IJPSR (2019), Volume 10, Issue 3 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 30 April 2018; received in revised form, 15 July 2018; accepted, 31 August 2018; published 01 March 2019

PHYTOCHEMICAL AND PHARMACOLOGICAL PROFILE OF *BACOPA MONNIERI* - AN ETHNOMEDICINAL PLANT

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Keywords:

Medicinal plants, *Bacopa monnieri*, Pharmacological activity, Tissue culture

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ABSTRACT: In recent times, the use of herbal products has increased tremendously in the developing as well as in developed countries. *Bacopa monnieri* is one of the most important medicinal plant that has been consumed for thousands of year as a memory enhancing, anti-inflammatory, analgesic, antipyretic, sedative and anti-epileptic agent. For many years, a lot of commercial and medicinal researches have been focusing their resources on this plant. The plant has been known to possess various activities such as, anti-bacterial, anti-fungal, anti-cancer, anti-oxidant, anti-inflammatory, anti-hyperglycemic, anti-depressant, anti-epileptic, memory enhancer, anti-ulcer, hepatoprotective, analgesic, anti-diarrheal, anti-hypertensive, anti-toxicity *etc*. Therefore step should be taken for its sustainable use and conservation. This review describes the phytoconstituents, traditional uses, and pharmacological activities of *Bacopa monnieri*. In brief, the biotechnological applications such as tissue culture, elicitation, genetic transformation for the advancement of this plant and its active components production have also been described.

INTRODUCTION: In human society from time immemorial medicinal plants have played an important role in the prevention and control of diseases. It has been confirmed by WHO that herbal medicines serve the health needs of about 80 percent of the world's population; especially for millions of people in the vast rural areas of developing countries. Development of science and technology and the side effect of modern medicine has resulted in increased and effective usage of plant-based medicines. Awareness of medicinal plants usage is a result of the many years of struggles against illnesses due to which man learned to pursue drugs in barks, seeds, fruit bodies, and other parts of the plants.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.10(3).1001-13

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.10(3).1001-13

In almost all the traditional medical systems, the medicinal plants play a major role and constitute their backbone. India has a rich heritage of traditional medicine and traditional health care system.

***Bacopa monnieri* L.:** *Bacopa monnieri* is an important medicinal plant of the family Scrophulariaceae used in traditional medicine to treat various nervous disorders and for promoting memory and intellect. This medicinal plant is locally known as Brahmi. It is known as a memory enhancer, and many preparations of Brahmi are now commercially available in the market. Some important medicinal uses of the plant *B. monnieri* for treatment of different diseases and the traditional formulation are given in **Table 1**.

Habitat, Geographical Distribution, and Ethnomedical Description: *Bacopa monnieri* is a perennial, creeping herb whose habitat includes wetlands and muddy shores. The leaves are succulent, relatively thick, oblanceolate and are

arranged oppositely on the stem. It is commonly found in wet marshy and damp places throughout India. It is also found in Nepal, Sri Lanka, China, Taiwan, Vietnam, and some southern states of USA [1]. *Bacopa monnieri* is a major constituent of the traditional Medhya Rasayana (Medhya - intelligence, Rasayana-rejuvenators) formulations, which are considered to facilitate learning and improve memory. In traditional medicine, the plant is used as a nervine tonic, diuretic, and to treat asthma, epilepsy, insanity, and hoarseness [2].

