampus of temporal lobe epileptic rats. Also showed positive effects in Pilocarpine induced epileptic models through the expression of NMDA R1 and glutamate receptor binding alterations to near-control levels. These data together indicate the neuroprotective role of *B. monnieri* extract in glutamate-mediated excito-toxicity during seizures and cognitive damage occurring in association with pilocarpine-induced epilepsy [13].

Nanteetip Limpeanchob, et al; 2008 reported that Brahmi extract is used for protection of neurons due to beta-amyloid induced cell death but glutamate induced toxicity doesn't reduce with brahmi extract. This neuronal protection effect is further due to its ability to lower oxidative stress by reducing level of reactive oxygen species and also due to reduced cellular acetyl cholinesterase activity. Thereby, increases the life span of cultured neurons. The toxicity due to glutamate has not shown much reduced by brahmi extract. The brahmi extract increases the life span of cells. So, deaths due to oxidative stress can be reduced with brahmi extract [14].

Singh M, et al; 2010 reported that oxidative stress is one of the major causes of Alzeimer's disease. This oxidative stress is initiated by lipid peroxidation by-product Acrolein due its high reactivity towards cellular nucleophilic groups. This acrolein level is higher in Alzeimer's patients.

Beta amyloid peptide toxicity occurred through this oxidative stress produced by hydrogen peroxide. Hydrogen peroxide modifies proteins, lipids and DNA as seen in Alzeimer's disease. *Brahmi monniera* extract protect the human neuroblastoma cell line SK-N-SH against the oxidative stress stimulators by prevented their generation along with preservation of mitochondrial membrane potential. In addition, brahmi extract prevent modifications of proteins regulated by redox reactions like NF-kappa B, Sirt 1, ERK ½ and p66Shc that further favours cell survival due to oxidative stress [15].

Saraf M.K, et al; 2011 reported anti-amnesic effect of *Brahmi monniera* in scopolamine (anti-cholinergic agent) induced in mice. Anti-cholinergic agent, Scopolamine induced amnesia in mice. The water maze mouse model is used to study amnesic activity of scopolamine and anti-amnesic activity of brahmi. To screen muscle coordination activity, Rotarod test was done. Brahmi extract treats anterograde and retrograde amnesia.

Piyabhan P, etal; 2019 reported that decreased GABA ergic neurons in brain is corrected to some extent by brahmi extract. This GABAergic neuron is responsible for cognitive impairment in schizophrenia. The result showed brahmi increased discrimination ratio (DR), calbindin(CB), parvalbumin (PV) and calretinin (CR). This study was conducted on PCP induced schizophrenia model [16].

Jadiya, et al; 2011 studied the anti-Parkinsonian effects of Bacopamonnieri. Plant reduces alpha synuclein aggregation, prevents dopaminergic neurodegeneration and restores the lipid content in nematodes, thereby proving its potential as a possible anti-parkinsonian agent.

Kamkaew N, et al; 2011 reported precognitive effect and as a alternative to nootropic drug, Bacopamonnieri. The CBF (cerebral blood flow) effect is measured by laser Doppler method on rats. Also, systolic blood pressure was monitored using tail cuff method. Brahmi extract (40mg/kg) increases CBF by 25% ($2927 \pm 123$ PU). Dose dependent hypotensive effects are also seen in rats on brahmi extract if it is given intravenously, that decreases CBF by 15% [17].

Ahirwar S, et al; 2012 reported ethanolic extract of brahmi has inhibitory activity on acetylcholinesterase. This effect is done in vivo in male albino rats having discrete brain regions. Brahmi ethanolic extract in 100mg/kg concentration is given to albino rats. The inhibitory acetylcholinesterase activity (AchE) data in various regions of brain of albino rats is as: Cerebral cortex (51.6 %), Cerebellum (51%), Pons (44 %), Thalamus (41.6 %), Hippocampus (38.1 %), Brain stem (34.3 %), Striatum (24.9 %). Also, enhanced Km values for AchE in each brain region is calculated by enzyme kinetic studies which is due to inhibitory effect of brahmi extract [18].

Kalyani Bai Kunte, et al; 2013 reported brahmi extract helps in restoring memory and learning skills in D-Galactose and sodium nitrite induced mice. Brahmi extract shows neuroprotection effect in alzeimer's induced mice. This neuroprotection effect is due to maintainance of ion gradients across cell membrane and thereby the structural and functional integrity of alzeimer's induced mice cell membrane. The neuroprotection action is confirmed by calculating activity levels of $Na^+/K^+$ -ATPase ,$Mg^{2+}$ -ATPase and $Ca^{2+}$ -ATPase along with estimation of Inorganic phosphates. The brahmi extract reduces the levels of all ATPase mediated ions significantly [19].

