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Research Article

A review on the potential of bacosides as therapeutic lead molecules

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Abstract

The Ayurvedic medicinal system employs a holistic approach to health, utilizing the synergistic properties of organic resources. The Ayurvedic herb *Bacopa monnieri* (L.) Wettst. (Brahmi) contains several phytoconstituents mainly saponins (bacosides) and flavonoids. Among the saponins, bacosides are the main active phytoconstituent that can be extracted from Brahmi. The most potent small molecule component that has been utilized for Computer Aided Molecular Docking experiments is Bacoside –A. The aim of this current review is to critically summarize the successful investigations regarding the role of bacosides and their effects against several diseases, which can be further utilized in the drug industry.

Keywords: *Bacopa monnieri*, phytoconstituents, saponins, bacoside, drug.

INTRODUCTION

In the folklore of Indian medicine, several herbs have been used traditionally as health tonics. Phytochemicals are different non-nutritive substances that are derived from these plants that do have some health benefitting properties (Craig, 1997). The different plant products that are consumed as foods are rich in different types of terpenoids, phenolic compounds, pigments and natural antioxidants that have the capacity to protect the body from different diseases like heart ailments, diabetes, hypertension, hypercholesterolemia, osteoporosis, cancer and different other medical conditions (Craig, 1997; Murkies, et al, 1998).

Bacopa monnieri (L) Wettst, is a well-known plant having several common names which evidences its continuous use as a nootropic; such as water hyssop, Brahmi, Bramabhi, and Nirabarhmi. Morphologically it is a creeping plant generally abundant in warm, marshy wetlands, often colonial in their distribution. Members have been reported from Indian subcontinent, East Asia, Australia, and the United States. *Bacopa* has white to light purple flowers and small leaves, and is a rich genera with over 100 species attributed to it (Lurie, 2015; Russo & Borrelli, 2005; Shinomol & Muralidhara, 2011; Williamson, 2002). Ayurvedic physicians and the practitioners of the traditional system of medicine

of India have relied on *Bacopa* for more than thousand years, and we can find scriptures such as Charaka Samhita (2500 B.C.) and the Susrata Samhita (2300 B.C.) containing references of the use of this plant, where it has been reported to impart action on the central nervous system (CNS) (PV Sharma, 2011; Rai, et al, 2003). Over the years it has been described as a brain tonic and recommended for the management of anxiety, poor cognition, and lack of concentration (Russo and Borrelli, 2005). *Bacopa* has also been reported for its efficacy towards the treatment of numerous inflammatory conditions such as asthma, bronchitis, dropsy, and rheumatism (Channa et al., 2006).

According to the summary report that was submitted to the Department of Ayush, Ministry of Health and Family Welfare in August 2008, *Bacopa monnieri* is considered as one of the most popular medicinal plants due to its broad range of therapeutic properties and generally desired for export development (Saini et al., 2012). Animal research has shown that the *Bacopa monnieri* extracts modulate the expression of certain enzymes involved in generation and scavenging of reactive oxygen species in the brain (Gohil & Patel., 2009). It was suggested that the adaptogenic properties of the herb would be beneficial in the management of stress related conditions also. The pharmacological properties of Brahmi were studied thoroughly and its activities were mainly due to the presence of a special type of saponin

called “*bacosides*” (Behera et al., 2016). Bacoside-A, a family of compounds extracted from this plant, is a folk-medicinal substance believed to exhibit therapeutic properties, particularly enhancing cognitive functions and improving memory (Malishev et al., 2017). Bacosides are the putative bioactive component which was placed second in the most important medicinal plants’ list by the Export-Import Bank of India. Among the bacoside components, Bacoside-A was found to be more pharmacologically active than Bacoside-B (Majumdar et al., 2013). Bacosides are rich antioxidants that terminate the attack of free radicals and thus reduce the risk of certain disorders like cancer, emphysema, cirrhosis, atherosclerosis, arthritis etc. proving its efficiency as a therapeutic (Murthy et al., 2006).

This review focuses on demonstrating the comparative binding pattern of bacosides with the responsible protein molecule as a drug target, hence understanding the possible interactions and/or mechanism of action and portraying Bacoside-A constituent as a potential inhibitor of different disease modifier proteins. Thus, as the gradual requirement of natural product-based drug discovery increases due to their less potential side effects, bacosides will have to be investigated towards virtual screening-based pipelines of drug discovery.

CHEMICAL ANALYSIS

Researchers performed several techniques for the chromatographic separation of different Bacosides present in the extracts of *Bacopa monnieri*. They successfully developed a simple, sensitive and reproducible HPTLC method for the determination of Bacoside-A from the methanolic extract of *Bacopa monnieri* by performing TLC on stationary phase i.e. Silica gel 60 F₂₅₄ with a solvent system Toluene : Ethylacetate : Methanol : Glacial acetic acid (3:4:3:1 v/v). The major Bacosides in *B. monnieri* as bacoside I, bacoside A₃, bacoside II, bacosasaponin C isomer and bacosasaponin C, of which the last four saponins constituted Bacoside-A (Table 1) (Pawar and

Jadhav, 2015; Sekhar, et al, 2019). Bacoside-A along with Bacosides I constitute more than 90% w/w of the total saponins present in Brahmi (Lal & Baraik, 2019).

Quantification of Bacoside-A by HPTLC method and fingerprinting of the in-house mother tincture (*Bacopa monnieri*) were developed and samples of homeopathic medicines were marketed in India by using Dichloromethane: Methanol: Water as a solvent system (Pawar & Jadhav, 2015). Chemically, bacosides are dammarane-type tritreprenoid saponins. Bacoside-A usually co-occurs with Bacoside-B; the latter differing only in optical rotation and probably an artifact produced during the process of isolating Bacoside-A (Gohil & Patel, 2009; Behera et al., 2016).

Computational Studies using Active principles of *Bacopa* with special reference to Bacosides

The process of drug discovery includes the initial construction of a library of natural compounds from various sources which typically has a size of approximately 1 lakh compounds. Following this the library is screened based on the properties of Lipinski’s rule of five and ADMET properties followed by analysis of quantitative structure activity relationships (QSAR).

