Pharmacogn. Res., 2023; 15(3):410-454.
https://www.phcogres.com

Review Article

In Quest of the Mysterious Holistic Vedic Herb *Bacopa monnieri* (L.) Pennell

Sumanta Mondal[1,*], Kausik Bhar[1], Prasenjit Mondal[2], Naresh Panigrahi[1], Suvendu Kumar Sahoo[1], Pydi Swetha[1], Subhadip Chakraborty[1], Nooka Yaswanth Teja[1], Neha Parveen[1]

[1]Department of Pharmaceutical Chemistry, School of Pharmacy, GITAM (Deemed to be University), Visakhapatnam, Andhra Pradesh, INDIA.
[2]Department of Pharmaceutical Technology, Brainware University, Kolkata, West Bengal, INDIA.

ABSTRACT

Throughout history, complementary and alternative therapies have been widely utilised. In recent years, there has been a surge in interest in the usage of herbal treatments all around the world. Various natural chemicals, such as those produced from plants, have been investigated as potential therapies for a myriad of ailments. The essence of this review was to methodically describe everything we know about *Bacopa monnieri* (L.) Pennell, a mysterious holistic Vedic herb belonging to the Plantaginaceae family, a well-known nootropic and effective memory enhancer, which has recently emerged as one of the most important medical herbs, widely used therapeutically in the Orient and growing in popularity around the world. Literature was gathered from sources such as Scopus, PubMed, Google Scholar, and ScienceDirect, and reviewed using the Prisma quality metacritic paradigm. It is now plainly obvious that current therapies fall short of meeting the demands of the vast majority of individuals with health problems, and traditional medicines are gaining appeal as a result of their reduced toxicity. Bacopa is a traditional herb used in Ayurvedic medicine to treat brain and nerve weariness, as well as in Siddha medicine to treat impaired memory. It's also used to cure brain and nerve exhaustion in Unani medicine. We improved Brahmi micropropagation and secondary metabolite biosynthesis by compiling pharmacobotanical and pharmacognostical descriptions, as well as ethnoarchaeological data and nanotechnology domination. This critique also highlights our contemporary information of pharmacological activity, preclinical and clinical investigations, significant bioactives, reported mechanisms of action, clinical effectiveness, safety, and the potential for herb-drug interactions. At the same time, the current incarnation of research at the plant is reviewed, as well as future research possibilities. Brahmi offers a lot of potential for treating a range of illnesses, including neuro-pharmacological, depression, inflammation, hepatoprotective, antidiabetic, and others. According to the presumptions of this review, further clinical trials and research are needed. While the impact of Brahmi as an anxiolytic and antidepressant has to be explored further, its potential as an anti-epileptic therapy and a treatment for antiepileptic drugs side effects is also being researched. Furthermore, Brahmi's antioxidant ability may explain, at least in part, the antistress, immunomodulatory, cognition-facilitating, anti-inflammatory, and anti-aging benefits documented in experimental animals and clinical circumstances, necessitating further study into its other therapeutic characteristics.

Keywords: *Bacopa monnieri*, Cheminformatics, Clinical trials, *Herpestis monnieri*, Pharmacological testimony, Plantaginaceae, Phytomolecules.

Correspondence:
Dr. Sumanta Mondal
Associate Professor and NSS Programme Officer (Unit-IX), School of Pharmacy, GITAM (Deemed to be University), Visakhapatnam, Andhra Pradesh, INDIA.
Email: mondalresearch@gmail.com

Received: 27-01-2023;
Revised: 23-02-2023;
Accepted: 30-03-2023.

INTRODUCTION

Throughout history, complementary and alternative therapies have been widely utilised. The Vedic period (2500 BC to 600 BC) was the time in Indian history when the Vedas, the country's earliest scriptures, were written. Plant categorization and naming in India is older than that of the Greeks and Romans, dating back to the Vedic period. Three types of plants have been identified in the Rigveda: trees (Vriksha), herbs (Osadhi), and creepers (Virudh). Plant types, shape, and morphology are also mentioned in the Atharvaveda. Four categories of medicinal plants are documented in Yajurveda.[1]

In recent years, interest in the usage of herbal products has exploded in both developed and developing countries. The study of plants (plant taxonomy and study of medicinal plants) may have arisen during this contemporary age, based on the aforementioned historical eras of recording in India from ancient documents and literature.[2]

DOI: 10.5530/pres.15.3.045

Alternative medicine is becoming increasingly popular across the world. The hunt for effective and safe medications is never-ending, as are novel applications for existing drugs. Brahmi is an Ayurvedic herb that has been used for ages in Ayurvedic medicine. Because Western medicine has limited therapy choices for some neurological illnesses, hospitals and research institutions throughout the world are increasingly turning to Ayurvedic science for effective and safer alternatives. Brahmi is a well-known nootropic plant with a long history of usage in neurological and psychiatric illnesses. Research and thousands of years of knowledge and experience back up its efficacy and safety.[3]

In India, *Bacopa monnieri* is a tiny perineal creeping plant also known as *Herpestis monnieri*, water hyssop, or Jalanimba. From 3000 years Brahmi has been used in Indian Ayurveda system, a holistic system of medicine. The name Brahmi is derived from word "Lord Bramha" mythically the creator of world according to Hindu pantheon. As brain is known as a major part of human body for creative activities, so any compound that help in increase the brain power and keep it healthy by means of "bringing knowledge of the supreme reality" is known as Brahmi. It is a major constituent of the traditional Medhya Rasayana formulations. In Charaka Samhita Ayurvedic system since 6th century AD it is used in the management of a variety range of mental conditions including anxiety, poor cognition and lack of concentration, which are considered to facilitate learning and improve memory. In traditional medicine, the plant is used as a nervine tonic, an energizer for the nervous system and heart, diuretic, to treat asthma, epilepsy, insanity, as a digestive aid, hoarseness, and respiratory functions.[4-7]

Classically Brahmi was described in Yajurveda as Santhanothpadaka, and in Atharva parisista and others as Medhya. Brahmi is also mentioned in Kausika sutra. Brahmi is described in Prajastapana Mahakashya, Garbhasthapana Dravya. Aindriya Rasayana, Apasmara Chikista, Kustha Chikista, Acharya Vagbhata suggested Brahmi as the best remedy for Apasmara Chikistsa in Uttara Sthana.[8-10]

According to Shodhala-nighantu, Brahmi and Mendukaparni (*Cantella asiatica* L. Urban; Family: Apiaceae) both are same in pharmacological property, but Brahmi is superior to Mandukaparni. Priya-Nighantu mentioned Brahmi in ShatapushpadiVarga whereas *Mighantu adarsha* mentioned Brahmi in Tiktalonikavarga. Botanically Brahmi is known as *Bacopa monnieri* (L.) Pennell, belongs to the family Plantaginaceae.[11-15]

In parayapadani Brahmi is mentioned as Medhya Janakatwath Brahmi hita which means the one which helps in development of brain is known as Brahmi. Classically Brahmi is also called as "Jalasaya" that available in water, "Toyavalli" that grows efficiently in presence of water. Brahmi is also called as "Tiktalonika" means a bitter type of lonika and "Somavalli" as a creeper prefers marshy areas for its growth.[16] The aim of current review was to systematically summarize our current knowledge about the mysterious holistic Vedic herb *Bacopa monnieri*.

TAXONOMIC POSITION, SYNONYMS AND VERNACULAR NAMES

In ancient Sanskrit books such as the Great Trilogy (Caraka Samhita, Sushrita Samhita, and Astanga Hridaya) and texts from Atharva-Veda, *B. monnieri* was first mentioned around the 6th century A.D. *Bacopa monnieri* is categorised by these texts as a Medhya Rasayana, a genus of herbs known for enhancing memory and intelligence. Over the years, Brahmi has been so respected that the Hindus used it to consecrate new-born babies in their ceremonies, claiming it would open the gateways to wisdom.[17]

B. monnieri is a non-aromatic herb and one of the most widespread species. Its ability to grow in water makes it a popular aquarium plant. Genus Bacopa contains more than 100 plant species of aquatic herbs, distributed throughout the warmer regions of the world. The details of the taxonomic position with synonyms[18-20] of *B. monnieri* are listed in Table 1[2,3] and vernacular names are depicted in Table 2.[1,3]

GEOGRAPHICAL DISTRIBUTION AND CULTIVATION

B. monnieri is a perennial plant and sometimes it can be cultivated as annual crop. It is widely spread with stable populations in all over the world. The plant has shown to flourish in a variety of soil and climate conditions. It flourishes in subtropical climates, particularly in areas with poor drainage and flooding. Plants grow faster at high temperatures and humidity (65-80%), thus it's best to plant it during the summer and rainy season. It is able to grow well in brackish water. It is cultivated in all over the India in Assam, Bengal, Bihar, Haryana, Himachal Pradesh, Karnataka, Maharashtra, Punjab and Tamil Nadu, Uttaranchal and Uttar Pradesh. Other than India, Bacopa plants are mostly occurs in warmers regions of the world, mainly grows in Asia, Australia and north and South America. In India it is found in wetlands, marshy tracts, near streams and on the border of ponds.[17,18]

If the environment supports moist and semi-shade conditions, the plant may grow in a range of soil types. It may be found at elevations of up to 1300 metres. The optimal conditions for *B. monnieri* growth are near-neutral clayey loams to clayey soils. It can grow in a broad range of temperatures (15-40°C) and soil pH in North India (5-7.5). It may, however, thrive on soils with a pH of 7.5 or higher. Except when cultivated near flowing water, it goes dormant over the winter months. The months of May through July are ideal for planting. There have been no reports of major pests, insects, or illnesses affecting the crop, however *Anartia jatrophae*, a white peacock butterfly caterpillar feeding

Table 1: Taxonomical classification and synonyms of *B. monnieri*.

Domain	Eukaryota
Kingdom	Plantae (Plants)
Subkingdom	Tracheobionta (Vascular plants)
Infrakingdom	Streptophyta
Division	Magnoliophyta (Flowering plants)
Superdivision	Embryophyta
Subdivision	Spermatophytina
Class	Magnoliopsida (Dicotyledonae)
Subclass	Asteridae
Order	Lamiales
Superorder	Asteranae
Family	Plantaginaceae
Genus	*Bacopa*
Species	*Monnieri*
Binomial name	*Bacopa monnieri* (L.) Pennell
Preferred common name	Water hyssop
Synonyms	*Anisocalyxlimnanthiflorus Hance* *Bacopa monnieri* Hayata and Matsum. *Capraria monnieria* (L.) Roxb. *Gratiola monnieria* L. *Gratiola parviflora* Willd. ex Schltdl. and Cham. *Gratiola portulacacea* Weinm. *Gratiola tetrandra* Stokes *Herpestes monnieria* (L.) Kunth *Herpestis fauriei* H. Lev *Herpestis monniera* *Herpestris monnieria* *Lysimachia monnieri* L. *Moniera cuneifolia* Michx. *Monniera pedunculosa* Persoon *Septas repens* Lour.
Allied species	*Centella asiatica* Linn. (Family: Apiaceae); *Bacopa floribunda* (R.Br.) Wettst. (Family: Plantaginaceae)
Plant type	Annual Aquatic Herbaceous Perennial Seed propagated Succulent Vegetatively propagated

plant, is a natural nemesis of *B. monnieri*. The tobacco cutworm, *Spodoptera litura*, has been documented causing damage in greenhouse settings. *Bacopa monnieri* belongs to the *Meloidogyne* genus and is a nematode host.[19,20]

Because *Bacopa monnieri* is a vegetatively propagated medicinal plant that is threatened, micropropagation techniques must be developed to protect germplasm and transfer it to new cultivars during growth in new locations. The particular growth factor for root and shoot induction, transplanting and acclimation of explants, and DNA separation from explants was recently described in research. Callus induction and regeneration from *B. monnieri* protoplasts. The results revealed that the plants are the identical.[21]

Freshly collected shoot cuttings of 5-10 cm length with internodes and rootlets are the best planting material for cultivation, according to recent studies, *B. monnieri* was ranked second in a priority list of the major Indian medicinal plants assessed based on medicinal significance, potential candidate, and commercial value for further research and development. During the wet season, when the propagates expand quickly, the plant displays sumptuous growth. Seeds are quite small and appear in October/November. Seed germination research has shown disappointing results.[22]

The crop can be harvested 75-90 days after planting. September-October is the best time for harvesting. The crop should be harvested when plants attain a length of 20-30 cm. The entire plant should be physically taken out, uprooted, or scraped off. The aerial portions of the plant stop growing almost completely even after irrigation and fertiliser treatment, and the field is overrun by winter weeds in the extreme cold temperatures of North India, making ratoon production unfeasible. Micropropagation using axillary meristems and de novo organogenesis have been extensively studied of this species due to its multipurpose therapeutic potential, and bioreactor based micropropagation has also been reported to increase the multiplication rate of shoot cultures for commercial propagation of *B. monnieri* plants, with the maximum content of bacosides recorded in shoot biomass using an airlift bioreactor system.[23]

PHARMACOBOTANICAL AND PHARMACOGNOSTICAL DESCRIPTION

Bacopa monnieri is an aquatic plant often found in marshy areas [Figure 1]. It is a small creeping, spreading, succulent herb with numerous branches and small fleshy, oblong leaves. Flowers are white purple and fruits appear in summer and the whole plant is medicinally important [Figure 2].[24]

Leaves are simple, opposite, and decussate, somewhat sessile, glabrous, obovate oblong to spatulate in shape, 0.6-2.5 cm in length and 3-8 mm in width, entire lower surface are dotted with minute specks, obscurely 1-3 nerved, colour faint green and leaf are arranged oppositely on the stem, with no petiole [Figures 3 and 4]. The epidermis, mesophyll, and vascular tissue make up

the three basic components of the leaf. The epidermis is separated into two layers: the top epidermis and the lower epidermis, both of which are covered by cuticle. Numerous palisade parenchyma cells are joined together with spongy parenchyma cells on the underside of the top epidermis. The pigment chlorophyll is present in both types of cells. Xylem and phloem make up the vascular tissue present in the leaf's midrib. The top and bottom epidermis are nearly identical. The stomata are anomocytic type and guard cell on stomata is 30-45 µm long and 18-25 µm wide. Stomatal numbers on upper and lower epidermis are 118 and 130 whereas the trichomes (glandular) number 25 and 13 respectively.[25] Epidermis, parenchyma with starch grains, anomocytic stomata, lignified fibres, sieve tubes, and scalariform vessels were reported as microscopic characteristics of powdered Brahmi. The guard cells of the stoma on powdered Brahmi are comparable in form and size to those on fresh Brahmi leaves.[26-28] The reported power characteristics of the plant narrated in Table 3.[12,29]

Stems are cylindrical, glabrous with prominent nodes and numerous branches. Internodes about 1-1.5 cm in length and 3-4 mm in diameter, pale yellowish green and with purplish tinge and often showing sprouting rootlets. The reported microscopical character of the stem is composed of epidermis, cortex, and stele. The epidermis is the outermost thin wall, layered with the cuticle with few stomata, two to three layers of hypodermis consisting of parenchyma cells with chlorophyll pigments and tannin content cells and cortex which are below this layer. The cortex layer comprises parenchyma tissue with big airspaces. In the stele layer there is an endodermis, vascular tissue and pith which is in the centre of the stem and this layer area is less than half the thickness of the cortex layer. A single layered endodermis connects with the cortex but is separate from the vascular tissue, forming a ring and consists of phloem. The pith is situated above the xylem and innermost stem contains compactly arranged parenchyma cells.[25,27,30] The pericycle is made up of barrel-shaped cells with thin walls that are compactly packed. Vascular bundles are distributed radially in the vascular tissue system. The phloem sits on top of the xylem. Xylems are many, with metaxylem pointing toward the pericycle and protoxylem pointing into the pith with xylem parenchyma and fibres.[31]

Figure 1: An aquatic Herb *Bacopa monnieri*.

Roots are thin, small, branched creamish-yellow cylindrical, about 5 mm in diameter, longitudinally wrinkle and off white in colour. The root is irregularly circular to angular at places in outline, shows outermost piliferous layer, parenchymatous cortex with intervening air spaces and a centrally located solid core of xylem encircled by narrow phloem. The proclaimed transverse section of *B. monnieri* roots shows piliferous layer occasionally at places getting replaced by formation of cork cells, cortex is wide, parenchymatous, traversed with simple and compound starch grains and intervened with air spaces, endodermis is distinct, a narrow band of phloem surrounding the centrally located solid core of xylem composed of radially arranged isolated vessels, fibres, parenchyma and medullary rays. Prismatic calcium oxalate cluster crystals, starch grains, and oil globules are spotted throughout and entrenched in the parenchymatous cells.[32]

The flowers are tiny, purple or pinkish white, axillary and solitary on pedicels that are 1.0-1.5 cm long, generally longer than the leaves, with two linear bracteoles that are shorter than pedicels [Figure 5]. The calyx is glabrous, and the pedicels are thin. The corolla is 8-10 mm long, with 5 petals and 3 sepals, a dark purple didynamous stamen, and a brilliant green capitate stigma. Corolla is 0.8 cm wide with violet and green streaks inside the throat, 5 mm tube, 5 lobes, obscurely 2-lipped, obtuse or emarginated. Four stamens, one pair filament, and 2.5 mm oblong anthers with continuous filaments are didynamous (1.5 mm). Style dilated towards the top, two chambered ovaries with numerous ovules. The ovaries are oblong globose with a slightly deflexed style of 5.5 mm length, and the stigma is a flat capsule with four valves, septicidal or loculicidal.[26,33,34]

Fruits are small globose to ovoid capsule form, less than 0.5 inch in length enclosed with persistent calyx, pedicel 1-3 cm long purplish when fresh. Seeds are numerous, very minute, less than 1 cm wide, oblong or irregular.[26,35] The details reported physicochemical properties and organoleptic characters of *B. monnieri* depicted in Tables 4 and 5.

ETHNOARCHAEOLOGICAL INFORMATION

In traditional medicine, *Bacopa monnieri* is an extremely useful medicinal plant for the treatment of many nervous disorders and the promotion of memory and intellect. Plant resources are mainly relied on by rural communities, particularly for herbal medicine, fruit, forage, household appliances, fire and shade.[36] The use of medicinal plants as traditional medicinal products is well known in the rural areas of many developing nations. Low-income people use traditional medicine to treat common illnesses in

Figure 2: *B. monnieri* plant in its existing form.

Figure 3: *Bacopa monnieri* leaves.

Figure 4: *Bacopa monnieri* leaflet (upper side and lower side).

Figure 5: Flower of *Bacopa monnieri*.

developing countries, such as farmers, smallisolated villages and indigenous peoples.[37] In alternative therapies, *Bacopa monnieri* is used as a nervous tonic, diuretic, asthma, epilepsy, insanity and hoarseness. For culinary and cosmetic purposes, it is often used.[38] Fresh plant juice serves as a cardiac tonic for memory enhancement and when used orally as diuretics.[39,40] Brahmi is used for oxidative damage from various ethnic groups and acts as a potent antioxidant agent, reducing back pain, mental illness, epilepsy, intestinal inflammation, and joint pain.[41] Elephantiasis is handled using the Brahmi root ointment.[42] Brahmi leaf powder mixed with milk is used to treat gonorrhoea, a sexually transmitted disease.[43] For the treatment of jaundice and fever, Brahmi's leaf extract is used, and its other applications are neurological tonics that often serve as neuroprotective properties; even asthma and bronchitis are cured.[44] It is also treated for dysentery in infants. Brahmi leaf juice is administered to raise the blood and to strengthen the nervous system.[45] The leaves are useful for blood purification and are also used for the prevention or curing of mental illness, cholera, home medicine for piles and amenorrhea.[46] To minimise hair dropping, thinning of hair and headache, mixture juice of leaves, roots and white flowers were used.[39,47] It is used against indigestion, leprosy and anaemia and

Table 2: Vernacular names of *B. monnieri*.

Sanskrit	Aindri, brahmi, gundala, indravalli, jalasaya, manduki, matsyaksi, nirabrahmi, sarasvati, tiktalonika, toyavalli, vami, jala-brahmi, jalaprimmi, mandukamata, matsyakshi, medhya, sureshta, survarchala, swayambhuvi, vaidhatri, vallari, vara, vira.
Hindi	Brahmi, jalbuti, jalnim, nirbrahmi, safedchamani.
Urdu	Brahmi buti, Jalanim, nirabrahmi.
English	Water hyssop.
Bengali	Brahmisaka.
Telugu	Neerisambraanimokka, sambraanichettu, sambranichettu, sambrareniaaku, sambrani-aku, sambrani-chettu, sambranichettu.
Oriya	Brahmi, prusniparnni.
Marathi	Brahmi, jalabrahmi, nirbrahmi.
Tamil	Nir-p-pirami, ahazndapoozndu.
Assamese	Brahmi.
Gujarati	Baam, jalanevari, kadaviluni.
Kannada	Jala brahmi, nirubrahmi.
Punjabi	Brahmibuti.
Konkani	Brahmi.
Malayalam	Barna.
Manipuri	Brahmi-sak.
Nepali	Medhagiree.
German	Kleinefettblatt.
Japanese	Bakopa.
French	Petite bacopa.
Chinese	Jia ma chi xian.
Thai	Phrommi.
Vietnamese	Rau dang bien.
Arabic	Farfakh.
Polish	Bakopadrobnolistna.
Persian	Jaranab.

Table 3: Powder characteristics of *B. monnieri*.

Whole plant powder	
Starch grain	Simple, round to oval shaped
Stomata	Anomocytic and diacyctic
Calcium oxalate crystal	Prismatic
Xylem vessel	Spiral thickenings
Trachids	Pitted
Root powder	
Colour	Brown
Starch grain	Simple
Xylem vessel	Spiral thickening
Trachids	Pitted xylem
Stem powder	
Color	Light green color
Taste	Bitter
Xylem vessels	Spiral thickening
Trachids	Pitted xylem
Starch grain	Simple, oval, round
Leaf powder	
Color	Green
Taste	Bitter
Stomata	Anomocyctic and diacytic
Mesophyll tissue	Prismatic calcium oxalate crystal
Starch grain	Simple

is used for treating spleen disease and skin disorders. It is also used as an approach to treating ulcers, Alzheimer's disease, and tumours.[48] The leaf juice is also believed to reduce the effect of snakebite when mixed with castor oil and applied locally as well as daily oral intake of leaf powder with hot cow's milk.[49] In Nepal, fresh juice is used to treat burns. Boiling leaves are applied to the abdomens of new mothers in Rajasthan to relieve postpartum agony, and warmed leaves are used as a poultice to alleviate edema. Tribal inhabitants in Maharashtra claim that stuttering can be strengthened by eating 5 leaves daily for a span of 1 month,[50] thus confirm the use of different parts of *Bacopa monnieri* for more than 30 diseases through the mapping of traditional knowledge in Indian communities in different regions of India. Table 6 summarizes the ethno-medicinal uses of Brahmi by different ethnic groups reported indifferent regions of India[51] and the list of important uses of *Bacopa monnieri* and its components as medicinal products for the treatment of different diseases, either directly or in the formulation, is given in Table 7.[39,40,47,49,50,52]

INDIGENOUS SYSTEMS OF MEDICINES

In many Ayurvedic preparations, *B. monnieri* is an essential ingredient and is considered an herb of Rasayana (Rasa: primordial tissue or plasma; Ayana: path), which is believed to prevent ageing, restore youth, prevent disease, promote healthy longevity, and strengthen life, brain, and mind. Bacopa is recommended for treating skin diseases, fever, edema, anaemia, increased frequency, and turbidity of urine, as well as psychological disorders in the Ayurvedic system of medicine. It is used for constipation, painful urination (dysuria), edema, nervous deficiency, and impaired memory in Siddha medicine, and in Unani medicine for brain and nervous fatigue treatment.[53-56]

Table 4: Physico-chemical parameters of *B. monnieri*.

Parameter	Aerial parts (%w/w)	Leaf (%w/w)	Roots (%w/w)
Total Ash Values	11.05	12.685	6.35
Acid Insoluble Ash Values	1.01	1.3	1.2
Water Soluble Ash Values	18.93	14.6	10.1
Loss on Drying	9.07	12.54	12.5
Water Soluble Extractive Values	23.5	22.704	21.7
Alcohol Soluble Extractive Values	10.89	27.344	9.06
Foreign matter	Less than 2%	Less than 2%	Less than 1.8%

Table 5: Organoleptic characters of *B. monnieri*.

Plant parts	Parameters	Perception
Flowers	Colour	Blue or white
	Consistency	Soft, smooth
	Odour	Slightly aromatic
	Taste	Bitter
Fruits	Colour	Green
	Consistency	Soft, smooth
	Odour	Bitter
	Taste	Bitter
Leaves	Colour	Greenish brown
	Consistency	Smooth
	Odour	Pungent
	Taste	Bitter-astringent
Stem	Colour	Brownish green
	Consistency	Soft, smooth
	Odour	Pungent
	Taste	Bitter
Roots	Colour	Brown
	Consistency	Smooth
	Odour	Pungent
	Taste	Bitter-Astringent

In several countries, including Bangladesh, India, Malaysia, Pakistan, and Sri Lanka, where Ayurvedic, Siddha, and/or Unani therapeutic systems are part of the national health care system, Bacopa is regulated as an active aspect in pharmaceutical assets and prescriptions. In Australia, Bacopa is regulated by the Therapeutic Goods Administration as an active ingredient in specified medicines with authorised Ayurvedic declarations of use, including *B. monnieri* has a history of being used for memory weakness in Ayurvedic medicine. Normal memory functioning can help.[57] Despite the US Food and Drug Administration (FDA) has not categorised it as generally recognised as safe for use in food items, it is authorised as a dietary supplement component under the Dietary Supplement Health and Education Act of 1994.[58] As a result, the USP has quality criteria monographs that specify the dried stems and leaves containing not less than 2.5 percent triterpene glycosides, as well as the powdered extract of the stems and leaves with a drug-to-extract ratio of 10–20:1.[59]

Brahmi Rasayana is a molecular nutrient and nutrition boosting substance described in ancient Ayurvedic scriptures. Rasayana treatment, according to Acharya Charaka, enhances the body's nutritional state, resulting in the production of improved cell and tissue qualities that can withstand age and stress.[60] Brahmi Rasayana is described by Sage Sushruta as an elixir and therapeutic agent that increases memory and mental skills while also lengthening human life. Sushruta mentions a therapy using fresh Brahmi juice and a very light diet at a specified time of day for 21 days after thorough cleaning of the body. Every week of therapy enhances memory and mental aptitude. The comprehensive 21-day therapy eliminates all negative aspects of the body and mind. The Goddess of Learning arrives in the user's consciousness, and the soul is inundated with many sorts of information. It also serves as a cardiac rejuvenator, allowing a person to live for 500 years, as stated in heart disease therapy.[61] Acharya Charaka also used Brahmi as one of the herbs in preparation of Aindra Rasayana to treat Svitra (leucoderma), kustha (skin diseases including leprosy), Jathara (abdominal diseases including ascites), Gulma (phantom tumor), Purana pliha (chronic splenic disorders), Visamajvara (irregular fever); and in Indrokta Rasayana to improve longevity, youth, voice, complexion, nourishment, intellect, memory and strength and be disease free.[3]

Medhya Rasayana, cognition Rasayana, slows the ageing process and aids in neural tissue regeneration, as well as having anti-stress, adaptive, and memory-improving properties.[60] Its soothing repercussions on the nervous system, as well as its potential to improve memory, are legendary. It is the most significant Nervine plant used in Ayurvedic therapy, according to Dr. Frawely; it promotes memory and attention. It rejuvenates brain cells by clearing toxins and obstructions from the neurological system while also providing a caring impact. Brahmi, a Himalayan plant, is vital nourishment for yogis who practise meditation. A modest portion of its fresh leaves is consumed daily to help the mind relax and promote meditation. Brahmi balances the right and left hemispheres of the brain[62,63] and helps to activate the crown

Table 6: Ethnic medicative uses of *B. monnieri* by numerous autochthonous communities in India.

State/ Region	Ethnic groups	Parts Used	Type of Uses
Andhra Pradesh	Yanadis, Chenchus, Iruliga, Erukala, Sugalis, Koyas, Konda Kapu, Kattunayakar, Manne Dora, and Gadabas.	Whole plant	Neurotronic, powder is given for nervous debility and as brain tonic, asthma, diuretic.
		Leaves	Whole plant as, leaves use to get relief from urinary problems.
Assam	Kalita, Koch, Boro, Kosari, Rajbonshi, Nath, Brahmin, Ahom, Bobo, Rabha, Rajbonghi, Kharia, Kachari and Nepali.	All parts of plant, leaf juice	All parts of plant are used as blood purifier, leaf juice is used as memory booster.
		Leaves and stem juice	Blood purifier.
		Whole plant	Epilepsy, asthma, ulcers, tumors, ascites, enlarged spleen, indigestion,inflammations, leprosy, anemia, biliousness, Brain tonic, Diabetics, Tonic for nerves, leaf juice is given to infants in bronchitis; leaves used as vegetables.
		Tender shoot	Leaf and shoot as vegetable and extract taken to treat liver complaints.
Chhattisgarh	Kanwar, Gonds, Muria and Halba.	Whole plant	Nerve tonic, asthma, snake bite.
		Leaves	Leaves are eaten as vegetable, Fever.
Himachal Pradesh	Gaddis, Gujjar.	Root, shoot	Bilious disorders, chronic and acute liver disorders associated with hepatomegaly.
		Leaves	Nervous tiredness.
Jammu and Kashmir	Gujjars, Bakarwal, Gaddis, Sibis and Pahadi.	Leaves	Stomachache.
		Whole plant	Poor production of milk in cows.
Jharkhand	Local inhabitants, Munda, Santhal, Kurukh, Kharia, Gond, Kol, Kanwar and Sabar people.	Whole plant	Nerve tonic, asthma, snake bite.
		Leaves	Skin diseases.
Kerala	Mullukuruma, Mudugar, Kattunayakar, Irular, Kurumbar and Dodurga.	Whole plant	Asthma, epilepsy.
		Leaves, stem	Enhance memory.
Madhya Pradesh	Kol, Korku, Saharia, Baiga, Bhil, Bhilala, Tadvi Bhil, Banjara, Gonds, Korku, Mankar, Halba, Kaul, Pawara, Oraon, Kanwar, Nandi, Chikalthana, Sakura.	Whole plant	Jaundice, to increase sexual power, bone fracture, improvement of mental functions, promotes memory and urinary disorders, diuretic, blood purifier, laxative, epilepsy, fever, brain tonic, rheumatism, diarrhea, abdominal diseases, anti-inflammatory, leprosy, cardiotonic, elephantiasis.
		Leaves	Memory, to cure back-ache after delivery, to prevent hair fall, epilepsy, menstrual disorder, to cure nephrotoxicity/kidney problems.
		Leaves, fruits, and stem	Hair growth.

State/ Region	Ethnic groups	Parts Used	Type of Uses
Odisha	Savara, Bhumia, Bonda, DangariaKandha, Didayi, Gadaba, Koya, Paika, Paraja, Sabar, Sora, Kolha, Munda, Santal andLanjia-Saura.	Leaves	Against malaria.
		Young shoots	As vegetable.
		Leaves	Memory power, to treat chickenpox.
Tamil Nadu	Malayali tribals.	Whole plant	Paste of the whole plant applied externally for dog bite, Memory power, Epilepsy, mental disorder, nervous weakness.
Telangana	Yerukala and Lambani.	Whole plant	Cooling effect.
Tripura	Tripuri, Jamatia, Halam, Santhal and nontribal community.	Leaf	Jaundice.
Uttarakhand	Gujjar and Bhotiyas.	Leaves	Epilepsy, to cure flatulence in children
		Whole plant	Whole plant crushed and applied externally on eczema.
Uttar Pradesh	Local people.	Whole plant	Spermatorrhoea.
West Bengal	Santhals, Kurukh, Mal Paharia people, Lodha and Munda.	Whole plant	Nerve tonic, asthma, insanity, diuretic, tranquilizer, Gonorrhea, Improvement of intelligence & memory, youthful vitality.
		Tender or young shoot	Green vegetable.

chakra (Sahasrara; the seventh spiritual chakra in the head). Since Vedic times, Brahmi has been utilised as a Medhya Rasayana, and it is still well-researched in today's medical world.

The Ayurvedic pharmacopoeia of India mentions important formulas of Brahmi as Sarasvataristha, Brahmi Ghrita, Ratnagiri Rasa, Brahmi Vati, Sarasvata Curna and Smrtisagara Rasa. Brahmi vati is a common Ayurvedic treatment for mental illnesses. According to Ayurveda sarasangraha, Brahmi vati can help with Alpamedha (weak memory), Manshikklam (mental fatigue), Tanav (stress disorder), Avasaad (depression), Manoroga (psychotic condition), and Anidra (Sleeplessness)[53] The herb can be taken as ghrita (medicated Ghee), medicated oil, churna (powder), svarasa (fresh juice), infusion, decoction, tincture (fermented beverage), syrup, tea, lepa (paste), pill or eaten fresh (leaves). As a milk decoction, Brahmi is a good brain tonic, particularly if combined with Aswagandha.[62] Sarasvatarishtam is a fermented lager (tincture) containing Brahmi, which is used to cure infertility, epilepsy, and mental illnesses.[64] It relieves joint pain, headaches, and helps to relax the mind when used as medicinal oil. It acts as a brain tonic and encourages hair growth when rubbed into the scalp.[9] Cough and pneumonia, especially in youngsters, might benefit from Brahmi paste applied to the neck.[12] Topical use also treats diaper rash in infants.[30] Swellings can be reduced by Brahmi lepa (paste). In children with acute bronchitis and other coughs, a poultice prepared of boiling plant is applied to the chest. To treat hoarseness, its leaves are cooked in ghee (purified butter) and eaten. Its leaves are juiced to treat diarrhoea in children. When administered to rheumatic symptoms, Brahmi juice combined with petroleum can improve.[20] As neti, Brahmi is one of the best herbs to normalize the absorption of prana through the sinus. A cup of freshly brewed Brahmi tea with honey before meditation is also beneficial.[62] For battling against sunburn, Brahmi is useful. Sunburn, according to Ayurveda, happens because of continuous exposure to the sun due to the aggravation of Pitta dosha. Applying Brahmi oil has a great cooling effect and decreases the feeling of burning. This is because of the essence of its Sita (cold) and Ropan (healing). When applied to the scalp, Brahmi oil helps to control hair drops and encourage hair growth. This is because hair loss is primarily caused in the body by an aggravated Vata dosha. By balancing Vata dosha, Brahmi oil works on hair decay. It helps to remove unnecessary dryness as well. This is due to its properties in Snigdha (oily) and Ropan (healing). In particular, a massage with Brahmi leaf paste or its oil on the head helps to reduce the headache. This is because of the potency of Brahmi's Sita (cold). It helps to eradicate aggravating factors from Pitta and eliminates the headache.[53,55] Table 8 displays the prescribed dosage of Brahmi as per Indigenous Systems of Medicines.

Ayurvedic scriptures allude to Brahmi Ghrita or Ghrta (Brahmi medicated ghee) as a common formulation. Brahmi Ghrita is made from one-part old cow's ghee, four parts Brahmi juice, and a quarter part total of vaca, kustha, and sankhapuspi paste,

Table 7: Important traditional uses of *B. monnieri*.

Plant parts	Preparation procedure and application	Medicinal importance
Whole Plant	Plant paste used externally three times daily.	Blisters
	Plant juice mixed with ginger, sugar and *Moringa oleifera* bark extract.	Stomach disorders in children
	Joyawake tea (combination of *B. monnieri* and *Camellia sinensis*) is considered as main rejuvenating herb.	Nervine tonic
	Plant juice is applied orally.	Memory enhancer, Cardiac tonic, Diuretic.
	8 ml plant juice or ½ gm plant powder is traditionally used once daily to increase learning speed and boost memory power.	Memory enhancement
	B. monnieri powder and *Saraca indica* bark powder were mixed in equal amounts and 5 gm of this formulation were administered to a patient every day.	Memory enhancer
	Fresh plant material is crushed, and the obtained extract is administered orally.	Malaria
	A mixture of leaves, roots and white flowers juice taken orally.	As hair tonic especially for thinning and falling of hairs, Headache.
	Plant juice mixed with castor oil is externally applied. Leaf powder mixed with hot cow's milk and taken orally.	Snakebite.
Leaves	Directly eaten	Memory enhancement.
	Leave juice is applied orally.	Epilepsy, Bronchial and Diarrheal ailments.
	Leaves were fried with ghee and taken orally.	Hoarseness of voice.
	Its Ghrita or medicated ghee is given with Pushkar Amul (Sauserialappa's root).	Memory enhancement.
	Powdered leaves about 5 gm with 2 or 3 black peppers are given in a single dose.	Bone fracture.
	Leaf paste externally used 3 times daily for animals.	Swelling of legs.
	Leaves and stem are boiled in water, filtered, about 100 ml filtrate taken orally twice daily for 5 to 10 days.	Asthma.
	Warmed paste applied on abdomen.	Abdominal pain, Urinary tract infections.
	Leave juice mixed with petroleum and applied locally.	Rheumatism.
	Brahmi leaves, Piper longum seeds and almond mixed with water and sugar and taken orally.	Memory enhancement.
Root	Fresh root decoction.	Snake Bite.
	Root juice mixed with milk and given 3 times daily.	Rheumatism.
	Dried root and fruit powder burnt and inhaled as smoke 3 times daily.	bronchitis.

according to Charaka. Insanity, inauspiciousness, epilepsy, and the results of wicked acts are all treated with this medicinal ghee.[3] Brahmi Ghrta is listed in Astanga Hrdayam among herbs such as vyosa, syama, trivit, danti, sankhapuspi, nrpadruma, saptala, and krmihara for the treatment of insanity, leprosy, and epilepsy, as well as to enhance speech, voice, memory, intelligence, and to bestow sons to barren women.[6] In the treatment of mental illnesses, Brahmi Ghrita can be used as a nasya in dosages of five drops each nostril. Before sleeping, massage Brahmi Ghrita made with sesame or coconut oil on the feet, major joints, and ears to relieve anxiety and melancholy.[65]

Swami Sivananda described a very remarkable treatment called Brahmi Kalpa treatment in his book 'The Practice of Ayurveda'. It is a 'Kaya Kalpa' therapy, where 'Kaya' refers to the body and 'Kalpa' refers to change or rejuvenation. He describes Kaya Kalpa therapy using fresh Brahmi leaves' juice and fresh cow milk for 45 days after going through pancha karma. The therapy restores the freshness and energy of the elderly and decrepit body, as well as the comprehensive potential of the senses and exquisite health. It both extends and enhances the quality of life. It puts the function of the sapta (seven) dhatus back to normal and heals many incurable ailments by restoring the natural balance of the three doshas.[66]

Table 8: The prescribed dosage of Brahmi as per Indigenous Systems of Medicines.

