Brahmi: A Detailed Review

Raj Kumar Mishra* PhD scholar, I.K. Gujral Punjab Technical University Jalandhar, Punjab

Associate Professor Department of Pharmacy IEC College of Engineering &Technology Greater Noida G,B. Nagar India

Email:dr.rajmishra2103@gmail.com

Jagdeep singh Dua Associate Professor Shivalik college of Pharmacy Nangal

Dr. Utpal Jana ,Principal Shiva Institute of Pharmacy Bilaspur H.P.

Abstract

Nano forms of formulations are becoming so popular in solving the problems of herbal extract absorption due to which herbal extract)are showing enormaous potential to cure many neuro degenerative disorder more efficiently to their allopathy counterpart as anxiety epilepsy and dementia.Encapsulating poorly water soluble herbals in nanoparticles, nanoemulsion or any other nanoforms is one of the methods that helps pharmaceutical researcher to solve community people health issues in more profound way as compared to conventional dosage forms. and is a effective innovative approach that assists to overcome the multiple limitations of various diseases, particularly neurodegenerative disorders (NDs).Bacopa monnieri belonging to the family plantaginaceae. Bacopa monnieri is a promising drug being used in Ayurveda since long time for treating cognitive disorder and curing various types of anxiety and dementia. .Along with the many active therapeutic entities bacosids A is the main active agent which consists of nootropic action and antioxidant property which conserve the neurons by getting inactive by its action through various pathways,bacosides consisting of neuroprotective action by acting on beta

amyloid plaques and prevent nerve cell death but not glutamate induced excitotoxicity in primary cortical culture . nanoparticle. being one of the useful delivery tool to deliver poorly soluble drug in brain by crossing the blood brain barrier nowadays showing trustfull response for getting therapeutic action from herbal extract targeted to brain due to smaller size and high lipid solubility which makes them easily cross membranes..The current review aimed to develop potent scientific literature which can actively deliver accurate facts regarding pharmacological action of herbal extract and modern formulative aspects generally used in current scenario.

Keywords: Ayurvedic herbs, nanoformulation, neurodegenerative disorder, therapeutic effect

Introduction **(1,2,3)**

The importance of Bacopa monnieri (Bacopa monniera Linn.) (**Ballard C et al 2011)** in perfecting memory and neuron strengthening work was first published in 1982 (Singh and Dhawan, 1982). After that many studies have been conducted in animal model to determine potential efficacy displayed by the medicinal active agent . The eventuality of Bacopa monnieri in shielding neuronal structure and or function has also been estimated in a number of growing studies. Bacopa monnieri is a well-known Ayurvedic medicinal condiment, which isre-emerging as a expedient to treatment of memory related diseases. Its medicinal energy is reported both in Indian as well as Chinese traditional literature. Although numerous chemical composites

have been isolated from Bacopa monnieri, the active fragments of this medicinal factory contain bacoside-A and bacoside-B. A number of other phytochemicals similar as alkaloids, glycosides, flavonoids, saponinsetc. are the ingredients of Bacopa monnieri (Dutta and Basu, 1963; Chatterji etal., 1965; Basu etal., 1967).

Examinations conducted so far have revealed that Bacopa monnieri exerts numerous pharmacological goods including memory boosting effect in the treatment of Alzheimer Disease and Schizophrenia, besides displaying antiparkinson, antistroke, and anticonvulsant capabilities. The present review discusses the chemical ingredients of Bacopa monnieri together with in vitro and in vivo studies grounded on its molecular and pharmacological goods .

figure:1 image of bacopa monnieri rastogi et al

Chemical constituents of bacopa monnieri(4,5)

Bacopa monniera is recognized by its complex chemical composition which particularly includes compounds like dammarane-type triterpenoid saponins called as bacosides, with jujubogenin or pseudo-jujubogenin moieties as their aglycone units. Based on the structural similarity, 12 analogs from the family of Bacosides are elucidated. In the recent past, bacopasides I–XII, a special class of saponins are identified as a crucial constituent of the herbal extract (Rauf et al., 2013). Apart from hersaponin, apigenin, D-mannitol, monnierasides I-III, plantainoside B and cucurbitacin; the alkaloids bacopa monnierine, herpestine and nicotine have also been classified within the chemical constituents of Bacopa monniera. Bacoside A is that the most studied and potent constituent of Bacopa, which consists of bacoside A3, bacopasaponin C, bacopaside II and bacopaside X (Srivastava et al., 2012; Deepak and Amit, 2013; Singh et al., 2014;.

Various research groups have separated the constituents of Bacopa monnieri through HPLC. Several mobile phase systems are used for the aim of separating various chemical constituents of Bacopa monnieri like methanol and water (Ganzera et al., 2004); mixture of acetonitrile and 0.05 M sodium sulfate (pH 2.3; 68.5:31.5; Sivaramakrishna et al., 2005; Murthy et al., 2006); 0.25% orthophosphoric acid in water and acetonitrile (Phrompittayarat et al., 2007; Sumathi and Devaraj, 2009); but till now no consensus mobile phase system has come up for the analysis of Bacopa monnieri constituents.Active componentsThe therapeutic effects of Bacopa monniera are believed to be exerted through triterpenoid saponins present within the plant extract. Bacosides are the triterpenoid saponins of prime importance. They have been shown to reinforce impulse transmission. The bacosides promote the repair of damaged neurons by upregulating neuronal

synthesis and kinase activity. The bacosides also aid within the restoration of synaptic activity, which ultimately results in impulse transmission (Singh and Dhawan, 1997). The impulse transmission, plays an important role in promoting healthy cognitive functions like span , focus, concentration, learning and memory. There is evidence which suggests that Bacopa, by the virtue of containing active constituents like bacosides, influences the synthesis and availability of the neurotransmitter, Serotonin; therefore, Bacopa helps to maintain neurotransmitter balance (Charles et al., 2011; Rauf et al., 2012a).

Pharmacological effects(7,6,8)

Memory booster in Alzheimer's disease and schizophrenia

Bacopa monnieri *(Bacopa monniere)* has been used in the form of memory booster from ancient eraby indian health practitioners and china based health care system also used this herb for numerous purposes for many years. The accreditation of the traditional assertion of Bacopa monnieri was initiated by investigating the effect of an alcoholic extract of this herb on acquisition, consolidation and retention in different conditioning schedules in rats. These included shock driven brightness-discrimination response, continuous avoidance and active conditioned response. It was found that motor skills, acquisition and consolidation were improved and newly acquired behavior was retained for a long period of time in all the three learning responses by the introduction of the CDRI-08 (KeenMind; 40 mg/kg, po. × 3d) in mice (Singh and Dhawan, 1982, 1997). To discern the efficacy of Bacopa monnieri in causing the reversal of amnesia, several behavioral studies have been conducted by inducing amnesic agents in animals. Some of the potential amnesic agents including benzodiazepines, scopolamine, quinoline derivatives and phenytoin cause amnesia by interrupting long-term potentiation (LTP).

