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Original Article

Medhya Rasayana Ghrita to Phytosome Approach-*Centella asiatica* and *Bacopa monnieri* Bioactive Enriched Fractions

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ABSTRACT

Background Phytosomes overcome solubility, absorption, and stability limitations of crude extracts, leading to enhanced bioavailability, better therapeutic effect, and reduced required dose. **Purpose:** Conventional Ayurvedic formulations of Centella asiatica and Bacopa monnieri are administered as churna or ghrita, requiring prolonged high doses that reduce compliance in geriatric patients due to swallowing difficulties and gastrointestinal intolerance. Phytosomal systems, inspired by ghrita carriers, may enhance bioavailability, ensure consistent therapy, and enable dose reduction with improved adherence. **Methodology:** Phytosomes comprising bioactive rich fractions of traditionally well-known nootropic plants, *Bacopa monnieri* and *Centella asiatica* phytosome formulation were prepared, characterized, and evaluated for their neuroprotective and cognitive efficacy and potency using in-vitro methods. **Results:** Results of acetylcholinesterase inhibition at 78%, LOX inhibition potency at 48.67%, SOD activity at 28.39±5.84 and GSH potency at 42% found significant. The optimised batch showed particle size 169.2-185.3 nm with zeta potential values of -18.3 to -20.1 mV indicating higher stability. **Conclusion:** Thus, phytosomes of selected botanical extracts were found to mitigate the risk factors associated with Alzheimer's disease such as acetylcholinesterase, oxidative stress and inflammatory influences. Centella and Bacopa phytosomes as potential adjunctive or preventive interventions for cognitive decline, aligning traditional knowledge with modern pharmaceutical innovation.

Keywords: Asiaticosides, Bacopa, Bacosides, Centella, Neurocognitive.

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INTRODUCTION

Both *Centella asiatica* and *Bacopa monnieri* herbs have a long history of being described as "brain tonics" and were often given together in traditional prescriptions to support memory, intellect, and overall nervous system health. Their recognition as Medhya Rasayanas provides the historical foundation for their current exploration as neuroprotective and cognitive-enhancing agents in modern pharmacology (Deore *et al*., 2023).

Ayurvedic conventional neuroprotective formulations of the selected plants- *Centella asiatica* and *Bacopa monnieri* are mostly in the form of powder, syrups, and tablets which need to be consumed orally in high doses in the form of Churna (powder) or Ghrita (Semisolid dosage form) for long duration to achieve the desired pharmacological effect. This is inconvenient for many geriatric patients. Elderly patients often face difficulty in swallowing multiple or bulky dosage forms, and increased sensitivity to gastrointestinal side effects. The need for frequent or high-dose administration of herbal formulations negatively affects patient compliance, undermining their long-term therapeutic value in chronic neurodegenerative conditions such as Alzheimer's or Parkinson's disease. These challenges highlight the need for advanced delivery systems, such as phytosomes mimicking conventional "Ghrita" carrier system, can improve solubility, bioavailability, and therapeutic consistency while reducing the required dose and improving overall compliance (Bhattacharya, 2009).

Hence, the hypothesis for the present research work is that phytosomes comprising bioactive rich fractions of these Indian traditional medicinal plants will help to cross the blood brain barrier and provide enhanced neuroprotective efficacy in Alzheimer's patients by improving nerve function, promoting cognitive health and reducing fatigue by incorporating bioactive enriched fractions at minimum doses. Phytosomes will increase oral bioavailability and enhance in vivo neuroprotection/ cognitive performance compared with the same dose of crude extract.

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MATERIALS AND METHODS

The selected herbs *Centella asiatica* and *Bacopa monnieri* were collected from the Medicinal and Aromatic Plant-AYUSH (MAPA) Garden, Government College of Pharmacy, Amravati, Maharashtra, India. The identification and authentication of both plants were performed by HOD, Pharmacognosy department, Govt. College of Pharmacy, Amravati based on organoleptic/ macroscopic (organ and sense), microscopic, phytochemical and physicochemical parameters complying with pharmacopeial and equivalent standards. The herbarium voucher specimen number is GCOPA/2021/02.

Reagents and Chemicals

Thio Barbituric Acid (TBA), reduced glutathione, oxidized glutathione and NADPH were procured from Hi-Media Laboratories (Mumbai, India). 5,5-Dithio-bis (2-nitrobenzoic acid) (DTNB). All chemicals were obtained from Sigma Aldrich (Bangalore, India) and CDH (Central Drug House (P) Ltd., New Delhi, India), and the remaining chemicals and reagents used were of analytical quality from CDH, Delhi and LobaChemie, Mumbai.

Extraction and Isolation of Bioactive rich fractions

Centella asiatica and *Bacopa monnieri* whole plants were dried and crushed into a powder. A 100 g sample of each plant powder was extracted using several solvents, including distilled water, 70 % ethanol, 95% ethanol, 80% methanol. The solvent was selected based on the solubility of the selected neuroprotective phytoconstituents. Bacosides 13.19 % by HPLC and 40% by UV spectroscopy found in final bioactive enriched *Bacopa* extract (Deore *et al.*, 2021). Asiaticoside 12.89% by HPLC and 25.14% by UV spectroscopy found in final bioactive enriched *Centella* extract (Deore *et al.*, 2021).

