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Recent Progress on Chemical Composition and Bioactivities of *Bacopa monnieri* (Linn.) a Plant of Ayurveda

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ABSTRACT

Bacopa monnieri (Linn.) is a highly regarded medicinal plant in Indian traditional Ayurvedic medicine for centuries owing to its broad spectrum bioactivities. The biological effects of *B. monnieri* are documented in traditional as well as scientific literature. The plant possess many important bioactivities like memory enhancing, anti-oxidant, anti-inflammatory, analgesic, antipyretic, hepatoprotective, sedative, antiepileptic and still many more are constantly being discovered. An ample amount of research on *B. monnieri* and its major constituents has unraveled its tremendous bioactive potential in the treatment of many serious disorders *viz.* Alzheimer's disease, cognitive functions, memory impairment, hepatic carcinoma and cigarette smoking-associated diseases. Since 2005, when the last review on *B. monnieri* was written, many more new bioactivities have been discovered, although they have not been compiled in one publication. In the present article we describe many new useful bioactivities of *B. monnieri* and its active chemical constituent bacoside and new chemical constituents that have been isolated and characterized.

Keywords: anti-Alzheimer's, antiamneatic, *Bacopa monnieri*, bacoside, neuroprotective, saponin, *Scrophulariaceae*

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INTRODUCTION

Bacopa monnieri (Linn.) belongs to the Scrophulariaceae family and has been a reputed medicinal plant in Indian traditional Ayurvedic system for 3000 years. It is a perennial creeping plant distributed in Fujian, Taiwan, and in Guangdong, Yunnan, and Sichuan Provinces in China. The plant is found throughout the Indo-Pakistan subcontinent in wet, damp and marshy areas and is locally known as Brahmi (Satyavati *et al*. 1976). The plant improves the brain health hence it has been given the name Brahmi which is derived from the word Brama (Russo and Borrelli 2005).

The tremendous medicinal and pharmacological significance of *B. monnieri* and chemical constituents therein has always attracted the attention of researchers. Many previously published reports have documented the use of *B. monnieri* for insanity, nervous breakdown, dermatitis and in memory enhancement (Chopra *et al*. 1998) antiulcerogenic, adaptogenic activities and hepatoprotective effect against morphine induced liver toxicity in rats (Russo and Borrelli 2005; Sumathi and Nangbri 2008). It helps in prevention of neurological diseases (Vohora *et al*. 2000) and possessed anti-inflammatory, analgesic, antipyretic, sedative (Kishore and Singh 2005), free radical scavenging and lipid peroxidative activities (Anbarasi *et al*. 2005a, 2005b). The plant also possess anti-addictive and mast cell stabilizing properties (Samiulla *et al.* 2001).

In recent years, many newer bioactivities of *B. monnieri* plant and pure chemical constituents have been rapidly deciphered; as a result, the pharmacological and medicinal value of the plant has been tremendously increased. Potential effects of *B. monnieri* on nitrobenzene induced liver damage in rats have been reported (Menon *et al*. 2010). Several recent studies have indicated beneficial effects of *B. monnieri* on cognitive functions, against the β-amyloid protein and glutamate-induced neurotoxicity in primary cortical cultured neurons in Alzheimer's disease (AD) patients (Dhansekaran *et al.* 2007; Limpeanchob *et al.* 2008; Uabun-

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Mini-Review

Table 1 Bioactivities of *Bacopa monnieri* (L.) and its active constituents.