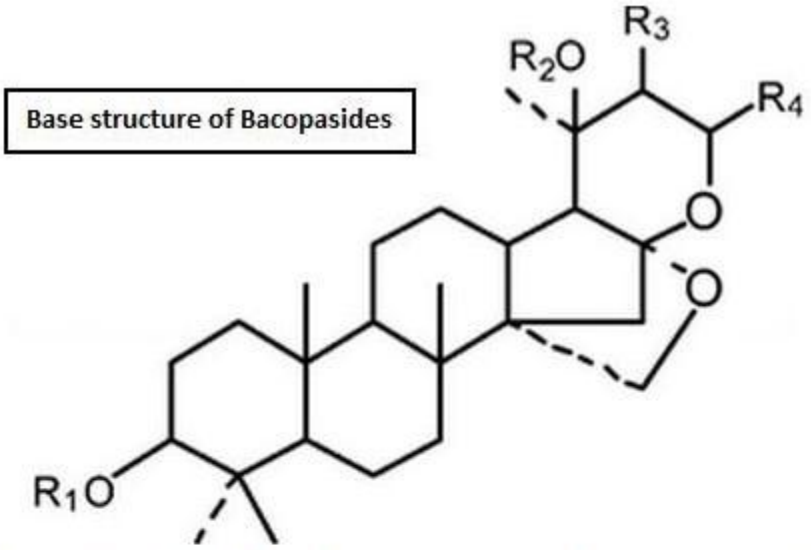
The process of LTP is probably interfered by the involvement of gamma-aminobutyric acid-benzodiazepine pathway. Saraf et al. demonstrated that amnesia induced by diazepam (1.75 mg/kg) was significantly reversed by Bacopa monnieri (120 mg/kg) which was provided orally in mice (Prabhakar et al., 2008). Subsequently, the same group later examined the influence exerted by Bacopa monnieri on the downstream signaling molecules related to LTP in amnesic mice, which were developed by diazepam (Saraf et al., 2008). The molecular tests revealed that diazepam upregulated the gene expression of inducible nitric oxide synthase (iNOS), mitogen activated protein kinase (MAP kinase) and phosphorylated CREB (pCREB) whereas reduced the expression levels of cAMP response element binding protein (CREB), cyclic adenosine monophosphate (cAMP), total nitrite and nitrate. The levels of calmodulin remained unaltered with diazepam induction. On the contrary, administration of Bacopa monnieri inhibited the increased expression of iNOS, pCREB and MAP kinase molecules and restored nitrite level to normal, the expression of which was altered by diazepam. The levels of cAMP, total CREB, total nitrite, nitrate and PDE were found to be unaffected by Bacopa monnieri. These behavioral findings provide tempting conclusion that Bacopa monnieri reverses amnesia induced by diazepam and can be used in the treatment of Alzheimer's Disease and Schizophrenia.

GABAergic and cholinergic system plays a vital role in reversing the amnesic behavior shown by diazepam and scopolamine. To assess the effect of Bacopa monnieri on downstream signaling molecules, amnesia was induced in mice by administrating of MK-801 and N(w)-nitro-L-arginine (L-NNA; Saraf et al., 2009). MK-801 is a NMDA receptor antagonist while L-NNA inhibits the production of nitric oxide that eventually results in memory loss. Morris water maze scale was selected to assess memory and learning skills in animals. It was found that supplementation of both of the amnesic agents in mice resulted in anterograde and retrograde

amnesia and that Bacopa monnieri significantly reversed the L-NNA induced anterograde and retrograde amnesia. On the contrary, exposure of MK-1 induced mice to Bacopa monnieri didn't influence anterograde and reterograde amnesia. This suggests that Bacopa monnieri reverses the amnesic effect caused by L-NNA but not with MK-1. In yet another disquisition, scopolamine was used to induce amnesia in mice and the effect of Bacopa monnieri was delved on downstream signaling motes (Saraf etal., 2010a). The findings revealed that the situations of protein kinase C and iNOS were downregulated whereas that of protein kinase A, Chart kinase, cAMP, calmodulin, pCREB, CREB and nitrite remained in normal range with the induction of scopolamine. Bacopa monnieri overruled the effect of scopolamine in amnesic mice by significantly adding protein kinase C, calmodulin and pCREB situations. This shows that Bacopa monnieri contributes to help memory loss intermediated by calmodulin. In addition, Bacopa monnieri is reported to significantly reverse L-NNA convinced anterograde amnesia rather of MK-801 convinced anterograde amnesia (Anand etal., 2010). Also, Bacopa monnieri ameliorates spatial memory in amnesic model of mice created using scopolamine (Saraf etal., 2011). In this study, the probing group tested theanti-amnesic effect of Bacopa monnieri on amnesia convinced by scopolamine using Morris water maze test. Muscle collaboration exertion in the creatures was assessed using the rotarod test. The results revealed that both anterograde and retrograde amnesia produced by scopolamine were reversed by Bacopa monnieri treatment. These compliances were suggestive of Bacopa monnieri's promising eventuality in the development of alternate approaches in the remedy of Alzheimer's complaint. Also, Bacopa monnieri perfected memory impairment convinced by phenytoin which further provides substantiation for its part as an antiamnesic agent (Vohora etal., 2000). In addition, BN52021 which is a platelet- cranking factor receptor antagonist was used to induce retrograde amnesia in mice was also perfected by Bacopa

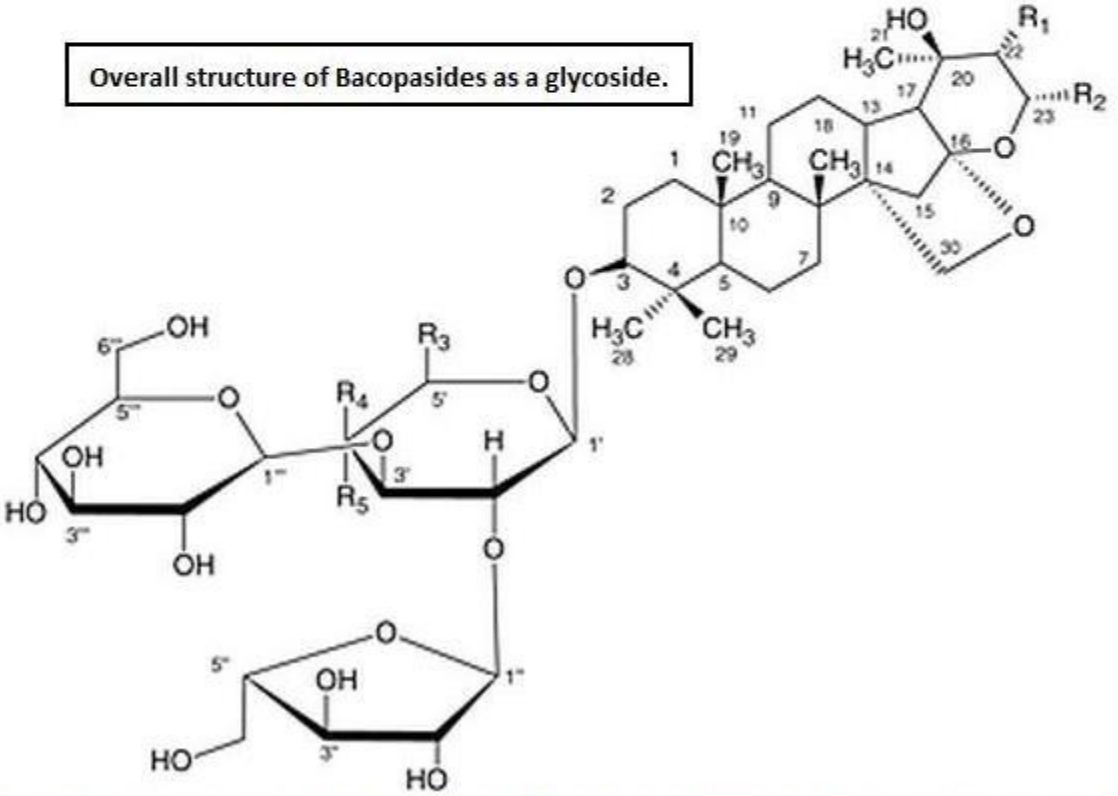
monnieri treatment. The reason for this might be an increase in glutamate position in the brain, which further increases platelet cranking factor conflation (Kishore and Singh, 2005). Bacopa monnieri also plays a neuroprotective part in rat by maintaining the position of mitochondrial enzymes, which got swerved due to morphine induction(Sumathietal.,2011.

Base structure of Bacopasides



(Modified from: Zhou Y, et al. Triterpene saponins from Bacopa monnieri and their antidepressant effects in two mice models. J Nat Prod. (2007))

Overall structure of Bacopasides as a glycoside.



