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Revisión / Review

Bacopa monnieri: Historical aspects to promising pharmacological actions for the treatment of central nervous system diseases

[*Bacopa monnieri*: Aspectos históricos de las acciones farmacológicas prometedoras para el tratamiento de enfermedades del sistema nervioso central]

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Section Review

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Abstract: *Bacopa monnieri* (L.) Wettst. (Plantaginaceae), also known as Brahmi, has been used to improve cognitive processes and intellectual functions that are related to the preservation of memory. The objective of this research is to review the ethnobotanical applications, phytochemical composition, toxicity and activity of *B. monnieri* in the central nervous system. It reviewed articles on *B. monnieri* using Google Scholar, SciELO, Science Direct, Lilacs, Medline, and PubMed. Saponins are the main compounds in extracts of *B. monnieri*. Pharmacological studies showed that *B. monnieri* improves learning and memory and presents biological effects against Alzheimer's disease, Parkinson's disease, epilepsy, and schizophrenia. No preclinical acute toxicity was reported. However, gastrointestinal side effects were reported in some healthy elderly individuals. Most studies with *B. monnieri* have been preclinical evaluations of cellular mechanisms in the central nervous system and further translational clinical research needs to be performed to evaluate the safety and efficacy of the plant.

Keywords: Alzheimer; *Bacopa monnieri*; Epilepsy; Parkinson; Schizophrenia.

Resumen: *Bacopa monnieri* (L.) Wettst. (Plantaginaceae), también conocida como Brahmi, se ha utilizado para mejorar los procesos cognitivos y las funciones intelectuales que están relacionadas con la preservación de la memoria. El objetivo de esta investigación es revisar las aplicaciones etnobotánicas, composición fitoquímica, toxicidad y actividad de *B. monnieri* en el sistema nervioso central. Se revisaron artículos sobre *B. monnieri* utilizando Google Scholar, SciELO, Science Direct, Lilacs, Medline y PubMed. Las saponinas son los principales compuestos de los extractos de *B. monnieri*. Los estudios farmacológicos mostraron que *B. monnieri* mejora el aprendizaje y la memoria y presenta efectos biológicos contra la enfermedad de Alzheimer, la enfermedad de Parkinson, la epilepsia y la esquizofrenia. No se informó toxicidad aguda preclínica. Sin embargo, se informaron efectos secundarios gastrointestinales en algunos ancianos sanos. La mayoría de los estudios con *B. monnieri* han sido evaluaciones preclínicas de los mecanismos celulares en el sistema nervioso central y es necesario realizar más investigaciones clínicas traslacionales para evaluar la seguridad y eficacia de la planta.

Palabras clave: Alzheimer; *Bacopa monnieri*; Epilepsia; Parkinson; Esquizofrenia.

LIST OF ABBREVIATIONS

COMT: catechol-*O*-methyltransferase
PEP: prolyl endopeptidase
PARP: poly (ADP-ribose) polymerase
5-HT: 5-hydroxytryptamine (serotonin)
PARP: poly (ADP-ribose) polymerase
T2VO: transient two-vessel occlusion
PKC: protein kinase C
PI3K/AKT: phosphoinositide-3-kinase-protein kinase
BDNF: brain-derived neurotrophic factor
cAMP: cyclic adenosine monophosphate
CREB: cAMP response element binding protein
AChE: acetylcholinesterase
PSAPP: amyloid-peptide overproducing transgenic mouse model
IL-6: interleukin-6
TNF-α: tumor necrosis factor α
MCP-1: monocyte chemoattractant protein-1
COX-2: cyclooxygenase-2
iNOS: inducible nitric oxide synthase
MAPK: mitogen-activated protein kinase
6-OHDA: 6-hydroxydopamine
PINK1: melanogaster transgenic model
MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
Bcl-2: B-cell lymphoma-2
GABA: γ-aminobutyric acid
mGIuR8: metabotropic glutamate receptor 8
NMDA: *N*-methyl-D-asparate
VGLUT: vesicular glutamate transporter

INTRODUCTION

In the 1950s, 250 million people worldwide were older than 60 years of age (WHO, 2011). In 2015, this number nearly quadrupled to 901 million (12% of the world's population). In 2050, the global elderly population is projected to reach 2.1 billion (22% of the world's population) (WHO, 2011). Aging is associated with declines in memory and cognitive skills, with a concomitant increase in the incidence of aging-related neurodegenerative diseases (Murman, 2015; Castelli *et al*., 2019; Gentile *et al*., 2021). In fact, cognitive function refers to multiple mental abilities, including motor function, attention, language, memory, executive control, vision, emotion, sensory function, and consciousness. Furthermore, cognitive impairment is a common characteristic of several diseases, such as Alzheimer's disease, Parkinson's disease, epilepsy, and schizophrenia (Kean *et al.*, 2016).

Alzheimer's disease, a chronic and neurodegenerative disease, has the highest incidence among neurodegenerative diseases, followed by Parkinson's disease and is associated with aging. It is a progressive and fatal neurodegenerative disorder that is characterized by the massive loss of neural cells and manifested by cognitive impairment, progressively worse psychological and behavioral manifestations, neurological signs, a decline in daily-living activities, and various neuropsychiatric and behavioral symptoms (Alzheimer's Association, 2016; Apostolova, 2016). The disease is characterized by the progressive atrophy of brain areas that are responsible for cognitive function, such as the cerebral cortex, entorhinal cortex, hippocampus, and ventral striatum. Brain lesions that are caused by the disease produce histopathological characteristics in the cerebral parenchyma, including amyloid fibrillary deposits in the walls of blood vessels that are associated with senile plaques, the accumulation of abnormal filaments of tau protein, the activation of glia, and inflammation (Kumar & Ekavali, 2015; Alzheimer's Association, 2016).

Parkinson's disease is a chronic and progressive disorder of the central nervous system that results from the loss of dopaminergic neurons in the substantia nigra, with consequent dopamine depletion (Balestrino & Schapira, 2020). These neurons have cell bodies in the substantia nigra pars compacta and send axons to the nuclei of the base. As the disease progresses and neurons degenerate, they develop cytoplasmic bodies (Lewy bodies) that arise from the deposition of α-synuclein anomalous protein (Schrag & Schott, 2006). The disease is characterized by cardinal signs of stiffness, bradykinesia, postural instability, and tremor. In addition to motor symptoms, sleep disorders, cognitive dysfunction, and depression may also occur, resulting in poor quality of life and making the disease even more disabling with a shortened life expectancy (Mhyre *et al.*, 2012). Complex interactions between genetic, environmental, and pathological factors that involve mitochondrial dysfunction, oxidative stress, inflammation, and excitotoxicity result in Parkinson's disease. In the 1960s, the first successful treatment emerged, paving the way for the development of new effective therapies. The introduction of levodopa represented the greatest therapeutic breakthrough in Parkinson's disease treatment, which produced clinical benefits for virtually all patients and reduced mortality. However, soon after levodopa was introduced, it became apparent that long-term treatment was complicated by the development of adverse effects, including motor fluctuations, dyskinesias, and

neuropsychiatric complications. Additionally, as the disease progresses, patients experience manifestations that do not respond adequately to levodopa treatment, such as episodes of freezing, postural instability, autonomic dysfunction, and dementia. Thus, the search is ongoing for new drugs and safe and effective adjuvants that are capable of acting on dopaminergic, cognitive, and motor alterations (Lang, 2009; Olanow *et al*., 2009; Armstrong & Okun, 2020).

Other nervous system conditions beyond neurodegenerative diseases, such as epilepsy and schizophrenia, significantly impair patients' quality of life. Epilepsy is a neurological disease that can be prevented and controlled in up to 70% of patients (Thijs *et al.*, 2019; Beghi, 2020). Failure to treat is a risk factor for sudden death and trauma. The causes of epilepsy are either genetic or acquired. Acquired causes comprise the vast majority of cases and include head trauma, perinatal injury, and brain infections, including neurocysticercosis and stroke. In some cases, the cause is unknown. Epileptic seizures that are caused by transient changes in neuronal activity may manifest in different ways, but the common form is seizure (WHO, 2005; Stafstrom & Carmant, 2015). This clinical condition is produced by a sudden, abnormal, and disordered electrical discharge of neurons that can manifest as focal seizures when restricted in regions bordering on the brain or generalized seizures when discharges originate within the brain and are distributed bilaterally. Such seizures may or may not cause the loss of consciousness (Sokhi *et al.*, 2016). These imbalances are related to the depolarization of excitatory neurons that activate nearby inhibitory interneurons that suppress the activity of stimulated cells and adjacent neurons, where neurotransmitters are involved in the inhibition process, such as glycine, glutamate and γ-aminobutyric acid (GABA), the main neurotransmitter inhibitory effects of the brain (Valenzuela *et al.*, 2011). Treatment of epilepsy are generally due with monotherapy (i.e., benzodiazepinics) and although each treatment has its own unique adverse effect profile, central effects are prominent and can affect quality of life (Liu *et al.*, 2017a).