As a result of these screening, the potential library size is reduced to around 1000 compounds which are known as the hits. These hits are then analyzed for their efficacy in binding and interacting with the target protein associated with the disease, which involves the processes of docking, simulation and post docking scoring. This results in the proposal of 2 or 3 potential leads, which can be explored using conventional clinical trial experiments; which if successful, results in a new drug being released into the market following FDA approval. The process of *in silico* screening not only brings down the costs of the experimental procedures but also reduces the time taken to experimentally justify the conformational, chemical and biological efficacy of the compound(s) in question. Thus,

Table 1: Chemistry of Bacosides

Compound	Constituents	Chemical name	Chemical Formula
Bacoside A (Mundkinajeddu, and Agarwal, 2012; Behera, et al, 2016; Sekhar, et al, 2019)	Bacoside A3	[α-L-arabinofuranosyl-(1→2)-{β-D-glucopyranosyl-(1→3)}-glucopyranosyl] β-D-	C ₄₁ H ₆₈ O ₁₃
	Bacoside II	[α-L-arabinofuranosyl-(1→2)-{β-D-glucopyranosyl-(1→3)}-glucopyranosyl] β-D-	
	Bacosasaponin C	α-L-arabinofuranosyl-(1→2)-{β-D-glucopyranosyl-(1→3)}-α-L-arabinopyranosyl]	
	Jujubogenin isomer of bacosasaponin C	[α-L-arabinofuranosyl-(1→2)-{β-D-glucopyranosyl-(1→3)}-α-L-arabinopyranosyl]	
	Bacoside N1	β-D-glucopyranosyl-(1→3)-β-D-glucopyranosyl]	C ₄₁ H ₆₈ O ₁₃
Bacoside B (Mundkinajeddu, and Agarwal, 2012; Behera, et al, 2016; Sekhar, et al, 2019)	Bacoside N2	β-D-glucopyranosyl-(1→3)-glucopyranosyl] β-D-	C ₄₇ H ₇₆ O ₁₈
	Bacoside IV	β-D-glucopyranosyl-(1→3)-α-L-arabinopyranosyl]	C ₄₁ H ₆₆ O ₁₃
	Bacoside V	β-D-glucopyranosyl-(1→3)-arabinopyranosyl] α-L-	C ₄₁ H ₆₆ O ₁₃

this process of virtual screening is an established and well documented area of research.

Reverse virtual screening, is nowadays being employed which enables us to find the unknown protein targets of active compounds or additional targets of existing drugs (drug repositioning) (Ranjan, et al, 2015). Almost 20% of the total 84 new drugs that were approved by the FDA for market use in the year 2013 were existing drugs, a data which implies that that drug repositioning plays a key role in drug discovery. Over the years as virtual screening studies are reaching their crescendo, more and more chemical compounds are exhibiting promiscuous activity and binding to multiple proteins, thus making specific target identification an important step in the fields of drug discovery and biomedical research (Majumdar et al., 2013). Many reverse screening methods can be used to search for the protein targets of molecules, of which the earliest approach was the use of expensive and time-consuming biological assays (Rajani, 2008). However, with the spontaneous development of Big Data and computational techniques, computer-aided reverse screening methods are playing an immensely important role in predicting the off-target effects and side effects of the drugs as well as in drug repositioning (Sato et al., 2006).

The result of study of the antimicrobial activity of terpenoid-based plant extracts against antibiotic resistant

microorganisms. The study involved use of phytochemicals from herbal medicinal plants *Bacopa monnieri* and *Andrographis paniculata*. Initially, phytochemical tests were performed for both the plants to screen for the presence of phytochemicals. *In silico* analysis of phytochemicals was studied against multidrug resistant (MDR) strains of methicillin resistant *Staphylococcus aureus*; where target proteins were identified using database mining. Subsequently, molecular docking revealed the interaction of chosen terpenoid (Bacoside, Bacopa saponin, andrographin and β -sitosterol) against the identified target proteins (PDB entry 2X4K & 2IHY) of MRSA.

Careful analysis of interactions revealed that Andrographin and Bacoside were more specific towards their interactions with the chosen targets from *Staphylococcus aureus*. This study documents the antimicrobial property of medicinal extracts of *Bacopa monnieri* and *Andrographis paniculata* against methicillin resistance *Staphylococcus aureus* and establishes the interaction of current phytochemicals involved in antimicrobial activity through an in-silico approach to reduce the cost incurred in experimental efforts.

The following section contains disease specific insights (Table 2 and Table 3); where bacosides have been used as an important phyto-constituent and potential modulator of cognate target proteins.

Table 2: Therapeutic uses of Bacoside as proved by in silico studies and pre-clinical application as extract.

SI No	Disease	Pre-clinical application of bacoside	Computer aided designing of drugs using bacoside
1	Breast cancer, colon and prostate cancer	A combination dose of bacoside I and bacoside II confirmed apoptosis (Palethorpe, et al, 2018).	Estimated free energy of ligand-protein interaction was found < -5.2 for MDM2-p53 auto-regulatory loop, Caspase-3, p53, Bcl2 alpha isoform, checkpoint kinase-1, palmitoyl protein thioesterase 1, indicating that expression of these proteins might be changed after oral administration of DCM fraction (Mallick, et al, 2015) which is mainly due to bacosides (Peng, et al, 2010; Kalachaveedu, et al, 2015).
2	Glioblastoma tumor cell	24h dose of 150 μ g/ml extract on GBM cell line (John, et al, 2017).	Docking and 50ns simulation of Bacoside A binding to CAMK2A. CAMK2A (Figure 2) is direct target for Bacoside A (John, et al, 2017).
3	Pancreatic cancer	MMPs are up regulated in every type of cancer and poor survival rate is associated with high MMP. Direct application Bacopa extract on MMP s are not studied (Sharath, et al, 2010).	MMP2 and MMP 9 (Figure 2) have been successfully docked with bacoside A3- Myricetin combination structure with a high docking score of 9276 and 11180 respectively. This combination can be useful for future drug designing (Desai and Gore, 2012).
4	Alzheimer's Disease	10 μ Amyloid Beta 42 added with bacoside showed increasing cell viability by 40%.	Significantly interacts with 1B4F (Figure 2) protein in silico with a number of more rotatable bonds and with a high score of GPCR ligand showing high binding affinity. High docking score (-6.84) and binding energy (-48.86) was also found with the target molecules found in literature (Ravel and Jency, 2013).
		Standardized extract (Baconize@300 mg) twice a day orally for 6 months results in improvement in cognitive function (Goswami, et al, 2011).	
		-	Target site 1: Significant interaction between bacoside and LRRK ₂ with binding affinity -7.5Kcal/mol. Binding produces 10H bonds at receptor ligand site.
5	Parkinson's Disease	-	Target site 2: Bacoside A interacted at the reported active binding site of protein DJ-1 and binding atomic coordination is similar with the template complex coordination (Chandrasekhar, et al, 2013).

Table 3: Therapeutic intervention of bacoside with reference drugs.

Disease	Purpose of Drug	Reference drug	Mode of action of bacoside	Adverse effect of reference drug	Reference
Diabetes	Reducing liver oxidative stress	Glibenclamide	Decreasing the liver enzyme Aspartate Aminotransferase (AST) and Alanine transaminase ALT	Patients with renal impairment and elderly with age related decline in renal function at a great risk of developing severe long-lasting hypoglycemia.	Giribabu, et al, 2015; Shanmugam and Ramalingam, 2019.
Hypo thyroidism	Increase T4 concentration without enhancing hepatic lipid peroxidation	Levothyroxin	Increase T4 concentration by 41% without enhancing LPO.	Levothyroxin induced liver dysfunction in few cases.	Ohmori, et al, 1999.
Epilepsy	Increase in GAD and GABA binding resulting in anticonvulsant	Benzodiazepine	Reverse the receptor alteration of GABA and GAD gene expression to near control.	Long term use include drug dependence and neurotoxicity	Feldblum, et al, 1990; Mathew, et al, 2012.