Extracts/compounds	Activity	Experimental model	Reference
B. monnieri extract	Anti-Alzheimer's	PSAPP mice	Holcomb *et al.* 2006
B. monnieri alcoholic extract, Bacosides	Anti-amnesic	Mice with induced amnesia	Kishore and Singh 2005
B. monnieri (L.)	Anti-amnesic	Mice induced with diazepam	Saraf *et al.* 2008
B. monnieri	Anti-amnesic	Scopolamine induced amnesia in mice	Saraf *et al.* 2010
B. monnieri	Anti-amnesic	Mice induced with diazepam and scopolamine	Anand *et al.* 2010
Bacoside-A	Anti-apoptosis	Adult male albino rats of Wistar strain	Anbarasi *et al.* 2006b
B. monnieri ethanol extract	Apoptopic/cytotoxic	In mouse S-180 cells	Rohini and Devi 2008
B. monnieri methanol extract	Anti-inflammatory	Carrageenan-induced rat paw edema	Viji and Helen 2008
B. monnieri extract	Anti-inflammatory	Rats induced with adjuvant	Vijayan *et al.* 2010
B. monnieri methanol extract, triterpenoids and bacoside enriched fractions	Anti-inflammatory	Lipopolysaccharide (LPS)-activated peripheral blood mononuclear cells and peritoneal exudate cells in vitro	Viji and Helen 2010
Betulinic acid	Anti-inflammatory	Cultured peripheral blood mononuclear cells	Viji *et al.* 2010a
B. monnieri extract	Antioxidant activity	Diabetic rats	Kapoor *et al.* 2009
B. monnieri extract	Anti-rheumatic	Rats induced with Type-II collagen	Viji *et al.* 2010b
B. monnieri methanol extract of the whole plant; bacopaside E; bacopaside VII	Anti-tumor	Human tumor cell lines MDA-MB-231, SHG-44, HCT-8, A-549 and PC-3M	Peng *et al.* 2010
B. monnieri	Cardioprotective effects	Rats with Ischaemia-reperfusion injury	Mohanty *et al.* 2010
Bacoside-A	Chemopreventive	Rats induced with N-nitrosodiethylamine	Janani *et al.* 2010
Bacoside-A	Hepatoprotective	Rats induced with N-nitrosodiethylamine	Janani *et al.* 2009
Bacoside-A (B-A)	Hepatoprotective	Rats induced with D-GalN	Sumathi and Nangbri 2008
B. monnieri ethanol extract	Improving learning and memory	Serotonergic system of postnatal rats	Charles *et al.* 2011
B. monnieri standardized extract	Memory enhancer	Healthy human	Raghav *et al.* 2006
Bacoside-A	Neuroprotective/antioxidant	Rats brain exposed to cigarette smoke	Anbarasi *et al.* 2005a, 2005b, 2006a
Bacosine (a triterpene)	Anti-hyperglycemic	Alloxanized induced diabetic rats	Ghosh *et al*. 2011
B. monnieri methanolic extract and bacoside-A	Wound healing	Swiss albino rats	Sharat *et al*. 2010
B. monnieri n-butanol extract	Acquisition and expression of morphine tolerance	Mice	Rauf *et al*. 2011
Bacopa monnieri alcohol extract	Cognitive function enhancer and neuroprotective	Male Wistar rats induced by ethylcholine aziridinium ion (AF64A)	Uabundi *et al*. 2010
B. monnieri	Seizure/convulsion Suppressing activity	*Caenorhabditis elegans*	Pandey *et al*. 2010
B. monnieri and bacoside-A	Anti-epileptic	Pilocarpine-induced epileptic rats	Mathew *et al*. 2010b, 2010c, 2010d

dit *et al*. 2010; Goswami *et al*. 2011). A number of reports have been published on neuro-pharmacological and nootropic effects of the whole plant, plant extract and phyto-constituents mainly mixtures of bacosides (Stough *et al.* 2008; Hota *et al.* 2009; Lohidasan *et al.* 2009; Zhou *et al.* 2009a). Mathew *et al*. (2010a) in their recent review article have discussed the use of *B. monnieri* and bacoside-A in ameliorating epilepsy associated behavioral deficits. *B. monnieri* appreciably reduce an expression and development of tolerance to morphine analgesia in mice and enhances antinocieptive effect of morphine in intolerant mice (Rauf *et al*. 2011). A recent study has revealed that *B. monnieri* modulates endogenous markers of oxidative stress in brain tissue of prepubetaral mice (Shinomol and Muralidhara 2011). Daily dietary intake of *B. monnieri* leaf powder has neuroprotective benefits and is expected to serve as prophylactic/therapeutic agent for neurodegenerative disorders (Shinomol and Muralidhara 2011). Bacosine, a triterpene present in *B. monnieri* showed antihyperglycemic activity in alloxan induced diabetic rats (Ghosh *et al.* 2011). *B. monnieri* may be useful in suppressing the seizure/convulsion in worms (Pandey *et al*. 2010). Bacoside-A isolated from *B. monnieri* (Wettest) is reported to have more effective wound healing and protease inhibition activities compared to the standard skin ointment nitrofurazone (Sharath *et al*. 2010). Horizon of bioactivities of *B. monnieri* and its chemical constituents from its traditional use to treat complicated disorders or diseases has been rapidly expanding. Researchers have unraveled the antiarthritic (Viji *et al*. 2010a) and antitumor (Rohini and Devi 2008; Peng *et al.* 2010) potential of *B. monnieri*. Bacoside-A is effective in the prevention of DEN-induced hepatocellular carcinoma (Janani *et al.* 2010).

At least 70 chemical constituents have been isolated from the whole plant of *B. monnieri* (Zhou *et al.* 2009b). The major chemical constituents identified are dammarane-type of triterpenoid saponins with jujubogenin or pseudojujubogenin moieties as aglycone units (Chillara *et al.* 2005). The biological activities of *B. monnieri* have been mainly attributed to these saponins especially, bacoside-A and bacoside-B (Deepak and Amit 2005). Compounds like polyphenols and sulfhydryl having endogenous antioxidant activity have been responsible for anti-AD property of *B. monnieri*. Bioactive potential of *B. monnieri* accessions to biosynthesize bacoside-A has been studied using $^{14}CO_2$ (Ganjewala *et al.* 2000a). Significant ontogenic and seasonal variation in accumulation pattern of bacoside-A in five different accessions of *B. monnieri* have also been reported (Ganjewala *et al.* 2000b). Dammarane triterpene saponins such as bacopasides E and VII possess potential antitumor and cytotoxic activities (Peng *et al*. 2010).