(Modified from: Srivastava P, et al. Stability Studies of Crude Plant Material of Bacopa monnieri and Quantitative Determination of Bacopaside I and Bacoside A by HPLC. Phytochem Anal. (2012)

Recently, the neuroprotective effect of Bacopa monnieri was studiedd in a rat model of schizophrenia (Piyabhan and Wetchateng, 2014). The authors evaluated discrimination ratio as a measure of cognitive ability from novel object recognition task. N-methyl-D- aspartate receptor subtype 1 (NMDAR1) density was also measured in different areas of brain including prefrontal cortex, striatum, cornu ammonis fields I (CA1) and 2/3 (CA2/3) of hippocampus and dentate gyrus (DG). The findings revealed a significant reduction in discrimination ratio in schizophrenia induced group compared to control. NMDAR1 showed upregulated expression in CA2/3 and DG but not in prefrontal cortex, striatum or CA1. Upon Bacopa monnieri administration, the DR score increased up to normal with considerable downregulation of NMDARI in CA2/3 and DG. The mechanism for memory impairment in schizophrenia induced rats appeared to be mediated by upregulation of NMDAR1 in CA2/3 and DG areas of brain. Interestingly, administration of Bacopa monnieri could restore this memory impairment by decreasing NMDAR1 in these brain areas. Therefore, Bacopa monnieri could be regarded as a novel frontier for the prevention of memory impairment in schizophrenia. The same group previously measured the vesicular glutamate transporter type 1 (VGLUT1) density in same areas of brain and found a significant decrease in the expression of this transporter of rat model of schizophrenia (Piyabhan and Wetchateng, 2013). As expected administration of Bacopa monnieri upregulated the expression of this transporter to normal level thereby proving its effectiveness in the treatment of Schizophrenia. Bacopa monnieri also possesses anti-epileptic property as evidenced by reducing the dopamine levels of dopaminergic neurons in the frontal cortex region of the rat brain (Jash and Chowdary, 2014). These observations suggest that Bacopa monnieri may possess the property to alleviate the positive symptoms of schizophrenia.

Khan et al. demonstrated the therapeutic efficacy of Bacopa monnieri on intellectual impairment and oxidative damage, induced by streptozotocin in rat models (Khan et al., 2015). The data showed that streptozotocin deteriorated memory and learning skills in these animals, which were significantly improved by Bacopa monnieri supplementation. Furthermore, increase in the amount of thiobarbituric acid reactive substances, indicative of lipid peroxidation, were visualized in the brain of these animals. Antioxidant status was also found disturbed in the hippocampus region of the brain along with a decrease in copper and zinc concentration in these experimental animals. Bacopa monnieri significantly ameliorated all of these alterations induced by streptozotocin in rats. The data suggests that formation of free radicals and increased rate of lipid peroxidation as a result of streptozotocin induction might cause neurotoxicity in these animals which can be prevented by the use of Bacopa monnieri. The study demonstrates the usefulness of Bacopa monnieri for the treatment of intellectually impaired patients.

Bacopa monnieri has been reported to increase the level of serotonin, trigger 5-HT3A receptors and CREB in hippocampus of postpartum rats thereby facilitating its learning abilities (Rajan et al., 2011). To identify the mechanism by which Bacopa monnieri acts on sodium butyrate (NaB) induced rat pups, the animals were subjected to fear conditioning test (Preethi et al., 2014). Fear conditioning is a behavioral paradigm in which an organism learns to envisage to an aversive stimulus. This stimulus is associated with neutral stimulus that elicits a state of fear response in the organism. The results revealed that Bacopa monnieri treatment in NaB induced rats facilitated the freeze response and triggered extracellular ERK/CREB signaling transduction. The levels of HAT containing coactivators such as p300, acetylated histones (e.g., Ac-H3 and Ac-H4) showed up regulated expression whereas HDACs (1, 2) and protein phosphatases (PP1α, PP2A) showed down regulated expression in hippocampus after fear conditioning test.

Subsequently, the expression of brain-derived neurotrophic factor (Bdnf) (exon IV) mRNA was found to be increased indicating that Bacopa monnieri enhances hippocampus-dependent contextual memory by modulating the expression of histone acetylated proteins and protein phosphatases in hippocampus.

Antiparkinson's effects(9-14)

Apart from alleviating memory, Bacopa monnieri is demonstrated to play a role in treating Parkinson's disease, which is a neurodegenerative disorder marked by the loss of neurons which produce dopamine in substancia nigra and alpha-synuclein protein, is accumulated in the inclusion bodies known as lewy bodies (Feany and Bender, 2000). To study the mechanism underlying PD pathogenesis various experimental models have been employed. However, research on evaluating the effect of Bacopa monnieri and other plant extracts in PD models is limited. Recently, Siddique et al. studiedd the effect of CDRI-08 (KeenMind) in transgenic Drosophila fruit fly (PD model) which expressed normal human alpha synuclein in their neurons. Different parameters including climbing skills, activity pattern, oxidative stress and apoptosis were measured to study the effect of Bacopa monnieri in the brain of fruit fly. Their findings revealed an improved climbing ability as well as activity pattern, reduced oxidative stress and apoptosis upon exposure of flies to Bacopa monnieri. These findings were dose dependent and suggest that the herb attenuates behavioral deformities, reduces the oxidative stress and neuronal cell death in the brains of PD model flies. Similar findings were obtained by Jansen et al., who also demonstrated the efficacy of Bacopa monnieri in alleviating the climbing activity of fruit flies compared to non-treated fruit flies (Jansen et al., 2014).

In line with previous research Jadiya et al., employed *Caenorhabditis elegans* model of Parkinson's disease to studied the efficacy of this herb. Their findings revealed that Bacopa monnieri exposure reduced alpha synuclein accumulation, prevented dopaminergic cell death and restored the lipid content in this PD model. These data provide an evidence for Bacopa monnieri to be considered as a possible anti-Parkinsonian medication and further research on the potential use of herbal plants, compounds, and extracts in treating Parkinson's disease is required (Jadiya et al., 2011).

Antistroke effects(15)

The medicinal potency of Bacopa monnieri in treating Alzheimer's Disease and Parkinson's Disease has already been established. To explore its role in treating brain stroke, few investigations have been conducted by Rehni et al., who explored the role of this herbal plant on ischemia and reperfusion induced brain injury in experimental mice (Rehni et al., 2007). Ischemic-reperfusion induction lead to the increase in infarct size and impairment of short-term memory and motor balance. On the other hand, administration of Bacopa monnieri in these mice significantly reduced the infarct size and attenuated their short-term memory and motor balance. In line with this report, Saraf et al. studiedd the role of Bacopa monnieri in ischemic induced brain injury in rats. Bacopa monnieri was supplemeted at a dosage of 120, 160, and 240 mg/kg in these animals and various behavioral and biochemical analysis were done to screen the efficacy of this herb (Saraf et al., 2010b). Their findings showed a protective role of Bacopa monnieri in reducing infarct size in the ischemic brain and ameliorating memory dysfunction as shown in the plus maze task. Additionally, administration of Bacopa monnieri improved the muscle coordination and catalase activity in rats exposed to ischemic insult. Levels of nitrite, nitrate and rate of lipid peroxidation were also significantly decreased. These observations indicate that

Bacopa monnieri protects brain against ischemia-induced insults and further research in this direction is warranted.Furthermore, brain ischemia reduces blood flow in cerebral arteries due to the lack of oxygen supply. To studied whether Bacopa monnieri exerts any effect on cerebral blood flow (CBF) Kamkaew et al., measured this parameter in rats (Kamkaew et al., 2013). Rats were treated with a dose of 40 mg of Bacopa monnieri for a period of 8 weeks and thereafter, the CBF was measured via Doppler. Interestingly, the herb was found to increase the cerebral blood flow (CBF) by 25% in rats without affecting their blood pressure. These findings further confirm the efficacy of this herb in the treatment of neurological disorders and further research in this direction is required.

Anticonvulsant effects in the treatment of epilepsy(16)

Epileptic seizures represent a cardinal feature of the neurological syndrome named epilepsy. This disease may affect people of all ages. In recent years, an immense interest has been generated in the search of herbal drugs and formulations that may be used in the treatment of epilepsy. Bacopa monnieri is one such widely used herbal drug that alleviates nervous function, enhances memory, and reduces convulsions and inflammation. It has been reported that CDRI-08 (KeenMind) produces anticonvulsive action (Reas et al., 2008). Paulose et al., studied the role played by metabotropic glutamate-8 receptor (mGluR8) and NMDA receptor 1 (NMDAR1) gene expression in pilocarpine induced epilepsy and during neonatal hypoxia (Paulose et al., 2008). During epilepsy, mGluR8 gene was downregulated whereas NMDAR1 gene showed increased expression in hypoxic neonates. To explore the neuroprotective role of Bacopa monnieri, epileptic rats were supplemented with the herbal medication and hypoxia induced rats were supplemented with glucose, oxygen and epinephrine. The findings revealed that Bacopa monnieri treatment significantly reversed the downregulation of mGluR8 gene to normal level.