Formulation	Dose
Brahmi Juice	2-4 teaspoons once a day
Brahmi Churna	¼-½ teaspoon twice a day
Brahmi Capsule	1-2 capsules twice a day
Brahmi Tablet	1-2 tablets twice a day
Brahmi Infusion	3-4 teaspoons once or twice a day

Table 9: *Bacopa monnieri* genes have been isolated and characterized.

Acetyl-CoA C-acetyltransferase, 3-hydroxy-3-methylglutaryl-CoA reductase, Mevalonate kinase, Mevalonate-5-pyrophosphate decarboxylase, Farnesyl diphosphate synthase, Squalene synthase, 3-deoxy- D -arabino-heptulosonate -7-phosphate synthase, Glycosyltransferases, Pathogenesis-related protein 1.

DOMINATION IN NANOTECHNOLOGY

Nanomedicine has been a popular technique for improving medical care in recent years. The use of ecofriendly nanoparticles has created new possibilities for improving medicinal effectiveness while lowering pessimistic effects. Jayshree *et al.*, reported that the rapid formation of platinum nanoparticles using leaf extract of *B. monnieri* and its Neurorescue effect on MPTP induced on experimental Parkinsonism in Zebrafish. This simple procedure helps for the biosynthesis of platinum nanoparticles which has several advantages such as cost effectiveness, compatibility, and eco friendliness for biomedical and pharmaceutical applications.[67] C. Krishnaraj *et al.*, announced that the interaction of Silver nanoparticles (AgNPs) with the growth and metabolism of *B. monnieri*. It is an apparent from of morphological and anatomical studies that AgNPs significantly decrease in the root and shoot length along with disappearance of air chamber in root cortex, alteration of shape, size and distribution of xylem elements in the stems of *B. monnieri*.[68] Mani Suganya *et al.*, reported the phytofabrication of silver nanoparticles with *B. monnieri* leaf extract, as well as its antibacterial efficacy and oxidative stress-induced lung cancer apoptosis. The entire paper emphasises the cost-effective, one-step, and eco-friendly acceptable synthesis of silver nanoparticles with a wide range of applications in drug administration and cancer diagnostics and therapy.[69] Kumar and Garg focused on bacoside rich extract loaded solid lipid nanoparticles as a therapy option for Alzheimer's disease. The formulation was found to have 24-hr drug release and 3 months stability, confirming the effectiveness of formed solid lipid nanoparticles.[70] Priya *et al.*, reported the effect of silver nanoparticles incorporated in Murashige and Skoog medium for callus induction in *B. monnieri*.[71] Mahitha *et al.*, outline a reliable and eco-friendly process for synthesis of metallic nanoparticles in the field of the nanotechnology. Here the ethanolic extract of the whole plant of *B. monnieri* used to produce silver nanoparticles by reduction of silver nitrate. It was observed that the synthesis process was quite rapid and silver nanoparticles were formed within minutes of silver ion coming in contact with the plant filtrate. Simultaneously the silver nanoparticles using *B. monnieri* proved excellent antimicrobial activity and these AgNPs may be used in food and pharmaceuticals industries.[72] Punuri *et al.*, reported the green synthesis of crystalline gold nanoparticles using UV irradiation and ethanolic leaf extract of *B. monnieri*, this method is eco-friendly, amenable to large scale production and has potential to be employed for synthesis of other metallic nanoparticles.[73] Khot Uttamkumar Vitthal *et al.*, studied Solid Lipid Nanoparticles (SLNs) loaded with Bacoside were prepared by microemulsion probe sonicator method. SLNs have been proposed as suitable colloidal carriers for delivery of drugs with limited solubility. Bacoside used as a model drug which was incorporated into SLNs prepared from stearic acid using Tween 80 as emulsifiers.[74] Badrelden *et al.*, also reported the formation of silver nanoparticles from aqueous extracts of whole plants of *B. monnieri, C. blumei* and *C. intybus* using oxidation-reduction method. The products were characterized using UV- Visible, FTIR Zeta potential and HR-TEM. The morphology of AgNPs is a spherical shape.[75] Khan *et al.*, also synthesized silver nanoparticles from *B monnieri* leaf and performed antibacterial activity against *Staphylococcus aureus* and *E. Coli* bacterial species and it was proved that plant coated AgNPs extract showed relatively higher antibacterial activity against Gram-ve bacteria as compared to Gram+ve bacteria.[76] Mahitha *et al.*, also reported that the antioxidant property of *B. monnieri* stabilized Silver Nanoparticles (BmSNPs) against aluminium induced toxicity in albino mice. Evidence certainly indicates that BmSNPs can eliminate oxidative stress and prevent tissue damage in mice exposed to aluminium.[77]

IMPROVED MICROPROPAGATION AND ENHANCEMENT OF SECONDARY METABOLITE BIOSYNTHESIS

Plant tissue culture strategies are the most widely used biotechnological tools for a variety of basic and applied purposes, including plant developmental studies, functional gene studies, commercial plant micropropagation, generation of transgenic plants with specific industrial and agronomical traits, plant breeding and crop improvement, virus removal from infected materials to render high-quality healthy plant material, preservation and conservation of plant material. It's a technique for growing plantlets *in vitro* from any portion of the plant in an appropriate nutritional media under aseptic circumstances.[78] Plant tissue culture research from the recent era have also been conducted for the preservation of medicinal plant resources as well as the effective generation of pharmaceutically relevant secondary metabolites. Approximately 70% of India's medicinal

Table 10: List of biologically active plant-derived molecules from *B. monnieri* from the Pub Chem database.

Sl. No.	Bioactive Compounds
1	Nicotine
2	D-Mannitol
3	Bacoside A
4	Bacopasaponin A
5	Bacopasaponin B
6	Bacopasaponin C
7	Bacopasaponin D
8	Bacopasaponin E
9	Bacopasaponin F
10	Bacopasaponin G
11	Bacopaside I
12	Bacopaside II
13	Bacopaside III
14	Bacopaside IV
15	Bacopaside V
16	Bacopaside VIII
17	Bacopaside XII
18	Plantainoside B
19	Betulinic acid
20	Cucurbitacin A
21	Cucurbitacin B
22	Cucurbitacin C
23	Cucurbitacin D
24	Cucurbitacin E
25	Stearic acid
26	Rosavin
27	3,4Dimethoxycinnamic acid
28	Ascorbic acid
29	Asiatic acid
30	Brahmic acid
31	Wogonin
32	Oroxindin
33	Loliolide
34	Stigmasterol
35	β-sitosterol
36	Ebelin lactone
37	Stigmastanol
38	Bacosterol
39	Bacosine
40	Heptacosane
41	Octacosane
42	Nonacosane
43	Triacontane
44	Hentriacontane
45	Dotriacontane
46	Apigenin
47	Quercetin
48	Ursolic acid
49	Luteolin
50	Asiaticoside
51	Bacopaside VI
52	Bacopaside VII
53	1,2-Benzenedicarboxylic acid, mono(2-ethylhexyl) ester
54	2,6,10-Trimethyl,14-ethylene-14-Pentadecne
55	2-Cyclohexen-1-one,3-(3-hydroxybutyl)-2,4,4trimethyl
56	2-Cyclohexen-1-one, 4-hydroxy-3,5,5-trimethyl-4-(3oxo1-butenyl)-
57	2-Nonenal, 2-Pentyl
58	2-Pentadecanone, 6,10,14-Trimethyl
59	3,7,11,15-tetramethyl-2-Hexadecen-1-ol
60	3A(1H)-Azulenol,2,3,4,5,8,8A-hexahydro-6,8Adimethyl3-(1-M
61	9-Octadecenoic acid (Z)
62	Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4hydroxy-, methyl ester
63	Cis-9-Hexadecenal
64	Cis-10-Nonadecenoic acid
65	Dodecane
66	Heneicosane
67	Hexadecanoic acid, 2-hydroxy-1-(hydroxymethyl) ethyl ester
68	Hexadecanoic acid, methyl ester
69	Icosanoic acid
70	Nonacosane
71	Octadecanoic acid
72	Octadecanoic acid, ethyl ester
73	Phenol, 2-methoxy-4-(2-Propenyl)
74	Phytol
75	Tridecane
76	Vitamin E
77	Cladribine
78	Cyclophosphamide
79	Mitoxantrone

Table 11: The various saponins and their IUPAC names.

Compounds	IUPAC name
Bacoside A_1	3-O-[α-L-arabinofuranosyl (1→3)-α-L-arabinopyranosyl]-jujubogenin
Bacoside A_2	3β-O-[α-L-arabinofuranosyl (1→6)-O-[α-L-arabino-pyranosyl-(1→5)-O-α-D-glucofuranosyl)oxy] pseudojujubogenin
Bacoside A_3	3β-[O-β-D-glucopyranosyl-(1→3)-O-[α-L-arabi-nofuranosyl-(1→2)]-O-β-D-glucopyranosyl) oxy] jujubogenin
Bacopasaponin A	3-O-α-L-arabinopyranosyl-20-O-α-L-arabinopyra-nosyl-jujubogenin
Bacopasaponin B	3-O-[α-L-arabinofuranosyl (1→2)-α-L-arabinopyr-anosyl] pseudojujubogenin
Bacopasaponin C	3-O-[β-D-glucopyranosyl-(1→3)-{α-L-arabinofu-ranosyl-(1→2)}-α-L-arabinopyranosyl] pseudoju-jubogenin
Bacopasaponin D	3-O-[α-L-arabinofuranosyl (1→2)-β-D-glucopyra-nosyl] pseudojujubogenin
Bacopasaponin E	3-O-[β-D-glucopyranosyl-(1→3)]-{α-L-arabinofu-ranosyl-(1→2)-α-L-arabinopyranosyl]-20-O-α-L-arabinopyranosyl) jujubogenin
Bacopasaponin F	3-O-[β-D-glucopyranosyl-(1→3)-{α-L-arabinofura-nosyl-(1→2)}-β-D-glucopyranosyl]-20-O-(α-L-ara-binopyranosyl) jujubogenin
Bacopasaponin G	3-O-[α-L-arabinofuranosyl-(1→2)-α-L-arabinopyr-anosyl] jujubogenin
Bacopaside I	3-O-[α-L-arabinofuranosyl-(1→2)-{6-O-sulfonyl-β-D-glucopyranosyl-(1→3)}-α-L-arabinopyranosyl pseudojujubogenin
Bacopaside II	3-O-[α-L-arabinofuranosyl-(1→2)-{β-D-glucopyr-anosyl-(I→3)}-β-D-glucopyranosyl] pseudojujubogenin
Bacopaside III_a	3-O-[{6-O-sulfonyl-β-D-glucopyranosyl-(1→3)}-α-L-arabinopyranosyl] pseudojujubogenin
BacopasideIII_b	3-O-[α-L-arabinofuranosyl-(1→2)-{β-D-glucopyra-nosyljujubogenin
Bacopaside IV	3-O-[β-D-glucopyranosyl-(1→3)-α-L-arabinopyra-nosyl] jujubogenin
Bacopaside V	3-O-[β-D-glucopyranosyl-(1→3)-α-L-arabinopyra-nosyl] pseudojujubogenin
Bacopaside VI	3-O-[6-O-sulfonyl-β-D-glucopyranosyl (1→3)]-α-L-arabinopyranosyl] pseudojujubogenin
BacopasideVII	3-O-{β-D-glucopyranosyl-(1→3)-[α-L-arabinofurano-syl-(1→2)]-α-L-arabinopyranosyl} jujubogenin
Bacopaside VIII	3-O-{β-D-glucopyranosyl-(1→3)-[α-L-arabinofurano-syl-(1→2)]-β-D-glucopyranosyl}-20-α-L-arabinopyra-nosyl jujubogenin
Bacopaside X	3-O-α-L-arabinofuranosyl-(1→2)-{β-D-glucopyrano-syl-(1→3)}-α-L-arabinopyranosyl] jujubogenin
Bacopaside N_1	3-O-[β-D-glucopyranosyl-(1→3)-β-D-glucopyranosyl] jujubogenin
Bacopaside N_2	3-O-[β-D-glucopyranosyl-(1→3)-β-D-glucopyranosyl] pseudojujubogenin
Monnieraside I	α-O-[2-O-(4-hdroxybenzoyl)-β-D-glucopy ranosyl]-4-hydroxyphenylethanol
Monnieraside II	α-O-[2-O-(3-methoxy-4-hdroxycinn amoyl)-β-D-gluco-pyranosyl]-3,4-dihydroxyphenylethanol
Monnieraside III	α-O-[2-O-(4-hdroxybenzoyl)-β-D-glucopyranosyl]-3,4-dihydroxyphenylethanol
Bacosterol glycoside	Bacosterol-3-O-β-D-glucopyranoside
Brahmoside	8,10,11-trihydroxy-9-(hydroxymethyl)-1,2,6a,6b,9,12a-hexamethyl-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicene-4a-carboxylic acid

plants are found in tropical locations, primarily in the Western and Eastern ghats, the Vindhyas, the Chotta Nagpur plateau, the Aravalis, and the Himalayas. Although temperate and alpine zones at higher altitudes contain fewer than 30% of medicinal plants, they do contain species with considerable medicinal potential. A number of therapeutic plants are already endangered, uncommon, or threatened. Plant tissue culture is a new method for propagating and conserving economically significant crops that are categorised as endangered, uncommon, or vulnerable, therefore one of our goals is to outline the *in vitro* approach for *Bacopa monnieri* conservation.

Recently Anuja Koul and Sharada Mallubhotla reported the enhancement of bacoside production in cell suspension cultures using suitable elicitors and precursors.[79] Ruchi Chauhan and Poonam Shirkot also evaluated and developed successfully for micropropagation of *B. monnieri* genotype, which can be further used for mass production of this genotype of this threatened plant species.[80] In addition, Neelam *et al.*, evaluated and

standardised biomass production in different vessels and bioreactors using explants and media for growth, total phenolic content, and antioxidant capacity of Bacopa shoot culture, and found that the Growtek bioreactor was an effective system for producing *B. monnieri* biomass in culture without losing antioxidant properties.[81] Haque *et al.*, also standardize and improved the method for micropropagation and *in vitro* biomass production of *B. monnieri*. Micropropagation was performed by using standard tissue culture method. The effect of different concentrations of 6-Benzylaminopurine (BAP) and Kinetin (KIN) alone on *in vitro* adventitious shoot multiplication from leaf explants was investigated. The cytokinin BAP or KIN alone was sufficient for induction of adventitious shoot buds from the leaf explants of *B. monnieri*. Higher concentration of cytokinin had reduced the number of shoots. BAP was found to be more effective than KIN for adventitious shoot induction. In addition of spermidine along with the optimum concentration of BAP has proven helpful in increasing the adventitious shoot bud induction rate.[82] *Bacopa* micropropagation from a variety of explants is employed in several countries. Plant regeneration was routinely achieved in tissue culture studies so far using various explants as the raw material. A few investigations on shoot regeneration from various explants have been published. The plant were produced from explant of leaves,[83-85] axillary node,[86] nodal segments,[87-89] internodes, shoot apex, root and stem.[90] In medicinal plants roots of micro-shoots have been obtained in MS medium with Indole-3-Acetic Acid (IAA), Indole-3-Butyric Acid (IBA), 1-Naphthaleneacetic Acid (NAA) used singly or in combination or when transferred to hormone free medium. The role of Auxins in root development was established and reviewed by John G. Torre.[91,92] Singh *et al.*, reported rooting in *B. monnieri* on MS medium supplemented with 6-Benzylaminopurine (BAP) (0.5 mg/l).[93] Root induction has also been reported in Bacopa using MS medium supplemented with a concentration of 1.0 mg/l of IAA and 1.0mg/l IBA.[94] Sharma *et al.*, reported best rooting in *B. monnieri* with IBA when incorporated in MS at different concentrations (0.1 - 0.3 mg/l).[95] Tiwari *et al.*, tried rooting on different media in Bacopa, i.e., MS media with or without hormones and found that rooting was highest (90%) on full-strength MS medium containing 2.46 mM IBA.[96] Shoot proliferation was achieved on MS media supplemented with various growth regulator viz. BAP, Kinetin, IBA, IAA, 2,4-Dichlorophenoxyacetic acid (2,4-D). The efficiency of BAP for shoot culture initiation and multiplication in *B. monnieri*, reported by several Authors.[97,98] These multiple shoots became dwarfish and excellent form to fit to culture tubes. Cytokinins are known to be very effective in promoting shoot proliferation and their role in shoot organogenesis is well established.[99] Several studies also showed that media supplemented with NAA and 6-Benzylaminopurine (BAP) has also useful for production of shoots. Success of regeneration depends not only on the type of the explant chosen, but also the way explants are placed on the culture medium.[100] Mohapatra and Rath reported maximum shoot multiplication on MS medium supplemented with BAP and NAA.[101] Effectiveness of MS medium for optimum shoot multiplication in different species have also noted by various Researchers.[87,102,103] Simultaneously, Methyl jasmonate stimulated the production of bacoside A, a valuable triterpenoid saponin with nootropic therapeutic potential, in *B. monnieri* shoot cultures developed *in-vitro*.[104] Bhanwar *et al.*, 2016, also reported the *in-vitro* culture established retained the inherent capability to synthesize bacosides under tissue culture conditions.[105] Similarly, the adventitious shoot cultures of *B. monnieri* has shown that both the biomass and bacoside-A was influenced by subculture.

Table 12: GC-MS analysis of *B. monnieri* extract.

Types of Compounds	Name of Chemicals
Saturated hydrocarbon	Dodecane; Tridecane; 2,6,10-Trimethyl,14-ethylene-14-Pe ntadecne; Heneicosane; Nonacosane; 2,6,10-Trimethylpentadecane.
Allylbenzene class	2-Methoxy-3-allylphenol (Eugenol)
Sesquiterpene	3-Isopropyl-6,8a-dimethyl-2,3,4,5,8,8a-hexahydro-3a(1H)-azulenol (Carotol); (6s)-6-hydroxy-3-oxo-alpha-ionone (Dehydrovomifoliol);
Acyclic diterpene alcohol	6,10,14-Trimethyl-,3,7,11,15-tetra methyl-2-Hexadecen-1-ol (Phytol)
Fatty acid	Oleic acid; Palmitic acid; Stearic acid; cis-10-Nonadecenoic acid; Arachidic acid; Palmitic acid; Pentadecanoic acid
Fatty acid esters	Ethyl octadecanoate
Ester of phthalic acid	Mono(2-ethylhexyl) phthalate; Dibutyl phthalate; Butyl isobutyl phthalate
Unsaturated aldehyde	2-Pentyl-2-nonenal; Cis-9-Hexadecenal;
Organic ketones	2-Pentadecanone
Enone	2-Cyclohexen-1-one
Phenol class	Benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-, methyl ester (Metilox);
Sterols	(3β)-Cholesta-4,6-dien-3-ol; (3β)-Ergost-5-en-3-ol; Stigmasterol; β-Sitosterol
Vitamin and its derivatives	Vitamin E; 1-(+)-Ascorbic acid 2, 6 dihexadeconate.
Miscellaneous	3-(3-hydroxybutyl)-2,4,4-trim ethylcyclohex-2-en-1-one; Levoglucosan; 1,6-Anhydro-beta-D-talopyranose; Oxirane

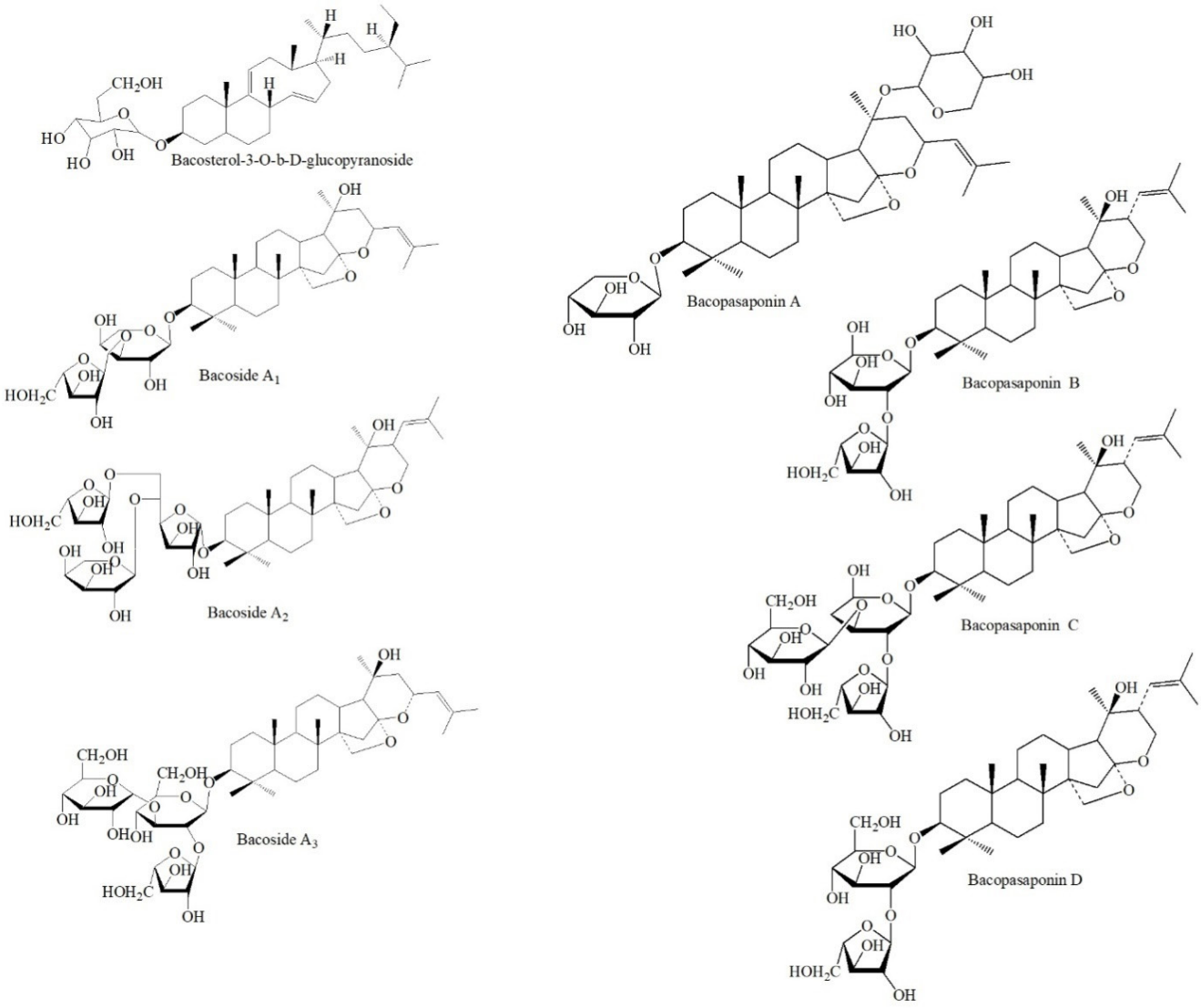

Figure 6: The chemical constituents and their structures obtained from *B. monnieri*.

The highest number of adventitious shoots, fresh weight, dry weight and the production of Bacoside A content was also reported, and these results are also useful for the large-scale cultivation of *B. monnieri* adventitious shoots for the production of bacoside A.[106] Łojewsk *et al.*, evaluated the content and concentration of magnesium and other metals in *in vitro* shoot cultures of *B. monnieri* and their influence on bacoside levels.[107] Monica *et al.*, reported that cell suspension culture in synthetic media offers an alternative way for producing metabolites of interest to the traditional cultivation in fields or greenhouses. Here enhanced the production of total saponins was obtained from 40-day old suspension cultures of *B. monnieri*. The callus yielded not only a 166% increased concentration of saponins but also produced two novel prominent bands of saponins compared to the natural plant system.[108] B. Muszy Nska *et al.*, proved that through *in-vitro* cultures, the essential micronutrients (zinc and magnesium) and organic compounds (anthranilic acid, L-tryptophan and serine) had an influence on biomass growth and the levels of metabolites. Phenolic compounds identified in biomass from the same variants of MS medium were chlorogenic acid (ranging from 0.20 to 0.70mg/g dry weight), neochlorogenic acid (ranging from 0.11 to 0.40mg/g dry weight) and caffeic acid (ranging from 0.01 to 0.04mg/g dry weight). The multi-therapeutic effect of *B. monnieri* is expressed by the activity of bacosides. Information about the presence of indole and phenolic compounds and fatty acids in this plant is limited.[109] Secondary metabolites are known to play a major role in the adaptation of plants to their environment, but also represent an important source of active pharmaceuticals. The accumulation of such metabolites appears often in plants exposed to various elicitors or signal molecules. Pratibha Anil Chaturvedi and Lal Hingorani reported that the enhancement of active principal Bacoside of *B.*

Table 13: Mineral composition and biochemical profile of *B. monnieri*.

Parameters	Quantity
Protein	2.1 g/100 g
Fat	0.6 g/100 g
Carbohydrate	5.9 g/100 g
Crude fibres	1.05 g/100 g
Flavonoids	575.4 µg/mL
phenolic content	587.6 µg/mL
Moisture	88.4 g/100 g
Calcium	0.202 g
Iron	7.8 mg/100 g
Sodium	0.501 g/100 g
Potassium	1.360 g/ 100g
Copper	7.0mg/kg
Aluminium	4.39 l mg/g
Phosphorous	16.0 g/100 g
Food energy value	38kcal/g
Zinc	68.7mg/kg
Manganese	78.4mg/kg
Magnesium	347.6mg/kg
Aluminium	4.39 mg/g
Ascorbic acid	63.0 mg/100gm
Nicotinic acid	0.3 mg/100gm
Cl	2.83 mg/g
carotenoid	0.0353 g/100 mL

monnieri by using stress ($ZnCl_2$, $CoCl_2$, and $CuSO_4$) and precursor (phenylalanine and tyrosine) compound. After analysing the results conclude that Tyrosin incorporation is the best enhancer treatment than phenylalanine in Bacoside production. $CoCl_2$ is effective stress generating compound that favours the Bacoside biosynthesis in *B. monnieri*. Tyrosine is comparable cheap compound than cobalt chloride that gives the same results.[110] Growth and bacopa saponin content of transgenic plants were also significantly improved. Transgenic plants bearing the cryptogein gene produced the most bacopasaponin D (1.4–1.69%). Ri crypt-transformed plants had considerably more bacoside A_3, bacopasaponin D, bacopaside II, bacopaside III, and bacopaside V accumulation than Ri-transformed plants. The transgenic lines that were created can be exploited for additional study on elicitation in crypt-transgenic plants as well as large-scale saponin production.[111] Similarly, the effect of precursor feeding and LED light exposure on the enhancement of bioactive chemicals in *B. monnieri in vitro* cells. L-alanine and L-phenylalanine were used as precursors to increase the accumulation of triterpenoids saponin glycosides. The optimal duration for precursor feeding was obtained after treatment for 6 days. Total triterpenoids saponin glycosides production increased 2.4-fold to 46.98 (mg/g dry wt.) and 2.6-fold to 49.41 (mg/g dry wt.), by adding 5mM L-alanine and 150 µM L-phenylalanine for 6 days. In addition, triterpenoids saponin glycosides reached the maximum level (58.53 dry wt.) after treatment with a combination of precursors (1.0mM L-alanine and 100 µM L-phenylalanine for 6 days). Furthermore, blue and red light on day 28 of treatment increased triterpenoids saponin glycosides (24.11, 22.18 mg/g dry wt.) 1.7-fold and 1.5-fold higher than that obtained with white light. This study indicated that bioactive compounds in *B. monnieri in vitro* cultures can be enhanced by feeding precursors and LED light exposure. These techniques can be applied at the industrial level of crops and food supplements.[112] S. Kamonwannasit *et al.*, reported that MS medium supplemented with 0.1 mg/l thidiazuron can be used for the induction of high shoot formation and increased yields of pseudojujubogenin glycosides in *B. monnieri*. In addition, chitosan and yeast extract are suitable as elicitors for increased accumulation of pseudojujubogenin glycosides in *B. monnieri* whole plant cultures.[113] As we known that *B. monnieri* is a valuable medical plant well recognised for its memory-enhancing properties, metal contamination has a significant impact on its active ingredients. The impact of Cadmium (Cd) on the triterpenoids Bacoside A and Bacopaside I saponins in this plant has been described. It has also been noted that the metal has an effect on growth indices like as protein, chlorophyll content, and biomass. It is interesting to note that the bacoside A and Bacopaside I gradually increased by the Cd treatment up to 10 µM and then decreased at higher concentrations, that is, 50 and 100 µM, but the concentration of these components was more in all the treated plants as compared to control. Simultaneously the protein, chlorophyll content and biomass decreased with the increase in metal concentration and exposure duration due to metal toxicity. This indicates that the synthesis of secondary metabolites enhances initially up to a certain limit due to abiotic stress and then decreases due to Cd toxicity in higher concentrations.[114] Elicitation is one of the most successful strategies for increasing secondary metabolite development, biomass stimulation, and bacoside production in *Bacopa monnieri in-vitro* culture.[115,116] The triterpenoid saponins collectively known as bacosides are the pharmaceutically essential compounds in the medicinal herb *Bacopa monnieri*, and they are present in very small quantities. As a result, developing designer Bacopa plants with altered triterpenoid content is critical. Thus, at the CSIR-National Chemical Laboratory in Pune, India, various genes involved in bacoside biosynthesis in Bacopa were isolated and characterized [Table 9]. These findings suggest that developing elite lines of Bacopa overexpressing pathway genes may provide insight into the bacoside biosynthesis regulatory mechanism.[117] As a result, we can predict that *B. monnieri* will become a very important plant for phytoremediation and removing Cadmium from polluted sites, and it is a good indication that its active constituents will increase in this condition, and pharmaceutical companies will use these plants for extracting its

active compounds, even if grown on polluted sites, and as the demand for Bacopa is met by natural population, putting heavy strain on existing natural population and thus slowing down the process. To achieve quick multiplication of the elite clones and germplasm conservation of *B. monnieri*, tissue culture techniques can be applied.

EXPLORATION OF BIOACTIVE COMPOUNDS AND PHYTOMOLECULES

Series of biochemical like alkaloids (brahmine, nicotine, herpestineandhydrocotyline), bacosides, flavonoids, glycosides, triterpenoids, sterols (β-sitosterol, stigma-sterol), saponins, chalcone type compound 2,4,6-trihydroxy-5-(3,3-di-Me propenyl)-3-(4-hydroxyphenyl) propiophenone respectively, are the potential therapeutic constituents of this plant identified by various Researchers.[118] A total of 79 biologically active plant-derived molecules from *Bacopa monnieri* from the PubChem database are shown in Table 10[119-121] and in Table 11, the various saponins and their IUPAC names are given.[122] The main constituents of Brahmi are triterpene saponins that have been called bacosides and bacopasaponins of the dammarane class. Bacosides are a complex blend of structurally closely related compounds, either jujubogenin or pseudojujubogenin glycosides, all of which vary only in the form of the sugar units in the glycoside chain and the position of the olefin side chain in the aglycone. Bacoside A is the major component that is responsible for the memory enhancement effect. On acid hydrolysis of Bacoside A, it gives bacogenins A_1, A_2, A_3, A_4.[123] These saponins, namely bacosides (A_1 and A_3) and bacopasaponins A-G, are a complex blend of closely related structures.[124-128] There have also been identified two new dammarane types of jujubogeninbisdesmosides, bacopasaponins E and F,[129] pseudojujubogenin glycosides, bacopasides I and II,[130] phenylethanoid glycosides, namely monnierasides I-III with the recognised analogue plantainoside B,[131] and bacopasides III, IV, and V.[132] Bacoside A is mixture of four triglycoside that is bacoside A_3, bacoside II, jujubogenin. Saponin A identified as 3-O-α-L-arabinopyranosyl-20-O-α-L-arabinopyrasonyl-jujubogenin, saponin B is 3-O-[α-Larabinofuranosyl (1→2)-α-L-arabinopyranosyl] pseudojujubogenin, and saponin C is 3-O-β-D-glucopyranosyl(1→3)-{α-L-arabinofuranosyl-(1→2)}-α-Larabinopyrasonyl] pseudojujubogenin and Pseudojujubogenin glycoside as 3-O-[α-Larabinofuranosyl-(1→2)-β-D-glucopiranosyl] pseudojujubogenin.[24] These Bacoside-A steroidal saponins glycoside are laevorotatory, and Bacoside-B is dextrorotatory, assumed to be among the most therapeutic constituents.[133] Bacoside B is composed of four minor saponins: bacopasides N_1, N_2, IV, and V. Simultaneously Bhandari *et al.*, reported a new sterol glycoside, bacosterol-3-O-ß-D-glucopyranoside along with bacopasaponin-C, bacopaside-I, bacopaside-II, bacosterol, bacosine, luteolin-7-O-ß-glucopyranoside and four cucurbitacins, bacobitacin A (I)-D, a known cytotoxic, cucurbitacin E, together with three known phenylethanoid glycosides, monnieraside I, III and plantioside B from *B. monnieri* and the use of cucurbitacin E in various experimental models as one of the most promising therapeutic natural molecules against cancer proliferation, as an immunomodulators and for the prevention of neurodegeneration.[134] Similarly, Chia-Chung Hou *et al.*, also reported two new saponins, 3-O-[6-O-sulfonyl-beta-d-glucopyranosyl-(1→3)]-alpha-l-arabinopyranosyl pseudojujubogenin and 3-O-[alpha-l-arabinofuranosyl-(1→2)]-alpha-l-arabinopyranosyljujubogenin, along with a new matsutaka alcohol derivative, (3R)-1-octan-3-yl-(6-O-sulfonyl)-beta-d-glucopyranoside and a new phenylethanoid glycoside viz., 3,4-dihydroxyphenylethyl alcohol (2-O-feruloyl)-beta-d-glucopyranoside and a new glycoside, phenylethyl alcohol [5-O-p-hydroxybenzoyl-beta-d-apiofuranosyl-(1→2)]-beta-d-glucopyranoside.[128] In addition, three new triterpene glycosides, bacopasides VI-VIII, have been identified by Yun Zhou *et al.*, from the whole plant and, when tested on forced swimming and tail suspension in mice, showed antidepressant activity.[135] In nature, Bacosides A and B are lipophilic, meaning they can be integrated with or dissolved in lipids, giving them the ability to cross the blood-brain barrier.[136] Other major compounds reported in this plant include flavonoids (luteolin, wogonin, oroxindin, hispidulin, eriodictyol, naringenin, cirsimaritin,clitorin, quercetinand apigenin), carnosol (phenolic diterpene), betulinic acid, brahmoside (triterpenoids), asiatic acid, brahmic acid, isobrahmicacid,cucurbitacin, asiaticoside, thanakunicide, D-mannitol, amino acids (alpha-alanine, aspartic acid glutamic acid), brassinosteroid,loliolide, rosavin, feruloyl glucoside, methocarbamolandrosmarinic acid.[137-141] Figure 6 demonstrate the chemical constituents and their structures obtained from *B. monnieri*. In addition, Table 12 also encompass the evidence of GC-MS analysis of methanolic extracts of the entire plant and their phytoconstituents.[142,143]

STOCKPILES OF TRACE ELEMENTS AND BIOCHEMICAL CONTOUR

The rising incidence of environmental pollution, particularly heavy metal poisoning of soil, has resulted in their absorption into human food chains *via* plant components. Heavy metal accumulation and amplification in human tissues caused by herbal medicine intake can have disastrous health consequences. The World Health Organization has thus defined some quality control standards for heavy metals and pesticide residues. The presence of trace components in *Bacopa monnieri* has been confirmed and recorded by several researchers as such, Lavu RVS *et al.*, stated that, for use as raw medicinal plant material or direct use, aboveground parts of plant Bacopa samples exceeded the threshold limits of Cd, Pb, Cu and Zn.[144] Brahmi leaves are

also enriched in K, Ca, P, Fe, as minor constituents and trace amounts of Mn, Zn, Co, Cr and Se, but concentration of all heavy metals, except Cr, was within permissible limits in both stem and leaf.[145,146] Furthermore, A. N. Garg *et al*., reported that aqueous, methanolic and aqueous–methanolic (1:1) extracts of Brahmi leaves contain seven minor (Al, Fe, Na, K, Ca, P, Cl) and eighteen trace (As, Au, Ba, Br, Co, Cr, Cu, Hf, Hg, La, Mn, Rb, Se, Sm, Sr, Th, V, Zn) elements whereas aqueous–methanolic extract showed maximum contents of Na, K, Cl and significant amounts of Mn, Co, Zn.[147] Amrita Mishra *et al*., also reported heavy metals and pesticide residues of various Ayurvedic formulations, including Brahmi Vati, Brahmi Ghrita and Saraswat Churna, where Pb, Cd, Cr and Ni were present in all samples but below the permissible limit. Whereas atrazine, aldrin, dialdrin are also identified but within the limits, ancillary pesticides are also prevalent in samples within permissible limits such as oxamyl, hexachlorocyclohexane, dichlorodiphenyl trichloroethane and dichlorodiphenyl dichloroethylene.[148] Recent research has suggested that the levels of metal accumulation and heavy metal contamination with *Bacopa monnieri* are attributable due to natural and anthropogenic activities. The results also showed that all of Brahmi's edible parts contain many nutritionally important minerals that have been connected to the promotion of good health and are highly beneficial in the treatment of different diseases. It is advisable that proper consumption of plants can contribute to minimize disease shortfalls.[149,150] The mineral composition and biochemical profile of *B. monnieri* are shown in Table 13.