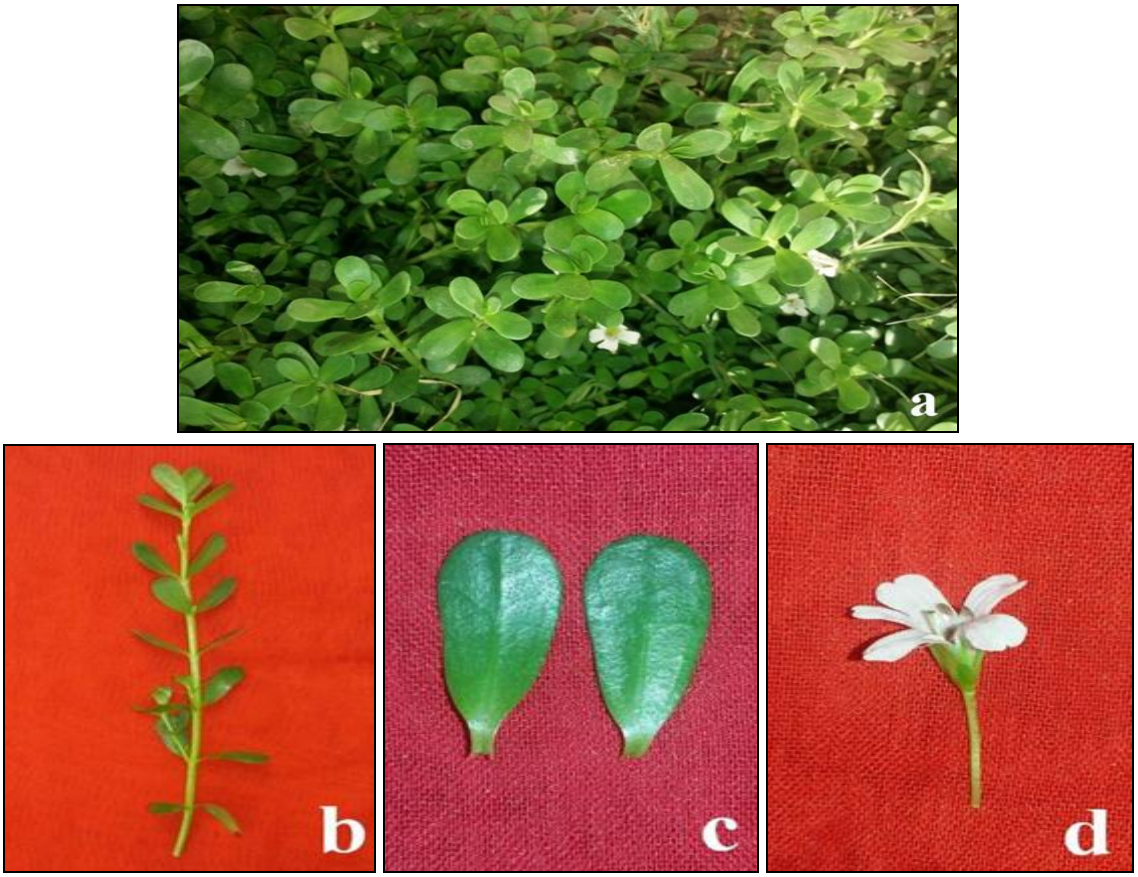

FIG. 1: *BACOPA MONNIERI* (a) PLANT IN NATURAL HABITAT, (b) TWIG, (c) LEAF, (d) FLOWER

TABLE 1: IMPORTANT ETHNO MEDICINAL USE OF *BACOPA MONNIERI* L.

Medicinal Use	Traditional Formulation	Reference
Memory enhancer, Cardiac tonic	Plant juice is given orally as a diuretic, cardiac tonic and memory enhancer	3, 4
Memory enhancer	Mix *Bacopa monnieri* powder with *Saraca indica* bark powder in equal amounts. Administer 5g of this formulation to the patient every day	5
Epilepsy, bronchial and diarrheal ailments	Leave juice is used as a remedy of epilepsy, bronchial and diarrheal ailments	6
Malaria	Fresh plant material is crushed, and the extract is given orally	7
Hair fall	Plant juice is given as hair tonic especially in thinning and falling hairs	3
	Juice obtained from a mixture of crushed leaves, roots and white flowers is taken orally	8
Headache	Juice obtained from a mixture of crushed leaves, roots and white flowers is taken orally	8
Snakebite	Plant Juice mixed with castor oil is applied externally to treat. Leaf powder decoction mixed with hot cow's milk taken orally	9

Propagation: The plant *Bacopa monnieri* L. is not capable of producing seeds and well registered for their regeneration using their mature stem cuttings. Sandy soil/black soil is more suitable for this plant to regenerate in a wide range. Stem cuttings used for regeneration requires to present 4-6 nodes. In the initial stage of its cultivation, it requires a moderate irrigation. Each one mature nodular part

of this plant is efficiently producing new root and shoot system in a favorable environmental condition which further support to develop its new individuals like their parental ones. After establishment, plant spread rapidly around the sites of its cultivation [10].

Phytochemistry: The pharmacological properties of *Bacopa monnieri* were studied extensively, and the activities were attributed mainly due to the presence of characteristic saponins called "bacosides." Bacosides are a complex mixture of structurally closely related compounds, glycosides of either jujubogenin or pseudojujubogenin [11]. Bacosides comprise a family of 12 known analogs. Major bacopasaponins were bacosides A3, bacopaside II, bacopaside I, bacopaside X, bacopasaponin C, bacopaside N2 and the minor components were bacopasaponin F, bacopasaponin E, bacopaside N1 bacopaside III, bacopaside IV and bacon aside V [12].

Four cucurbitacins, bacitracin A-D, a known cytotoxic, cucurbitacin E and three phenylethanoid glycosides, monnieraside I, III and plant inside B were isolated from the aerial part of *Bacopa monnieri* [13]. Two common flavonoids, luteolin, and apigenin, have also been detected in *B. monnieri* [14]. A simple reversed-phase HPLC method has been developed and successfully analyzed for the simultaneous determination of all 12 *Bacopa* saponins present in the extracts of *B. monnieri* [12].

Pharmacological Activity: Demands of the scientific community have necessitated experimental evidence to underline the medicinal importance of Bacopa monnieri further. Taking a cue from the traditional ethnomedicinal use of this highly valuable plant, scientific studies have been designed and conducted to pharmacologically validate these claims. *Bacopa monnieri* has been found to possess significant anti-depressant activity, anti-anxiety, anti-convulsant, anti-cancer, anti-inflammatory, antioxidant, anti-bacterial, anti-fungal, anti-ulcer, anti-diarrheal, anti-hypertensive, analgesic and anti-toxicity activity.