Similarly, glucose supplementation together with oxygen supply in hypoxic neonates rescued the NMDAR1 gene expression to normal level. These observations suggest a neuroprotective role of Bacopa monnieri in glutamate-mediated excitotoxicity during seizures in pilocarpine-induced epilepsy. A study employed a number of convulsion inducing models including pentylenetetrazol, strychnine, hypoxic stress and pilocarpine to studied the anticonvulsive activity of Bacopa monnieri in rats and mice. Bacopa monnieri was administered orally (50 and 55 mg/kg) in these animals, 2 and 4 h prior to receiving convulsive stimuli. It was found that the herb produced a significant anticonvulsant activity like benzodiazepines in different convulsion inducing models studied (Kaushik et al., 2009).

CDRI-08 (KeenMind) has been reported to ameliorate pilocarpine induced epilepsy through regulation of 5-HT2C and NMDA receptors in cerebral cortex (Khan et al., 2008; Krishnakumar et al., 2009a,b, 2015). During epileptic condition, the expression of glutamate receptors is altered. 5-HT2C receptor and IP3 (a signal transduction molecule) shows an elevated expression during epileptic state. On the other hand, NMDA receptor shows a downregulated expression in the brain of epileptic animals whereas mGlu5 and GLAST shows an upregulated expression leading to glutamate mediated excitotoxicity. It has been shown that treatment of epileptic rats with Bacopa monnieri reverses the changes observed in 5-HT2C, NMDA receptor expression and IP3 content thereby effectively managing the neurotransmitter balance in the cerebral cortex. These observations suggest the neuroprotective role of CDRI-08 (KeenMind) in glutamate-mediated excitotoxicity via regulating altered neurotransmitter receptor expression during seizures observed in pilocarpine induced epilepsy.

Antidepressant effects(17)

Bacopa monnieri appears to play a plethora of functions in the central nervous system. In addition to its diverse role in treating the diseased brain, the herb shows anti-depressant property. When mice supplemented with CDRI-08 (KeenMind) were subjected to tail suspension test (TST) and forced swimming (FST), the herbal drug exerted antidepressant activity (Shen et al., 2009). The drugs were given orally for 5 days that significantly minimized the immobility time span both in FST and TST. The antidepressant activity of Bacopa monnieri was believed to have occurred by some of its components like Bacosides A and B, bacopasaponin C, bacopasides I and II and its plant extract. However, bacopaside VII, a constituent of Bacopa monnieri, did not reveal any antidepressant activity when analyzed using tail suspension and forced swimming tests (Sairam et al., 2002; Sheikh et al., 2007; Zhou et al., 2007). Banerjee et al. studiedd whether treatment with Bacopa monnieri produces any antidepressant activity in rats which were made to undergo chronic unpredictable stress based depression (Banerjee et al., 2014). The group used some behavioral tests like sucrose consumption test, shuttle box escape test and open field test to validate this hypothesis. Stress was induced in rats for a period of 4 weeks. This resulted in decreased consumption of sucrose, locomotor activity and escape latency in the animals. In addition, both mRNA and protein content of brain-derived neurotrophic factor (BDNF) showed downregulated expression in both the frontal cortex and hippocampus in CUS treated rats. Supplementation with Bacopa monnieri (80–120 mg/kg) greatly suppressed the behavioral changes and attenuated BDNF content to normal in the frontal cortex and hippocampus areas of the rat brain confirming its antidepressant activity.

The antidepressant activity of Bacopa monnieri was reported in morphine induced depression in rats (Rauf et al., 2014). Morphine, an opioid analgesic drug, when administered in rats cause

depression. The drug was administered everyday two times at a dose of 20–65 mg/kg for 8 consecutive days. Three days after last morphine administration forced swimming test (FST) was conducted to assess the withdrawal effect of the drug. It was found that Bacopa monnieri treatment inhibited the withdrawal effect of the morphine induced depression. Altogether, Bacopa monnieri can be considered as a useful adjunct to cure depression like illnesses.

Antianxiety effects(18)

CDRI-08 (KeenMind) consists of antianxiety effects, antidepressant activity, anticonvulsive action and antioxidant activity (Reas et al., 2008). Supplementation of Bacopa monnieri normalized the levels of corticosterone hormone which were imbalanced due to acute and chronic stress induction in rats. The levels of 5-HT, noradrenalin (NA) and dopamine in cortex and hippocampus regions of rats were also brought to normal in acute and chronic unpredictable stress induced animals (Sheikh et al., 2007). Bacopa monnieri modulates the cholinergic system and produces metal chelating effects. Cognitive abnormalities produced by neurotoxins, colchicine and ibotenic acid were improved by Bacopa monnieri administration in a dose dependent manner in rats (Bhattacharya et al., 2000; Rauf et al., 2012b). Also norepinephrine levels declined and 5-hydroxytryptamine levels were increased in hippocampus, cerebral cortex and hypothalamus by Bacopa monnieri treatment. Anxiety was relieved to a greater extent with higher doses of CDRI-08 (KeenMind), which was comparable to lorazepam, a standard drug used in the treatment of anxiety (Bhattacharya and Ghosal, 1998). However, treatment with lower dose of CDRI-08 (KeenMind; 10, 20, or 30 mg/kg supplemented for 1 week period) did not affect serotonin (5-HT) and dopamine levels in mice brain (Rauf et al., 2012b).

Antioxidant effects(19,20,21)

Free radical stress and subsequent formation of ROS has been implicated in the development of several diseases. Bacopa monnieri, a traditionally reputed herbal drug, has been reported to exert antioxidant activity. There are many factors that produce free radical mediated oxidative stress *in vivo*. Smoke formed from crackers increases the risk of the development of many lung diseases that ultimately results in the formation of oxidative stress. Pandareesh M. and Anand assessed whether Bacopa monnieri ameliorates the neuronal damage and physiological changes in rats upon smoke exposure (Pandareesh M. and Anand, 2014). The group exposed the rats to smoke for 1h for 3 weeks and treated the animals with Bacopa monnieri with three different dosages viz., 10, 20, and 40 mg/kg body weight. This treatment quenched reactive oxygen species formed as a result of smoke exposure and normalized the pathological changes observed in rat brain. Also, the rate of acetylcholine esterase activity, lipid peroxidation and brain neurotransmitter levels were found to be normal upon Bacopa monnieri treatment. The herb also down regulated iNOS expression thereby inhibited nitric oxide generation and HO-1 expression. Antioxidant enzyme concentration and monoamine oxidase activity were also enhanced which were depleted upon smoke exposure. These findings suggest the antioxidant and neuroprotective properties of Bacopa monnieri and may be considered as a possible remedy in the treatment of several neurodegenerative disorders.

Furthermore, oxidative stress generated by lead exposure is ameliorated by Bacopa monnieri in various areas of rat brain (Velaga et al., 2013). Lead exposure raised the levels of reactive oxygen species (ROS). Also the rate of lipid peroxidation, the carbonyl content in total protein and metal content in different tissues of rat brain. However, Bacopa monnieri treatment mitigated the levels of these proteins to normal suggesting its antioxidant property. Similarly,

oxidative stress generated by sodium nitroprusside (SNP) was ameliorated by Bacopa monnieri treatment in PC12 cells (Pandareesh M. D. and Anand, 2014). In this study, Bacopa monnieri inhibited the generation of NO via down regulating iNOS expression. Heat shock proteins together with apoptotic markers such as Bax, Bcl-2, cytochrome-c and caspase-3 were also modulated to normal, the level of which was imbalanced by SNP exposure in PC12 cells. In addition, sodium nitroprusside (SNP) induced damage to plasma membrane, nuclear membrane and mitochondrial integrity of PC12 cells was ameliorated by Bacopa monnieri treatment. These findings suggests a protective and antioxidant role Bacopa monnieri exhibits to PC12 cells by mitigating the SNP induced toxicity.