CANCER

Test-tube and animal studies have found that *Bacopa monnieri* may have anti-cancer properties. Bacosides, have been shown to inhibit the growth of breast cancer and colon cancer in test-tube studies (Ryan Raman, 2019). The anti-cancer activity of the ethanolic extract of *Bacopa monnieri* against human breast cancer cell line (MDA-MB-468) may be due to the synergistic effect of the secondary metabolites present in the extract. Increased permeability by over-expression of AQP 1, a transmembrane protein responsible for water transport is a distinct feature of many human cancer cells including those of breast, colon, and prostate cancer (Figure 1).

Aquaporin-1 (AQP1) has been proposed as a dual water and cation channel that when upregulated in cancers enhances cell migration rates (De lesio et al., 2019). Bacoside II inhibits the activity of aquaporins AQP 1, thus reducing endothelial cell migration and induces apoptosis (Patil et al., 2014; Leung et al., 2017; Palethorpe et al., 2018; De lesio et al., 2019). Different cell lines like Colon (HT29, Colo320, and Caco2), Lung (A549), Cervix (HeLa, SiHa), and Breast (MCF-7, MDAMB-231) are tested *in vitro* and *in silico* with the application of *B. monnieri* extract (Mallick, et al, 2015). Interaction of protein ligand studies showed that the proteins have changed after bacoside administration (Peng et al., 2010; Kalachaveedu et al., 2015; Mallick et al., 2015) Table 2. Glioblastoma multiforme is a highly malignant brain tumor. Herbal extracts of *Bacopa monnieri* having anticancer properties has been used for the development of brain cells because of its neuroprotective properties which have shown to be promising in treating cancer. Bacoside A induced cell cycle arrest and apoptosis by considerably exhibiting cytotoxicity on U-87 MG cells. The fraction of early apoptotic cells in control was low that increased substantially after Bacoside A treatment. Thus, it indicated that Bacoside A has a possible anticancer activity that could be inducing cell cycle arrest in sub-G0 phase and apoptosis in GBM *in vitro* (Aithal & Rajaswari, 2019). Another study showed that the extracts of *Bacopa monnieri* and its bioactive component Bacoside A can generate dosage associated tumor specific disturbances in the hydrostatic

pressure balance of the cell (Figure 1) via a mechanism involving excessive phosphorylation of calcium/calmodulin dependent protein-kinase IIA (CaMKIIA/CaMK2A) enzyme which is further involved in the release of calcium ions from the smooth ER networks. High intracellular calcium stimulated massive macropinoscytotic extracellular fluid intake which in turn caused cell hypertrophy in the initial stages followed by excessive macropinosome enlargement and fluid accumulation associated with organelle congestion, cell rounding, cell swelling and rupture of glioblastoma cell membranes. All these events culminated into a non-apoptotic, physical non-homeostasis associated glioblastoma tumor cell death. These results identified glioblastoma tumor cells to be specific target of the tested herbal medicine and therefore can be exploited as a safe anti-GBM therapeutic (John et al., 2017). *In silico* studies concluded that, bacosides are the probable molecule for CaMK2A phosphorylation regulation and it binds to CaMK2A activation domain with the highest glide ratio (John et al., 2017) Table 2. Potentiality of bacosides a therapeutic (Sharath et al., 2010) has also being established by the *in silico* study of pancreatic cancer matrix metalloproteinase enzyme (MMP 2 and MMP 9). These two enzymes have been successfully docked with Bacoside A-Myricetin combination (Desai & Gore, 2012) (Table 2, Figure 2).

COGNITIVE impairment–Alzheimer’s disease

When fat molecules react with free radicals, they undergo a process called lipid peroxidation. Lipid peroxidation is linked to several conditions such as Alzheimer’s, Parkinson’s and other neurodegenerative disorders which affect the neurons in the human brain (Ryan Raman, 2019). Until now ND has no cure and represents a high cost for the health system and patients’ families (Behera et al., 2016).

Alzheimer’s disease is an age-associated, irreversible, progressive neurodegenerative disease, characterized by severe memory loss, behavioral changes, and a notable decline in cognitive function. Beta amyloid toxicity to neuronal cells has been identified as one of the major features in Alzheimer’s disease and these oligomers might damage the neuronal NMDA type glutamate receptors (Urdaneta et al., 2018). The NMDA type glutamate receptors

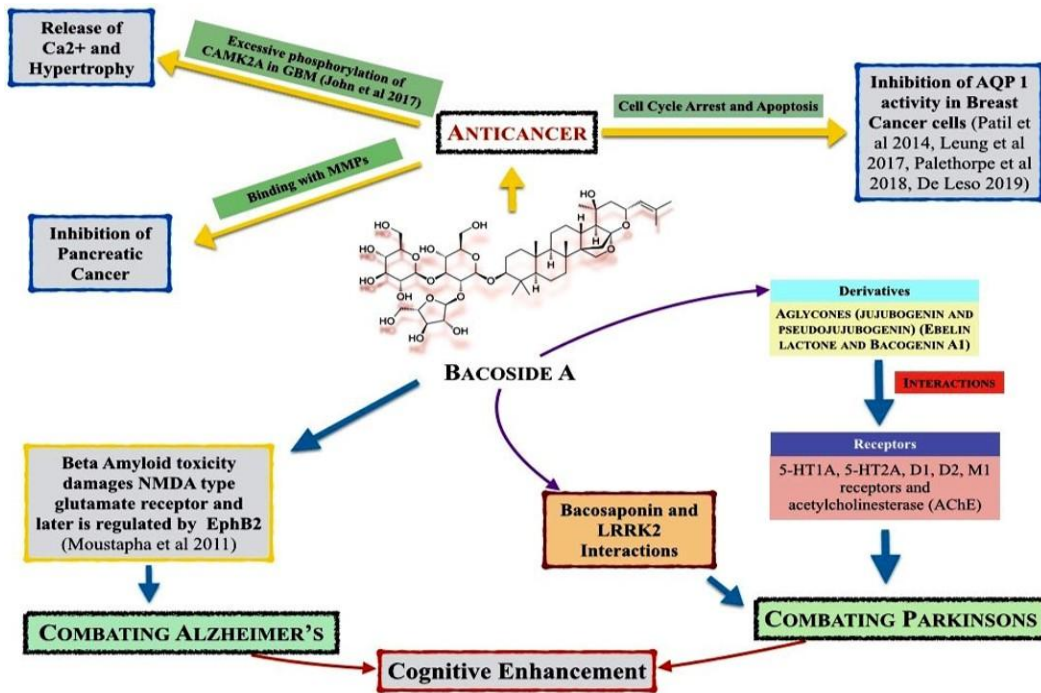


Figure 1. Mode of action of bacosides in combating some common diseases.