Siddiqui YH, et al; evaluated the anti-parkinson effect of baccopa in Drosophila fly, Baccopa improves the neuronal survival by obstructing oxidation of cells, and improving functional capacity of the cell [20].

Pritsana P, et al; (2014) experimentally proved that Bacopamonnieri can show significant enhancement in memory in psychotic patients. The experiment was performed on a three groups of rats assigned as Group A (Control), Group B (Phencyclidine) (PCP) and group C (Brahmi + PCP). NMDAR1 density was measured in prefrontal cortex, striatum and cornuammonis field. Memory impairment observed in rats receiving PCP was mediated by NMDAR1 up regulation in CA2/3 and DG. Rats receiving Brahmi before administration of PCP can restore this cognitive deficit by lowering NMDAR1 in those brain areas. So Brahmi can be a new neuroprotective agent for the prevention of memory loss in schizophrenia.{}
Pandey S P, et al; (2015) proved the positive effect of Bacopamonnieriin models with memory impairments due to neurological disorders. In this research it was demonstrated that mice with STZ-induced diabetes when treated with low dose (50- or 100 mg/kg BW) of Brahmi extract showed significant improvements in cognitive skills. When Brahmi extract was given in higher doses (150 mg/kg BW or above), improvement in diabetic condition as well as spatial memory loss was observed. These improvements were correlated to reduction in oxidative stress and up regulation of AMPA receptor GluR2 subunit gene expression in the hippocampus [21].

Rai R, et al; (2015) revealed the significant effect of Bacopamonnieri on the scopolamine induced memory loss in mice. RT-PCR and immunoblotting data has showed that scopolamine dignificantly downregulated the NMDAR GluN2B subunit expression in prefrontal cortex and hippocampus. Oral administration of Bacopamannieri to scopolamine-treated amnesic mice improved the spatial memory which was correlated with upregulation of GluN2B subunit expression [22].

Dhanoop M A, et al; 2015 reported neuroprotective effects of brahmi in rats. Firstly, toxicity is induced in the rats by damaging mitochondria with methyl mercury. This damage causes oxidative stress in them that further decreases glutathione level, inhibit catalase enzyme activity and increase thiobarbituric acid reactive substances levels in rat's brain. Brahmi in 250 µg/mL dose prevented this mitochondrial damage to brain in rats. The levels of glutathione are increased with decrease in thiobarbituric acid reactive substances levels and undergo catalase enzyme activity. This effect of brahmi is due to presence phenols and flavonoids in them [23].

Preethi J, et al; (2016) investigated the discrimative capability of rats for old and novel objects after the administration of Bacopamonniera extract. Rats were given the daily oral dose of Brahmi extract (80 mg/kg) in 0.5% gum acacia (per-orally, p.o.; PND 15–29)/three doses of 5-azacytidine (5-azaC; 3.2 mg/kg) in 0.9% saline (intraperitoneally, i.p.) on PND-30.

Rats treated with Brahmi extract/5-azaC showed better discrimination towards old and novel objects. It was concluded from behavioral tests that upregulation of reelinalong with activation of NMDAR leads to BDNF (brain-derived neurotropic factor). These changes may be linked with improved novel object recognition memory [24].

Kanthamma S. L, et al; 2018 reported the in silico studies of bacopamonnieri compounds by targeting multi-proteins for Alzheimer's disease. The lipinski's properties of three compounds i.e apigenin, rosavin and luteolin are calculated. The lipinski's rule of five is a set of molecular discriptors that are essential for drug like molecules. This includes partion coefficient logP<=5, molecular weight <=500 daltons, no of hydrogen bond acceptors <=10, and no of hydrogen donors <=5. These molecular discriptors are calculated by using Discovery studio 4.1 visualizer along with

DruLiTo software that shows satisfactory results. These results are correlated with the synthesis of novel compounds for treating Alzhemer's disease [25].

Chandrasekar S, et al; (2020) proved the protective function of Bacoside-A on 6-OHDA caused lesions in the striatum by modulation of GluR1 AMPA and NR1 NMDA. RT-PCR was used to reverse the conditions induced by 6-OHDA and significant reduction in GluR1 mRNA was observed but NR1 mRNA expression was found to increased which was reversed by Bacoside-a treatment after 2 weeks. Impaired Mitochondrial Complex I activity and MTT assay in 6-OHDA induced rats was attenuated by Bacoside – A treatment. Bacoside-a treatment also reduced the levels of TNF– α and IL-6 [26].