Schizophrenia is one of the most serious and challenging psychiatric disorders. It is defined as a complex clinical syndrome that consists of various psychopathological manifestations that involve thought, perception, emotion, movement, and behavior. It is very prevalent among psychiatric conditions without pathognomonic symptoms but with distortions of thought and perception, and a dulling of affect without impairments in intellectual capacity. Over time, however, cognitive impairment may appear (Vannorsdall & Schretlen, 2019). Limitations that are imposed by the disease result from the deterioration of various mental processes that causes positive and negative symptoms. Positive symptoms are additional behaviors that occur during times of psychiatric crisis, such as delusions, hallucinations, changes in speech, and behavioral alterations (e.g., catatonia and movement disorders). Negative symptoms consist of a loss of function, characterized by lower motor and psychic activity, flat affect, and anhedonia (Khan *et al*., 2013). The course of schizophrenia is variable. Approximately 30% of cases have complete or almost complete recovery. Approximately 30% of cases experience incomplete remission or partial functional impairment, and approximately 30% of cases exhibit significant and persistent impairments in professional, social, and affective function (Lambert *et al*., 2010). The most common medications for treating schizophrenia are risperidone, olanzapine, and quetiapine. However, psychiatrists currently need 4-6 weeks to determine the efficacy of these drugs, thus possibly delaying adequate treatment (Tandon *et al*., 2008). Drugs that are used to treat schizophrenia can cause serious side effects, including movement disorders, weight gain, and metabolic dysfunction (Leucht *et al*., 2013).

Since above mentioned, therapeutic alternatives for these diseases are quite limited. Although effective in some cases, the available drugs act only in a palliative manner and have many side effects, thus making the search and development of new drugs extremely necessary (Khan *et al*., 2013; DeMaagd & Philip, 2015; Stafstrom & Carmant, 2015; Apostolova, 2016). Therefore, new pharmacological targets and therapeutic agents, including medicinal plants, are a potential alternative to treat these pathophysiologies.

Several plants have been studied with regard to their memory properties. *Bacopa monnieri* (L.) Wettst. (Family Plantaginaceae) has several notable biological activities that are related to memory, brain function, and intellectual capacity. *B. monnieri* extracts have been used for neurological treatment to improve concentration, control impulsivity, and exert calming actions, among other benefits (Ahn *et al.*, 2016). Preclinical and clinical studies that have sought to improve the cognition-enhancing effects of

B. monnieri extracts have reported promising results (Gohil & Patel, 2010). Clinical studies reported positive effects on memory formation, learning, attention, concentration, and adaptation to environmental stressful situations that affect cognition (Aguiar & Borowski, 2013). Extracts of *B. monnieri* have also been used to treat digestive complaints and skin disorders, and antiepileptic, antipyretic, and analgesic effects have also been observed (Bammidi *et al.*, 2011).

Thus, considering the importance of *B. monnieri*, this review discusses the ethnobotanical applications, phytochemical composition, and activity of this species in the central nervous system, with a focus on cognitive performance, epilepsy, schizophrenia, Alzheimer's disease, and Parkinson's disease. Studies that evaluated the safety of *B. monnieri* are also discussed.

MATERIALS AND METHODS

It was reviewed articles on *Bacopa monnieri* that were published from January 1991 to August 2020 using online journals and books that were published in English, Portuguese, and Spanish. The bibliographic survey was performed using Google Scholar, SciELO, Science Direct, Lilacs, Medline, and PubMed. The data that have been published on this species consist of its history, ethnobotany, ethnopharmacology, phytochemistry, pharmacology, and toxicity. We used the following keywords in our search: *B. monnieri*, ethnobotany, ethnopharmacology, chemical composition, pharmacological action, and toxicity.

History, organoleptic characteristics, and ethnobotanical uses of *Bacopa monnieri*

Bacopa monnieri (L.) Pennell is also referred to as the "herb of grace," "Brahmi," "Aindri" and "Hissopo of water". It is a creeping perennial plant with a small stature. Its scientific name has several synonyms, including *Anisocalyx limnanthiflorus* Hance, *Bacopa monnieri* (L.) Hayata & Matsum., *Bacopa monnieri* (L.) Wettst., *Bramia indica* Lam., *Bramia monniera* (L.) Drake, *Bramia monnieri* (L.) Pennell, *Calytriplex obovata* Ruiz & Pav., *Capraria monnieri* (L.) Roxb., *Gratiola monnieri* (L.) L., *Gratiola parviflora* Willd. ex Schltdl. & Cham., *Gratiola portulacacea* Weinm., *Gratiola tetrandra* Stokes, *Habershamia cuneifolia* (Michaux) Raf., *Herpestis africana* Steud., *Herpestis brownei* Steud., *Herpestis calytriplex* Steud., *Herpestis cuneifolia* Pursh, *Herpestis monnieri* (L.) Rothm., *Herpestis monnieria* (L.) Humb., *Herpestis monnieria* (L.) Kunth, *Herpestis moranensis* Kunth, *Herpestis pedunculosa* Steud., *Herpestis procumbens* Hort. Berol. ex Spreng., *Herpestis spathulata* Bl., *Hydrotrida beccabunga* Willd., *Limosella calycina* Forsk., *Lysimachia monnieri* L., *Monniera africana* Persoon, *Monniera brownei* Persoon, *Monniera cuneifolia* Michx., *Monniera monniera* (L.) Britton, and *Monniera pedunculosa* Persoon (Hassler, 2018). It has a wide geographical distribution. In India and the tropics, it grows naturally in moist soils, shallow water, and marshes. It is easily cultivated. It produces fruits and pale blue or white flowers in summer. Each part of the plant has organoleptic characteristics such as color, odor, taste, and consistency (Figure No. 1).

B. monnieri is an adaptogenic plant that is used in Ayurvedic medicine. *B. monnieri* was named after Lord Brahma, the creator of the mythology of a world that is surrounded by medicinal plants and the originator of the science of Ayurveda. It is an important plant in India that has been used in religious, social, and medical practices since the Vedic civilization. Its antiquity can be traced back to the time of Athar Ved (the science of well-being) that was written in 800 BC, which mentioned this plant in the first verse of the third chapter of Athar Samhita (compilation on factors that promote well-being) (Kean *et al.*, 2015).

All parts of *B. monnieri* have been used for medicinal purposes. It has been reported to have antiepileptic, antidepressant, anxiolytic, gastrointestinal, muscular, cardiovascular, and antitumor effects (Bammidi *et al*., 2011; Aguiar & Borowski, 2013). The oral use of *B. monnieri* leaves for the treatment of epileptic seizures is widespread in India as a decoction, juice, and powder, and it is used as an infusion in Egyptian communities (Shanmugasundaram *et al.*, 1991; Poonam & Singh, 2009; Sharma *et al.*, 2013; Silambarasan & Ayyanar, 2015; Emilie *et al.*, 2019). In the Himalayas in Nepal, juice of the entire plant is given orally as a diuretic, cardiac tonic, memory enhancer, and hair tonic (Singh *et al.*, 2012). Its antioxidant actions are notable (Mukherjee *et al*. 2011; Shinomol *et al.*, 2012), with neuroprotective actions that increase cognitive and motor performance (Uabundit *et al.*, 2010; Saini *et al.*, 2012; Aguiar & Borowski, 2013).