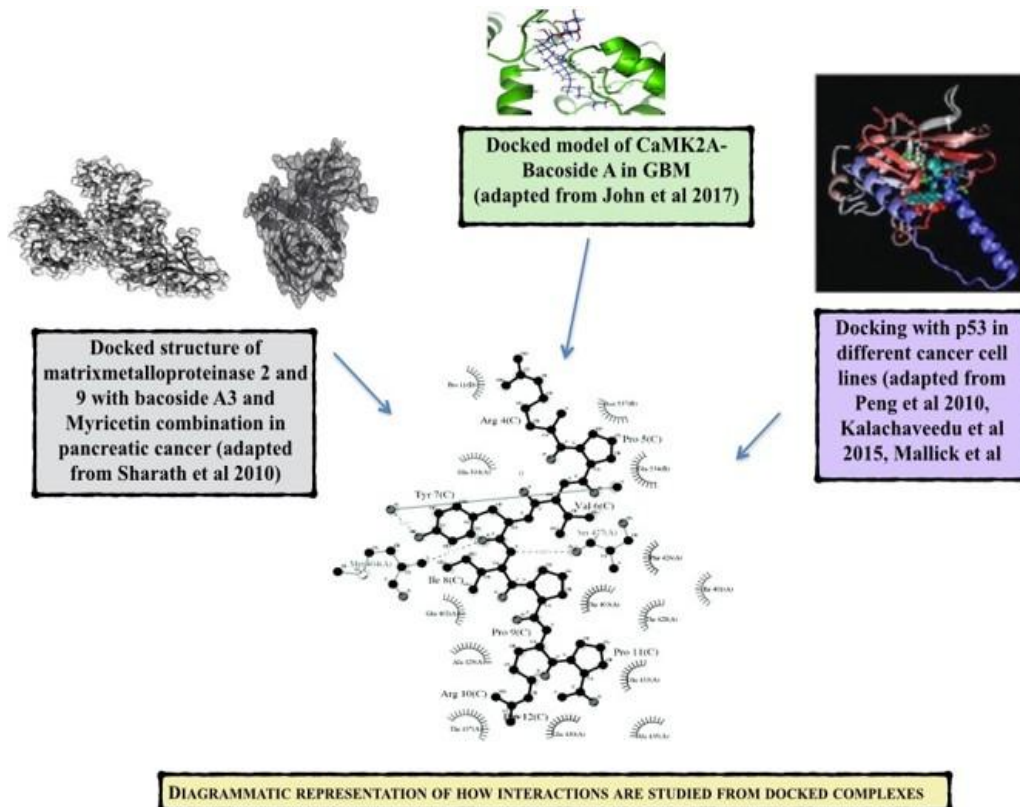


Figure 2. Docked complexes of bacosides with target protein.

is regulated by the receptor tyrosine kinase EphB2 (PDB ID: 1B4F) Figure 1. *Bacopa monnieri* as one of the top three herbs in Alzheimer's disease has been suggested as it functions by stabilizing the structural and functional integrity of the membrane (Lal & Barik, 2019). Bacoside-A exerted

significant inhibitory effects upon cytotoxicity, fibrillation, and particularly membrane interactions of amyloid-beta(1-42) (Aβ42), the peptide playing a prominent role in Alzheimer's disease progression and toxicity. Specifically, researchers showed that pre-incubation of Bacoside-A

with A β 42 significantly reduced cell toxicity and inherited fibril formation. In parallel, spectroscopic and microscopic analyses revealed that Bacoside-A blocked membrane interactions of A β 42, while formation of A β 42 oligomers was not disrupted. These interesting phenomena suggested that inhibition of A β 42 oligomer assembly into mature fibrils and blocking membrane interactions of the oligomers were likely the underlying factors its putative physiological benefits (Malishev, et al., 2017).

The need for development of therapeutics came from the study that, amyloid modulators scylloinositol (ELN005) and Resveratrol are presently in clinical trial for Alzheimer's disease but safety concerns have been raised for each (Salloway et al., 2011; Mullane & Williams, 2013). Current drugs used to treat the diseases like Donepezil also have unpleasant side effects and doctors are in search of alternatives (Ravel & Jency, 2013). Dementia is associated with Alzheimer's disease and EPH2 gene play a crucial role in NMDA signaling pathway helping to restore cognitive functions. In silico analysis indicates that Bacoside A has a high docking score and it shows significant interaction with 1B4F protein which is abundantly found in cytoplasm, but drug likeness is moderate (Ravel & Jency, 2013; Manakadan et al., 2015) (Table 2).

COGNITIVE impairment–Parkinson's disease

Neurodegenerative Parkinson's disease (PD) is associated with aggregation of protein alphasynuclein and selective death of dopaminergic neurons, thereby leading to cognitive and motor impairment in patients. Bacosides reduces alphasynuclein aggregation, prevents dopaminergic neurodegeneration and restores the lipid content (Chandrasekhar et al., 2013; Lal & Barik, 2019). Another cause of PD is higher activity of Leucine rich repeat kinase 2 (Jain et al., 2013). Two chemicals in *Bacopa*, bacosides A and B, improve the transmission of impulses between nerve cells in our brain. The neurobiological effects of these isolated molecules were found to increase protein kinase activity and new protein synthesis, specifically in cells in region of the brain associated with long-term memory (Kumar, et al, 2016).

Bacopa monnieri may provide a platform for future drug discoveries and novel treatment strategies in PD and can act as anti-parkinsonian agent (Lal & Barik, 2019).

Target site 1 (Table 2): From the KEGG pathway database it was found that probably inhibiting the activity of DJ-1 may effectively reduce the Parkinson's symptoms. Investigation of active binding sites with DJ-1 protein and docking Bacoside-A with active binding sites gives the idea of the target site and drug interaction with high affinity and this study can be used to investigate the effect of inhibitors on the functional active site of enzyme.

Target site 2: Bacoside-A is a potential inhibitor of leucine rich Repeat Kinase 2 was proved by the in-silico studies

proving its efficiency as a therapeutic (Jain et al., 2013; Jain et al., 2017). It has been proposed as a major constituent in inhibiting enzymatic activities of LRRK₂ (Table 2).