NEW CHEMICAL CONSTITUENTS FROM *BACOPA MONNIERA*

Zhou *et al.* (2009b) isolated a new triterpenoid saponin, bacopaside IX (3-*O*-{β-D-glucopyranosyl (1→4) [α-L-arabinofuranosyl-(1→2)]-β-D-glucop-yranosyl}-20-*O*-α-L-arabinopyranosyljujubogenin) from the whole plant of *B. monniera* (L.) Earlier, Chillara *et al.* (2005) have isolated two new triterpenoid glycosides 3-*O*-[β-D-glucopyranosyl-(1→3)-β-D-glucopyranosyl] jujubogenin and 3-*O*-[β-D-glucopyranosyl-(1→3)-β-D-glucopyranosyl] pseudojujubogenin along with 10 known saponins from *B. monnieri*. Two new dammarane-type triterpenoid saponins, bacopaside-XI (3-*O*-[α-L-arabinofuranosyl(1→3)]-6-*O*-sulfonyl-β-D-gluco-

pyranosyl pseudojujubogenin) and bacopaside-XII (3-*O*-{β-D-glucopyranosyl(1→3)[α-L-arabinofuranosyl(1→2)]-β-D-glucopyranosyl}-20-*O*-α-L-arabinopyranosyl pseudojujubogenin), together with known compounds, bacopaside IV, bacopaside V, and apigenin have been reported from the aerial parts of the *B. monnieri* (Bhandari *et al.* 2009).

BIOACTIVITIES OF *BACOPA MONNIERI*

B. monnieri is an excellent medicinal plant offering many promising pharmacological activities useful for the treatment of many complex diseases/disorders. The newer most promising bioactivities are antiamneatic, anti-inflammatory, neuroprotective/antioxidant, hepatoprotective, cardioprotective, anti-Alzheimer's, nootropic, anti-aging, memory enhancing, anti-arthritic and anti-tumor, cytotoxic and chemopreventive (**Table 1**). In the following sections these bioactivities with brief information of their mechanism have been discussed.

Protective effects/antioxidant activities

Nearly 35-40% of the world's population used to smoke. The number of people exposed to environmental tobacco smoke is increasing rapidly. Free radicals and oxidative damage plays crucial roles in the pathogenesis of smoking-related diseases. Cigarette smoking causes free radical-mediated lipid peroxidation (LPO) leading to increased membrane permeability and cellular damage in the heart and brain (Anbarasi *et al.* 2005a, 2005b). Bacoside-A, a dammarane type of triterpenoid isolated from *B. monnieri* has been known for its strong antioxidant potential is useful in protection against cigarette smoking-induced toxicity as well as in diabetic complications such as neuropathy, nephropathy and cardiopathy occurred due to excessive oxidative damages (Anbarasi *et al.* 2005a, 2005b; Kapoor *et al.* 2009).

Protective effect of bacoside-A against smoking-induced toxicity in rat brain has been reported (Anbarasi *et al.* 2005a, 2005b). For the assessment of antioxidant potential of bacoside-A against cigarette smoking-induced toxicity, activities of enzymes such as lactate dehydrogenase (LDH), creatine kinase (CK) with their isoenzymes have been monitored in rats (Anbarasi *et al.* 2005a, 2005b). Bacoside-A being a powerful free radical scavenger and anti-lipid peroxidative agent prevented the release of LDH (Anbarasi *et al.* 2005a). A similar study by Anbarasi *et al.* (2005b) reported protective effects of bacoside-A; however, in this study CK and its isoenzymes were used as sensitive markers for the assessment of cardiac and cerebral damage occurred due to oxidative damage. Results of the study revealed that cigarette induced smoking in albino male causes a significant increase in activities of the serum CK and isoenzymes, but decreases in the heart and brain. Exposure to cigarette smoking leads to an increase in LPO, membrane permeability and cellular damage in the heart and brain causing release of CK into the circulation (Anbarasi *et al.* 2005b). Bacoside-A prevents the leakage of CK from the respective tissues as it has protective effects on the structural and functional integrity of the membrane.

