OPEN ACCESS PEER REVIEW
DOI: https://doi.org/10.52756/bhietm.2023.e02.001
Chapter- 1

Deciphering the pharmacotherapeutic aspects of an ethnomedicinal plant *Bacopa monnieri* (Brahmi)

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Keywords: *Bacopa monnieri* (Brahmi), Medhya Rasayana, Ethnomedicines, Neuroprotection, Cancer.

Abstract:

Indian Ayurveda is the birthplace of traditional classical medicines from ancient ages as it has vast reservoir of medicinal plants. Amongst all medicinal plants, *Bacopa monnieri* or Brahmi is an ethno-medicinal herb abundantly found in tropical and sub-tropical regions of India. This herb is composed of enormous bioactive phytochemicals like bacosides, alkaloids, glycosides, sterols and flavonoids. Bacosides are the most significant among all and bear enormous neuromedicinal properties and protect brain from neuronal damage and modulate the imbalance of neurotransmitter signalling. Extracts of Brahmi can prevent brain aging, enhance memory learning and perception ability. Notably, it's reactive oxygen species (ROS) quenching, antioxidant properties, anticancer, anti-inflammatory, anti-epileptic, anti-depressant, anti-stress, gastrointestinal, endocrinological, cardioprotective, hepatoprotective features are experimentally proven in animal model. Administration of Brahmi extract can restore the cognition and other neuronal disorders in Alzheimer's and Parkinson's patients. To avoid few adverse effects of *Bacopa*, combination with synthetic drugs or formation of its nanoparticulate form may be recommended. The immense important pharmacological role of *Bacopa* will be concised in this chapter.

Introduction:

Plants are the major sources of ethnomedicines that play a pivotal role in drug discovery (Banerjee et al., 2014; Acharya, 2021a, 2021b, 2022a, 2022b, 2023; Bhattacharjee, 2021; Basu et al., 2022). India is well known for its rich heritage of herbs or medicinal plants (Bose, 2018; Erfani, 2021; Bhowmik et al., 2022; Ghosh et al., 2022; Darro & Khan, 2023; De & Sharma, 2023; De et al., 2023; Dhakar & Tare, 2023; Jyotirmayee et al., 2023). Indian Ayurvedic is one of the great representatives of traditional medical practices (Madhu & Sarkar, 2015; Maiti et al., 2010, 2013; Pyne & Santra, 2017; Choudhary et al., 2021; Kar et al., 2022; Raha et al., 2022;

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Mrs. Bhanumati Sarkar, Dr. (Professor) Surjyo Jyoti Biswas, Dr. Alok Chandra Samal & Dr. Akhil Pandey (eds.), The Basic Handbook of Indian Ethnobotany and Traditional Medicine [Volume: 2]. ISBN: 978-81-962683-5-0; pp. 01-13; Published online: 15th December, 2023
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Mandal, 2022; Pal et al., 2022; Pimple et al., 2023). Charak Samhita, Sushruta Samhita and Veda describe specific effects or "Prabhava" of several ethnopharmacological plant species. *Bacopa monnieri* or Brahmi is the most popular succulent annual herb, which belongs to the member of Scrophulariaceae family (Choudhary et al., 2021). Nearly 146 species of the genus *Bacopa* are abundantly distributed in subtropical countries (Manap et al., 2019). Fleshy green leaves of Brahmi consist of various bioactive phytochemicals like alkaloids, terpenes, flavonoids etc. Brahmi has immense clinical and economic importance. Brahmi is considered a "Medhya Rasayana" and was used by Vedic scholars in the ancient period for its various pharmacological properties. It is described in Ayurveda as Brahmirasayan, Brahmighritam etc., for its anti-aging and anti-seizures effect (Choudhary et al., 2021). Brahmi leaves extracts are widely used as a brain tonic for their memory-boosting and neuroprotective properties (Fatima et al., 2022). Application of natural products in modern treatment against serious life-threatening diseases is gaining importance nowadays (Sarkar et al., 2016; Sarkar, 2017; Sarkar et al., 2021; Sanyal, 2022a,b). Several studies reported that Brahmi is used as a traditional medicine to treat various neurological diseases. Brahmi root extracts have anti-venom properties and are used to treat eye problems like cataracts. Leaves of Brahmi act as anti-asthmatic compound. Its extract has free radical scavenging properties. It also has an anti-mutagenic effect and anti-tumour activity against various cancers (Ghosh et al., 2021). The nontoxic Brahmi and its phytochemicals offer new hope for patients suffering from several complex disorders.