OTHER therapeutic interventions using Bacoside (Table 3)

In Ayurveda, *Bacopa* is used as a nootropic and has been reported to improve intellect and memory and thus finds its way as an essential component of numerous Ayurvedic herbal formulations that target the CNS and manage conditions such as memory, lack of concentration, and anxiety (Aguiar & Borowski, 2013). Cardio tonic, nervine and diuretic properties of *Bacopa* have also been documented along with its effects on memory and cognition (Pase et al., 2012; Stough et al., 2013; Kongkeaw et al., 2014). Ayurvedas also used *Bacopa* to treat inflammatory conditions such as asthma and arthritis and several studies have documented the anti-inflammatory properties of *Bacopa* in animal models of arthritis (Viji & Helen, 2008; Viji & Helen, 2011; Viji et al., 2010a,b). These studies demonstrate that *Bacopa* is able to modulate systemic inflammation. Apart from these Bacoside-A helps in promotion of glycolysis by elevating Hexokinase A and G-3-P dehydrogenase as well as it has an important effect on hepatic key enzymes for carbohydrate metabolism. Bacoside-A has been proved to have therapeutic activity which infers in modulating hepatic key enzymes by preventing defect in carbohydrate metabolism against T2DM (Type 2 Diabetes mellitus) comparing with a reference drug (Table 3) (Gurubabu et al., 2015; Shanmugam & Ramalingam, 2019).

Researchers showed that T4 concentration was increased by Brahmi suggesting its thyroid-stimulating role. Bacosides could increase T4 concentration by 41% without enhancing hepatic lipid peroxidation (LPO) suggesting that it can be used as a thyroid-stimulating drug. Hepatic LPO was decreased and superoxide dismutase (SOD) and catalase activities were increased by administration of bacoside which is the main constituent of *Bacopa monnieri* extract. It is thus suggested that Brahmi may be used in the regulation of hypothyroidism (Table 3) (Kar et al., 2002).

Bacoside proves in efficiency in the treatment of epilepsy also. Gama aminobutyric acid (GABA) is a naturally occurring amino acid that works as a major inhibitory neurotransmitter in the central nervous system (Joseph et al., 2002; Jin et al., 2003). In TLE (Temporal Lobe Epilepsy) there is an imbalance between excitatory and inhibitory synaptic transmission key brain areas as a result of decrease in GABA mediated inhibition. It exerts an inhibitory action in all forebrain structures and plays a pathogenesis role in epilepsy (Smart, 1997). Decarboxylation of glutamate to GABA is carried out by an enzyme Glutamate decarboxylase (GAD). GAD is the rate limiting enzyme of GABA synthesis and is used as a marker for GABAergic activity (Sophie et al., 1990). There is significant decrease in GAD and GABA

binding in epileptic and histologically damaged cortex (Lloyd et al., 1981). Bacoside treatment showed anticonvulsant property (Table 3) and potentially proves its efficiency as therapeutic (Mathew et al., 2012). Thus, in summary, it can be stated that Bacosides can be used for interventions in diseases such as cancer and neurodegenerative disorders such as Parkinson's and Alzheimer's as well as an anti-inflammatory component to treat asthma and arthritis. Thus, with the world health organization emphasizing the necessity to improve the livelihood quotient of the elder members of the society, *Bacopa* and Bacoside based intervention strategies presents exciting opportunities for explorations using traditional high throughput screening as well as computer aided strategies for finding fresh targets and modulation of molecular pathways.

Computational Prediction of Molecular Properties and Bioactivity

To predict the molecular properties and bioactivity of the two major classes of bacosides, we performed a simple in silico check using Molinspiration using canonical SMILES obtained from PUBCHEM and found that both Bacoside A and Bacoside B had more than the acceptable standard of Lipinski violations (total 3 which is greater than the acceptable 1) (Figure 3). Further, the bioactivity scores of both the compounds were not satisfactory (Figure 4). This analysis leads us to comment that bacosides in their original form would not be suitable lead molecules but that need to be chemically modified to achieve the proper bioactive form which may serve as a lead for future drug discovery studies.

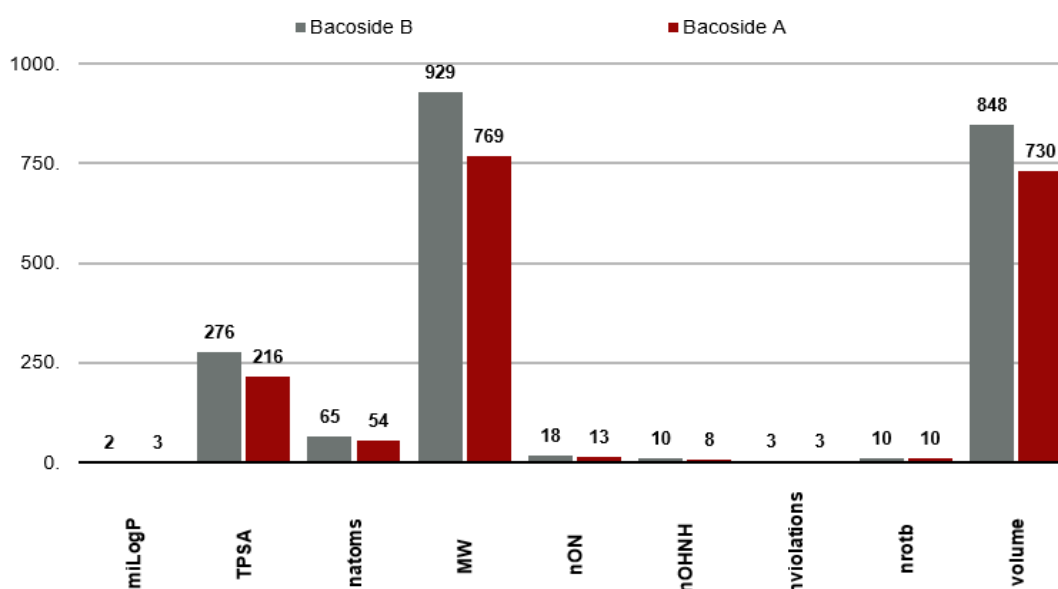


Figure 3. Graphical representation of molecular property data of Bacosides.