Bacopa monnieri also ameliorates decabrominated diphenyl ether (PBDE-209) provoked toxicity in neonate and young female mice (Verma et al., 2014). Different doses of Bacopa monnieri (40, 80, or 120 mg/kg) in combination with PBDE-209 (20 mg/kg body weight) were administered orally in mice from postnatal day 3 to day 10. Levels of oxidative stress indicators (malondialdehyde, and protein carbonyl) and antioxidant markers (superoxide dismutase and glutathione peroxidase) were measured. The results showed that the dose of 120 mg/kg of Bacopa monnieri restored the levels of oxidants and activities of antioxidant enzymes in the hippocampus and frontal cortex of neonates against PBDE-209-induced toxicity. This data suggests that Bacopa monnieri renders the brain resistant to PBDE-209 induced toxicity and thus may be better exploited as a preventive approach to protect against oxidative-mediated neuronal dysfunctions.

Another paraquat (PQ) mediated oxidative stress and neurotoxicity was ameliorated by Bacopa monnieri treatment in different brain regions of pre-pubertal mice (Hosamani et al., 2014). Mice were administered CDRI-08 (KeenMind) daily (200 mg/kg body weight) for 4 consecutive

weeks along with PQ (15 mg/kg body weight, intraperitoneally) after 3 h of last dose of extract. Within 2 days PQ administration resulted in the up regulation of oxidative stress indicating molecules (such as reactive oxygen species (ROS), hydroperoxides (HP) and malondialdehyde (MDA). However, Bacopa monnieri restored PQ induced oxidative stress back to normal via suppression of these markers in various brain regions.

Previous studies have demonstrated increased reactive oxygen species formation and cytotoxicity in cells exposed to hydrogen peroxide (H_2O_2). Hence, H_2O_2 has been greatly used to study the effects of antioxidant and cytoprotective role of herbal extracts. Pandareesh et al. studied the effect of Bacopa monnieri on H_2O_2mediated oxidative stress in PC12 and L132 cells (Pandareesh et al., 2014). In this study, cells were treated with H_2O_2 for 24 h with or without Bacopa monnieri pretreatment. A couple of tests including cell viability assay, ROS estimation, lipid peroxidation, mitochondria membrane potential assay, comet assay and gene expression studies were conducted to measure the cytoprotective activity of Bacopa monnieri. Bacopa monnieri scavenged free radicals formed during the process thereby assisting in cytoprotection. Moreover, H_2O_2 induced mitochondrial and plasma membrane damage was repaired by Bacopa monnieri in both of these cell lines.

Stress is a common and sometimes unavoidable problem that may lead to serious health effects. Investigators are attempting to explore the role of phytochemicals, plant extracts and compounds in modulating the activities of stress associated biomarkers. The levels of stress biomarkers namely Hsp, SOD, and cyt P450 were evaluated to study the effect of Bacopa monnieri in stress induced animals. To studied the antistress effect, the herbal medicine was orally administered (20 and 40 mg/kg) in rats for 7 successive days (Chowdhuri et al., 2002). Stress induction elevated Hsp expression in brain. However, the protein expression remain unaltered at both

doses of Bacopa monnieri in all brain regions. Interestingly, pretreatment of animals with Bacopa monnieri (7 days period) before stress induction resulted in decreased Hsp expression in all brain areas with more significant reduction in hippocampus region. At the same time, lower dose of Bacopa monnieri decreased SOD activity whereas its higher dose increased it in the hippocampus region of the rat brain. Similarly, pretreatment with a lower dose of Bacopa monnieri further reduced the SOD activity in each of the brain regions. However, higher dose of Bacopa monnieri led to elevation in the enzyme activity in all areas of the brain except cerebellum and hippocampus where it dropped significantly. Similarly stress increased the activity of Cyt P450 in all the brain regions. Almost similar results were observed with both the doses, but the P450 expression reduced with a higher dose of Bacopa monnieri. Likewise, animals pretreated with the higher dose of Bacopa monnieri followed by stress induction restored the activity of P450 enzymes to near normal levels in animals. These findings indicated the effectiveness of Bacopa monnieri in regulating stress biomarker levels and suppoting the brain to combat stressful conditions.

Mathur et al. used DPPH radical scavenging method to studied the antioxidant nature of four different extracts of CDRI-08 (KeenMind) in male wistar rats. It was found that all the four different extracts possessed the maximum antioxidant activity (Mathur et al., 2010). Bacopa monnieri has also been considered as a valuable supplement in the treatment of cancer and tumor. Janani et al. studied the effects of Bacopa monnieri on chemoprevention of liver cancer in an animal model (Janani et al., 2010). The group treated the animals with a carcinogen, which led to an increase in their lipid peroxidation, tumor biomarkers and markers corresponding to liver damage. Eventually, hemolysate and antioxidant status dropped markedly in the liver. Bacopa monnieri supplementation recovered the enzyme levels to normal, suppressed lipid

peroxidation and enhanced its antioxidant status suggesting its chemoprotective role in the treatment of liver cancer. Similarly, the antioxidant and tumor inhibiting property of Bacopa monnieri was studied in 3-methylcholanthrene induced fibrosarcoma rats (Rohini et al., 2004). The levels of the antioxidant enzymes such as glutathione peroxidase, superoxide dismutase, catalase and glutathione, the rate of lipid peroxidation (LPO) were determined in the liver and kidney tissues. Sarcoma induction in rats resulted in a marked increase in the rate of LPO and a decrease in the antioxidant enzyme status. Furthermore, tumor markers such as lactate dehydrogenase, alanine transaminase, aspartate transaminase, creatine kinase, and sialic acid showed an upregulated expression in the serum. Bacopa monnieri supplementation enhanced the antioxidant enzyme status, reduced the rate of lipid peroxidation and downregulated tumor development markers.

Similar to many previous reports, an investigating group measured the antioxidant and lipid peroxidative status in response to Bacopa monnieri supplementation in streptozotocin induced diabetic rats. They provided CDRI-08 (KeenMind) orally to these diseased animals daily for 15 days (dosage: 50, 125, and 250 mg/kg). Thereafter, the enzymatic activity of catalase, SOD and GPx, levels of GSH and rate of lipid peroxidation were measured in kidney and brain, with special attention to cerebrum, cerebellum and midbrain. It was found that antioxidant status and peroxidative damage was totally reversed by the administration of plant extract. Activities of SOD, catalase, GPx and levels of GSH were significantly increased in diabetic rats treated with extract (Kapoor et al., 2009). To studied the antidiabetic effect of this herb, Ghosh et al., treated alloxan induced hyperglycemic rats with CDRI-08 (KeenMind). They found that blood glucose level went down when single and multiple doses of Bacopa monnieri were provided to the animals. Weight of the rats was also recovered to normal with Bacopa monnieri treatment which

was lost during diabetes. CDRI-08 (KeenMind) also inhibited the increase in glycosylated hemoglobin *in vitro* and reduced thiobarbituric acid reactive substances (TBARS) content. It also increased the levels of glutathione, SOD, catalase activity in liver of diabetic rats. The effect of extract was such that the peripheral glucose utilization was found to be increased *in vitro* in the diaphragm of diabetic rats, which was proportionate to the effect of insulin (Ghosh et al., 2010). The effects of CDRI-08 (KeenMind) (40 mg/kg) were studied on aluminum induced oxidative stress and hippocampus damage in rats (Nannepaga et al., 2014). Electron microscopy was used to evaluate any structural changes occurred as a result of aluminum intoxication in the hippocampus region of the rat brain. The enzyme activities of antioxidants such as catalase, glutathione peroxidase and SOD were determined. Aluminum administration induced oxidative damage, which was confirmed by finding increased levels of thiobarbituric acid reactive substances in the rat brain. Treatment with Bacopa monnieri for a period of 1 month decreased the levels of thiobarbituric acid reactive substances, and restored antioxidant enzyme levels. Furthermore, electron microscopy results of Bacopa monnieri treated rats revealed attenuated vacuolation, lipofuscin deposition and pyramidal cell degeneration in the hippocampus which was induced via aluminum induction. These findings further demonstrate Bacopa monnieri an important supplement useful for ameliorating the antioxidant status and inhibiting the oxidative damage occurred in aluminum intoxicated animals.