Preparation of Phytosomes

Different ratios of lecithin and botanical extract (1:1, 2:1, and 1:2) and methods-rotary evaporation, mechanical dispersion, anti-solvent precipitation, and continuous evaporation were used for optimization. Phytosome batches of bioactive-rich extracts of *B. monnieri* (BM), *C. asiatica* (CA), and a combination of both extracts (BCM) were prepared using Lecithin with ≥70% phosphatidylcholine at different molar ratios (1:1, 1:2, and 2:1). The bioactive enriched fractions and lecithin in different ratios were added to a 100 mL round bottom flask containing 30 mL of tetrahydrofuran. It was stirred for 3 hr at 40°C, followed by 2 hr of magnetic stirring. The solution was then evaporated to remove the tetrahydrofuran, and 15 mL of n-hexane and 2 mL ethanol was added (Wardana *et al.*, 2022). The obtained complex was precipitated, filtered, and vacuum dried to yield the phytosome complex.

Pharmaceutical Evaluation of Phytosomes

The physicochemical compatibility of the extract-polymer mixture was studied by comparing FTIR scans of the bioactive rich fraction and the phytosomes complex. Solubility was measured in various solvents such as DCM, n-hexane, ethyl alcohol and pH 6.8 phosphate buffer (Freag *et al.*, 2018). Particle Size was measured using Dynamic Light Scattering (DLS) and photon correlation spectroscopy. One millilitre of phytosomes was mixed with 10 mL of water and transferred into a cuvette, and the zeta potential was determined using a zeta-sizer (Zetasizer, Nano-ZS, Malvern Instruments, UK). The transition temperature was determined using a Differential Scanning Calorimeter (DSC, Mettler Toledo). The thermogram of the phytosome formulation was compared with that of bioactive rich fraction.

Entrapment Efficiency

The phytosome complex was solubilized in 10 mL ethyl acetate and centrifuged (5000 rpm) for 30 min at 30°C. The supernatant was mixed with ethanol to rupture the vesicles, and an adequate dilution was prepared to evaluate the extracted content using a UV spectrophotometer (UV-1700 Pharma Spec Shimadzu Corporation) at 278 nm. The entrapped drug content was determined by using a standard calibration curve. The equation for calculating entrapment efficiency is as follows:

$$\text{Entrapment Efficiency} = \frac{\text{Absorbance of Phytosomes} - \text{Absorbance of supernatant}}{\text{Absorbance of Phytosomes}} \times 100$$

Stability study

The formulations were sealed in glass vials and stored at a temperature of 40±2°C and a Relative Humidity (RH) of 75±5%. The samples were drawn at 0, 1, 2, 3 and 6 months in triplicate to assess the key changes in the physical, chemical, and microbiological properties of phytosomes over time. Particle size, PDI, zeta potential, entrapment efficiency, drug release profile, and chemical assay of phytoconstituents are evaluated.

In vitro dissolution and drug release study

The dissolution test was achieved according to the dissolution test method II (paddle) of the United States of Pharmacopoeia (USP 43). To mimic intestinal fluid, phosphate buffer pH 6.8 was used. The dissolution bowls were filled with 900 mL of dissolution media and positioned in a dissolution apparatus to control the temperature at 37±0.5°C and the paddle speed was set at 150 rpm to achieve uniform dispersion of phytosomes. Weighed sample (10 mg) of phytosomes was added to the dissolution media. At different time intervals, 5 mL of the sample was withdrawn and sink condition maintained. After every 1 hr same procedure was repeated (Udapurkar *et al.*, 2018). The collected samples were filtered using Whatman filter paper and analyzed at λ_{max} 278 nm using a UV-visible spectrophotometer against 0.1N HCl and phosphate buffer 6.8 pH as blank. The outcome metric is derived from the average of three values.

Ex vivo permeation study

An *ex vivo* permeation study was conducted using goat buccal mucosa and a Franz diffusion cell (Kumar *et al.*, 2024). The goat buccal mucosa was obtained freshly from Local Animal Slaughterhouse and used within 2 hr. Mucosa mounted between the donor and receptor compartments of the diffusion cell. The receptor compartment was filled with isotonic phosphate buffer solution with a pH of 6.8, and the temperature was maintained at 37±0.2°C. A stirrer was employed to maintain hydrodynamics within the receptor compartment. The sample, previously moistened, was placed in the donor compartment. The donor compartment was filled with 13 mL of phosphate buffer solution with a pH of 6.8. Periodic sample withdrawals were performed from the receptor compartment at appropriate time intervals, and an equal volume of fresh phosphate buffer solution was added to maintain sink conditions (Mazumder *et al.*, 2016). The percentage of drug that appeared in the receptor compartment was determined by measuring the UV absorbance of the withdrawn samples.

In vitro Neuroprotective Study

The neuroprotective potency and efficacy of bioactive rich fractions is determined using *in vitro* methods. Stock solutions of extracts and derived phytosomes were prepared by dissolving 10 mg of each extract or phytosome in 10 mL of ethanol, resulting in a final concentration of 1 mg/mL. The stock solutions were serially diluted to 10, 20, 30, 40, and 50 µg/mL. The same dilutions were used for following assay.