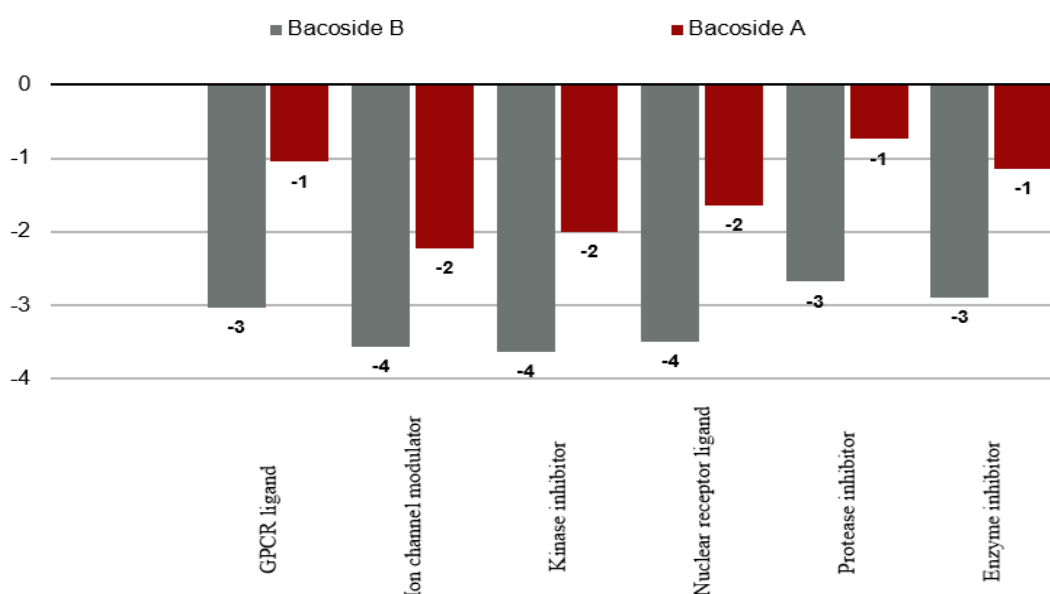


Figure 4. Graphical representation of predicted bioactivity data of Bacosides.

CONCLUSION

It is concluded by the above literature that *Bacopa monnieri* is a highly potential medicinal plant that is being used for a long time. It was established from the pharmacological studies that bacosides were responsible for the biological activity of *Bacopa monnieri*. The present review attempts to summarize the chemistry and various health beneficial properties of bacosides against various diseases. Extensive researches still required in the future to validate its effectiveness in various other disorders and to find out the impact of the extracts on gene expression. Researchers are also now trying biotechnological tools to obtain higher yields of bacosides from the plant as it is the exclusive source of these immensely useful compounds. Many studies indicated that there may exist interactions between herbal medicines and synthetic drugs. So, stringent clinical experiments are necessary to negotiate these issues. Drug discovery and development is a costly, long and difficult process. The emphasis now is not just on finding new ways to treat human disease, but also on improving the quality of people's life in general. The use of new computer-aided drug design techniques has the ability to accomplish both of these goals and can improve the efficiency of the process as well as it reduces costing. Thus, there is still a lot of scope in these fields for better utilization of this wonder plant.

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REFERENCES

- Aguiar S, & Borowski T(2013). Neuropharmacological review of the nootropic herb *Bacopa monnieri*. *Rejuvenation Res.* 16(4): 313–326. <https://dx.doi.org/10.1089%2Fnej.2013.1431>
- Aithal MGS, & Rajeswari N(2019). 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.* 7(1): 25-32. <https://dx.doi.org/10.14791%2Fbtr.2019.7.e21>
- Behera S, Mallick B, Tiwari TN, & Mishra PC(2016). A Short Review on Physico-Chemical Properties of *Bacopa monnieri* L. *Int J of Medicinal Plants.*110: 735-741.
- Chandrasekar S, Thangarajan S, Loganathan S, Sundaram S, & Kumarasamy P(2013). Molecular docking studies of Bacoside-A, an active component of *Bacopa monnieri* with DJ1 for Anti-Parkinson's drug design. *Biomirror.* 4:67-70.
- Channa S, Dar A, Anjum S, Yaqoob M, & Atta UR(2006). Anti-inflammatory activity of *Bacopa monnieri* in rodents. *J Ethnopharmacol.* 104: 286–289. <https://doi.org/10.1016/j.jep.2005.10.009>
- Craig WJ(1997). Phytochemicals: guardians of our health. *Journal of the American Dietetic Association.* 97: S199-S204. [https://doi.org/10.1016/S0002-8223\(97\)00765-7](https://doi.org/10.1016/S0002-8223(97)00765-7)
- De Ieso ML, Pei JV, Nourmohammadi S, Smith E, Chow PH, Kourghi M, Hardingham JE, & Yool AJ(2019). Combined Pharmacological administration of AQP1 ion channel blocker AqB011 and water channel blocker Bacopaside II amplifies inhibition of colon cancer cell migration. *Scientific Reports.* 9(1): 12635. <https://doi.org/10.1038/s41598-019-49045-9>
- Desai NS, & Gore M(2012). 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 SysBiol.* 5(1): 1-8. Doi:10.4172/jcsb.1000083
- Feldblum S, Ackermann RF, & Tobin AJ(1990). Long term increase of glutamate decarboxylase mRNA in a rat model of temporal lobe epilepsy. *Neuron.* 5(3): 361-371. [https://doi.org/10.1016/0896-6273\(90\)90172-c](https://doi.org/10.1016/0896-6273(90)90172-c)
- Giribabu N, Eswar Kumar K, Swapna Rekha S, Muniandy S, & Salleh N(2015). *Vitis vinifera* (Muscat Variety) Seed Ethanolic Extract Preserves Activity Levels of Enzymes and Histology of the Liver in Adult Male Rats with Diabetes. *Evid Based Complement Alternat Med.* 2015: 542026. <https://doi.org/10.1155/2015/542026>
- Gohil KJ, & Patel AJ(2009). A review on *Bacopa monnieri*. Current research and future prospects. *Int J of Green Phar.* 4(1): 1-9. DOI: 10.4103/0973-8258.62156
- Goswami S, Saoji A, Kumar N, Thawani V, Tiwari M, & Thawani M(2011). Effect of *B monnieri* on cognitive functions in Alzheimer's disease patients. *International Journal of Collaborative Research on Internal Medicine and Public Health.* 3(4): 285-293. <http://iomcworld.com/ijcrimph/ijcrimph-v03-n04-01.htm>
- Jain C.K, Gupta A, Tewari A, Sharma V, Kumar VS, Mathur, & Sharma SK(2013). Molecular docking studies of bacoside from *Bacopa monnieri* with LRRK₂ receptor. *Biologia* 68(6): 1068-1071. DOI: 10.2478/s11756-013-0277-0
- Jain P, Sharma HP, Basri F, Priya K, & Singh P(2017). Phytochemical analysis of *Bacopa monnieri* (L.) Wettst. and their anti-fungal activities. *Indian Journal of Traditional Knowledge.* 16(2): 310-318. <http://nopr.niscair.res.in/handle/123456789/40107>
- Jin H, Wu H, Osterhaus G, Wei J, Davis K, Sha D, Floor E, Hsu C, Kopke RD, & Wu JY(2003). Demonstration of functional coupling between γ -aminobutyric acid (GABA) synthesis and vesicular GABA transport into synaptic vesicles. *Proc Natl Acad Sci.* 100(7): 4293-4298. <https://doi.org/10.1073/pnas.0730698100>
- John S, Sivakumar KC, & Mishra R(2017). Bacoside A induces tumor cell death in human Glioblastoma cell lines through catastrophic macropinocytosis. *Front Mol Neurosci.* 10(171): 1-22. <https://doi.org/10.3389/fnmol.2017.00171>
- Joseph J, Niggemann B, Zaenker KS, & Entschladen F (2002). The neurotransmitter γ -aminobutyric acid is an inhibitory regulator for the migration of SW 480 colon carcinoma cells. *Cancer Res.* 62(22): 6467-6469.
- Kalachaveedu M, Papacchan S, Sanyal S, Koshy T, & Telapolu S(2015). Isolation and evaluation of cytogenetic effect of Brahmi saponins on cultured human lymphocytes exposed *in vitro*. *Nat Prod Res.* 29 (12): 1118–1121. <https://doi.org/10.1080/14786419.2014.979416>
- Kar A, Panda S, & Bharti S(2002). Relative efficacy of three medicinal plant extracts in the alteration of thyroid hormone concentrations in male mice. *J Ethnopharmacol.* 81(2): 281-285. [https://doi.org/10.1016/s0378-8741\(02\)00048-x](https://doi.org/10.1016/s0378-8741(02)00048-x)
- Kongkeaw C, Dilokthornsakul P, Thanarangsarit P, Limpeanchob N, & Norman Scholfield C(2014). Meta-analysis of randomized controlled trials on cognitive effects of *Bacopa monnieri* extract. *J Ethnopharmacol.* 151(1): 528–535. <https://doi.org/10.1016/j.jep.2013.11.008>

