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ORIGINAL RESEARCH

Liposomal Delivery as a Strategy to Improve Berberine Bioavailability: A Double-Blind, Crossover, Randomized Pilot Study in Healthy Males

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Purpose: Berberine, despite broad therapeutic potential, exhibits poor intestinal absorption and can cause gastrointestinal discomfort at higher doses. This pilot study compared the absorption, metabolic responses, and safety of a liposomal berberine formulation against standard unformulated berberine powder.

Patients and Methods: In a randomized, double-blind, crossover design, six healthy males (n = 6; age: 37.8 ± 3.3 years; height: 174.8 ± 5.0 cm; weight: 74.6 ± 2.9 kg) ingested a single 400 mg dose of berberine, either as unformulated or liposomal berberine (Specnova LLC, Tysons Corner, VA, USA). Venous blood samples were collected at 0, 0.33-, 0.67-, 1-, 1.5-, 2-, 4-, 6-, 8-, 12-, and 24-hours post-ingestion and analyzed for plasma berberine concentrations. Metabolic and safety markers were assessed over 24 hours.

Results: Liposomal berberine produced significantly higher pharmacokinetic responses compared with unformulated berberine, including a 70.1% increase in Cmax ($p = 0.03$) and a 42.8% increase in AUC_{0-24} ($p = 0.03$). No significant differences were observed between conditions in 24-hour changes in metabolic or safety markers.

Conclusion: Liposomal delivery substantially enhances berberine absorption without negatively affecting metabolic or safety parameters in healthy male subjects. These findings support liposomal formulation as a promising strategy for improving berberine's bioavailability and potential clinical utility. Given the small sample size and the inclusion of males only, these findings should be interpreted as exploratory and may not be generalizable to females or broader populations.

Keywords: liposomal delivery, pharmacokinetics, bioavailability, herbal alkaloids, nutraceuticals

Introduction

Berberine is a naturally occurring benzylisoquinoline alkaloid found in the stems, roots, and rhizomes of various medicinal plants, including *Berberis aristata, B. darwinii, B. petiolaris*, and *B. vulgaris*.[1–5] In its extracted form, berberine has been widely used in traditional Chinese and Ayurvedic medicine.[6] As a phytonutrient, it exhibits broad therapeutic potential, including benefits related to metabolic health (eg, hyperglycemia, lipid regulation, blood pressure, body composition, and polycystic ovary syndrome), modulation of inflammatory markers, enhancement of liver and kidney function, gastrointestinal support, and neuroprotection.[7] Despite its extensive pharmacological properties and clinical utility, berberine's poor intestinal absorption and low in vivo bioavailability necessitate the development of strategies to overcome these limitations.[8]

Two preclinical studies reported an absolute bioavailability of only 0.68% and 0.36%, concluding that intestinal first-pass metabolism is the primary barrier, with rapid hepatic extraction and distribution further contributing to low systemic concentrations.[9,10] These findings have been confirmed in human studies. In one trial, the mean maximum plasma

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concentration following 400 mg berberine ingestion reached approximately 0.4 ng/mL.[11] Another study reported an even lower peak concentration of ~0.02 ng/mL after a 500 mg oral dose in healthy subjects.[12] Although intravenous administration can increase berberine's systemic availability, it has been associated with serious adverse effects, including respiratory arrest, making oral administration the preferred route.[8] Accordingly, formulation strategies aimed at improving gastrointestinal absorption represent a critical pathway to optimizing berberine's efficacy and safety.

A variety of absorption-enhancement technologies have been investigated, including salt formation, spheronization, nanoencapsulation, self-microemulsifying systems, co-administration with P-glycoprotein inhibitors such as silymarin, and mucoadhesive microparticle formulations, among others, without altering the berberine molecule itself.[13–18] Since the late 1990s, liposomal delivery systems have gained commercial and scientific traction, demonstrating improved bioavailability for both hydrophilic and hydrophobic compounds compared with conventional powdered forms. This enhanced performance is attributed to protection from gastrointestinal degradation and improved transmucosal uptake and absorption.[19] Liposomal delivery systems may further enhance the oral bioavailability of alkaloids by facilitating incorporation into mixed micelles and promoting uptake via intestinal lymphatic pathways, thereby reducing exposure to presystemic intestinal metabolism and hepatic first-pass clearance. Encapsulation within a phospholipid bilayer may also improve aqueous dispersibility and protect labile compounds from degradation in the gastrointestinal environment. These mechanisms provide a rationale for evaluating liposomal formulations as a strategy to improve systemic exposure of poorly absorbed alkaloids such as berberine. Nevertheless, limited data exist regarding how liposomal formulations affect the pharmacokinetic profile of berberine specifically. Recent evidence has shown that vitamin C incorporated into a liposomal system demonstrates significantly improved absorption into plasma and leukocytes.[20]

Prior work using the same liposomal platform demonstrated enhanced absorption of CoQ10 under similar controlled conditions.[21] The present study aimed to investigate the absorption characteristics of berberine delivered via a standardized liposomal formulation and to examine factors influencing its bioavailability under fasted conditions. By comparing liposomal and conventional berberine, this study provides insight into strategies for maximizing berberine's metabolic potential across diverse clinical applications. This study builds upon our previously published liposomal CoQ10 pharmacokinetic trial using the identical excipient system.[21]

Materials and Methods

Methods

The study was approved by the Medstar Specialty Hospital Ethics Committee (IRB Number: ECR/1324/Inst/KA/2019) on August 22, 2024 (Approval Number: RRS/CL/BA/BER/2024) and registered with the Clinical Trials Registry - India (CTRI Registration Number: CTRI/2024/11/076293) on November 5, 2024. The research was conducted at Medstar Specialty Hospital, Bengaluru, Karnataka, India. The study adhered to international ethical standards, including the Declaration of Helsinki (Edinburgh, 2000), ICH-GCP guidelines, and the Ethical Guidelines for Biomedical Research on Human Participants (ICMR, 2006). Written informed consent was obtained from all participants prior to any study procedures.