Neuroprotective Role of *Bacopa monnieri*: Neuro-degenerative disease (ND) such as Alzheimer's disease, Parkinson's disease, and prion disease affect the neurons in the human brain. These are chronic and incurable conditions which mostly affect the aging population. They cause progressive deterioration of neurons, sensory information transmission disruption, and movement control [15]. Until now ND has no cure and represent a high cost for the health system and patients families. Alzheimer's disease is an age-associated, irreversible, progressive neurodegenerative disease, characterized by severe memory loss, behavioral changes, and a notable decline in cognitive function. Management of the neurodegenerative disorder like Alzheimer's disease and increasing memory enhancement power is considered as one of the greatest challenges. *Bacopa monnieri* as one of the three top herbs in Alzheimer's disease has been suggested [16]. Treating patients with Brahmi extract may be an alternative direction for ameliorating neurodegenerative disorders associated with the overwhelming oxidative stress as well as Alzheimer's disease [17]. *Bacopa monnieri* extract shows a significant neuroprotective effect against Alzheimer's disease by stabilizing the structural and functional integrity of the membrane [18].

The bacoside establish a healthy anti-oxidant environment in liver and brain. The neuroprotective activity is attributed to the regulation of mRNA translation & surface expression of neuroreceptors such as AMPAR, NMDAR, and GABAR in the various parts of the brain [19].

Neurodegenerative Parkinson's disease (PD) is associated with aggregation of protein alpha-synuclein and selective death of dopaminergic neurons, thereby leading to cognitive and motor impairment in patients. *B. monnieri* reduces alpha-synuclein aggregation, prevents dopaminergic neurodegeneration and restores the lipid content in two different strains of nematodes *C. elegans*; a transgenic model expressing "human" alpha-synuclein, and a pharmacological model expressing green fluorescent protein (GFP) specifically in the dopaminergic neurons treated with selective catecholaminergic neurotoxin 6-hydroxydopamine (6-OHDA), thereby proving its potential as a possible anti-parkinsonian agent [20]. *Bacopa monnieri* showed a better response than levodopa in case of rotenone-induced rodent model of Parkinson disease. Thus, the *B. monnieri* may provide a platform for future drug discoveries and novel treatment strategies in PD and can act as anti-parkinsonian agent [21].

Prions are transmissible pathogens that cause a group of fatal neurodegenerative which may be genetic, infectious of sporadic in origin. In the human, it is responsible for transmissible spongiform encephalopathies (TSE), fatal diseases characterized by loss of motor control, dementia, and paralysis. The prion hypothesis proposes that the scrapie form of prion protein (PrP^{sc}) is the misfolded form of native protein (PrP^{c}) [22]. The misfolded protein can induce conformational changes in the native protein causing deposition of insoluble toxic aggregates of fibrillar protein amyloidosis. The membrane interaction affects the misfolding pathways of amyloidogenic protein fibrillation. Bacoside A has an anti-amyloid property. It accelerated fibril formation in the presence of lipid bilayer which reduced the concentration of membrane active prefibrillar species of prion fragment. The induction of fibril formation and corresponding inhibition of membrane interaction are likely factors for ameliorating amyloid protein toxicity by BacosideA [23].

Memory Enhancer: Many researchers are in the direction of developing a drug, or finding a source of natural compounds that might improve our capacity to remember. Traditional knowledge says that *Bacopa monnieri* has memory-enhancing the property and such traditional beliefs have now been scientifically tested by some researcher [24]. Now it is a well-known fact that *Bacopa monnieri* enhances memory. Improvement in spatial learning performance and enhanced memory retention in neonatal rat treated with an extract of *Bacopa monnieri* was observed [25]. It was observed that the animals treated with oral administration of *B. monnieri* (100 and 200 mg/kg) show significant protection against $AlCl_3$-induced memory impairment. Further, the neuroprotective effect of *B. monnieri* (100 and 200 mg/kg) was significantly improved when supplemented with rivastigmine (5 mg/kg) [26].

A study on human memory in adults (aged between 40 and 65 years) show a significant effect of the *Bacopa monnieri* on a test for the retention of new information. Follow-up tests showed that the rate of learning was unaffected, suggesting that Brahmi decreases the rate of forgetting of newly acquired information [27]. Role of *Bacopa monnieri* as a cognitive enhancer and use of *Bacopa monnieri* in polyherbal preparation for improving cognitive and behavioral outcome on child and adolescent have been suggested [28]. Oral administration of *Bacopa monnieri* extract to Adult male Wistar rats for 60 days was found to be associated with enhanced learning dependent hippocampal long-term synaptic potentiation which plays a critical role in learning and memory [29].

Anti-depressant and Anti-anxiety activity: Psychiatric disorder is a life-threatening illness that affects millions of people worldwide. Depression can lead to suicide. Studies carried out by researcher suggest the antidepressant property of *Bacopa monnieri* [30, 31, 32, 33, 34]. Significantly reduced escape latency and plasma corticosterone level along with the significant restoration of body weight among the stressed rats has been observed on acute treatment with *Bacopa monnieri* extract. Such properties of *Bacopa* extract coincides with the effects of well-accepted antidepressant drug fluoxetine hydrochloride and prominently forecast the antidepressant property of *Bacopa monnieri* in stress-related neuropsychiatric disorders [35]. Different doses of Brahmi exhibited antidepressant activity in mice in forced swimming test (FST), and shock-induced depression (SID) models [32].