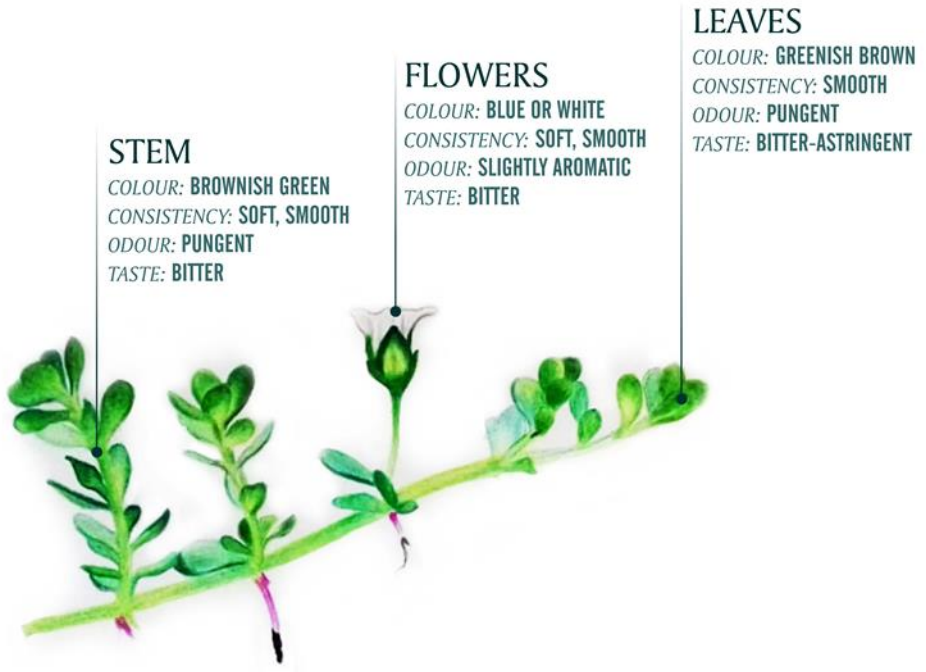

Figure No. 1
***Bacopa monnieri* and its organoleptic characteristics**

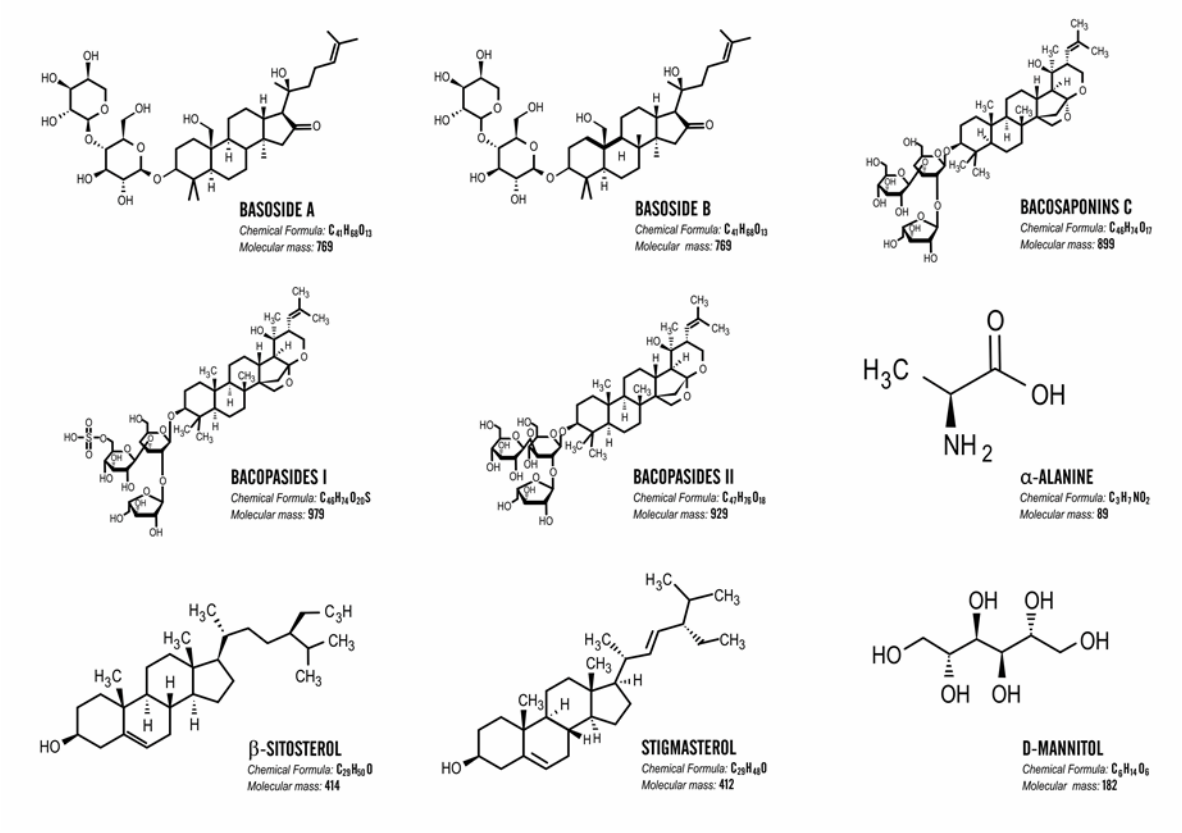

Figure No. 2
Main chemical constituents of *Bacopa monnieri*

Main bioactive constituents of Bacopa monnieri

The chemical constituents of *Bacopa monnieri* have been identified in its stems, leaves, flowers, fruits, and roots. Its bioactive metabolites are mainly concentrated in the stems and leaves. The main bioactive constituents of *B. monnieri* (Figure No. 2) are tetracyclic triterpene saponins (jujubogenin and pseudojujubagenin), bacoside-A and -B (including bacoside-A1 and -A3), bacopasaponin-A, -B, -C, -D, -E, and -F, alkaloids (herpestine, brahmin, and nicotinin), flavonoids (luteolin-7 glucoside, glucuronyl-7-apigenin, glucortonyl-7-luteolin, and common phytosterols), D-mannitol, glutamic acid, glycoside, stigmasterol, α-alanine, β-sitosterol, cucurbitacin-B, cucurbitacin-E, bittulinic acid, bacobitacin-A, -B, -C, and -D, cucurbitacin-E, monnieraside-I and -III, and plantioside-B (Deepak & Amit, 2004; Deepak *et al.*, 2005; Sivaramakrishna *et al.*, 2005; Bhandari *et al.*, 2007; Zhou *et al.*, 2007; Rastogi *et al.*, 2012b; Aguiar & Borowski, 2013; Jain & Das, 2016; Mallick *et al.*, 2017).

The pharmacological properties of *B. monnieri* are attributed to its high content of active principle bacosides that have high efficacy in the central nervous system (Menon *et al.*, 2010). Among its metabolites, the most studied is bacoside-A, which is found in different concentrations in different parts of the plant (Pandey *et al.*, 2010; Mathew *et al.*, 2010a; Mathew *et al.*, 2010b; Mathew *et al.*, 2011; Rastogi *et al.*, 2012b; Aguiar & Borowski, 2013).

Pharmacological effects of Bacopa monnieri on the central nervous system

The pharmacological activity of *Bacopa monnieri* has been exploited to improve learning and memory and treat depression, emotional stress, fatigue, anxiety, insomnia, Alzheimer's disease, Parkinson's disease, epilepsy, and schizophrenia (Ahn *et al.*, 2016). The effects of *B. monnieri* on the central nervous system detailed in this review are summarized in Figure No. 3. To explore and summarized the *B. monnieri* effects on central nervous system and its safety, it was revised 52 articles previously published in scientific literature.

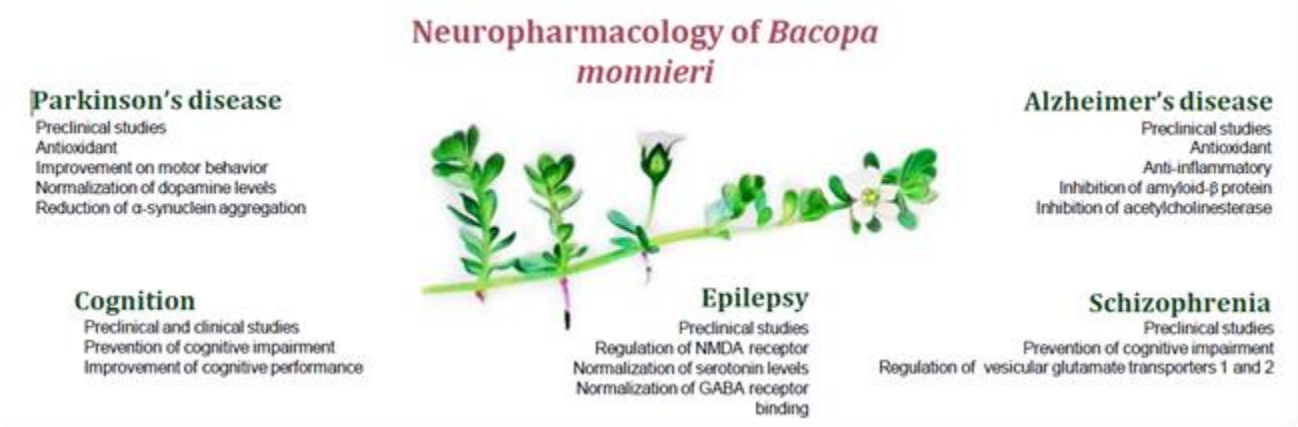

Figure No. 3
Pharmacological effects of *Bacopa monnieri* on the central nervous system

Improvement in cognitive performance

Several *in vitro* and *in vivo* studies have investigated the pharmacological properties of *B. monnieri*, reporting neuroprotective effects and improvements in cognitive function (Aguiar & Borowski, 2013). These effects are attributed to its antioxidant, antiapoptotic, and anti-inflammatory actions (Bhattacharya *et al.*, 2000; Shinomol *et al.*, 2011). Several reviews have highlighted its effects on cognitive function (Shinomol *et al.*, 2011; Pase *et al.*, 2012; Aguiar & Borowski, 2013, Kongkeaw *et al.*, 2014; Kean *et al.*, 2016; McPhee *et al.*, 2016; Kean *et al.*, 2017; Cicero *et al.*, 2018; Kenedy, 2019; Sukumaran *et al.*, 2019). Table No. 1 shows *in vitro* and *in vivo* studies that evaluated the effects of *B. monnieri* on cognitive function.

Dethe *et al.* (2016), investigated the molecular mechanism by which a standardized extract of *B. monnieri* enhances memory based on a panel of cell-free and receptor-transfected cell assays *in vitro*. The solvent for the extract was not specified in this study, but *B. monnieri* was shown to inhibit catechol-*O*-methyltransferase (COMT), prolyl endopeptidase (PEP), and poly (ADP-ribose)

polymerase (PARP) and antagonize serotonin 5-hydroxytryptamine-2A (5-HT_{2A}) and 5-HT_6 receptors, which have been shown to be associated with learning and memory deficits and aging-associated memory impairments.

Table No. 1
Effects of *Bacopa monnieri* on cognitive function

Type of study	Extract	Dose	Time of treatment	Main effects	Origin of study	Source
Preclinical (*in vitro*)	Standardized (solvent not specified)	5, 10, 25, and 100 µg/ml	—	• Inhibition of COMT, PEP, ADP-ribose, and PARP • Antagonism of 5-HT_{2A} and 5-HT_6 receptors	India	(Dethe *et al.*, 2016)
Preclinical (*in vitro* and *in vivo* in T2VO mice)	Ethanolic	50 mg/kg	1 week before and 3 days after surgery	• Prevention of cognitive deficits related to cerebral ischemia • Amelioration of T2VO-induced impairments in non-spatial short-term memory performance in the object recognition test through PKC and PI3K/Akt mechanisms	Japan	(Le *et al.*, 2015)
Preclinical (Swiss mice)	Ethanolic	50 mg/kg	2-4 weeks	• Amelioration of cognitive impairments • Enhancement of neuroregeneration in trimethyltin-treated mice in object location test and modified Y maze test	Japan	(Pham *et al.*, 2019)
Preclinical (C57BL/6 mice)	Standardized (solvent not specified)	200 mg/kg	4 weeks	• Improvement in memory via increase in cell proliferation and neuroblast differentiation in the dentate gyrus	Korea	(Kwon *et al.*, 2018)

Preclinical (neonatal hypoglycemic rats)	Aqueous extract and bacoside-A	50 and 100 mg/kg	10 days	• Improvement in alterations of D_1 and D_2 receptor expression, cAMP signaling, and oxidative stress-induced cell death	India	(Thomas *et al*., 2013)
Clinical	Standardized methanolic	150 mg	6 weeks	• Improvement in tests of cognitive function	India	(Kumar *et al.*, 2016)
Clinical	Standardized ethanolic	300 mg/day	12 weeks	• Improvement in verbal learning, memory acquisition, and delayed recall	Thailand	(Piyabhan & Wetchateng, 2014)
Clinical	Standardized ethanolic	300 and 600 mg/day	12 weeks	• Improvements in attention, cognitive processing, and working memory partially through the suppression of AChE activity	Thailand	(Peth-Nui *et al*., 2012)
Clinical	Standardized methanolic	300 mg/day	12 weeks	• Enhancement of auditory verbal learning, delayed word recall, and Stroop task performance	USA	(Calabrese *et al*., 2008)
Clinical	Standardized ethanolic	160 and 320 mg/day	16 weeks	• Improvements in hyperactivity, inattention, mood, sleep, and cognition	Australia	(Kean *et al.*, 2015)

The effects of an ethanolic extract of *B. monnieri* that contained 22% bacoside-A and 11% bacopaside on cognitive performance were evaluated *in vitro* and *in vivo* by Le *et al*. (2015). In the *in vitro* experiments, organotypic hippocampal slice cultures were used to evaluate neurophysiological activity in the hippocampus and pathophysiology that is relevant to ischemia. The results suggested that *B. monnieri* was beneficial for the prevention of cerebral ischemia-related cognitive deficits. In the *in vivo* experiments, mice were subjected to transient two vessel occlusion (T2VO)-induced cognitive deficits, an animal model of vascular dementia. The T2VO mice were orally treated daily with a standardized extract of *B. monnieri* (50 mg/kg) 1 week before and then continuously 3 days after surgery. *B. monnieri* treatment ameliorated T2VO-induced impairments in non-spatial short-term memory performance in the object recognition test. The mechanism of action was shown to involve protein kinase C (PKC) and the phosphoinositide-3 kinase/protein kinase B (PI3K/Akt) pathway.

Another study evaluated the beneficial effects of daily treatment with an ethanolic extract of *B. monnieri* (50 mg/kg, orally, once daily for 2-4 weeks) on cognitive impairments and neuroregeneration in male Swiss albino mice. The extract contained 22% bacoside-A and 11% bacopaside. This mouse model involves neurodegeneration that is induced by trimethyltin, an organotin compound with potent neurotoxic effects that induces neuronal degeneration in humans and rodents. The *B. monnieri* extract ameliorated cognitive impairments and enhanced neuroregeneration in trimethyltin-treated mice in an object location test and modified Y maze test. The improvement in spatial memory deficits was confirmed by the Nissl staining of hippocampal tissues and propidium iodide staining of organotypic hippocampal slice cultures (Pham *et al.*, 2019).

Kwon *et al.* (2018), found that a standardized extract of *B. monnieri* (solvent not specified; 200 mg/kg, orally, for 4 weeks) improved memory in male C57BL/6J mice by increasing cell proliferation and neuroblast differentiation in the dentate gyrus. The authors suggested that this effect may be related to higher levels of brain-derived neurotrophic factor (BDNF) and cyclic adenosine monophosphate (cAMP) response element binding protein (CREB) phosphorylation in the dentate gyrus.

Thomas *et al*. (2013), investigated alterations of dopaminergic system function (dopamine D_1 and D_2 receptor subtypes) in hypoglycemic neonatal rats that were orally treated with an aqueous extract of *B. monnieri* (100 mg/kg for 10 days) and bacoside-A (50 mg/kg for 10 days). Neonatal hypoglycemia triggered a series of events that resulted in neuronal death, impairments in spatial learning and memory and cognition, and a decrease in the number of dopamine D_1 receptors. Neonatal hypoglycemic rats that were treated with *B. monnieri* and bacoside-A exhibited improvements in D_1 and D_2 receptor expression and cAMP signaling and the attenuation of oxidative stress-induced cell death.

Kumar *et al.* (2016), conducted a randomized, double-blind, placebo-controlled, non-crossover, parallel clinical trial to evaluate the effect of *B. monnieri* on memory in medical students. The 60 participants of both genders received placebo or 150 mg of a standardized methanolic extract of *B. monnieri* twice daily for 6 weeks. *B. monnieri* significantly improved performance on tests of cognitive function. In 46 health volunteers (age between 18-60 years) that received a standardized ethanolic extract of *B. monnieri* (300 mg for 12 weeks) it was observed an improved speed of visual information, learning rate and memory consolidation and state anxiety (Stough *et al.*, 2001).

Roodenrys *et al*. (2002), also reported the effects of *Bacopa monnieri* on human memory in a double-blind randomized and placebo control study. Seventy-six adults (age between 40-65 years) received a standardized extract of *B. monnieri* (300 mg for 12 weeks) presented an increasing in on a test for the retention of new information. The rate of learning, assessing attention, verbal and visual short-term memory, everyday memory function and anxiety levels were unaffected.

Morgan & Stevens (2010), investigated the effects of *B. monnieri* on memory performance in healthy elderly subjects in a randomized, double-blind, placebo-controlled study. The study included 98 healthy participants (> 55 years old, 46 males and 52 females) who were randomized to receive placebo or a standard ethanolic extract of *B. monnieri* (300 mg/day daily for 12 weeks). Neuropsychological and subjective memory assessments were performed at baseline and after treatment. The extract of *B. monnieri* significantly improved verbal learning, the acquisition of memory, and delayed recall. However, *B. monnieri* treatment caused adverse gastrointestinal effects, including an increase in stool frequency, abdominal cramps, and nausea.

Peth-Nui *et al*. (2012), performed a randomized, double-blind, placebo-controlled study to investigate the effects of *B. monnieri* on attention, cognitive processing, working memory, and cholinergic and monoaminergic function. The study included 60 healthy elderly subjects (mean age: 62.6 years, 23 males and 37 females) who received a standardized ethanolic extract of *B. monnieri* (300 and 600 mg daily for 12 weeks) or placebo. Working memory, attention, and cognitive processing were assessed before treatment, every 4 weeks throughout the study period, and at 4 weeks after the cessation of treatment. *B. monnieri* improved attention, cognitive processing, and working memory, partially by suppressing acetylcholinesterase (AChE) activity. *B. monnieri* did not cause adverse effects, changes in hematological or biochemical parameters, or electrocardiographic abnormalities.

Calabrese *et al*. (2008), studied the effects of a standardized methanolic extract of *B. monnieri* on cognitive performance, anxiety, and depression in a randomized, double-blind, placebo-controlled trial. The study included 48 participants (mean age: 73.5

years) without clinical signs of dementia who orally received placebo or a *B. monnieri* extract (300 mg/day for 12 weeks). *B. monnieri* enhanced auditory verbal learning, delayed word recall memory, and performance on the Stroop task. The dose was well tolerated, with no changes in blood pressure and only a few adverse events that primarily involved stomach upset.

The effects of *B. monnieri* on cognitive performance were also investigated in a randomized controlled trial that included 120 male children and adolescents (6-14 years old) with hyperactivity and inattention. The participants were orally treated with placebo or a standardized ethanolic extract of *B. monnieri* (160 and 320 mg/day for 16 weeks) with ≥ 55% bacosides. *B. monnieri* improved hyperactivity, inattention, mood, sleep, and cognition (Kean *et al.*, 2015).

Anti-Alzheimer's disease activity

B. monnieri has been suggested to be a promising treatment for Alzheimer's disease, in which a *B. monnieri* extract was shown to counteract neuronal deterioration (Ahn *et al.*, 2016). Several research groups have reviewed the preclinical effects of *B. monnieri* on Alzheimer's disease (Chaudhari *et al.*, 2007; Howes & Houghton, 2012; Srivastav & Yadav, 2016). Table No. 2 summarizes the anti-Alzheimer's disease effects of *B. monnieri*.

Table No. 2
Effects of *Bacopa monnieri* on Alzheimer's disease

Type of study	Extract	Dose	Time of treatment	Main effects	Origin of study	Source
Preclinical (*in vitro*)	Ethanolic	Several	—	• Inhibition of amyloid-β and AChE • Antioxidant effects	Thailand	(Limpeanchob *et al*., 2008)
Preclinical (i*n vitro*)	Ethanolic	Several	—	• Inhibition of amyloid-β	Estonia	(Witter *et al*., 2018)
Preclinical (i*n vitro*)	Methanolic	Several	—	• Inhibition of amyloid-β	India	(Mathew & Subramanian, 2012)
Preclinical (PSAPP mice)	Ethanolic	40 and 60 mg/kg	4 or 32 weeks	• Inhibition of amyloid-β • Improvement in hyperlocomotion	USA	(Dhanasekaran *et al*., 2007)
Preclinical (Wistar rats)	Ethanolic	20, 40, and 80 mg/kg	3 weeks	• Improvement in escape latency • Decrease in retention time • Increasing in cholinergic neuron densities	Thailand	(Uabundit *et al.*, 2010)
Preclinical (Wistar rats)	Standardized (solvent not specified)	50 mg/kg	2 weeks	• Reversal of memory impairment • Inhibition of AChE • Antioxidant effects	India	(Saini *et al.*, 2012)
Preclinical (Wistar rats)	Standardized (solvent not specified)	50 mg/kg	2 weeks	• Anti-inflammatory effects	India	(Saini *et al*., 2019)

Preclinical (*in vitro* and in Swiss mice)	Ethanolic	30 mg/kg	1 week	• Inhibition of AChE • Antidementia effects	India	(Das *et al*., 2002)
Preclinical (Swiss mice)	Standardized (solvent not specified)	120 mg/kg	Single dose	• Improvements in calmodulin and memory	India	(Saraf *et al*., 2009)
Preclinical (Wistar rats)	Bacosides	200 mg/kg	12 weeks	• Improvements in neurotransmitter systems, behavioral paradigms, and hippocampal neuronal loss • Antioxidant effects	India	(Rastogi *et al.*, 2012b)
Preclinical (Wistar rats)	Bacoside	50, 100, 200, 400, and 800 mg/kg	12 weeks	• Neuroprotective effects through pleiotropic actions for the prevention of aging-related complications and senile dementia of Alzheimer's progression	India	(Rastogi *et al.*, 2012a)

Limpeanchob *et al*. (2008), evaluated the *in vitro* neuroprotective effects of an extract of *B. monnieri* against amyloid-β_{25-35} protein and glutamate-induced neurotoxicity in primary cortical cultured neurons. The ethanolic extract at different concentrations protected neurons from cell death but not glutamate-induced excitotoxicity. This effect was mediated by the suppression of AChE activity, a decrease in intracellular oxidative stress, and a decrease in lipid peroxidation. The inhibitory effects of ethanolic and methanolic extracts of *B. monnieri* on amyloid-β oligomerization and fibrillation were also investigated by Witter *et al*. (2018) and Mathew and Subramanian (2012), respectively.

The anti-amyloidogenic potential of *B. monnieri* was evaluated in a transgenic amyloid-β peptide-overproducing PSAPP mouse model of Alzheimer's disease. Male and female PSAPP mice were treated with an ethanolic extract of *B. monnieri* (40 and 60 mg/kg, orally, for 4 or 32 weeks). Treatment with the extract decreased amyloid-β_{1-40} and amyloid-β_{1-42} levels in the cortex by as much as 60% and reversed hyperlocomotion in PSAPP mice (Holcomb *et al.*, 2006). The effects of *B. monnieri* in reduce beta-amyloid levels in *ex vivo* brain of PSAPP mice were also evaluated by Dhanasekaran *et al*. (2007). The ethanolic extract of *B. monnieri* (50 - 1000 µg) reduced components of the oxidative stress cascade and decreased lipoxygenase activity.

Uabundit *et al*. (2010), investigated the effect of an ethanolic extract of *B. monnieri* on cognitive function and neurodegeneration in an animal model of Alzheimer's disease that was induced by ethylcholine aziridinium. Male Wistar rats were orally treated with the extract (20, 40, and 80 mg/kg) for 2 weeks before and 1 week after induction of the model. Treatment with all doses of the extract improved the escape latency and decreased retention time in the Morris water maze. The low dose of the *B. monnieri* extract increased cholinergic neuron densities in all areas of the hippocampus. No correlation was found between the cognition-enhancing effect and neuroprotective effect of the extract, suggesting different mechanisms of action of *B. monnieri*.

The effects of *B. monnieri* on colchicine-induced dementia (i.e., a model of Alzheimer's disease) were also evaluated. Male Wistar rats

received colchicine (3 µg/µL, intracerebroventricularly) and then were orally treated with a standardized extract of *B. monnieri* (solvent not specified; 50 mg/kg/day for 2 weeks). Cognitive performance was evaluated in the elevated plus maze, and motor function was evaluated in the rotarod test. Colchicine induced neurobehavioral deficits, increased AChE activity, inhibited Na^+/K^+ ATPase activity, and induced brain oxidative stress, reflected by higher levels of lipid peroxidation and protein carbonyls and a decrease in the activity of antioxidant enzymes. Supplementation with the *B. monnieri* extract reversed memory impairments, restored the activity of antioxidant enzymes, and attenuated oxidative damage (Saini *et al.*, 2012).

Using the same model of colchicine-induced dementia, Saini *et al*. (2019), evaluated the anti-inflammatory effects of a standardized extract of *B. monnieri* (solvent not specified; 50 mg/kg for 2 weeks) in male Wistar rats. Colchicine increased β-amyloid production, induced oxidative stress, increased the expression of proinflammatory cytokines (interleukin-6 [IL-6] and tumor necrosis factor α [TNF-α]) and chemokines (monocyte chemoattractant protein-1 [MCP-1]), and increased the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) in the brain. Treatment with the *B. monnieri* extract reversed all of these alterations.

Das *et al*. (2002), evaluated the antidementia activity of *B. monnieri* against deficits that were induced by the anticholinergic drug scopolamine (3 mg/kg, intraperitoneally) in the passive avoidance test. In male Swiss mice, oral administration of an ethanolic extract of *B. monnieri* (30 mg/kg for 1 week) significantly increased the transfer latency and no transfer response in the second trial after scopolamine treatment, thus attenuating its antidementia effect. The extract dose-dependently inhibited AChE activity *in vitro*.

Saraf *et al*. (2009), investigated the protective mechanism of action of *B. monnieri* against scopolamine-induced amnesia in male Swiss mice. In the brain, scopolamine downregulated PKC and iNOS without affecting cAMP, PKA, calmodulin, mitogen-activated protein kinase (MAPK), nitrite, CREB, or phosphorylated CREB. Treatment with a standardized extract of *B. trimera* (solvent not specified; 120 mg/kg, single dose, orally or intraperitoneally) reversed scopolamine-induced amnesia by significantly increasing calmodulin levels and partially decreasing PKC and pCREB levels.

In addition to crude and standardized extracts of *B. monnieri*, bacopasides have also been evaluated in an animal model of Alzheimer's disease. Bacoside (200 mg/kg) was orally administered for 12 weeks in male Wistar rats (17-18 months old or > 2 years old). The treatment protected animals against aging-associated alterations of neurotransmission systems, behavior, hippocampal neuronal loss, and oxidative stress (Rastogi *et al.*, 2012b).

Rastogi *et al*. (2012b), used the isolated compound bacoside that was dissolved in sodium sulphate buffer (0.05 M, pH 2.3) and acetonitrile (50:50, volume/volume). Long-term oral bacoside administration significantly decreased age-dependent elevations of proinflammatory cytokines, iNOS protein expression, total nitrite, and lipofuscin content in the cortex in middle-aged and aged female Wistar rats. These results suggest that bacoside may have potential as a neuroprotective agent based on its pleiotropic actions in preventing aging-associated complications and Alzheimer's-type senile dementia.

Despite the promising preclinical effects of *B. monnieri* against Alzheimer's disease, no clinical studies have yet investigated the plant's effects on the disease. One study investigated the effects of treatment with *B. monnieri* combined with other medicinal species (*Hippophae rhamnoides* and *Dioscorea bulbifera*), reporting positive effects on cognitive function in human patients with Alzheimer's-associated senile dementia (Sadhu *et al.*, 2014).

Antiparkinson activity

The antiparkinsonian activity of *B. monnieri* has been investigated *in vitro* and in several models of neurodegenerative disease. The antioxidant and neuroprotective effects of *B. monnieri* confer anti-Parkinsonian activity of the plant that is associated with lower α-synuclein protein aggregation and the selective death of dopaminergic neurons. Table No. 3 summarizes the antiparkinsonian effects of *B. monnieri*.

In N27 cell lines (dopaminergic cells) that were pretreated with an ethanolic extract of *B. monnieri*, a cytoprotective effect was observed, reflected by the attenuation of rotenone-induced oxidative stress and cell death (Shinomol *et al.*, 2012).

Jadiya *et al*. (2011), evaluated the anti-Parkinsonian effects of a concentrated mother tincture of a *B. monnieri* extract in two different *Caenorhabditis elegans* nematode models. The

transgenic model expressed human αa-synuclein, and the pharmacological model expressed green fluorescent protein specifically in dopaminergic neurons that were treated with the selective catecholaminergic neurotoxin 6-hydroxydopamine (6-OHDA). *B. monnieri* reduced α-synuclein aggregation, prevented dopaminergic neurodegeneration, and restored lipid content in nematodes, demonstrating the possible anti-Parkinsonian potential of this species.

Table No. 3
Effects of *Bacopa monnieri* on Parkinson's disease

Type of study	Extract	Dose	Time of treatment	Main effects	Origin of study	Source
Preclinical (*in vitro*)	Ethanolic	2-6 μg/L	24 h	• Cytoprotective effect, revealed by the attenuation of rotenone-induced oxidative stress and cell death	India	(Shinomol *et al.*, 2012)
Preclinical (*C. elegans*)	Mother tincture	The mother tincture was diluted tenfold in OP50	—	• Reduction of α-synuclein aggregation • Prevention of dopaminergic neurodegeneration • Restoration of lipid content in nematodes	India	(Jadiya *et al.*, 2011)
Preclinical (*Drosophila*)	Standardized (solvent not specified)	0.05% and 0.1%	1 week	• Reduction of endogenous markers oxidative stress • Inhibition of dopamine depletion • Lower incidence of mortality	India	(Hosamani & Muralidhara, 2009)
Preclinical (*Drosophila*)	Standardized (solvent not specified)	0.05% and 0.1%	24 h	• Restoration of electron transport chain and antioxidant and neuroprotective activity	India	(Hosamani & Muralidhara, 2010)
Preclinical (*Drosophila*)	Standardized (solvent not specified)	11 mg/100 g of food	2 weeks	• Improvement in climbing ability • Normalization of markers of oxidative stress	UK	(Jansen *et al.*, 2014)
Preclinical (*Drosophila*)	Acetone	0.25, 0.50, and 1.0 μl/ml	24 days	• Improvement of behavioral abnormalities • Normalization of markers of oxidative stress	India	(Siddique *et al.*, 2014)
Preclinical (*Drosophila*)	Standardized (solvent not specified)	0.1% in the diet	48 h	• Reduction of paraquat-induced toxicity • Optimization of active JNK protein and cleaved caspase-3 activity • Stabilization of oxidative	India	(Srivastav *et al.*, 2018)

				and apoptotic processes		
Preclinical (zebrafish)	Standardized aqueous extract encapsulated in nanoparticles	0.3, 0.4, and 0.5 μmol/kg	5 days	• Neuroprotection against MPTP-induced toxicity	India	(Nellore *et al.*, 2013)
Preclinical (Swiss mice)	Ethanolic	10 mg/kg	1 week	• Normalization of markers of oxidative stress • Restoration of antioxidant enzyme activity, neurotransmitter activity, and dopamine levels	India	(Shinomol *et al.*, 2012)
Preclinical (Swiss mice)	Standardized (solvent not specified)	200 mg/kg	4 weeks	• Prevention of oxidation-mediated neuronal dysfunction	USA	(Hosamani *et al.,* 2016)
Preclinical (Swiss mice)	Ethanolic	40 mg/kg	30 days	• Increase in locomotor activity • Increase in tyrosine hydroxylase and caspase-3 activity and gene expression in the substantia nigra	India	(Singh *et al.*, 2016)
Preclinical (Swiss mice)	Ethanolic	40 mg/kg	30 days	• Improvement in motor behavior through a decrease in oxidative stress and apoptosis and increase in dopamine level and Bcl-2 protein expression	India	Singh *et al.*, 2017)
Preclinical (Swiss mice)	Standardized (solvent not specified)	200 mg/kg	3 weeks	• Decrease in paraquat-induced cognitive deficits and oxidative stress • Restoration of dopamine levels and decreased cholinergic activity in the striatum	India	(Krishna *et al.*, 2019)

The neuroprotective effects of a standardized extract of *B. monnieri* (solvent not specified; provided in the diet for 1 week) against rotenone-induced oxidative damage and neurotoxicity were also evaluated in a *Drosophila melanogaster* model of Parkinson's disease. In flies that were exposed to the extract, significantly lower levels of endogenous oxidative markers were observed, with the inhibition of dopamine depletion and a lower incidence of mortality, suggesting the neuroprotective potential of *B. monnieri* (Hosamani & Muralidhara, 2009).

A study of adult male *Drosophila melanogaster* evaluated the prophylactic efficacy of a standardized extract of *B. monnieri* (solvent not specified; provided in the diet for 24 h) that contained approximately 40% bacoside against paraquat-induced oxidative stress, mitochondrial dysfunction, and lethality. The *B. monnieri* extract prevented paraquat-induced oxidative stress and neurotoxicity and restored the activity of electron transport chain

complexes, suggesting a specific effect on mitochondria and neuroprotective efficacy (Hosamani & Muralidhara, 2010).

The therapeutic potential of a standardized extract of *B. monnieri* (solvent not specified; provided in the diet for 2 weeks) to relieve motor symptoms of Parkinson's disease was studied in a simple model with two types of flies. Improvements in climbing ability were observed only in the PINK1 *D. melanogaster* transgenic model, which may be explained by the presence of antioxidants in *B. monnieri* that decreased the sensitivity to oxidative stress. PINK1 flies are usually more sensitive to oxidative stress. Moreover, in PINK1 flies, higher plasma levodopa levels improved locomotion, whereas healthy wildtype flies did not exhibit such positive results, which can be attributed to a higher likelihood of side effects from treatment resulting in dyskinesia resulting in decreased ability to climb wild-type flies (Jansen *et al.*, 2014).

Siddique *et al*. (2014), evaluated the effects of an acetone extract of *B. monnieri* (0.25, 0.50, and 1.0 µL/mL for 24 days) in a *Drosophila* sp. transgenic line that expressed human α-synuclein. *B. monnieri* improved behavioral abnormalities and reduced oxidative stress and apoptosis in this fly model of Parkinson's disease.

Srivastav *et al*. (2018), investigated the effects of a standardized extract of *B. monnieri* (solvent not specified; 1% concentration provided in the diet for 48 h) against paraquat-induced toxicity in a *D. melanogaster* model of Parkinson's disease. *B. monnieri* decreased acute paraquat-induced toxicity by optimizing redox balance and mitochondrial function, decreasing apoptosis, optimizing active c-Jun N-terminal kinase (JNK) protein and cleaved caspase-3 activity, and stabilizing the transcriptional regulation of genes that are responsible for regulating apoptosis and oxidative stress. These findings further demonstrated the potential of *B. monnieri* as a neuroprotective agent.

Nellore *et al*. (2013), evaluated the neuroprotective effects of a platinum nanoparticle-encapsulated aqueous extract of *B. monnieri* (alternating days of treatment for 5 days) in a zebrafish model of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinson's disease. *B. monnieri* pretreatment significantly reversed the toxic effects of MPTP, increased the levels of dopamine and its metabolites, increased glutathione levels, increased glutathione peroxidase, catalase, superoxide dismutase, and mitochondrial complex I activity, decreased malondialdehyde levels, and increased locomotor activity. These findings suggest that the protective potential of *B. monnieri* against MPTP-induced neurotoxicity occurs through dual actions on mitochondrial complex I and antioxidant activity.

Treatment with an ethanolic extract of *B. monnieri* (10 mg/kg, intraperitoneally, for 7 days) exerted neuroprotective effects in male Swiss mice that received rotenone. Treatment with the extract restored the activity of cytosolic antioxidant enzymes, restored reduced glutathione levels, and normalized oxidative markers, protein carbonyl content, neurotransmitter function, and cellular dopamine levels, thus further demonstrating the potent neuroprotective effects of the plant (Shinomol *et al.*, 2012).

Treatment with a standardized extract of *B. monnieri* (solvent not specified; 200 mg/kg for 4 weeks) in prepubertal male Swiss mice exerted significant antioxidant effects. Treatment with the extract improved oxidative homeostasis, decreased paraquat-induced reactive oxygen species, reduced mitochondrial dysfunction, and decreased malondialdehyde and hydroperoxide levels in various brain regions (Hosamani *et al.*, 2016).

Singh *et al*. (2017), evaluated the neuroprotective effects of an ethanolic extract of *B. monnieri* (40 mg/kg, orally, for 30 days) in a model of MPTP-induced Parkinson's disease in male Swiss mice. Treatment with *B. monnieri* improved motor behavior, reduced oxidative stress and apoptosis, increased dopamine levels, and increased B-cell lymphoma 2 (Bcl-2) protein expression, indicating a dopaminergic neuroprotective effect against Parkinson's disease that occurred through the modulation of oxidative stress and apoptotic factors.

Singh *et al*. (2016), also evaluated the therapeutic effects of an ethanolic extract of *B. monnieri* in a model of MPTP-induced Parkinson's disease in male Swiss mice that were orally treated with an extract of *B. monnieri* (40 mg/kg, orally, for 30 days). *B. monnieri* significantly decreased oxidative stress, increased locomotor activity, and increased tyrosine hydroxylase and caspase-3 activity and gene expression in the substantia nigra. These results indicate that *B. monnieri* promotes neurogenesis, reduces apoptosis, and restores the concentration of dopamine and its metabolites.

Male Swiss mice were orally supplemented with a standardized extract of *B. monnieri* (solvent not specified; 200 mg/kg for 3 weeks), and anxiety-

like behavior, motor function, and biochemical changes in specific brain areas were examined. Supplementation with *B. monnieri* decreased paraquat-induced cognitive deficits and oxidative stress, increased dopamine levels, and reversed cholinergic activity in the striatum (Krishna *et al.*, 2019).

Antiepileptic activity

Many drugs that are used to treat epilepsy may cause cognitive deficits (Kwan & Brodie, 2001). A renewed interest has been seen in the use of traditional medicinal plant formulations to treat epilepsy and exert neuroprotective effects. However, despite the widespread therapeutic use of medicinal plants, little is known about their effectiveness and toxicity (Liu *et al.*, 2017b). *B. monnieri* exerts interesting preclinical antiepileptic effects on many pathways that are involved in epilepsy, but robust preclinical research and clinical studies are still lacking to fully evaluate the therapeutic potential of this species. The antiepileptic effects of *B. monnieri* are summarized in Table No. 4.

Table No. 4
Effects of *Bacopa monnieri* on epilepsy

Type of study	Extract	Dose	Time of treatment	Main effects	Origin of study	Source
Preclinical (Wistar rats)	Aqueous	300 mg/kg	2 weeks	• Regulation of NMDA receptor 1 • Increase in glutamate dehydrogenase activity • Increase in escape latency	India	(Khan *et al.*, 2008)
Preclinical (Wistar rats)	Aqueous	150 mg/kg	2 weeks	• Regulation of mGluR8 expression	India	(Paulose *et al.*, 2008)
Preclinical (Wistar rats)	Aqueous and bacoside-A	150 and 300 mg/kg	2 weeks	• Normalization of GABA levels, $GABA_A$ and $GABA_B$ receptor binding, and CREB gene expression in the striatum	India	(Mathew *et al.*, 2010a)
Preclinical (Wistar rats)	Aqueous and bacoside-A	150 and 300 mg/kg	2 weeks	• Normalization of GABA levels, $GABA_A$ and $GABA_B$ receptor binding, and CREB gene expression in the hippocampus	India	(Mathew *et al.*, 2011)
Preclinical (Wistar rats)	Aqueous and bacoside-A	150 and 300 mg/kg	2 weeks	• Antiepileptic effects by attenuating impairments in the peripheral nervous system	India	(Mathew *et al.*, 2010b)
Preclinical (*C. elegans*)	Bacoside-A	0.25%, 0.1%, and 0.01%	—	Antiepileptic	India	(Pandey *et al.*, 2010)
Preclinical	Aqueous	150	2 weeks	• Normalization of	India	(Krishnakumar *et*

(Wistar rats)		mg/kg		cerebellar 5-HT content, 5-HT_{2C} gene expression, and 5-HT_{2C} receptor binding		*al*., 2009a)
Preclinical (Wistar rats)	Aqueous	150 mg/kg	2 weeks	• Normalization of hippocampal 5-HT content, 5-HT_{2C} gene expression, and 5-HT_{2C} receptor binding	India	(Krishnakumar *et al*., 2009b)

Khan *et al*. (2008), evaluated the neuroprotective effects of an aqueous extract of *B. monnieri* in male Wistar rats. Epilepsy was induced by an intraperitoneal injection of pilocarpine, and seizures were assessed by observing behavioral postures. Treatment with *B. monnieri* (300 mg/kg for 2 weeks) reversed the expression of *N*-methyl-D-aspartate (NMDA) receptor 1 and glutamate receptor binding alterations in the hippocampus, increased the activity of glutamate dehydrogenase, and reversed the increase in escape latency in the Morris water maze.

Paulose *et al*. (2008), investigated the involvement of metabotropic glutamate receptor 8 (mGluR8). During epilepsy, mGluR8 gene expression was downregulated, and the time spent in the platform quadrant decreased in the Morris water maze. Oral treatment with an aqueous extract of *B. monnieri* (150 mg/kg for 2 weeks) reversed mGluR8 gene expression and the time spent in the platform quadrant to control levels.

Using the same animal model of pilocarpine-induced epilepsy, Mathew *et al*. (2010b) and Mathew *et al*. (2011) evaluated the effects of an aqueous extract of *B. monnieri* (300 mg/kg for 2 weeks) and bacoside-A (150 mg/kg for 2 weeks) in male Wistar rats. Oral treatment with *B. monnieri* and bacoside-A reversed the alterations of GABA levels, $GABA_A$ and $GABA_B$ receptor binding, and CREB gene expression in the striatum and hippocampus, resulting in an increase in the GABA-mediated inhibition of overstimulated neurons in the cerebral cortex in rats. Mathew *et al*. (2010a) used the same model, animals, and treatment conditions and found that repetitive seizures resulted in an increase in metabolism and excitability, and treatment with the *B. monnieri* extract and bacoside-A exerted antiepileptic effects by attenuating impairments in the peripheral nervous system. Bacoside-A was also evaluated by Pandey *et al*. (2010) in a *C. elegans* model of epilepsy, who found that 0.25%, 0.1%, and 0.01% bacoside-A reduced seizures/convulsions.

In addition to the actions of *B. monnieri* on GABA receptors, the involvement of 5-HT receptors has also been investigated. In a male Wistar rat model of pilocarpine-induced epilepsy, Krishnakumar *et al*. (2009a) found that treatment with an aqueous extract of *B. monnieri* (150 mg/kg for 2 weeks) normalized cerebellar 5-HT content, 5-HT_{2C} gene expression, 5-HT_{2C} receptor binding, and motor dysfunction that were induced by pilocarpine. The same effects were observed in the hippocampus in rats that were orally treated with an aqueous extract of *B. monnieri* (150 mg/kg for 2 weeks) (Krishnakumar *et al*., 2009b).

Anti-schizophrenia activity

Since the most common drugs for treating schizophrenia can cause serious side effects, more effective and safe drugs are needed, especially to address cognitive impairments (Piyabhan *et al.*, 2016). In this line, *B. monnieri* is a promising medicinal plant for the treatment of schizophrenia (Table No. 5).

Piyabhan *et al*. (2016), and Piyabhan & Wetchateng (2015), evaluated the cognitive and neuroprotective effects of *B. monnieri* in a model of phencyclidine-induced schizophrenia in male Wistar rats. The animals orally received a standardized extract of *B. monnieri* (40 mg/kg for 2 weeks) before (neuroprotective study) and after (therapeutic study) phencyclidine administration. *B. monnieri* prevented cognitive impairment by elevating vesicular glutamate transporter 3 (VGLUT3) immunodensity in the prefrontal cortex and striatum and VGLUT2 immunodensity in the prefrontal cortex. Therapeutic treatment with the extract also effectively reversed cognitive deficits by decreasing NMDA receptor 1 in the CA2 and CA3 areas of the hippocampus (Piyabhan & Wetchateng, 2014).

Sarkar *et al*. (2012), reported a case study of the effects of *B. monnieri* in schizophrenia. A 34-year-old man with a diagnosis of paranoid schizophrenia received two tablets of *B. monnieri* daily for 4 weeks. Each tablet contained 250 mg of *B. monnieri* extract. *B. monnieri* reduced psychopathology without any treatment-emergent adverse effects.

Table No. 5
Effects of *Bacopa monnieri* on schizophrenia

Type of study	Extract	Dose	Time of treatment	Main effects	Origin of study	Source
Preclinical (Wistar rats)	Standardized	40 mg/kg before and after model induction	2 weeks	• Prevention of cognitive impairment by elevating VGLUT3 immunodensity in the prefrontal cortex and striatum	Thailand	(Piyabhan *et al.*, 2016)
Preclinical (Wistar rats)	Standardized	40 mg/kg before and after model induction	2 weeks	• Prevention of cognitive impairment by elevating VGLUT2 immunodensity in the prefrontal cortex	Thailand	(Piyabhan and Wetchateng, 2015)
Preclinical (Wistar rats)	Standardized	40 mg/kg before and after model induction	2 weeks	• Restoration of cognitive deficits by decreasing NMDA receptor 1 in the CA2 and CA3 areas of the hippocampus	Thailand	(Piyabhan & Wetchateng, 2014)
Clinical	Standardized	500 mg/day	4 weeks	• Reduction of psychopathology	India	(Sarkar *et al*., 2012)

TOXICOLOGICAL EVALUATIONS

The acute oral toxicity of *B. monnieri* extract was evaluated in female Sprague-Dawley rats that received a single dose of 5000 mg/kg and were monitored for toxic signs for 14 days. Chronic oral toxicity was evaluated in female and male rats that were treated daily with *B. monnieri* extract (30, 60, 300, or 1500 mg/kg for 270 days). Alterations of clinical signs were monitored. No signs of toxicity were observed with either acute or chronic exposure (Sireeratawong *et al.*, 2016).

Allan *et al*. (2007), also performed a safety evaluation of a standardized extract of *B. monnieri* in male and female Sprague-Dawley rats. The results showed a median lethal dose of 2400 mg/kg (single oral administration) and mild lowering of body weight gain but no other signs of toxicity after 14 days of treatment with 500 mg/kg. No evidence of toxicity was seen after 90 days of treatment with 85, 210, and 500 mg/kg.

Rastogi *et al*. (2012b), orally treated male Wistar rats with bacoside for 12 weeks and observed no changes in body mass, liver function, or kidney function in animals that received 200 mg/kg. However, hematological alterations were observed at doses of 50, 100, and 200 mg/kg. At higher doses (400 and 800 mg/kg), a slight decrease in body mass, decrease in albumin and protein content, and increase in plasma aspartate transaminase, alanine transaminase, and alkaline phosphatase were observed.

In humans who were treated with a therapeutic dose of *B. monnieri* for 12 weeks, some healthy elderly individuals exhibited gastrointestinal side effects (e.g., diarrhea, nausea, increase in stool frequency, and abdominal cramps), with no changes in hematological, biochemical, blood pressure, or electrocardiographic parameters (Calabrese *et al*., 2008, Peth-Nui *et al*., 2012, Piyabhan & Wetchateng, 2014).

CONCLUSION

Bacopa monnieri is a creeping perennial plant with a small stature that is distributed in India and other tropical regions. All parts of the plant are used for medicinal purposes. It is prepared as a decoction, infusion, juice, and powder, mainly in India. Its biologically active ingredients are concentrated in the stems and leaves. Its biological actions have been mainly attributed to its high content of bacosides, mainly bacoside-A. *B. monnieri* has been used to improve cognitive performance. Its preclinical biological actions include effects in Alzheimer's disease, Parkinson's disease, epilepsy, and schizophrenia. No acute toxicity was reported in a preclinical study of a *B. monnieri*. However, gastrointestinal side effects were reported in some healthy elderly individuals who received a therapeutic dose of *B. monnieri*. Although research on *B. monnieri* has been expanding, most studies have been preclinical evaluations of cellular mechanisms in the central nervous system. Further translational clinical research needs to be performed to evaluate the safety and efficacy of the plant in patients with Parkinson's disease, Alzheimer's disease, epilepsy, and schizophrenia. Controlled clinical trials also need to be conducted over long periods of time to affirm the beneficial biological activity of *B. monnieri*.

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