Participants

Subjects were eligible to participate if they met all of the following conditions: male or female (non-pregnant), aged 18–45 years; weighing at least 50 kg; in good health, with no evidence of underlying disease, as determined by medical history, physical examination, ECG, chest X-ray (PA view), and laboratory tests performed within 7 days before study initiation; screening laboratory values within normal ranges or judged by the Principal Investigator as not clinically significant. Subjects were excluded if they met any of the following conditions: known allergies to berberine products, food, or any drugs; use of fat-reducing medications, statins, or vitamin supplements (including vitamin E) within the past month; resting hypotension (BP <90/60 mmHg), hypertension (BP >140/90 mmHg), or abnormal pulse rate (below 50/min or above 100/min); a history or current presence of significant cardiovascular, pulmonary, hepatic, renal, hematological, gastrointestinal, endocrine, immunologic, dermatologic, neurological, musculoskeletal, or psychiatric conditions, or hospitalization/surgery within the past 4 weeks; a history of myocardial infarction (MI), stroke, peripheral arterial

disease, gastrointestinal bleeding, hepatic impairment, asthma, renal impairment, epilepsy, or intracranial hemorrhage; use of over-the-counter or prescribed medications, including any enzyme-modifying drugs, within the past 14 days; history of alcoholism, drug abuse, or smoking; hypersensitivity to heparin; participation in any other clinical study within the past 3 months; difficulty with blood donation, swallowing, or repeated venipuncture, or the presence of unsuitable veins for venipuncture.

During the initial screening visit, subjects underwent several diagnostic assessments, including an electrocardiogram (ECG), chest X-ray (PA view), and hematological tests (RBC count, hemoglobin, total and differential leukocyte count, platelet count). Serum chemistry tests were performed, including Random Blood Sugar Test (RBS), Renal Function Tests (RFT): creatinine and urea, and Liver Function Tests (LFT): total bilirubin, ALT (SGPT), and AST (SGOT). Serological tests included an HIV test and screening for Hepatitis B Surface Antigen. Urine analysis consisted of a physical examination (including color, appearance, and specific gravity), a chemical examination (pH, protein, glucose, bile salts, and bile pigments), and a microscopic examination (including pus cells, epithelial cells, bacteria, RBCs, casts, and crystals).

Study Procedure

This study was conducted as a randomized, double-blind, crossover trial. Eligible participants were randomly assigned to two groups using simple randomization. Study materials were centrally coded, and randomization numbers were generated using a computer-based randomization schedule.

Participants were admitted to the clinical research facility on the evening prior to dosing to ensure fasting and control over environmental conditions. After placement of an indwelling catheter, a baseline blood draw was obtained and the assigned study product was administered with 240 mL of water at room temperature. Blood samples were collected at predetermined intervals across a 24-hour period following ingestion. To minimize confounding variables, participants remained on site, followed a standardized low-polyphenol diet, and refrained from additional food intake outside scheduled meals. After a washout period of at least five days, participants returned to complete the alternate intervention under the same controlled conditions (see Figure 1). Throughout the study, participants consumed a standardized berberine-free diet consisting of 200 mL apple juice, two bread rolls, and 15 g butter. All subjects remained in the clinical facility for at least 24 hours following each dose.