PHARMACOLOGICAL TESTIMONY

Antioxidant and Adaptogenic Activity

Reactive oxygen species are by-products of normal cell action. They are produced in a number of cellular compartments and serve a crucial function in signalling. Overproduction of reactive oxygen species (ROS) has been related to the advancement of a number of human illnesses, including cancer, respiratory, neurological, and metabolic disorders, as well as inflammation and ageing. Antioxidants aid in the prevention of free radical oxidative damage. The antioxidant properties of *Bacopa monnieri* are well-known and have been investigated in several studies. *Bacopa monnieri* has good nitric oxide radical scavenging, reducing strength, and DPPH function, making it a promising natural antioxidant with therapeutic potential in preventing or halting the progression of aging and age-related oxidative stress-related degenerative diseases.[151] *Bacopa monnieri* extract or bacosides strengthen the system's defense against oxidative stress by reducing the development of free radical aggregation, according to many histological (*in-vitro*) and animal research.[17,65] *In vitro* antioxidant efficacy of *Bacopa monnieri* aerial parts ethanolic extract was reported by Ghosh *et al*., As comparison to the reference drug, the antioxidant, nitric oxide scavenging, and superoxide radical scavenging behaviour were found to be concentration dependent.[152] In addition, an *in-vitro* study by Russo and researchers examined at how an ethanol extract of Bacopa caused hydrogen peroxide-induced cytotoxicity and DNA damage in human non-immortalized fibroblast cells. They also explored into the ability of hydrogen peroxide to scavenge free radicals and its effect on DNA cleavage. Bacopa showed a dose-dependent inhibition of superoxide anion formation, indicating free radical scavenging capacity, as well as a protective effect against hydrogen peroxide cytotoxicity and DNA damage.[153] Shinomol and his colleagues amply suggested that *Bacopa monnieri* leaf powder can modulate endogenous levels of oxidative stress markers in the brains of prepubertal mice in an *in-vivo* and *in-vitro* trials. Based on these findings, it is proposed that the alcoholic extract of Bacopa may help shield the brain from oxidative-mediated neurodegenerative diseases caused by oxidative stress. Based on these findings, it is hypothesized that consuming Bacopa leaf powder in the diet provides neuroprotection and could be useful as a prophylactic/therapeutic agent for neurodegenerative diseases caused by oxidative stress.[154,155] According to recent findings, Brahmi is a strong antioxidant. Brahmi's responsiveness was dose-dependent. In trials, 100 micrograms of alcoholic Brahmi extract was equal to 247 micrograms of EDTA and 58 micrograms of vitamin E. On lower doses of 100 micrograms/ml and below, Brahmi only marginally covered autooxidation and ferrous Sulphate mediated oxidation of reduced glutathione, but at higher concentrations it accelerated the rate of oxidation.[45] In another research, diabetic rats' antioxidant function was modulated by a substantial increase in superoxide dismutase, catalase, glutathione peroxidase, and glutathion amounts, indicating a significant reversal of redox imbalance and peroxidative harm to improve the defense mechanism toward reactive oxygen species.[156] Other studies show that bacosides of Brahmi reduce the formation of free radicals, implying a free radical scavenging process.[157,158] The methanol extracts of the entire plant, meanwhile, were suggested to have potent antioxidant, antimicrobial, and anti-inflammatory effects. In contrast to methanol extracts, aqueous extracts of the plant were found to have fewer operations. In addition to the above extracts, petroleum ether and hexane extracts displayed marginal activity. The cellular toxicity of these active crude methanol extracts was tested on fresh sheep erythrocytes and found to be negligible.[159] Consequently, antioxidant components such as ascorbic acid, complete phenols, and tannins were present in higher concentrations in *Bacopa monnieri*; leading to the conclusion that Bacopa can help cure neurological problems caused by free radical disruption as a supplement.[160]

Memory Tub-Thumper and in Opposition to Amnesia

Bacopa dramatically increased visual information processing speed, learning rate, memory consolidation, and lessened maximum anxiety. Several studies have shown that higher-order

cognitive functions, such as learning and memory, may be improved. Bacopa alcoholic extract increases motor learning, development, and retention in animals, as well as delaying the extinction of newly learned behaviours, according to animal behavioural research.[161] Bacosides present in the alcoholic extract of *B. monnieri* caused retrograde amnesia, possibly due to an increase in platelet activating factor synthesis by increasing the amount of cerebral glutamate.[162] Memory loss caused by scopolamine may be reversed by treatment with Bacopa. In cognitively intact cohorts, Bacopa enhanced memory functioning, with Pycnogenol improving working memory.[163] The behavioural study proved that *Bacopa monnieri* significantly overcome the diazepam induced amnesia.[164] Bacopa extract administration (40 mg/kg x 7 days) with phenytoin repairs Phenytoin induced cognitive dysfunction, which was found to enhance memory acquisition and retention in mice.[165] Improvements in spatial learning efficiency and improved memory retention were observed in neonatal rats treated with *Bacopa monnieri* alcoholic extract.[166] Similarly, 60 days of oral administration of *Bacopa monnieri* ethanolic extract to adult male Wistar rats showed enhanced long-term synthetic potentiation based on learning that played a critical role in learning and memory.[167] In addition, supplementation with *B. monnieri* increases both the learning capacity and the short-term memory retention of both non-sleep-deprived and sleep-deprived fruit flies (Drosophila melanogaster), and both behaviours have beneficial dose-dependent effects.[168] Furthermore, Bacopa alcoholic extract also enhances spatial working memory by promoting hippocampal neurogenesis in healthy adolescent mice and the effects may be due to bacopaside I in significant quantities.[169] CDRI 08 is a unique extract of *Bacopa monnieri* that restores spatial memory by upregulating the NMDA subunit GluN2B receptor expression in the brain of scopolamine-induced amnesiac mice.[170] Similarly, CDRI-08 (containing 55% of Bacosides A and B) provides evidence towards molecular basis for memory enhancement in streptozotocin-induced type II diabetes mellitus mice by modulating the expression of the AMPA (alpha-amino -3-hydroxy-5-methyl-4-isoxazolepropionic acid) type glutamate receptor by way of reversing the increased blood glucose level to normal by decreasing the insulin resistance and decreasing the oxidative stress in dose-dependent manner.[171] The standardized *Bacopa monnieri* extract exerts major antioxidant effects by attenuating the Superoxide Dismutase (SOD) suppression caused by diazepam in mice, whereas the extract did not attenuate the SOD activity in L-NNA treated mice, but partially decreased the SOD activity in pre-treated scopolamine and Dizocilpine mice, and the report documented that the antiamnesic effect mechanism of *Bacopa monnieri* may differ depending on the type of amnestic agent used.[172] Brahmi alcoholic extract also facilitates anterograde memory and attenuates experimental anterograde amnesia induced in mice by scopolamine and sodium nitrite, possibly by improving the level of acetylcholine and hypoxic conditions, respectively, due to an increase in synthesis of platelet activating factor by increasing thelevel of cerebral glutamate.[162] Using Morris water maze, *Bacopa monnieri* has the ability to elicit antiamnesic effect against diazepam-induced amnesia in mice and this effect is mediated by the GABAergic system and extensively supplemented by its known antioxidant and antiapoptotic properties, which potentiate long-term potential in hippocampus and piriform cortex slices.[173] Additionally, alcoholic extract of *B. monnieri* (50 mg/kg, p.o.) also enhanced Olfactory Bulbectomized (OBX) induced mice cognition dysfunction *via* a mechanism involving enhancement of synaptic plasticity-related signaling and brain-derived neurotrophic factor transcription and protection of cholinergic systems from OBX-induced neuronal damage.[174] Habbu *et al.*, stated that in comparison to bacopa extract at the studied dose, the Bacopa-phospholipid complex showed improved antiamnesic activity. This may be attributed to the stronger absorption of bacopaside from the complex in amnesic mice induced by natural aging.[175]

Cognition and Neuro-Pharmacological Activity

Bacopa monnieri has been reported to enhance memory in different animal models because of its therapeutic potential in the treatment of neurological diseases. The key constituents responsible for cognitive activity are Bacosides. It has been identified that the main chemical compound Bacoside A is responsible for the neuropharmacological effects of *Bacopa monnieri*.[65,161,176] Bacoside A and B were proved to be useful in cognition as well as triterpenoid saponins were responsible to enhance nerve impulse transmission.[128,129] Bacosides were also proved to repair damaged neurons by enhancing kinase activity, neuronal synthesis, restoration of synaptic activity andnerve impulse transmission.[161] In a phencyclidine-induced schizophrenic rat model, Piyabhan *et al.*, recorded that both partial restoration of cognitive deficit and neuroprotection, *via* Brahmi supplement daily at 40 mg/kg, p.o., for 14 days, and explained its underlying mechanism of action through increasing GABAergic neurons.[177] Bacoside A_3 and bacopaside II showed comparatively higher neuroprotective response among four different components of bacoside A, analysed as higher cell viability and decreased intracellular ROS and suggesting better regulation of cyto-(neuronal) protection of Neuro-2a cells.[178] Brahmi is a reputed nerve tonic in Ayurvedic literature. By providing an aqueous solution of an alcoholic extract (40 mg/kg, p.o.) for three or more days, its effects on the learning output of rats have been examined in various conditioning regimes. A labile behaviour using a shock-motivated brightness-discrimination response was induced by the first schedule. Better acquisition, improved retention and delayed extinction were shown by the brahmi-treated group.[138] Bacosides A and B tend to be promising compounds with a facilitative effect on mental retention ability by enhancing both positive and negative reinforcement responses in rats.[179] Bacoside A and bacopaside X seemed to have binding

affinity for the D_1 receptor and stimulated the memory and cognition-related receptors M_1 and 5-hydroxytryptamine, and ebelin lactone had the strongest binding energy, the highest BBB penetration, and binding affinity for the receptors M_1 and 5-HT_{2A}, indicating that *Bacopa monnieri* was responsible for the cognitive effects.[180] *Bacopa monnieri* extract also improves the cognitive impairment of Trimethyltin (TMT) in mice, primarily by shielding the hippocampal neurons from TMT-induced hippocampal lesions and partly by encouraging neurodegeneration in the regions of the dentate gyrus.[181] *Bacopa monnieri* also acts against toxicants such as glutamate, aluminium and nitric oxide as a neuroprotective agent. Antioxidant effects of *Bacopa monnieri* have been reported in various memory-involved areas of the rat brain, such as the hippocampus, frontal cortex, and striatum.[182]

Anti-Depressant Stratagems

Antidepressant activity using the Forced Swimming Test (FST) and Tail Suspension Test (TST) in mice for several fractions of *Bacopa monnieri* methanol extract and the research indicates that the fraction of methanol, ethanol and butanol decreases the immobility duration in FST and TST in mice for 5 consecutive days after oral administration.[183] Similarly, in the forced swimming test and shock-induced depression, Brahmi showcased antidepressant activity, while the tail suspension test did not showcase any activity on Albino Mice at 10, 20, 30 mg/kg p.o., doses.[184] Significant chemical constituents of *B. monnieri*, namely bacosides A and B, bacopasides I and II, developed antidepressant activity with bacopasaponin C, but bacopaside VII has no antidepressant activity in experimental animals (rats) using the FST and TST.[135,185,186] Bacopa aqueous extract (80 and 120 mg/kg, p.o.), significantly decreased escape latency and level of plasma corticosterone, as well as substantial body weight restoration among stressed rats. These Bacopa extract properties clearly coincide with the effects of a well-accepted antidepressant drug.[187] Similarly, Shader *et al*., also proved that, compared to imipramine, *B. monnieri* extract at a dosage of 20-40 mg/kg, p.o., provokes anti-depressant activity in rodent animals.[188] Antidepressant activity of *Bacopa monnieri* leaves alcoholic extract compared with standard drug imipramine in Tail Suspension Test (TST) and Forced Swim Test (FST) in mice model has been reported by Wasnik *et al*.[189] Similarly, Mannan *et al*., reported anti-depressant-like activity of *Bacopa monnieri* leaves methanolic extract using Forced Swimming Test (FST), locomotor activity test measurement and tail suspension test where, compared to standard drug imipramine hydrochloride, obtained results showed substantial antidepressant-like activity.[190] In behavioural models of depression in mice, acute treatment with methanolic extract of the entire plant mediated an antidepressant-like effect. The evidence documented suggests that the antidepressant-like impact of *Bacopa monnieri* is induced by interaction with the serotonergic and noradrenergic systems in the forced swimming test.[191]

Anticonvulsant Maneuvers

No anticonvulsant activity was observed when extract of *Bacopa monnieri* was administered in mice and rats at lower doses, but intraperitoneal high-dose injecting developed anticonvulsant effect for 15 days of treatment.[192] while bacosides also registered promising anticonvulsant activity.[193] In addition, in various models with similar mechanisms of action like benzodiazepines, the ethanolic extract of *Bacopa monnieri* leaves produced substantial anticonvulsant activity.[194] The anticonvulsant function of different medicinal plants, including *Bacopa monnieri*, was studied by Kasthuri *et al*.[195] Giramkar *et al*., have documented the anticonvulsant activity of two polyherbal formulations of *Bacopa monnieri* and Saraswatarishta against seizures caused by maximal electroshock in rats.[196] Glutaminergic transmission or blockage of the sodium channel can involve the recorded anticonvulsant activity of *Bacopa monnieri* leaves ethanol extract.[197] *B. monnieri* has a neural pathway that prevents epileptic fits. Bacoside promotes acetylcholine, which activates GABA, and balances chemicals within the brain that control seizure activity. It also increases GABA activity and reduces cognitive problems.[198]

Anxiolytic Activity

Because of its anxiolytic property (anti-anxiety), Brahmi can be helpful in controlling anxiety. Although increasing the memory span, it may reduce the symptoms of anxiety and mental exhaustion. Neuroinflammation (inflammation of the nervous tissue) responsible for anxiety can also be prevented by Brahmi. It's called an adaptogenic herb, which means it enhances the resistance of the body to stress.[199] One rodent experiment showed that *Bacopa monnieri* had anti-anxiety effects close to those of lorazepam (benzodiazepine), a prescription medication used to relieve anxiety.[200] Highly effective as an adaptogen, these plants induced increases in corticosterone as normalized acute and chronic stress, normalized noradrenaline, 5-hydroxy tryptamine and dopamine in acute and chronic unpredictable stress in rats in the cortex and hippocampus. Bacopa can be reversed by cognitive deficiencies caused by neurotoxins, colchicine and ibotenic acid in a dose-related manner.[201-203] In contrast to lorazepam, higher doses of *Bacopa monnieri* extracts displayed better effects. In addition, acute and sub chronic treatment of *B. monnieri* aerial parts methanolic extract does not affect dopamine and serotonin turnover in mice whole brain at a dose of 10, 20 and 30 mg/kg, p.o..[204] BacoMind (30 and 60 mg/kg oral) is a standardized phytochemical composition derived from *B. monnieri* that, via the use of Elevated Plus Maze (EPM) and open field test, has significant anxiolytic activity in rats.[205] Similarly, using light/dark box, elevated plus maze, marble burial and rota rod trials in mice at doses of 50, 100 and 200 mg/kg, p.o., the methanolic extract of the arial parts also has anxiolytic effects.[206] Himalaya Herbals Brahmi tablets demonstrated an anxiolytic effect in

general as well as in ethanol withdrawal triggered by anxiety in rats.[207]

Sedative and Tranquillizing Benefaction

A sedative effect of glycosides called hersaponins has been documented in earlier systematic reviews.[208] A subsequent study showed that there were tranquillizing effects on albino rats and dogs with the alcoholic extract and, to a lesser degree, the aqueous extract of the whole plant.[209] Furthermore, the plant's alcoholic extract and chlorpromazine have been found to boost the efficiency of rats in motor learning.[210]

Antiepileptic Effect

Epilepsy is a chronic disease of the central nervous system that arises not only with the imbalance of Glutamatergic Neurons and Gamma-aminobutyric Acid (g-GABA) inhibitory neurons, but also with impaired neuronal central cholinergic control. Since Brahmi is rich in antioxidants that protect the cells of the brain. The development and function of certain genes and their proteins is decreased during an epileptic attack. These genes, proteins and pathways are activated by Brahmi, thereby reversing the possible cause and effects of epilepsy. Hersaponin, an active constituent of *Bacopa monnieri*, demonstrated defense against seizures in mice and alluded to the possibility of its use in the treatment of epilepsy as an adjuvant.[211] An experiment was conducted in rats to determine the pharmacological interaction of the whole *Centella asiatica* and *Bacopa monnieri* plant with standard antiepileptic drugs such as Phenytoin, Phenobarbitone and Carbamazepine. The results showed that herbal plant products such as *C. asiatica* and *B. monnieri* interact with conventional anti-epileptic drugs and that caution should be exercised to avoid possible adverse interactions.[212] Similarly, Khan *et al.*, reported neuroprotective role of *B. monnieri* extract in epileptic rats which showed glutamate mediated excitotoxicity during seizures and cognitive damage along withpilocarpine induced epilepsy.[213] In addition, Mathew *et al.*, experimented the effect of *Bacopa monnieri* whole plant aqueous extract on (Gamma Amino Butyric Acid) GABA binding and gene expression in cerebral cortex region of epileptic rats.[214] During PTZ-induced epilepsy, various extracts of the entire plant represented anti-seizure activity as evidence in the rat brain with reference to the cholinergic system and ATPases. The reversal of down-regulated mgluR8 gene expression to the control level was significantly brought about by *Bacopa monnieri* treatment in epileptic rats. In neonatal rats, hypoxia caused expressive and functional changes in neuronal cell $NMDAR_1$ receptors, which are reversed by glucose alone or glucose supplementation accompanied by oxygen during resuscitation to prevent neuronal damage associated with glutamate. According to the test findings, *Bacopa monnieri* has clinical imports and therapy for epilepsy and hypoxia.[215] Similarly, Jobin Mathew and Gireesh Gangadharan (2011), reported that *Bacopa monnieri* and Bacoside-A are beneficial against memory impairment in epileptic rats. Here *Bacopa monnieri* enhances the therapeutic effect against epilepsy by reversing changes in GABA, $GABA_A$ receptor binding, $GABA_A$ receptor subunits and GAD gene expression that occur during epilepsy, resulting in increased GABA mediated inhibition of over-stimulated hippocampal neurons.[216] Bacoside-A also prevents epileptic rat seizures, minimizing impairment of GABAergic function or alteration of the GABA receptor in the striatum of epileptic rats, motor learning, and memory deficiency.[217,218]

Antilocomotive and Anti-Compulsive Accoutrements

Bacopa monnieri leaf ethanolic extract attenuated the marble-burying activity in mice, and the effect was comparable to that shown by the reference standard drug, fluoxetine. This study concludes that ethanolic extract has an anti-compulsive effect in a dose-dependent manner.[219] Similarly, the anti-locomotive activity recorded in mice with *B. monnieri* hydroethanolic extract suggested that the extract (80 mg/kg) developed a significant anti-locomotive activity that was unaffected by naloxone.[220]

Anti-Parkinsonian Effects

Parkinson's disease is a progressive, neurodegenerative disease that is believed to slaughter dopaminergic neurons through mitochondrial dysfunction and oxidative stress, in which *Bacopa monnieri* reduces alpha synuclein aggregation, prevents dopaminergic neurodegeneration and restores lipid content in nematodes, thereby demonstrating its potential as a possible anti-Parkinsonian agent.[221] Ethanolic extract of the whole plant (including roots) of *Bacopa monnieri* modulate catecholamine system in different brain regions of rotenone induced rodent model of Parkinson's disease and thus offers protection. The extract is better than the reference drug Levodopa when compared overall, and the study indicated that Bacopa might provide a forum for potential drug discoveries and innovative treatment methods for Parkinson's disease and may act as an antiparkinsonian agent.[222] Similarly, the ethanolic extract of the whole plant has significantly improved morphological damage, cell viability and decreased apoptosis of rotenone exposed PC12 cells, indicating that in an *in-vitro* model of Parkinson's disease, *B. monnieri* has the potential to provide neuroprotection against rotenone toxicity.[223] Swathi *et al.*, also suggested the ability of *B. monnieri* whole plant ethanol extract for modulating glutamate metabolism in several brain regions of induced rodent model of Parkinson's disease.[224] The cluster of alpha-synuclein protein in the substantia nigra, the dopamine producing cell of the brain is reduced by Brahmi. It kills dopamine producing cells. Brahmi prevents the death of dopamine cells and symptoms of Parkinson's.[29] For one month, treatment with whole plant extract (40 mg/kg body wt., p.o.) substantially reduced the elevated oxidative stress levels observed in Parkinsonian mice. The comparative effect of *Bacopa*

monnieri in Parkinsonian mice, suggest that due to the presence of bacosides.[225] The cytoprotective effect of *Bacopa monnieri* against rotenone-induced oxidative stress and cell death has been clearly demonstrated by pre-treatment of dopaminergic (N27 cell lines) cells. The prophylactic neuroprotective effect of the ethanolic extract of the whole plant was clearly demonstrated mostly by data gathered in the mice model, as evidenced by the abrogation of rotenone-mediated oxidative stress and neurotoxicity and the data suggested that *Bacopa monnieri* could provide a better platform for future drug discoveries and novel therapeutic approaches to Parkinson's disease.[226]

Anti-Alzheimer's Chattels

The bioactive components of Brahmi are Bacoside A, Bacoside B, Bacosaponins and Betulinic acid etc. Each known chemical ingredient plays an important role in neuroprotection. The neuroprotective properties of Brahmi and its bioactive components include reactive oxygen species reduction, neuroinflammation, amyloid-β aggregation inhibition, and cognitive and learning activity enhancement. As we know that Amyloid-β and Tau are the hallmarks of many neuronal dysfunctions that lead to Alzheimer's disease, the inhibitory effect of Brahmi against Tau-mediated toxicity can be hypothesized, and Brahmi can be used as a lead formulation for the treatment of Alzheimer's disease and other neurological disorders.[227] In earlier systematic studies, *Bacopa monnieri* was successful and helpful for the treatment of Alzheimer's.[228] *Bacopa monnieri* extract was shown to minimise brain amyloid beta levels in the cortex during short- and long-term therapy and to reverse behavioural defects in mice.[229] Subchronic administration (14 days) of bacoside A (82%) was evaluated for animal models of Alzheimer's disease caused by intra-cerebro-ventricular colchicine administration and ibotenic acid nucleus basalismagnocellularis lesion. Similarly, subchronic administration of *Bacopa monnieri* alcoholic extract (10 mg/kg) decreased the severity of memory deficits, while the results were visible only on day 14 at the lower dose. This same research showed reversed acetylcholine depletion, decreased activity of choline acetylase, and decreased binding of the muscarinic cholinergic receptor in the frontal cortex and hippocampus.[179] The documented neuroprotective properties of whole plant methanol extract *Bacopa monnieri* (100 mg/kg, p.o.) for 180 days of application resulted in memory deficits and biochemical changes in the Alzheimer's disease-induced mice ATPase system. By stabilising the structural and functional integrity of the membrane, they also demonstrated important neuroprotective effects of *Bacopa monnieri* against Alzheimer's disease.[230] An animal experiment was conducted by Chaudhari *et al.*, which clearly shows the importance of brahmi as a promising agent in Alzheimer's disease and other types of cognitive impairment.[231] Roy *et al.*, one of the three herbs in Alzheimer's disease, also suggested *Bacopa monnieri*.[232] Brahmi extract, reported by Limpeanchob *et al.*, 2018, may be an alternative way to improve neurodegenerative disorders such as Alzheimer's disease.[158]

Cardiovascular Recreation

Cardiovascular disease is the name of the heart and blood vessel disorders group and includes hypertension, coronary heart disease, and cerebrovascular disease. As Brahmi contains naturally occurring nitric oxide, this nitric oxide plays a key role in the cardiovascular system. It dilates the arteries, relaxes the blood vessels and increases oxygen and blood flow, making it a supplement to high blood pressure, heart disease, asthma, bronchitis, and many other cardiovascular diseases.[233] Srimachai *et al.*, reported an ethanolic extract of *B. monnieri* aerial parts as a cardiac protection against ischemia/reperfusion injury using cardiac function and coronary circulation as endpoints. Results have shown that the ethanol extract improves myocardial function following ischemia/reperfusion injury by recovering coronary blood flow, contractile strength and decreasing infarct size.[234] Similarly, when administered intravenously at a dose of 20-60 mg/kg, the effect of *Bacopa monnieri* extract on arterial blood pressure and heart rate of anaesthetized rats was found to decrease systolic and diastolic pressure without disturbing the heart rate[235] and, at the same time, broncho-vasodilatory activity of different fractions of *Bacopa monnieri* in anaesthetized rats was recorded. The activity was observed because of calcium ion inhibition.[236] Documented cardiac depressive activity of whole plant ethanolic extract *B. monnieri* on left ventricular contractility, heart rate, and coronary flow in isolated rabbit heart, which appeared to be similar toquinidine in extract activity.[237] Bacopa has also been shown to calming effects in experimental animals on the pulmonary arteries, aorta, trachea, ileal and bronchial smooth muscles, and these effects may have been mediated by inhibition of the influx of calcium ions influx into cell membranes.[236,238,239] Several researchers have shown that *Bacopa monnieri* active compounds such as saponins and flavonoids have produced vasodilatory effects on rats isolated mesenteric arteries through endothelial dependent vasodilator release as well as direct effects on vascular smooth muscle cells by preventing transmission of calcium ion.[240] In parallel, a concentration-dependent increase in coronary flow, promoted cardiac function, and decreased infarction area resulting from ischemia and reperfusion in isolated rat perfused hearts was induced by the aerial part of *B. monnieri* ethanol extract.[234] Bacopa has also shown cardio protection, increased coronary blood flow and protection against reperfusion damage to myocardial ischemia[234,241] and regular oral administration of *Bacopa monnieri* extract (40 mg/kg) to rats for eight weeks has shown a substantial improvement in cerebral blood flow, suggesting cerebrovascular dilation.[242] Furthermore, *In vitro* thrombolytic activity of ethanolic, methanolic, acetone and aqueous extract of various parts (root, stem and leaf) of *Bacopa monnieri* is also reported and the study indicated that the ethanolic leaf extract showed the highest thrombolysis followed

by aqueous extract, methanol and acetone, and this finding may have important implications for the treatment of cardiovascular disease.[243] Hydro-alcoholic lyophilized extract of entire Brahmi also serves as a cardioprotectant against myocardial necrosis induced by isoproterenol in rats.[241] A. Onsa-ard, *et al.*, compared to clinically used captopril, documented anti-hypertensive action of bacopa ethanolic extract and the extract elicited independent endothelial vasorelaxation, which indicated that it acts directly on the vascular smooth muscle cells and showed a clear, prompt, and constant antihypertensive action on NG-Nitroarginine methyl ester hydrochloride induced Rats.[41]

Relaxant Effects on Smooth and Cardiac Muscles

The bronchodilator effect of *Bacopa monnieri* (50 mg/kg) ethanol extract on anaesthetized rats is also reported and the extract has antagonised the bronchoconstrictor action of carbachol. This same bronchodilator property shown by the plant extract is reflected by a decrease in expiratory pressure which, compared to isoprenaline, was more like a salbutamol-induced effect. The plant extract's bronchodilator action is likely to be mediated jointly by β-adrenoceptor-dependent and independent mechanisms. Thus, a justification for its conventional use in the treatment of asthma is given.[244] Subsequently, in anaesthetized rats, different fractions and sub-fractions isolated from *Bacopa monnieri* developed substantial inhibition of carbachol-induced bronchoconstriction, hypotension and bradycardia, and different fractions were predicted to have broncho-vasodilatory activity, which is primarily due to calcium ion inhibition.[236] The ethanol extract of *B. monnieri* spontaneously inhibited the movements of both guinea-pig ileum and rabbit jejunum, where there was a marked reduction in the reactions caused by acetylcholine and histamine in the ileum in the presence of the extract. The concentration-dependent inhibition of the acetylcholine mediated contraction in the ileum was also inhibited by the extract, this report indicated that the spasmolytic effect of the extract in smooth muscles is mainly due to the inhibition of calcium influx through the cell membrane's both voltage and receptor-operated calcium channels.[239] The relaxant action of *Bacopa monnieri* ethanol extract was also explored in rabbit and guinea pig pulmonary arteries, aorta and trachea. Plant extracts have a significant relaxation effect on all tissue levels in a dose-dependent manner. However, the relaxant response of the plant extract was not affected by either atropine or propranolol pretreatment of the blood vessels, while the response was partially blocked by propranolol in tracheal preparations. Indomethacin reduced plant extract-induced relaxation in all tissues and the report suggested that relaxation induced by *B. monnieri* may involve prostacycline compounds in all tissues and β-adrenoceptors in trachea. In addition, this relaxation is independent of endothelial and muscarinic receptor activation.[239] The stabilising effect of mast cells was also tested *in vitro*, with the exception of different extracts of *B. monnieri*, while the methanol fraction exhibited potent activity comparable to disodium cromoglycate, a known stabiliser of mast cells.[245] *Bacopa monnieri* extract is an abundant source of bioactive compounds, including saponins (bacoside A and bacopaside I) and flavonoids (luteolin and apigenin) which caused vasorelaxation in a concentration-dependent manner, but in endothelial intact vessels, luteolin and apigenin have developed vasorelaxation with greater efficacy than bacoside A and bacopaside I.[240] Brahmi has been shown to induce relaxation in blood vessels through an impact on both endothelial cells and a direct effect on vascular smooth muscle from a wide variety of tissues, Intravenous treatment with brahmi extract (20–60 mg/kg) reduces the blood pressure in anaesthetised rats by releasing NO from the endothelium and modulating vascular smooth muscle Ca^{2+} homeostasis.[235]

Anti-Stroke Ramification

A stroke occurs when a portion of the brain is cut off by the flow of blood. Most are caused by a clot that blocks the flow, or something else, which is known as ischemic strokes. About 10 percent are caused by brain bleeding. These are haemorrhagic strokes. But there has been little research into the role of Brahmi in the treatment of brain stroke. *Bacopa monnieri* aqueous extracts attenuated ischaemia-reperfusion induced cerebral injury in mice in terms of decreased infarct size, improved short-term memory, coordination motor and lateral push response, and the study indicated that Brahmi aqueous extracts prevent cerebral injury induced by ischaemia-reperfusion with comparable potency.[246] The role of Brahmi in ischemic induced brain injury in Wistar rats was also investigated by Saraf *et al*. In these animals, Brahmi was supplemented with doses of 120, 160, and 240 mg/kg, and several behavioural and biochemical tests were performed to assess the efficacy of this herb. As seen in the plus maze test, their findings showed Brahmi's protective role in reducing infarct size in the ischemic brain and improving memory impairment. In addition, Brahmi administration enhanced the behaviour of muscle coordination and catalase in rats exposed to ischaemic insult. The levels of nitrite, nitrate and lipid peroxidation levels were also massively diminished. These results show that Brahmi protects the brain from insults caused by ischemia.[247] Bacopaside I (3, 10 and 30 mg/kg) has also been documented to increase the brain ATP content, energy charge, total adenine nucleotides, nitric oxide level, Na^+K^+ATPase and $Ca^{2+}Mg^{2+}$ATPase activity, along with improved antioxidant enzyme activities including brain superoxide dismutase activity, for its neuroprotective effect against injury caused by cerebral ischemia over adult male Sprague-Dawley rats. In addition, the increased malondialdehyde content of the brain was substantially inhibited by bacopaside I.[248] In addition, because of the lack of oxygen supply, brain ischemia decreases blood flow in the cerebral arteries. Kamkaew *et al*., tested this parameter in rats to investigate whether Brahmi has any effect on cerebral blood flow. Rats were treated with a 40 mg dose of Brahmi for 8 weeks, and cerebral blood flow was

measured by Doppler methods. Interestingly, without influencing their blood pressure, the herb has been found to increase cerebral blood flow by 25 percent in rats. Furthermore, these results affirm the effectiveness of this herb in the treatment of neurological disorders.[242] Xoan Thi Le *et al*., reported that *Bacopa monnieri* triterpenoid saponins (bacosides I) were also beneficial for the prevention of cognitive deficits related to cerebral ischemia in the mouse model. The neuroprotective effects of bacopaside I were blocked by the PKC inhibitor Ro-31-8220 and the PI3K inhibitor LY294002, but not by the ERK inhibitor U0126. In addition, treatment with bacopaside I itself was able to increase the p-Akt level in OHSCs.[249]

Gastrointestinal Workout

Brahmi has been clearly proven to help with a number of gastrointestinal issues. On castor oil-induced diarrhoea in rats, an ethanol extract of the entire plant of *Bacopa monnieri* demonstrated antidiarrheal effects. At an oral dosage of 500 mg/kg, it dramatically increased mean latent period and decreased frequency of defecation, equivalent to loperamide (50 mg/kg, p.o.).[250] Furthermore, Sairam *et al*., recorded that, at a dosage of 10-50 mg/kg, p.o., twice daily for 5 days, Bacopa methanolic extract showed dose-dependent anti-ulcer on different gastric ulcer models induced by ethanol, aspirin, cold restraint stress and pylorus ligation, and the extract showed no impact on acid-pepsin secretion, increased mucin secretion and decreased cell shedding without any effect on cell proliferation.[251] From then on, Sairam and Goel *et al*., further reported that in different gastric ulcer models, the prophylactic and curative effects of standardized Bacopa extract. The 1000 microg/ml dose extract showed *in-vitro* anti-*Helicobacter pylori* activity and the 10 microg/ml dose showed increased *in-vitro* prostanoid activity in human colonic mucosal incubates andconcluded that these factors may contribute to the extract's anti-ulcerogenic activity.[252] Similarly, the significant ulcer protective effect of fresh *Bacopa monnieri* juice (100 and 300 mg/kg) may also be due to its role on mucosal defensive factors such as increased mucin secretion, mucosal glycoprotein and reduced cell shedding, rather than on offensive factors such as acid and pepsin.[253] Prince *et al*., also reported ulcerative potential of commercially available *B. monnieri* methanol extract on wistar albino rats (Indomethacin-induced ulceration) and extract at doses of 500 mg/kg/b.w, had minimal gastric lesions.[254] In normal and NIDDM rats, Bacopa methanol extract (50 mg/kg) also exhibited significant anti-ulcer and ulcer-healing activities.[255] It has recently been documented that *Bacopa monnieri* is currently used in Indian medicine as a probiotic and phytomedicine in alternative therapies for *Helicobacter pylori*. Additionally, a standardised Bacopa extract at a dosage of 40 mg/kg, p.o., reversed ulcer development caused by stress, and higher doses (80 mg/kg) prevented adrenal gland weight increases in rats.[199] Plant extracts are used as medical products or health-promoting agents, but in most cases, the molecular mode of action of the active ingredients in these herbal extracts is unknown. Inhibition of the *H. pylori* urease enzyme, bacterial cell membrane disintegration, and host immune system regulation are all possible mechanisms.[256] *Bacopa monnieri* also has both antidiarrheal and laxative activities. The ethanolic leaf extract of the castor oil-induced diarrheal system in mice showed that the extract decreased the mean number of defecations and indicated that the extracts reduced diarrhoea by inhibiting castor oil-induced intestinal fluid accumulation at a dose of 500 mg/kg, p.o..[257] Similarly, the laxative role of polar and non-polar fractions of the entire plants was reported by S. Nikhil *et al*., where the non-polar fraction demonstrated the highest diarrhoea effect in drug-induced constipation in mice.[258] Subhan *et al*., claimed that hydroethanolic extract of *Bacopa monnieri* impaired GIT motility in rats, which was reversed with naloxone therapy, suggesting that plant constituents interact with α-2 adrenoceptors and GABA receptors.[259]