In vitro Acetyl cholinesterase inhibition activity

The *in vitro* neuroprotective evaluation of BMP, CAP and BCMP was conducted using Ellman's colorimetric method (Ellman *et al.,* 1961). In this study, Acetylthiocholine Iodide (ATCI) at a concentration of 0.075 M served as the substrate, while Acetyl cholinesterase (AChE) derived from *Electrophorus electricus* eel, with an enzyme concentration of 0.5 U/mL, was used. The chromophore employed was 5, 5-Dithio- His-(2-Nitrobenzoic Acid) (DTNB) at a concentration of 0.01 M. The experimental protocol was as follows: in cuvettes, a mixture of 3 mL phosphate buffer (pH 8), 100 µL AChE enzyme, and 100 µL of the phytosome formulation such as BMP, CAP, BCMP or standard Donepezil hydrochloride was incubated at 37°C for 5 min to facilitate the binding of the enzyme with the phytosome and phytoconstituents. After 5 min, 100 µL of DTNB was added to the mixture and allowed to stand for a brief period. Subsequently, 20 µL of ATCI was added to initiate the reaction. Readings were taken at 412 nm using a UV Spectrophotometer after 2 min of ATCI addition. For the control, the test compound solution was replaced with 100 µL of water. This protocol allowed for the assessment of the inhibitory activity of the formulation against AChE using the colorimetric method, with the absorbance readings serving as an indicator of the inhibitory potential. Measure the absorbance at 412 nm and calculate the % inhibition by the following formula:

$$\text{Acetyl cholinesterase inhibition} = \frac{\text{Absorbance of Control} - \text{Absorbance of treated sample}}{\text{Absorbance Control}} \times 100$$

In vitro Antioxidant Activity

Weigh accurately 11.2 mg of DPPH (2,2 diphenyl-1-picrylhydrazyl hydrate) dissolved in ethanol within a 100 mL volumetric flask, which was then wrapped in aluminium foil to prevent light exposure. Stock solutions of BMP, CAP and BCMP phytosome were prepared by dissolving 10 mg of the respective phytosome formulation in 10 mL of ethanol, resulting in a final concentration of 1 mg/mL. From these stock solutions, further serial dilutions of 10, 20, 30, 40, and 50 µg/mL were prepared. Similarly, serial dilutions of Ascorbic acid were prepared by dissolving 10 mg of Ascorbic acid in ethanol to obtain a stock solution with a concentration of 1 mg/mL. From this stock solution, serial dilutions of 10, 20, 30, 40, and 50 µg/mL were made. For the *in vitro* activity, 3 mL of each serial dilution of phytosome and 1 mL of DPPH solution were mixed in a test tube, followed by incubation in darkness for 20 min. After the incubation period, the absorbance of the mixture was measured at 517 nm (Khadabadi *et al.*, 2019). The same process was carried out for the diluted ascorbic acid samples. % RSA inhibition was calculated by following:

$$\%\ \text{RSA} = \frac{\text{Abs. of Control} - \text{Abs. of treated sample}}{\text{Abs. of Control}} \times 100$$

In vitro Anti-inflammatory activity

The anti-inflammatory activity was determined spectrophotometrically by monitoring the production of conjugated diene hydroperoxides at a wavelength of 234 nm. To prepare the substrate for the activity, 28 mg of linoleic acid was accurately weighed and placed in a 10 mL glass measuring cylinder. An equal weight of Tween-20, along with 2 mL of distilled water, was added. To achieve a clear solution, 50 µL of 2N NaOH was added. The volume of the solution was then adjusted to 10 mL. using distilled water. Fresh substrate was prepared for each enzyme activity. The reaction mixture consisted of 2.7 mL. of 0.2 M sodium phosphate buffer at pH 6.5 and 0.3 mL. of the prepared substrate. The reaction was initiated by adding the enzyme and the respective phytosome formulation BMP, CAP, BCMP respectively. The change in absorbance at 234 nm (Huang *et al.*, 2024) was recorded for duration of 3 min using a UV spectrophotometer. The enzyme activity was expressed as a change in the absorbance 234nm Formula used for calculations:

$$\%\ \text{LOX inhibition} = \frac{\text{Abs. of Control} - \text{Abs. of treated sample}}{\text{Abs. Control}} \times 100$$

Superoxide Dismutase activity

SOD enzyme facilitates the simultaneous oxidation and reduction of superoxide radicals into molecular O_2 and H_2O_2. SOD activity

was assessed according to the standard protocol. The experimental protocol for assessing SOD activity was as follows: The reaction mixture for this method consisted of 0.1 mL of phenazine methosulfate (18 µL of 100 mM of phenazine methosulfate add in 10 mL water (100 mM phenazine methosulphate prepared by 306 mg of phenazine methosulphate add in 10 mL water)) and 0.1 mL of formulation BMP, CAP, BCMP to it. Add 1.2 mL sodium pyrophosphate, 0.3 mL of 300 µM nitro-blue tetrazolium. Reaction was started by addition of 0.2 mL of NADH (750 Mm). After incubation at 30°C for 90 sec. Addition of 0.1 mL glacial acetic acid to stop the reaction. Reaction mixture was stirrer vigorously with 4 mL of n-butanol and then mixture was allowed to stand for 10 min, centrifuged and n-butanol layer was separated (Parveen RO *et al.*, 2016). The color intensity of chromogen in n-butanol layer was measured at 560 nm spectrophotometrically. The results were expressed in units per milligram of protein (units/mg protein), indicating the specific activity of SOD.