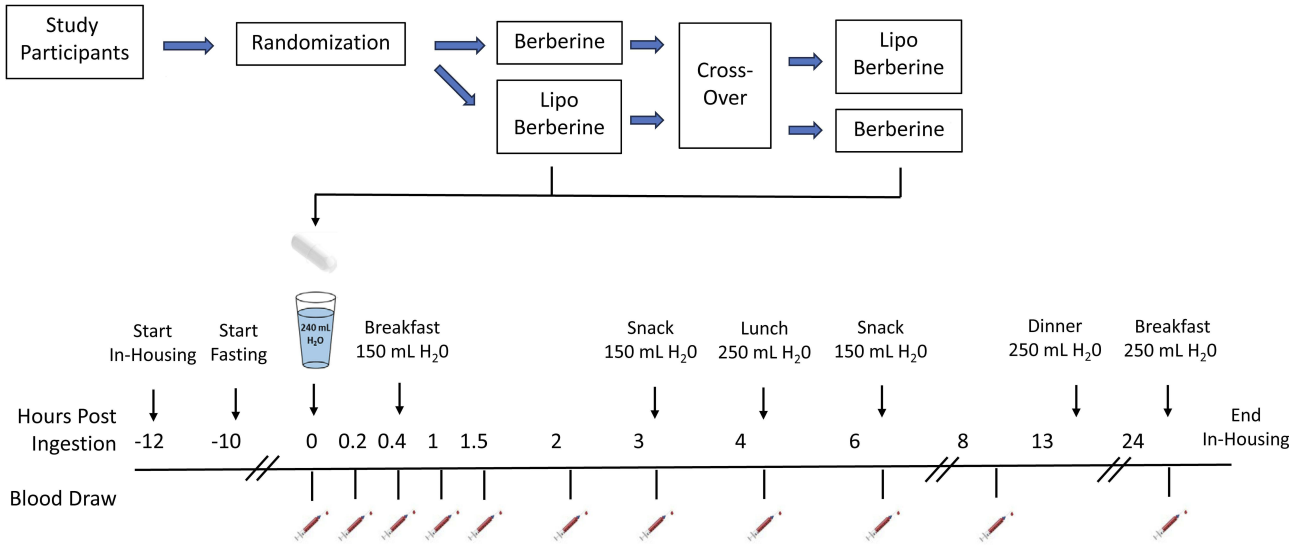

Figure 1 Schematic Overview of Research Design.

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Study Materials

Unformulated berberine and liposomal berberine capsules (LipoVantage®, Specnova, LLC, Tyson Corner, VA, USA) were obtained from Molecules Food Solutions Pvt Ltd (Kerala, India). At each visit, subjects ingested two optically identical hard-gel capsules of the assigned study material, providing 200 mg berberine per capsule (400 mg total per administration). The 400 mg berberine dose was selected based on prior human pharmacokinetic studies demonstrating that this dose yields measurable but low plasma berberine concentrations following conventional (unformulated) administration.[11] Because systemic exposure at this dose is limited by poor oral absorption, 400 mg represents a validated and sensitive probe dose for evaluating whether liposomal formulation enhances berberine bioavailability at an equivalent dose. The berberine content of both formulations was verified by independent third-party analysis (Interfield Laboratories, Kochi, India). In addition, the liposomal product was characterized using a combination of physicochemical and imaging techniques. All analyses were performed at the International and Inter University Centre for Nanoscience and Nanotechnology (Mahatma Gandhi University, Priyadarshini Hills, Kottayam-686 560, Kerala, India), except for cryogenic transmission electron microscopy (cryo-TEM), which was conducted at the Colorado School of Mines (Department of Chemical and Biological Engineering, Golden, CO 80401, USA). Hydrodynamic particle size and polydispersity index (PDI) were measured by dynamic light scattering (DLS) using standard operating procedures. Measurements were performed at 25°C following appropriate dilution to minimize multiple scattering effects. The formulation exhibited a mean hydrodynamic particle size in the range of 140–170 nm with a PDI < 0.2, indicating a narrow particle size distribution. Zeta potential was determined by electrophoretic light scattering to assess surface charge and colloidal stability under controlled temperature and ionic conditions. The particles demonstrated a zeta potential of approximately −35 mV, consistent with good electrostatic stability of the dispersion. Encapsulation efficiency was determined using validated analytical methods based on dialysis separation of free (unencapsulated) compound from the liposomal fraction, followed by quantitative chemical analysis of the encapsulated and non-encapsulated fractions. The formulation achieved an encapsulation efficiency of approximately 83%. Cryo-TEM was employed to visualize particle morphology and nanoscale structure under near-native hydrated conditions. Samples were vitrified and imaged without staining. Cryo-TEM analysis revealed intact nanoscale liposomal vesicles with clearly resolved lipid bilayers and particle sizes in the same range as those measured by DLS. Multiple vesicle architectures were observed, including unilamellar vesicles (ULV, Figure 2A and B), multilamellar vesicles (MLV, Figure 2C), and multivesicular vesicles (MVV, Figure 2D), consistent with a structurally intact but morphologically heterogeneous liposomal formulation. Representative cryogenic transmission electron microscopy (cryo-TEM) images of the liposomal berberine formulation are provided in Figure 2 to confirm vesicle morphology, bilayer integrity, and the presence of multiple vesicle architectures.

The liposomal formulation used in this study incorporates a sunflower-lecithin–based phospholipid matrix combined with plant-derived polysaccharides, including gum arabic and alginate. Together, these components form a lipid bilayer surrounding a hydrated interior, creating a vesicle structure that improves stability and dispersibility in aqueous environments. This delivery platform has been previously applied in our investigations of liposomal vitamin C[20] and liposomal CoQ10,[21] in which the same excipient system supported enhanced oral absorption. For the current study, the liposomal berberine ingredient was manufactured under identical quality specifications, and the structural features of the vesicles were confirmed through cryogenic electron microscopy performed by an independent analytical laboratory. The description of the liposomal excipients and the general methodological approach used here aligns with our prior absorption studies on liposomal vitamin C[20] and CoQ10,[21] which employed the same liposomal delivery system.