Hepatoprotective Feat

Drugs and dietary supplements have been linked to unusual hepatotoxicity, but a vigorous causality assessment using a quantitative approach has not always been conducted. The determination of the respective hepatotoxicity class is an important for subsequent causality assessment. Since the liver is the body's largest detoxification organ, the compounds in Brahmi support the liver in this respect. It helps by helping the liver convert toxins into harmless ones and waste products in its conversion.[260] The ethanolic extract of the whole plant of *Bacopa monnieri* demonstrated strong hepatoprotective activity in rats with morphine, carbon tetrachloride and nitrobenzene-induced liver toxicity. The extract significantly attenuated hepatotoxin induced changes in biochemical parameters (sera AST, ALT, and ALP) and histopathological changes in liver tissues.[261-263] In similar fashion, Nagendra Kumar *et al*., stated that at a dosage of 200 mg/kg, p.o., ethanolic extract of the entire plant has the potential as an adjunct therapy to inhibit liver complications due to alcohol-induced hepatotoxicity in rats. The extract achieved significantly reduces the activity of Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), malondialdehyde and also increases liver antioxidant enzymes.[264] Furthermore, Tirtha Ghosh *et al*., delineated that ethanol extract and its different fractions of the aerial parts of the plant preserved liver cells, perhaps by its antioxidant effect on hepatocytes, from both paracetamol and alcohol-induced liver impairment in rats.[152,265,266] Sumathi and Nongbri proposed that Bacoside-A has a hepatoprotective impact against hepatotoxicity caused by d-galactosamine (d-GalN) in rats and in addition, bacoside-A also significantly normalises decreased vitamin C and E levels.[267] Subsequently, whole plant ethanol and aqueous extracts also possesses hepatoprotective effects and maintain the structural integrity of the hepatocellular membrane against d-GalN mediated and paracetamol induced hepatotoxicity.[268,269]

In addition, the methanol extract of the whole plant restored the serum elevation of ALT, AST and creatinine, and also protected the liver and kidneys of Male Sprague Dawley rats from the toxicological influence of morphine and street heroin at doses of 40 mg/kg/day, *ip*., for 14 and 21 days of treatment.[270] Seed based ethanolic extract (400 mg/kg, p.o) also prevented carbon tetrachloride induced hepatic damage in albino mice model.[271]

Antihypercholesterolemic Cascade

The findings of several studies have shown that *Bacopa monnieri*, based on experiments, animal studies and observational clinical experiences, can substantially reduce LDL cholesterol or bad cholesterol. As such, Venkatakrishnan Kamesh *et al*., reported that in hypercholesterolemic rats, whole plant ethanolic extract extended protection against various biochemical changes and aortic pathology,[272] likewise the leaves also decrease serum cholesterol, triglycerides, LDL in rats. Seasonal variation in the hypolipidemic effect of *B. monnieri* leaves has also been recorded in normal rats and the maximum hypolipidemic effect of the leaves in July and August was already registered.[273] In atherogenic diet-induced hyperlipidemic rats, the recorded ethanolic extract of the entire plant effectively decreases plasma cholesterol, triglycerides, LDL, and VLDL and increases plasma HDL levels.[274] The whole plant ethanol extract also acts as a renoprotective agent by attenuating the renal oxidolipidemic stress by regulating the NOS signaling pathway and by protecting the nephron in hypercholesterolemic rats.[275]

Antidiabetic Prospective

Diabetes mellitus is a metabolic disorder that impacts the metabolism of carbohydrates, fat and protein. A global survey has estimated that almost 10 percent of the population is affected by diabetes mellitus every year. This leads to increased demand for antidiabetic factor herbal products with little side effects, as reported by Tirtha Ghosh *et al*., the possible impact on hemoglobin glycosylation and *in vitro* peripheral use of ethanolic extract glucose from the aerial parts of *Bacopa monnieri*. Compared to controls in alloxan-induced hyperglycemic rats, the extract produced a significant decrease in blood glucose levels, both in single dose and multiple doses.[276] Equally, whole-plant methanol extracts have important antihyperglycemic potential in streptozotocin-induced diabetic rats and oral glucose tolerance trials in glucose-impaired mice and have substantially blocked dose-dependent rises in serum glucose concentrations.[277,278] Triterpene saponin bacosine extracted from the ethyl acetate fraction of the ethanol extract from the aerial parts of the plant, increased glycogen content in the liver of diabetic rats and *in-vitro* peripheral glucose utilization in the diaphragm of diabetic rats, which is comparable to insulin operation.[279] Isolated stigmasterol from Bacopa aerial parts that also have renoprotective effects in STZ-nicotinamide-induced diabetic nephropathy through inhibition of advanced glycation end products and oxidative stress.[280] Interestingly, in experimental rats, the recorded antidiabetic ability of Brahmi ghrita also indicates its role in the successful management of diabetes.[281] According to one study, using hydroalcoholic extract of *B. monnieri* leaves was used to treat a group of rats with streptozotocin-induced diabetes mellitus type II, and it exhibited significant myocardial salvaging effect.[282] Pandey *et al*., reported that standardized extract of *Bacopa monnieri* called CDRI-08 (containing 55±5% of Bacosides A and B) showed anti-diabetic activity in streptozotocin-induced diabetes mellitus type II mice.[171] An active compound isolated from *Bacopa monnieri* leaves which reduced elevated levels of serum cholesterol, triglycerides, LDL and VLDL in diabetic rats, but increased HDL cholesterol. This illustrates the potential use of *Bacopa monnieri* extract for the treatment of hyperlipidemia in diabetics.[283] Interestingly, *In-vitro* approaches on alpha amylase and alpha glucosidase activity revealed that the leaves inhibited 41.2-49.9% of alpha amylase and alpha glucosidase activity.[284]

Anticancer / Cytotoxic Attentiveness

Research indicates that its cancer-fighting effects could be responsible for the high levels of antioxidants and compounds like bacosides in *Bacopa monnieri*. In test-tube and animal studies, *Bacopa monnieri* has been shown to block the growth and spread of cancer cells, but human research is needed to validate these effects. Through disastrous macropinocytosis of GBM animal models, Bacoside-A induces tumour cell death in human glioblastoma cell lines.[285] In fact, cytotoxic ability and therapeutic efficacy against Ehrlich ascites carcinoma tumor-bearing mice were shown by the hydroalcoholic extract and all other fractions of the whole plant while providing safety against malignancy prompted changed physiological conditions.[286] Equally, whole plant ethanol extract showed substantial retardation of solid tumour growth and restored near-normal altered hematological parameters in mouse-induced tumour cells of Daltons lymphoma ascites.[287] Stigmasterol is known to have anti-cancer properties through triggering apoptosis through ceramide-mediated activation of protein phosphatase 2A. T. Ghosh *et al.*, investigated the anticancer effect of stigmasterol, which was derived from *Bacopa monnieri*, on Ehrlich Ascites Carcinoma in Swiss albino mice, and reported that stigmasterol increased the life duration of tumor-bearing animals by reducing tumour volume and viable cell count.[288] Agrawal *et al*., reported anticarcinogenic and antimutagenic activities of the *B. monnieri* methanol extract inhibited the development of micronucleus and chromosomal aberrations caused by known mutagen in Swiss albino mice bone marrow cells.[289] Bacoside A rich fraction also exhibits substantial anticancer activity against EAC tumour bearing mice at doses of 250 and 500 mg/kg body weight over 10 days, showed a significant decrease in body weight, tumour volume, packed cell volume, viable tumour cell count, and increased non-viable cell count percentage rise.[290] Bacoside A has been demonstrated to

suppress lipid peroxidation and increase the levels of antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase in the Wister albino rat model, however the specific mechanism remains unclear.[291] The extract of Bacopa (20 mg/kg body wt, sc) also promotes antioxidant status, decreases the rate of lipid peroxidation and tumour progression markers in rats carrying fibrosarcoma.[292] Similarly, the aqueous extract of whole plant can also induce apoptosis in tumor cells of Ehrlich ascites through *Bax*-related activation of caspase-3 in mouse mammary carcinoma cells. Treatment with the aqueous extract raised the expression of the *Bax* pro-apoptotic gene while decreasing the expression of the Bcl-2 anti-apoptotic gene.[293] Practically major phytoconstituent found in *Bacopa monnieri* has been demonstrated in cancer cells to exhibit anti-metastatic, anti-angiogenic, and anti-proliferative effects.[294]

Immune Modulation

Immunodeficiency disorders are severe and debilitating diseases that affect a large number of people. Although research continues to shed light on genetic as well as hormonal and environmental risk factors that lead to the general population's causes of these autoimmune diseases, they remain among the most poorly understood and poorly recognized types of disease. Many adaptogens exert immunomodulatory properties, but the plant *B. monnieri* is one of the promising candidates for treating immunodeficiency disorders and boosting immune response.[295] *Bacopa monnieri*'s neuro-endocrine immunomodulation has been supported by an immense number of investigations. In both normal and amnesic human subjects and animals, the medication and its components had strong neuroprotective, nootropic, and anti-stress effects. In experimental mice, strong proliferative effects on several immune system components, such as NK cell counts, phagocytosis, antigen processing and presentation, and cytokine generation, have been demonstrated. Stress-induced increases in adrenal weight, plasma cortisol, blood glucose, triglyceride, and total WBC count are all decreased when *B. monnieri* is used in stress models. The neuro-endocrine-immune modulation of *Bacopa monnieri* is brought into consideration.[296] Juvekar AR *et al*., reported that saponin rich *Bacopa* fraction had *in vitro* stimulation effects on the release of immune mediators from murine peritoneal cells and proliferative effects on *in-vitro* immune cells.[297] Brahmi acts and slows down the activity of stress on the central nervous system. People usually get paranoid in cases of global distress or epidemic, so it might be useful to reduce stress and anxiety. An *in vitro* study suggests that by controlling the Th1 polarized immune responses while suppressing NO (and TNFα) by macrophages and IFN by innate lymphocytes, bacoside-rich ethanolic extracts have anti-inflammatory effects. It also showed sustained IL-10 production, which is indicative of neutralizing the activation of Th1 and favoring the activation of regulatory T cells.[298] *In-vitro* and *in-vivo*, similar beneficial effects were observed in rats treated with Brahmi. Comparative analysis of age-related immunosenescence reversal strategies using synthetic drugs and natural remedies has shown significant immunomodulatory effects through modulation of MAPK and NF-kB signaling cascades in middle-aged and elderly rats.[299] The implications of the *B. monnieri* extract on the *in-vitro* ICR mice immune system study showed that the extract slightly suppressed the proliferation of splenocytes and decreased the proliferation of T-lymphocytes but slightly increased the activity of the lysosomal enzyme, suggesting a poor effect on phagocytic activation.[300]

Intendancies on Pains, Inflammation and Pyrexia

Medicinal plants and their secondary metabolites are increasingly being employed in the treatment of ailments as a supplemental therapy. Inflammation and hyperalgesia are pathologic disorders that cause a broad variety of illnesses, including rheumatic and immune-mediated diseases, diabetes, cardiovascular disease, and so on. The herbs *Bacopa monnieri* have been studied in clinical and pre-clinical contexts for their anti-inflammatory, analgesic, and antipyretic properties. With the aid of *Bacopa monnieri* and lifestyle improvements, this review aims to achieve a multidimensional therapeutical approach towards inflammation, pain, and pyrexia. In additament, using various nociception models such as the hot-plate, tail-flick, writhing reflex system, and formalin experiments, several authors stated that various extracts of Brahmi produced significant analgesic activity in rodents at the tested dose levels.[254,301,302] *Water hyssop* preclude experimentally induced inflammatory reactions by inhibiting prostaglandin synthesis and partially stabilising lysosomal membranes at anti-inflammatory doses, and it did not cause gastric irritation. The anti-inflammatory effects of various Brahmi extracts on carrageenan-induced oedema in rat hind paws were reported, and the oedema paw volume was reduced significantly.[303,304] According to Shahid *et al*., the methanol extract of the whole plant significantly reduced allodynia and hyperalgesia caused by chronic constriction injury, as evidenced by increased paw withdrawal threshold, paw withdrawal latency to light brushing and heat, and decreased paw withdrawal time to pin prick and cold stimuli. By raising the pain threshold to that of pre-surgery baseline, the extract counterbalanced the chronic constriction injury-induced aberrations in nociceptive behaviours.[305] *Bacopa monnieri*'s triterpenoid and bacoside fractions also have anti-inflammatory activity, as shown by their ability to reduce pro-inflammatory cytokine and NOx development during LPS-induced inflammation *in vitro*, and enriched fractions also have anti-oedematogenic activity in carrageenan-induced hind paw oedema assay and adjuvant-induced arthritic mice.[306] Since *Bacopa monnieri* significantly inhibited the activities of 5-*lipoxygenase*, 15-*lipoxygenase*, and *cyclooxygenase*-2, the plant has anti-inflammatory activity in carrageenan-induced rat paw oedema, with an oedema inhibition of 82% when compared to indomethacin. All at the same, bacoside fractions also resulted

in a significant decrease in *ex-vivo* release of TNF-α.[307,308] Similarly, at 400 mg/kg body weight methanol extract of the leaves demonstrated substantial anti-inflammatory activity in both the carrageenan and histamine-induced oedema studied models in rats, with 62.73 percent and 61.99 percent reductions in paw volume, respectively[309] while an ethanolic leaf extract showed significant antinociceptive activity in mice with acetic acid-induced writhing.[257] Michelle and his collaborators recently reiterated that bacopa tea, infusion, and alkaloid extracts, as well as Bacoside A, significantly reduced TNF-α and IL-6 release from activated N9 microglial cells *in vitro*. Furthermore, the tea, infusion, and alkaloid extract of Bacopa effectively inhibited caspase 1 and 3 as well as matrix metalloproteinase-3 in a cell free assay, indicating that Bacopa can reduce inflammation in the CNS and may be a potential source of novel therapeutics for a variety of CNS disorders.[309] Bacopa also has anti-inflammatory effects on innate immune system cells, according to an *in-vitro* proposed research, by reducing NO and TNF-α in stimulated RAW 246.7 macrophages and IFN-γ in stimulated human blood cells. In addition, in human blood cells, IL-10 was slightly elevated indicating polarization towards the regulatory T-cell phenotype. These results highlighted additional supporting evidence to justify Bacopa's clinical assessment of chronic systemic and brain inflammation disorders drivenby the innate immune system.[310] Analogously, whole plant methanolic extract reduced the amount of acetic acid-induced gastric constrictions in mice at four doses in a dose-dependent manner in antinociceptive activity studies.[277] Abbas and his co-workers delineate that a hydroethanolic extract and its fraction specially n-butanol fraction of the aerial parts has antinociceptive properties and inhibits locomotor activity through a non opioidergic mechanism, despite the fact that both activities were unaffected by the opioid receptor antagonist naloxone.[220,311] In writhing and hot plate trials, Subhan *et al.*, claimed that the LD_{50}, ED_{50}, and therapeutic index of hydroethanolic extract of Bacopa aerial parts were 67.778, 67.22 and 232, 232 and 3.42, 3.45, respectively.[259] Concurrently, in the acetic acid induced abdominal constriction experiment and the hot plate test in mice, hydroethanolic extract was compared to morphine and diclofenac for antinociceptive action, and the extract demonstrated dose-related activity that was naloxone-reversible. Furthermore, the extract has been shown to minimize the *in-vitro* effects of morphine withdrawal in the guinea-pig ileum, implying that this plant extract may be useful in reducing morphine withdrawal symptoms in humans.[312] Vohora *et al.*, speculated for the first time that Bacosine-I is opiodergic in nature but has only mild analgesic effects, with no effects on barbiturate narcosis, haloperidol-induced catalepsy, spontaneous motor activity, or the conditioned avoidance response.[313] In monosodium urate crystal-induced inflammation in Wistar albino female rats, the commercially available dry powder of Bacopa demonstrated anti-arthritic properties against gouty arthritis, which reducing paw swelling as well as lipid peroxidation and normalising the antioxidant enzyme, liver biomarker levels, and histopathological changes.[314] *Bacopa monnieri* extract significantly reduced footpad swelling and arthritic symptoms, according to Viji *et al.*, in arthritic rats; it inhibits the activities of cyclooxygenase and lipoxygenase. Reduced myeloperoxidase activity indicated a decline in neutrophil infiltration, and histopathological evidence showed an increase in joint architecture. At the same time, serum anti-collagen IgM and IgG levels were steadily reduced.[315] In parallel, Sabina *et al.*, also found that a dosage of 500 mg/kg/b.w., of commercially available *B. monnieri* had significant antipyretic efficacy in yeast-induced pyrexia albino rats as compared to indomethacin.[254] Furthermore, Rauf *et al.*, asserted that *Bacopa monnieri* was successful in neuropathic pains based on different preclinical profiles. It also has a potent anti-inflammatory impact *via* COX-2 inhibiting mechanism. It has been well documented to be a safe and well tolerated herbal therapy in several clinical trials involving people of various ages, and it inhibits opioid withdrawal induced hyperalgesia, as well as the acquisition and expression of morphine tolerance, with a strong protective effect against opiates' toxic effects on major organs such as the brain, kidneys, and heart.[316]

Realizing the Importance of Urinary and Respiratory Tract Infections

A major concern of medical research is actually Multidrug-resistant (MDR) over bacterial pathogens. New sources for developing antibacterial agents may be considered to be medicinal plants. *Bacopa monnieri* methanolic extract has possible antimicrobial activity against MDR-urinary and respiratory tract bacterialstrains in clinical isolates.[82] Bacopa can also increase secretions in the urinary tract. There is concern that urinary obstruction could exacerbate this. An important protective effect against morphine-induced kidney toxicity was also exerted by *B. monnieri* extract (40 mg/kg, p.o.).[317] The possible impact of ethanolic extract of Bacopa on tacrolimus-induced nephrotoxicity in rats was stated by Oyouni *et al.*,(2019), the report also indicated that characteristic morphological findings such as glomerular atrophy, renal tubule degeneration, necrosis, and vacuolation have been shown in the kidneys of tacrolimus-treated rats and also prevent damage to cellular DNA.[318] Consequently, infusing gentamicin-intoxicated rats with two dosages of ethanolic extract of *Bacopa monnieri* whole plant (100 and 200 mg/kg) restored renal damage in a dose-dependent manner, indicating a nephroprotective effect that might be mediated by boosting antioxidant activity with natural antioxidants and scavenging free radicals.[319] Likewise, in a rat model, the methanolic fraction of *Bacopa monnieri* inhibits potassium bromate-induced renal carcinogenesis. Oral supplementation of Bacopa prior to potassium bromate exposure resulted in a substantial decrease in COX-2 and p53 protein expression, proinflammatory cytokine secretion, ornithine decarboxylase function, and [3H]-thymidine incorporation into DNA, all of which are well-known indicators

of inflammation and tumor promotion.[320] According to various preclinical assessments, Brahmi possesses antiasthmatic properties. This helps to relax the respiratory system and control allergic responses.[321]

Legitimacy in Spermatogenesis and Fertility

In mice of the Parkes (P) strain, Bacopa treatment (250 mg/kg body weight/day for 28 and 56 days) had no effect on body weight, testis, epididymis, or seminal vesicle weights, but epididymis weight was significantly reduced while libido was unaffected. Fertility was significantly reduced in mice treated with the plant for 28 days compared to the control group.[322] Similarly, the standardized *Bacopa monnieri* extract (CDRI-08) improves the consistency of sperm and the density of spermatogenic cells and the steroidogenic indices of Parkes mice in the testis at doses of 40 and 80 mg/kg p.o., respectively.[323] CDRI-08 has also been shown to enhance reproductive health in male Parkes mice by enhancing the function of antioxidant enzymes, including upregulation of MAP2K1 and MAP2K2 and suppression of MKK4.[324] Treatment with Bacopa had no effect on the release of testosterone by Leydig cells in Parkes mice, since there were no differences in blood testosterone levels between treated animals. As a result, it's possible that Bacopa operates directly on the seminiferous tubules. Sertoli cells are recognised to play a vital part in spermatogenesis maintenance, and any injury to these cells might cause spermatogenesis suppression. The presence of intraepithelial vacuoles in the damaged seminiferous tubules in the testes of treated mice revealed that Bacopa's anti-spermatogenic effect was mediated through Sertoli cells.[325]

Role in Cigarette Smoking Induced Brain Changes

Smoking prohibitions or restrictions can protect non-smokers from passive smoking while simultaneously lowering tobacco consumption among smokers. Cigarette smoking is a serious health hazard that has a variety of physiological and biochemical repercussions that are mediated by the components present and formed during smoking. Several empirical investigations have found that both active and passive cigarette smoke exposure has a variety of biological repercussions.[326] This review presents the results of a controlled experiment that examined the influence of bacoside A on the causative role of passive/second-hand smoke exposure in inducing pathological and neurological alterations in rats' brains. In the brains of rats, chronic cigarette smoke exposure resulted in severe histological and neurotransmitter abnormalities, as well as lipid peroxidation states, mitochondrial functioning, membrane modifications, and apoptotic damage. Bacoside A, a neuroactive molecule isolated from *B. monnieri*, proved successful in combating these alterations as a neuroactive agent.[327] Bacoside A administration avoided structural and functional impairment of mitochondria following cigarette smoke exposure. Which indicated that exposure to chronic cigarette smoke causes damage to the mitochondria and that by preserving the structural and functional integrity of the mitochondrial membrane; bacoside A protects the brain from this damage.[328] Similarly, when rats were exposed to cigarette smoke, serum creatine kinase activity increased significantly, with a corresponding reduction in the heart and brain. Cigarette smoke exposure generated a significant increase in all three serum isoforms, which were avoided following Bacoside A treatment. Cigarette smoking is said to cause free radical-mediated lipid peroxidation, which leads to increased membrane permeability and cell damage in the heart and brain, as well as the release of creatine kinase into the circulation. Bacoside A's protective impact on the membrane's structural and functional integrity prevented creatine kinase from leaking out of the tissues, perhaps due to its free radical scavenging and antioxidant properties.[329] Administration of bacoside A (10 mg/kg b.w./day, oral) for 12 weeks also prevented expression of hsp70 and neuronal apoptosis when cigarette smoke was exposed to adult male albino rats of the Wistar strain. The brain can be shielded from the harmful effects of cigarette smoking by Bacoside-A.[330] Likewise, Bacoside A also increased the antioxidant status and retained trace element (copper, iron, zinc and selenium) levels when adult male albino rats were exposed to cigarette smoke for 12 weeks while obtaining bacoside A (10 mg/kg b.w./day, p.o.) at the same time.[331] Consequently, when rats were exposed to cigarette smoke while also receiving bacoside A, the organs were protected by stabilising cell membranes and blocking the release of Lactate dehydrogenase isoenzyme, likely due to its free radical scavenging and anti-lipid peroxidative activities.[332]

Wound Healing Aptitude

For its wound healing activity, the ethanolic extract of the aerial parts of *B. monnieri* has been studied using various rat models, which have significant increases in wound contraction and skin breaking strength in both excision and incision wound models, respectively.[333] Similarly, dried whole plant ethanolic extract also outlines the healing effects that seemed to be due to decreased damage to tissue generated by free radicals, promoting effects on antioxidant status, faster deposition of collagen, and formation of other constituent connective tissue, and antibacterial activity.[334] In addition, Bacoside-A was more efficient in different wound models compared to the usual Nitrofurazone skin ointment.[335] Bacoside-A gel topical treatment substantially decreases the scarring area and scarring thickness of the rabbit ear following a thermal wound in a dose-dependent manner by decreasing the content of collagen, hydroxyproline and hexosamine, along with the Scar elevation index and the index of epidermal thickness levels. Therefore, in the development of pharmaceuticals for the suppression of scar formation, Bacoside-A has the potential for use.[336]

Endocrine Effects

Bacopa extract (200 mg/kg orally) has increased the thyroid hormone T_4 by 41% in mice, while T_3 has not been stimulated, implying that the extract is capable of directly stimulating the synthesis and/or release of T_4 at the glandular level without affecting the conversion of T_4 to T_3.[337] Besides this, in hypothyroid and euthyroid animals, ethanolic extract of the whole plant increased both T_4 and T_3 and decreased TSH level, which revealed that Bacopa's thyrogenic activity is not only localized in the thyroid gland, but that certain central or peripheral actions may be taken by the herb.[338]

The Benefit of Regenerative Hair Fringe

Brahmi has external advantages, such as curing dandruff and associated scalp problems, preventing hair loss and split ends, and stimulating hair growth. In Brahmi, the alkaloids bind to the hair shaft proteins, creating stronger and thicker hair. While comprehensive study is limited to animal studies with regard to Brahmi as a growth aid, the research has been enlightening. In order to increase hair length and density, one study tested eight different styles of ointments on rodents. The greatest increase in hair density and length was seen by the singular herbal extract of Brahmi.[339] Interestingly, Brahmi Oil stimulates hair growth as well. It enhances the health of the scalp and even the health of individual hair strands. Brahmi Oil has been used in ayurvedic systems for over a thousand years to avoid hair falls. Consuming Brahmi extracts and applying Brahmi Oil topically is an effective way of reducing blood pressure. It facilitates relaxation, lowers tension and thereby helps to lower blood pressure. Brahmi Oil massage is often recommended by some Ayurveda doctors as a standalone procedure to reduce blood pressure.[26] Herbal hair oil made from alcoholic extracts of *Emblica officinalis, Bacopa monnieri*, and *Cyperus rotundus*, or the whole thing. Individual hair oils were made with varied concentrations of all three herbs or a mixture of all three herbs, with coconut oil as a base in predetermined proportions. The hair oil formulation exhibited the best results among the other formulations studied by displaying follicular size increase and anagen phase lengthening when applied topically to the shaved skin of albino rats.[340-342] *Bacopa monnieri*, this water plant has hair-growing components. The antioxidant empowers hair follicles to regenerate. Pleasant sleep inducer and herb wonder to be treated Alopecia because it was identified as a potential candidate for the treatment of Androgenic alopecia on the basis of its 5α-R1-inhibiting activity.[343,344]

Cell Lines as *in vitro* Models

Cell lines are commonly used for research purposes. Cell lines have been the workhorse of programmes for the identification and investigation of mechanisms of action, the discovery and/or testing of drugs/compounds/factors and the relevance of findings to human disease for decades. Bacopasides, a triterpenoid saponin found in abundance in the *Bacopa monnieri* plant, are the major ingredient. This component is primarily responsible for the plant's facilitation and modulatory actions.[179] When applied to human tumour cell lines MDA-MB-231, SHG-44, HCT-8, A549 and PC-3M at 50 μM doses, Bacoside E and Bacopaside VII may have antitumor efficacy[345] and inhibit prostaglandin synthesis and lysosomal membrane stabilisation in a non-toxic way.[309,346,347] The triterpene saponins Bacopaside I (BAC I) and Bacopaside II (BAC II) have demonstrated synergistic effects in reducing breast cancer cell proliferation and blocking *in-vitro* migration and invasion, whereas bac I and bac II in combination can induce G2/M arrest and apoptosis at high dosages. In contrast to other subtypes, the synergistic apoptosis-inducing potential of BAC I and BAC II is more prevalent in TNBC and HER2-positive breast cancer cells.[348] Cucurbitacin, another pivotal constituent of this plant, has been demonstrated to have cytotoxic properties when combined with betulinic acid against two MCF-7 and MDA-MB-231 breast cancer cells.[349] Cucurbitacins have been reported to be a potent anti-tumor and anti-proliferative agent in the murine sarcoma-180 cell line, capable of triggering cell cycle arrest during the G2/M phase, suppressing uncontrolled cell multiplication, and inducing cell death by activating apoptosis.[350] It is known that the leaf extract of Bacopa has neuroprotective function. Through the ERK and PI3K pathways, the extract extends its protective action against THBP-induced neuroblastoma cell death, whereas the ethanol extract of the aerial component at a concentration of 250 μg/ml has been demonstrated to be efficacious against THBP-mediated cytotoxicity. The extract is responsible for phosphorylation of ERK1/2 and Akt. These findings imply that *Bacopa monnieri* protects neuroblastoma cell lines by targeting two survival pathways (Akt and ERK)[351] Bacoside A has gained sufficient consideration substantially in recent research on anticancer therapeutic advancement for making possible anticancer activity to Glioblastoma multiforme cell lines, inducing cell cycle arrest and apoptosis through Notch pathway.[285,316,352] Bacopaside I and II have been reported for anticancer efficacy in low and high aquaporins expressing HT29 colon cancer cells, and it is crucial to note that Bacopaside II exclusively blocks the Aquaporins-1 water channel, whereas Bacopaside I inhibits both the Aquaporins-1 ion and water channel.[353-355] In DU145 prostate cancer cell lines, both methanol extract and various artificial digestive juice extracts of Bacopa have shown a cytotoxic and anti-invasive effect, but in the case of methanol extract, a strong cytotoxicity and anti-migration activity is shown.[356,357] MD. Nasar Mallick *et al.*, performed *in vitro* anticancer activity of whole plant hydroalcoholic extract and its fraction against different human cancer cell lines, namely Colon (HT29, Colo320, and Caco2), Lung (A549), Cervix (HeLa, SiHa), rhabdomyosarcoma (RD) and Breast (MCF-7, MDAMB-231), stating that *B. monnieri* has great potential for anticancer phytopharmaceuticals development.[358,359] In contrast,

endophytic fungi isolated from *Bacopa monnieri* recorded potent cytotoxic activity against HCT-116, MCF-7, PC-3, and A-549 cell lines respectively.[360] Using deep sequencing (RNA-Seq) to uncover transcriptome alterations in SH-SY5Y human neuroblastoma cells following treatment with Bacopa, How-Wing Leung *et al.*, revealed numerous genes whose Bacopa-regulated expression levels can mediate nootropic and neuroprotective effects.[361] Analogously, Krishna *et al.*, by DNA fragmentation method, documented *Bacopa monnieri's* genotoxicity potential on oral cancer cell lines, inhibition of HeLa cell proliferation and ascites accumulation and induction of apoptosis on KB cells by ethanolic extract, validated by DNA fragmentation analysis using the technique ofagarose gel electrophoresis.[362]

Antimicrobial Potential

A large variety of bacteria can cause infection. Herbal medicines are less costly and have fewer side effects than prescription pills. Antimicrobial properties of *Bacopa monnieri* are susceptible to *Staphylococcus aureus, Escherichia coli, Acinetobacter baumannii, Streptococcus faecalis, Shigella dysenteriae, Klebsiella pneumoniae, Bacillus subtilis, Bacillus cereus, Pseudomonas aeruginosa, Bacillus pumilus, Salmonella typhi, Salmonella Typhimurium, Vibrio cholera, Proteus vulgaris, Enterococcus faecalis, Shigella sonnei, Streptococcus pneumoniae, Proteus mirabilis*, and *Salmonella enterica*. In-addition, *Bacopa monnieri* also has antifungal properties against *Aspergillus flavus, Aspergillus niger, Candida albicans, Alternaria alternata, Fusarium fusiformis, Penicillium notatum* and *Saccharomyces cerevisiae*.[50,363-366]

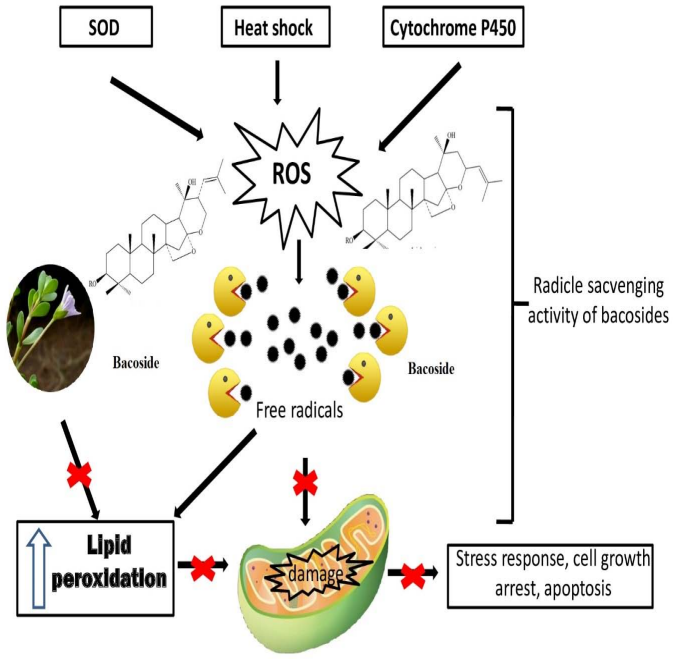

Figure 7: Neuroprotective effects of *Bacopa monnieri* bacoside.

In vitro Anthelmintic Activity

Worm infestation in the gastrointestinal tract is referred to in Ayurveda as *Krimiroga*. For the treatment of *Krimiroga*, many Ayurvedic medicinal plants are traditionally used. Severe toxic side effects in humans are caused by the use of synthetic anthelmintic medicines to treat parasitic infestations. There are no such side effects and, economically, the use of Ayurvedic plants.[367] This review paper thus highlights the *in-vitro* anthelmintic role of *Bacopa monnieri* in different pharmacological models. When their anthelmintic activity was conducted separately on adult Indian earth worms (*Pheretima posthuman*), Ghosh *et al.*, concluded that the n-butanol fraction and ethanolic extract of Bacopa aerial parts were more potent than ethyl acetate and aqueous fractions, but the petroleum ether extract did not show anthelmintic activity when compared to the reference drugs piperazine citrate and albendazole.[368,369]

In vitro Thrombolytic Manoeuvres

Myocardial or cerebral infarctions are severe atherothrombotic diseases caused by thrombus formation in blood vessels. Thrombolytic agents are used to remove clots that have already coalesced in blood vessels; however, these therapies come with a slew of hazards that can be life-threatening. *In-vitro* thrombolytic activity of ethanolic, methanolic, acetone, and aqueous extracts of different parts (root, stem, and leaf) of *Bacopa monnieri* was documented by Sai Sandeep *et al.*, The highest degree of thrombolysis was found in the leaf ethanolic extract, which was followed by aqueous, methanol, and acetone extracts.[243] Sweta Prasad *et al.*, also catalogued *in-vitro* thrombolytic activity of six aqueous herbal extracts but *B. monnieri*, the most interesting of

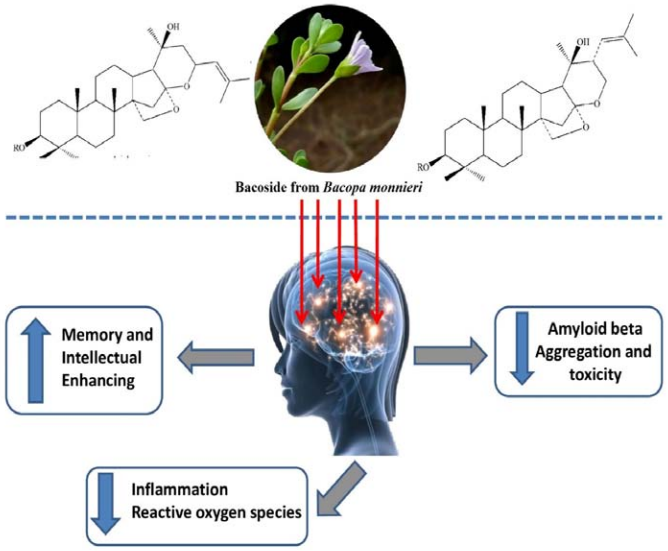

Figure 8: The mechanism of action of bacoside against ROS induces mitochondrial damage. (ROS indicates reactive oxygen species; SOD, superoxide dismutase).

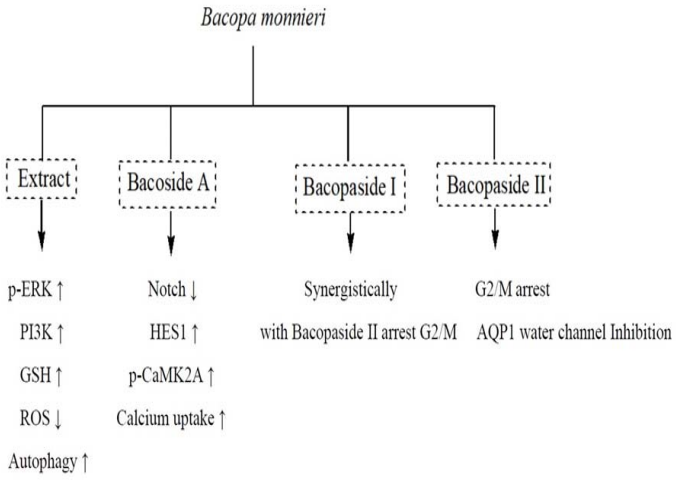

Figure 9: Major targets of the extract of *Bacopa monnieri* and its bioactive constituents for anticancer activity. Upregulation and downregulation are shown by the up (↑) and down (↓) arrows, respectively.