Two more studies have reported similar protective roles of bacoside-A against oxidative stress in the brain of rats exposed to cigarette smoke (Anbarasi *et al.* 2006a, 2006b). The brain is highly susceptible to free radical attack; however, it produces more free radicals per gram of tissue than does any other organs but lack sufficient enough amounts of protective antioxidants (Arivazhagan *et al.* 2002). Application of bacoside-A as being a strong antioxidant could be a very effective strategy for brain to overcome effects of oxidative damages (Anbarasi *et al.* 2006a). A study by Anbarasi *et al.* (2006a) confirmed the neuroprotective effects of bacoside-A against chronic cigarette smoking induced oxidative damage in rat brain. Antioxidant status of rat brain after treatment with bacoside-A have been evaluated by measuring the changes in the level of reduced glutathione, vitamin C, E, and A, superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase as well as copper, iron, zinc and selenium in brain and serum ceruloplasmin activity (Anbarasi *et al.* 2006a). A substantial increase in the antioxidant status while maintaining the levels of trace elements has been observed in rats following bacoside-A treatment (Anbarasi *et al.* 2006a). These studies have clearly suggested that cigarette smoking associated diseases might be prevented by application of an oxidant like bacoside-A (Anbarasi *et al.* 2006a). A study has described that cigarette smoking exceptionally increases oxidative damages and induces expression of heat shock protein-70 (hsp-70) and apoptosis (Anbarasi *et al.* 2006b). Expression of hsp-70 and apoptosis becomes pronounced during cigarette smoking toxicity and pathogenesis. Since the bacoside-A hinders both expression of hsp-70 and apoptosis it may provide protection to the brain of smoking-induced rats from the toxic effects of cigarette smoking (Anbarasi *et al.* 2006b).

Concurrently, the bacoside-A has shown similar protective roles in diabetic complications such as neuropathy, nephropathy and cardiopathy which occurs as result of oxidative stress damages (Kapoor *et al.* 2009). A study performed with streptozotocin induced diabetic rats has revealed the protective effect of *B. monnieri* extract on tissue antioxidant defense system and LPO (Kapoor *et al.* 2009). Extract of *B. monnieri* most likely shield tissues from the attack of reactive oxygen species (ROS) in diabetic rats *via* modulation of antioxidant defense system (Kapoor *et al.* 2009). Protective effect of *B. monnieri* extract in this study has been substantiated by measuring activities of enzymes of antioxidant status such as, superoxide dismutase (SOD) catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GSH) in diabetic rats after administration of bacopa extract. Vijayan and Helen (2007) studied the geneoprotective effect of *B. monnieri* aqueous extract in nicotine-induced toxicity Swiss mice (Vijayan and Helen 2007). Nicotine an active component of cigarettes smoke exert devastating effects by generation of free radicals on important biomolecules of the cell leading to genomic instability. For the investigation of effects of *B. monnieri* aqueous extract on genomic stability and LPO, micronucleus assay was performed and the levels of malondialdehyde (MDA) measured (Vijayan and Helen 2007).

Aluminium and its salts have been reported to cause oxidative damages to bio-molecules like lipids, proteins and nucleic acids which lead to neurotoxicity. Extracts of *B. monnieri* have shown protective effects against aluminium-induced oxidative stress in the hippocampus and cerebral cortex in male Wister rats (Jyoti and Sharma 2006). Also, *B. monnieri* has demonstrated beneficial effects against neurotoxicity in brain occurred due to oxidative stress damages in male Wister rats (Jyoti *et al.* 2007).

For the first time potential of *B. monnieri* to modulate endogenous markers of oxidative stress in brain tissue of prepubertal (PP) mice has been evaluated recently by Shinomol and Muralidhara (2011). Their study suggested that the dietary intake of *B. monnieri* leaf powder confers neuroprotective advantage and might be used as a prophylactic/therapeutic agent for neurodegenerative disorders involving oxidative stress (Shinomol and Muralidhara 2011). Dietary intake of *B. monnieri* significantly diminished basal oxidative markers (MDA levels, ROS generation, hydroperoxide levels and protein carbonyls) with corresponding increase in the levels of reduced glutathione, thiol and activities of antioxidant enzymes (catalase, glutathione peroxidase, superoxide dismutase) in both cytoplasm and mitochondria in various brain regions of prepubertal (PP) mice. Also, *B. monnieri* leaf powder has a property to modulate cholinergic function by significantly reducing the activity of acetyl cholinesterase in all regions of the brain. Examination of cortical/cerebellar synaptosomes of normal and *B. monnieri* fed mice exposed to 3-nitropropionic acid (3-NPA) have provided more evidence that dietary intake of *B. monnieri* leaf powder confers the prepubertal brain with

additional capacity to cope with neurotoxic pro-oxidants. The results showed that control mice exhibited a concentration related LPO and ROS generation while synaptosomes obtained from *B. monnieri* fed mice showed only a marginal induction at the highest concentration clearly suggesting their increased resistance to 3-NPA-induced oxidative stress (Shinomol and Muralidhara 2011).