Safety

Safety evaluations included routine clinical chemistry, hematology, and vital signs monitoring performed at baseline and 24 hours after dosing. Parameters were assessed by an accredited clinical laboratory using standardized procedures. The panels incorporated markers of liver and kidney function, lipid status, glucose regulation, electrolyte balance, and complete blood counts. All laboratory testing was performed by Radiant Research Services Private Limited (#99/A, 8th Main, III Phase, Peenya Industrial Area, Bangalore, Karnataka 560058, India). Vital signs, including blood pressure, heart rate, and temperature, were recorded at multiple time points throughout each study visit: admission, pre-dose (0 hours), 15 minutes, 30 minutes, 60 minutes, 120 minutes, 4 hours, 8 hours, 12 hours post-dose, and at checkout

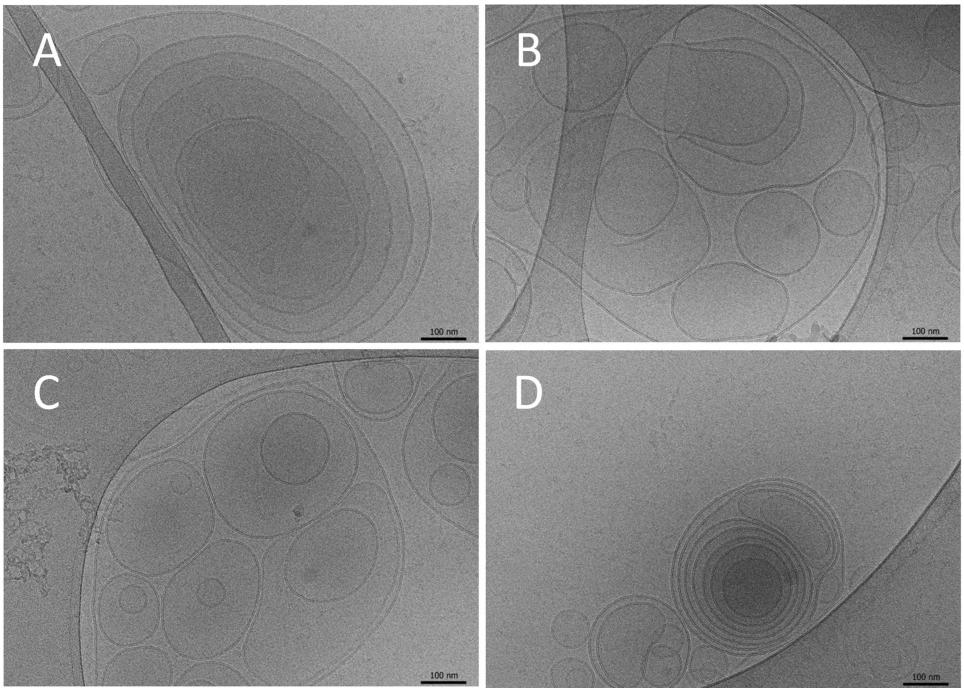

Figure 2 Representative cryogenic transmission electron microscopy (cryo-TEM) images of the liposomal berberine formulation. Images demonstrate intact nanoscale liposomal vesicles with clearly resolved lipid bilayers and particle sizes consistent with those measured by dynamic light scattering (DLS). Multiple vesicle architectures are observed, including multivesicular vesicles (MVV) (**A** and **B**), unilamellar vesicles (ULV) (**C**), and multilamellar vesicles (MLV) (**D**), confirming a structurally intact but morphologically heterogeneous liposomal formulation. Scale bars = 100 nm.

(24 hours post-dose). A ±15-minute window was permitted for post-dose vital sign measurements. Physical examinations were conducted at admission and at 2, 4, and 8 hours after dosing. Potential adverse events were documented and evaluated by the clinical investigator.

Sample Collection

At each scheduled time point, whole blood was drawn into chilled EDTA tubes and immediately placed on ice. Samples were processed promptly by centrifugation to separate plasma, which was then transferred into labeled microtubes. Interim storage occurred at −20°C until batches of samples were moved to a −80°C freezer for long-term preservation. All specimens were transported under controlled conditions to the analytical laboratory following completion of both study periods.

Sample Preparation and LC-MS/MS Analysis

Plasma berberine concentrations were quantified using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method performed on a Shimadzu LC-MS/MS system equipped with an electrospray ionization (ESI) source operating in positive ion mode. Before analysis, frozen plasma samples were thawed at room temperature and subjected to protein precipitation using acidified acetonitrile. Briefly, plasma samples were mixed with precipitation solvent, vortexed to ensure complete protein removal and analyte extraction, and then centrifuged to obtain clarified supernatants. The supernatants were transferred to autosampler vials, and 3 µL was injected into the LC–MS/MS system for analysis.

Chromatographic separation was achieved on a Thermo C18 column (100 × 4.6 mm, 3 µm) maintained at 40 °C using isocratic elution. The mobile phase consisted of 10 mM ammonium formate (pH 6.0) in water (solvent A) and acetonitrile (solvent B), mixed at a 50:50 (v/v) ratio and delivered at a flow rate of 0.45 mL/min. The total run time was 3.0 minutes. Mass spectrometric detection was performed in multiple reaction monitoring (MRM) mode using positive ESI. Quantification was based on monitoring the berberine precursor-to-product ion transition m/z 336.5 →

321.2, selected for optimal sensitivity and selectivity. Optimized source parameters included an interface temperature of 300°C, desolvation temperature of 526°C, DL temperature of 250°C, nebulizing gas flow of 3.0 L/min, and heating/drying gas flow of 10.0 L/min, ensuring stable ionization and high analytical sensitivity. The method was fully validated, demonstrating excellent linearity ($R^2 = 0.99$), a lower limit of quantification (LOQ) of 1.0 pg/mL, and a limit of detection (LOD) of 0.4 pg/mL for berberine in human plasma. Extracted ion chromatograms obtained by LC–MS/MS at the lower limit of quantification (1.0 pg/mL) and the highest calibration concentration (50,000 pg/mL) are provided in Supplementary Figure S1 to demonstrate assay sensitivity, peak integrity, and chromatographic performance across the validated concentration range.