Anti-depressant property comparable with standard anti-depressant drug imipramine of the alcoholic extract of *Bacopa monnieri* in tail suspension test (TST) and forced swim test (FST) mice model has been reported [33]. Similarly, anti-depressant - like effect of methanolic extract in all the classic models such as forced swimming test (FST), measurement of locomotor activity test (MLAT) and tail suspension test (TST) was reported, where it was found to possess significant antidepressant-like activity comparable to the standard drug imipramine hydrochloride [34]. The antidepressant-like the action of bacon aside I (BS I) was investigated using a mouse model of behavioral deficits induced by chronic unpredictable mild stress (CUMS) for 5 weeks to induce depression. The oral administration of BS ameliorated CUMS-induced depression-like behaviors in mice reversed the increased level of plasma corticosterone and decreased mRNA and protein expressions of glucocorticoid receptor induced by CUMS exposure, indicating that hypothalamic-pituitary-

adrenal (HPA) axis hyperactivity of CUMS-exposed mice was restored by BS-I treatment [36].

Anxiety is the displeasing feeling of fear and concern. When anxiety becomes excessive, it may be considered an anxiety disorder. Anti-anxiety property of *Bacopa monnieri* has been reported. *Bacopa* extract produced a dose-related anxiolytic activity in a rat model of clinical anxiety, qualitatively comparable to that of lorazepam, in all the test parameters. The advantage of *Bacopa monnieri* over the widely used benzodiazepine anxiolytics lies in the fact that it promotes cognition unlike the amnesic action of the latter [37].

Anti-convulsant/Anti-epileptic Activity: Epilepsy is a neuropsychological disorder, caused due to over discharge of neurotransmitter substances, which affects an estimated 7 million people in India and 50 million people worldwide. Several, medicinal plants including *Bacopa monnieri* have been studied for anticonvulsant activity [38]. The ethanolic extract of *Bacopa monnieri* leaves administered at 50 mg/kg orally produced significant anticonvulsant activity for all the different models studied with a mechanism of action similar to that of benzodiazepines (GABA agonist) [39]. The anticonvulsant activity of two polyherbal formulations of *B. monnieri, i.e.* Brahmi Ghrita (BG) and Saraswatarishta (SW) against seizures induced by maximal electroshock (MES) in rats is also reported [40]. The anticonvulsant activity of alcoholic extract of *Bacopa monnieri* in albino rats, using pentylenetetrazole (PTZ) models have also been reported and suggested that the anticonvulsant activity of *Bacopa monnieri* may involve glutaminergic transmission or sodium channel blockage [41].

Therapeutic Effects of *Bacopa monnieri*: The plant extracts have become interesting candidates as therapeutic agents due to their anti-oxidant, anti-inflammatory properties.

Anti-cancer Activity: Cancer remains as one of the most common causes of mortality worldwide. Cancer chemoprevention by natural products is well accepted nowadays. Phytosterols are natural products, showing anticancer activity, besides other activities. Stigmasterol, a phytosterol isolated from aerial parts of *Bacopa monnieri* show anticancer activity against ehrlich ascites carcinoma (EAC) in Swiss albino mice. Stigmasterol decreased tumor volume, packed cell volume and viable cell count, and increased mean survival time thereby increasing the life span of EAC tumor-bearing mice. The antitumor activity of stigmasterol might be mediated through the activation of protein phosphatase 2A by ceramide causing apoptosis [42]. Cytotoxic activity of ethanolic and dichloromethane (DCM) extract of *Bacopa monnieri* against MCF-7, and MDA-MB 231 cell line have been observed. Cytotoxic activity in DCM fraction in both the cell lines may be due to the presence of cucurbitacins and betulinic acid in DCM fraction [43].

The anti-cancer activity of the ethanolic extract of *Bacopa monnieri* against human breast cancer cell line (MDA-MB-468) is may be due to the synergistic effect of the secondary metabolites present in the extract [44]. Study on the effect of *Bacopa monnieri* extract on gene expression in SH-SY5Y human neuroblastoma cells have revealed that several genes are regulated by *Bacopa monnieri* including genes for regulation of mRNA translation, and transmembrane transport, responses to oxidative stress and protein misfolding thus suggesting that *Bacopa monnieri* may protect against brain damage and improve brain development [45]. Increased permeability by over-expression of AQP 1, a transmembrane protein responsible for water transport is a distinct feature of many human cancer cells including those of breast, colon, and prostate. Bacopaside II inhibits the activity of aquaporins AQP 1, thus reducing endothelial cell migration and induces apoptosis [46].