Nootropic, anti-aging and memory-enhancing activities

B. monnieri has been used in India for centuries as an anti-aging and memory-enhancing ethnobotanical therapy (Holcomb *et al.* 2006). The standardized extract of *B. monnieri* have been reported to improve behavioural learning information processing in subjects with age-associated memory impairment without any evidence of dementia or psychiatric disorder (Raghav *et al.* 2006). Three new saponins from *B. monnieri* namely, bacopaside 3, bacopaside I and bacopasaponin C are reported to have nootropic activity and improves scopolamine-induced memory impairment in mice (Zhou *et al.* 2009b). *B. monnieri* leaf extract rich in the bacoside content has therapeutic potential of improving the memory functions in hypobaric conditions simulating an altitude of 25,000 ft for different durations in male Sprague Dawley rats (Hota *et al.* 2009). Beneficial effect of administration of bacoside on apoptosis, cytochrome c oxidase activity, ATP levels, and oxidative stress markers and on plasma corticosterone levels has been reported. Bacosides are excellent therapeutic agent in ameliorating hypobaric hypoxia induced cognitive dysfunctions and other related neurological disorders (Hota *et al.* 2009). The mechanism of the bacoside action was elucidated by studying expression of NR1 subunit of *N*-methyl-d-aspartate receptors, neuronal cell adhesion molecules and cAMP response element-binding protein phosphorylation. A recent study revealed that *B. monnieri* leaf ethanol extract is useful for memory enhancement through up-regulation of expression of tryptophan hydroxylase (TPH2) and serotonin transporter system (Charles *et al.* 2011). Techniques like enzyme linked immunosorbent assay and semi-quantitative polymerase chain reaction has been used to evaluate the effects of *B. monnieri* leaf ethanol extract on neurotransmitter system in rats.

Although, *B. monnieri* has been known for centuries in Ayurveda for cognitive improving effects several recently published reports have consolidated these findings. A special extract (Stough *et al.* 2008) and lipid-based extract of *B. monnieri* (Lohidasan *et al.* 2009) have been reported to demonstrate nootropic effects. Neuropsychological effects of *B. monnieri* have been tested using the Cognitive Drug Research cognitive assessment system. *B. monnieri* special extract significantly improved performance of the 'Working Memory' factor, more specifically spatial working memory accuracy (Stough *et al.* 2008). *B. monnieri* plants have the property of prevention of formation of MDA and lipofuscin pigments in prostate gland of D-galactose induced aging mice, *Mus musculus* (Kalamade *et al.* 2008).

Anti-amnesic activities

Several research groups working on *B. monnieri* have investigated anti-amnesic properties for the development of new potential drugs for amnesia. Amnesia is a condition results from ageing, chronic drug abuse or head injury for which currently limited therapeutics are available. However, recent studies have revealed potential anti-amnesic properies of *B. monnieri* that could be useful in alleviating amnesia (Anand *et al.* 2010). Studies have revealed that administration of *B. monnieri* extract may reverse both diazepam and scopolamine induced amnesia in mice (Saraf *et al.* 2008, 2010). Most likely *B. monnieri* antagonizes MK801, an NMDA receptor antagonist and N(ω)-nitro-L-arginine (L-NNA), a nitric oxide synthase inhibitor. The antiamnesic effect *B. monniera* on L-NNA induced amnesia are possibly mediated by nitric oxide (NO) pathway with involvement of calmodulin (CaM), which is required for long-term potentiation (LTP) sustenance (Anand *et al.* 2010). Scopolamine has been known as anticholinergic drug produce amnesia by interference of LTP. It is used for discerning the efficacy of various antiamnesic drugs (Saraf *et al.* 2008). *B. monnieri* has been found to improve CaM significantly and it partially attenuates activity of protein kinase C and pCREB, these properties has been postulated for anti-amnesic effects in scopolamine induced amnesia in rats. These studies have clearly indicated major role of CaM in anti-amnesic effects of *B. monnieri*. Kishore and Singh (2005) have reported antiamnesic effects of alcoholic extract of *B. monnieri* and the bacosides on experimental amnesia in mice induced by scopolamine, sodium nitrite, and BN52021. Properties of bacosides to improve acetylcholine level and hypoxic conditions are the most likely factors responsible for anti-amnesic effects of *B. monnieri* (Kishore and Singh 2005). Bacosides are also found to increase synthesis of platelet activating factor by enhancing cerebral glutamate level (Kishore and Singh 2005).