Phytogeographical distribution of *Bacopa monnieri*:

Brahmi is highly distributed in both tropical and subtropical nations like Nepal, China, USA etc. and native to India. It is abundantly found in West Bengal and other states like Kerala, Uttar Pradesh, Orissa, Karnataka, Himachal Pradesh, Bihar, Tamil Nadu, Panjab, Gujarat etc. (Fig. 1) (Choudhary et al., 2021). This plant generally grows in marshy- wetlands areas, ponds, river side and in humid weather where the temperature is 30-40°C. They are cultivated in sandy soil at pH 7-8 (Choudhary et al., 2021; Pal et al., 2022).

Plant morphology:

It is a creeping herbaceous species about 60-90 cm long and consists of a soft -succulent stem with several long branches (10-35 cm) and ceramic-yellow roots. It has green, oval, sessile leaves arranged in pairs along the branches and are generally 8-15mm in size with strong medicinal values. Flowers are small-sized and whitish-purple in colour. It has purple colour fruits that are ovate pointed at the top (Choudhary et al., 2021; Pal et al., 2022).

Active phytochemical constituents of *B. monnieri*:

Brahmi is the godown of numerous bioactive compounds with various pharmacological attributes. Saponins like bacosides are the most significant secondary metabolites among them and are related to cognition enhancement and neuroprotection (Sukumaran et al., 2019). Bacoside A, bacoside B, bacopasides, bacosaponins, betulinic acid are the most important saponines of Brahmi

(Banerjee et al., 2021). Chemical name of bacoside is 3-(a-L-arabinopyranosyl)-O-b-D-glucopyranoside-10, 20-dihydroxy- 16-keto-dammar- 24-ene (Saha et al., 2020) (Fig 2) and it possess immense neuromedicinal properties. Apart from that, saponins can promote apoptosis, superoxide quenching, lipid peroxidation reduction and antioxidant enzyme stimulation (Banerjee et al., 2021).

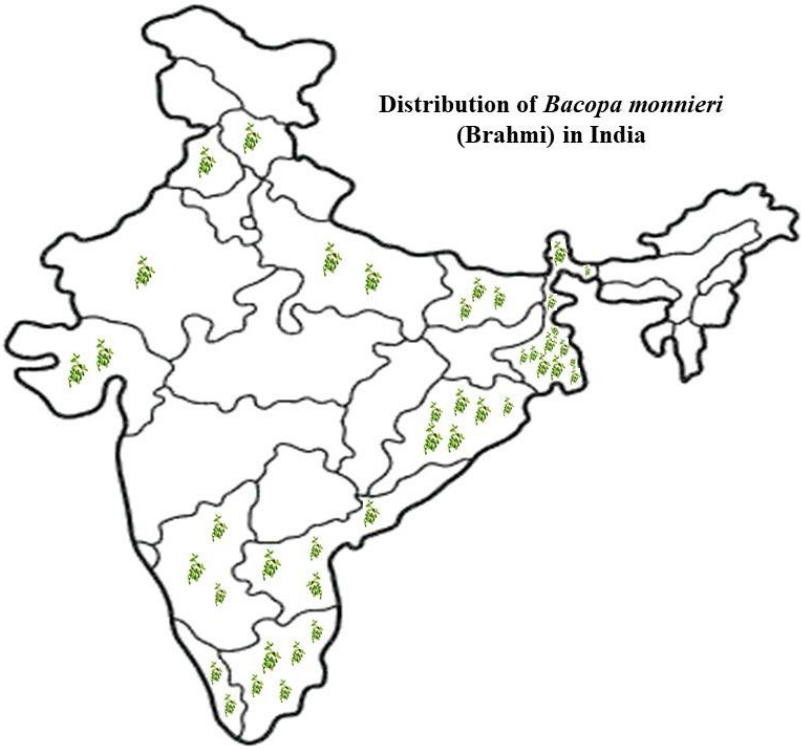

Figure 1. Distribution of *Bacopa monnieri* in India

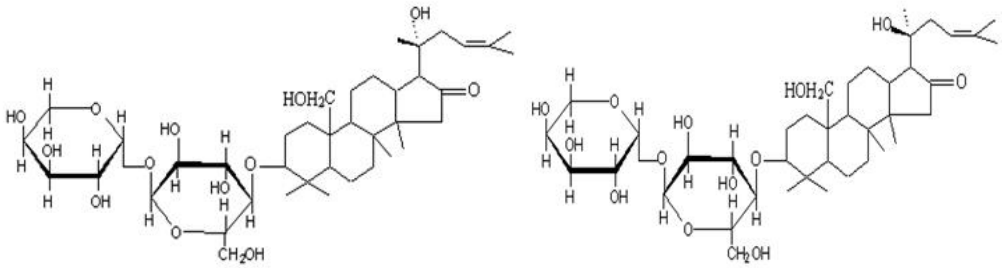

Figure 2. Structure of Bacoside A and Bacoside B

Other important phytochemicals include phenolic compounds, alkaloids, flavonoids, glycosides, phenylethanoid glycosides, alcohols, cucurbitacins, sterols etc. (Fatima et al., 2022; Jain et al., 2016). Nicotine, brahmin, and herpestine are some known alkaloids and pseudo-jujubogenins are glycosides extracted from Brahmi (Saha et al., 2020). Aspartic acid, stigmasterol, hydrocotyline, D-mannitol, serine, glutamic acid and alanine are also included among the phytoactive components of Brahmi (Fatima et al., 2022).

Important therapeutic attributes of *Bacopa monnieri*:

As discussed, Brahmi has been used immensely in traditional therapies to treat different mental illnesses like memory dysfunction, anxiety, depression, Alzheimer's disease, Parkinson's disease, insanity, psychosis, dementia, amnesia, schizophrenia etc. It also cures other physical and physiological maladies like, diabetes, cancer, inflammation, oxidative brain damage, skin infection, epilepsy, digestive problems, asthma, allergies etc. (Ghosh et al., 2021; Sukumaran et al., 2019). Some therapeutic properties of Brahmi are concised below.

Cognition enhancement:

Brahmi has traditionally been used to revitalize intellectual properties and as memory booster. As reported earlier, bacosides can enhance memory and calm the brain in hypoxic conditions. Bacosides can also induce cognitive function and learning ability. Oxidative damage initiates aging and age-related neural dysfunctions. Bacosides can destroy ROS accumulation in the brain and protect the brain from further deterioration (Banerjee et al., 2021; Vishnupriya et al., 2017).

Neuroprotection:

One of the most known and popular actions of Brahmi is neuroprotection. According to reports, Brahmi's phytochemicals can reduce lipid peroxidation rate and nitric oxide-induced damage in rodent brain (Vishnupriya et al. 2017). Saponins from this plant can also modulate the activity of dopamine D1 receptor and its expression in hypoglycemic neonatals. Bacoside A and B can balance SOD (Superoxide dismuatse) content by scavenging free radicals and preventing cortical cell death in the brain. Thus it can relief the brain from stress by inhibiting ROS aggregation (Jain et al., 2016).

Brain aging, oxidative stress and *B. monnieri*:

The prooxidants and antioxidants in our body maintain a state of equilibrium and allow cells to function properly (Simpson et al., 2015). With increasing age, this chemical equilibrium gets disrupted and hampers normal functioning. Like other cells and nerves, the brain is also affected by ROS imbalance occurred by unusual accumulation of free radicals. Due to high metabolism, glutamate cytotoxicity, higher amount of unsaturated fatty acids and decreased functioning of glutathione peroxidase, the brain is more prone to oxidative damage. Both *in vitro* and *in vivo* experiments proved bacosides' free radical scavenging property protects brain cells from superoxide damage and improves its functional ability in cognition management and memory enhancement (Simpson et al., 2015). Bacosides exert anti-oxidant activities in the brain's frontal cortex, hippocampus and striatum region. Brahmi extract can also trigger the expression of heat-shock-protein 70 and cytochrome 450 in the brain. It also can increase the SOD level in the brain and helps the brain in adapting stressed conditions (Jain et al., 2016).

Alzheimer's disease treatment:

Alzheimer's disease is a chronic neural degeneration associated with dementia, memory loss and cognitive disorders like impaired perception, learning and thinking incapability in patients. Unusual aggregation of β-amyloid peptides and abnormal phosphorylation of tau proteins in brain are the main reason of this disease (Fatima et al., 2022; Saha et al., 2020). Though there is no such drug discovered to cure this malady. Acetyl choline esterase (AChE) inhibitors and glutamate modulators can make this disease less severe. Increased amount of acetyl choline can reverse pathogenicity of this disease. Researchers demonstrated that ethanolic extract of *Bacopa* can reduce the activity of AChE in the cerebral cortex and other brain regions. It has been clinically proven that ethanolic extract of *Bacopa* can ameliorate the cognitive function of the brain of Alzheimer's patients (Saha et al., 2020).

According to a study, phytochemicals from *Bacopa* can inhibit the generation of β-amyloid fibrils. There is clear evidence that it could be a novel anti-Alzheimer agent in future (Saha et al., 2020). In silico research study reported that two important saponin Bacopasaponin G and Bacosaponin N_2 would be more beneficial in Alzheimer's disease treatment (Fatima et al., 2022). Cigarette smoking makes Alzheimer's disease related dementia worse in patients. *Bacopa* extract can prevent lipid peroxidation rate in the brain induced by nicotine from cigarettes (Aguir et al., 2013).

In the treatment of Parkinson's disease:

Parkinson's disease is another frequent neurodegenerative sickness assisted by abnormal accumulation of α-synuclein protein and degradation of dopaminergic neurons in the nervous system. Bacosides have the ability to protect the neural degeneration in Parkinson's disease. Researchers demonstrated the neuroprotective effect of Bacopa extract in an experimental model using *Caenorhabditis elegans.* It can prevent neuronal degradation by inducing SOD, reduce lipid peroxidation and prevent α-synuclein accumulation (Banerjee et al., 2021).

Anti-epileptic property:

Epilepsy is a neural disease that affects the CNS and cognitive abilities. It is the imbalanced chemistry of neurotransmitter molecules and their signalling. Gamma-amino butyric acid (GABA) is the chief inhibitory neurotransmitter that regulates the nervous excitation. In epileptic patients, GABA receptors get decreased in number and obstruct the normal function of GABA. Defatted alcoholic extract of *B. monnieri* containing bacoside A, can treat the epileptic seizures by protecting the peripheral nervous system from neuronal impairments (Banerjee et al., 2021). Researchers have done an experimental research with epileptic patients, and they found that alcoholic extracts of Brahmi can ameliorate temporal lobe epilepsy and petit mal epilepsy (Jain et al., 2016).

Anti-cancer property:

Cancer is a very complicated, deadly human disease, showing multifaceted clinical features and leading to the death of millions of people worldwide every year. Brahmi extract has potent anti-

neoplastic properties against various cancer including breast, colon, glioblastoma, liver, neuroblastoma, prostate etc. The combination of Bacopaside (I and II), which are two active triterpene compound derived from leaf extract of *Bacopa*, synergistically inhibits the breast cancer cells (MCF-7, MDA-MB-231, T47D cell lines) proliferation and metastasis by blocking G2-M phase transition and aquaporin 1 (AQP1) expression (Ghosh et al., 2021). Higher activation of AQP1 is found in many cancers that significantly induce cancer migration and invasion. Study showed that Bacopaside II can effectively reduce overexpression of AQP1 in HT29 colon cancer cell line. It can also exhibit apoptotic effects both in breast and colon cancer cells (Ghosh et al., 2021). Bacoside A is another promising anti-cancer secondary metabolite of *Bacopa* that can suppress self-renewal, progression of glioblastoma multiforme (GBM) & U87MG cell line by downregulating Notch1 signaling pathway and enhance the HES1 (hairy and enhancer of split-1) expression in dose dependant manner (Aithal and Rajeswari, 2019).

Studies showed that the higher expression of un-phosphorylated CaMK2A (Calcium/Calmodulin Dependent Protein Kinase II A) protein is responsible for the development of aggressive, malignant brain tumor GBM. Bacoside A can block the function of CaMK2A by converting it to the phosphorylated form (Ghosh et al., 2021). In addition, Bacoside A is considered as hepatoprotective agent that reduces hepatocarcinoma growth by mitigating lipid peroxidation and increasing the antioxidants enzymes (glutathione peroxidase, superoxide dismutase etc.) production. The leaf extract of *Bacopa* (250 mg/ml) has potential anti-cancer activity against neuroblastoma, which is a pediatric cancer. This leaf extract significantly increases neuroblastoma cell death by downregulating the ERK1/2 and AKT pathways (Fatima et al., 2022). Methanolic extract of Brahmi has cytotoxic effect against prostate cancer cell (DU145) and it also significantly reduces cancer cells invasion and migration (Ghosh et al., 2021). Mallick et al. reported that the dichloromethane fraction of Brahmi is a strong anti-cancer agent against various cancers, including lung, cervical, colon, and breast. This study also demonstrated that orally administrated dichloromethane fraction of Brahmi (40 mg/kg dose) significantly reduced tumor size, weight and cancer cell number in Ehrlich ascites carcinoma (EAC) bearing mice model (Mallick et al., 2017).

Anti-diabetic effect:

Diabetes mellitus is a lethal chronic metabolic disorder associated with hyperglycemia and hyperlipidemia. According to International Diabetes Federation report (2015) nearly 415 million patients are suffering from diabetes all over the world. Currently, many treatments are available to treat diabetes, but they are unable to cure diabetes completely. Several research demonstrated that alcoholic extract of *Bacopa* significantly reduce hyperglycemia and are effective against diabetic nephropathy. Another study reveals that *Bacopa* can reduce the mice model's body weight and blood glucose levels (Fatima et al., 2022).

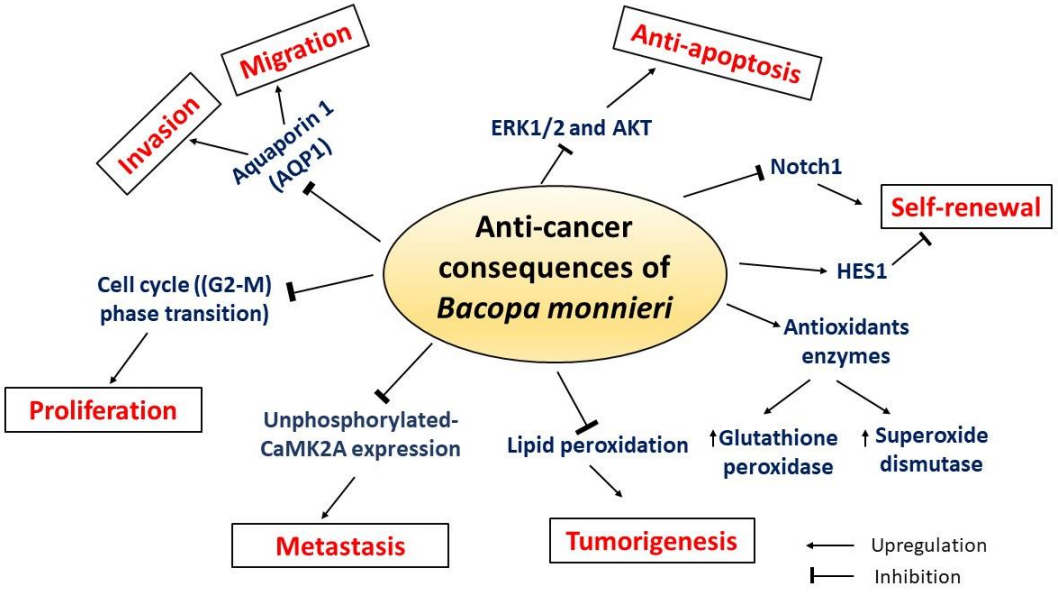

Figure 3. Anti-cancer effects of *Bacopa monnieri*

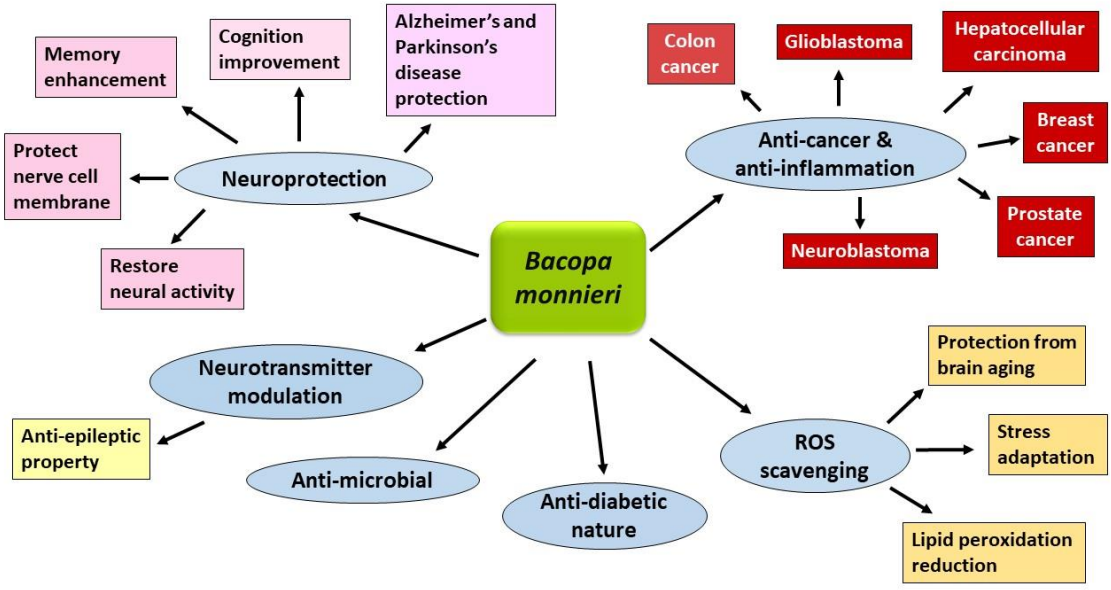

Figure 4. Pharmacological effects of *Bacopa monnieri* and its use in treating several diseases

Antimicrobial effect:

Extract of Bacopa possesses antimicrobial property. Methanol, ethanol, chloroform and ether extract of *B. monnieri* can kill *Salmonella typhi*, *Aspergillus niger*, *Micrococcus luteus*, *Bacillus pumilus* and *Bacillus subtilis* respectively (Jain et al., 2016).

Antidepressant and anti-anxiolytic effect:

Experimental evidence from forced swim test and learned helplessness tests (using animal model) suggests that ethanol extract of *Bacopa* bears anxiolytic and antidepressant activities (Banerjee et al., 2021).

Hormonal effect:

In mice model, *Bacopa* extract can increase the level of T4 and can also regulate spermatogenesis. *Bacopa* leaves also elevate level of serotonin in human brain and reduce stress (Pal et al., 2022).

Negative impact of *Bacopa* upon health:

Bacopa exerts some unfavourable effects upon health like loose motion, abdominal cramp, nausea, flu like symptoms etc. (Kongkeaw et al., 2013).

Conclusion:

Brahmi is an important ethno-medicinal plant with various pharmacological perspectives. Phytochemicals of Brahmi are used as a potent neuromedicine. Superoxide scavenging property of bacosides helps in neuroprotection, memory and cognition power enhancement. As discussed epilepsy, Alzhiemer's disease and Parkinsons's disease can be treated with phytochemicals of Brahmi. Anticancer, anti-inflammatory, anti-diabetic, anti-microbial properties of *Bacopa* are well-known. Though there are some negative impacts of Brahmi extract like nausea, abdominal cramp, diarrhoea still the other efficacies of this plant made it a "wonder plant". In conclusion it maybe stated bioavailability and efficacy of Brahmi may be increased by nanoparticle mediated phytomedicinal delivery instead of direct application. Extensive research work should be required to decipher other medicinal attributes of Brahmi in future.

Acknowledgement:

Authors would like to acknowledge Diamond Harbour Women's University for the support. We would like to acknowledge the publisher, editors and support staff of "The Basic Handbook of Indian Ethnobotany and Traditional Medicine", for their help in different stages of developing and producing the chapter.

Conflict of interest:

The authors declare no conflict of interest.

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HOW TO CITE

Sunita Jhulki, Sukanya Kundu and Aparajita Pal (2023). Deciphering the pharmacotherapeutic aspects of an ethnomedicinal plant *Bacopa monnieri* (Brahmi). © International Academic Publishing House (IAPH), Mrs. Bhanumati Sarkar, Dr. (Professor) Surjyo Jyoti Biswas, Dr. Alok Chandra Samal & Dr. Akhil Pandey (eds.), *The Basic Handbook of Indian Ethnobotany and Traditional Medicine [Volume: 2]*, pp. 01-13. ISBN: 978-81-962683-5-0. DOI: https://doi.org/10.52756/bhietm.2023.e02.001