$$\text{SOD \% inhibition} = \frac{\text{Abs. of Control} - \text{Abs. of treated sample}}{\text{Abs. Control}} \times 100$$

Reduced Glutathione Activity

Reduced glutathione plays an important role in reducing oxidative stress. The potential of the selected bioactive rich fractions to increase the level of reduced glutathione was tested using a standard protocol: 1 mL of phytosome formulation BMP, CAP and BCMP (100 mg/mL) was mixed with 0.8 mL of distilled water and 0.2 mL of 50% trichloroacetic acid in tube. The tube was shaken intermittently for 10-15 min and centrifuged for 15 min at 3000 rpm. 0.6 mL of supernatant was mixed with 0.8 mL of 0.4 M Tris buffer (pH 8.9) and 20 µL of 0.1 mL of DTNB in absolute alcohol and the sample was shaken. The absorbance was read within 5 min of the addition 40 µL of DTNB at 412 nm (Parveen RO *et al.*, 2016) against the reagent blank with no sample. All values are expressed as µg mg^{-1} protein. For determination of IC_{50}, 50% inhibition of LOX activity was calculated from:

$$\text{Glutathione \% inhibition} = \frac{\text{Abs. of Control} - \text{Abs. of treated sample}}{\text{Abs. Control}} \times 100$$

Statistical analysis

The results are presented as Mean± SD. Statistical comparisons were made using one-way ANOVA followed by Tukey's *t*-test using GraphPad Prism version 10.0, USA. ($p<0.05$) was considered statistically significant.

RESULTS

Phytosomes containing bioactive-rich fractions of Indian medicinal plants will enhance blood-brain barrier penetration, improve oral bioavailability, and provide superior neuroprotective efficacy in Alzheimer's disease. Compared to crude extracts, phytosomes are expected to enhance cognitive performance and enable ≥30% dose reduction without added toxicity.

The size of the particles can vary between 50 and 200 µM. Zeta potential was used to determine the physical stability of the product. The particle size of optimized batch H (BMP, CAP, BCMP) was found to be 169.2, 172.6, and 185.3 nm with zeta potential values of-18.3, -20.1, and -18.2 mV respectively indicating higher stability. Higher Zeta potential values (electrostatic repulsion between particles) indicate increased stability. A zeta potential of±20 mV indicated that the phytosomal preparation was more

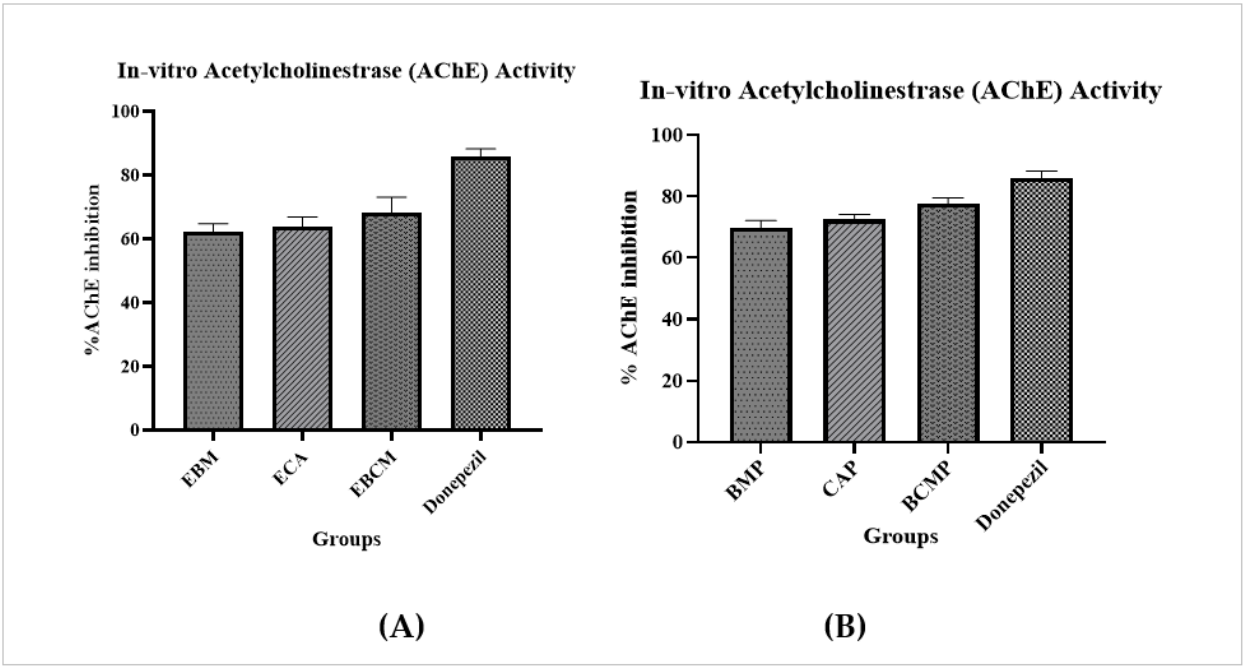


Figure 1: *In vitro* Acetylcholinesterase Inhibition Activity of (A) Bioactive Enriched Fractions BM, CA, BCM, (B) Phytosomes BMP, CAP, BCMP. All values are expressed as triplicate measurements (n=3) and presented as mean±SD.

physically stable. The entrapment efficiency of the BMP 85.18%, CAP 90.18%, BCMP 95.94% respectively.