Statistical Analysis

Outcomes of interest included blood berberine responses, as indicated by pharmacokinetic variables (Cmax, AUC_{0-24}, Tmax) and raw concentrations; selected metabolic parameters (glucose and insulin); and safety markers, including hemodynamics and standard clinical panels. To account for outliers and potential normality violations, data with one value per condition (eg, pharmacokinetic variables and percent changes in safety markers) were analyzed using the non-parametric Wilcoxon signed-rank test, with treatment (liposomal berberine and non-liposomal berberine) specified as a within-subjects factor. Linear mixed-effects models were employed to investigate the effects of treatment and time on outcomes with multiple values per condition (eg, raw berberine concentrations and hemodynamic variables). Models included fixed effects for the interaction between treatment and time point, with a random intercept and slope for time point nested within subjects. Restricted maximum likelihood (REML) estimation was used, incorporating an autoregressive correlation structure. Joint tests of fixed effects were conducted. For all tests, statistical significance was considered at $p < 0.05$. Unless otherwise noted, descriptive data are presented as median ± interquartile range (IQR). Percent differences were calculated by dividing the absolute difference between values by the mean of the values, then multiplying by 100 to express the result as a percentage. Data were analyzed using R software version 4.4.2 with the rstatix package version 0.7.2.[22,23]

Results

Participant Characteristics

Six male participants completed the present pilot study and were included in the analysis (Table 1 and Figure 3).

Pharmacokinetic Analysis

C_{max} significantly differed between conditions (liposomal berberine: 22,302 ± 3405 pg/mL, non-liposomal berberine: 10,721 ± 842 pg/mL; $p = 0.03$; Figure 4A). The median C_{max} with liposomal berberine was 70.1% higher than that of non-liposomal berberine, as measured by percent difference. AUC_{0-24} significantly differed between conditions (liposomal berberine: 97,222 ± 26,265 pg/mL × 24 h, non-liposomal berberine: 62,975 ± 2,655 pg/mL × 24 h; $p = 0.03$; Figure 4B). The median AUC_{0-24} with liposomal berberine was 42.8% higher than that of non-liposomal berberine, as

Table 1 Participant Characteristics

	All (n=6)	
	Mean	**SD**
Age (y)	37.8	3.3
Height (cm)	174.8	5.0
Weight (kg)	74.6	2.9
BMI (kg/m^2)	24.4	1.0
SBP (mmHg)	125.0	8.5
DBP (mmHg)	76.8	3.8

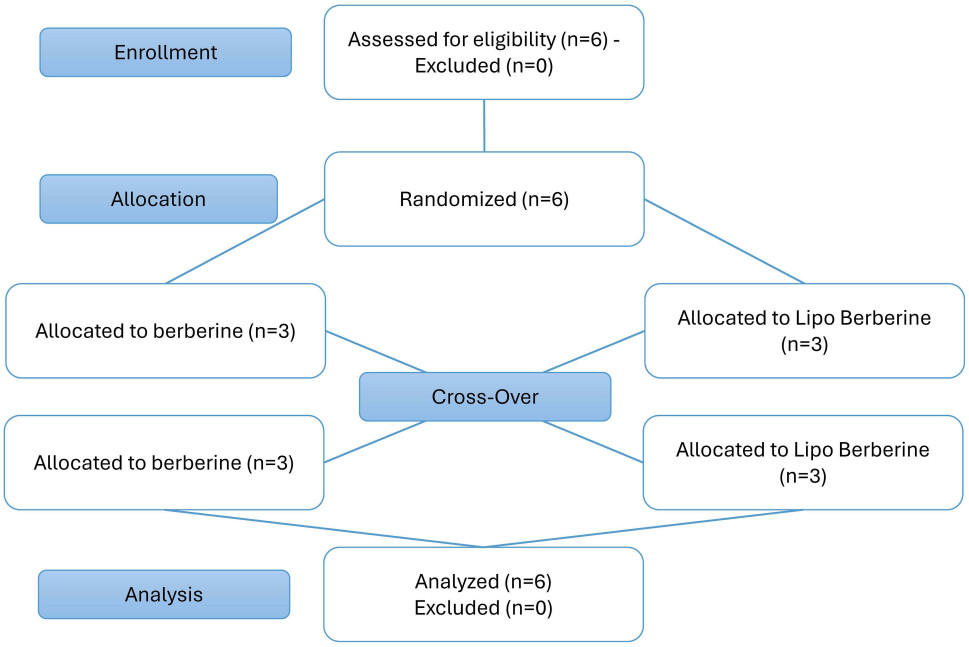

Figure 3 CONSORT flow diagram.