Anti-hyperglycemic Activity: Methanolic extract of the plant possess significant anti-hyperglycemic potential. In OGTT (Oral glucose tolerance tests) conducted with glucose-challenged mice, the extract, administered at four doses of 50, 100, 200 and 400 mg per kg body weight, dose-dependently and significantly inhibited the increase in serum glucose concentrations, respectively, by 33.3, 34.2, 42.1 and 44.2% [47]. The anti-diabetic potential of *Bacopa monnieri* in streptozotocin-induced diabetic rats was reported. The elevated levels of blood glucose and glycated hemoglobin, whereas the reduced level of hemoglobin, total white blood cell count and platelet count in diabetic rats were normalized on treatment with Brahmi (500 mg/kg

b.w.) and were comparable with that of the glibenclamide (600 µg/kg b.w./day) treated rats [48]. This study shows that *Bacopa monnieri* possesses significant antihyperglycaemic effects in streptozotocin-induced diabetic rats. An active compound (BM-1) isolated from leaves of *Bacopa monnieri* causes a significant fall in serum cholesterol, triglycerides, LDL and VLDL in normal rats. In diabetic rat BM-1 also decreased the raised levels of serum cholesterol, triglycerides, LDL and VLDL but increased HDL cholesterol. It shows the possible use of *Bacopa monnieri* extract to treat hyperlipidemia in diabetics [49].

Anti-inflammatory Activity: *Bacopa monnieri* possesses significant anti-inflammatory activity that may well be relevant to its effectiveness in the healing of various inflammatory conditions in traditional medicine. The ethanol extract selectively inhibited prostaglandin E(2)-induced inflammation [50]. The methanolic and aqueous extract of *Bacopa monnieri* caused a significant reduction in the edema paw volume. However, no such inflammatory reduction was observed in petroleum ether, and hexane extracts [51]. The anti-inflammatory activity of *Bacopa monnieri* is due to the triterpenoid and bacoside present in plant [52]. Significant anti-inflammatory activities of methanolic extract have also been observed both in the carrageenan and histamine-induced edema test models in rats [53].

Anti-oxidant Activity: Numerous studies have been carried out have shown the antioxidant potential of *Bacopa monnieri* extract. It was observed that the methanol and aqueous extracts show maximum antioxidant activity. The anti-oxidant activity of petroleum ether and hexane extracts was also observed. Methanol, aqueous, petroleum ether and hexane extracts reduce superoxide dismutase (SOD) levels with 65.68% and 62.34%, 56.67% and 54.18% inhibition and showed antioxidant activity [51]. *B. monnieri* extracts exhibit antioxidant activity in dose-dependent manner [54]. The anti-oxidant potential in streptozotocin-induced diabetic rats was reported [48]. The elevated levels of lipid peroxidation in the diabetic rats were normalized on treatment with *Bacopa* (500 mg/kg b.w.). It was observed that the stigmasterol, a phytosterol isolated from aerial parts of *Bacopa monnieri* decreased the levels of lipid peroxidation and increased the levels of glutathione, superoxide dismutase and catalase in the liver of ehrlich ascites carcinoma (EAC) bearing mice [42].

Anti-bacterial Activity: The susceptibility of the bacteria to the crude extracts varied according to the microorganism and extracting solvent. Methanolic extracts of *Bacopa monnieri* was found to possess maximum inhibitory effects against both gram positive and gram negative organisms tested compared to chloroform and ethanolic extract. *Bacillus pumilis* was found to be highly sensitive in all the extracts whereas *Salmonella typhe* was found to be highly resistant [55]. Methanol, hexane and petroleum ether extracts showed antimicrobial activity against *E. coli*, *Salmonella typhimurium*, *Staphylococcus aureus*, and *Saccharomyces cerevisiae*. However, aqueous extract showed no activity against any of the microorganism [51]. Ethanol and dichloromethane extracts of *B. monnieri* possess significant anti-microbial activity towards the bacterial species *S. pneumonia, E. faecalis, P. mirabilis,* and *K. pneumoniae*. The study shows that ethanol and dichloromethane extracts of *B. monnieri* can be used as a potential source of antimicrobial agents [56]. Antimicrobial activity of *B. monnieri* ethanol extracts against *Providencia pseudo mallaei* was also reported [57].

Anti-fungal Activity: Methanolic extract showed significant antifungal activity against *Candida albicans* and *Aspergillus niger* [58]. The phytochemicals betulinic acid, wogonin and oroxindin isolated from the aerial parts of *Bacopa monnieri* possess significant antifungal activity against the two fungi *Alternaria alternate* and *Fusarium fusiformis* [59]. *B. monnieri* whole plant extracts in methanol and ethanol: methanol solvent possesses better *in-vitro* anti-fungal activity against *A. niger*, *Candida albicans* and *Malassezia furfur*as compared with the extract in other solvents. The GC-MS analysis confirms the presence of the various phytochemicals contributing for the antifungal activity [60]. *Bacopa monnieri* also exhibits antifungal activity against dermatophytic fungi. Both aqueous and ethanolic extract of *B. monnieri* exhibited a very good anti-fungal activity against the dermatophyte fungi namely *Aspergillus niger, Aspergillus flavus, Trichophyton rubrum* and *Microsporum* [61].