Anti-inflammatory activities

For very long time *B. monnieri* has been described as a therapeutically useful herb for the treatment of inflammation. Channa *et al*. (2006) have reported potential anti-inflammatory properties of *B. monnieri*. The ethanol extract of *B. monnieri* has demonstrated strong anti-inflammatory activity against carrageenan-induced paw edema in mice and rats. The anti-inflammatory action of the ethanol extracts however has been observed only in rats those treated with chemical mediator prostaglandin E2 but not against carrageenan, in histamine, serotonin, bradykinin and arachidonic acid)-induced edema in rats (Channa *et al*. 2006). Most defined work on anti-inflammatory potential of *B. monnieri* and its mechanism of action have been carried out by Viji and coworkers (Viji *et al.* 2008, 2010a, 2010b). Efficacy of *B. monnieri* methanol extracts in modulating key mediators of inflammation using carrageenan-induced rat paw edema, rat mononuclear cells and human whole blood assay have been evaluated (Viji and Helen 2008). Methanol extract of *B. monniera* demonstrated a strong anti-inflammatory activity which has been attributed to its tendency to inhibit activities of cyclooxigenase-2 and lipooxygenase and down regulation of tumor necrosis factor (TNF)-α and interleukin-6 (IL-6) (Viji and Helen 2008). A similar study has reported the anti-inflammatory activity of *B. monnieri* methanol extract rich in triterpenoid and bacosides content (Viji and Helen 2010). The inhibitory properties of *B. monnieri* methanol extract on the production of pro-inflammatory cytokines such as, TNF-α and IL-6 is assumed to be responsible for anti-inflammatory activity (Viji and Helen 2010). Both the triterpenoid and bacosides present in methanol extract of *B. monnnieri* demonstrated anti-oedematogenic effect in carrageenan-induced hind paw oedema mice; however, a methanol extract containing triterpenoid only showed anti-arthritic activity in the arthritis model (Viji and Helen 2010). Betulinic acid a pentacyclic triterpenoid present in the *B. monniera* also possesses anti-inflammatory activity (Viji *et al.* 2010b). Betulinic acid suppresses the production of IL-6 as a result of lipopolysaccharide induction in blood mononuclear cells both *in vivo* and *in vitro*. It inhibits production of IL-6 by preventing 65kD protein nuclear factor κB (p65 NF-κB) nuclear translocation. Other factors p38 and extracellular-signal-regulated kinases and mitogen-activated protein kinases are also involved in prevention of p65 NF-κB nuclear translocation (Viji *et al.* 2010a).

Anti-epileptic activities

Epilepsy is a neuronal disorder characterized by learning, cognitive and memory impairments (Mathew *et al*. 2010a). *B. monnieri* has been used for long time as nervine tonic for improving the mental performance. The plant molecules

from *B. monnieri* have beneficial properties of suppressing the seizure/convulsion in worms (*Caenorhabditis elegans*) (Pandey *et al*. 2010). The 1-mm long *Caenorhabditis elegans* is one of the prime research tools to study different human neurodegenerative diseases. The occurrence of seizures causing the impairment of peripheral nervous system in pilocarpine-induced epileptic rats could be well prevented by application of *B. monnieri* and the bacoside-A (Mathew *et al*. 2010b). Application of *B. monnieri* and the bacoside-A in epileptic rats was found to increase acetylcholine esterase and malate dehydrogenase activity in the muscle and decrease in the heart. The bacoside-A treatment also significantly influence insulin and T3 content in the serum of the epileptic rats (Mathew *et al*. 2010b). Recent studies have indicated the roles of gamma-aminobutyric acid-A (GABA-A) receptors in epilepsy associated motor learning deficits (Mathew *et al*. 2010c, 2010d). The group of Mathew and coworkers has carried out the most defined work on GABA receptors and their association with learning deficit in epileptic rats. A study aimed to evaluate potential of *B. monnieri* and the bacoside-A on spatial recognition memory deficit and alterations of GABA receptor in the striatum of epileptic rats has revealed that application of *B. monnieri* and bacoside-A can reverse the changes in memory deficit and alterations of GABA-A receptor (Mathew *et al*. 2010c). Another study by this group has found the similar effects of *B. monnieri* and bacoside-A, on motor deficit and alterations of GABA-A receptor functional regulation in the cerebellum of epileptic rats (Mathew *et al*. 2010d). The study suggested that the occurrences of repetitive seizures induce GABAergic activity, motor learning, and memory deficit in epileptic rats. Application of *B. monnieri* and bacoside-A most likely prevents the occurrence of seizures and may reduce the impairment of GABAergic activity, motor learning, and memory deficit in epileptic rats. In these studies, total GABA and GABA-A receptor numbers in the control and epileptic rats have been evaluated using [(3)H]GABA and [(3)H]bicuculline binding. Also studied the GABA(Aα1), GABA(Aα5), GABA(Aγ3) and GABA(AΔ) gene expressions levels. Please refer an article by Mathew *et al*. (2010a) for details on beneficial effect of *B. monnieri* on epilepsy-associated behavioral deficits.

