The pharmacology of Bacopa monniera. A review

Ali Esmail Al-Snafi
Department of Pharmacology, College of Medicine, Thi qar University, Nasiriyah, P O Box42, Iraq.
Cell: +9647801397994.
Email: aboahmad61@yahoo.com

Abstract:

Bacopa monniera was distributed in the warmer and wetlands regions of the world. It was widely used in traditional medicine to treat various complains. *Bacopa monniera* contained alkaloid brahmine , nicotinine, herpestine, bacosides A[3-(α-L-arabinopyranosyl)-*O*-β-D-glucopyranoside-10, 20-dihydroxy-16-keto-dammar-24-ene] , triterpenoid saponins , saponins A, B and C, betulinic acid , D-mannitol , stigmastanol , β-sitosterol , stigmasterol. and pseudojujubogenin glycoside. The pharmacological studies showed that *Bacopa monniera* possessed many pharmacological effects included central nervous effects (memory enhancement , antidepressant , anxiolytic , anticonvulsant and antiparkinsonian) , antioxidant , gastrointestinal , endocrine , antimicrobial , anti-inflammatory , analgesic , cardiovascular and smooth muscle relaxant effects. The present review focused on the chemical constituents and pharmacological effects of *Bacopa monniera*.

Keywords: *Bacopa monniera*, chemical constituents, pharmacology

Introduction:

Plant derivates had been employed by population to prevent different kind of diseases for centuries. The knowledge of plant properties was acquired by ancient civilization that passed down from generation to generation until today. *Bacopa monniera* (synonyms: *Lysimachia monnieri L. Cent., Gratiola monnieri L., Monniera cuneifolia and Herpestis monniera L.*) [(1),] which commonly known as (bacopa, brahmi, and thyme leaved gratiola), belongs to the scrophulariaceae family, was distributed in the warmer and wetlands regions of the world. It was used in traditional medicine to treat various nervous disorders, as a brain tonic to enhance memory development, learning, and concentration, and to provide relief to patients with anxiety; it is also used in digestive complains, for skin disorders, and as an antiepileptic, antipyretic, and analgesic [(1-2)]. *Bacopa monniera* contained alkaloid brahmine , nicotinine, herpestine, bacosides A[3-(α-L-arabinopyranosyl)-*O*-β-D-glucopyranoside-10,20-dihydroxy-16-keto-dammar-24-ene], triterpenoid saponins , saponins A, B and C, betulinic acid , D-mannitol , stigmastanol , β-sitosterol , stigmasterol and pseudojujubogenin glycoside[(5-12)]. The pharmacological studies showed that *Bacopa monniera* possessed many pharmacological effects included central nervous effects (memory enhancement, antidepressant, anxiolytic, anticonvulsant and antiparkinsonian), antioxidant, gastrointestinal, endocrine, antimicrobial, anti-inflammatory, analgesic, cardiovascular and smooth muscle relaxant effects. The present review aimed to highlight the chemical constituents and pharmacological effects of *Bacopa monniera*.

Chemical constituents:

Bacopa monniera contained alkaloid brahmine , nicotinine, and herpestine[(5-6)]. Bacosides A [3-(α-L-arabinopyranosyl)-*O*-β-D-glucopyranoside-10, 20-dihydroxy-16-keto-dammar-24-ene] was isolated from Bacopa monniera. Triterpenoid saponins, saponins A, B and C and pseudojujubogenin glycoside were also isolated from Bacopa monniera. They identified as 3-*O*-α-L-arabinopyranosyl-20-*O*-α-L-arabinopyrasonyl-jujubogenin,3-*O*-[α-L-arabinofuranosyl-(1→2)-α-L-arabinopyranosyl] pseudojujubogenin , 3-*O*-β-D-glucopyranosyl(1→3)-{α-L-arabinofuranosyl-(1→2)}-α-L arabinopyrasonyl] pseudojujubogenin and 3-*O*-[α-L-arabinofuranosyl-(1→2)-β-D-glucopiranosyl] pseudojujubogenin. Bacopasides I , II , III, IV and V were also isolated from *Bacopa monniera* , which identified as 3-*O*-α-L- arabinofuranosyl-(1→2)-β-D-glucopyranosyljujubogenin, 3-*O*-β-D-glucopyranosyl-(1→3)-α-L-arabinopyranosyl jujubogenin, 3-*O*- β-D-glucopyranosyl-(1→3)-α-L-arabinofuranosyl pseudojujubogenin[(7-11)].