The optimized formulation BMP (1:1) CAP (1:1) BCMP(1:1) this batches was maintained at both freezing and room temperature for 90 days. No significant changes were observed in the formulations. The drug remained stable under different storage conditions, including varying temperatures and humidity levels, with no significant changes observed in its physicochemical properties, potency, or overall quality.

Thermal analysis of phospholipid complexes was performed using DSC60 at an increased temperature of 10°C/min from 30°C to 300°C under nitrogen protection. Peak shifts or disappearance in DSC occur because hydrogen bonding, van der Waals forces, and polar interactions between phytoconstituents and phospholipids disrupt crystalline structures. This reduces the energy needed for thermal transitions, leading to lower melting points, reduced enthalpy, and new amorphous thermal profiles. These changes are a thermodynamic signature of phytosome formation, differentiating it from mere physical mixtures.

The FTIR spectrum of each sample was observed in the wavenumber range 4000-400 cm^{-1}. For BMP, CAP, and BCMP, i.e. C=N stretching and C=O stretching (1651.14 cm^{-1}), C-H bending (1471.69 cm^{-1}), N-O stretching (1899 cm^{-1}), O-H bending (3365 cm^{-1}), C=N stretching (1714.79 cm^{-1}), and C=C stretching (1634.74 cm^{-1}), respectively. Peak shifts (mainly in O-H, C=O, and P=O regions), reduced intensities, and broadening in FTIR spectra confirm phytosome complexation.

During accelerated stability studies, phytosomal formulations exhibited minimal variation in particle size and zeta potential, indicating good physical stability. The formulations retained ≥90% of the bioactive-enriched fractions after 6 months under accelerated storage conditions. Based on these findings, the projected shelf life of the optimized phytosomes is estimated to be greater than 1.5 years, confirming their long-term stability and suitability for pharmaceutical development.

The neuro-cognitive potential of bioactive-rich fractions and their corresponding phytosomal formulations was evaluated through antioxidant, anti-acetylcholinesterase, anti-inflammatory, and permeation studies. Antioxidant activity demonstrated the following order of efficacy: Ascorbic acid > BCM > CA > BCMP > CAP > BM > BMP, as illustrated in Figure 1. Acetylcholinesterase (AChE) inhibition studies revealed that phytosome formulations exhibited greater enzyme inhibition compared to their respective bioactive-rich fractions. The order of inhibition was: Donepezil > BMP > BCMP > BCM > CAP > BM > CA, as shown in Figure 2. This

Table 1: Comparative *ex vivo* Permeation Study Results.

Permeation study of BMP						
Permeability parameter	**BMP (1:1) MDM**	**BMP (1:2) MDM**	**BMP (2:1) MDM**	**BMP (1:1) RET**	**BMP (1:2) RET**	**BMP (2:1) RET**
Area	3.46	3.46	3.46	3.46	3.46	3.46
Flux (J)	0.032	0.0217	0.0193	0.094	0.028	0.0263
Permeability Coefficient	0.00032	0.000217	0.000193	0.00094	0.00028	0.000263
Permeation study of CAP						
Permeability parameter	CAP (1:1) MDM	CAP (1:2) MDM	CAP (2:1) MDM	CAP (1:1) RET	CAP (1:2) RET	CAP (2:1) RET
Area	3.46	3.46	3.46	3.46	3.46	3.46
Flux (J)	0.0089	0.0089	0.0068	0.0324	0.0324	0.0097
Permeability Coefficient	0.000089	0.000089	0.000068	0.000324	0.000324	0.000097
Permeation study of BCMP						
Permeability parameter	BCMP (1:1) MDM	BCMP (1:2) MDM	BCMP (2:1) MDM	BCMP (1:1) RET	BCMP (1:2) RET	BCMP (2:1) RET
Area	3.46	3.46	3.46	3.46	3.46	3.46
Flux (J)	0.0111	0.0142	0.0094	0.0469	0.0133	0.0122
Permeability Coefficient	0.000111	0.000142	0.000094	0.000469	0.000133	0.000122