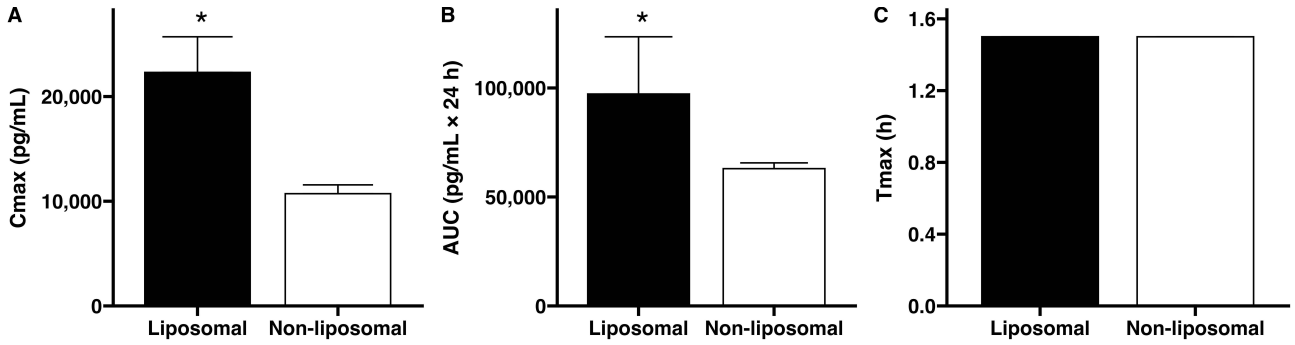

Figure 4 Pharmacokinetic comparison of berberine absorption. (**A**) significant benefit of liposomal delivery for maximal concentrations (C_{max}, **A**) and area under the curve over 24 hours (AUC_{0-24}, **B**) was observed, while T_{max} (**C**) was no different between groups. * indicates significant difference compared to standard, non-liposomal berberine. Bars indicate median values ± IQR.

measured by percent difference. For T_{max}, all participants in both the liposomal berberine and non-liposomal berberine conditions demonstrated a T_{max} value of 1.5 hours (Figure 4C); therefore, no statistical analysis was performed. Raw concentrations of berberine are displayed in Figure 5. When evaluating raw concentrations, a trend for a significant effect of time ($p = 0.09$) was observed, without significant effects of treatment ($p = 0.19$) or treatment × time ($p = 0.30$).

Metabolic and Safety Markers

No differences between groups were observed for 24-hour changes in glucose (p=0.69) or insulin ($p = 0.69$; Figure 6). No significant effects of supplementation on hemodynamic variables were observed. Specifically, no significant effect of treatment ($p = 0.75$), time ($p = 0.49$), or the treatment × time interaction ($p = 0.82$) was observed for systolic blood pressure. Similarly, for diastolic blood pressure, no significant effect of treatment ($p = 0.91$), time ($p = 0.81$), or the treatment × time interaction ($p = 0.65$) was observed. Additionally, no significant effect of treatment ($p = 0.52$), time ($p = 0.61$), or the treatment × time interaction ($p = 0.38$) was observed for heart rate. No significant differences between conditions were observed for a variety of other safety markers, whose percent changes between the pre-ingestion time point and 24 hours after supplement ingestion were evaluated (Table 2).

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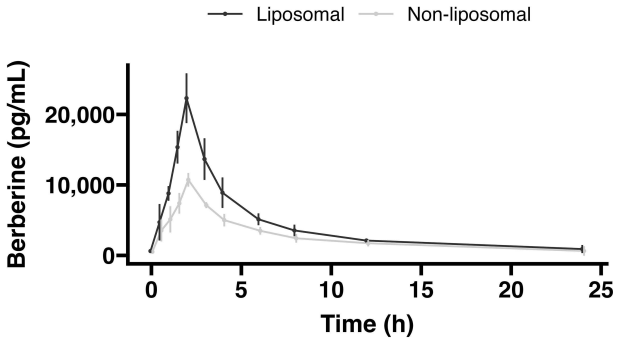

Figure 5 Effects of liposomal delivery on berberine absorption. Raw concentrations of berberine are displayed for 24 hours following ingestion of liposomal berberine or standard, non-liposomal berberine. Points indicate median values, and error bars indicate IQR.

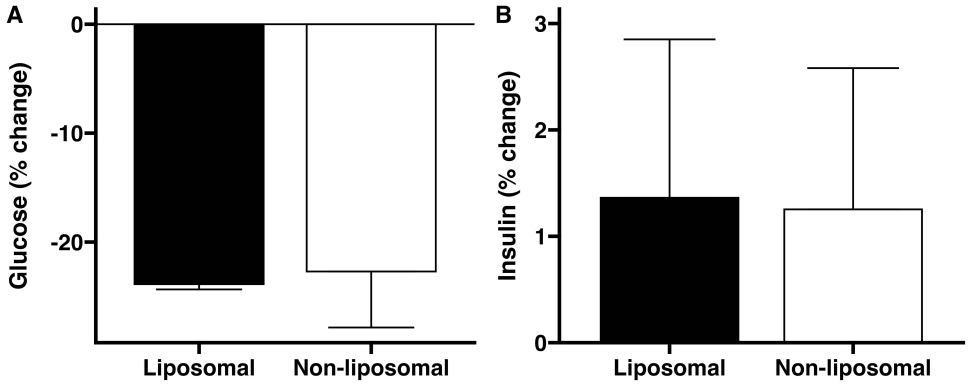

Figure 6 Metabolic biomarker changes after supplement ingestion. The potential effects of liposomal and standard delivery of berberine were examined for glucose (**A**) and insulin (**B**). Bars indicate median values ± IQR.