Bacopa monniera also contained betulinic acid , D-mannitol , stigmastanol , β-sitosterol and stigmasterol[(12)].

Pharmacological effects:

Central nervous effects:

Memory enhancement:

Behavioral studies in animals have shown that Bacopa improves motor learning, acquisition and retention, and delay extinction of newly acquired behavior [(13)]. The methanol extract and different fractions of *B. monniera* were evaluated for antidepressant activity in the forced swimming test (FST) and tail suspension test (TST) in mice. The results showed that the methanol extract, ethanol and butanol fraction significantly reduced

the immobility times both in FST and TST in mice after being administrated orally for 5 consecutive days. All tested samples, in the effective doses for FST and TST, showed no inhibitory effect against locomotor activity (LA) in mice [14]. On the other hand, it was found that bacosides facilitates anterograde memory and attenuate anterograde experimental amnesia induced by scopolamine and sodium nitrite possibly by improving the acetylcholine level and hypoxic conditions, respectively. In addition, bacosides also reversed BN52021 (a platelet-activating factor receptor antagonist) induced retrograde amnesia, probably due to increase in platelet activating factor synthesis by enhancing cerebral glutamate level [15]. Memory deficits following cholinergic blockade by scopolamine were reversed by Bacopa treatment. Bacopa improved memory functioning in cognitively intact cohorts, with Pycnogenol improving working memory [16]. Benzodiazepines are known to produce amnesia by the involvement of GABAergic system and by the interference of long term potentiation. The behavioral study showed that Bacopa monniera significantly reversed the diazepam induced amnesia [17]. Bacopa administration with phenytoin significantly reversed phenytoin-induced cognitive impairment, as noted by improved acquisition and retention of memory [18]. A clinical trial was carried out to assess the effects of 12-weeks administration of *Bacopa monnieri* (300mg/day) on memory performance in people over the age of 55-years. Bacopa significantly improved memory acquisition and retention in older persons [19]. Significant cognitive enhancing benefits have been demonstrated with chronic administration of Bacopa extracts. A double-blind, placebo-controlled, 12-week trial utilizing the same patient selection criteria and the same dose of Bacopa extract (300 mg daily) containing 55% combined bacosides, was carried out. Forty-six healthy volunteers (ages 18-60) were randomly and evenly divided into treatment and placebo groups. The same series of tests administered in the acute dosage trial were administered at baseline, five, and 12 weeks after treatment began. At the end of the 12-week study, results indicated a significant improvement in verbal learning, memory consolidation, and speed of early information processing in the treatment group compared to placebo. These effects were not observed at baseline or at five weeks [20].

The Bacopa supplement was commercially available as KeenMind™ (Flordis). This product is manufactured from the stems, leaves and roots of Bacopa and is extracted with 50% ethanol. It is standardized to contain active bacosides at levels of 55% ± 5%. KeenMind™ help develop novel preventative health practices and nutritional/pharmacological targets in the elderly for cognitive and brain health. Bacopa appeared to have multiple modes of action in the brain, all of which may be useful in ameliorating cognitive decline in the elderly. These include: (i) direct pro-cholinergic action; (ii) anti-oxidant (flavonoid) activity; (iii) metal chelation; (iv) anti-inflammatory effects; (v) improved blood circulation; (vi) adaptogenic activity; and (vii) removal of b-amyloid deposits [21]. However , in a double-blind randomized, placebo control study performed on 76 adults aged between 40 and 65 years, in which various memory functions were tested and levels of anxiety was measured , the rate of learning was unaffected by *Bacopa monnieri* suggesting that *Bacopa monnieri* decreases the rate of forgetting of newly acquired information. Tasks assessing attention, verbal and visual short-term memory and the retrieval of pre-experimental knowledge were unaffected. Questionnaire measures of everyday memory function and anxiety levels were also unaffected [22].

Antidepressant:

Bacosides A and B, bacopasides I and II and bacopasaponin C and the extract of *Bacopa monniera* exhibited antidepressant activity, while bacopaside VII did not have any antidepressant activity when tested on forced swimming and tail-suspension models in experimental animals [23-25].

Anxiolytic:

Crude plant extract of *Bacopa monnieri* or bacosides have also shown anxiolytic effects, antidepressant activity, anticonvulsive action and antioxidant activity [26]**.** *Bacopa monnieri* was highly effective as an adaptogen, it normalized acute and chronic stress induced corticosterone changes in rats. It also normalized noradrenalin (NA), 5-HT, and DA in cortex and hippocampus of rats in acute and chronic unpredictable stress [27]. Bacopa modulated the cholinergic system and have antioxidant and metal chelating effects. In an animal model, there was a dose-related reversal by Bacopa of cognitive deficits produced by the neurotoxins, colchicine and ibotenic acid [28-29]. *Bacopa monniera* lowered norepinephrine and increases the 5-hydroxytryptamine levels in hippocampus, hypothalamus and cerebral cortex. The higher doses of *Bacopa monniera* extracts produced significantly greater anxiolytic effects compared to lorazepam, a standard anxiolytic drug from benzodiazepine group [30]. However, acute and sub chronic (one week) treatment of *Bacopa monnieri* methanolic extract (10, 20 or 30 mg/kg) didn't affected dopamine (DA) and serotonin (5-HT) turnover in mice whole brain [31].

Antiparkinson:

Bacopa monnieri, on pharmacological *Caenorhabditis elegans* models of Parkinson's, reduced alpha synuclein aggregation, prevents dopaminergic neurodegeneration and restores the lipid content in nematodes, thereby proving its potential as a possible anti-Parkinsonian agent [32].

Anticonvulsant:

Crude plant extract of *Bacopa monnieri* or bacosides have also shown anticonvulsive action [26].

It possessed neuroprotective effects in glutamate-mediated excitotoxicity during seizures and cognitive damage occurring in association with pilocarpine-induced epilepsy [33]. The ethanolic extract of *Bacopa monniera* was tested for anticonvulsant activity using different convulsive models (pentylenetetrazol, maximal electroshock and strychnine-induced convulsion in rats, as well as hypoxic stress-induced convulsions in mice and lithium–pilocarpine-induced status epilepticus). The ethanolic extract of *Bacopa monniera* was administered as 50 and 55 mg/kg orally for rats and mice, respectively, 2 and 4 hours before the respective convulsive stimuli. The ethanolic extract of leaves produced significant anticonvulsant activity for all the different models studied with a mechanism of action similar to that of benzodiazepines (GABA agonist) [34].

Antioxidant:

The total phenolic content of aqueous extract of *Bacopa monniera* measured by Folin ciocalteau was found to be 58 mg gallic acid equivalent/g , while, in hydrogen peroxide scavenging method the IC_{50} value was found to be 254.70 µg/ml [35]. The antistress effect of bacosides of Brahmi (*Bacopa monnieri*) was studied in adult male Sprague Dawley rats by administering oral doses of 20 and 40 mg/kg for 7 consecutive days. Bacosides, at both doses, didn't induce significant changes in the expression of Hsp70 in all studied brain region, while stress alone produced significant increase in the Hsp70 expression in all brain regions. A significant decrease in the activity of superoxide dismutase (SOD) was evident in the hippocampus with the lower dose of bacosides, while an increase in the activity of SOD was observed in the brain regions with the higher dose An increase in the activity of cytochrome P450 (P450) dependent 7-pentoxyresorufin-o-dealkylase (PROD) and 7-ethoxyresorufin-o-deethylase (EROD) was observed in all the brain regions after exposure to stress alone and with both doses of bacosides , although the magnitude of induction of P450 expression was less with a higher dose of bacosides. Interestingly, stress in the animals pretreated with bacosides for 7 days resulted in a decrease in Hsp70 expression in all the brain regions with a significant decrease occurring only in the hippocampus. Likewise the activity of SOD was found to be further reduced in all the brain regions in the animals treated with the lower dose of bacosides followed by stress. However, when animals exposed to stress after treatment with the higher dose of bacosides, a significant increase in the enzyme activity was observed in the cerebral cortex and in the rest of the brain while the activity of SOD was reduced to a much greater extent in the cerebellum and in the hippocampus. Likewise, the activity of P450 enzymes was found to be restored to almost control levels in the animals exposed to stress and pretreated with the higher dose of bacosides, while a lesser degree of induction, compared with animals treated with bacosides or stress alone, was observed in the animals pretreated with the lower dose of bacosides and exposed to stress. These data indicated that bacosides has potential to modulate the activities of Hsp70, P450 and SOD and allowing the brain to be prepared to act under adverse conditions such as stress [36].

Bacopa monniera alcoholic extract exerted a hepatoprotective effect against the inhibition of antioxidant enzymes and reduction in GSH level induced by morphine in rats [37].

Four extracts of *Bacopa monnieri* (whole plant) tested for antioxidant activity using DPPH radical scavenging**.** The methanol and aqueous successive extracts showed the maximum antioxidant activity with IC_{50} values of 46.00 µg/ml and 43.10 µg/ml, respectively [38].

Methanolic extract of *Bacopa monnieri* callus exerted scavenging activity with IC_{50} value of 0.739 mg/ml [39]. Bacoside-A administration improved the antioxidant status and maintained the levels of trace elements. *Bacopa monnieri* extract promoted the antioxidant status, reduces the rate of lipid peroxidation and the markers of tumor progression in the fibrosarcoma bearing rats [40].

The protective effect of *Bacopa monnieri*, on tissue antioxidant defense system and lipid peroxidative status in streptozotocin-induced diabetic rats was investigated. Extract of *B. monnieri* was administered orally, once a day for 15 days (at doses 50, 125 and 250 mg/kg bw) to diabetic rats. Activity of antioxidant enzymes (SOD, Catalase, and GPx), levels of GSH and lipid peroxidation were estimated in kidney, cerebrum, cerebellum and midbrain of diabetic rats and compared to reference drug, glibenclamide. Administration of plant extract to diabetic rats showed significant reversal of disturbed antioxidant status and peroxidative damage. Significant increase in SOD, CAT, GPx activity and levels of GSH was observed in extract treated diabetic rats [41]. In studying, the antihyperglycaemic activity, *in vivo* antioxidant potential, effect on glycosylation of hemoglobin and *in-vitro* peripheral utilization of glucose, of the ethanolic extract of the aerial parts of *Bacopa monnieri*, it was found that the extract produced significant decrease in the blood glucose level in alloxan induced hyperglycemic rats both in the single dose as well as multiple dose experiments. The ethanolic extract also reversed the weight loss of the diabetic rats which returned to near normal. The extract prevented significant elevation of glycosylated hemoglobin *in vitro*, with IC_{50} value of 11.25 µg/ml that is comparable with the reference drug, α-tocopherol. Administration of the extract and glibenclamide significantly decreased the levels of TBARS, increased the content of GSH and increased the activity of SOD and CAT in liver of diabetic rats.

The extract increased peripheral glucose utilization in the diaphragm of diabetic rats *in vitro*, which is comparable with the action of insulin [42].

Anti-inflammatory and analgesic effects:

Bacopa monniera effectively suppressed experimentally induced inflammatory reaction effect by inhibiting the prostaglandins synthesis and partly by stabilizing lyosomal membranes and didn't cause gastric irritation at anti-inflammatory doses [43]. The ethanol extract of the whole plant of *Bacopa monnieri* produced significant writhing inhibition in acetic acid induced writhing in mice at the oral dose of 250 and 500 mg/kg ($P<0.001$) comparable to diclofenac sodium 25mg/kg [44]. The anti-inflammatory effects of the many extracts of *Bacopa monnieri* were investigated on carrageenan induced edema in rat's hind paws**.** The methanol extract and aqueous fractions (100 mg/kg) showed a significant reduction in the edema paw volume, while, petroleum ether and hexane extracts didn't reduced inflammation [38].

Human red blood cell (HRBC) membrane stabilization method was used to assay the in vitro anti-inflammatory activity of *Bacopa monnieri*. Methanolic extract and the callus (100, 200, 300 µg) produced membrane stabilization better than diclofenac sodium [39]. The anti-inflammatory activity of *Bacopa monnieri* is due to the triterpenoid and bacoside present in the plant. *Bacopa monniera* has the ability to inhibit inflammation through modulation of pro-inflammatory mediator release. The fractions containing triterpenoids and bacosides inhibited the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha and interleukin-6 [45].

Gastrointestinal effects:

The ethanol extract of the whole plant of *Bacopa monnieri* was showed antidiarrhoeal effect on castor oil induced diarrhea in mice. It increased mean latent period and decreased frequency of defecation significantly at the oral dose of 500 mg/kg comparable to loperamide 50mg/kg [44].

Fresh *Bacopa monniera* juice exerted significant antiulcerogenic activity [46]. Bacopa have a protective and curative effect for gastric ulcers. In rats, the Bacopa extract standardized for bacoside-A was evaluated for its prophylactic and healing effects in five models of gastric ulcers. At a dose of 20 mg/kg for 10 days, Bacopa extract significantly healed penetrating ulcers induced by acetic acid, significantly strengthened the mucosal barrier, and decreased mucosal exfoliation. The extract also alleviated stress-induced ulcers as observed by significant reduction in lipid peroxidation in rat gastric mucosa. It was also exerted anti *H. pylori* effect [47-48]. A double-blind, randomized, placebo controlled trial of 169 patients with irritable bowel syndrome , effects of an Ayurvedic preparation containing *Bacopa monniera* and *Aegle marmelos* was compared with standard therapy (clidinium bromide, chlordiazepoxide, and psyllium). Subjects were randomly assigned to standard drug treatment, botanical treatment, or placebo for six weeks. Treatment was administered orally as drug, botanical, or placebo three times daily. Ayurvedic therapy was superior to placebo, however, the two botanicals were not given separately, and the benefit could not link specifically to the Bacopa portion of the Ayurvedic preparation [49].

Antimicrobial effects:

Methanol extracts were found to be the most potent antimicrobial agent in comparison to other extracts. Aqueous extracts showed no activity against any of the microorganisms. Hexane and petroleum ether extracts showed similar antimicrobial activity but less significant in comparison to methanol extracts. The MIC of the methanol extracts was found to be the lowest against *E.coli*, *Salmonella typhimurium*, *Staphylococcus aureus* and *Saccharomyces cerevisae* [38]. Methanolic extract (1mg/ml) of callus of *Bacopa monnieri* shows good activity against *Staphylococcus aureus*, *Salmonella typhi* and *E. coli* and maximum activity was observed against *Staphylococcus aureus*. No activity was observed against *K. pneumoniae* [39]. Ether extract of Bacopa *monnieri* showed antimicrobial activity against four bacteria and one fungus, *Salmonella typhi, Pseudomonas aeruginos***,** *Staphylococcus aureus, Vibrio cholera* and *Candida albicans* [50]**.**

Endocrine effects:

Bacopa extract (200 mg/kg orally) increased the thyroid hormone, T4, by 41% in mice. T3 was not stimulated, suggesting that the extract may directly stimulate synthesis and/or release of T4 at the glandular level, while not affecting conversion of T4 to T3[51].

Bacopa monniera extracts caused reversible suppression of spermatogenesis and fertility. The treatment caused reduction in motility and viability of the sperms and reduced the number of spermatozoa in caudaepididymidis and testis, and caused alterations in the somniferous tubules in mice [52].

Other effects:

Ethanolic extract of whole plant of *Bacopa monnieri* has shown cardiac depressive activity on left ventricular contractility, heart rate and coronary flow in isolated rabbit heart and it appeared that, the activity of ethanolic *Bacopa monnieri* extract was similar to that of quinidine on heart [53]. Bacopa has relaxant effects on pulmonary arteries, aorta, trachea, ileal, and bronchial smooth muscles in experimental animals. These effects possibly

mediated by inhibition of calcium-ion influx into cell membranes [54-56]. The methanol extract of Bacopa possessed potent mast cell stabilizing activity comparable to disodium cromoglycate [57].

Contraindications and adverse effects:

Therapeutic doses of Bacopa are not associated with any known side effects, and Bacopa has been used safely in Ayurvedic medicine for several hundred years. The clinical studies have confirmed the safety of the bacosides in healthy male volunteers at both single and multiple doses administered over a period of 4 weeks. Concentrated bacosides given in single (20-30 mg) and multiple (100-200 mg) daily doses were well tolerated and without adverse effects [13].

The LD50 of Bacopa extracts administered orally to rats was 5 g/kg for aqueous extracts and 17 g/kg of the alcohol extract. Neither alcoholic nor aqueous extract resulted in gross behavioral changes at these concentrations [58].

Dosage:

Daily doses of Bacopa are 5-10 g of non-standardized powder, 8-16 mL of infusion, and 30 mL daily of syrup. Dosages of a 1:2 fluid extract are 5-12 mL per day for adults and 2.5-6 mL per day for children ages 6-12. For Bacopa extracts standardized to 20-percent bacosides A and B, the dosage is 200-400 mg daily in divided doses for adults, and 100-200 mg daily in divided doses for children [59].

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