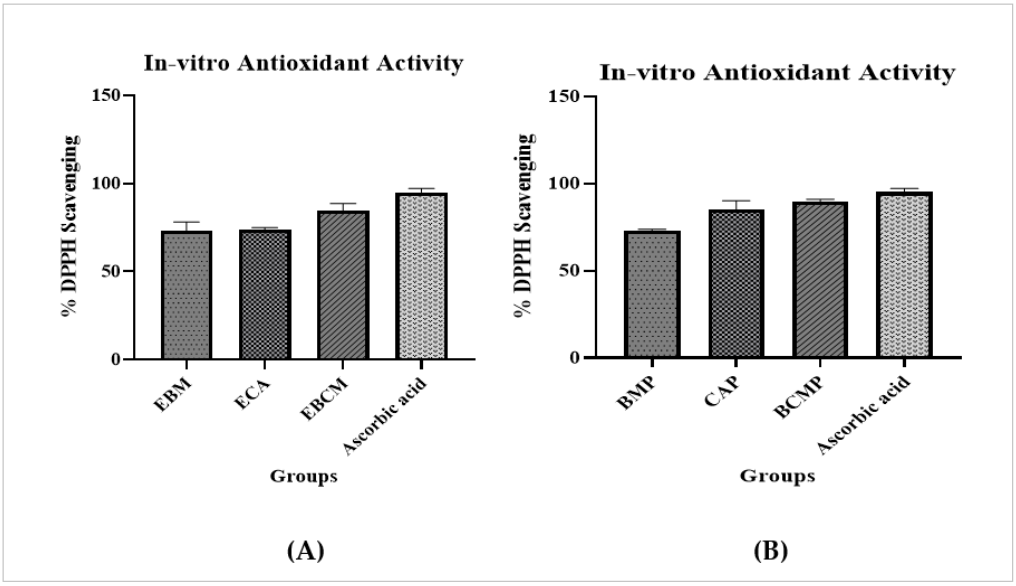


Figure 2: *In vitro* Antioxidant Activity by DPPH Method of (A) Bioactive Enriched Fractions- BM, CA, BCM (B) Phytosomes BMP, CAP, BCMP. All values are expressed as triplicate measurements (*n*=3) and presented as mean±SD.

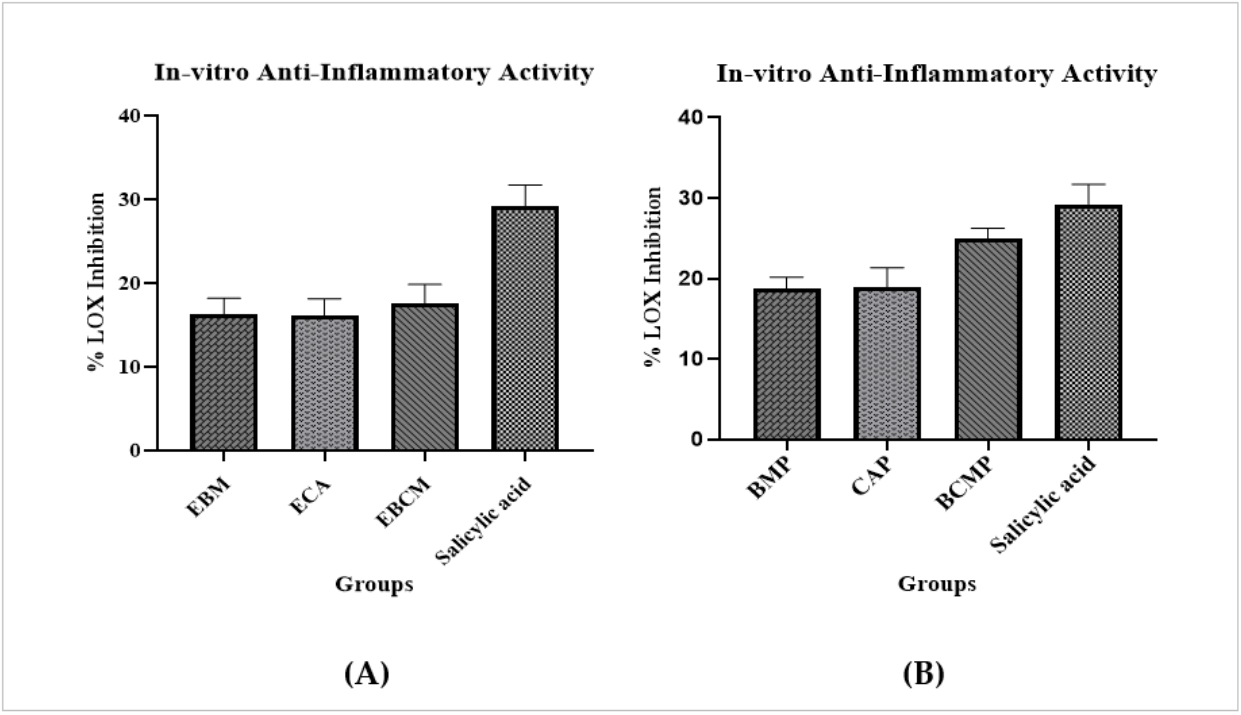


Figure 3: *In vitro* Anti-inflammatory (LOX) activity of (B) Phytosomes- BMP, CAP, BCMP (A) Bioactive Enriched Fractions-BM, CA, BCM. All values are expressed as triplicate measurements (*n*=3) and presented as mean±SD.

indicates enhanced neuroprotective potential of the phytosomal formulations.

Lipoxygenase (LOX) inhibition, a marker of anti-inflammatory activity, showed that BMP, CAP, and BCMP inhibited LOX expression in a concentration-dependent manner. At 50 µg/mL, the percentage inhibition was: BMP: 46.48%, CAP: 45.24%, BCMP: 48.67%.

These findings are summarized in Figure 3. A significant reduction ($p<0.05$) in Superoxide Dismutase (SOD) activity was observed with: BMP2: 6.96±4.67, CAP: 26.90±6.97, BCMP: 28.39±5.84. Figure 4 similarly, Glutathione (GSH) levels decreased significantly ($p<0.05$), as depicted in Figure 5.