An *in vitro* study exploring the potential of Bacopa monnieri in cytokine regulation, quenching of reactive oxygen species (ROS), and ameliorating intracellular signaling pathway markers was conducted in splenocytes of F344 rats (different age groups; Priyanka et al., 2013). Firstly, concanavalin exposure induced proliferation of lymphocytes acquired from spleen of F344 rats of specific age groups (3-month-old, 8–9 month old, and 18 month old). These proliferated

splenocytes were thereafter treated with different dosages of Bacopa monnieri (0.001, 0.01, 0.05, 0.1, and 1%) and donepezil (5, 10, 25, 50, and 100 μg/ml). The effect of these drugs was studied via measuring the levels of cytokines, antioxidant markers and different intracellular molecules. It was found that donepezil alone but not Bacopa monnieri reduced the lymphocyte proliferation in young rats. Cytokines such as IL-2 and IFN-γ showed elevated expression with lower doses of Bacopa monnieri whereas their expression reduced due to donepezil in rats which were young and early middle-aged. Concanavalin exposure also reduced the activity of antioxidant markers (SOD, CAT, GPx, and GST) in these cells. On the contrary, enhancement in CAT activity was observed in all age groups with Bacopa monnieri supplementation whereas in older rats donepezil increased the SOD activity. Likewise the action of GPx and GST biomarkers was enhanced in lymphocytes via both Bacopa monnieri and donepezil administration all age groups. Whereas in splenocytes there was an enhancement in the rate of lipid peroxidation and age-related suppression in NO generation. Bacopa monnieri along with donepezil raised up NO production in the lymphocytes of early middle-aged and older rats. It is important to note that donepezil could suppress lipid peroxidation splenocytes of only old rats whereas Bacopa monnieri could do the same in both early-middle-aged and old rats. Similarly the reversal in decline of the p-Akt expression was achived by Bacopa monnieri in both early middle aged and old rats' lymphocytes. We can conclude that Bacopa monnieri alongwith donepezil exert various age-related effects on cytokine generation, antioxidant status and intracellular targets which may further manipulate the therapeutic efficiency of these drugs in various diseases.

Gastrointestinal and hepatoprotective effects (22,23,24)

Bacopa monnieri has been shown to treat a number of gastrointestinal disorders. A dose of 500 mg/kg of CDRI-08 (KeenMind) when supplied orally prevented the development of diarrhea in mice. As compared to loperamide (50 mg/kg) Bacopa monnieri was able to decrease the frequency of defecation suggesting its role as an anti-diarrhoeal herb (Siraj et al., 2012). Also, the fresh juice of this herbal medicine has been shown to prevent the formation of ulcers (Rao et al., 2000). In this study, the group assessed the prophylactic and healing effects CDRI-08 (KeenMind) exerts in five different models of gastric ulcers. It was found that the extract (20 mg/kg for 10 consecutive days) alleviated acetic acid induced penetrating ulcers, strengthened mucosal barrier and reduced mucosal exfoliation by reducing the rate of lipid peroxidation in gastric mucosa of rat. The extract has also been reported to produce anti-Helicobacter pylori activity (Sairam et al., 2001; Goel et al., 2003). A randomized, double-blind, placebo controlled clinical trial of 169 irritable bowel syndrome patients, was conducted to assess the therapeutic capacity of an Ayurvedic preparation containing Bacopa monnieri and *Aegle marmelos* herbs. These herbal drugs were provided orally to the patients three times daily for a period of 6 weeks. The effect of ayurvedic treatment was highly beneficial in curing the disease. However, the extent of Bacopa monnieri's efficacy could not be predicted as both the drugs were given at the same time to the patients (Yadav et al., 1989).

CDRI-08 (KeenMind) has been found to exert hepatoprotective effect in rats by alleviating antioxidant enzymes status induced by morphine (Sumathi et al., 2011). It was found that morphine induction increased the rate of lipid peroxidation and decreased antioxidant enzyme status in rats. This toxicity induced as a result of morphine induction was nullified by the supplementation of Bacopa monnieri.

Endocrine effects(25-30)

The efficay of Bacopa monnieri in treating endocrine related abnormalities has been documented in a few animal studies. CDRI-08 (KeenMind; 200 mg/kg orally) has been shown to alter the secretion of thyroid hormone in male mice (Kar et al., 2002). The synthesis of T4 hormone was increased by 41% via Bacopa monnieri intake. However, T3 synthesis was unaffected by the drug supplement indicating that the drug might not be involved in T4 to T3 conversion. Furthermore, Bacopa monnieri has been demonstrated to possess the anti-fertility ability in male mouse (Singh and Singh, 2009).

Antimicrobial effects

Methanolic extracts of CDRI-08 (KeenMind) have been reported to possess antimicrobial activity as compared to other extracts (Azad et al., 2012; Katoch et al., 2014). In this study, hexane and petroleum ether extracts inhibited the growth of microbes in a similar manner but the effect was less considerable in comparison to methanolic extracts whereas the aqueous extract of CDRI-08 (KeenMind) did not show anti-microbial activity (Hosamani et al., 2014). The growth of Staphylococcus aureus was inhibited to a greater extent by the methanolic extract (1mg/ml) of CDRI-08 (KeenMind) in comparison to Salmonella typhi and Eschirichia coli. However, the extract did not suppress the growth of K. pneumonia microbe (Rohini et al., 2004).

Anti-inflammatory and painkiller effects

Bacopa monnieri, known for its anti-inflammatory and pain relieving effects, acts by selectively inhibiting cyclo-oxygenase-2 enzyme, and consequently reducing prostaglandins synthesis. Jain et al. demonstrated that CDRI-08 (KeenMind) could effectively suppress the experimentally

produced inflammatory reaction by quenching the synthesis of prostaglandins and preventing lyosomal membranes from rupture. Also, treatment with anti-inflammatory dose of Bacopa monnieri didn't cause any gastric problems (Jain et al., 1994). Writhing produced by acetic acid in mice was reduced using whole plant ethanol extract of CDRI-08 (KeenMind) (250 and 500 mg/kg; Rao et al., 2000). Mathur et al. used different extracts of CDRI-08 (KeenMind) and studied their anti-inflammatory effects in edema caused by carrageenan in rat's hind paws. Supplements including methanolic and aqueous extract (100 mg/kg) of Bacopa monnieri were found to significantly reduce inflammation, while, petroleum ether and hexane extracts produced no effect (Janani et al., 2010). Also, it was found that methanolic extract (100, 200, 300 μg) assisted in membrane stabilization as compared to diclofenac sodium (Rohini et al., 2004). Interleukin-6 and tumor necrosis factor-alpha synthesis was inhibited by the fractions of Bacopa monnieri containing triterpenoids and bacosides (Viji and Helen, 2011). Furthermore, proinflammatory cytokines such as nitric oxide and TNF-α showed down regulated expression in stimulated macrophages and IFN-γ in stimulated human blood cells (Williams et al., 2014). These results provide further evidences that confirm the efficacy of Bacopa monnieri in the treatment of brain inflammation.

Relaxant effects on smooth and cardiac muscles

Investigations exploring the efficay of CDRI-08 (KeenMind) in relaxing cardiac and smooth muscles have been demonstrated in experimental animals. The herbal extract ameliorates left ventricular contractility, coronary blood flow and heart rate in rabbit's heart (Rashid et al., 1990). It also relaxes bronchial smooth muscles, pulmonary arteries, aorta, and trachea. Apparently, the mechanism of action Bacopa monnieri exerts on the cardiac muscles is quite similar to that of quinidine. These effects possibly were mediated by accumulation of calcium ions in the

extracellular space (Dar and Channa, 1997, 1999; Channa et al., 2003). Furthermore, CDRI-08 (KeenMind) stabilizes the activity of mast cells comparable to disodium cromoglycate (Samiulla et al., 2001).