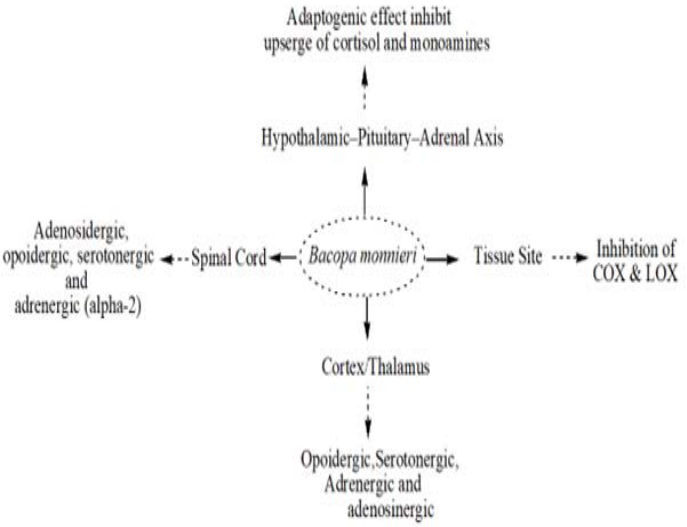

Figure 10: Feasible *Bacopa monnieri* mechanism of action in chronic pain monitoring.

the six herbs, demonstrated nearly 50% clot lysis.[370] Likewise, in different blood samples, the chloroform extract of leaf displayed pertinent clot lytic properties, with a mean percent clot lytic activity of 48.39%.[371] According to one study, *Bacopa monnieri*'s thrombolytic activity could be very promising and beneficial for Bangladeshi traditional medicine because its *in-vivo* clot dissolving property and active component(s) for clot lysis could lead to the plants' therapeutic uses.[372]

Bacopa monnieri Toxicity Spectrum and Herb-Drug Interactions

A toxicological exploration is essential for the development of novel drugs. The US Food and Drug Administration (FDA) believes that testing novel compounds in animals for toxicity

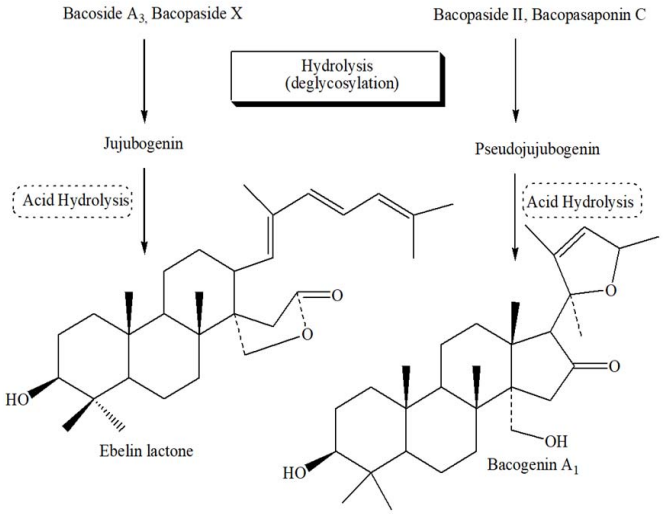

Figure 11: Deglycosylation of bacoside A components yields the aglycones jujubogenin and

and pharmacological activity is critical. Many underdeveloped countries rely on herbs and herbal products to suit their healthcare requirements. It is vital to properly assess the safety and efficacy of these therapeutic plants in order to maximise their advantages to mankind.[373] Sireeratawong *et al.*, explored the acute and chronic toxicity of crude ethanolic extract of *B. monnieri* aerial part at dosages of 30, 60, 300, or 1500 mg/kg in Sprague-Dawley rats over a 270-day period, finding no significant differences in the acute toxicity test between the experimental and control groups. In the chronic toxicity test, the experimental rats' behaviour and health were normal, the same as the control rats. The values of the other tested parameters were all within accepted ranges.[374] Furthermore, various researchers conducted toxicity studies on various *Bacopa monnieri* formulations, such as Deo *et al.*, compiled acute and subchronic toxicity studies of Brahmi ghrita in rodents and concluded that Brahmi ghrita is safe in rodents and mice at doses of 1, 2.5, and 5 g/kg, p.o.[375] Similarly, no evidence of toxicity was found in a 90-day subchronic oral toxicity study in rats of BacoMind, an enriched phytochemical composition derived from *Bacopa monnieri*, at doses of 85, 210, and 500 mg/kg, in terms of clinical effects, neurological examination, weight gain, or hematological parameters. There were no signs of degradation after a necropsy and histopathological examination.[376] Furthermore, Parihar Deepak and his teammates assessed the subacute toxicity of a new Brahmi formulation, finding no morbidity or mortality at the tested dose level, as well as no significant changes in body weight, food consumption, organ weight, urine analysis, haematology, histopathology, or biochemical parameters. Researchers concluded that the new formulation is safe.[377] For clearer vision, Pravina *et al.*, performed a safety evaluation of BacoMind in healthy volunteers in a phase I study, in which each of 23 participants was orally given one single capsule of BacoMind daily for 30 days, with 300

mg for the first 15 days and 450 mg for the next 15 days. In each of the treated volunteers, a thorough review of physiological, hematological, biochemical, and electrocardiographic parameters obtained before and after treatment revealed no adverse effects. Mild gastrointestinal system side effects were seen in the study, but they went away on their own.[57] According to a comprehensive article, the medicinal herb Bacopa has the ability to alter the pharmacokinetics of amitriptyline in rats, *via* inhibition of CYP2C and CYP3A enzymes, *Bacopa monnieri* mediated increased intestinal absorption and decreased first-pass metabolism of amitriptyline in the intestine and liver, indicating an herb–drug interaction.[378]

Speculative Based Mechanisms of Action and Safeguards Credentials

Bacopa monnieri extract's pharmacological effects in multiple dimensions have been investigated in research laboratories all over the world over the past 50 years, particularly as a nerve tonic and memory enhancer. Bacopa therapy has been shown in animal studies to reduce dementia, boost memory, and have anti-hyperglycaemic, hepatoprotective, and anti-hyperlipidaemia properties, as well as cardio protection with increased coronary blood flow and protection against myocardial ischemia reperfusion injury. *Bacopa monnieri* extract has also been shown to have antimutagenic and free radical scavenging activities on human lymphocytes *in-vitro*, without causing any genotoxicity. Several authors express differing views on the mechanism of action of *Bacopa monnieri* extract and its active phytoconstituents bacoside. According to Rajan *et al.*, Bacopa predominantly acts as an antioxidant (i.e., neuroprotection) or changes a variety of neurotransmitters such as serotonin (5-hydroxytryptamine, 5-HT), dopamine, acetylcholine, and γ-aminobutyric acid to carry out its pharmacological activity. 5-HT has been shown to fine-tune synaptic plasticity, which is a substrate for memory nucleation.[176] [Figure 7] depicts the neuroprotective effects of bacoside from *Bacopa monnieri* as seen in various studies.[231,379,380] [Figure 8] summarizes the pathways involved in the neuroprotection from bacosides, which include detoxification and binding of free radical scavenging metal ions, as well as growing antioxidant properties.[158,198,381,382] *Bacopa monnieri* also inhibits three enzymes like Catechol-O-Methyl Transferase (COMT), Prolyl Endopeptidase (PEP), and Poly (ADP-ribose) Polymerase (PARP), according to Shekhar Dethe *et al.*, It also had an antagonistic effect on serotonin (5-HT_6 and 5-HT_{2A}) receptors, which are known to affect various neuronal pathways and are linked to memory and learning disabilities, as well as age-related memory loss.[383] *Bacopa monnieri* possesses anticancer potential in malignancies including colon, breast, liver, prostate, and neurological tumours. Certain studies argued that the ingredients extracted from the *B.monnieri* extract showed unique activity against various cancer cell types, ultimately resulting to cell death by altering specific signalling pathways, halting at key phases of the cell cycle, or simply providing cytotoxicity, or even by activating the autophagic pathway in a nontoxic approach to normal cells [Figure 9].[294] The effect of Bacoside-A in acute and chronic models of Experimental Autoimmune Encephalomyelitis (EAE) in mice was stated by K. Madhu *et al.*, The researchers found that Bacoside-A-treated mice had a significantly decreased inflammation rating than control mice in both models, and the Author hypothesised that Bacoside-A treatment inhibited the development of inflammatory cytokines and inflammatory chemokines in EAE mice.[384] Bacopa also benefits against neuropathic pain and has a potent anti-inflammatory impact via COX-2 inhibitory mechanism. It also suppresses opioid withdrawal-induced hyperalgesia, as well as the development and manifestation of morphine tolerance [Figure 10]. Naloxone has also been shown to reverse the analgesic effect in several trials, both in tonic and acute pain models. These results point to an opioidergic pathway being involved. This effect may be due to Bacopa's indirect action on opioid receptors via 5-HT and Gamma Amino Butyric Acid (GABA). The aglycone portion of Bacoside A_3 was docked into the COX-2 active site to investigate the possible role of Bacopasides in direct COX-2 inhibition. Bacoside A_3 and other associated compounds are classified as a new class of Phospholipase A_2 (PLA_2) inhibitors since their chemical structures are like those of steroidal anti-inflammatory drugs. Bacoside A_3 is also well-suited to the active site of PLA_2, due to favourable electrostatic and steric interactions. Bacopasides are superior to established steroidal anti-inflammatory drugs so there are less chances of unwanted interactions with steroid binding globulins, especially androgen and oestrogen receptors.[316,385] *Bacopa monnieri* has also been shown to inhibit Hsp70 expression in chronic stress and to modulate several enzymes involved in Hsp70 expression, such as superoxide dismutase and cytochrome P450, during chronic stress. Prolonged use of Bacopa has also been shown to improve hippocampal dendritic arborization.[306,386] In multiple clinical trials including healthy volunteers, aged people with and without memory impairments, anxiety, and depression, *B. monnieri* were exemplified to be an effective and well tolerated medication. It has also been proven to have ulcer-protecting and ulcer-curing properties, with apparent results in ulcer treatment. Simultaneously, *Bacopa monnieri* exerts some of its analgesic effects through adenosine A_1 receptor activation in all reported clinical trials, especially in neuropathic pain models. *B. monnieri* has been observed to be devoid of potentially catastrophic adverse effects, particularly those involving the cardiovascular system and headaches, which are frequent side effects of several direct acting adenosinergic medications. Considering *Bacopa monnieri*'s complex pharmacological profile as a potent analgesic with central and peripheral effects mediated by adenosinergic, serotonergic, and adrenergic pathways, at last, *Bacopa monnieri* has anti-inflammatory, anti-depressant, and adaptogenic properties. It's past time to look at *Bacopa monnieri*'s potential in the treatment of chronic pain.[94,95,251] *Bacopa monnieri* extracts

have been found to inhibit some human Cytochrome P450 (CYP) drug metabolizing enzymes, according to a latest report. It may also change the expression of rat CYP drug metabolizing enzymes in the liver and intestine, as well as intestinal P-glycoprotein. It's possible that the bacoside constituents in *Bacopa monnieri* extracts are metabolized to active forms in the body before exerting their pharmacological effects. Bacoside A_3, bacopaside II, bacopaside X, and bacopasaponin C can be converted to their aglycones jujubogenin or pseudojujubogenin by sequential deglycosylation. Then ebelin lactone and bacogenin A_1 are generated by further acid hydrolysis of jujubogenin and pseudojujubogenin, respectively [Figure 11].[387,388]

CLINICAL TRIALS DELINEATION

Various researchers have conducted multiple clinical trials and investigations to determine the nootropic benefits of *Bacopa monnieri*. The majority of recent clinical research on Bacopa focused on its impact on cognition, memory, anxiety, and/or depression in healthy volunteers (either elderly or of unspecified age) or Alzheimer's patients. In 1996 a special extract of *Bacopa monnieri* was launched by the Indian Government's Central Drug Research Institute, Lucknow, termed CDRI 08. It was thought at the time that this particular standardised extract had been subjected to the most research and was the most promising extract for medical conditions.[389] In one 2011 open-label, prospective, uncontrolled, non-randomized study, thirty-nine Alzheimer's patients (60-65 years) were given 300 mg Bacognize (alcohol extract standardized by HPLC for 10-20% Bacopa glycosides; Verdure Sciences, Noblesville, Indiana) twice daily for 6 months. Twenty-three patients showed significant improvements in various areas, including attention, orientation of person, place, and time, and in reading, writing, and comprehension.[390] Similarly, A randomized, double-blind, placebo-controlled study in 2010 investigated Bacopa efficacy in improving memory performance in older healthy people. Ninety-eight participants over 55 years of age were randomized to receive 300 mg/day BacoMind (20:1 alcohol extract standardized to contain 40-50% bacosides; Natural Remedies Pvt. Ltd., Bangalore, India) or placebo for 12 weeks. The Bacopa group showed significantly improved memory acquisition and retention. An additional study on the safety of BacoMind resulted in no major adverse effects.[57,391] In 2008, the whole plant standardized dry extract of Bacopa (methanol-extracted extract with a minimum of 50% bacosides A and B) on cognitive function and safety. Each of forty-eight healthy participants (65 years older), who completed the study were given either 300 mg once a day of the Bacopa extract or placebo for 12 weeks. Over the course of the study, the Bacopa group had improved delayed recall memory and while the placebo group experienced no change. The Bacopa group also experienced decreased depression and anxiety while the placebo recipients increase in both.[392] Similarly, sixty-two healthy individuals were given either 300 mg KeenMind (a dry extract standardised to at least 55% bacosides) or placebo daily for 90 days, and the Bacopa group had significantly enhanced spatial working memory accuracy at the end of the trial.[393] Roodenrys *et al*., reported the effect of Bacopa on anxiety and various memory functions. Total seventy-six healthy participants were given 300 mg-450 mg and thirty-nine were given placebo. After the trial ended the authors posited that it was the antioxidant effect of Bacopa on the hippocampus that was responsible for the improved retention.[394] Bacopa was also found to have strong psychotropic activity in research comparing it to Gotu Kola, as demonstrated by excessive sleep including alterations in the brain and blood.[395] Drug *B. monnieri* was also proved by the Central Council for Research in Homoeopathy through randomized, double-blind, placebo-controlled method. The pathogenetic responses elicited during the proving trial expands the scope of use of the drug *B. monnieri* extract is efficacious in subjects with age-associated memory impairment with significant improvement on mental control, logical memory and impaired associated learning. The reported studies also provide further evidence that *B. monnieri* has potential for safely enhancing cognitive performance in aging.[396] Navneet *et al.*, studied the effectiveness of B. monnieri on medical students by administering 150 mg of standardised extract (Bacognize) twice day for six weeks with a matched placebo. The extractsignificantly enhances memory skills and raises serum calcium levels.[397] James *et al*., reported that *B. monnieri* which has been subjected to hundreds of scientific studies and has been shown in human randomized controlled trials to improve memory, attention and mood. It also hypothesized that chronic administration *B. monnieri* will improve attention, concentration and behaviour in children with high levels of hyperactivity and/or inattention.[398] C. Kongkeaw *et al*., reported that randomized, placebo controlled human intervention trials on chronic dosing of standardized extracts of *B. monnieri* without any co-medication, suggests that *B. monnieri* has the potential to improve cognition, particularly speed of attention and improve the memory function in terms of picture recognition, numeric working memory, word recognition, and spatial working memory and also efficacy on healthy or dementia patients.[399] J.D. Kean *et al*., highlight the safe use of *B. monnieri* in child and adolescent populations for improving elements of cognition as well as behaviour and attention-deficit domains.[64] *Bacopa* intensifies memory free recall, according to Matthew *et al*., but evidence for improvement in other cognitive capacities is still missing, possibly because to uneven metrics used by research across various cognitive domains. The study of Bacopa's nootropic effects is still in its early stages, with more research needed to look at the impacts of Bacopa across all human cognitive capacities.[400] Srinibash Sahoo *et al*., also reported the efficacy of Brahmi ghrita and Jyotishmathitaila in cognitive deficit children's. Brahmi ghrita has given orally in a dose of 10 gms twice daily with warm water/milk before food and Jyotishmatitaila given as Pratimarsha Nasya (2-2 drops) in each nostril twice daily for a period of 12

weeks to evaluate the effect on clinical symptoms of cognitive deficit and changes in mini-mental state examination. Seventy-six cognitive deficit children were selected for these studies. The trials provided significant data on all clinical symptoms and at the end of the 84th days of the study it also provided significant effect on attention, concentration and sensory perception, simultaneously lab reports show that no significant changes occur in almost all hematological parameters which indicates that these medicines are safe for administration and also effective to improve the clinical symptoms of the cognitive deficit children.[401] Tatimah Peth-Nui *et al.*, trialled a randomised double-blind placebo-controlled design on sixty healthy senior adults, 23 males and 37 females, who were given either a standardised extract of *B. monnieri* (300 or 600 mg) or a placebo once daily for 12 weeks. The inhibition of AChE activity increased attention, cognitive processing, and working memory in the *B. monnieri*-treated group. The health benefits of *B. monnieri* for healthy elderly individuals were also validated in this study. In addition, no toxicity or side effects were observed throughout the trials and suppression of AChE activity resulting in enhanced cholinergic function, which in turn enhances attention and memory processing and gives rise to the increased working memory.[402] Simillarly, James D. Kean *et al.*, also highlighted that the use of *B.monnieri* in polyherbal preparations for improving cognitive and behavioural outcomes in child and adolescent populations.[403] Simultaneously, Raghav *et al.*, also reported the efficacy of standardized *B. monnieri* extract (125 mg twice a day) in subjects with age-associated memory impairment without any evidence of dementia or psychiatric disorder. The standardized extract of Brahmi produced significant improvement on mental control, logical memory and paired associated learning during the 12-week drug therapy.[404] Recently Sane R *et al.*, reported that capsule Artyl (500 mg twice a day orally for 28 days) significantly decreasing the blood pressure in hypertensive patients, without any adverse effects. Capsule Artyl is a polyherbal Ayurvedic oral formulation which is made from the aqueous extracts of Brahmi (Bacoside 30%) and Shunthi (Gingerol 2.5%).[405] D. Mishra and B.R. Tubaki, reported a randomized double blind clinical studies effect of Brahmi vati (500 mg) and Sarpagandha Ghana vati (500 mg) in management of essential hypertension. Both the Vati produced improvement in most of the variables and were comparable. Improvements were seen in various variables like systolic blood pressure, diastolic blood pressure, mean arterial pressure, Hamilton anxiety rating scale, subjective sleep profiles and total cholesterol. However, Brahmi vati showed increase in weight and Body Mass Index. Sarpagandha Ghana vati produced reduction in total cholesterol and LDL. Both groups had an acceptable safety profile as determined by serum creatinine levels.[406] Interestingly, it was stated in a recent study that 1-month administration of Brahmi extracts (500 mg/day) in addition to antipsychotic drugs could minimise psychopathology in schizophrenic patients without triggering additional side effects.[407] Likewise, using the same patient selection parameters and the same dosage of Bacopa extract (300 mg/day), Stough *et al.*, conducted a 12-week double-blind, placebo-controlled study. The treatment group showed a substantial increase in verbal learning, memory consolidation, and speed of early information processing at the end of the 12-week trial.[408] According to Sathyaseela R. *et al.*, applying *Bacopa monnieri* paste topically to the ankle joint of the patients with arthritis reduced swelling. Bacopa is known for its anti-arthritic properties, and it is mostly used to treat swelling caused by increased synovial effusion.[409] In another, James D. Kean and his colleagues found that nine trials met the inclusion criteria in a systematic review of *Bacopa monnieri* dominant poly-herbal formulations in children and adolescents. Five trials provided enough evidence for an impact size study, with the majority of changes in behavioural outcomes. Six investigations looked at true cognitive ability and behavioural constructs, with visual perception, impulsivity, and concentration showing the most breakthroughs. Inconsistent methodological nature and under-reporting of protection and tolerability data (44%) compromise the veracity of the evidence for the formulations examined.[403] The effects of *Bacopa monnieri* on memory, attention, and cognitive function in children have been studied less thoroughly in controlled trials. As compared to children who received placebo, those who received Bacopa syrup (350 mg) three times daily for three months showed increased exploratory drive, enhanced perceptual images of patterns, and increased perceptual organization and reasoning skill.[410] Over the course of 16 weeks, a randomized, double-blind, placebo-controlled study testing *Bacopa monnieri* in 36 children with attention deficit hyperactivity disorder was performed. As compared to the 17 children who received placebo, the 19 children who received Bacopa (50 mg twice daily for 12 weeks, followed by 4 weeks of placebo) showed substantially greater outcomes in sentence repetition, rational memory, and paired associate learning tasks at 12 weeks. These improvements were also continued after 16 weeks.[411] According to a systematic review of *Bacopa monnieri* trials in children and adolescents, the herb has the ability to enhance memory. Despite these promising findings, research on the impact of *Bacopa monnieri* on cognitive performance in children and adolescents is still lacking.[412,413] In contrast, according to the first research, a four-month supplementation with a combination of *Bacopa monnieri* extract and several micronutrients resulted in significantly better cognitive functions, such as memory and attention, when compared to a control product.[414]

BACOPA MONNIERI AND THEIR BIOACTIVE COMPOUNDS: A CHEMINFORMATICS APPROACH IN A MULTI-TARGET MINISTRATION SCENARIO

One of the most important mechanisms in the pharmaceutical industry is drug production. The time and complexity of drug development have been greatly reduced due to a number of statistical approaches. In the detection and production of novel promising molecules, integrating quantitative and experimental methods has proved to be highly helpful. With the vast variety of docking algorithms available today, knowing the advantages and disadvantages of each strategy is crucial to developing good strategies and generating relevant data. Bacosides and their aglycones in 5-HT_{1A}, 5-HT_{2A}, D_1, D_2, M_1 receptors, and acetylcholinesterase were analysed *in silico* using AutoDock. Discovery Studio 4.0 was used to forecast ADMET and Druglikeness. According to the data collected, aglycones have a higher binding ability to the target than Bacosides.[180] In addition, *in silico* analyses of phytocompounds found in *B. monnieri* on two receptors, CASP-3 and tau-protein kinase I (PDB IDs: 3KJF and 1J1B), as possible causes of Alzheimer's symptoms. The PyRx tool was used to perform molecular docking in order to determine the most desirable binding affinity and capacity. On CASP-3 and TPK I receptors, phytoligands including Bacopasaponin G and Bacopasaponin N_2 have a lower binding energy than the synthetic analog Donepezil, according to the statements.[415] In fact, *in-silico* molecular docking tests of Bacopa constituents as LRRK2 antagonists as a possible Parkinson's disease therapy. Bacosaponin was found to be a stronger ligand than the other triglycosidic saponins tested, with a binding affinity of −7.5 kcal/mol and major interactions at the receptor-ligand interface. As a consequence, it's being proposed as a possible Parkinson's disease therapy.[416] S. Chandrasekar *et al.*, on the other hand, used Discovery Studio methods to explore the binding affinity of bacoside-A with the DJ-1 receptor *in-silico* and explored that bacoside-A interacts with DJ-1.[417] Three separate docking algorithms were used to consider the relationship of the bacoside-TPH complex, including Hex-Dock, PatchDock, and AutoDock. Bacoside A_3 and A, which are the main active compounds, form hydrogen bonds with various residues of TPH, enhancing learning and memory functions.[418] Concurrently, active phytocompounds from various Ayurvedic medicinal plants were used to conduct *in silico* pharmacophore screening and docking trials against the α-amino-3-hydroxy-5-methy l-4-isoxazolepropionic acid (AMPA) receptor. Bacopaside-II, Quercetin, and Asiatic acid were shown to have beneficial associations and may be used to treat Alzheimer's disease.[419] Latest molecular docking experimental data studies suggested that phytocompounds found in *B. monnieri* are selective against the two target proteins AChE and MAGL (Monoacylglycerol Lipase), both of which have been related to the treatment of Alzheimer's disease. On comparative molecular docking experiments using Schrodinger to classify possible Anti-Alziehmers drugs from flavonoids, xanthonoids, and saponins, it was established that bacoside-A showed successful binding for both AChE and MAGL targets, which was substantially higher than that of the synthetic drug Donepezil. Luteolin and Bacopaside were shown to have high binding affinities in many CDK5 (Cyclin-dependent Kinase 5) receptors.[420,421] The selection of new compounds to propose as drugs and the selection of potential targets to be inhibited in order to prevent disease prognosis are also part of the drug development process. Using computer-aided drug development, the antimicrobial action of phytoconstituents found in *Bacopa monnieri* on the Outer Membrane Protein X (OMPX) receptor *in vitro* and *in silico*. Bacopaside-I had the best docking score against OMPX of all phytoconstituents, followed by bacopaside II, bacopaside A, β-sitosterol, luteolin and apigenin.[422] In addition, Emran *et al.*, used the GOLD 4.12 kit to conduct molecular docking tests of potent phytochemicals on two key drug-target-pathways, namely penicillin binding protein and *S. aureus* DNA gyrase. The evidence from the Molecular Binding Interactions showed that luteolin has a higher specificity for the DNA gyrase binding site and may be a powerful antimicrobial entity.[423] In a related vein, Eswari *et al.*, crawled molecular docking simulations between essential *Bacopa monnieri* phytochemicals and explored novel MRSA targets PDB entry 2X4K and 2IHY. Bacoside and bacopa saponin had higher binding affinities and docking ratings for target proteins, suggesting that they could be used as effective antimicrobial agents.[424] Glioblastoma multiforme is a type of brain tumor that is particularly aggressive and has a poor prognosis. Via docking and molecular dynamic modeling experiments on the anticancer target CaMK2A (Calcium/calmodulin-dependent Protein Kinase Type IIα) enzyme, recent evidence has shown that the structure-function relationship of the "bioactive components" of the *Bacopa monnieri* plant extract. Bacoside A, the primary bioactive constituent of *B. monnieri*, had the highest GlideScore in the T-site, indicating a high affinity for binding. Bacoside A will sterically fit well in the enzyme pocket and induces tumor cell death in human glioblastoma cell lines by catastrophic micropinocytosis, according to complex simulations of Bacoside A binding to CaMK2A.[285] Analogously, computational research using molecular docking suggests that bacoside-histone protein interactions could be important in arresting mitosis during prophase,[425] and various bioinformatics techniques such as homology modelling and active docking of Bacoside A3 and Myricetin in proteins implicated in pancreatic cancer, namely MMP2 and MMP9. The combination structure's docking scores show that it may be used to treat advanced pancreatic cancer.[426] The Zika virus is an arbovirus of the flavivirus family that poses a major global challenge. The compounds Galloylquinic acid, Bacopaside III, and Bacopaside A were known as leads against Zika virus during the recent epidemic. The compounds were also shown to have attractive quantum chemical and ADMET properties.[427] In the pancreas, immunohistochemistry showed that Brahmi ghrita was able to restore cell mass and function to levels comparable to the usual regulation. Apigenin and quercetin displayed substantial interactions with protein kinase C *in-silico*

trials, while clitorin, bacopaside I and II, and CD38 showed significant interactions. The highest percentage inhibition of the α-amylase enzyme was found in quercetin.[428] Accordingly, Rauf *et al.*, docked the aglycone portion of Bacoside A_3, (a standard bacopaside) into the COX-2 active site using OEDocking tools to investigate the possible involvement of Bacopasides in direct COX-2 inhibition. The findings revealed a strong and beneficial molecular association between Bacopasides and Arg120 and Met522, which is essential for analgesic and anti-inflammatory activities.[316]

SUMMARY OF FINDINGS: PROSPECTIVE AND FUTURE EXPECTATIONS

Traditional medicines are gaining popularity owing to their reduced toxicity, while contemporary therapies fail to address the needs of the great majority of people suffering from health problems. Bacopa is a traditional plant used in Ayurvedic and Siddha therapy to alleviate brain and nerve weariness, as well as memory problems. In Unani medicine, it's also utilised to treat neuroglial atrophy. The therapeutic qualities of Brahmi have been extensively studied by several research teams. Bacosides are thought to be active components of herbal extracts that are primarily engaged in exerting nootropic effects in both animals and humans. Bacoside A treatment also prevented mitochondrial structural and functional damage after exposure to cigarette smoke. We compiled the pharmacobotanical and pharmacognostical descriptions, as well as ethnoarchaeological data and nanotechnology dominance, and enhanced Brahmi micropropagation and secondary metabolite biosynthesis. This review covers both current phytochemical and pharmacological findings on *Bacopa monnieri* (L.) Pennell. Brahmi has a lot of promise for treating a variety of neuro-pharmacological, depression, inflammation, hepatoprotective, antidiabetic, and other conditions. The vast diversity of neuropharmacological effects of Brahmi opens up fascinating paths for further research and offers new prospects in the treatment of various disorders, especially in light of several publications indicating important activities of *Bacopa monnieri* extract. Larger clinical trials and further research are required to corroborate the findings of this review. While the activity of Brahmi as an anxiolytic and antidepressant has to be researched further, its potential as an anti-epileptic therapy and a treatment for antiepileptic medication side effects is also something that will be looked into in the future. Furthermore, Brahmi's antioxidant ability may explain, at least in part, the antistress, immunomodulatory, cognition-facilitating, anti-inflammatory, and anti-aging benefits documented in experimental animals as well as clinical circumstances, necessitating further study into its other therapeutic characteristics. Consequently, because of its antioxidant action, this experimental evidence implies that it may be beneficial in the treatment of human diseases in which free radical generation is a significant factor. *Bacopa monnieri*'s antifertility potential was recently discovered in male mice, where it was found to produce reversible reduction of spermatogenesis and fertility without causing any obvious side effects. In recent *in-vitro* research, *Bacopa monnieri* was also found to exhibit thrombolytic action. Herb-drug and herb-herb interactions of *Bacopa monnieri* should be investigated in addition to the pharmacological research described above. Interactions between herbal medications and synthetic pharmaceuticals are known to exist and can have significant implications, according to several research. To summarise, there is minimal clinical evidence that *B. monnieri* enhances memory in healthy people or those with age-related memory problems. Furthermore, clinical evidence for the therapy of Alzheimer's disease and depression with *B. monnieri* is limited, since just a few studies have looked into Alzheimer's disease using a single herb formulation of *Bacopa monnieri*, and none have looked into depression patients. Furthermore, bigger, long-term trials comparing *B. monnieri* to existing conventional medicines are needed to establish whether *B. monnieri* is a viable alternative therapy for the illnesses mentioned above. Simultaneously, further progress toward bench-to-bedside translation, or the mechanisms underlying the effects of Brahmi in various disease conditions, requires a better understanding of the pathophysiological nature of various diseases associated with cognitive science, as well as insight into the interaction of nanomaterials with biological systems at various levels. The use of targeted nanoparticles based on liposomes, polymeric micelles, and polymersomes might be considered a crucial strategy for delivering extracts and active ingredients to the brain.

Thus, biomedical research on *Bacopa monnieri* is still in its early stages, but preliminary insights like documented in this review will definitely open the floodgates for additional research, among many others, that will undoubtedly benefit mankind.

ACKNOWLEDGEMENT

We are thankful to GITAM (Deemed to be University), Visakhapatnam, Andhra Pradesh, India for providing necessary facilities to carry out this research.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

Financial Support and Sponsorship

This study was supported by GITAM Institute of Pharmacy, GITAM (Deemed to be University), Visakhapatnam, Andhra Pradesh, India.

ABBREVIATIONS

***B. monnieri*:** *Bacopa monnieri*; **cm:** Centimetre; **mm:** Millimeter; **FDA:** Food and Drug Administration; **AgNPs:** Silver nanoparticles; **$AgNO_3$:** Silver Nitrate; **SLNs:** Solid Lipid Nanoparticles; **UV-visible:** Ultraviolet-visible; **FTIR:** Fourier Transform Infrared; **HR-TEM:** High-Resolution Transmission

Electron Microscopy; ***S. Aureus*:** *Staphylococcus aureus*; ***E. coli*:** *Escherichia coli*; **Gm+ve:** Gram Positive; **Gm-ve:** Gram Negative; **BmSNPs:** *B. monnieri* stabilized silver nanoparticles; **BAP:** 6-benzylaminopurine; **KIN:** Kinetin; **IAA:** Indole-3-Acetic Acid; **IBA:** Indole-3-Butyric Acid; **NAA:** 1-Naphthaleneacetic Acid; **BAP:** 6-Benzylaminopurine; **mg/l:** Milligram/liter; **mM:** Millimolar; **2,4-D:** 2,4-Dichlorophenoxyacetic acid; **mg/g:** Milligram/gram; **$ZnCl_2$:** Zinc Chloride; **$CoCl_2$:** Cobalt Chloride; **$CuSO_4$:** Copper Sulphate; **LED:** Light-Emitting Diode; **µM:** Micrometer; **Cd:** Cadmium; **IUPAC:** International Union of Pure and Applied Chemistry; **GC-MS:** Gas Chromatography–Mass Spectrometry; **ROS:** Reactive Oxygen Species; **DNA:** Deoxyribonucleic Acid; **EDTA:** Ethylenediaminetetraacetic Acid; **CDRI:** Central Drug Research Institute; **NMDA:** N-Methyl-D-Aspartic Acid; **AMPA:** Alpha-Amino-3-Hydrox y-5-Methyl-4-Isoxazolepropionic Acid; **SOD:** Superoxide Dismutase; **L-NNA:** Nomega-Nitro-L-Arginine; **GABA:** Gamma-aminobutyric acid; **mg/kg:** Milligrams/Kilogram; **OBX:** Olfactory Bulbectomy; **BBB:** Blood Brain Barrier; **TMT:** Trimethyltin; **FST:** Forced Swimming Test; **TST:** Tail Suspension Test; ***p.o.*:** *per os*; **EPM:** Elevated Plus Maze; **PTZ:** Pentylenetetrazole; **NMDAR:** N-Methyl-D-Aspartate Receptor; **GAD:** Glutamate Decarboxylase; **PC12 cells:** Pheochromocytoma Cells 12; **ATP:** Adenosine Triphosphate; **NO:** Nitric oxide; **PKC inhibitor:** Protein Kinase C Inhibitor; **PI3K inhibitor:** Phosphoinositide 3-Kinase inhibitor; **ERK inhibitor:** Extracellular Signal-Regulated Kinase inhibitor; **NIDDM:** Non-Insulin-Dependent Diabetes Mellitus; **AST:** Aspartate Aminotransferase; **ALT:** Alanine Aminotransferase; **ALP:** Alkaline Phosphatase; **d-GalN:** d-galactosamine; **LDL:** Low-density Lipoprotein; **VLDL:** Very Low-density Lipoprotein; **HDL:** High-density Lipoprotein; **NOS:** Nitric Oxide Signaling; **STZ:** Streptozotocin; **GBM:** Glioblastoma Multiforme; **EAC:** External Auditory Canal; **DEN:** N-nitrosodiethylamine; **NK cell:** Natural Killer cell; **WBC:** White Blood Cells; **Th1:** T helper type 1; **TNF:** Tumor Necrosis Factor; **IFN:** Interferon; **IL-10:** Interleukin 10; **MAPK:** Mitogen-activated Protein Kinase; **NF-kB:** Nuclear Factor Kappa-light-chain-enhancer of activated B cells; **ICR:** Institute of Cancer Research; **CNS:** Central Nervous System; **IFN-γ:** Interferon Gamma; **LD50:** Lethal Dose 50; **ED50:** Effective Dose 50; **IgM:** Immunoglobulin M; **IgG:** Immunoglobulin G; **COX-2:** Cyclooxygenase-2; **MDR:** Multidrug-Resistant; **DNA:** Deoxyribonucleic Acid; **MAP2K1:** Mitogen-Activated Protein Kinase Kinase 1; **MAP2K2:** Mitogen-Activated Protein Kinase Kinase 2; **MKK4:** Mitogen-activated protein Kinase Kinase 4; **T_4:** Thyroxine; **T_3:** Triiodothyronine; **TSH:** Thyroid-Stimulating Hormone; **5α-R1:** 5α-Reductase-1; **THBP:** Tert-Butyl Hydroperoxide; **5-HT:** 5-hydroxytryptamine; **COMT:** Catechol-O-methyl transferase; **PEP:** Prolyl endopeptidase; **PARP:** Poly (ADP-ribose) polymerase; **EAE:** Experimental Autoimmune Encephalomyelitis; **PLA2:** Phospholipase A_2; **LRRK2:** Leucine-Rich Repeat Kinase 2; **CDK5:** Cyclin-Dependent Kinase 5; **OMPX:** Outer Membrane Protein X; **MRSA:** Methicillin-resistant *Staphylococcus aureus*; **MMP2:** Matrix Metallopeptidase 2; **MMP9:** Matrix Metallopeptidase 9; **CD38:** Cluster of Differentiation 38.