Anti-ulcer Activity: Methanolic extract of *Bacopa monnieri* (BME) standardized to bacoside-A content (percentage-38.0 ± 0.9), when given in the dose of 10-50 mg/kg, twice daily for 5 days, showed dose-dependent anti-ulcerogenic on various gastric ulcer models induced by ethanol, aspirin, 2h cold restraint stress and 4h pylorus ligation. BME in the dose of 20 mg/kg, given for 10 days, twice daily showed healing effects against 50% acetic acid-induced gastric ulcers [62]. Significant anti-ulcer and ulcer-healing activities of *Bacopa monnieri* extract (50 mg/kg) in normal and NIDDM rats were observed. Further, the ulcer protective effects of *B. monnieri* extract was more pronounced in non-diabetic. The anti-ulcer and ulcer-healing activities of extract may be due to their effects on the various mucosal offensive and defensive factors [63].

Hepatoprotective Activity: Ethanolic extract of *Bacopa monnieri* (EBM) at the dose of 300 mg/kg/day produced a significant hepatoprotective effect in the paracetamol-induced hepatotoxic rats by decreasing the activity of serum enzymes serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase ALP and bilirubin. As *B. monnieri* contains large amounts of saponins, it may be suspected that the hepatoprotective activity may be due to the presence of saponins in the extract [64].

A similar finding was also observed for ethyl acetate fraction (EAF) and *n*-butanol fraction (NBF) of ethanolic extract of *Bacopa monnieri* on ethanol-induced hepatotoxicity in rats [65]. The hepato-protective function of the ethanolic extracts of *in-vitro* grown *B. monnieri* containing bacoside-A was observed in carbon tetrachloride (CCl_4) - intoxicated albino mice. Administration of *Bacopa* ethanolic extract from either source (*in-vitro* or natural) markedly prevented CCl_4-induced hepatic damage in albino mice model as indicated by the levels of serum markers (SGPT, SGOT, and bilirubin) of hepatic damage [66].

Anti-diarrheal Activity: The anti-diarrheal activity of ethanolic extract of *B. monnieri* on Castor oil induced diarrheal mice was observed. The result showed that extract reduces the mean number of defecation which was 35.42% and 47.92% at the doses of 250 mg/kg and 500 mg/kg respectively. The latent period for the extract treated group was increased as compared to the control group. Tannins and phenolics present in the plant extract might be responsible for the anti-diarrhoeal activity of *B. monnieri* ethanol extract [67].

Anti-hypertensive Activity: *Bacopa monnieri* (Brahmi) provides traditional cognitive treatments possibly reflecting improved cerebral hemo-dynamics. However, little is known about the cardiovascular actions of Brahmi. Intravenous Brahmi extract (20-60 mg/kg) decreased systolic and diastolic pressures without affecting heart rate in anesthetized rats. Brahmi reduces blood pressure partly via releasing nitric oxide from the endothelium, with additional actions on vascular smooth muscle Ca^{2+} homeostasis [68]. A clear, prompt and constant anti-hypertensive action of *Bacopa* and at least as effective as the clinically used captopril has been observed [69]. Recently, the cardioprotectant activity of *Bacopa* extract was studied against ischemia/reperfusion injury using cardiac function and coronary flow as end-points. It was revealed that *Bacopa monnieri* improves myocardial function following ischemia/ reperfusion injury through the recovery of coronary blood flow, contractile force and a decrease in infarct size [70]. Thus, this extract or an active ingredient may lead to an efficacious and novel treatment for primary human hypertension.

Anti-toxicity Activity: Addictive drugs when interacting with brain systems affect physiological stimuli such as water, food and social interaction, which are critical for survival [71]. The pretreatment with methanolic BM extract protected morphine-induced reduction in body weight. The protective effect of *Bacopa monnieri* against opioid-induced body weight loss might be due to its adaptogenic effect mediated by the hypothalamic-pituitary axis. The pretreatment with *Bacopa monnieri* restore the elevation of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and creatinine and protect liver and kidneys from the toxicological influence of morphine and street heroin. Thus, *Bacopa monnieri* due to its content of bacoside-A which possessed strong antioxidant potential may provide a beneficial herbal remedy for the management of opioid-related hepatotoxicity and nephrotoxicity [72].

Regeneration Studies and *in-vitro* Production of Bacosides in *Bacopa monnieri*: Plant tissue culture techniques offer an integrated approach for the production of standardized quality phytopharmaceutical through mass-production of consistent plant material for physiological characterization and analysis of active ingredients [73]. Some studies have been conducted utilizing tissue cultures and other biotechniques for plantlet regeneration and bacoside production in agarified and liquid culture medium using different explants. Adventitious shoot buds were induced from leaf and stem explants of *Bacopa monnieri* on Murashige and Skoog (MS) medium supplemented with benzyladenine. Further, it was observed that the source of the explants as well as different gelling agents in the medium influence shoot induction and eventual shoot growth in *B. monnieri* shoot culture [74].

A maximum number of shoots per ex-plant, higher explants response irrespective of the type of explants and higher shoot length were observed in MS medium containing BAP (2.5 mg l^{-1}) and IAA (0.01 mg l^{-1}) with 3 % sucrose [75]. MS media was found to be superior over B5 media for *in-vitro* shoot multiplication and plantlet regeneration of *B. monnieri* [76]. MS basal + 0.5 mg/l IAA and MS basal + 0.5 mg/l NAA was found as best culture medium for culture initiation and axillary shoot proliferation. Compact globular callus was best initiated and proliferated on MS+0.5 mg/l BAP+1 mg/l 2,4 D and best regeneration on MS + 1.0 mg/l BAP + 1 mg/l IAA [77].

The medicinal plants exhibit seasonal variations in their active component quality as well as quality. Seasonal variations in harvest index and total bacoside contents were observed in wild populations of *Bacopa monnieri*. Principal component analysis showed that samples of summer were positively correlated with both the harvest index and total bacoside content thus suggesting an appropriate time for the harvest [78]. The efficient multiple shoots regeneration system developed may help in mass production of this most valuable plant and it will help to explore a suitable culture condition for large scale propagation for improving the production of commercially and therapeutically important bacosides all-round the year irrespective of season.

Enhanced Secondary Metabolite Production in *Bacopa monnieri* by Elicitation: Elicitation is one of the most effective techniques currently used for improving the biotechnological production of secondary metabolites. The effect of different abiotic elicitors such as salicylic acid, jasmonic acid and copper sulphate ($CuSO_4$) on the stimulation of biomass and bacoside production in *in-vitro Bacopa monnieri* culture has been studied [79, 80]. The shoot cultures treated with 45 mg L^{-1} of $CuSO_4$ enhanced bacoside content by 1.42-fold than in control cultures [79]. About two and three-fold higher quantity of bacoside A production in plant culture on elicitation with 50 µM methyl jasmonate and 50 µM salicylic acid respectively have been reported.

In plant culture highest accumulation *i.e.*, 59.18 mg/g DW (dry weight) of bacoside A_3 (3.5-fold higher), 95.30 mg/g DW of bacopaside II (5.2-fold higher), 46.11 mg/g DW of Jujubogenin isomer of bacopasaponin C (4.8-fold higher) and 68.16 mg/g DW of bacopasaponin C (5.9-fold higher), altogether accounting for the production of 269.71 mg/g DW (almost fivefold higher) of bacoside A in a combination of 25 µM MJ + 25 µM SA treated for 3 weeks duration has been reported [80]. These studies indicate the effectiveness of abiotic elicitation on bacoside production in *in-vitro* shoot cultures of this medicinally important herb known for its memory-enhancing properties. Thus the protocol formulated can be used as an efficient alternative for mass production of whole plants with increased metabolite content.

Microbial Modulation and Bacoside Production: Microbes associated with plant play a very important role in plant growth and development, and phyto- disease management. These microbial interactions with plant also increase the resistance against abiotic and biotic stress. In a study, rhizospheric microbe, namely *Bacillus megaterium*, *Glomus intraradices*, *Trichoderma harzianum* were evaluated for bacoside content enhancement in *B. monnieri* var. CIM-Jagriti. The combined treatment of *B. megaterium* and *T. harzianum* showed significant enhancement (1.40-fold) in total bacoside contents (active plant molecule) as compared to control [81]. In *Bacopa* plants treated with microbes as bio-inoculants *Pseudomonas monteilii, Cedecea davisae, Cronobacter*

dublinensis, Advenella spp. and *P. aeruginosa*, there was a significant enhancement in the biomass and secondary metabolite content of *Bacopa monnieri.* A significant improvement in nutrients (NPK) concentration was also noticed in bioinoculants treated plants compared to the un-inoculated ones [82]. The co-cultivation of *B. monnieri* with axenically cultivated root endophyte *Piriformospora indica* resulted in growth promotion, increase in bacoside content, antioxidant activity and nuclear hypertrophy of this medicinal plant [83]. Chitinolytic microbes *viz*., *Chitiniphilus* sp. MTN22 and *Streptomyces* sp. MTN14 singly as well as in combination modulated the biosynthetic pathway of bacoside A and systemic defense mechanism against *Meloidogyne incognita* in *Bacopa monnieri.* These microbes not only augmented bacoside A production (1.5 fold) but also strengthened host resistance *via* enhancement in chlorophyll a, defense enzymes and phenolic compounds like gallic acid, syringic acid, ferulic acid and cinnamic acid [84].

Molecular Studies on Genetic Diversity: The information of genetic similarities and diversity among Brahmi accessions is necessary for their conservation and breeding programs. Genetic variation among different accessions of *B. monnieri* collected from different locations of Southern India and Central India has been evaluated using RAPD and inter-simple sequence repeats (ISSR) marker systems [85, 86]. RAPD analysis showed a low level of genetic diversity in 24 geographically distinct accessions of *Bacopa monnieri* [87]. A RAPD based SCAR marker system has also been developed to identify *B. monnieri* from its adulterant candidates namely *Centella asiatica*, *Eclipta alba,* and *Malva rotundifolia* [88].

In another study, quantification of the major bioactive principle of *B. monnieri*, bacoside A, was performed to evaluate chemodiversity in the plants collected from different ecogeographical locations. The analysis of 75 accessions showed a wide range of significant variation in bacoside A content. However, there was less significant genetic diversity among the high and low yielding accessions thus indicating that there is a critical role of agroclimatic condition on differential bacoside accumulation [89].