Anti-Alzheimer's activities

Several recently published reports have recognized the anti-AD potential of *B. monnieri*. AD is one of the most common neurodegenerative disorders affects many elderly people worldwide (Limpeanchob *et al.* 2008). Presently, there is no drug or therapy is available as definite solution for treatment of AD except that the acetyl cholin esterase inhibitors (AChEI) and the glutamate modulators available to maintain cognitive functions of patients (Knopman 2006). Several research groups have investigated *B. monnieri* and its phytoconstituents if they possess anti-AD properties. The results of their studies have unraveled anti-AD properties of *B. monnieri* and may pave the way for the development of new therapeutics/drugs for curing AD. Perhaps, a deeper understanding of the AD and mechanism of progression would be required for development of new effective therapeutics/drugs. Our understanding of AD has suggested that a 40-42 amino acids long β-amyloid peptide (A-β, 1-40, 42) derived from proteolysis of amyloid precursor protein (APP) has been a major component in the formation of senile plaque found in brains of AD patients, therefore this peptide could be an attractive target for new therapeutics/drugs (Glenner and Wong 1984). A study by Holcomb *et al.* (2006) has revealed the potential of *B. monnieri* extract to reduce amyloid (A-β) levels in transgenic (PSAPP) mouse models over expressing mutant forms of presenilin (PS) and amyloid precursor protein (APP). A similar study has supported anti-AD property of *B. monnieri* (Dhansekaran *et al.* 2007). The polyphenols and sulfhydryl with endogenous antioxidant activity present in *B. monnieri* extract have been recognized as the major compounds that demonstrate anti-AD properties. These compounds have ability of reducing β-amyloid deposits in the brain of an AD doubly transgenic mouse model of rapid amyloid deposition (PSAPP mice) (Dhansekaran *et al.* 2007). *B. monnieri* extract has been reported to provide protection against the β-amyloid protein and glutamate-induced neurotoxicity in primary cortical cultured neurons (Limpeanchob *et al.* 2008). Higher level of acetylcholine esterase activity and neuronal oxidative stress are often believed to be responsible for neurotoxicity, however their levels could be substantially suppressed by application of *B. monnieri*. These properties of *B. monnieri* to suppress acetylcholine esterase activity and neuronal oxidative stress are attributed for its neuroprotective behaviour (Limpeanchob *et al.* 2008). The alcohol extract of *B. monnieri* enhanced the cognitive function and neuroprotective agent in male Wistar rats of AD induced by ethylcholine aziridinium ion (AF64A) (Uabundi *et al*. 2010). For the study, *B. monnieri* alcoholic extract at doses of 20, 40 and 80 mg/kg BW was fed orally with needle to male Wistar rats for 2 weeks before and 1 week after the intra cerebroventricular administration of AF64A bilaterally. The effects of *B. monnieri* extract on spatial memory was analyzed using Morris water maze test, whereas the density of neurons and cholinergic neurons was determined using histological techniques 7 days after AF64A administration (Uabundi *et al*. 2010). Certainly, these astonishing properties of *B. monnieri* extract and its constituents could be exploited for ameliorating neurodegenerative disorders associated with the overwhelming oxidative stress as well as AD (Limpeanchob *et al.* 2008).

Anti-arthritic activities

Recent study using a type II collagen-induced arthritis rat model has revealed *B. monnieri* potential to treat rheumatoid arthritis (Viji *et al.* 2010b). Antiarthritic potential of plant extract has been evaluated after inducing arthritis in male Wistar rats by immunization with bovine type II collagen in complete Freund's adjuvant. *B. monnieri* extract have shown beneficial effects on several selected parameters *viz.* paw swelling, arthritic index, cyclooxygenase, lipoxygenase, myeloperoxidase and serum anti-collagen immunoglobulins (IgG and IgM) levels in Wistar rats (Viji *et al.* 2010b). The ability of *B. monnieri* in alleviating lysosomal instability in adjuvant-induced arthritis in rats has been reported (Vijayan *et al.* 2010). It has been suggested that *B. monnieri* extract may stabilize lysosomal membranes and decrease the spread of inflammation.

Anti-tumor/cytotoxic/chemopreventive activities

Anti-tumor activity is one of the most important activities of *B. monnieri* plant that has been recognized recently (Rohini and Devi 2008; Peng *et al.* 2010). The ethanolic extract of *B. monnieri* can induce cell death by apoptosis in mouse S-180 cells (Rohini and Devi 2008). Peng *et al.* (2010) reported anti-tumor activities of *B. monnieri* extract and four different fractions prepared in petroleum ether, chloroform, ethyl acetate and butanol. Dammarane triterpene saponins *viz.*, bacopasides E and VII present in the butanol fraction of *B. monnieri* have potential anti-tumor and cytotoxic effects against human tumor cell lines (MDA-MB-231, SHG-44, HCT-8, A-549 and PC-3M). Anti-tumor effects were assessed by performing a 3-(4,5,-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide assay *in vitro* and in mouse implanted with sarcoma S180 *in vivo* (Peng *et al*. 2010). Still, the mechanism of action of these bacopasides remains to be elucidated. Previously, Pawar *et al.* (2007) isolated two new dammarane glycosides, the 20-deoxy derivatives of jujubogenin and pseudojujubogenin along with 8 new compounds and tested them for cytotoxic, antileishmanial, antimalarial, antioxidant, and anti-inflammatory activities. Not all, but some of these compounds demonstrated mild to moderate cytotoxic activity against

non-cancerous kidney cell lines. Bacoside-A has been quite effective in preventing DEN-induced hepatocellular carcinoma by quenching LPO, enhancing antioxidant status, and protecting endogenous enzymatic and non-enzymatic antioxidant activity (Janani *et al.* 2010). Thus, the chemopreventive properties of the bacoside-A would be an effective alternative approach to control hepatocarcinogenesis.

Hepatoprotective and cardio-protective activities

Several reports have described the hepatoprotective properties of *B. monnieri* and its major constituent bacoside-A against liver and kidney injury in rats induced by selected compounds. Bacoside-A has been found to be a highly effective hepatoprotective agent against liver injury induced using D-GalN in rats (Sumathi and Nangbri 2008). With the application of bacoside-A in D-GalN induced rats, a sharp decrease was observed in the activities of enzymes, serum alanine transaminase, aspartate transaminase, alkaline phosphatase, g-glutamyl transferase, LDH and 50nucleotidase. Bacoside-A, however, helped to restore normal levels of vitamins C and E in the liver and plasma of D-GalN-induced rats (Sumathi and Nangbri 2008). Very similar hepatoprotective effects of *B. monnieri* leaf extract against morphine-induced liver and kidney toxicity in rats have also been reported (Sumathi and Devraj 2009). To assess the hepatoprotective effects, these authors studied the histopathological changes of liver and kidney as well as the activities of several relevant enzymes after administration of bacoside-A in morphine-induced rats. Pretreatment of bacoside-A prevents an elevation of LPO and activity of serum marker enzymes and maintains the antioxidant status during DEN-induced hepatotoxicity in the rats (Janani *et al.* 2009). The notorious carcinogen DEN is reported to induce oxidative stress and cellular injury causing generation of ROS. In addition to its hepatoprotective properties, *B. monnieri* has also demonstrated cardioprotective effects in rat hearts following ischaemia-reperfusion (I-R) injury perfused in a Langendorff model (Mohanty *et al.* 2010). Cardioprotective effects of *B. monnieri* have been validated after measurement of activity of myocardial creatine phosphokinase and histopathological examination in the experimental model of ischaemia-reperfusion injury (Mohanty *et al.* 2010). These studies provide a basis for the alleged therapeutic use of *B. monnieri* and bacoside-A in liver and kidney injury as well as ischaemic heart diseases.

Other useful bioactivities

Besides the above important bioactivities, some other useful bioactivities of *B. monnieri* have also been investigated. Bacosine, a triterpene isolated from the ethyl acetate fraction of the ethanolic extract of *B. monnieri*, demonstrated antihyperglycemic activity in diabetic rats (Ghosh *et al*. 2011). Bacosine might have insulin-like activity and its antihyperglycemic effect might be due to an increase in peripheral glucose consumption as well as protection against oxidative damage in alloxanized diabetes (Ghosh *et al*. 2011). Sharath *et al*. (2010) described the wound-healing properties of the methanolic extract of *B. monnieri* and bacoside-A in excision, incision and dead space wounds on Swiss albino rats. The wound-healing activity of bacoside-A has been more effective in various wound models compared to the standard skin ointment Nitrofurazone. The effect of *B. monnieri* in the acquisition and expression of morphine tolerance in mice has been reported (Rauf *et al*. 2010). Acute and chronic administration of 5, 10 and 15 mg/kg *n*-butanolic extract of *B. monnieri* resulted in a significant decrease both in expression and development of tolerance to morphine analgesia in mice. Also, *B. monnieri* enhanced the antinociceptive effect of morphine in intolerant animals.

CONCLUSION

Pharmacological and medicinal significance of *Bacopa monnieri* (Brahmi) is rapidly increasing. In this article we have discussed many newer useful bioactivities of *B. monnieri* and its major chemical constituents. The plant of *B. monnieri* has been in the center of researches since very long time owing to its tremendous pharmaco-active potential. Since ancient times *B. monnieri* has been an integral part of Indian and many other traditional medicinal systems used as nerve tonic, memory-enhancing, anti-inflammatory, analgesic, antipyretic, sedative, antiepileptic and antidote to snake venom. In the past few years researches conducted on *B. monnieri* and its major constituents have elucidated many important bioactivities like antiamneatic, anti-inflammatory, neuroprotective/ antioxidant, hepatoprotective, antiepileptic, cardio protective, nootropic, anti-aging, memory enhancing, anti-arthritic and anti-tumor/cytotoxic/chemopreventive activities. These new developments in pharmacological and medicinal research has evoked considerable interest in *B. monnieri* for its future development as potential drugs for AD and amnesia, respectively for which currently limited or no treatment is available. Concomitantly, significant progress has been made towards elucidation of the mechanism of action of *B. monnieri* extracts and its active ingredients. Perhaps more efforts are still needed to be devoted for deeper understanding of mechanism of action as in case of Anti-Alzheimer, anti-tumor and chemopreventive properties of this plant. It is important to mention that until now most of the studies were aimed to investigate bioactivities of either *B. monnieri* leaf/whole plant extract or active constituent bacosides; however, no study were undertaken to evaluate the efficacy of *B. monnieri* if given together with other plants. Therefore, it is important to initiate studies to investigate if *B. monnieri* extract and its active constituents chronically exert more potent effects in combination with extracts of plants with similar medicinal value in the experimental models. Surprisingly, herbal formulations/medicines are completely not devoid of side effects/ serious clinical consequences. Therefore complete clinical investigations of the herbal formulations must be encouraged in order to evidence any possible side effects.

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