REFERENCES

1. Balkrishna A, Mishra RK, Srivastava A, Joshi B, Marde R, Prajapati UB. Ancient Indian rishi's (Sages) knowledge of botany and medicinal plants since Vedic period was much older than the period of Theophrastus, A case study who was the actual father of botany? Int J Unani Integr Med. 2019;3(3):40-4.
2. Mondal S, Bhar K, Kumari R, Mondal P, Chakraborty S, Teja NY. An Insight into the Elusive Healer Plant "*Luffa echinata* Roxb." Pharmacognosy Res. 2023;15(1):26-41.
3. Sharma RK, Dash B, Samhita C. Chowkhamba Sanskrit series office. Vol III45, 58, 447, 456; Vol IV; 2009;167-8.
4. Mukherjee GD, Dey CD. Clinical trial on Brahmi. I. J Exp Med Sci. 1966;10(1):5-11. PMID 5337552.
5. Chopra RN. Indigenous drugs of India. 2nd ed. Calcutta, India: united nations Dhur and Sons; 1958;341.
6. Nadkarni KM. The Indian materia medica. Columbia, MO: South Asia Books; 1988;624-5.
7. Kirtikar KR, Basu BD. Indian medicinal plants, Part II. Allahabad: Indian Press; 1918;930-1.
8. Anonymous, Agnivesa CS, Revised by Charaka and Drdhabala. Commentary by Sastri K, Chaturvedi G. Varanasi: Chaukhamba Bharati Academy; 2004;738.
9. Anonymous, Sushrutha SS, Nibandhasangraha W. Commentary of Dalhanacharya and Nyayachandrika Panjika of Gayadasacharya on Nidanasthana Acharya JT, Ram N, Acharya V, Prakashan CS, editors. 2012;824.
10. Vagbhata A, Sangraha A. Varanasi, Chaukhamba orientalia. 2nd ed Srikanthamurthy K, translator. 1999;2:627.
11. Keshava V. Siddhamantra. Commented by Prakasha. 1st ed Sharma PV, editor. Varanasi: Chaukhamba Amarabharathi Prakashan; 1977;113.
12. Rajanighantu NP. Written by Tripathi I. Edited with Dravyagunaprakasha Hindi commentary. rev ed. Varanasi: Chowkhambha Krishnadas Academy; 2010;703.
13. Kaiyadeva A, Nighantu K. Varanasi, Chaukhambha orientalia. PathyapathyaVibhodhaka, Edited by Prof. Sharma PV, Sharma GP. 1st ed. 1979;696.
14. Madanapala NR, Madanapala N Srikrishnadasa G, editor. 1961;296.
15. Kirtikar KR, Basu BD. Indian medicinal plants with illustrations, Revised by Blatter E. Caius JF, Mhaskar KS. 2nd ed. Oriental Enterprises. 2001;1724.
16. Ashalatha M, Shenoy LN. A critical review on Brahmi. International Ayurvedic. Med J. 2016;4(2):141-52.
17. Gohil KJ, Patel JJ. A review on *Bacopa monnieri*: current research and future prospects. Int J Green Pharm. 2010;4(1):1-9. doi: 10.4103/0973-8258.62156.
18. Samaddar T, Nath S, Halder M, Sil B, Roychowdhury D, Sen S, *et al*. Karyotype analysis of three important traditional Indian medicinal plants, *Bacopa monnieri, Tylophora indica* and *Withania somnifera*. Nucleus. 2012;55(1):17-20. doi: 10.1007/s13237-012-0048-2.
19. Vopadeva HHD. Commented by Prakasa. 1st ed Prof Sharma PV, editor. Varanasi: Chaukhamba Amarabharathi Prakashan; 1977;44.
20. Nadkarni KM. Indian materia medica. Mumbai: Popular Press Prakashan Pvt. Ltd., 2010:624-5.
21. Soundarara T, Karrunakar CM. Micropropagation of *Bacopa monnieri* through protoplast. Asian J Biotechnol. 2011;3(2):135-52. doi: 10.3923/ajbkr.2011.135.152.
22. Baruah A, Gogoi PK, Barua IC, Baruah D. Agronomic manipulation in Brahmi (*Bacopa monnieri*) cultivation for higher productivity in Assam plains. J Krishi Vigyan. 2014;2(2):11-3.
23. Saha PS, Sarkar S, Jeyasri R, Muthuramalingam P, Ramesh M, Jha S. *In vitro* propagation, phytochemical and neuropharmacological profiles of *Bacopa monnieri* (L.) Wettst.: a review. Plants (Basel). 2020;9(4):411. doi: 10.3390/plants9040411, PMID 32224997.
24. Roy A. A review on pharmaceutically important medicinal plant: *Bacopa monnieri*. J. Nat. Prod. Plant Resour. 2017;7(4):11-7.
25. Aparna V, V MS, P S, Kn SK. Comparative pharmacognosy of two medhyadravyas, Brahmi (*Bacopa monnieri* Linn.) and Mandukaparni (*Centella asiatica* Linn.). J Phytopharmacol. 2015;4(1):1-5. doi: 10.31254/phyto.2015.4101.
26. Jain PK, Das D, Jain P, Jain P. Pharmacognostic and pharmacological aspect of *Bacopa monnieri*: a review. Innov J Ayruvedic Sci. 2016;4(3):7-11.
27. Saesong T, Temkitthawon P, Nangngam P, Ingkaninan K. Pharmacognostic and physico-chemical investigations of the aerial part of *Bacopa monnieri* (L.) Wettst. Songklanakarin J Sci Technol. 2019;41(2):397-404.
28. Ashalatha M, Shenoy LN. Preliminary pharmacognostic study of Brahmi. International Ayurvedic. Med J. 2015;3(12):2465-9.
29. Kaarthik RA, Jeganath S, Priya EP, Azhagi RI, Suchithra AB. Pharmacological activity of Brahmi – a review. Drug Des Discov Research. 2020;1(1):4-11.

30. Charoenphon N, Anandsongvit N, Kosai P, Sirisidthi K, Kangwanrangsan N, Jiraungkoorskul W. Brahmi (*Bacopa monnieri*): up-to-date of memory boosting medicinal plant: a review. Indian J Agric Res. 2016;50(1):1-7.
31. Gubbannavar JS, Chandola HM, Harisha CR, Khanpara K, Shukla VJ. A comparative pharmacognostical and preliminary physico-chemical analysis of stem and leaf of *Bacopa monnieri* (L.) Pennel and *Bacopa floribunda* (R. BR.) Wettst. Ayu. 2013;34(1):95-102. doi: 10.4103/0974-8520.115441, PMID 24049413.
32. Gubbannavar JS, Harisha CR, Chandola HM. A comparative study of roots of *Bacopa monnieri* (L.) Pennel and *Bacopa floribunda* (R. Br.) wettst. Int J Pharmacogn Phytochem Res. 2012;4(1):8-11.
33. Manisha NT, Khemani A, Urmila DV, Charmi PS, Santani DD. Comparative pharmacognostic and phytochemical investigation of two plant species valued as Medhya Rasayanas. Int J Appl Biol Pharm Technol. 2011;2(3):28-36.
34. Datta SC, Mukerji B. Pharmacognosy of Indian leaf drugs. Bull No. 2. Calcutta: Ministry of Health, Government of India; 1952;62.
35. Nadakarni KM, Nadakarni AK. Indian materia medica. Bomaby Popul Prakashan. 1976;579.
36. Gupta MP, Solís PN, Calderón AI, Guionneau-Sinclair F, Correa M, Galdames C, *et al*. Medical ethnobotany of the tribes of Bocas del Toro, Panama. J Ethnopharmacol. 2005;96(3):389-401. doi: 10.1016/j.jep.2004.08.032, PMID 15619557.
37. Mota-Rojas D, Martinez-Burnes J, Alonso-Spilsbury ML, Lopez A, Ramirez-Necoechea R, Trujillo-Ortega ME, *et al*. Meconium staining of the skin and meconium aspiration in porcine intra partum still births. Livest Sci. 2006;102(1-2):155-62. doi: 10.1016/j.livsci.2006.01.002.
38. Shukla SD, Bhatnagar M, Khurana S. Critical evaluation of Ayurvedic plants for stimulating an intrinsic antioxidant response. Front Neurosci. 2012;6:112. doi: 10.3389/fnins.2012.00112, PMID 22855669.
39. Singh AG, Kumar A, Tewari DD. An ethnobotanical survey of medicinal plants used in Terai Forest of Western Nepal. J Ethnobiol Ethnomed. 2012;8:19. doi: 10.1186/1746-4269-8-19, PMID 22591592.
40. Rout SD, Panda SK. Ethnomedicinal plant resources of Mayurbhanj District, Orissa. Indian J Trad Knowl. 2010;9(1):68-72.
41. Onsa-ard A, Scholfield CN, Ingkaninan K, Srimachai S, Kamkaew N, Chootip K. Oral *Bacopa monnieri* is antihypertensive in rats chronically treated with L-NAME. J Physiol Biomed Sci. 2012;25(1):23-6.
42. Mukherjee A, Gombar V, Shamsi Y, Gupta M, Sinha S. Effectiveness of Brahmi in various illnesses: review paper. Herb Med. 2017;3(2):1-4. doi: 10.21767/2472-0151.100030.
43. Rae C, Scott RB, Lee M, Simpson JM, Hines N, Paul C, *et al*. Brain bioenergetics and cognitive ability. Dev Neurosci. 2003;25(5):324-31. doi: 10.1159/000073509, PMID 14614259.
44. Patil A, Vadera K, Patil D, Phatak A, Juvekar A, Chandra N. *In vitro* anticancer activity and phytochemical analysis of *Bacopa monnieri* (L.) Wettst. Int J Pharm Sci Res. 2014;5(10):4432-8.
45. Tripathi YB, Chaurasia S, Tripathi E, Upadhyay A, Dubey GP. *Bacopa monnieri* Linn. as an antioxidant: mechanism of action. Indian J Exp Biol. 1996;34(6):523-6. PMID 8792640.
46. Phrompittayarat W, Wittaya-Areekul S, Jetiyanon K, Putalun W, Tanaka H, Ingkaninan K. Stability studies of saponins in *Bacopa monnieri* dried ethanolic extracts. Planta Med. 2008;74(14):1756-63. doi: 10.1055/s-0028-1088311, PMID 18951336.
47. Mukti M, Rahmatullah M. Treatment with aquatic plants by a Bagdi tribal healer of Rajbari District, Bangladesh. Anc Sci Life. 2013;33(1):22-6. doi: 10.4103/0257-7941.134562, PMID 25161326.
48. Chatterjee TK, Chakraborty A, Pathak M, Sengupta GC. Effects of plant extract *Centella asiatica* (Linn.) on cold restraint stress ulcer in rats. Indian J Exp Biol. 1992;30(10):889-91. PMID 1293014.
49. Upasani SV, Beldar VG, Tatiya AU, Upasani MS, Surana SJ, Patil DS. Ethnomedicinal plants used for snakebite in India: a brief overview. Integr Med Res. 2017;6(2):114-30. doi: 10.1016/j.imr.2017.03.001, PMID 28664135.
50. Verma M. Ethnomedicinal and antimicrobial screening of *Bacopa monnieri* (L.) Pennell. J Phytol. 2014;6:1-6.
51. Sainuddin FV, Kakkara A, Vasundharan SK, Parambath SN, Rajan SC, Raghunathan J. Spatial mapping of ethno medicinal knowledge with specific reference to *Bacopa monnieri* (L.) Pennell in India. J Ayurveda Med Sci. 2017;2(3):219-24. doi: 10.5530/jams.2017.2.18.
52. Bhowmik D, Chiranjib TP, Tripathi KK, Kumar KPS. Traditional Indian memory enhancer herbs and their medicinal importance. Annals Biol Res. 2010;1(1):41-6.
53. Anonymous, Ayurveda Pharmacopoeia Committee. Brahmi (Whole plant). The Ayurveda pharmacopoeia of India, Part I. 1st ed. New Delhi, India: Department of Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy (AYUSH). Ministry of Health and Family Welfare, Government of India; 1999;2.
54. Anonymous, Unani Pharmacopoeia Committee, Brahmi J (Whole plant). The Unani pharmacopoeia of India, Part I. New Delhi, India: Department of Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy (AYUSH). Ministry of Health and Family Welfare, Government of India; 2007;4.
55. Anonymous, Siddha Pharmacopoeia Committee. PirammiValukkai (Whole plant). The Siddha pharmacopoeia of India, Part I. 1st ed. New Delhi, India: Department of Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy (AYUSH). Ministry of Health and Family Welfare, Government of India; 2008;1.
56. Engels G, Bacopa BJ. *Bacopa monnieri*. Herb Gram (The Journal of the American Botanical Council). 2011;91:1-4.
57. Pravina K, Ravindra KR, Goudar KS, Vinod DR, Joshua AJ, Wasim P, *et al*. Safety evaluation of BacoMind™ in healthy volunteers: a phase I study. Phytomedicine. 2007;14(5):301-8. doi: 10.1016/j.phymed.2007.03.010, PMID 17442556.
58. Mills S, Bone K. The essential guide to herbal safety. St. Louis: Elsevier/Churchill Livingstone; 2005.
59. 59. Anonymous. Rockville, MD: United States Pharmacopeial Convention. 34th revision, National Formulary. 29th ed (USP 34-NF 29), 2nd Supplement. In:. U S A Pharmacopeial Convention. Bacopa. United States Pharmacopeia; 2011;5327.
60. Singh RH, Narsimhamurthy K, Singh G. Neuronutrient impact of Ayurvedic Rasayana therapy in brain aging. Biogerontology. 2008;9(6):369-74. doi: 10.1007/s10522-008-9185-z, PMID 18931935.
61. Bhishagratna KKL. An English translation of the SUSHRUTA SAMHITA. Bharat Mihir Press; 1911;2:522-6.
62. Frawley D, Lad V. Yoga of herbs. Lotus press; 2001;239-41.
63. Pole S. Ayurvedic Medicine- The principles of traditional practice. Singing Dragon. 2013;149-50.
64. Kean JD, Downey LA, Stough C. A systematic review of the Ayurvedic medicinal herb *Bacopa monnieri* in child and adolescent populations. Complement Ther Med. 2016;29:56-62. doi: 10.1016/j.ctim.2016.09.002, PMID 27912958.
65. Russo A, Borrelli F. *Bacopa monnieri*, a reputed nootropic plant: an overview. Phytomedicine. 2005;12(4):305-17. doi: 10.1016/j.phymed.2003.12.008, PMID 15898709.
66. Sivananda S. Practice of Ayurveda. A divine life society: Rishikesh, India. 2006;121:205-7.
67. Nellore J, Pauline C, Amarnath K. *Bacopa monnieri* phytochemicals mediated synthesis of platinum nanoparticles and its neurorescue effect on 1-methyl 4-phenyl 1,2,3,6 tetrahydropyridine-induced experimental parkinsonism in zebrafish. J Neurodegener Dis. 2013;2013:972391. doi: 10.1155/2013/972391, PMID 26317003.
68. Krishnaraj C, Jagan EG, Ramachandran R, Abirami SM, Mohan N, Kalaichelvan PT. Effect of biologically synthesized silver nanoparticles on *Bacopa monnieri* (Linn.) Wettst. plant growth metabolism. Process Biochem. 2012;47(4):651-8. doi: 10.1016/j.procbio.2012.01.006.
69. Suganya M, Kavitha S, Mythili Gnanamangai BM, Ponmurugan P. Phytofabrication of silver nanoparticles using *Bacopa monnieri* leaf extract and its antibacterial activity as well as oxidative stress-induced apoptosis of lung cancer. IET Nanobiotechnol. 2018;12(3):318-24. doi: 10.1049/iet-nbt.2017.0146.
70. Kumar R, Garg R. Formulation and evaluation of solid lipid nanoparticles loaded with bacoside rich extract. Int J Pharm Sci Res. 2020;11(1):371-7.
71. Kalsaitkar P, Tanna J, Kumbhare A, Akre S, Warade C, Gandhare N. Silver nanoparticles induced effect on *in vitro* callus production in *Bacopa monnieri*. Asian J Biol Life Sci. 2014;3(3):167-72.
72. Mahitha B, Raju BDP, Dillip GR, Reddy CM, Mallikarjuna K, Manoj L, *et al*. Biosynthesis, characterization and antimicrobial studies of AgNPs extract from *Bacopa monnieri* whole plant. Dig J Nanomater Biostructures. 2011;6(1):135-42.
73. Babu PJ, Sharma P, Saranya S, Bora U. Synthesis of gold nanoparticles using ethonolic leaf extract of *Bacopa monnieri* and UV irradiation. Mater Lett. 2013;93(15):431-4. doi: 10.1016/j.matlet.2012.11.034.
74. Vitthal KU, Pillai MM, Kininge P. Study of solid lipid nanoparticles as a carrier for bacoside. Int J Pharm Biol Sci. 2013;3(3):414-26.
75. Badrelden AM, Elmaksoud AIA, El-Maaty REA, Hassan A, Mohamed AAB, Elebeedy D. Green synthesis of silver nanoparticles mediated extract of various *in vitro* plants (*Bacopa monnieri, Coleus blumei, Cichorium intybus*). J Bio Sci Research. 2018;15(1):01-11.
76. Khan NS, Dixit AK, Mehta R. Verdure synthesis of AgNPs from *Bacopa monnieri* L., and its antibacterial efficacy. World J Pharm Pharm Sci. 2015;4(9):1122-32.
77. Mahitha B, Deva Prasad Raju B, Mallikarjuna K, Durga Mahalakshmi ChN, Sushmal NJ. *Bacopa monnieri* stabilized silver nanoparticles attenuates oxidative stress induced by aluminum in albino mice. J Nanosci Nanotechnol. 2015;15(2):1101-9. doi: 10.1166/jnn.2015.8995, PMID 26353618.
78. Krikorian AD, Berquam DL. Plant cell and tissue cultures: the role of Haberlandt. Bot Rev. 1969;35(1):59-67. doi: 10.1007/BF02859888.
79. Koul A, Mallubhotla S. Elicitation and enhancement of bacoside production using suspension cultures of *Bacopa monnieri* (L.) Wettst. biotech. 2020;10(6):1-4.
80. Chauhan R, Shirkot P. Micropropagation of endangered medicinal plant *Bacopa monnieri* (L.) Pennell. J Pharmacogn Phytochem. 2020;9(2):1614-20.
81. Jain N, Sharma V, Ramawat KG. Shoot culture of *Bacopa monnieri*: standardization of explant, vessels and bioreactor for growth and antioxidant capacity. Physiol Mol Biol Plants. 2012;18(2):185-90. doi: 10.1007/s12298-012-0103-0, PMID 23573056.
82. Haque SM, Chakraborty A, Dey D, Mukherjee S, Nayak S, Ghosh B. Improved micropropagation of *Bacopa monnieri* (L.) Wettst. (Plantaginaceae) and antimicrobial activity of *in vitro* and *ex-vitro* raised plants against multidrug-resistant clinical isolates of Urinary Tract Infecting (UTI) and Respiratory Tract Infecting (RTI) bacteria. Clin Phytosci. 2017;3:1-10.
83. Praveen N, Naik PM, Manohar SH, Nayeem A, Murthy HN. *In vitro* regeneration of Brahmi shoots using semisolid and liquid cultures and quantitative analysis of bacoside A. Acta Physiol Plant. 2009;31(4):723-8. doi: 10.1007/s11738-009-0284-5.

84. Joshi AG, Pathak AR, Sharma AM, Singh S. High frequency of shoot regeneration on leaf explants of *Bacopa monnieri*. Environ Experiment Biol. 2010;8:81-4.
85. Vijayakumar M, Vijayakumar R, Stephen R. *In vitro* propagation of *Bacopa monnieri* L. A multipurpose medicinal plant. Indian J Sci Technol. 2010;3(7):781-6. doi: 10.17485/ijst/2010/v3i7.17.
86. Banerjee M, Modi P. Micropropagation of *Bacopa monnieri* using cyanobacterial liquid medium. Plant Tissue Cult Biotechnol. 2010;20(2):225-31. doi: 10.3329/ptcb.v20i2.6917.
87. Tiwari V, Deo Singh B, Nath Tiwari K. Shoot regeneration and somatic embryogenesis from different explants of Brahmi [*Bacopa monnieri* (L.) Wettst.]. Plant Cell Rep. 1998;17(6-7):538-43. doi: 10.1007/s002990050438, PMID 30736632.
88. Ramseh M, Marx R, Mathan G, Pandian SK. Effect of bavistin on *in vitro* plant conversion from encapsulated unimodal microcuttings of micropropagated *Bacopa monnieri* (L.) – an ayurvedic herb. J Environ Biol. 2007;30(3):441-4.
89. Behera S, Nayak N, Shasmita BDP, Naik SK. An efficient micropropagation protocol of *Bacopa monnieri* (L.) Pennell through two-stage culture of nodal segments and *ex vitro* acclimatization. J Appl Biol Biotechnol. 2015;3(3):16-21.
90. Binita BC, Ashok MD, Yogesh TJ. *Bacopa monnieri* (L.) Pennell: A rapid, efficient and cost effective micropropagation. Plant Tissue Cult Biotechnol. 2005;15(2):167-75.
91. Torrey JG. Auxin control of vascular pattern formation in regenerating pea root meristems grown *in vitro*. Am J Bot. 1957;44(10):859-70. doi: 10.1002/j.1537-2197.1957.tb08272.x.
92. Torrey JG. Endogenous and exogenous influences on the regulation of lateral root formation. In: Jackson MB, editor. New root formation in plants and cuttings. Dordrecht: Martinus-Nijhoff; 1986;31-66.
93. Singh S, Ray BK, Mathew S, Buragohain P, Gogoi J, Gogoi S, *et al*. Micropropagation of a few important medicinal plants. Ann Biol. 1999;15(1):1-7.
94. Tiwari V, Tiwari KN, Singh BD. Comparative studies of cytokinins on *in vitro* propagation of *Bacopa monnieri*. Plant Cell Tissue Organ Cult. 2001;66(1):9-16. doi: 10.1023/A:1010652006417.
95. Sharma S, Kamal B, Rathi N, Chauhan S, Jadon V, Vats N, *et al. In vitro* rapid and mass multiplication of highly valuable medicinal plant *Bacopa monnieri* (L.) Wettst. Afr J Biotechnol. 2010;9(49):8318-22.
96. Tiwari V, Tiwari KN, Singh BD. Suitability of liquid culture for *in vitro* multiplication of *Bacopa monnieri* (L.) Wettst. Phytomorphology. 2000;50(3/4):337-42.
97. Shrivastava N, Rajani M. Multiple shoot regeneration and tissue culture studies on *Bacopa monnieri* (L.) Pennell. Plant Cell Rep. 1999;18(11):919-23. doi: 10.1007/s002990050684.
98. Tiwari V, Tiwari KN, Singh BD. Shoot bud regeneration from different explant of *Bacopa monnieri* (L.) Wettst. by trimethoprim and bavistin. Plant Cell Rep. 2007;25(7):629-35.
99. Evans DA, Sharp WR, Ammirato PV, Yamada. Handbook of plant cell culture. Techniques for propagation and breeding. New York, London: Macmillan Publishing Co.. 1986;1.
100. Gurnani C, Kumar V, Mukhija S, Dhingra A, Rajpurohit S, Narula P. *In vitro* regeneration of Brahmi (*Bacopa Monneiri* (L.) Penn.) – A threatened medicinal plant. Kathmandu Univ J Sci Eng Technol. 2012;8(1):97-9. doi: 10.3126/kuset.v8i1.6048.
101. Mohapatra HP, Rath SP. *In vitro* studies of *Bacopa monnieri* – an important medicinal plant with reference to its biochemical variations. Indian J Exp Biol. 2005;43(4):373-6. PMID 15875724.
102. Tejavathi DH, Sowmya R, Shailaja KS. Micropropagation of *Bacopa monnieri* using shoot tip and nodal explant. J Trop Medi Plants. 2001;2(1):39-45.
103. Sharma N, Satsangi R, Pandey R, Devi S, Vimala S. *In vitro* clonal propagation and medium-term conservation of Brahmi (*Bacopa monnieri*). J Plant Biochem Biotechnol. 2007;16(2):139-43.
104. Sharma P, Yadav S, Srivastava A, Shrivastava N. Methyl jasmonate mediates upregulation of bacoside A production in shoot cultures of *Bacopa monnieri*. Biotechnol Lett. 2013;35(7):1121-5. doi: 10.1007/s10529-013-1178-6, PMID 23504481.
105. Jat BL, Panwar R, Gena D, Bhat TS, Rawat RS. *In vitro* production of bacosides in tissue cultures of *Bacopa monnieri*. World J Pharm Res. 2016;5(7):1087-107.
106. Naik PM, Patil BR, Jaggal LG, Jangid VK. The effect of subculture on the Bacoside A content in adventitious shoot cultures of *Bacopa monnieri* (L.). Res J Pharm Biol Chem Sci. 2013;4(4):1111-6.
107. Łojewski M, Krakowska A, Reczyński WR, Szewczyk A, Muszyńska B. Analysis of elements and bacosides in *in vitro* shoot culture of *Bacopa monnieri*. Acta Physiol Plant. 2016;38(7):1-10. doi: 10.1007/s11738-016-2182-y.
108. Monica J, Ritika R, Anamika M. Enhancement of secondary metabolite biosynthesis in *Bacopa monnieri*: an *in-vitro* study. Res J Recent Sci. 2013;2(1):13-6.
109. Muszyńska B, Łojewski M, Sułkowska-Ziaja K, Szewczyk A, Gdula-Argasińska J, Hałaszuk P. *In vitro* cultures of *Bacopa monnieri* and an analysis of selected groups of biologically active metabolites in their biomass. Pharm Biol. 2016;54(11):2443-53. doi: 10.3109/13880209.2016.1158843, PMID 27046025.
110. Chaturvedi PA, Hingorani L. Media standardization for enhanced production of bacoside of *Bacopa monnieri In situ* Condition. Pharmacogn Mag. 2018;14(55)(55-Supplement 1):S32-5. doi: 10.4103/pm.pm_328_17.
111. Majumdar S, Garai S, Jha S. Use of the cryptogein gene to stimulate the accumulation of bacopa saponins in transgenic *Bacopa monnieri* plants. Plant Cell Rep. 2012;31(10):1899-909. doi: 10.1007/s00299-012-1303-3, PMID 22733208.
112. Watcharatanon K, Ingkaninan K, Putalun W. Improved triterpenoid saponin glycosides accumulation in *in vitro* culture of *Bacopa monnieri* (L.) Wettst. with precursor feeding and LED light exposure. Ind Crops Prod. 2019;134(8):303-8. doi: 10.1016/j.indcrop.2019.04.011.
113. Kamonwannasit S, Phrompittayarat W, Ingkaninan K, Tanaka H, Putalun W. Improvement of pseudojujubogenin glycosides production from regenerated *Bacopa monnieri* (L.) Wettest. Z Naturforsch C J Biosci. 2008;63(11-12):879-83. doi: 10.1515/znc-2008-11-1216, PMID 19227838.
114. 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. Scientific World Journal. 2014. doi: 10.1155/2014/824586, PMID 24672380.
115. Sharma M, Ahuja A, Gupta R, Mallubhotla S. Enhanced bacoside production in shoot cultures of *Bacopa monnieri* under the influence of abiotic elicitors. Nat Prod Res. 2015;29(8):745-9. doi: 10.1080/14786419.2014.986657, PMID 25485652.
116. Largia MJV, Pothiraj G, Shilpha J, Ramesh M. Methyl jasmonate and salicylic acid synergism enhances bacoside A content in shoot cultures of *Bacopa monnieri* (L.). Plant Cell Tiss Organ Cult. 2015;122(1):9-20. doi: 10.1007/s11240-015-0745-z.
117. Vishwakarma RK, Kumari U, Khan BM. Memory booster plant *Bacopa monnieri* (Brahmi): biotechnology and molecular aspects of bacoside biosynthesis. In: Tsay HS, Shyur LF, Agrawal D, Wu YC, Wang SY, editors. Medicinal plants – recent advances in Research and Development. Singapore: Springer; 2016;167-89.
118. Basu N, Rastogi PR, Dhar ML. Chemical examination of *Bacopa monnieri* Wettst. Part III: the constitution of Bacoside-B. Indian J Chem. 1967;5:84-6.
119. Bolton EE, Wang Y, Thiessen PA, Bryant SH. Chapter 12. PubChem: integrated platform of small molecules and biological activities. In: Annual reports in computational chemistry. 2008;4:217-41.
120. Jeyasri R, Muthuramalingam P, Suba V, Ramesh M, Chen JT. *Bacopa monnieri* and their bioactive compounds inferred multi-target treatment strategy for neurological diseases: a cheminformatics and system pharmacology approach. Biomolecules. 2020;10(4):1-19. doi: 10.3390/biom10040536, PMID 32252235.
121. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, *et al*. PubChem 2019 update: improved access to chemical data. Nucleic Acids Res. 2019;47(D1):D1102-9. doi: 10.1093/nar/gky1033, PMID 30371825.
122. 122. Chapter RM 9. *Bacopa monnieri*, a nootropic Drug. In: Ramawat KG, Mérillon J-M, editors. Bioactive molecules and medicinal plants. Berlin, Heidelberg, New York: Springer-Verlag; 2008;175-95.
123. Kulshreshtha DK, Rastogi RP. Bacogenin-A1: A novel dammarane triterpene sapogenin from *Bacopa monnieri*. Phytochemistry. 1973;12(4):887-92. doi: 10.1016/0031-9422(73)80697-1.
124. Jain P, Kulshreshtha DK. Bacoside A1, A minor saponin from *Bacopa monnieri*. Phytochemistry. 1993;33(2):449-51. doi: 10.1016/0031-9422(93)85537-2.
125. Rastogi S, Pal R, Kulshreshtha DK. Bacoside A3-a triterpenoid saponin from *Bacopa monnieri*. Phytochemistry. 1994;36(1):133-7. doi: 10.1016/s0031-9422(00)97026-2, PMID 7764837.
126. Garai S, Mahato SB, Ohtani K, Yamasaki K. Bacopasaponin D-a pseudojujubogenin glycoside from *Bacopa monnieri*. Phytochemistry. 1996;43(2):447-9. doi: 10.1016/0031-9422(96)00250-6, PMID 8862037.
127. Garai S, Mahato SB, Ohtani K, Yamasaki K. Dammarane-type triterpenoid saponins from *Bacopa monnieri*. Phytochemistry. 1996;42(3):815-20. doi: 10.1016/0031-9422(95)00936-1, PMID 8768327.
128. Hou CC, Lin SJ, Cheng JT, Hsu FL. Bacopaside III, bacopasaponin G and bacopasides A, B and C from *Bacopa monniera*. J Nat Prod. 2002;65(12):1759-63. doi: 10.1021/np020238w, PMID 12502309.
129. Mahato SB, Garai S, Chakravarty AK. Bacopasaponins E and F: two jujubogenin bisdesmosides from *Bacopa monnieri*. Phytochemistry. 2000;53(6):711-4. doi: 10.1016/s0031-9422(99)00384-2, PMID 10746885.
130. Chakravarty AK, Sarkar T, Masuda K, Shiojima K, Nakane T, Kawahara N. Bacopaside I and II: two pseudojujubogenin glycosides from *Bacopa monnieri*. Phytochemistry. 2001;58(4):553-6. doi: 10.1016/s0031-9422(01)00275-8, PMID 11576596.
131. Chakravarty AK, Sarkar T, Nakane T, Kawahara N, Masuda K. New phenylethanoid glycosides from *Bacopa monnieri*. Chem Pharm Bull (Tokyo). 2002;50(12):1616-8. doi: 10.1248/cpb.50.1616, PMID 12499603.
132. Chakravarty AK, Garai S, Masuda K, Nakane T, Kawahara N. Bacopasides III-V: three new triterpenoid glycosides from *Bacopa monnieri*. Chem Pharm Bull (Tokyo). 2003;51(2):215-7. doi: 10.1248/cpb.51.215, PMID 12576661.
133. Pushkar G, Pushkar B, Sivabalan R. A review on major bioactivities of *Bacopa monnieri*. Annals Appl Bio-Sci. 2014;2(2):R1-11.
134. Bhandari P, Kumar N, Singh B, Kaul VK. Bacosterol glycoside, a new 13,14-seco-steroid glycoside from *Bacopa monnieri*. Chem Pharm Bull (Tokyo). 2006;54(2):240-1. doi: 10.1248/cpb.54.240, PMID 16462073.
135. Zhou Y, Shen YH, Zhang C, Su J, Liu RH, Zhang WD. Triterpene saponins from *Bacopa monnieri* and their antidepressant effects in two mice models. J Nat Prod. 2007;70(4):652-5. doi: 10.1021/np060470s, PMID 17343408.
136. Parveen R, Shamsi TN, Kumar H, Fatima S. Phytochemical analysis and *in vitro* biological characterization of aqueous and methanolic extract of *Bacopa monnieri*. Int J Pharm Pharm Sci. 2016;8(12):90-6. doi: 10.22159/ijpps.2016v8i12.14739.
137. Deepak M, Sangli GK, Arun PC, Amit A. Quantitative determination of the major saponin mixture Bacoside A in *Bacopa monnieri* by HPLC. Phytochem Anal. 2005;16(1):24-9. doi: 10.1002/pca.805, PMID 15688952.

138. Singh HK, Dhawan BN. Effect of *Bacopa monnieri* linn. J Ethnopharmacol. 1982;5(2):205-14. doi: 10.1016/0378-8741(82)90044-7, PMID 7057659.
139. Tripathi S, Sharma P. Characterization of brassinosteroid isolated from *Bacopa monnieri* L. and their free radical scavenging activity. Int J Sci Res. 2013;4(4):2738-42.
140. Abbas G, Al Harrasi AA, Hussain H, Hamaed A, Supuran CT. The management of diabetes mellitus-imperative role of natural products against dipeptidyl peptidase-4, α-glucosidase and sodium-dependent glucose co-transporter 2 (SGLT2). Bioorg Chem. 2019;86:305-15. doi: 10.1016/j.bioorg.2019.02.009, PMID 30738330.
141. Ahirrao RA, Kadambande DS, Chavan GM. Herbal drugs used in treatment of cancer. Int J Pharm Chem Res. 2017;3(2):182-9.
142. Udgire M, Pathade GR. Preliminary phytochemical and antifungal screening of crude extracts of the *Bacpoa monnieri*. Univers J Environ Res Technol. 2012;2(4):347-54.
143. Jain P, Sharma HP, Basri F, Priya K, Singh P. Phytochemical analysis of *Bacopa monnieri* (L.) Wettst. and their antifungal activities. Indian J Trad Knowl. 2017;16(2):310-8.
144. Srikanth Lavu RV, Prasad MN, Pratti VL, Meißner R, Rinklebe J, Van De Wiele T, *et al*. Trace metals accumulation in *Bacopa monnieri* and their bioaccessibility. Planta Med. 2013;79(12):1081-3. doi: 10.1055/s-0032-1328713, PMID 23824547.
145. Kumar A, Garg AN, Reddy AVR. Availability of essential trace elements in the extract of *Bacopa moneiri* (Brahmi) leaves. Board of research in nuclear sciences. Mumbai, India: Department of Atomic Energy; 2007;435-6.
146. Kulhari A, Sheorayan A, Bajar S, Sarkar S, Chaudhury A, Kalia RK. Investigation of heavy metals in frequently utilized medicinal plants collected from environmentally diverse locations of north western India. SpringerPlus. 2013;2:676. doi: 10.1186/2193-1801-2-676, PMID 24386622.
147. Garg AN, Kumar A, Nair AGC, Reddy AVR. Elemental analysis of Brahmi (*Bacopa monnieri*) extracts by neutron activation and its bioassay for antioxidant, radio protective and anti-lipid peroxidation activity. J Radioanal Nucl Chem. 2009;281(1):53-8. doi: 10.1007/s10967-009-0081-z.
148. Mishra A, Mishra AK, Tiwari OP, Jha S. Studies on metals and pesticide content in some Ayurvedic formulations containing *Bacopa monnieri* L. J Integr Med. 2016;14(1):44-50. doi: 10.1016/S2095-4964(16)60241-8, PMID 26778228.
149. Kalpana P, Balasubramanian K, Kalaivani RA. Evaluation of heavy metals in selected medicinal plants and their corresponding soils collected from environmentally diverse locations of India. Res J Pharm Technol. 2018;11(8):3489-93. doi: 10.5958/0974-360X.2018.00645.5.
150. Gogoi. P, Kalita JC. Mineral content of some edible medicinally important leafy vegetables of kamrup district of Assam, India. Int J Pharm Pharm Sci. 2014;6(9):404-6.
151. Volluri SS, Bammidi SR, Chippada SC, Vangalapati M. *In vitro* antioxidant activity and estimation of total phenolic content in methanolic extract of *Bacopa monnieri*. Rasāyan J Chem. 2011;4(2):381-6.
152. Ghosh T, Maity TK, Das M, Bose A, Dash DK. *In vitro* antioxidant and hepatoprotective activity of ethanolic extract of *Bacopa monnieri* Linn. Aerial parts. Iran J Pharmacol Ther. 2007;6(1):77-85.
153. Russo A, Izzo AA, Borrelli F, Renis M, Vanella A. Free radical scavenging capacity and protective effect of *Bacopa monnieri* L. on DNA damage. Phytother Res. 2003;17(8):870-5. doi: 10.1002/ptr.1061, PMID 13680815.
154. Shinomol GK, Bharath MMS, 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(2):102-14. doi: 10.1007/s12640-011-9303-6, PMID 22203611.
155. Shinomol GK, Muralidhara. *Bacopa monnieri* modulates endogenous cytoplasmic and mitochondrial oxidative markers in prepubertal mice brain. Phytomedicine. 2011;18(4):317-26. doi: 10.1016/j.phymed.2010.08.005, PMID 20850955.
156. Kapoor R, Srivastava S, Kakkar P. *Bacopa monnieri* modulates antioxidant responses in brain and kidney of diabetic rats. Environ Toxicol Pharmacol. 2009;27(1):62-9. doi: 10.1016/j.etap.2008.08.007, PMID 21783922.
157. Dhanasekaran M, Tharakan B, Holcomb LA, Hitt AR, Young KA, Manyam BV. Neuroprotective mechanisms of ayurvedic antidementia botanical *Bacopa monnieri*. Phytother Res. 2007;21(10):965-9. doi: 10.1002/ptr.2195, PMID 17604373.
158. Limpeanchob N, Jaipan S, Rattanakaruna S, Phrompittayarat W, Ingkaninan K. Neuroprotective effect of *Bacopa monnieri* on beta-amyloid-induced cell death in primary cortical culture. J Ethnopharmacol. 2008;120(1):112-7. doi: 10.1016/j.jep.2008.07.039, PMID 18755259.
159. Mathur A, Verma SK, Purohit R, Singh SK, Mathur D, Prasad GBKS, *et al*. Pharmacological investigation of *Bacopa monnieri* on the basis of antioxidant, antimicrobial and anti-inflammatory properties. J Chem Pharm Res. 2010;2(6):191-8.
160. Meena H, Pandey HK, Pandey P, Arya MC, Ahmed Z. Evaluation of antioxidant activity of two important memory enhancing medicinal plants *Baccopa monnieri* and *Centella asiatica*. Indian J Pharmacol. 2012;44(1):114-7. doi: 10.4103/0253-7613.91880, PMID 22345883.
161. Singh HK, Dharwan BN. Neuropsychopharmacological effects of the Ayurvedic nootropic *Bacopa monnieri* Linn (Brahmi). Indian J Pharmacol. 1997;29:S359-65.
162. Kishore K, Singh M. Effect of bacosides, alcoholic extract of *Bacopa monnieri* Linn. Indian J Exp Biol. 2005;43(7):640-5. PMID 16053272.
163. Ryan J, Croft K, Mori T, Wesnes K, Spong J, Downey L, *et al*. An examination of the effects of the antioxidant Pycnogenol® on cognitive performance, serum lipid profile, endocrinological and oxidative stress biomarkers in an elderly population. J Psychopharmacol. 2008;22(5):553-62. doi: 10.1177/0269881108091584, PMID 18701642.
164. Saraf MK, Prabhakar S, Pandhi P, Anand A. *Bacopa monnieri* ameliorates amnesic effects of diazepam qualifying behavioural-molecula partitioning. Neuroscience. 2008;155(2):476-84. doi: 10.1016/j.neuroscience.2008.05.043, PMID 18585439.
165. Vohora D, Pal SN, Pillai KK. Protection from phenytoin-induced cognitive deficit by *Bacopa monnieri*, a reputed Indian nootropic plant. J Ethnopharmacol. 2000;71(3):383-90. doi: 10.1016/s0378-8741(99)00213-5, PMID 10940574.
166. Vollala VR, Upadhya S, Nayak S. Learning and memory enhancing the effect of *Bacopa monnieri* in the neonatal rat. Bratisl Lek Listy. 2011;112(12):663-9. PMID 22372329.
167. Promsuban C, Limsuvan S, Akarasereenont P, Tilokskulchai K, Tapechum S, Pakaprot N. *Bacopa monnieri* extract enhances learning-dependent hippocampal long-term synaptic potentiation. NeuroReport. 2017;28(16):1031-5. doi: 10.1097/WNR.0000000000000862, PMID 28885486.
168. Ong BAG, Villanueva MCN, Medina PMB. *Bacopa monnieri* supplementation increases learning and short-term memory retention of sleep-deprived *Drosophila melanogaster*. J Appl Pharm Sci. 2020;10(12):104-10.
169. Pham HTN, Tran HN, Nguyen PT, Le XT, Nguyen KM, Phan SV, *et al. Bacopa monnieri* (L.) Wettst. extract improves memory performance via promotion of neurogenesis in the hippocampal dentate gyrus of adolescent mice. Int J Mol Sci. 2020;21(9):3365. doi: 10.3390/ijms21093365, PMID 32397562.
170. Rai R, Singh HK, Prasad S. A special extract of *Bacopa monnieri* (CDRI-08) restores learning and memory by upregulating expression of the NMDA receptor subunit GluN2B in the brain of scopolamine-induced amnesic mice. Evid Based Complement Alternat Med. 2015;2015:254303. doi: 10.1155/2015/254303, PMID 26413117.
171. Pandey SP, Singh HK, Prasad S. Alterations in hippocampal oxidative stress, expression of AMPA Receptor GluR2 subunit and associated spatial memory loss by *Bacopa monnieri* extract (CDRI-08) in streptozotocin-induced diabetes mellitus type 2 mice. PLOS ONE. 2015;10(7):e0131862. doi: 10.1371/journal.pone.0131862, PMID 26161865.
172. Prabhakar S, Saraf MK, Banik A, Anand A. *Bacopa monnieri* selectively attenuates suppressed superoxide dismutase activity in diazepam induced amnesic mice. Ann Neurosci. 2011;18(1):8-13. doi: 10.5214/ans.0972.7531.1118104, PMID 25205911.
173. Prabhakar S, Saraf MK, Pandhi P, Anand A. *Bacopa monnieri* exerts antiamnesic effect on diazepam-induced anterograde amnesia in mice. Psychopharmacology. 2008;200(1):27-37. doi: 10.1007/s00213-007-1049-8, PMID 18193203.
174. Le XT, Pham HTN, 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(10):2201-15. doi: 10.1007/s11064-013-1129-6, PMID 23949198.
175. Habbu P, Madagundi S, Kulkarni R, Jadav S, Vanakudri R, Kulkarni V. Preparation and evaluation of Bacopa-phospholipid complex for antiamnesic activity in rodents. Drug Invent Today. 2013;5(1):13-21. doi: 10.1016/j.dit.2013.02.004.
176. Rajan KE, Preethi J, Singh HK. Molecular and functional characterization of *Bacopa monnieri*: A retrospective review. Evid Based Complement Alternat Med. 2015;945217.
177. Piyabhan P, Tingpej P, Duansak N. Effect of pre- and post-treatment with *Bacopa monnieri* (Brahmi) on phencyclidine-induced disruptions in object recognition memory and cerebral calbindin, parvalbumin, and calretinin immunoreactivity in rats. Neuropsychiatr Dis Treat. 2019;15:1103-17. doi: 10.2147/NDT.S193222, PMID 31118643.
178. Bhardwaj P, Jain CK, Mathur A. Comparative evaluation of four triterpenoid glycoside saponins of bacoside A in alleviating sub-cellular oxidative stress of N2a neuroblastoma cells. J Pharm Pharmacol. 2018;70(11):1531-40. doi: 10.1111/jphp.12993, PMID 30073654.
179. Singh HK, Rastogi RP, Srimal RC, Dhawan BN. Effect of bacosides A and B on avoidance responses in rats. Phytother Res. 1988;2(2):70-5. doi: 10.1002/ptr.2650020205.
180. Ramasamy S, Chin SP, Sukumaran SD, Buckle MJC, Kiew LV, Chung LY. *In silico* and *in vitro* analysis of Bacoside A aglycones and its derivatives as the constituents responsible for the cognitive effects of *Bacopa monnieri*. PLOS ONE. 2015;10(5):e0126565. doi: 10.1371/journal.pone.0126565, PMID 25965066.
181. Pham HTN, Phan SV, Tran HN, Phi XT, Le XT, Nguyen KM, *et al. Bacopa monnieri* (L.) ameliorates cognitive deficits caused in a trimethyltin-induced neurotoxicity model mice. Biol Pharm Bull. 2019;42(8):1384-93. doi: 10.1248/bpb.b19-00288, PMID 31366873.
182. Bhattacharya SK, Bhattacharya A, Kumar A, Ghosal S. Antioxidant activity of *Bacopa monnieri* rat frontal cortex, striatum and hippocampus. Phytother Res. 2000;14(3):174-9. doi: 10.1002/(sici)1099-1573(200005)14:3<174::aid-ptr624>3.0.co;2-o, PMID 10815010.
183. Shen YH, Zhou Y, Zhang C, Liu RH, Su J, Liu XH, *et al*. Antidepressant effects of methanol extract and fractions of *Bacopa monnieri*. Pharm Biol. 2009;47(4):340-3. doi: 10.1080/13880200902752694.
184. Kadali SR, M C D, Rao A S R S, Sri G KAntidepressant activity of brahmi in albino mice. J Clin Diagn Res. 2014;8(3):35-7. doi: 10.7860/JCDR/2014/7482.4098, PMID 24783074.
185. Sairam K, Dorababu M, Goel RK, Bhattacharya SK. Antidepressant activity of standardized extract of *Bacopa monnieri* in experimental models of depression in rats. Phytomedicine. 2002;9(3):207-11. doi: 10.1078/0944-7113-00116, PMID 12046860.
186. Singh HK, Srimal RC, Srivastava AK, Garg NK, Dhawan BN. Proceedings of the fourth conference on ther neurobiology of learning and memory, CA. 1990;79.

187. Hazra S, Banerjee R, Das BK, Ghosh AK, Banerjee TK, Hazra US, *et al*. Evaluation of antidepressant activity of *Bacopa monnieri* in rat: a study in animal model of depression. Drug Discov. 2012;2:8-13.
188. Shader RI, Greenblatt DJ. Pharmacotherapy of acute anxiety. In: Bloom FE, Kupfer DJ, editors. Psycopharmacolo-gy: fourth generation of progress. New York: Raven Press; 1995;1341-8.
189. Wasnik U, Singh V, Ali M. Evaluation of the antidepressant effects of *Bacopa monieri* in mice. Int J Pharm Sci Res. 2015;6(2):890-4.
190. Mannan MA, Abir AB, Rahman MR. Antidepressant-like effects of methanolic extract of *Bacopa monnieri* in mice. Complement Altern. Med. 2015;15:337.
191. Girish C, Oommen S, Vishnu R. Evidence for the involvement of the monoaminergic system in the antidepressant-like activity of methanolic extract of *Bacopa monnieri* in albino mice. Int J Basic Clin Pharmacol. 2016;5(3):914-22. doi: 10.18203/2319-2003.ijbcp20161545.
192. Ganguly DK, Malhotra CL. Some behavioural effects of an active fraction from *Herpestis monniera*, Linn. (Brahmi). Indian J Med Res. 1967;55(5):473-82. PMID 6065425.
193. Reas SK, Amee K, Paulose CS. Decreased glutamate receptor gene expression and binding studies in pilocarpine induced epileptic rat: neuroprotective role of *Bacopa monnieri* extract. Epilep Behav. 2008;12(4):54-60.
194. Kaushik D, Tripathi A, Tripathi R, Ganachari M, Khan SA. Anticonvulsant activity of *Bacopa monnieri* in rodents. Braz J Pharm Sci. 2009;45(4):643-9. doi: 10.1590/S1984-82502009000400006.
195. Kasthuri S, Karthigadevi K, Manjulakshmi P, Kavimani S. Medicinal plants with anticonvulsant activity – a review. Int J Pharm Biol Sci. 2013;2(3):285-97.
196. Giramkar SA, Kulkarni OP, Jagtap SD, Kuvalekar AA, Mukherjee S, Jagtap RR, *et al*. Anticonvulsant potential of commonly practiced formulations of Brahmi (*Bacopa monnieri* Linn.) in Wistar rats. J Pharm Res. 2013;7(9):787-91.
197. Wasnik U, Singh V, Ali M. Evaluation of anticonvulsant activity on leaves of alcoholic extract of *Bacopa monnieri* Linn. Int J Pharm Sci Rev Res. 2012;17(2):1-5.
198. Chowdhuri DK, Parmar D, Kakkar P, Shukla R, Seth PK, Srimal RC. Antistress effects of bacosides of *Bacopa monnieri*: modulation of Hsp70 expression, superoxide dismutase and cytochrome P450 activity in rat brain. Phytother Res. 2002;16(7):639-45. doi: 10.1002/ptr.1023, PMID 12410544.
199. Rai D, Bhatia G, Palit G, Pal R, Singh S, Singh HK. Adaptogenic effect of *Bacopa monnieri* (Brahmi). Pharmacol Biochem Behav. 2003;75(4):823-30. doi: 10.1016/s0091-3057(03)00156-4, PMID 12957224.
200. Bhattacharya SK, Ghosal S. Anxiolytic activity of a standardized extract of *Bacopa monnieri*: an experimental study. Phytomedicine. 1998;5(2):77-82. doi: 10.1016/S0944-7113(98)80001-9, PMID 23195757.
201. Sheikh N, Ahmad A, Siripurapu KB, Kuchibhotla VK, Singh S, Palit G. Effect of *Bacopa monnieri* on stress induced changes in plasma corticosterone and brain monoamines in rats. J Ethnopharmacol. 2007;111(3):671-6. doi: 10.1016/j.jep.2007.01.025, PMID 17321089.
202. Agrawal A. A comparative study of psychotropic drugs and bio-feedback therapy in the prevention and management of psychosomatic disorder [thesis] Varanasi: Banaras Hindu University; 1993.
203. Bhattacharya SK, Kumar A, Ghosal S. Effect of *Bacopa monnieri* on animal models of Alzheimer's disease and perturbed central cholinergic markers of cognition in rats. Res Commun Pharmacol Toxicol. 1999;4(3-4):1-12.
204. Rauf K, Subhan F, Abbas M, Haq IU, Ali G, Ayaz M. Effect of acute and sub chronic use of *Bacopa monnieri* on dopamine and serotonin turnover in mice whole brain. Afr J Pharm Pharmacol. 2012;6(39):2767-74.
205. Rathore R, Arora T, Mamadi RK. Evaluation of anxiolytic properties of Baco Mind extract of plant *Bacopa monnieri* Linn. in comparison with diazepam in rodent model. Int J Basic Clin Pharmacol. 2019;8(11):2506-11. doi: 10.18203/2319-2003.ijbcp20194793.
206. Mannan MA. Anxiolytic effects of the methanolic extract of *Bacopa monnieri* in mice. Pharmacol Pharm. 2019;10(6):298-308.
207. Sudershan B, Chowta MN, Ullal SD, Rajeshwari S, Sayeli VK, Shivaprasad S, *et al*. Effect of *Bacopa monnieri* on ethanol-induced anxiolysis and withdrawal anxiety in Wistar rats. Indian J Physiol Pharmacol. 2018;62(3):339-46.
208. Malhotra CL, Das PK. Pharmacological studies of *Herpestis monniera* Linn (Brahmi). Indian J Med Res. 1959;47(3):294-305. PMID 13664331.
209. Aithal HN, Sirsi M. Pharmacological investigation on *Herpestis monniera*. Ind J Pharmacol. 1961;23:2-5.
210. Prakash JC, Sirsi M. Comparative study of the effects of Brahmi (*Bacopa monnieri*) and chlorpromazine on learning in rats. J Sci Ind Res. 1962;21:93-6.
211. Martis G, Rao A, Karanth KS. Neuropharmacological activity of *Herpestis monniera*. Fitoterapia. 1992;63:399-404.
212. Sudha S, Bindu R, Joyce G, Amit A, Venkataraman BV. Pharmacological interaction of *Centella asiatica* and *Bacopa monnieri* with antiepileptic drugs – an experimental study in rats. J Nat Rem. 2005;5(1):63-9.
213. Khan R, Krishnakumar A, Paulose CS. Decreased glutamate receptor binding and NMDA R1 gene expression in hippocampus of pilocarpine-induced epileptic rats: neuroprotective role of *Bacopa monnieri* extract. Epilepsy Behav. 2008;12(1):54-60. doi: 10.1016/j.yebeh.2007.09.021, PMID 18086456.
214. Mathew J, Balakrishnan S, Antony S, Abraham PM, Paulose CS. Decreased GABA receptor in the cerebral cortex of epileptic rats: effect of *Bacopa monnieri* and Bacoside-A. J Biomed Sci. 2012;19(1):25. doi: 10.1186/1423-0127-19-25, PMID 22364254.
215. Paulose CS, Chathu F, Khan SR, Krishnakumar A. Neuroprotective role of *Bacopa monnieri* extract in epilepsy and effect of glucose supplementation during hypoxia: glutamate receptor gene expression. Neurochem Res. 2008;33(9):1663-71. doi: 10.1007/s11064-007-9513-8, PMID 17940877.
216. Mathew J, Gangadharan G, Kuruvilla KP, Paulose CS. Behavioral deficit and decreased GABA receptor functional regulation in the hippocampus of epileptic rats: effect of *Bacopa monnieri*. Neurochem Res. 2011;36(1):7-16. doi: 10.1007/s11064-010-0253-9, PMID 20821261.
217. Mathew J, Peeyush Kumar TP, Khan RS, Paulose CS. Behavioral deficit and decreased GABA receptor functional regulation in the cerebellum of epileptic rats: effect of *Bacopa monnieri* and bacoside A. Epilepsy Behav. 2010;17(4):441-7. doi: 10.1016/j.yebeh.2010.01.012, PMID 20153260.
218. Mathew J, Soman S, Sadanandan J, Paulose CS. Decreased GABA receptor in the striatum and spatial recognition memory deficit in epileptic rats: effect of *Bacopa monnieri* and bacoside-A. J Ethnopharmacol. 2010;130(2):255-61. doi: 10.1016/j.jep.2010.04.043, PMID 20451596.
219. Nimburkar TA, Wankhade AM, Wanjari MM. Evaluation of anti-compulsive effect of ethanolic extract of *Bacopa monnieri* L. leaves in mice. Indo Am J Pharm Res. 2018;8(12):1409-14.
220. Abbas M, Subhan F, Rauf K, Haq IU, Mohani SNUH. The involvement of non opioidergic mechanism in the antinociceptive and antilocomotive activity of *Bacopa monnieri*. Iran J Pharmacol Ther. 2012;11(1):15-9.
221. Jadiya P, Khan A, Sammi SR, Kaur S, Mir SS, Nazir A. Anti-parkinsonian effects of *Bacopa monnieri*: insights from transgenic and pharmacological Caenorhabditis elegans models of Parkinson's disease. Biochem Biophys Res Commun. 2011;413(4):605-10. doi: 10.1016/j.bbrc.2011.09.010, PMID 21925152.
222. Swathi G, Rajendra W. Protective role of *Bacopa monnieri* on induced Parkinson's disease with particular reference to catecholamine system. Int J Pharm Pharm Sci. 2014;6(7):379-82.
223. Gunduluru S, Ramaiah CV, Rajendra W. Protective role of *Bacopa monnieri* against rotenone-induced Parkinson's disease in PC 12 cell lines. Int J Phytomed. 2017;9(2):219-22.
224. Swathi G, Visweswari G, Rajendra W. Evaluation of rotenone induced Parkinson's disease on glutamate metabolism and protective strategies of *Bacopa monnieri*. Int J Plant Ani Environ Sci. 2013;3:62-7.
225. Singh B, Pandey S, Verma R, Ansari JA, Mahdi AA. Comparative evaluation of extract of *Bacopa monnieri* and *Mucuna pruriens* as neuroprotectant in MPTP model of Parkinson's disease. Indian J Exp Biol. 2016;54(11):758-66. PMID 30179419.
226. Shinomol GK, Mythri RB, Srinivas Bharath MMS, Muralidhara. *Bacopa monnieri* extract offsets rotenone-induced cytotoxicity in dopaminergic cells and oxidative impairments in mice brain. Cell Mol Neurobiol. 2012;32(3):455-65. doi: 10.1007/s10571-011-9776-0, PMID 22160863.
227. Dubey T, Chinnathambi S. Affiliations expand Brahmi (*Bacopa monnieri*): an ayurvedic herb against the Alzheimer's disease. Arch Biochem Biophys. 2019;676(15):108153.
228. Bammidi SR, Volluri SS, Chippada SC, Avanigadda S. Vanga-lapati M. A review on pharmacological studies of *Bacopa monnieri*. J Chem Biol Phys Sci. 2011;1(2):250-9.
229. Aloe L, Alleva E, Fiore M. Stress and nerve growth factor: findings in animal models and humans. Pharmacol Biochem Behav. 2002;73(1):159-66. doi: 10.1016/s0091-3057(02)00757-8, PMID 12076735.
230. Kunte KB, Kuna Y. Neuroprotective effect of *Bacopa monnieri* on memory deficits and ATPase system in Alzheimer's Disease (AD) induced mice. J Sci Inn Res. 2013;2(4):719-35.
231. Chaudhari KS, Tiwari NR, Tiwari RR, Sharma RS. Neurocognitive effect of nootropic drug Brahmi (*Bacopa monnieri*) in Alzheimer's disease. Ann Neurosci. 2017;24(2):111-22. doi: 10.1159/000475900, PMID 28588366.
232. Roy A, Lakshmi T, Geetha RV. Top three herbs in Alzheimer's disease – a review. Int J Pharm Biol Sci. 2011;2(4):362-75.
233. Mukherjee S, Dugad S, Bhandare R, Pawar N, Jagtap S, Pawar PK, *et al*. Evaluation of comparative free-radical quenching potential of Brahmi (*Bacopa monnieri*) and Mandookparni (*Centella asiatica*). Ayu. 2011;32(2):258-64. doi: 10.4103/0974-8520.92549, PMID 22408313.
234. Srimachai S, Devaux S, Demougeot C, Kumphune S, Ullrich ND, Niggli E, *et al*. *Bacopa monnieri* extract increases rat coronary flow and protects against myocardial ischemis/reperfusion injury. BMC Complement Altern Med. 2017;17(117):1-10.
235. Kamkaew N, Scholfield CN, Ingkaninan K, Maneesai P, Parkington HC, Tare M, *et al*. *Bacopa monnieri* and its constituents is hypotensive in anaesthetised rats and vasodilator in various artery types. J Ethnopharmacol. 2011;137(1):790-5. doi: 10.1016/j.jep.2011.06.045, PMID 21762768.
236. Channa S, Dar A, Yaqoob M, Anjum S, Sultani Z, Atta-ur-Rahman. Broncho-vasodilatory activity of fractions and pure constituents isolated from *Bacopa monnieri*. J Ethnopharmacol. 2003;86(1):27-35. doi: 10.1016/s0378-8741(03)00013-8, PMID 12686438.
237. Rashid S, Lodhi F, Ahmad M, Usmanghani K. Cardiovascular effects of *Bacopa monnieri* (L.) pennel extract in rabbits. Pak J Pharm Sci. 1990;3(2):57-62. PMID 16414671.

238. Dar A, Channa S. Relaxant effect of ethanol extract of *Bacopa monnieri* on trachea, pulmonary artery and aorta from rabbit and guinea-pig. Phytother Res. 1997;11(4):323-5. doi: 10.1002/(SICI)1099-1573(199706)11:4<323::AID-PTR93>3.0.CO;2-H.
239. Dar A, Channa S. Calcium antagonistic activity of *Bacopa monnieri* on vascular and intestinal smooth muscles of rabbit and guinea-pig. J Ethnopharmacol. 1999;66(2):167-74. doi: 10.1016/s0378-8741(98)00240-2, PMID 10433473.
240. Kamkaew N, Paracha TU, Ingkaninan K, Waranuch N, Chootip K. Vasodilatory effects and mechanisms of action of *Bacopa monnieri* active compounds on rat mesenteric arteries. Molecules. 2019;24(12):2243. doi: 10.3390/molecules24122243, PMID 31208086.
241. Nandave M, Ojha SK, Joshi S, Kumari S, Arya DS. Cardioprotective effect of *Bacopa monneira* against isoproterenol-induced myocardial necrosis in rats. Int J Pharmacol. 2007;3(5):385-92. doi: 10.3923/ijp.2007.385.392.
242. Kamkaew N, Norman Scholfield CN, Ingkaninan K, Taepavarapruk N, Chootip K. *Bacopa monnieri* increases cerebral blood flow in rat independent of blood pressure. Phytother Res. 2013;27(1):135-8. doi: 10.1002/ptr.4685, PMID 22447676.
243. Sandeep YS, Panigrahi M, Divya GC, Beena DB. Evaluation of *in vitro* thrombolytic activity of phytochemicals in *Bacopa monnieri* Linn. J Pharm Res. 2012;5(1):100-1.
244. Dar A, Channa S. Bronchodilatory and cardiovascular effects of an ethanol extract of *Bacopa monnieri* in anaesthetized rats. Phytomedicine. 1997;4(4):319-23. doi: 10.1016/S0944-7113(97)80040-2, PMID 23195581.
245. Samiulla DS, Prashanth D, Amit A. Mast cell stabilising activity of *Bacopa monnieri*. Fitoterapia. 2001;72(3):284-5. doi: 10.1016/s0367-326x(00)00309-9, PMID 11295306.
246. Rehni AK, Pantlya HS, Shri R, Singh M. Effect of chlorophyll and aqueous extracts of *Bacopa monnieri* and *Valeriana wallichii* on ischaemia and reperfusion-induced cerebral injury in mice. Indian J Exp Biol. 2007;45(9):764-9. PMID 17907741.
247. Saraf MK, Prabhakar S, Anand A. Neuroprotective effect of *Bacopa monnieri* on ischemia induced brain injury. Pharmacol Biochem Behav. 2010;97(2):192-7. doi: 10.1016/j.pbb.2010.07.017, PMID 20678517.
248. Liu X, Yue R, Zhang J, Shan L, Wang R, Zhang W. Neuroprotective effects of bacopaside I in ischemic brain injury. Restor Neurol Neurosci. 2013;31(2):109-23. doi: 10.3233/RNN-120228, PMID 23160060.
249. Le XT, Nguyet Pham HT, Van Nguyen T, Minh Nguyen K, Tanaka K, Fujiwara H, *et al*. Protective effects of *Bacopa monnieri* on ischemia-induced cognitive deficits in mice: the possible contribution of bacopaside I and underlying mechanism. J Ethnopharmacol. 2015;164:37-45. doi: 10.1016/j.jep.2015.01.041, PMID 25660331.
250. Siraj MA, Chakma N, Rahman M, Salahuddin M, Kumar SS. Assessment of analgesic, antidiarrhoeal and cytotoxic activity of ethanolic extract of the whole plant of *Bacopa monnieri* Linn. Int Res J Pharm. 2013;3(10):98-101.
251. Sairam K, Rao CV, Babu MD, Goel RK. Prophylactic and curative effects of *Bacopa monnieri* in gastric ulcer models. Phytomedicine. 2001;8(6):423-30. doi: 10.1078/S0944-7113(04)70060-4, PMID 11824516.
252. Goel RK, Sairam K, Babu MD, Tavares IA, Raman A. *In vitro* evaluation of *Bacopa monnieri* on anti-*Helicobacter pylori* activity and accumulation of prostaglandins. Phytomedicine. 2003;10(6-7):523-7. doi: 10.1078/094471103322331494, PMID 13678238.
253. Rao CV, Sairam K, Goel RK. Experimental evaluation of *Bacopa monnieri* on rat gastric ulceration and secretion. Indian J Physiol Pharmacol. 2000;44(4):435-41. PMID 11214498.
254. Prince SE, Das AP, Arumugam G. *In vivo* appraisal of pharmacological activity of *Bacopa monnieri* and its HPLC analysis for Bacoside A. International journal of pharmaceutical science and research. 2019;10(5):2244-9.
255. Dorababu M, Prabha T, Priyambada S, Agrawal VK, Aryya NC, Goel RK. Effect of *Bacopa monnieri* and *Azadirachta indica* on gastric ulceration and healing in experimental NIDDM rats. Indian J Exp Biol. 2004;42(4):389-97. PMID 15088689.
256. Vítor JM, Vale FF. Alternative therapies for *Helicobacter pylori*: probiotics and phytomedicine. FEMS Immunol Med Microbiol. 2011;63(2):153-64. doi: 10.1111/j.1574-695X.2011.00865.x, PMID 22077218.
257. Hossain H, Howlader MSI, Dey SK, Hira A, Ahmed A. Evaluation of analgesic, antidiarrhoeal and cytotoxic activities of ethanolic extract of *Bacopa monnieri* (L.). Br J Pharm Res. 2012;2(3):188-96. doi: 10.9734/BJPR/2012/1951.
258. Nikhil S, Sudha S, Aruna B, Amarjeeth R, Guido S, Amit A. Preliminary evaluation of different components of *Bacopa monnieri* for laxative effect. J Nat Rem. 2007;7(1):174-82.
259. Subhan F, Abbas M, Rauf K, Baseer A. Anti git motility, toxicological and phytochemical studies on *Bacopa monnieri*. Pharmacologyonline. 2010;3:937-50.
260. Teschke R, Bahre R. Severe hepatotoxicity by Indian Ayurvedic herbal products: A structured causality assessment. Ann Hepatol. 2009;8(3):258-66. doi: 10.1016/S1665-2681(19)31777-6, PMID 19841509.
261. Menon BR, Rathi MA, Thirumoorthi L, Gopalakrishnan VK. Potential effect of *Bacopa monnieri* on nitrobenzene induced liver damage in rats. Indian J Clin Biochem. 2010;25(4):401-4. doi: 10.1007/s12291-010-0048-4, PMID 21966114.
262. Sumathy T, Subramanian S, Govindasamy S, Balakrishna K, Veluchamy G. Protective role of *Bacopa monnieri* on morphine induced hepatotoxicity in rats. Phytother Res. 2001;15(7):643-5. doi: 10.1002/ptr.1007, PMID 11746853.
263. Swathi G, Peddanna K, Bhuvaneswar C, Rajendra W. Antioxidant and hepatoprotective effects of *Bacopa monnieri* and *Vinca rosea* against carbon tetrachloride (CCl4) induced liver damage in rats. Int J Pharm Sci Rev Res. 2013;21(2):342-6.
264. Kumar DVN, Narasaiah KL, Rao SP. Ameliorative effect of *Bacopa monnieri* on alcohol induced hepatotoxicity and oxidative stress in albino rats. J Pharmacogn Phytochem. 2016;5(3):287-92.
265. Ghosh T, Maity TK, Das M, Bose A, Dash GK. Hepatoprotective activity of *Bacopa monnieri* L. against ethanol – induced hepatotoxicity in rats. Phcog Mag. 2007;3(10):95-9.
266. Ghosh T, Maity TK, Dash DK, Bose A. Effect of various fractions of *Bacopa monnieri* Linn. aerial parts on ethanol-induced hepatotoxicity in rats. Orient Pharm Exp Med. 2007;7(3):297-303. doi: 10.3742/OPEM.2007.7.3.297.
267. Sumathi T, Nongbri A. Hepatoprotective effect of Bacoside-A, a major constituent of *Bacopa monnieri* Linn. Phytomedicine. 2008;15(10):901-5. doi: 10.1016/j.phymed.2007.11.020, PMID 18222663.
268. Sumathi T, Ramakrishnan S. Hepatoprotective activity of *Bacopa monnieri* on D-galactosamine induced hepatotoxicity in rats. Nat Prod Sci. 2007;13(3):195-8.
269. Karim R, Khan AF, Yeasmin R, Akter J, Akter T. An evaluation of hepatoprotective activity of aqueous and ethanolic extracts of *Bacopa monnieri* (L.) against paracetamol induced hepatotoxicity in swiss albino mice. Eur J Biomed Pharm Sci. 2020;7(2):393-401.
270. Shahid M, Subhan F, Ullah I, Ali G, Alam J, Shah R. Beneficial effects of *Bacopa monnieri* extract on opioid induced toxicity. Heliyon. 2016;2(2):e00068. doi: 10.1016/j.heliyon.2016.e00068, PMID 27441247.
271. Gudipati T, Srivastava P, Bhadauria R, Prasad GBKS. Hepatoprotective potential of *in vitro Bacopa monnieri* L. against carbon tetrachloride – induced hepatotoxicity in albino mice. Int J Pharm Biol Sci. 2012;3(4):664-72.
272. Kamesh V, Sumathi T. Antihypercholesterolemic effect of *Bacopa monnieri* linn. Asian Pac J Trop Med. 2012;5(12):949-55. doi: 10.1016/S1995-7645(12)60180-1, PMID 23199712.
273. Mitra PK. Hypolipidemic effect of *Bacopa monnieri* (L.) Wettst. leaves in rats: seasonal variation. Eur J Mol Biol Biochem. 2014;1(4):124-7.
274. Thomas M, Rajani G, Reddy GN. Evaluation of anti-hyperlipdemic effect of *Bacopa monnieri* Linn. In atherogenic diet-induced hyperlipidemic rats. An Int J Adv Pharm Sci. 2014;5(5):2362-7.
275. Kamesh V, Sumathi T. Nephroprotective potential of *Bacopa monnieri* on hypercholesterolemia induced nephropathy via the NO signaling pathway. Pharm Biol. 2014;52(10):1327-34. doi: 10.3109/13880209.2014.891142, PMID 25068673.
276. Ghosh T, Maity TK, Sengupta P, Dash DK, Bose A. Antidiabetic and *in vivo* antioxidant activity of ethanolic extract of *Bacopa monnieri* Linn. aerial parts: a possible mechanism of action. Iran J Pharm Res. 2008;7(1):61-8.
277. Taznin I, Mukti M, Rahmatullah M. *Bacopa monnieri*: an evaluation of antihyperglycemic and antinociceptive potential of methanolic extract of whole plants. Pak J Pharm Sci. 2015;28(6):2135-9. PMID 26639482.
278. Lavinya BU, Sabina EP. Anti-hyperglycaemic effect of Brahmi (*Bacopa monnieri* L.) in streptozotocin induced diabetic rats: A study involving antioxidant, biochemical and haematological parameters. J Chem Pharm Res. 2015;7(10):531-4.
279. Ghosh T, Maity TK, Singh J. Antihyperglycemic activity of Bacosine, a triterpene from *Bacopa monnieri*, in alloxan-induced diabetic rats. Planta Med. 2011;77(8):804-8. doi: 10.1055/s-0030-1250600, PMID 21154199.
280. Kishore L, Kaur N, Singh R. Renoprotective effect of *Bacopa monnieri* via inhibition of advanced glycation end products and oxidative stress in STZ-nicotinamide-induced diabetic nephropathy. Ren Fail. 2016;38(9):1528-44. doi: 10.1080/0886022X.2016.1227920, PMID 27784187.
281. Sabina EP, Baskaran UL, Martin SJ, Swaminathan M, Bhattacharya Y, Tandon S. Assessment of antidiabetic activity of the traditional Indian ayurvedic formulation brahmigritham in streptozotocin-induced diabetic rats. Int J Pharm Pharm Sci. 2014;6(11):347-51.
282. Ghatage AJ, Mohanty IR, Maheswari U, Suman RK, Urhekar AD, Deshmukh Y. Cardioprotective efficacy of *Bacopa monnieri* in experimental diabetes mellitus: biochemical and histopathological assessment. MGM J Med Sci. 2014;1(1):7-12. doi: 10.5005/jp-journals-10036-1002.
283. Mitra P, Ghosh T, Mitra PK. Effect of an isolated compound (BM-1) from *Bacopa monnieri* (L.) Wettst. Leaves on serum lipids in normal and diabetic rats. SMU. Med J. 2014;1(1):166-74.
284. Mitra PK, Ghosh T, Mitra P. Scientific validation of antidiabetic plants of Sikkim Himalaya. World J Pharm Res. 2012;1(2):386-97.
285. John S, Sivakumar KC, Mishra R. Bacoside A induces tumor cell death in human glioblastoma cell lines through catastrophic macropinocytosis. Front Mol Neurosci. 2017;10(171):171. doi: 10.3389/fnmol.2017.00171, PMID 28663722.
286. Mallick MN, Khan W, Parveen R, Ahmad S, Sadaf, Najm MZ, *et al*. Exploring the Cytotoxic Potential of Triterpenoids-enriched Fraction of Bacopa monnieri by Implementing *In vitro, In vivo*, and *in silico* Approaches. Pharmacogn Mag. 2017;13(Suppl 3):S595-606. doi: 10.4103/pm.pm_397_16, PMID 29142420.
287. Kumar EP, Elshurafa AA, Elango K, Subburaju T, Suresh B. Cytotoxic and anti-tumour properties of ethanolic extract of *Bacopa monnieri* (L.) Penn. Anc Sci Life. 1998;17(3):228-34. PMID 22556847.
288. Ghosh T, Maity TK, Singh J. Evaluation of antitumor activity of stigmasterol, a constituent isolated from *Bacopa monnieri* Linn. aerial parts against ehrlich ascites carcinoma in mice. Orient Pharm Exp Med. 2011;11(1):41-9. doi: 10.1007/s13596-011-0001-y.

289. Agrawal RC, Shilki V, Agrawal N. Modulation of carcinogenicity and mutagenicity by herbal medicinal plant *Bacopa monnieri* extract in swiss albino mice. J Mol Oncol Res. 2017;1(1):1-3.
290. Prakash NS, Sundaram R, Mitra SK. *In vitro* and *in vivo* anticancer activity of Bacoside A from whole plant of *Bacopa Monnieiri* (Linn). Am J Pharmacol Toxicol. 2011;6(1):11-9.
291. Janani P, Sivakumari K, Geetha A, Ravisankar B, Parthasarathy C. Chemopreventive effect of bacosideA on N-nitrosodiethylamine-induced hepatocarcinogenesis in rats. J Cancer Res Clin Oncol. 2010;136(5):759-70. doi: 10.1007/s00432-009-0715-0, PMID 19916024.
292. Rohini G, Sabitha KE, Devi CS. *Bacopa monnieri* Linn. extract modulates antioxidant and marker enzyme status in fibrosarcoma bearing rats. Indian J Exp Biol. 2004;42(8):776-80. PMID 15573526.
293. Kalyani MI, Lingaraju SM, Salimath BP. A pro-apoptotic 15-kDa protein from *Bacopa monnieri* activates caspase-3 and downregulates Bcl-2 gene expression in mouse mammary carcinoma cells. J Nat Med. 2013;67(1):123-36. doi: 10.1007/s11418-012-0661-z, PMID 22467255.
294. Ghosh S, Khanam R, Chowdhury AA. The evolving roles of *Bacopa monnieri* as potential anti-cancer agent: a review. Nutr Cancer. 2020;5:1-11.
295. Gohil KJ. Exploring the potential of *Centella asiatica* and *Bacopa monnieri* in immunodeficiency disorders in women: two herbs as Holy Grail. International Journal of Minor Fruits. Med Aromat Plants. 2020;6(2):01-12.
296. Brahma SK. Neuroendocrine-immune modulation by Ayurvedic Rasayana Drugs. Int. J. Ayur. Pharm Res. 2020;8(12):51-71.
297. Hule AK, Juvekar AR. *In vitro* immune response of saponin rich fraction of *Bacopa monnieri*, Linn. Int J PharmTech Res. 2009;1(4):1032-8.
298. Pathania M, Bhardwaj P, Pathania N, Rathaur VK, Amisha. A review on exploring evidence-based approach to harnessing the immune system in times of corona virus pandemic: best of modern and traditional Indian system of medicine. J Fam Med Prim Care. 2020;9(8):3826-37. doi: 10.4103/jfmpc.jfmpc_504_20, PMID 33110775.
299. Priyanka HP, Nair RS. Strategies to overcome neuroendocrine immune deficits in aging: role of neuroendocrine-immune modulators and bioactive plant extracts. Turk J Immunol. 2019;7;Suppl 1:S99-107. doi: 10.25002/tji.2019.1027.
300. Saraphanchotiwitthaya A, Ingkaninan K, Sripalakit P. Effect of *Bacopa monnieri* Linn. extract on murine immune response *in vitro*. Phytother Res. 2008;22(10):1330-5. doi: 10.1002/ptr.2491, PMID 18688885.
301. Kumar S, Bajwa BS, Singh K, Kalia AN. Anti-inflammatory activity of herbal plants: a review. Int J Adv Pharm Biol Chem. 2013;2(2):272-81.
302. Basak A, Hossain ML, Parvin MN. Evaluation of phytochemical and pharmacological activities of *Bacopa monnieri* (L.). Int J Sci Rep. 2016;2(10):242-7. doi: 10.18203/issn.2454-2156.IntJSciRep20163394.
303. Bala S, Priya AJ, Devi RG. Physiological and pharmacological effects of *Bacopa monnieri*. Drug Invent Today. 2018;10(11):2179-82.
304. Channa S, Dar A, Anjum S, Yaqoob M, Atta-Ur-Rahman. Anti-inflammatory activity of *Bacopa monnieri* in rodents. J Ethnopharmacol. 2006;104(1-2):286-9. doi: 10.1016/j.jep.2005.10.009, PMID 16343831.
305. Shahid M, Subhan F, Ahmad N, Ullah I. A bacosides containing *Bacopa monnieri* extract alleviates allodynia and hyperalgesia in the chronic constriction injury model of neuropathic pain in rats. BMC Complement Altern Med. 2017;17(1):293. doi: 10.1186/s12906-017-1807-z, PMID 28583132.
306. Viji V, Helen A. Inhibition of pro-inflammatory mediators: role of *Bacopa monnieri* (L.) Wettst. Inflammopharmacology. 2011;19(5):283-91. doi: 10.1007/s10787-010-0046-4, PMID 20607614.
307. Viji V, Helen A. Inhibition of lipoxygenases and cyclooxygenase-2 enzymes by extracts isolated from *Bacopa monnieri* (L.) Wettst. J Ethnopharmacol. 2008;118(2):305-11. doi: 10.1016/j.jep.2008.04.017.
308. Hossain H, Al-Mansur A, Akter S, Sara U, Ahmed MR, Jahangir AA. Evaluation of anti-inflammatory activity and total tannin content from the leaves of *Bacopa monnieri* (Linn.). Int J Pharm Sci Res. 2014;5(4):1246-52.
309. Nemetchek MD, Stierle AA, Stierle DB, Lurie DI. The Ayurvedic plant *Bacopa monnieri* inhibits inflammatory pathways in the brain. J Ethnopharmacol. 2017;197:92-100. doi: 10.1016/j.jep.2016.07.073, PMID 27473605.
310. Williams R, Münch G, Gyengesi E, Bennett L. *Bacopa monnieri* (L.) exerts anti-inflammatory effects on cells of the innate immune system *in vitro*. Food Funct. 2014;5(3):517-20. doi: 10.1039/c3fo60467e, PMID 24452710.
311. Abbas M, Subhan F, Mohani N, Rauf K, Ali G, Khan M. The involvement of opioidergic mechanisms in the activity of *Bacopa monnieri* extract and its toxicological studies. Afr J Pharm Pharmacol. 2011;5(8):1120-4.
312. Subhan F, Abbas M, Rauf K, Arfan M, Sewell RDE, Ali G. The role of opioidergic mechanisms in the activity of *Bacopa monnieri* extract against tonic and acute phasic pain modalities. Pharmacologyonline. 2010;3:903-14.
313. Vohora SB, Khanna T, Athar M, Ahmad B. Analgesic activity of bacosine, a new triterpene isolated from *Bacopa monnieri*. Fitoterapia. 1997;68(4):361-5.
314. Simon JP, Gaopande PS, Praveen S, Reeja AA, Rajasekar A, Vidya R, *et al*. Influence of *Bacopa monnieri* in suppressing the arthritis induced by MSU crystal in Wistar albino female rats: through biochemical and histopathological approach. J App Pharm Sci. 2019;9(10):17-23. doi: 10.7324/JAPS.2019.91003.
315. Viji V, Kavitha SK, Helen A. *Bacopa monnieri* (L.) wettest inhibits type II collagen-induced arthritis in rats. Phytother Res. 2010;24(9):1377-83. doi: 10.1002/ptr.3135, PMID 20309843.
316. Rauf K, Subhan F, Al-Othman AM, Khan I, Zarrelli A, Shah MR. Preclinical profile of Bacopasides from *Bacopa monnieri* (BM) as an emerging class of therapeutics for management of chronic pains. Curr Med Chem. 2013;20(8):1028-37, PMID 23210787.
317. Sumathi T, Niranjali Devaraj SN. Effect of *Bacopa monnieri* on liver and kidney toxicity in chronic use of opioids. Phytomedicine. 2009;16(10):897-903. doi: 10.1016/j.phymed.2009.03.005, PMID 19403290.
318. Oyouni AAA, Saggu S, Tousson E, Mohan A, Farasani A. Mitochondrial nephrotoxicity induced by tacrolimus (FK-506) and modulatory effects of *Bacopa monnieri* (Farafakh) of Tabuk Region. Pharmacogn Res. 2019;11(1):20-4. doi: 10.4103/pr.pr_100_18.
319. Kannan NR, Sudha A, Manimaran A, Saravanan D, Natarajan E. Beneficial effect of *Bacopa monnieri* extract on gentamicin induced nephrotoxicity and oxidative stress in Albino rats. Int J Pharm Pharm Sci. 2011;3;Suppl 5:144-8.
320. Rehman MU, Tahir M, Khan AQ, Lateef A, Khan R, Hamiza OO, *et al*. Methanolic extract of *Bacopa monnieri* protects against $KBrO_3$-induced renal damage in Wistar rats by restoring antioxidant enzyme activities and suppressing inflammation and apoptosis. J Pharm Res. 2012;5(11):5231-8.
321. Sudharani D, Krishna KL, Deval K, Safia AK, Priya. Pharmacological profiles of *Bacopa monnieri*: a review. Int J Pharm. 2011;1(1):15-23.
322. Singh A, Singh SK. Evaluation of antifertility potential of Brahmi in male mouse. Contraception. 2009;79(1):71-9. doi: 10.1016/j.contraception.2008.07.023, PMID 19041444.
323. Patel SK, Singh S, Singh HK, Singh SK. Effect of standardized extract of *Bacopa monnieri* (CDRI-08) on testicular functions in adult male mice. J Ethnopharmacol. 2017;197:101-9. doi: 10.1016/j.jep.2016.07.026, PMID 27401287.
324. Patel SK, Singh S, Singh SK. Standardized extract of *Bacopa monnieri* (CDRI-08): effect on germ cell dynamics and possible mechanisms of its beneficial action on spermatogenesis and sperm quality in male mice. Biochem Biophys Res Commun. 2017;494(1-2):34-41. doi: 10.1016/j.bbrc.2017.10.089, PMID 29054405.
325. Mishra RK, Singh S, Singh SK. Natural products in regulation of male fertility. Indian J Med Res. 2018; (Suppl)148:S107-14. doi: 10.4103/ijmr.IJMR_1968_17, PMID 30964087.
326. Frazer K, McHugh J, Callinan JE, Kelleher C. Impact of institutional smoking bans on reducing harms and secondhand smoke exposure. Cochrane Database Syst Rev. 2016;2016(5):CD011856. doi: 10.1002/14651858.CD011856.pub2, PMID 27230795.
327. Vani G, Anbarasi K, Devi CSS, Bacoside A. Bacoside A: Role in cigarette smoking induced changes in brain. Evid Based Complement Alternat Med. 2015;2015(4):286137. doi: 10.1155/2015/286137, PMID 26413118.
328. Anbarasi K, Vani G, Devi CSS. Protective effect of bacoside A on cigarette smoking-induced brain mitochondrial dysfunction in rats. J Environ Pathol Toxicol Oncol. 2005;24(3):225-34. doi: 10.1615/jenvpathtoxoncol.v24.i3.80, PMID 16050806.
329. Anbarasi K, Vani G, Balakrishna K, Devi CSS. Creatine kinase isoenzyme patterns upon chronic exposure to cigarette smoke: protective effect of Bacoside A. Vasc Pharmacol. 2005;42(2):57-61. doi: 10.1016/j.vph.2005.01.003, PMID 15722250.
330. Anbarasi K, Kathirvel G, Vani G, Jayaraman G, Shyamala Devi CSS. Cigarette smoking induces heat shock protein 70-kDa expression and apoptosis in rat brain: modulation by bacoside. Neuroscience. 2006;138(4):1127-35. doi: 10.1016/j.neuroscience.2005.11.029, PMID 16472926.
331. Anbarasi K, Vani G, Balakrishna K, Devi CSS. Effect of bacoside A on brain antioxidant status in cigarette smoke exposed rats. Life Sci. 2006;78(12):1378-84. doi: 10.1016/j.lfs.2005.07.030, PMID 16226278.
332. Anbarasi K, Sabitha KE, Devi CSS. Lactate dehydrogenase isoenzyme patterns upon chronic exposure to cigarette smoke: protective effect of bacoside A. Environ Toxicol Pharmacol. 2005;20(2):345-50. doi: 10.1016/j.etap.2005.03.006, PMID 21783610.
333. Ghosh T, Maity TK, Dash DK, Boss A. A study on wound healing activity of *Bacopa monnieri* Linn. aerial parts. Orient Pharm Exp Med. 2007;7(2):150-6. doi: 10.3742/OPEM.2007.7.2.150.
334. Murthy S, Gautam MK, Goel S, Purohit V, Sharma H, Goel RK. Evaluation of *in vivo* wound healing activity of *Bacopa monnieri* on different wound model in rats. Biomed Res Int. 2013;2013;Special Issue:1-9.
335. Sharath R, Harish BG, Krishna V, Sathyanarayana BN, Swamy HMK. Wound healing and protease inhibition activity of bacoside-A isolated from *Bacopa monnieri* wettest. Phytother Res. 2010;24(8):1217-22. doi: 10.1002/ptr.3115, PMID 20213670.
336. Chen Z, Lu L. Suppressive effect of bacoside A on hypertrophic scar formation by downregulation of TGF-β1. Trop J Pharm Res. 2018;17(9):1725-31. doi: 10.4314/tjpr.v17i9.6.
337. Kar A, Panda S, Bharti S. Relative efficacy of three medicinal plant extracts in the alteration of thyroid hormone concentrations in male mice. J Ethnopharmacol. 2002;81(2):281-5. doi: 10.1016/s0378-8741(02)00048-x, PMID 12065164.
338. Vigneshwar R, Arivalagan A, Palanivel M. Thyrogenic, hypolipidemic and antioxidant effects of *Bacopa monnieri* (Brahmi) on experimental hypothyroidism in rats. J Pharmacogn Phytochem. 2021;10(1):454-8.
339. Banerjee PS, Sharma M, Neha RK. Preparation, evaluation and hair growth stimulating activity of herbal hair oil. J Chem Pharm Res. 2009;1(1):261-7.
340. Jain PK. Alternative herbal drugs used for treating hair disease. Asian J Pharm Clin Res. 2016;9(1):75-7.

341. Jain PK, Dass DJ. Evaluating hair growth potential of some traditional herbs. Asian J Pharm Clin Res. 2015;8(6):150-2.
342. Jain PK, Joshi H, Dass DJ. Drug that causes hair loss and promotes hair growth – a review. Int J Res Pharm Biomed Sci. 2012;3(4):1476-82.
343. Rashid K, Raj VBA, Kumar PSS, Nishad KM. Hair care promising herbs: a review. Indo Am J Pharm Res. 2020;10(3):677-88.
344. Jain R, Monthakantirat O, Tengamnuay P, De-Eknamkul W. Identification of a new plant extract for androgenic alopecia treatment using a non-radioactive human hair dermal papilla cell-based assay. BMC Complement Altern Med. 2016;16:18. doi: 10.1186/s12906-016-1004-5, PMID 26796631.
345. Peng L, Zhou Y, Kong de Y, Zhang WD. Antitumor activities of dammarane triterpene saponins from *Bacopa monnieri*. Phytother Res. 2010;24(6):864-8. doi: 10.1002/ptr.3034, PMID 19960417.
346. Jain P, Khanna NK, Trehan N, Pendse VK, Godhwani JL. Antiinflammatory effects of an ayurvedic preparation, Brahmi Rasayan, in rodents. Indian J Exp Biol. 1994;32(9):633-6. PMID 7814042.
347. Holcomb LA, Dhanasekaran M, Hitt AR, Young KA, Riggs M, Manyam BV. *Bacopa monnieri* extract reduces amyloid levels in PSAPP mice. J Alzheimers Dis. 2006;9(3):243-51. doi: 10.3233/jad-2006-9303, PMID 16914834.
348. Palethorpe HM, Smith E, Tomita Y, Nakhjavani M, Yool AJ, Price TJ, *et al*. Bacopasides I and II act in synergy to inhibit the growth, migration and invasion of breast cancer cell lines. Molecules. 2019;24(19):3539. doi: 10.3390/molecules24193539, PMID 31574930.
349. Mallick MN, Akhtar MS, Najm MZ, Tamboli ET, Ahmad S, Husain SA. Evaluation of anticancer potential of *Bacopa monnieri* L. against MCF-7 and MDA-MB-231 cell line. J Pharm Bioallied Sci. 2015;7(4):325-8. doi: 10.4103/0975-7406.168038, PMID 26681894.
350. Rohini G, Devi CSS. *Bacopa monnieri* extract induces apoptosis in murine sarcoma cells (S-180). Phytother Res. 2008;22(12):1595-98. doi: 10.1002/ptr.2515, PMID 19067376.
351. Petcharat K, Singh M, Ingkaninan K, Attarat J, Yasothornsrikul S. *Bacopa monnieri* protects SHSY5Y cells against tert-butyl hydroperoxide-induced cell death via the ERK and PI3K pathways. Siriraj Med J. 2015;67(1):20-6. PMID 29152617.
352. Aithal MGS, Rajeswari N. Bacoside A induced sub-G0 arrest and early apoptosis in human glioblastoma cell line U-87 mg through notch signaling pathway. Brain Tumor Res Treat. 2019;7(1):25-32. doi: 10.14791/btrt.2019.7.e21, PMID 31062528.
353. Papadopoulos MC, Saadoun S, Verkman AS. Aquaporins and cell migration. Pflugers Arch. 2008;456(4):693-700. doi: 10.1007/s00424-007-0357-5, PMID 17968585.
354. Stroka KM, Jiang H, Chen SH, Tong Z, Wirtz D, Sun SX, *et al*. Water permeation drives tumor cell migration in confined microenvironments. Cell. 2014;157(3):611-23. doi: 10.1016/j.cell.2014.02.052, PMID 24726433.
355. Schwab A, Fabian A, Hanley PJ, Stock C. Role of ion channels and transporters in cell migration. Physiol Rev. 2012;92(4):1865-913. doi: 10.1152/physrev.00018.2011, PMID 23073633.
356. Jurisic V, Radenkovic S, Konjevic G. The actual role of LDH as tumor marker, biochemical and clinical aspects. Adv Exp Med Biol. 2015;867:115-24. doi: 10.1007/978-94-017-7215-0_8, PMID 26530363.
357. Koczurkiewicz P, Łojewski M, Piska K, Michalik M, Wójcik-Pszczoła K, Szewczyk A, *et al*. Chemopreventive and anticancer activities of *Bacopa monnieri* extracted from artificial digestive juices. Nat Prod Commun. 2017;12(3):337-42. doi: 10.1177/1934578X1701200306, PMID 30549879.
358. Mallick MN, Khan W, Parveen R, Ahmad S, Sadaf NMZ, Ahmad I, *et al*. Exploring the cytotoxic potential of triterpenoids-enriched fraction of *Bacopa monnieri* by implementing *in vitro, in vivo*, and *in silico* approaches. Pharmacogn Mag. 2017;13(Suppl 3):S596-606:S595-606. doi: 10.4103/pm.pm_397_16, PMID 29142420.
359. Journal BS. Triterpenoid saponins investigation and pharmacological (cytotoxic and antioxidant) properties of *Bacopa monnieri* L. cultivated in Iraq. Baghdad Sci J. 2018;15(2):123-9. doi: 10.21123/bsj.15.2.123-129.
360. Katoch M, Singh G, Sharma S, Gupta N, Sangwan PL, Saxena AK. Cytotoxic and antimicrobial activities of endophytic fungi isolated from *Bacopa monnieri* (L.) Pennell (Scrophulariaceae). BMC Complement Altern Med. 2014;14:52. doi: 10.1186/1472-6882-14-52, PMID 24512530.
361. Leung HW, Foo G, Banumurthy G, Chai X, Ghosh S, Mitra-Ganguli T, *et al*. The effect of *Bacopa monnieri* on gene expression levels in SH-SY5Y human neuroblastoma cells. PLOS ONE. 2017;12(8):e0182984. doi: 10.1371/journal.pone.0182984, PMID 28832626.
362. Krishna RN, Gayathri R, Priya V. Genotoxicity potential of *Bacopa monnieri* on oral cancer cell lines by DNA fragmentation. Int J Pharm Sci Rev Res. 2016;39(1):240-2.
363. Kalaivani T, Sasirekha M, Arunraj D, Palanichamy V, Rajasekaran C. *In vitro* evaluation of antibacterial activity of phytochemical extracts from aerial parts of *Bacopa monnieri* (L.) Wettest (Scorphulariaceae). J Pharm Res. 2012;5(3):1636-9.
364. Sampathkumar P, Dheeba B, Vidhyasagar V, Arulprakash T, Vinothkannan R. Potential antimicrobial activity of various extracts of *Bacopa monnieri* (Linn.). Int J Pharm Res. 2008;4(3):230-2.
365. Fazlul MKK, Deepthi SP, Irfan M, Farzana Y, Munira B, Nazmul MHM. Antibacterial and antifungal activity of various extracts of *Bacopa monnieri*. Int J Pharm Res. 2019;11(1):1698-702.
366. Ghosh T, Maity TK, Bose A, Dash GK, Das M. A study on antimicrobial activity of *Bacopa monnieri* Linn. Aerial parts. J Nat Rem. 2006;6(2):170-3.
367. Bora M, Kawlni L, Upadhyay S, Mukherjee K, Hazra J. A comprehensive review on *in vitro* anthelmintic activities of some ayurvedic plants. Int J Ayurveda Pharm Res. 2017;5(11):62-5.
368. Ghosh T, Maity TK, Dash GK, Bose A. Anthelmintic activity of various fractions of ethanolic extract of *Bacopa monnieri*. Indian Drugs. 2006;43:760-2.
369. Ghosh T, Maity TK, Bose A, Dash GK. Anthelmintic activity of *Bacopa monnieri*. Indian J Nat Prod. 2005;21(2):16-9.
370. Prasad S, Kashyap RS, Deopujari JY, Purohit HJ, Taori GM, Daginawala HF. Effect of *Fagonia arabica* (Dhamasa) on *in vitro* thrombolysis. BMC Complement Altern Med. 2007;7:36. doi: 10.1186/1472-6882-7-36, PMID 17986325.
371. Das J, Rahman MM. Antioxidant and thrombolytic activity of chloroform extract of *Bacopa monnieri* (L.). Bull Pharm Res. 2014;4(3):133-9.
372. Emran TB, Rahman MA, Uddin MMN, Rahman MM, Uddin MZ, Dash R, *et al*. Effects of organic extracts and their different fractions of five Bangladeshi plants on *in vitro* thrombolysis. BMC Complement Altern Med. 2015;15:128. doi: 10.1186/s12906-015-0643-2, PMID 25902818.
373. Ghosh D, Mondal S, Ramakrishna K. Acute and sub-acute (30-day) toxicity studies of *Aegialitis rotundifolia* Roxb. leaves extract in Wistar rats: safety assessment of a rare mangrove traditionally utilized as pain antidote. Clin Phytosci. 2019;5(1):13. doi: 10.1186/s40816-019-0106-2.
374. Sireeratawong S, Jaijoy K, Khonsung P, Lertprasertsuk N, Ingkaninan K. Acute and chronic toxicities of *Bacopa monnieri* extract in Sprague-Dawley rats. BMC Complement Altern Med. 2016;16:249. doi: 10.1186/s12906-016-1236-4.
375. Reddy KRC, Kumar V, Yadav K. Acute and sub-chronic toxicity study of Brahmi ghrita in rodents. Int J Green Pharm. 2014;8(1):18-22. doi: 10.4103/0973-8258.126814.
376. Joshua Allan JJ, Damodaran A, Deshmukh NS, Goudar KS, Amit A. Safety evaluation of a standardized phytochemical composition extracted from *Bacopa monnieri* in sprague–dawley rats. Food Chem Toxicol. 2007;45(10):1928-37. doi: 10.1016/j.fct.2007.04.010, PMID 17560704.
377. Deepak P, Sushil K, Vijay T. Subacute oral toxicity of new formulation of *Bacopa monnieri* in rats. Toxicol Int. 2015;22(2):103-10.
378. Khurshid F, Govindasamy J, Khalilullah H, Nomani MS, Shahid M, Ain MR, *et al*. Effect of herb-drug interactions of *Bacopa monnieri* Linn. (Brahmi) formulation on the pharmacokinetics of amitriptyline in rats. Braz J Pharm Sci. 2017;53(4):e17072. doi: 10.1590/s2175-97902017000417072.
379. Malishev R, Shaham-Niv S, Nandi S, Kolusheva S, Gazit E, Jelinek R, *et al*. an Indian traditional-medicine substance, inhibits β-amyloid cytotoxicity, fibrillation, and membrane interactions. ACS Chem Neurosci. 2017;8:884-91.
380. Farooqui AA, Farooqui T. Contribution of diabetes and metabolic syndrome in the pathogenesis of Alzheimer's disease. In: Farooqui T, Farooqui AA, editors. Role of the Mediterranean diet in the brain and neurodegenerative diseases. London, England: Elsevier; 2018. p. 301-16.
381. Stough C, Scholey A, Cropley V, Wesnes K, Zangara A, Pase M, *et al*. Examining the cognitive effects of a special extract of *Bacopa monnieri* (CDRI08: Keenmnd): a review of ten years of research at Swinburne University. J Pharm Pharm Sci. 2013;16(2):254-8. doi: 10.18433/j35g6m, PMID 23958194.
382. Abdul Manap ASA, Vijayabalan S, Madhavan P, Chia YY, Arya A, Wong EH, *et al*. *Bacopa monnieri*, a neuroprotective lead in Alzheimer disease: a review on its properties, mechanisms of action, and preclinical and clinical studies. Drug Target Insights. 2019;13:1177392819866412. doi: 10.1177/1177392819866412, PMID 31391778.
383. Dethe S, Deepak M, Agarwal A. Elucidation of molecular mechanism(s) of cognition enhancing activity of Bacomind®: A standardized extract of *Bacopa monnieri*. Pharmacogn Mag. 2016;12(Suppl 4):S482-7. doi: 10.4103/0973-1296.191464, PMID 27761079.
384. Madhu K, T P, S M. Bacoside-A inhibits inflammatory cytokines and chemokine in experimental autoimmune encephalomyelitis. Biomed Pharmacother. 2019;109:1339-45. doi: 10.1016/j.biopha.2018.10.188, PMID 30551384.
385. Khan I, Nisar M, Shah MR, Shah H, Gilani SN, Gul F, *et al*. Anti-inflammatory activities of Taxusabietane A isolated from *Taxus wallichiana* Zucc. Fitoterapia. 2011;82(7):1003-7. doi: 10.1016/j.fitote.2011.06.003, PMID 21699963.
386. Viji V, Shobha B, Kavitha SK, Ratheesh M, Kripa K, Helen A. Betulinic acid isolated from *Bacopa monnieri* Wettst. suppresses lipopolysaccharide stimulated interleukin-6 production through modulation of nuclear factor-κB in peripheral blood mononuclear cells. Int Immunopharmacol. 2010;10(8):843-9. doi: 10.1016/j.intimp.2010.04.013, PMID 20430119.
387. Kulshreshtha DK, Rastogi RP. Identification of ebelin lactone from Bacoside A and the nature of genuine saponin. Phytochemistry. 1973;12(8):2074-6. doi: 10.1016/S0031-9422(00)91552-8.
388. Singh R, Panduri J, Kumar D, Kumar D, Chandsana H, Ramakrishna R, *et al*. Evaluation of memory enhancing clinically available standardized extract of *Bacopa monnieri* on P-glycoprotein and cytochrome P450 3A in Sprague-Dawley rats. PLOS ONE. 2013;8(8):e72517. doi: 10.1371/journal.pone.0072517, PMID 24015255.
389. Stough C, Singh H, Zangara A. Mechanisms, efficacy, and safety of *Bacopa monnieri* (Brahmi) for cognitive and brain enhancement. Evid Based Complement Alternat Med. 2015;2015:717605. doi: 10.1155/2015/717605, PMID 26413128.
390. Goswami S, Saoji A, Kuman N, Thawani V, Tiwari M, Thawani M. Effect of *Bacopa monnieri* on cognitive functions in Alzheimer's disease patients. Int J Collab Res Intern Med Public Health. 2011;3(3):179.

391. 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(7):753-9. doi: 10.1089/acm.2009.0342, PMID 20590480.
392. Calabrese C, Gregory WL, Leo M, Kraemer D, Bone K, Oken B. Effects of a standardized *Bacopa monnieri* extract on cognitive performance, anxiety, and depression in the elderly: a randomized, double-blind, placebo-controlled trial. J Altern Complement Med. 2008;14(6):707-13. doi: 10.1089/acm.2008.0018, PMID 18611150.
393. Stough C, Downey LA, Lloyd J, Silber B, Redman S, Hutchison C, *et al*. Examining the nootropic effects of a special extract of *Bacopa monnieri* on human cognitive functioning: 90-day double-blind placebo-controlled randomized trial. Phytother Res. 2008;22(12):1629-34. doi: 10.1002/ptr.2537.
394. Roodenrys S, Booth D, Bulzomi S, Phipps A, Micallef C, Smoker J. Chronic effects of Brahmi (*Bacopa monnieri*) on human memory. Neuropsychopharmacology. 2002;27(2):279-81. doi: 10.1016/S0893-133X(01)00419-5, PMID 12093601.
395. Singh RH, Sinha AN, Pandey HP. A comparative study of the psychotropic action of the Medhya drugs, Brahmi (*Bacopa monnieri*) and Mandukaparni (*Hydrocotyl asiatica*). J Res Indian Med. 1975;10:108-10.
396. Rajpal R, Singh V, Siddiqui V, Nayak C, Mal P, Sarkar D. *Bacopa monnieri* - A multicentric, randomized, double-blind homoeopathic pathogenetic trial. Indian J Res Homoeopathy. 2011;5(4):22-7. doi: 10.53945/2320-7094.1732.
397. Kumar N, Abichandani LG, Thawani V, Gharpure KJ, Naidu MUR, Venkat Ramana GV. Efficacy of standardized extract of *Bacopa monnieri* (Bacognize) on cognitive functions of medical students: a six-week, randomized placebo-controlled trial. Evid Based Complement Alternat Med. 2016;2016:4103423. doi: 10.1155/2016/4103423 , PMID 27803728.
398. Kean JD, Kaufman J, Lomas J, Goh A, White D, Simpson D, *et al*. A randomized controlled trial investigating the effects of a special extract of *Bacopa monnieri* (CDRI 08) on hyperactivity and inattention in male children and adolescents. BACHI study protocol (ANZCTRN12612000827831). Nutrients. 2015;7(12):9931-45. doi: 10.3390/nu7125507, PMID 26633481.
399. Kongkeaw C, Dilokthornsakul P, Thanarangsarit P, Limpeanchob N, Norman Scholfield CN. Meta-analysis of randomized controlled trials on cognitive effects of *Bacopa monnieri* extract. J Ethnopharmacol. 2014;151(1):528-35. doi: 10.1016/j.jep.2013.11.008, PMID 24252493.
400. 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(7):647-52. doi: 10.1089/acm.2011.0367, PMID 22747190.
401. Bhuyan G, Sudhakar D, Dua PK. Clinical evaluation of brahmighrita and jyotishmatitaila in the management of cognitive deficit in children. J Res Ayurvedic Sci. 2018;2(2):80-9. doi: 10.5005/jp-journals-10064-0043.
402. Peth-Nui T, Wattanathorn J, Muchimapura S, Tong-Un T, Piyavhatkul N, Rangseekajee P, *et al*. Effects of 12-week *Bacopa monnieri* consumption on attention, cognitive processing, working memory, and functions of both cholinergic and monoaminergic systems in healthy elderly volunteers. Evid Based Complement Alternat Med. 2012;2012:606424. doi: 10.1155/2012/606424, PMID 23320031.
403. Kean JD, Downey LA, Stough C. Systematic overview of *Bacopa monnieri* (L.) Wettst. dominant poly-herbal formulas in children and adolescents. Medicines (Basel). 2017;4(4):1-24. doi: 10.3390/medicines4040086, PMID 29165401.
404. Raghav S, Singh H, Dalal PK, Srivastava JS, Asthana OP. Randomized controlled trial of standardized *Bacopa monnieri* extract in age-associated memory impairment. Indian J Psychiatry. 2006;48(4):238-42. doi: 10.4103/0019-5545.31555, PMID 20703343.
405. Sane R, Dawkhar S, Ambulkar P, Mandole R. The effect of a polyherbal oral formulation in the management of essential hypertension: an open label, pilot clinical study. Int J Basic Clin Pharmacol. 2018;7(7):1427-31. doi: 10.18203/2319-2003.ijbcp20182694.
406. Mishra D, Tubaki BR. Effect of Brahmi vati and Sarpagandha Ghana vati in management of essential hypertension - A randomized, double blind, clinical study. J Ayurveda Integr Med. 2019;10(4):269-76. doi: 10.1016/j.jaim.2017.04.001, PMID 29242090.
407. Sarkar S, Mishra BR, Praharaj SK, Nizamie SH. Add-on effect of Brahmi in the management of schizophrenia. J Ayurveda Integr Med. 2012;3(4):223-5. doi: 10.4103/0975-9476.104448, PMID 23326095.
408. Stough C, Lloyd J, Clarke J, Downey LA, Hutchison CW, Rodgers T, et al. The chronic effects of an extract of *Bacopa monnieri* (Brahmi) on cognitive function in healthy human subjects. Psychopharmacol (Berl). 2001;156(4):481-4. doi: 10.1007/s002130100815, PMID 11498727.
409. Sathyaseela R, Kamalinie R, Bupesh G, Baskar M, Vasanth S. Anti-inflammatory effect of *Bacopa monnieri* (Brahmi) on Swollen Joints – A Case Study. Int J Res Pharm Sci. 2020;11(3):4074-7. doi: 10.26452/ijrps.v11i3.2607.
410. Sharma R, Chaturvedi C, Sharma R, Tewari P, Chaturvedi CM, Tewari PV, et al. Efficacy of *Bacopa monnieri* in revitalizing intellectual functions in children. J Res Educ Indian Med. 1987;1:12.
411. Negi K, Singh Y, Kushwaha K, Rastogi C, Rathi A, Srivastava J, et al. Clinical evaluation of memory enhancing properties of memory plus in children with attention deficit hyperactivity disorder. Indian J Psychiatry. 2000;42;Suppl 2:4.
412. Solon FS, Sarol JN, Bernardo AB, Solon JA, Mehansho H, Sanchez-Fermin LE, et al. Effect of a multiple-micronutrient-fortified fruit powder beverage on the nutrition status, physical fitness, and cognitive performance of schoolchildren in the Philippines. Food Nutr Bull. 2003;24(4);Suppl:S129-40. doi: 10.1177/15648265030244S210, PMID 17016955.
413. Nga TT, Winichagoon P, Dijkhuizen MA, Khan NC, Wasantwisut E, Wieringa FT. Decreased parasite load and improved cognitive outcomes caused by deworming and consumption of multi-micronutrient fortified biscuits in rural Vietnamese schoolchildren. Am J Trop Med Hyg. 2011;85(2):333-40. doi: 10.4269/ajtmh.2011.10-0651, PMID 21813856.
414. Mitra-Ganguli T, Kalita S, Bhushan S, Stough C, Kean J, Wang N, et al. A randomized, double-blind study assessing changes in cognitive function in Indian school children receiving a combination of *Bacopa monnieri* and micronutrient supplementation vs. placebo. Front Pharmacol. 2017;8:678. doi: 10.3389/fphar.2017.00678, PMID 29204115.
415. Roy S, Chakravarty S, Talukdar P. Identification of bioactive compounds present in *Bacopa monnieri* Linn. Against caspase-3 and Tau protein kinase I to Prevent Alzheimer's disease: an *in-silico* Study. J Pharm Innov. 2019;8:855-61.
416. Jain CK, Gupta A, Tewari A, Sharma V, Kumar VS, Mathur A, et al. Molecular docking studies of bacoside from *Bacopa monnieri* with LRRK2 receptor. Biologia. 2013;68(6):1068-71. doi: 10.2478/s11756-013-0277-0.
417. Chandrasekar S, Thangarajan S, Loganathan S, Sundaram S, Kumarasamy P. Molecular docking studies of Bacoside-A, an active component of *Bacopa monnieri* with DJ1 for anti-Parkinson's drug design. Biomirror. 2013;4:1-4.
418. Rajathei DM, Preethi J, Singh HK, Rajan KE. Molecular docking of bacosides with tryptophan hydroxylase: A model to understand the bacosides mechanism. Nat Prod Bioprospect. 2014;4(4):251-5. doi: 10.1007/s13659-014-0031-5.
419. Bagchi P, Anuradha M, Kar A. Pharmacophore modeling and docking studies of SNCA receptor with some active phytocompounds from selected ayurvedic medicinal plants known for their CNS activity. Adv Intell Syst Comput. 2018;672:1-9. doi: 10.1007/978-981-10-7512-4_1.
420. Leonard J, Seth B, Sahu BB, Singh VR, Patra N. Statistical optimization for enhanced Bacoside A production in plant cell cultures of *Bacopa monnieri*. Plant Cell Tiss Organ Cult. 2018;133(2):203-14. doi: 10.1007/s11240-017-1373-6.
421. Iqbal S, Balasubramanian ARK, Gunasekaran K. Efficacy of flavonoids and xanthonoids on alzhiemer's through multiple targeting as evidenced by cross docking. Am J Drug Deliv Ther. 2016;3:1-12.
422. Lavinya BU, Martin SJ, Jayakumar P, Jena B, Samarpita S, Sabina EP. *In-vitro* antimicrobial potential of *Bacopa monnieri* and *in-silico* OMPX inhibitory activity of its active components. J Chem Pharm Res. 2016;8:294-300.
423. Emran TB, Rahman MA, Uddin MMN, Dash R, Hossen MF, Mohiuddin M, et al. Molecular docking and inhibition studies on the interactions of *Bacopa monnieri's* potent phytochemicals against pathogenic *Staphylococcus aureus*. DARU J Pharm Sci. 2015;23:1-8.
424. Eswari JS, Yadav M. New perspective of drug discovery from herbal medicinal plants: *Andrographis paniculata* and *Bacopa monnieri* (terpenoids) and novel target identification against *Staphylococcus aureus*. S Afr J Bot. 2019;124:188-98. doi: 10.1016/j.sajb.2019.05.013.
425. Joardar S, Ghosh S, Gupta S, Ganguli S. *In-vitro* and computational assessment of genotoxic potential of active constituents present in three medicinally important plant extracts. Int J Curr Res Biosci Plant Biol. 2017;4(7):119-28. doi: 10.20546/ijcrbp.2017.407.015.
426. Desai NS, Gore M. Computer aided drug designing using Phytochemicals- Bacoside A3 and myricetin and nitric oxide Donors-S-nitroso N-acetylpenicillamine and nitroglycerin as a potential treatment of pancreatic cancer. J Comput Sci Syst Biol. 2012;05(1):1-8. doi: 10.4172/jcsb.1000083.
427. Kothandan S, Purushothaman I, George SP, Purushothaman SR, Sulochana MK. Molecular docking and density function theory studies of compounds from *Euphorbia hirta* and *Bacopa monnieri* to zika virus structural and nonstructural proteins. Phcog Mag. 2018;14(57):481-7. doi: 10.4103/pm.pm_89_17.
428. Lavinya B U, Swaminathan M, Bhattacharya Y, Tandon S, Evan Prince S. *In-vivo* anti-hyperglycemic potential of brahmigritham and docking studies of its active components against protein kinase C and CD38. J Food Biochem. 2015;39(6):642-52. doi: 10.1111/jfbc.12166.

Cite this article: Mondal S, Bhar K, Mondal P, Panigrahi N, Sahoo SK, Swetha P, *et al*. In Quest of the Mysterious Holistic Vedic Herb *Bacopa monnieri* (L.) Pennell. Pharmacog Res. 2023;15(3):410-54.