Genetic Transformation: *Agrobacterium*-mediated genetic transformation is the most preferred strategy utilized for plant genetic transformation. The development of efficient transformation protocol can lead to the genetic improvement of the plant for secondary metabolite content. Attempts have been made to induce Ti and Ri based genetic transformations in *Bacopa monnieri* by some researcher. *Agrobacterium*-mediated genetic transformation of *Bacopa monnieri* has been standardized using the *Agrobacterium tumefaciens* strain EHA105 that harbored the binary vector pBE2113 containing genes for β-glucuronidase (GUS) and neomycin phosphotransferase. Successful transformation was confirmed by histochemical assay for GUS activity, PCR analysis and RT–PCR [90, 91]. *B. monnieri* was transformed with three different strains of *A. tumefaciens viz.* LBA4404, EHA105, and GV3101 harboring expression vector pCAMBIA2301 containing β-glucuronidase (GUS) as a reporter gene.

However, no statistically significant difference in transformation efficiency was found for all the three strains. Interestingly, Gus expression was variable with LBA4404 plants showing highest GUS activity [92]. An efficient transformation system for *Bacopa monnieri*, using *Agrobacterium rhizogenes* strains LBA 9402 and A4 has also been developed. Transformed plants showed morphological features typically seen in transgenic plants produced by *A. rhizogenes*. The growth and biomass accumulation were significantly higher in the transformed shoots and roots than in the non-transformed plants. Further, in transformed plants, the content of active compound was enhanced significantly as compared to non-transformed plant [93]. The transformation protocol developed can be used for genetic engineering of *Bacopa monnieri* for enhancement of its pharmaceutically important metabolites.

Analysis of Metabolic Pathway Gene Expression: The widespread pharmaceutically important triterpenoid saponins (bacoside A, bacoside B, bacopasaponin C, bacopaside I, bacopaside II, bacopaside X, bacopaside N2) present in *Bacopa monnieri* are the prime source of its important medicinal properties and are formed by cytoplasmic mevalonate (MVA) pathway and plastid methylerythritol 4-phosphate (MEP)

pathways [94]. Oxidosqualenecyclases (OSCs) catalyzes the cyclization of 2, 3-oxidosqualene to various triterpene skeletons, the first committed step in triterpenoid biosynthesis [95].

Further, the formation of squalene is the key regulatory point in triterpene biosynthesis, catalyzed by squalene synthase (SQS). A full-length oxidosqualenecyclasec DNA from *Bacopa monnieri* oxidosqualenecyclases (BmOSC) has been isolated and characterized. Quantitative real-time PCR (qRT-PCR) data showed that BmOSC is expressed in all tissues examined with higher expression in stem and leaves as compared to roots and floral parts [96]. A full-length SQS gene has also been isolated from *B. monnieri* and characterized as *B. monnieri* squalene synthase (BmSQS) (1242 bp) encoding 414 amino acids. Phylogenetic analysis showed that BmSQS show the closest relationship with *Salvia miltiorrhiza*. BmSQS mRNA expression level was found to be higher in vegetative parts (roots) as compared to floral parts. Methyl jasmonate induces the BmSQS mRNA expression in all tissues tested, while salicylic acid, cold, and salt induce much higher expression in roots [97]. Comparative transcriptome analysis of shoot and root tissue of *Bacopa monnieri* identifies potential genes related to triterpenoid saponin biosynthesis. The transcript related to CYP450s and UDP-glucosyltransferases were specifically upregulated in shoot tissue as compared to root tissue [98].

CONCLUSION: It is concluded by the above literature that *Bacopa monnieri* is a highly potential medicinal plant that is being used in Ayurveda for a long time. The present review is a comprehensive literature analysis of the chemistry and various heath beneficial functional properties of the plant *Bacopa monnieri*. It was observed that the plant possess various pharmacological properties. The pharmacological activity of this plant might be due to the presence of different biologically active compounds. Numbers of research are still required in the future to validate its effectiveness in various disorders and to find out the impact of the extracts on its ultimate effect on gene expression. The tissue culture techniques developed for the propagation of this plant can be used for conservation of the germplasm of this medicinally important plant, which can enhance the rate of multiplication and can reduce the period and cost of production. The transformation protocol developed can be used for genetic engineering of *Bacopa monnieri* for enhancement of its pharmaceutically important metabolites. Further, the protocol formulated for enhances production of secondary metabolites can also be used as an efficient alternative for increased metabolite production. Thus, there is still a lot of scope in this field for better utilization of this wonder plant.

ACKNOWLEDGEMENT: The authors are thankful to the PG Department of Botany, Dr. Shyama Prasad Mukherjee University, Ranchi, Jharkhand for their valuable support and providing necessary facilities for writing the review article.

CONFLICT OF INTEREST: The authors declare no competing financial interests.

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How to cite this article:
Lal S and Baraik B: Phytochemical and pharmacological profile of *Bacopa monnieri* - an ethnomedicinal plant. Int J Pharm Sci & Res 2019; 10(3): 1001-13. doi: 10.13040/IJPSR.0975-8232.10(3).1001-13.

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