- Kumar J, Gond P, Dabas R, Tripathi JS, Byadgi PS, Tewari P, Kumar S, & Rao RK(2016). Medicinal importance of *Bacopa monnieri* (L.) Pennell. *Indian Journal of Agriculture and Allied Sciences*. 2(3): 89-96.
- Lal S, & Baraik B(2019). Phytochemical and Pharmacological profile of *Bacopa monnieri*- an ethnomedicinal plant. *International Journal of Pharmaceutical Sciences and Research*. 10(3): 1001-1013. DOI: 10.13040/IJPSR.0975-8232. 10(3).1001-13
- Leung HW, Foo G, Banumurthy G, Chai X, Ghosh S, Mitra-Ganguli T, & VanDongen AMJ(2017). The effect of *Bacopa monnieri* on gene expression levels in SH-SY5Y human neuroblastoma cells. *PLOS One*. 12(8): e0182984. <https://doi.org/10.1371/journal.pone.0182984>
- Lloyd KG, Munari C, Bossi L, Stoeffels C, Talairach J, & Morselli PL(1981). Biochemical evidence for the alterations of GABA-mediated synaptic transmission in pathological brain tissue (stereo EEG or morphological definition) from epileptic patients. *Neuro- transmitters, Seizures, and Epilepsy*. 325-338.
- Majumdar S, Basu A, Paul P, Halder M, & Jha M(2013). Bacosides and Neuroprotection. *Natural products*: 3639-3660
- Malishev R, S S Niv, S Nandi, S Kolusheva, E Gazit, & Jelinek R(2017). Bacoside-A an Indian Traditional-Medicine Substance, Inhibits β -Amyloid Cytotoxicity, Fibrillation, and Membrane Interactions. *ACS Chem Neurosci*. 8(4): 884-891. <https://doi.org/10.1021/acscchemneuro.6b00438>.
- Mallick MN, Akhtar MS, Najm MZ, Tamboli ET, Ahmad S, & Husain SA(2015). Evaluation of anticancer potential of *Bacopa monnieri* L. against MCF-7 and MDA-MB 231 cell line. *Journal of Pharmacy & Bioallied Sciences*. 7(4): 325-328. DOI: 10.4103/0975-7406.168038
- Manakadan AA, Suja ST, Silvipriya KS, & Chithra J (2015). A computational in silico approach for identification of Indian Herbs for the treatment of Alzheimer's disease. *Research Journal of Pharmaceutical, Biological and Chemical sciences*. 6(1): 414-422.
- Mathew J, Balakrishnan S, Antony S, Abraham PM, & Paulose CS(2012). Decreased GABA receptor in the cerebral cortex of epileptic rats: Effect of *Bacopa monnieri* and Bacoside A. *Journal of Biomedical Science* 19(25): 1-13. <http://www.jbiomedsci.com/content/19/1/25>
- Mullane K, & Williams M(2013). Alzheimer's therapeutics: Continued clinical failures question the validity of the amyloid hypothesis – but what lies beyond? *Biochem Pharmacol*. 85(3): 289-305. <https://doi.org/10.1016/j.bcp.2012.11.014>
- Mundkinajeddu D, & Agarwal A(2012). Bacoside B the need remains for establishing identity. *Fitoterapia*. 87(1): 7-10. <http://dx.doi.org/10.1016/j.fitote.2013.03.011>
- Murkies AL, Wilcox G, & Davis SR(1998). Phytoestrogens. *Journal of Clinical Endocrinology & Metabolism*. 83: 297-303. <https://doi.org/10.1210/jcem.83.2.4577>
- Murthy PBS, Raju VR, Ramakrisana T, Chakravarthy MS, KumarKV, Kannababu S, & Subbaraju GV(2006). Estimation of Twelve *Bacopa* Saponins in *Bacopa monnieri* Extracts and Formulations by High-Performance Liquid Chromatography. *Chem. Pharm. Bull*. 54(6): 907-911. <https://doi.org/10.1248/cpb.54.907>
- Ohmori M, Harada K, Tsuruoka S, Sugimoto K, Kobayashi E, & Fujimura A(1999). Levothyroxin induced liver dysfunction in a primary hypothyroid patient. *Endocr J*. 46 (4): 579-83. <https://doi.org/10.1507/endocrj.46.579>
- Palethorpe HM, Tomita Y, Smith E, Pei JV, Townsend AR, Price TJ, Young JP, Yool AJ, & Hardingham JE(2018). The aquaporin 1 inhibitor bacopaside II reduces endothelial cell migration and tubulogenesis and induces apoptosis. *Int J Mol Sci*. 19(3): 653. <https://dx.doi.org/10.3390%2Fijms19030653>
- Pase MP, Kean J, Sarris J, Neale C, Scholey AB, & Stough C(2012). The cognitive-enhancing effects of *Bacopa monnieri*: a systematic review of randomized, controlled human clinical trials. *J Altern Complement Med*. 18(7): 647–652. <https://doi.org/10.1089/acm.2011.0367>
- Patil A, Vadera K, Patil D, Phatak A, Juvekar A, & Chandra N(2014). *In-vitro* anticancer activity and phytochemical analysis of *Bacopa monnieri* (L.) Wettst. *Int J Pharm Sci Res*. 5(10): 4432- 38. [http://dx.doi.org/10.13040/IJPSR.0975-8232.5\(10\).4432-38](http://dx.doi.org/10.13040/IJPSR.0975-8232.5(10).4432-38)
- Pawar SS, & Jadhav MG(2015). Determination and Quantification of Bacoside a from *Bacopa monnieri* (L) By High Performance Thin Layer Chromatography. *International Journal of Pharmacognosy and Phytochemical Research*. 7(5): 1060-1065.
- Peng L, Zhou Y, Kong de Y, & Zhang WD(2010). Antitumor activities of dammarane triterpene saponins from *Bacopa monniera*. *Phytother Res*. 24(6): 864–8. <https://doi.org/10.1002/ptr.3034>
- Rai D, Bhatia G, Palit G, Pal R, Singh S, & Singh HK(2003). Adaptogenic effect of *Bacopa monniera* (Brahmi). *Pharmacol Biochem Behav*. 75: 823–830. [https://doi.org/10.1016/s0091-3057\(03\)00156-4](https://doi.org/10.1016/s0091-3057(03)00156-4)
- Rajan KE, Preethi J, & Singh HK(2015). Molecular and Functional Characterization of *Bacopa monniera*: A Retrospective Review. *Evid Based Complement Alternat Med*. 2015:945217. <https://doi.org/10.1155/2015/945217>
- Rajani, M(2008). *Bacopa monnieri* a nootropic drug: In: RamawatKG, Merillon JM, editors. *Bioactive molecules and medicinal plants*. Berlin: Springer. 175-195.
- Ravel AS, & Jency S(2013). QSAR and docking studies on phytocompounds as lead molecule against Alzheimer's disease. *International Journal of Current Research*. 5(5): 1198-1201.
- Russo A, & Borrelli F(2005). *Bacopa monniera*, a reputed nootropic plant: an overview. *Phytomedicine: international journal of phytotherapy and phytopharmacology*. 12: 305–317. <https://doi.org/10.1016/j.phymed.2003.12.008>
- Ryan Raman(2019). 7 emerging benefits of *Bacopa monnieri*. *Nutrition*. <https://www.healthline.com/nutrition/bacopa-monnieri-benefits>
- Saini N, Mathur R, & Agrawal SS(2012). Qualitative and quantitative assessment of four marketed formulations of Brahmi. *Indian J Pharm Sci*. 74(1): 24-28. <https://doi.org/10.4103/0250-474x.102539>
- Salloway S, Sperling R, Keren R, Porsteinsson AP, Dyck CH, Tariot PN, Gilman S, Arnold D, Abushakra S, Hernandez C, Crans G, Liang E, Quinn G, Bairu M, Pastrak A, & Cedarbaum JM(2011). A phase 2 randomised trial of ELND005, Scylloinositol in mild to moderate Alzheimer's disease. *Neurology*. 77(13): 1253-1262. <https://dx.doi.org/10.1212%2FWNL.0b013e3182309fa5>
- Sato H, Shewchuk LM, & Tang J(2006). Prediction of Multiple Binding Modes of the CDK2 Inhibitors, Anilino-pyrazoles, Using the Automated Docking Programs GOLD, FlexX, and LigandFit: An Evaluation of Performance. *J. Chem. Inf. Model*. 46: 2552–2562. <https://doi.org/10.1021/ci600186b>
- Sekhar VC, Viswanathan G, & Baby S(2019). Insights into the Molecular Aspects of Neuroprotective Bacoside A and Bacopaside. *Curr Neuropharmacology*. 17(5): 438-446. <https://dx.doi.org/10.2174%2F1570159X16666180419123022>

- Shanmugam DB, & Ramalingam S(2019). Bacoside-A diminishes liver functional enzymes and improves carbohydrate metabolic key enzymes in streptozotocin a rat model of T2DM. *Biocatalysis and agricultural Biology*. 21: 101331. <https://doi.org/10.1016/j.bcab.2019.101331>
- Sharath R, Harish BG, Krishna V, Sathyanarayana BN, & Swamy HM(2010). Wound healing and protease inhibition activity of Bacoside A, isolated from *Bacopa monnieri* wettest. *Phytother Res*. 24(8): 1217-1222. <https://doi.org/10.1002/ptr.3115>
- Shinomol G.K, & Muralidhara(2011). *Bacopa monnieri* modulates endogenous cytoplasmic and mitochondrial oxidative markers in prepubertal mice brain. *Phytomedicine: international journal of phytotherapy and phytopharmacology*. 18: 317–326. <https://doi.org/10.1016/j.phymed.2010.08.005>
- Smart TG(1997). Regulation of excitatory and inhibitory neurotransmitter-gated ion channels by protein phosphorylation. *Curr Opin Neurobiol*. 7(3): 358-67. [https://doi.org/10.1016/s0959-4388\(97\)80063-3](https://doi.org/10.1016/s0959-4388(97)80063-3)
- Stough C, Scholey A, Cropley V, Wesnes K, Zangara A, Pase M, Savage K, Nolidin K, Lomas J, & Downey LA(2013). Examining the cognitive effects of a special extract of *Bacopa monniera* (CDRI08: Keenmnd): A review of ten years of research at Swinburne University. *Journal of pharmacy & pharmaceutical sciences*. 16(2): 254–258. <https://doi.org/10.18433/J35G6M>
- Urdaneta KE, Castillo MA, Montiel N, Semprún-Hernández N, Antonucci N, & Siniscalco D(2018). Autism spectrum disorders: Potential neuro-psychopharmacotherapeutic plant-based drugs. *Assay Drug Dev Technol*. 16(8):433-444. <https://doi.org/10.1089/adt.2018.848>
- Viji V, & Helen A(2008). Inhibition of lipoxygenases and cyclooxygenase-2 enzymes by extracts isolated from *Bacopa monniera* (L.) Wettst. *J Ethnopharmacol*. 118(2): 305–311. <https://doi.org/10.1016/j.jep.2008.04.017>
- Viji V & Helen A(2011). Inhibition of pro-inflammatory mediators: role of *Bacopa monniera* (L.) Wettst. *Inflammopharmacology*. 19(5): 283–291. <https://doi.org/10.1007/s10787-010-0046-4>
- Viji V, Kavitha SK, & Helen A(2010)a. *Bacopa monniera* (L.) wettst inhibits type II collagen-induced arthritis in rats. *Phytother Res*. 24(9): 1377–1383. <https://doi.org/10.1002/ptr.3135>
- Viji V, Shobha B, Kavitha SK, Ratheesh M, Kripa K, & Helen A(2010)b. Betulinic acid isolated from *Bacopa monniera* (L.) Wettst suppresses lipopolysaccharide stimulated interleukin-6 production through modulation of nuclear factor-kappaB in peripheral blood mononuclear cells. *Int Immunopharmacol*. 10(8): 843–849. <https://doi.org/10.1016/j.intimp.2010.04.013>
- Williamson EM(2002). *Major Herbs of Ayurveda*. Churchill Livingstone, Elsevier Limited.