Phytosomes prepared in a 1:1 ratio using the rotary evaporation technique demonstrated the highest flux compared to other batches Table 1, indicating enhanced drug diffusion across the simulated

membrane. *In vitro* release studies revealed that phytosomes and enriched extracts exhibited a similar release pattern up to 45 min. However, phytosomes achieved maximum release up to 4 hr, followed by sustained release up to 8 hr. In contrast, enriched extracts showed comparatively limited sustained release. Kinetic modeling indicated that: The RET (1:1 ratio) followed first-order release kinetics. Other optimized phytosome batches followed zero-order release kinetics Table 2. The improved release profile of phytosomes may be attributed to enhanced solubility, wettability, and improved molecular dispersion of the enriched extract within the phospholipid matrix.

Table 2: Comparative Pharmacokinetic Parameters of Different Batches of Bioactive Enriched Fractions and Phytosomes.

Pharmacokinetic parameter of different batches of bioactive enriched fractions						
	Graph correlation		**EBM**	**ECA**	**B+C Extract**	
	First order release model (R2)		0.9732	0.9867	0.9835	
	Zero order release model(R2)		0.9733	0.9884	0.9884	
	Hixon Crowell release model(R2)		0.9732	0.9867	0.9835	
	Higuchi release model (R^2)		0.9007	0.9297	0.9204	
Pharmacokinetic Parameters of Different Batches of BMP						
Graph correlation	BMP (1:1) MDM	BMP (1:2) MDM	BMP (2:1) MDM	BMP (1:1) RET	BMP (1:2) RET	BMP (2:1) RET
First order release model	0.9827	0.9746	0.9826	0.9953	0.9919	0.9725
Zero order release model	0.9828	0.9753	0.9829	0.9855	0.9920	0.9726
Hixon Crowell release model	0.9827	0.9748	0.9827	0.9853	0.9919	0.9726
Higuchi release model	0.9192	0.9011	0.9165	0.9238	0.9401	0.8987
Pharmacokinetic Parameters of Different Batches of CAP						
Graph correlation	CAP (1:1) MDM	CAP (1:2) MDM	CAP (2:1) MDM	CAP (1:1) RET	CAP (1:2) RET	CAP (2:1) RET
First order release model	0.9880	0.9934	0.9866	0.9928	0.9899	0.9893
Zero order release model	0.9851	0.9935	0.9868	0.990	0.990	0.9894
Hixon Crowell release model	0.9877	0.9934	0.9866	0.9921	0.9899	0.9894
Higuchi release model	0.9297	0.944	0.9248	0.9401	0.9333	0.9322
Pharmacokinetic Parameters of Different Batches of BCMP						
Graph correlation	BCMP (1:1) MDM	BCMP (1:2) MDM	BCMP (2:1) MDM	BCMP (1:1) RET	BCMP (1:2) RET	BCMP (2:1) RET
First order release model	0.9968	0.9961	0.9976	0.9950	0.990	0.9920
Zero order release model	0.9969	0.9961	0.9976	0.9941	0.995	0.9948
Hixon Crowell release model	0.9968	0.9961	0.9976	0.9940	0.996	0.9920
Higuchi release model	0.953	0.9506	0.9564	0.9442	0.9534	0.9497

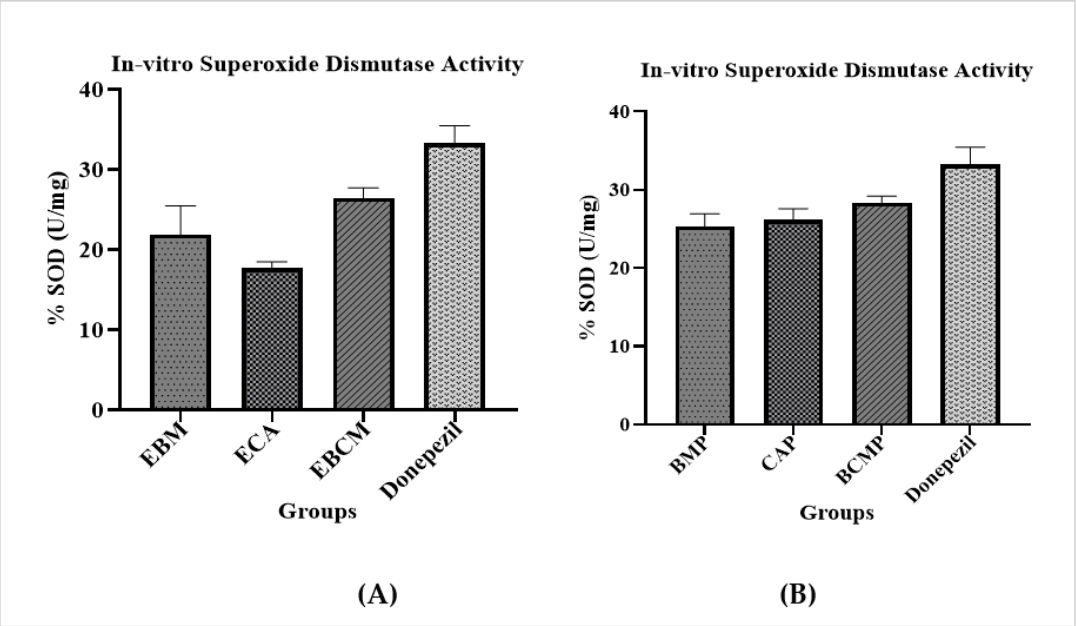


Figure 4: Percentage SOD activity (A) Bioactive Enriched Fractions BM, CA, BCM (B) Phytosomes-BMP, CAP, BCMP. All values are expressed as triplicate measurements (*n*=3) and presented as Mean±SD.

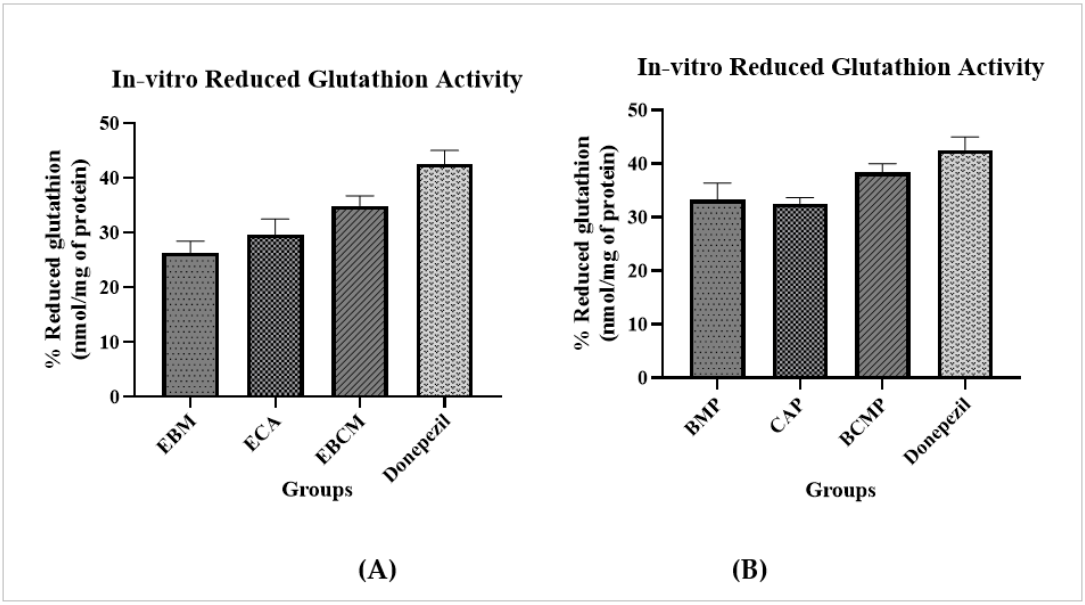


Figure 5: Percentage Glutathion Reductase Activity of (A) bioactive enriched fractions- BM, CA, BCMP (B) Phytosomes BMP, CAP, BCMP. All values are expressed as triplicate measurements (*n*=3) and presented as mean±SD.

DISCUSSION

Phytosomal delivery of bioactive-rich fractions from the Indian medicinal plants *Bacopa monnieri* and *Centella asiatica*, both widely used in Ayurveda (a traditional "science of life" system emphasizing holistic balance and natural therapies), offers a rational strategy to improve brain targeting and therapeutic efficacy in Alzheimer's disease. In Ayurveda, the concept of polyherbalism- combining multiple herbs to enhance efficacy and reduce toxicity and supports the use of such combined bioactive fractions in this study (Parasuraman *et al.*, 2014). The optimized BMP (1:1) CAP (1:1) BCMP(1:1) this batches (BMP, CAP, BCMP) exhibited nanosized particles (169-185 nm) with zeta potentials around-18 to-20 mV, indicating adequate electrostatic stabilization and colloidal stability, which are critical for enhanced intestinal absorption and potential blood-brain barrier permeation. High entrapment efficiencies (85-96%) further support effective phytoconstituent incorporation within the phospholipid matrix. DSC and FTIR analyses confirmed true complex formation through hydrogen bonding and polar interactions, evidenced by peak shifts and amorphous thermal transitions, distinguishing phytosomes from physical

mixtures. Stability studies demonstrated ≥90% drug retention under accelerated conditions, predicting extended shelf life. Functionally, phytosomes showed superior acetylcholinesterase and lipoxygenase inhibition compared to crude fractions, along with sustained release and higher membrane flux. These findings collectively support improved bioavailability, enhanced neuroprotection, and the feasibility of dose reduction without increased toxicity.

CONCLUSION

The findings provide valuable insights for improved delivery of asiaticosides and bacosides may amplify their antioxidant, anti-amyloid, and neuroinflammatory-modulating actions, supporting cognitive preservation and neuronal survival. Thus, integrating Indian traditional Ayurvedic wisdom with modern phytosome technology offers a promising translational research pathway for developing safe, effective, and accessible neuroprotective nutraceuticals.

ABBREVIATIONS

BM: *Bacopa monnieri*; **CA:** *Centella asiatica*; **BCM:** *Bacopa-centella* mix; **BMP:** *Bacopa monnieri* phytosome; **CAP:** *Centella asiatica* phytosome; **BCMP:** *Bacopa-centella* mix phytosome; **AChE:** Acetylcholinesterase; **MDM:** Mechanical Dispersion Method; **RET:** Rotatory Evaporation Technique.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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AUTHORS CONTRIBUTIONS

Ram Vighne: Performed *in vitro* experiment, analysis, data interpretation, and visualization. **Sharada Deore and Ram Vighne:** Wrote this manuscript, conceptualized and designed the study. **Bhushan Baviskar:** Contributed to the data analysis and interpretation. All the authors have read and agreed to the published version of the manuscript.

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