Discussion

This pilot study compared the bioavailability of liposomal versus standard, unformulated berberine. The findings demonstrate that liposomal delivery significantly enhances berberine absorption, with higher peak plasma concentrations and greater total exposure. The liposomal formulation produced a 70.1% higher Cmax and a 42.8% higher $AUC_{0\text{-}24}$ over

Table 2 Percent Changes in Safety Markers (Biochemical and Hematological) from Baseline to 24 Hours After Supplement Ingestion

Variable	Treatment	Median	IQR	$p^{\#}$
Albumin (g/dL)	Liposomal	4.7	3.7	0.28
	Non-liposomal	−1.9	4.5	
Alkaline phosphatase (U/L)	Liposomal	4.1	5.2	0.56
	Non-liposomal	2.1	4.5	
Bilirubin (mg/dL)	Liposomal	−4.1	17.9	0.69
	Non-liposomal	3.0	14.2	
Cholesterol (mg/dL)	Liposomal	−1.3	2.8	0.84
	Non-liposomal	0.5	2.7	

(*Continued*)

Table 2 (Continued).

Variable	Treatment	Median	IQR	$p^{\#}$
Creatinine (mg/dL)	Liposomal	4.2	18.8	0.11
	Non-liposomal	−9.1	1.4	
Eosinophils (%)	Liposomal	−25.0	25.0	0.60
	Non-liposomal	0.0	0.0	
Glucose (mg/dL)	Liposomal	−23.9	0.5	0.69
	Non-liposomal	−22.7	5.1	
HDL (mg/dL)	Liposomal	0.7	2.6	0.84
	Non-liposomal	0.5	3.3	
Hemoglobin (g/dL)	Liposomal	0.4	4.6	0.69
	Non-liposomal	−0.9	3.3	
Insulin (µIU/mL)	Liposomal	1.4	1.5	0.69
	Non-liposomal	1.3	1.3	
LDL (mg/dL)	Liposomal	−0.8	1.0	0.84
	Non-liposomal	−0.9	1.4	
Lymphocytes (%)	Liposomal	−11.4	11.3	0.84
	Non-liposomal	−8.5	13.9	
Monocytes (%)	Liposomal	−6.3	34.4	0.56
	Non-liposomal	−16.7	47.7	
Neutrophils (%)	Liposomal	−1.8	10.4	1.00
	Non-liposomal	−1.9	2.7	
Platelets ($\times 10^3/\mu L$)	Liposomal	−2.2	7.6	0.84
	Non-liposomal	−2.3	13.1	
RBC ($\times 10^6/\mu L$)	Liposomal	−1.9	5.9	1.00
	Non-liposomal	−1.9	9.5	
SGOT (U/L)	Liposomal	2.8	4.1	0.16
	Non-liposomal	−4.0	3.2	
SGPT (U/L)	Liposomal	−3.0	6.9	0.56
	Non-liposomal	−2.0	7.5	
Triglycerides (mg/dL)	Liposomal	−0.5	3.1	1.00
	Non-liposomal	0.1	1.9	
Urea (mg/dL)	Liposomal	−0.9	7.7	1.00
	Non-liposomal	1.5	13.0	

(*Continued*)

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Table 2 (Continued).

Variable	Treatment	Median	IQR	$p^{\#}$
Uric Acid (mg/dL)	Liposomal	−5.4	3.8	1.00
	Non-liposomal	−2.4	10.9	
VLDL (mg/dL)	Liposomal	0.3	7.3	1.00
	Non-liposomal	2.1	7.0	
WBC ($\times 10^3/\mu L$)	Liposomal	3.7	3.3	0.84
	Non-liposomal	6.4	6.7	

Notes: $^{\#}p$ values from Wilcoxon signed-rank tests on percent change values between baseline and 24 hours after supplement ingestion.
Abbreviations: AlkPhos, Alkaline Phosphatase; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; RBC, Red Blood Cells; AST (SGOT), Aspartate Aminotransferase; ALT (SGPT), Alanine Aminotransferase; VLDL, Very Low-Density Lipoprotein; WBC, White Blood Cells.

24 hours compared with the standard formulation ($p = 0.03$), confirming improved absorption. These outcomes align with prior work showing that liposomal formulation enhances nutrient bioavailability by improving solubility, protecting bioactives from gastrointestinal degradation, and facilitating membranes transport.[19] The same liposomal formulation has recently been demonstrated a significantly increase in vitamin C Cmax and AUC compared with conventional forms, supporting liposomal technology as an effective strategy for improving absorption.[20]

The randomized, double-blind, crossover design minimized interindividual variability, while fasting conditions, a controlled diet, and an adequate washout period reduced confounding factors. Subjects were in-housed for 24 hours during each study period, allowing for optimal control of dietary intake and environmental variables. A validated LC–MS/MS assay with picogram-level sensitivity enabled accurate quantification of berberine plasma concentrations across the 24-hour sampling window. Safety and biochemical monitoring confirmed that both formulations were well tolerated. Overall, these controlled conditions support the conclusion that liposomal encapsulation enhances systemic berberine exposure.

A range of formulation strategies has been explored to overcome berberine's poor bioavailability. For example, a berberine–phospholipid complex (BPC) in a solid dispersion system containing D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) and SiO_2 significantly improved the pharmacokinetic profile of berberine.[24] The BPC markedly increased berberine's liposolubility and intestinal absorption, with TPGS acting both as a dissolution enhancer and P-glycoprotein (P-gp) inhibitor. Perfusion tests showed a 2.0-fold increase in absorption, and oral administration produced a 322% increase in relative bioavailability.[24] TPGS further enhances bioavailability by inhibiting P-gp-mediated efflux.[25] These effects collectively improve dissolution, reduce efflux, and increase permeability.[24,26,27] Additional studies have explored emulsion-based delivery systems. An oil-in-water nanoemulsion of berberine hydrochloride improved intestinal permeability and reduced P-gp efflux, increasing bioavailability ~4.4-fold and maintaining strong six-month stability.[28] A self-nanoemulsifying system using squalene, RH-40, and 1,2-propanediol produced a 3.4-fold bioavailability increase in rabbits.[29] These nanoemulsions improved solubility and reduced efflux, increasing systemic availability. Human clinical data also support enhanced-delivery systems. A study in twelve volunteers found significantly higher berberine plasma concentrations and $AUC_{0\text{-}24}$ with a food-grade solid-dispersion formulation.[30] Another study showed that emulsified berberine delivered with TPGS or Quillaja extract significantly increased AUC and Cmax versus powder.[31] More recently, LipoMicel berberine produced significantly higher $AUC_{0\text{-}24}$ and Cmax than standard berberine in ten healthy adults.[32] Direct quantitative comparison of berberine pharmacokinetics across published delivery systems is limited by substantial heterogeneity in dose, formulation, analytical sensitivity, and study design; therefore, comparisons in the present study are intentionally qualitative and contextual rather than based on standardized effect sizes.

The results have meaningful implications for improving berberine supplementation in various populations, including athletes, individuals with metabolic or cardiovascular disorders, and those with impaired absorption. The increase in

Cmax and AUC_{0-24} demonstrate substantially higher bioavailability of liposomal berberine, making it a preferable option for individuals needing higher systemic exposure without increased dosing. This may be particularly beneficial for individuals with gastrointestinal diseases, pancreatic insufficiency, or bile acid deficiency, where lipid digestion is impaired.

Limitations of the Study

The study has several limitations. This exploratory study was designed to provide preliminary pharmacokinetic data and to assess formulation-related differences in berberine exposure. First, the small sample size of six healthy male participants limits statistical power and restricts the generalizability of the findings to other populations, including females, older adults, and individuals with metabolic or gastrointestinal conditions. Accordingly, the findings should be interpreted as hypothesis-generating rather than confirmatory. Second, the absence of a placebo control prevents differentiation between treatment effects and potential expectancy or procedural influences.

As a single-dose pharmacokinetic investigation, the study design does not provide information on steady-state pharmacokinetics, tissue distribution, or the long-term safety and tolerability of repeated supplementation. Additionally, this study was designed to evaluate absorption-related pharmacokinetic parameters (C_{max}, AUC, T_{max}) rather than elimination kinetics. The sampling schedule, optimized for absorption profiling, was not intended to characterize the terminal elimination phase and therefore does not support reliable estimation of half-life, apparent clearance, or volume of distribution. To avoid reporting unstable or potentially misleading estimates derived from insufficient terminal-phase data, elimination parameters were intentionally not calculated.

Although the randomized, double-blind, crossover methodology reduced interindividual variability, the possibility of residual carryover effects cannot be completely excluded despite the implemented washout period. Future studies with larger, more diverse cohorts and extended supplementation periods will be required to confirm these preliminary findings and to establish their broader clinical relevance.

Conclusion

Liposomal encapsulation was associated with greater oral absorption of berberine, as reflected by higher peak plasma concentrations and increased systemic exposure compared with the unformulated form at an equivalent dose. These findings indicate that liposomal delivery may help overcome the poor oral bioavailability that limits conventional berberine supplementation, likely through improved solubility, protection from gastrointestinal degradation, and enhanced intestinal uptake. This study was designed as an exploratory pharmacokinetic investigation, and the findings should be interpreted as hypothesis-generating. Larger studies and repeated-dose investigations will be required to confirm these results and to establish their clinical relevance.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study was conducted by the Declaration of Helsinki and approved by the Institutional Review Board of Medstar Specialty Hospital (IRB number: ECR/1324/Inst/KA/2019) on August 22, 2024 (IRB approval number: RRS/CL/BA/BER/2024). The study was prospectively registered with the Clinical Trials Registry - India (CTRI Registration Number: CTRI/2024/11/076293) on November 5, 2024.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Professor Grant Tinsley reports personal fees from Specnova LLC, during the conduct of the study; personal fees from Tinsley Consulting LLC, outside the submitted work. All authors declare that the research was conducted without any other commercial or financial relationships that could be construed as a potential conflict of interest.

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