Sivasangari K. et al; (2020) proved the significant effects of *Bacopa monnieri* extract on prenatal stress by amelioration of learning and memory capabilities of rats. Pregnant rats with PNS were given BME during gestation, on postnatal day and to their offsprings. The antioxidant property of BME possibly inhibited the PNS related symptoms like anxiety, behavioral and memory loss. It was concluded that BME can be used as strategy to prevent PNS related symptoms in off springs also [27].

Manisha V, et al; 2020 reported the effects of brahmi extract on behavioural changes in learning and memory of albino rats. The brahmi in 100 mg/kg dose is given to albino rats and changes are noted by use of morris water maze test. The escape latency of rats is recorded. Escape latency is the time taken by mouse to find the plateform for escaping the maze. This test showed their behavioural changes i.e how they learned new things and to recall memories from their brain. Brahmi can be used as brain enhancing drug due to its anti-inflammatory, anti-oxidant and beta amyloid aggregation inhibitory properties [28].

Witter S, et al; 2020 reported the brahmi ayurvedic drug as a nutraceutical supplement to enhance memory neurons. They identified inhibitors on three different variants of the Aβ peptide: methionine Aβ1–40, Aβ1–40, and Aβ1–42 that are found within nutraceuticals. These inhibitors study was done by fluorescence spectroscopy in vitro that diagnosis amyloid-β (Aβ) fibrillation and other bioactive compounds. The pathogen plague formation is inhibited and free Aβ levels are reduced naturally that showed positive effects of brahmi [29].

Qazi M.S, et al; 2020 reported the computational study correlation of brahmi and it's biological activity. This bioinformatics study helps in determining binding and molecular interactions between brahmi as a ligand and AChE, BuChE as a repectors. This docking analysis was done by MGL tools Autodock 4.2 module. The hydrophobic interactions, inhibition constants and hydrogen bonds analysis helps to find out active sites at the receptors. The favourable results i.e binding energy (ΔG) results showed that bacoside X, bacosideA, 3-beta-D-glucosylstigmasterol and daucosterol may be good inhibitors for the inhibition of AChE and BuChE activities [30].

Zhang B, et al; 2020 reported that bacoside-A has potentials for use in the management of Parkinson disease. Component showed a positive protective effect against Parkinson disease-induced oxidative damage and neuronal degeneration in rats through downregulation of iNOS, AChE, inflammatory cytokines and pro-apoptotic proteins.

P. K. Anamika, et al; 2021 reported that hydroalcoholic extract of brahmi shows remarkable nootropic and neuroprotective effects in propionic acid induced memory and behavior impairment in rats. This study is done on 27 Sprague Dawley rats which are adults. The propionic acid is given to adult rats through intracerebroventricular route and autism occurs in them. The hydroalcoholic extract of brahmi in a dose of 250mg/kg and 500mg/kg is given to autism adult rats. Actophotometer and marble burying test is conducted on them to study in vivo effects while to study in vitro effects, the levels of serotonin and Glutamate was estimated in affected rats. The hydroalcoholic extract of brahmi remarkable decreases the levels of serotonin and Glutamate that showed its neuroprotective and nootropic effects.

## SUMMARY AND CONCLUSION

Brahmi is a traditional ayurvedic drug used for memory enhancement, anti-inflammatory and antipyretic. Cognitive action and behavioral changes due to *Bacopa monnieri* was reported extensively by different experiments. The memory enhancement may be due to the downregulation of iNOS, AChE and agonistic action on NMDA receptors. The neuroprotective action is via anti-inflammatory activity on neurons which is the result of inhibition of beta Amyloid proteins and cytokines in various animal models. The oxidative stress is also reduced by Brahmi by inhibition of actylcholinesterase enzyme.

It can be concluded that nootropic and neuroprotective action of *Bacopa monnieri* can be enhanced by making Baccosides more lipophillic which will increase the bioavailability of the molecule in the brain. By acetylation of OH groups of Baccoside A, lipophillic character can be enhanced which will improve the capability to cross Blood brain barrier.

**Conflict of interest**

There is no conflict of interest.

**Abbreviations**

SAD: Sporadic Alzheimer's disease
PCP: Phencyclidine
ACE: Acetylcholinesterase
AD: Alzheimer's disease
iNOS :Inducible nitric oxide synthase
Aβ- Amyloid beta protein
RT-PCR: Reverse transcription polymerase chain reaction

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