Clinical trials(31-35)

Basically Bacopa monnieri is known to ameliorate cognitive function. This viewpoint has now been scientifically tested through a handful of randomized, double-blind, placebo-controlled clinical trials and nearly all have shown promising results. (Singh et al., 2014) found that supplementation of 12g of Bacopa monnieri improved the nervousness, concentration and memory in adults. The dose was given to 35 adults in the form of syrup for 4 weeks. There was no complaint of side effects (Singh and Singh, 1980). Similar observations were confirmed by Sharma et al. who studied the effect of Bacopa monnieri in 20 primary school children (Sharma et al., 1987). A dosage of 350 mg was given in syrup form three times a day for 3 months. The herb improved learning skills, perception, memory and reaction times in them without the occurrence of any side effects. A randomized and double-blind placebo-controlled trial in 36 children was conducted, who were affected with attention deficit hyperactivity disorder (ADHD) was conducted (Negi et al., 2000). The results were highly beneficial with Bacopa monnieri supplementation as it greatly improved the logical memory. In this study, freshly preperaed whole plant extract of Bacopa monnieri was administered at a dosage of 50 mg two times a day for a period of 12 weeks. Later, cognitive function tests were performed at various time points which included baseline, 4, 8, 12, and 16 weeks. Recovery was observed in the 12 weeks group, consolidated by different cognitive tests. A placebo controlled study demonstrated enhanced

learning and controlled abnormal behavior in 40 mentally retarded children consuming standardized extract of CDRI-08 (KeenMind; Dave et al., 1993). Another randomized, double-blind, placebo-controlled trial proved the effectiveness of Bacopa monnieri in ameliorating memory (Roodenrys et al., 2002). In this study, 76 healthy adults, 40–65 years old, were supplemented with Bacopa monnieri (dose 300 mg) and they all were benefitted by retaining the information in delayed recall of word pairs. However, there were a few parameters which failed to show the beneficial effect of Bacopa monnieri. These include attention, working memory, short-term memory tasks, psychological state and retrieval of prior knowledge. Likewise, no effect of Bacopa monnieri (300 mg dosage) on various measures of memory performance was found when it was administered 2 h after treatment suggesting that its benefits are obtained after long-term use (Nathan et al., 2001). The same group of investigators later found no significant effect of Bacopa monnieri (300 mg/day) on cognition and memory when provided in combination with *Ginko biloba* 120 mg/day for a period of 4 weeks. This was a randomized, placebo-controlled, double-blinded clinical trial, conducted in 85 healthy subjects (Nathan et al., 2004). Bacomind™ capsule when consumed orally (at a dose of 300 mg once a day for first 15 days and 450 mg once a day for next 15 days) improved mental functioning in 23 healthy adults (Pravina et al., 2007).

A placebo-controlled and double-blinded 12-week clinical trial was conducted out to studied the effectiveness of CDRI-08 (KeenMind) (300 mg daily for 12 weeks) on 46 healthy people aged between 18 and 60 years. A series of cognition function tests were conducted at baseline and later on after 5 and 12 weeks. At the end of 12 weeks, in the treatment group a significant enahncement in verbal learning and concentration was noticed compared to non-treated groups. These effects were not observed at baseline or at 5 weeks of treatment (Stough et al., 2001).

Likewise many other clinical trials were conducted to determine the effect of Bacopa monnieri on memory function in elderly people above the age of 55 years. They all used same criteria with same amount of dosage and period of administration. It was found that aged people were able to acquire, store and retain their memory over time by consuming Bacopa monnieri as a supplement (Calabrese et al., 2008; Morgan and Stevens, 2010). Another randomized double-blind placebo-controlled clinical trial examining the effect of Bacopa monnieri on cognitive, biochemical and cardiovascular performance was conducted in elderly people (Morgan and Stevens, 2010). This study involved a large number of randomly selected participants (465 participants) aged between 60 and 75 years. CDRI-08 (KeenMind) (300 mg/day) was given to them for a period of 12 months. The participants underwent a series of cognitive function tests at points: baseline, 3, 6, and 12 months and expectedly, the results revealed a significant improvement in their memory function which suggests the effectiveness of Bacopa monnieri to be used as a memory booster.

Peth Nui et al. studied different aspects of brain function like attention, cholinergic and monoaminergic functions, memory processing and working memory-using Bacopa monnieri. They recruited 60 healthy adults aged around 60 years for a randomized, double-blind, placebo-controlled clinical trial. The period of Bacopa monnieri administration and dosage was similar to previous studies (300 mg for 12 weeks; Peth-Nui et al., 2012). AChE and MAO activities were measured to evaluate the cholinergic and monoaminergic systems functions. On the contrary, percent accuracy and reaction time was examined to determine the working memory. Latencies and amplitude of N100 were used to measure attention and cognitive processing. The findings of this study revealed a reduction in both N100 and P300 latencies and improvement on working memory with Bacopa monnieri supplementation. Furthermore, AChE activity was also found to be decreased suggesting that Bacopa monnieri can ameliorate cognitive processing, working

memory and attention partly through the reduction of AChE activity. In another similar kind of clinical trial involving healthy elderly subjects and others suffering from senile dementia of Alzheimer's type (SDAT), behavioral and biochemical parameters like learning abilities, inflammatory markers and oxidative stress were measured (Sadhu et al., 2014). A number of cognitive function tests were employed after every 3 months to evaluate the efficay of Bacopa monnieri in these people. It was found that Bacopa monnieri treated SDAT patients improved memory performance when compared to controls. The levels of inflammatory markers like homocysteine, C-reactive protein, and tumor necrosis factor alpha; oxidative stress markers like glutathione peroxidase, glutathione, thiobarbituric acid reactive substances and SOD showed a marked decline in Bacopa monnieri treated SDAT patients. This suggests the significance of the herb in managing cognitive decline associated with the aging process. Another multicenter clinical trial involving patients with mild cognitive impairment used similar criteria and obtained favorable results establishing the role of Bacopa monnieri in improving cognitive function (Zanotta et al., 2014).

Currently , the acute effects of bacopa moneri (320 and 640 mg doses) on stress and mood swings generated by versatile were demonstrated in a double-blind, placebo-controlled clinical trial involving 17 healthy volunteers (Benson et al., 2014). Bacopa monnieri supplementation reduced stress as observed by reduction in cortisol levels and alleviated mood in these participants. Altogether, these studies demonstrate the clinical efficacy of Bacopa monnieri in alleviating various abnormalities hence can be considered as a trustful frontier to treat various diseases

Conclusion

Interests in the utilization of different herbal products increase day by day. As several studies show that utilization of synthetic drugs have side effects, so there is a need of alternative source of drugs which have low or negligible side effects. Medicinal plants contain wide range of bioactive compounds which is an alternative of synthetic drug for Alzheimer's disease treatment. Medicinal plants can boost life quality of patients with AD and memory deficits. This review provides the details about the role of medicinal plants against the Alzheimer's disease. However, mechanisms of action are still not clear. Future clinical trials involving larger sample sizes are require investigating role of different medicinal plants and the underlying mechanisms.

References

1. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. Lancet. 2011;377:1019–1031. [PubMed] [Google Scholar]

2. Ryman DC, Acosta-Baena N, Aisen PS, Bird T, Danek A, Fox NC, et al. Symptom onset in autosomal dominant Alzheimer disease: a systematic review and meta-analysis. Neurology. 2014;83:253–260. [PMC free article] [PubMed] [Google Scholar]

3. Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S, Van der Flier WM. Alzheimer's disease. Lancet. 2016;388:505–517. [PubMed] [Google Scholar]

4. Akiyama H. [Development of disease-modifying therapy for Alzheimer's disease] Brain Nerve. 2016;68:463–472. [PubMed] [Google Scholar]

5. Markowitsch HJ, Staniloiu A. Amnesic disorders. Lancet. 2012;380:1429–1440. [PubMed] [Google Scholar]

6. Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry. 1957;20:11–21. [PMC free article] [PubMed] [Google Scholar]

7. Alzheimer's Association. 2010 Alzheimer's disease facts and figures. Alzheimers Dement. 2010;6:158–194. [PubMed] [Google Scholar]

8. World Alzheimer Report 2015 The Global Impact of Dementia. http://www.alz.co.uk/research/worldreport2015

9. Selkoe DJ. Alzheimer's disease: genes, proteins, and therapy. Physiol Rev. 2001;81:741–766. [PubMed] [Google Scholar]

10. Brunkan AL, Goate AM. Presenilin function and gamma-secretase activity. J Neurochem. 2005;93:769–792. [PubMed] [Google Scholar]

11. Priller C, Bauer T, Mitteregger G, Krebs B, Kretzschmar HA, Herms J. Synapse formation and function is modulated by the amyloid precursor protein. J Neurosci. 2006;26:7212–7221. [PMC free article] [PubMed] [Google Scholar]

12. Cai Y, An SS, Kim S. Mutations in presenilin 2 and its implications in Alzheimer's disease and other dementia-associated disorders. Clin Interv Aging. 2015;10:1163–1172. [PMC free article] [PubMed] [Google Scholar]

13. Poirier J, Delisle MC, Quirion R, Aubert I, Farlow M, Lahiri D, et al. Apolipoprotein E4 allele as a predictor of cholinergic deficits and treatment outcome in Alzheimer disease. Proc Natl Acad Sci U S A. 1995;92:12260–12264. [PMC free article] [PubMed] [Google Scholar]

14. Masliah E, Mallory M, Deerinck T, DeTeresa R, Lamont S, Miller A, et al. Re-evaluation of the structural organization of neuritic plaques in Alzheimer's disease. J Neuropathol Exp Neurol. 1993;52:619–632. [PubMed] [Google Scholar]

15. Thal DR, Griffin WS, de Vos RA, Ghebremedhin E. Cerebral amyloid angiopathy and its relationship to Alzheimer's disease. Acta Neuropathol. 2008;115:599–609. [PubMed] [Google Scholar]

16. Kahol AP, et al. Council of Scientific and Industrial Research Process for the preparation of a extract rich in Bacosides from the herb Bacopa monniera. United States Patent US006833143B1 (December 21, 2004).

17. Kulkarni R, Girish KJ, Kumar A. Nootropic herbs (Medhya Rasayana) in Ayurveda: an update. Pharmacogn Rev. 2012;6:147–153. [PMC free article] [PubMed] [Google Scholar]

18. Aguiar S, Borowski T. Neuropharmacological review of the nootropic herb Bacopa monnieri. Rejuvenation Res. 2013;16:313–326. [PMC free article] [PubMed] [Google Scholar]

19. Singh HK, Dhawan BN. Neuropsychopharmacological effects of the Ayurvedic nootropic Bacopa Monniera Linn. (Bacopa monnieri) Indian J Pharmacol. 1997;29:359–365. [Google Scholar]

20. Gupta P, Khatoon S, Tandon PK, Rai V. Effect of cadmium on growth, bacoside A, and bacopaside I of Bacopa monnieri (L.), a memory enhancing herb. ScientificWorldJournal. 2014;2014:824586. [PMC free article] [PubMed] [Google Scholar]

21. Russo A, Borrelli F. Bacopa monniera, a reputed nootropic plant: an overview. Phytomedicine. 2005;12:305–317. [PubMed] [Google Scholar]

22. Barrett SC, Strother JL. Taxonomy and natural history of Bacopa (Scrophulariaceae) in California. Systematic Botany. 1978;3:408–419. [Google Scholar]

23. Basu NK, Lamsal PP. Investigations on Indian medicinal plants; Hydrocotyle asiatica Linn. Q J Pharm Pharmacol. 1947;20:135. [PubMed] [Google Scholar]

24. Rastogi S, Pal R, Kulshreshtha DK. Bacoside A3 – a triterpenoid saponin from Bacopa monniera. Phytochemistry. 1994;36:133–137. [PubMed] [Google Scholar]

25. Sairam K, Rao CV, Babu MD, Goel RK. Prophylactic and curative effects of Bacopa monniera in gastric ulcer models. Phytomedicine. 2001;8:423–430. [PubMed] [Google Scholar]

26. Kumar V. Efficay medicinal plants for CNS disorders: an overview. Phytother Res. 2006;20:1023–1035. [PubMed] [Google Scholar]

27. Pase MP, Kean J, Sarris J, Neale C, Scholey AB, Stough C. The cognitive-enhancing effects of Bacopa monnieri: a systematic review of randomized, controlled human clinical trials. J Altern Complement Med. 2012;18:647–652. [PubMed] [Google Scholar]

28. Jenny NS. Inflammation in aging: cause, effect, or both? Discov Med. 2012;13:451–460. [PubMed] [Google Scholar]

29. Floyd RA, Hensley K. Oxidative stress in brain aging. Implications for therapeutics of neurodegenerative diseases. Neurobiol Aging. 2002;23:795–807. [PubMed] [Google Scholar]

30. Parletta N, Milte CM, Meyer BJ. Nutritional modulation of cognitive function and mental health. J Nutr Biochem. 2013;24:725–743. [PubMed] [Google Scholar]

31. Bhattacharya SK, Bhattacharya A, Kumar A, Ghosal S. Antioxidant activity of Bacopa monniera in rat frontal cortex, striatum and hippocampus. Phytother Res. 2000;14:174–179. [PubMed] [Google Scholar]

32. Bourre JM. Effects of nutrients (in food) on the structure and function of the nervous system: update on dietary requirements for brain. Part 1: micronutrients. J Nutr Health Aging. 2006;10:377–385. [PubMed] [Google Scholar]

33. Sohal RS, Orr WC. The redox stress hypothesis of aging. Free Radic Biol Med. 2012;52:539–555. [PMC free article] [PubMed] [Google Scholar]

34. Simpson T, Pase M, Stough C. Bacopa monnieri as an antioxidant therapy to reduce oxidative stress in the aging brain. Evid Based Complement Alternat Med. 2015;2015:615384. [PMC free article] [PubMed] [Google Scholar]

35. Russo A, Izzo AA, Borrelli F, Renis M, Vanella A. Free radical scavenging capacity and protective effect of Bacopa monniera L. on DNA damage. Phytother Res. 2003;17:870–875. [PubMed] [Google Scholar]

36. Dhanasekaran M, Tharakan B, Holcomb LA, Hitt AR, Young KA, Manyam BV. Neuroprotective mechanisms of ayurvedic antidementia botanical Bacopa monniera. Phytother Res. 2007;21:965–969. [PubMed] [Google Scholar]

37. Rottkamp CA, Raina AK, Zhu X, Gaier E, Bush AI, Atwood CS, et al. Redox-active iron mediates amyloid-beta toxicity. Free Radic Biol Med. 2001;30:447–450. [PubMed] [Google Scholar]

38. Falangola MF, Lee SP, Nixon RA, Duff K, Helpern JA. Histological co-localization of iron in Abeta plaques of PS/APP transgenic mice. Neurochem Res. 2005;30:201–205. [PMC free article] [PubMed] [Google Scholar]

39. Kapoor R, Srivastava S, Kakkar P. Bacopa monnieri modulates antioxidant responses in brain and kidney of diabetic rats. Environ Toxicol Pharmacol. 2009;27:62–69. [PubMed] [Google Scholar]

40. Shinomol GK, Bharath MM, Muralidhara Neuromodulatory propensity of Bacopa monnieri leaf extract against 3-nitropropionic acid-induced oxidative stress: in vitro and in vivo evidences. Neurotox Res. 2012;22:102–114. [PubMed] [Google Scholar]

41. Jyoti A, Sharma D. Neuroprotective role of Bacopa monniera extract against aluminium-induced oxidative stress in the hippocampus of rat brain. Neurotoxicology. 2006;27:451–457. [PubMed] [Google Scholar]

42. Morgan A, Stevens J. Does Bacopa monnieri improve memory performance in older persons? Results of a randomized, placebo-controlled, double-blind trial. J Altern Complement Med. 2010;16:753–759. [PubMed] [Google Scholar]

43. Russo A, Borrelli F, Campisi A, Acquaviva R, Raciti G, Vanella A. Nitric oxide-related toxicity in cultured astrocytes: effect of Bacopa monniera. Life Sci. 2003;73:1517–1526. [PubMed] [Google Scholar]

44. Michaelis ML. Drugs targeting Alzheimer's disease: some things old and some things new. J Pharmacol Exp Ther. 2003;304:897–904. [PubMed] [Google Scholar]

45. Le XT, Pham HT, Do PT, Fujiwara H, Tanaka K, Li F, et al. Bacopa monnieri ameliorates memory deficits in olfactory bulbectomized mice: possible involvement of glutamatergic and cholinergic systems. Neurochem Res. 2013;38:2201–2215. [PubMed] [Google Scholar]

46. Uabundit N, Wattanathorn J, Mucimapura S, Ingkaninan K. Cognitive enhancement and neuroprotective effects of Bacopa monnieri in Alzheimer's disease model. J Ethnopharmacol. 2010;127:26–31. [PubMed] [Google Scholar]

47. Raghav S, Singh H, Dalal PK, Srivastava JS, Asthana OP. Randomized controlled trial of standardized Bacopa monniera extract in age-associated memory impairment. Indian J Psychiatry. 2006;48: