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Hypolipidemic, anti-inflammatory, and neurotrophic effects of a multicomponent nutraceutical containing berberine, bergamot, and amaranth in mild-to-moderate hypercholesterolemia

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Abstract

BACKGROUND: Nutraceutical combinations represent a potential strategy for managing mild hypercholesterolemia in patients who cannot tolerate or do not require statin therapy. In this two-group prospective comparative study, we evaluated the effects of a nutraceutical formulation containing berberine (500 mg), bergamot extract (200 mg), and *Amaranthus cruentus* extract (30 mg) on lipid, inflammatory, and neurotrophic parameters in low-risk subjects with mild-to-moderate hypercholesterolemia.
METHODS: Sixty subjects with low-density-lipoprotein cholesterol (LDL-C) 115–180 mg/dL, total cholesterol (TC) 200–260 mg/dL, triglycerides <250 mg/dL, and cardiovascular risk < 20% received either one tablet daily (Group 1, n = 30) or two tablets daily (Group 2, n = 30) of the study supplement for 8 weeks. Primary outcomes included TC, LDL-C, oxidized LDL (oxLDL), and high-density-lipoprotein cholesterol (HDL-C). Secondary outcomes were triglycerides, high-sensitivity C-reactive protein (hs-CRP), and serum brain-derived neurotrophic factor (BDNF).
RESULTS: Both regimens significantly reduced TC and LDL-C at 8 weeks. Group 2 demonstrated superior reductions in LDL-C (−25.2% *versus* −14.5%, $p < 0.05$), oxLDL (−23.1% *versus* −11.8%, $p < 0.05$), and hs-CRP (−31.3% *versus* −6.7%, $p < 0.001$) compared with Group 1. Group 2 also showed significant increases in HDL-C (+14.9% *versus* +2.2%, $p < 0.05$) and BDNF levels (+16.3% versus +2.7%, $p<0.001$). Both regimens were well-tolerated with no adverse events or hepatic/muscular parameter changes.

O R I G I N A L A R T I C L E

CONCLUSION: This nutraceutical formulation effectively and safely reduced TC and LDL-C in low-risk subjects with mild hypercholesterolemia. The twice-daily regimen provided superior lipid improvements and increased HDL-C and BDNF levels, indicating additional antioxidant, anti-inflammatory, and neuroprotective properties warranting further investigation.

Abbreviations:

BDNF	- Brain-derived neurotrophic factor
HMG-CoA	- 3-hydroxy-3-methylglutaryl-coenzyme A
CVD	- Cardiovascular disease
LDL-C	- Low-density lipoprotein cholesterol
CPK	- Creatine phosphokinase
LDLR	- LDL receptor
AMPK	- Adenosine monophosphate-activated protein kinase
TC	- Total cholesterol
Tg	- Triglycerides
HDL-C	- High-density lipoprotein cholesterol
oxLDL	- Oxidized low-density lipoprotein
hs-CRP	- High-sensitivity C-reactive protein
BMI	- Body mass index
ELISA	- Enzyme-linked immunosorbent assay
CsV	- Coefficients of variation
AST	- Aspartate aminotransferase
ALT	- Alanine aminotransferase
BUN	- Blood urea nitrogen
ULN	- Upper limit of normal
IL-6	- Interleukin-6
IL-1β	- Interleukin-1 beta

INTRODUCTION

Cardiovascular (Chong *et al.* 2025), metabolic (Zhang *et al.* 2024), and neuropsychiatric (Fan *et al.* 2025) diseases are among the leading causes of morbidity and mortality worldwide and are characterized by complex, bidirectional relationships (Deste & Lombardi, 2023; Singh *et al.* 2025). Multiple mechanistic pathways may explain the observed epidemiological associations, with growing evidence that dyslipidemia (Zorkina *et al.* 2024; Lang *et al.* 2025), systemic inflammation (Suffee *et al.* 2024; Upthegrove *et al.* 2025), and reduced circulating neurotrophins – particularly brain-derived neurotrophic factor (BDNF) (Geroldi *et al.* 2006; Motamedi *et al.* 2017; Pius-Sadowska & Machaliński, 2017) – act as key mediators across all three disease domains. Through inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, statins remain the gold standard for secondary prevention of cardiovascular disease (CVD) in patients with dyslipidemia (Rossini *et al.* 2022; Yang *et al.* 2023). Notably, beyond their established efficacy in lowering serum low-density lipoprotein cholesterol (LDL-C), statins may exert pleiotropic effects including anti-inflammatory (Koushki *et al.* 2021) and antioxidant (Mansouri *et al.* 2022) activity, as well as promotion of increased circulating BDNF levels (Zhang *et al.* 2017). However, approximately 10% of patients discontinue statin therapy within 12 months due to adverse effects, including statin-associated muscle symptoms – characterized by myalgia, asthenia, fatigue, and elevated creatine phosphokinase (CPK) levels (Newman *et al.* 2019). These limitations substantially restrict the widespread use of statins for primary CVD prevention, particularly in individuals at low cardiovascular risk with mild-to-moderate hypercholesterolemia (Durai & Redberg, 2022). Nutraceutical agents with lipid-modulating properties have therefore gained considerable attention as alternative strategies for primary CVD prevention in low-risk populations. Accordingly, these compounds offer favorable safety profiles while producing clinically meaningful reductions in atherogenic lipoproteins (Biagi *et al.* 2018; Cicero & Colletti, 2018; Minoretti *et al.* 2022). Among the most promising lipid-lowering nutraceuticals are berberine, bergamot extract, and amaranth extract – each possessing distinct but potentially complementary mechanisms of action.

Berberine – an isoquinoline alkaloid derived from *Berberis aristata* – exerts hypolipidemic effects through HMG-CoA reductase-independent pathways (Li *et al.* 2020). Accordingly, its primary mechanisms involve upregulation of hepatic LDL receptor (LDLR) expression and suppression of cholesterol biosynthesis via adenosine monophosphate-activated protein kinase (AMPK) activation (Asghari *et al.* 2025). Beyond lipid modulation, preclinical studies indicate that berberine can attenuate inflammation (Wang *et al.* 2024) and upregulate BDNF expression via PI3K/AKT/CREB-dependent pathways (Shen *et al.* 2016; Tang *et al.* 2024), though peripheral bioavailability constraints may limit translational validation (Asghari *et al.* 2025). Novel delivery systems, including liposomal formulations, have been therefore developed to overcome these pharmacokinetic limitations and optimize efficacy (Mujtaba *et al.* 2022). Bergamot (*Citrus bergamia*) extract has previously demonstrated multifaceted cardiometabolic benefits, including amelioration of atherogenic dyslipidemia (Toth *et al.* 2016) and potent antioxidant and anti-inflammatory effects (Adorisio *et al.* 2023). Its bioactive polyphenolic fraction can modulate lipid metabolism through multiple distinct pathways – including cholesterol synthesis inhibition, increased fatty acid oxidation, reduced cholesterol absorption, and activation of AMPK signaling (Huang *et al.* 2021) – which complement the mechanisms of berberine. Amaranth (*Amaranthus* ssp., including *A. cruentus*) has also demonstrated cholesterol-lowering and hypotriglyceridemic effects in preclinical hyperlipidemic models, with evidence suggesting favorable modulation of hepatic lipid metabolism and enhancement of antioxidant defense systems (Kim *et al.* 2006; Kabiri *et al.* 2011; Chmelík *et al.* 2019). Its biological properties – including HMG-CoA reductase inhibition, reduced cholesterol synthesis, enhanced bile acid conversion, AMPK activation, and modulation of the gut microbiota-liver axis (Yang *et al.* 2021) – position

Tab. 1. Baseline characteristics of study participants

Variable	Entire cohort (n = 60)	Group 1 (n = 30)	Group 2 (n = 30)	*p*
Men/women	32/28	16/14	16/14	0.82
Age, years	48.3 ± 8.2	47.8 ± 7.9	48.8 ± 8.6	0.63
Body mass index, kg/m^2	26.4 ± 2.8	26.1 ± 2.6	26.7 ± 3.0	0.42
Systolic blood pressure, mm Hg	126 ± 10	125 ± 9	127 ± 11	0.47
Diastolic blood pressure, mm Hg	79 ± 7	78 ± 6	80 ± 8	0.33
Fasting plasma glucose, mg/dL	92.4 ± 8.1	91.8 ± 7.8	93.0 ± 8.5	0.58

Data are given as counts for sex, whereas all other variables are summarized as means ± standard deviation.

amaranth as a potentially valuable adjunct in comprehensive dyslipidemia management.

Given the converging evidence regarding the individual benefits of berberine, bergamot, and amaranth, along with their potential additive and/or synergistic effects on lipid metabolism, inflammation, and neurotrophic signaling, we hypothesized that a multicomponent nutraceutical formulation combining these agents might offer comprehensive cardiometabolic and neurotrophic benefits. We therefore conducted an 8-week two-group prospective comparative study to evaluate the effects of this nutraceutical combination on lipid profiles, high-sensitivity C-reactive protein (hs-CRP), and serum BDNF levels in apparently healthy subjects at low cardiovascular risk with mild-to-moderate hypercholesterolemia.

METHODS

Study design and participants

This 8-week two-group prospective comparative study employed a two-group pretest-posttest design. Sixty Caucasian adults were enrolled based on the following criteria: (1) age > 18 years, (2) fasting serum LDL-C levels between 115 and 180 mg/dL, (3) total cholesterol (TC) levels between 200 and 260 mg/dL, (4) triglyceride (Tg) levels below 250 mg/dL, and (5) estimated 10-year cardiovascular risk < 20% according to the SCORE2 algorithm (Fontainhas *et al.* 2024). Exclusion criteria comprised (1) current or recent (within 3 months) use of lipid-lowering pharmacotherapy including statins, fibrates, ezetimibe, or bile acid sequestrants; (2) documented hypersensitivity or intolerance to berberine, bergamot, amaranth, or any excipient contained in the study supplement; (3) positive history of cardiovascular events including myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina; (4) diagnosis of familial hypercholesterolemia or other genetic dyslipidemia disorders; (5) familial history suggestive of high cardiovascular risk; (5) hepatic impairment or active hepatobiliary disease; (6) muscular disorders including myopathy, rhabdomyolysis, or unexplained elevated CPK levels; (7) renal insufficiency (estimated glomerular filtration rate < 60 mL/min/1.73 m^2); (8) diabetes mellitus or other endocrine disorders; and (9) pregnancy or lactation. Eligible participants were identified through review of outpatient medical records at Studio Minoretti srl (Oggiono, Italy), and subsequently contacted for in-person clinical visits and potential enrollment. Following comprehensive explanation of study objectives, procedures, potential benefits, and risks, all participants provided written informed consent prior to any study-related procedures. To minimize confounding from lifestyle modifications, participants were explicitly instructed to maintain their habitual dietary patterns and physical activity levels throughout the 8-week study period. The study protocol was conducted in accordance with the ethical principles of the Declaration of Helsinki and received approval from the local ethics committee (reference number: E778624).

Study supplement

The investigational nutraceutical formulation (Colestarmony Plus) was supplied by Bionativa SpA (Barberino Tavarnelle, Italy) in oral tablet form. Each tablet contained 500 mg of berberine in a 20% liposomal formulation, 200 mg of bergamot extract, and 30 mg of amaranth (*A. cruentus*) extract.

Procedures

A total of 60 apparently healthy subjects (32 men and 28 women, mean age: 48.3 ± 8.2 years) were included in the study. At the baseline visit, the following data were collected from all participants: medical history, physical examination, anthropometric measurements (height, weight, body mass index [BMI] calculation), and resting blood pressure values. Fasting venous blood samples (minimum 8-h overnight fast) were collected for baseline lipid profile, glucose determination, hs-CRP, BDNF, and safety parameters. Participants were subsequently assigned in a 1:1 ratio to one of two dosing regimens using a computer-generated allocation sequence. Group 1 (n = 30) received a once-daily regimen consisting of one tablet of the study supplement administered after the evening meal (total daily dose: berberine

Tab. 2. Changes in lipid profile, inflammatory markers, and BDNF

Biochemical variable	Group 1		Group 2		*p*‡
	Baseline	8 weeks	Baseline	8 weeks	
TC, mg/dL	227 ± 19	194 ± 16*	229 ± 17	187 ± 15*	NS
LDL-C, mg/dL	145 ± 17	124 ± 14*	147 ± 15	110 ± 12*	<0.05
OxLDL, U/L	51 ± 13	45 ± 11*	52 ± 14	40 ± 9*	<0.05
HDL-C, mg/dL	46 ± 7	47 ± 8	47 ± 8	54 ± 7*	<0.05
Tg, mg/dL	142 ± 38	136 ± 35	145 ± 41	138 ± 37	NS
Hs-CRP, mg/L	1.5 ± 0.7	1.4 ± 0.6	1.6 ± 0.8	1.1 ± 0.5†	<0.001
BDNF, ng/mL	22.1 ± 4.6	22.7 ± 4.4	22.7 ± 5.0	26.4 ± 5.3**	<0.001

Data are expressed as means ± standard deviations. *$p < 0.05$ versus baseline within group. †$p < 0.01$ versus baseline within group. ** $p < 0.001$ versus baseline within group. ‡Between-group comparison at week 8 (Group 2 versus Group 1). Abbreviations: TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; OxLDL, oxidized low-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; Tg, triglycerides; Hs-CRP, high-sensitivity C-reactive protein; BDNF, brain-derived neurotrophic factor; NS, not significant.

500 mg, bergamot extract 200 mg, amaranth extract 30 mg). Group 2 (n = 30) received a twice-daily regimen consisting of one tablet administered in the morning after breakfast and one tablet in the evening after dinner (total daily dose: berberine 1000 mg, bergamot extract 400 mg, amaranth extract 60 mg). Twice-daily dosing was implemented to probe potential dose-response relationships. Participants received detailed written and verbal instructions regarding proper supplement administration, storage requirements, and the importance of adherence to the assigned dosing regimen. Supplements were self-administered by participants at home throughout the 8-week study period. Compliance was assessed through tablet counting at the final visit and participant self-report. The final study visit was conducted at week 8 (± 3 days). The final visit replicated the baseline assessment protocol, including physical examination, anthropometric measurements, blood pressure determination, and fasting venous blood collection for evaluation of biochemical outcome parameters and safety assessments.

Outcome measures

The primary outcome measures were changes from baseline to week 8 in TC, LDL-C, high-density lipoprotein cholesterol (HDL-C), Tg, and oxidized low-density lipoprotein (oxLDL) – as a marker of atherogenic lipoprotein modification. Secondary outcomes comprised changes in hs-CRP and serum BDNF levels.

Laboratory assays

Biochemical analyses of fasting plasma glucose and routine lipid parameters (TC, LDL-C, HDL-C, Tg) were performed using enzymatic colorimetric methods on a Hitachi-912 Auto Analyzer (Hitachi, Mannheim, Germany) with commercially available Roche Diagnostics reagent kits (Roche Diagnostics, Mannheim, Germany) according to manufacturer specifications. LDL-C was calculated using the Friedewald formula. Oxidized LDL was quantified using a commercially available sandwich enzyme-linked immunosorbent assay (ELISA) (Mercodia AB, Uppsala, Sweden). Hs-CRP protein concentrations were determined by latex-enhanced immunonephelometric assay on a BN II nephelometer (Dade Behring, Newark, DE, USA), with interassay and intraassay coefficients of variation (CsV) of 6.7% and 3.8%, respectively. Serum BDNF concentrations were measured using a commercially available ELISA kit (FineTest Biotech Inc., Boulder, CO, USA). Interassay and intraassay CsV were 7.9% and 5.7%, respectively. All laboratory analyses were conducted by trained personnel blinded to group assignment.

Safety assessment

Changes from baseline in clinical laboratory safety parameters were evaluated, including hepatic transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), CPK as a marker of muscle injury, serum creatinine and blood urea nitrogen (BUN) for renal function assessment, and hematological parameters (hematocrit and hemoglobin). Participant-reported tolerability was evaluated through self-administered questionnaires administered at week 8, which assessed the presence, frequency, and severity of common gastrointestinal symptoms (nausea, gastric discomfort or pain, altered bowel habits) and muscular symptoms (myalgia, muscle weakness, exercise intolerance) using standardized rating scales. Clinically relevant changes in laboratory safety parameters were predefined according to established thresholds (Biagi *et al.* 2018; Minoretti *et al.* 2022): hepatic transaminases (AST and/or ALT) equal to or exceeding three times the upper limit of normal (ULN), CPK elevation greater than five times the ULN, serum creatinine equal to or exceeding 1.3 times the ULN, BUN equal to or exceeding two times the ULN, hematocrit decrease of five percentage points or more from baseline values, and hemoglobin decrease of 2.0 g/dL or more from baseline.

Statistical analysis

Categorical variables are expressed as frequencies and percentages and were compared between treatment groups using Pearson's chi-square test. Continuous variables are presented as means ± standard deviations. Paired Student's *t*-tests were used to evaluate within-group changes from baseline to week 8, whereas unpaired Student's *t*-tests were applied to compare continuous variables between Group 1 and Group 2 at baseline and week 8 to identify potential dose-dependent effects. Pearson's correlation coefficients were calculated to explore potential associations between changes in lipid parameters, hs-CRP, and BDNF levels. All analyses were performed using SPSS Statistics version 20.0 (IBM, Armonk, NY, USA). Statistical tests were two-tailed, with $p < 0.05$ considered statistically significant. Given the exploratory nature of this investigation and the evaluation of multiple biochemical endpoints, no adjustments for multiple comparisons were applied; accordingly, findings should be interpreted as hypothesis-generating pending confirmatory analysis.

RESULTS

Baseline characteristics

At baseline, Groups 1 and 2 demonstrated comparable profiles, with no significant differences in sex distribution, age, BMI, blood pressure measurements, or fasting plasma glucose concentrations (Table 1). All laboratory safety parameters were within established normal ranges for both groups (data not shown). The study population was therefore representative of individuals with mild-to-moderate hypercholesterolemia requiring primary CVD prevention.

Changes in lipid profiles

Changes in lipid parameters during the 8-week study period are summarized in Table 2. At baseline, no significant differences were observed between groups. Both dosing regimens produced significant reductions in TC and LDL-C at week 8 compared with baseline. In Group 1, TC decreased by 14.5% ($p < 0.05$) and LDL-C by 14.5% ($p < 0.05$). Group 2 demonstrated greater reductions, with TC decreasing by 18.3% ($p < 0.05$) and LDL-C by 25.2% ($p < 0.05$). Between-group comparisons revealed significantly greater LDL-C reduction in Group 2 than Group 1 ($p < 0.05$). Group 2 showed significant reductions in oxLDL concentrations from baseline (23.1%, $p < 0.05$) compared with a modest decrease in Group 1 (11.8%, $p < 0.05$), with the between-group difference reaching statistical significance ($p < 0.05$). Additionally, Group 2 demonstrated significant increases in HDL-C levels (+14.9%, $p < 0.05$) from baseline, whereas Group 1 showed minimal change (+2.2%), with Group 2 exhibiting significantly greater HDL-C elevation ($p < 0.05$). Percent changes from baseline in lipid parameters for both treatment groups are illustrated in Figure 1.

Changes in hs-CRP and BDNF levels

Group 2 exhibited a statistically significant 31.3% reduction in hs-CRP concentrations from baseline to week 8 ($p < 0.01$), whereas Group 1 showed a modest 6.7% decrease that did not achieve statistical significance. The between-group difference in hs-CRP reduction was significant ($p < 0.001$), indicating superior anti-inflammatory effects with the twice-daily regimen. Similarly, Group 2 demonstrated a significant increase in serum BDNF levels at week 8 (+16.3% from baseline, $p < 0.001$), whereas Group 1 showed only a minimal increase (+2.7%). The magnitude of serum

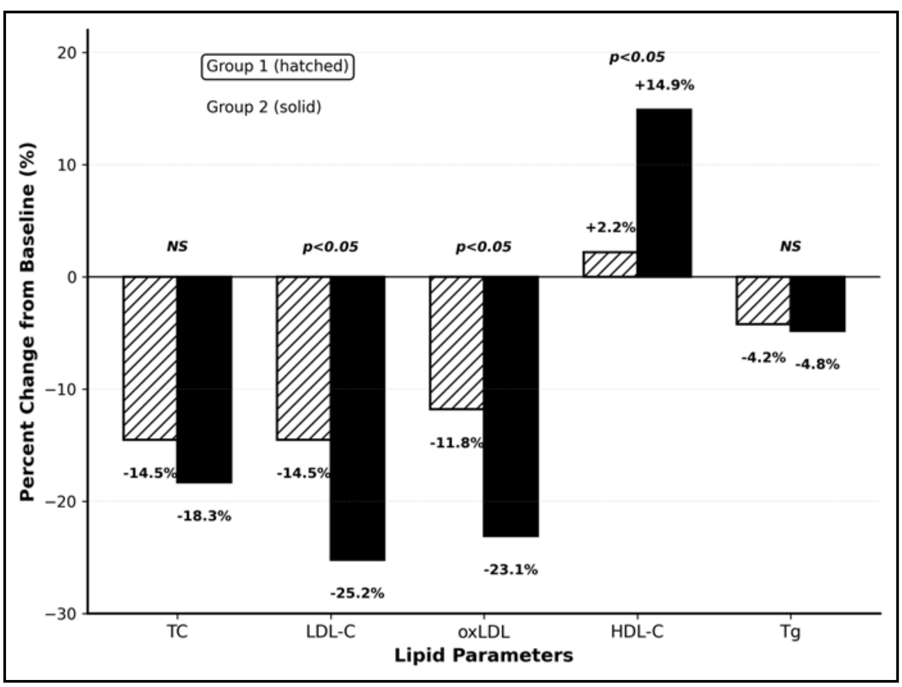

Fig. 1. Percent changes from baseline in lipid parameters following 8-week nutraceutical supplementation.

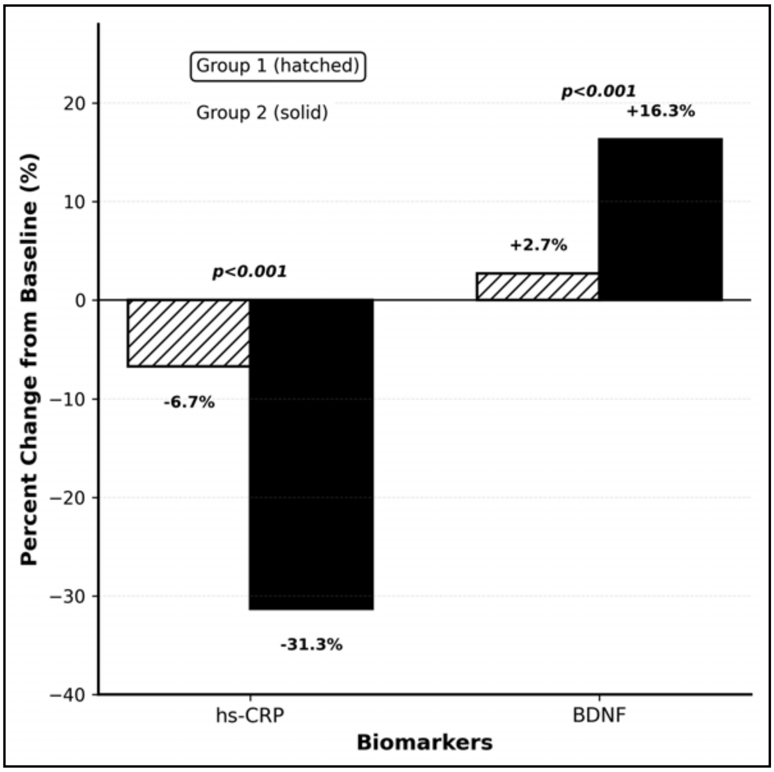

Fig. 2. Percent changes from baseline in high-sensitivity C-reactive protein (hs-CRP) and brain-derived neurotrophic factor (BDNF) following 8-week nutraceutical supplementation.

BDNF elevation was significantly greater in Group 2 compared with Group 1 ($p < 0.001$). Percent changes in hs-CRP and BDNF levels are depicted in Figure 2. Notably, correlation analysis revealed a positive association between the magnitude of BDNF elevation and improvements in HDL-C concentrations in Group 2 ($r = 0.42$, $p < 0.05$).

Safety and tolerability

Both dosing regimens were safe and well-tolerated throughout the 8-week study. No participants withdrew due to supplement-related adverse effects, and no cases of gastrointestinal or muscular symptoms were documented. All laboratory parameters remained within normal limits in all participants.

DISCUSSION

In this 8-week two-group prospective comparative study, we evaluated a multicomponent nutraceutical formulation containing berberine, bergamot extract, and amaranth extract in apparently healthy subjects with mild-to-moderate hypercholesterolemia at low CVD risk. Our results revealed that both once-daily and twice-daily regimens produced significant reductions in TC and LDL-C from baseline. However, the twice-daily schedule demonstrated significantly greater LDL-C reduction and was the only regimen to yield significant improvements in oxLDL, HDL-C, hs-CRP, and serum BDNF levels. A positive correlation between BDNF elevation and HDL-C improvements was also observed in Group 2. Collectively, these findings suggest that while both regimens provide meaningful lipid-lowering effects, the higher-dose regimen may offer additional antioxidant, anti-inflammatory, and neurotrophic benefits, positioning this combination as a viable option for hypercholesterolemic individuals at low CVD risk who are unsuitable candidates for or intolerant to statin therapy.

The observed reductions in TC and LDL-C across both study groups are in accordance with the established lipid-lowering properties of the individual supplement components. Clinical studies have demonstrated LDL-C reductions of approximately 20–30% with berberine at doses of 500–1000 mg daily over a treatment period of 8–12 weeks, with enhanced effects observed when treatment is extended beyond 3 months (Koppen *et al.* 2017; Wang & Zidichouski, 2018). Similarly, previous investigations have reported significant hypolipidemic effects of bergamot extracts over treatment periods ranging from 30 days to 6 months (Spina *et al.* 2024; Carpenito *et al.* 2025). The magnitude of lipid improvements observed in the present 8-week study – particularly the 25.2% LDL-C reduction in Group 2 – supports these prior findings and suggests additive or synergistic interactions between the formulation components. The superior efficacy of the twice-daily regimen in reducing oxLDL and elevating HDL-C warrants particular attention. OxLDL plays a central role in atherogenesis through promotion of endothelial dysfunction, foam cell formation, and inflammatory cascade activation (Munno *et al.* 2024). The significant oxLDL reduction observed in Group 2 suggests enhanced antioxidant capacity at higher supplementation dosage, likely attributable to the polyphenolic constituents of bergamot extract (Baron *et al.* 2021) and the antioxidant properties of amaranth (Sarker *et al.* 2020). It should be acknowledged, however, that direct mechanistic validation through established antioxidant capacity assays was not conducted in the present investigation, and the observed reductions in circulating oxLDL may reflect both direct radical-scavenging activity and indirect effects mediated through improvements in overall lipid metabolism. The concomitant HDL-C elevation in this group further supports the multifaceted benefits of higher-dose supplementation, as HDL-C particles facilitate reverse cholesterol transport and exert anti-inflammatory and antioxidant effects (Ouimet *et al.* 2019). The statistically significant reduction in hs-CRP concentrations observed in Group 2 represents another important finding, given the established relationship between systemic low-grade inflammation and CVD risk (Kälsch *et al.* 2020). Preclinical evidence indicates that berberine exerts anti-inflammatory effects through inhibition of nuclear factor-κB signaling pathways *in vitro*, while bergamot polyphenols have been shown to downregulate cyclooxygenase-2, inducible nitric oxide synthase, and pro-inflammatory cytokine expression (Zhang *et al.* 2025; Adorisio *et al.* 2023). The observed hs-CRP reduction in Group 2 may therefore reflect cumulative polyphenolic effects at higher doses; however, specific inflammatory mediators such as interleukin (IL)-6 and IL-1β were not directly quantified in this study, limiting our ability to fully characterize the mechanistic underpinnings of the anti-inflammatory response. The dose-dependent nature of hs-CRP reduction suggests that achieving clinically meaningful systemic anti-inflammatory effects requires sufficient circulating concentrations of bioactive compounds to engage multiple anti-inflammatory pathways simultaneously. Perhaps most intriguing is the significant elevation in circulating serum BDNF – a critical mediator of neuronal survival and synaptic plasticity with significant peripheral metabolic effects (Podyma *et al.* 2021) – observed exclusively in Group 2. Preclinical findings have shown that berberine can upregulate BDNF expression through PI3K/AKT/CREB-dependent signaling pathways (Tang *et al.* 2024), suggesting a mechanistic rationale for the observed neurotrophic effects. Nevertheless, translation of these findings to human subjects is complicated by berberine's well-documented bioavailability limitations, which may constrain the achievement of therapeutically relevant central nervous system concentrations following oral administration. The liposomal formulation employed in the present study was designed to enhance bioavailability; however, we acknowledge that comparative bioavailability data *versus* crystalline berberine preparations were not obtained. Notably, both berberine (Tian *et al.* 2023) and bergamot (Ferlazzo *et al.* 2020) possess neuroprotective properties through their antioxidant and anti-inflammatory effects, which may indirectly support BDNF production and signaling. The dose-dependent nature of BDNF elevation suggests that achieving therapeutic concentrations of active compounds sufficient to modulate central and peripheral neurotrophic pathways requires higher supplementation levels. Intriguingly, the positive correlation between BDNF and HDL-C levels identified in our study corroborates prior evidence from coronary artery disease cohorts demonstrating that BDNF deficiency parallels HDL reduction (Jiang *et al.* 2011; Monisha *et al.* 2020) – potentially supporting a functional link between neurotrophic signaling and atheroprotective lipid profiles. However, the exploratory correlation observed in our study ($r = 0.42$, $n = 30$, $p < 0.05$), while statistically significant, represents a modest effect size that limits definitive mechanistic inference. Moreover, the cross-sectional nature of the correlation analysis precludes determination of temporal relationships, and potential confounding variables were not controlled. In this scenario, the directionality of this association – i.e., whether BDNF elevation drives HDL-C improvements, HDL-C increases promote BDNF synthesis, or both parameters respond independently to shared upstream regulatory mechanisms – remains to be elucidated.

Both dosing regimens demonstrated excellent safety and tolerability profiles throughout the 8-week study period. No participants discontinued treatment due to adverse effects, and no significant self-reported symptoms were reported. Notably, the absence of clinically significant changes in hepatic or muscular enzymes represents a significant finding, particularly given the hepatotoxicity and myopathy concerns that limit statin use in primary CVD prevention (Durai & Redberg, 2022). Although our global results are encouraging, they should be considered within the context of several limitations. First, while the two-group prospective comparative design provides preliminary evidence of potential efficacy, it cannot establish definitive causal relationships between the intervention and observed outcomes. Second, the relatively short 8-week intervention period precludes comprehensive assessment of long-term efficacy and sustainability of effects. Specific questions that remain unanswered include whether BDNF elevation persists beyond treatment cessation or declines rapidly upon supplement discontinuation and whether compensatory neuroendocrine feedback mechanisms become engaged during extended treatment. Extended follow-up periods would be therefore essential to address these temporal dynamics and establish the durability of treatment effects. Third, the modest sample size ($n = 60$) limits statistical power for detecting more subtle treatment effects and restricts generalizability of findings. The study population comprised exclusively individuals of Caucasian ethnicity with mild-to-moderate hypercholesterolemia at low cardiovascular risk, which substantially limits extrapolation to other ethnic groups, patients with more severe dyslipidemia, or individuals at higher cardiovascular risk. In addition, given that ethnic-specific genetic polymorphisms in key lipid metabolism genes may influence individual responses to nutraceutical interventions, validation studies in ethnically diverse populations are essential to establish broader applicability. Fourth, compliance assessment relied exclusively on tablet counting at the final visit, without objective verification through urinary biomarker analysis or electronic monitoring systems. This approach may overestimate true adherence rates and introduces uncertainty regarding the consistency of supplement intake throughout the study period. Moreover, the twice-daily dosing regimen implemented in Group 2 – which doubled active compound concentrations relative to Group 1 – was designed to probe dose-response relationships. However, the absence of additional intermediate dosing groups precludes rigorous assessment of dose-response linearity and identification of potential threshold effects or saturation phenomena. Fifth, although participants were instructed to maintain habitual dietary patterns and physical activity levels, the study did not include objective assessments of dietary intake, physical activity levels, or other lifestyle factors that may influence lipid metabolism and cardiovascular risk. Such monitoring would enhance interpretation of treatment effects and control for potential confounding variables. Furthermore, systematic assessment of behavioral parameters relevant to BDNF interpretation – including sleep quality, mood states, and cognitive function – was not conducted. These neurobehavioral measures would provide valuable context for interpreting the observed neurotrophic effects and assessing their potential clinical significance. Finally, the mechanisms underlying the observed effects remain incompletely characterized. While preclinical and clinical data support the individual effects of berberine, bergamot, and amaranth on lipid metabolism, inflammation, and neurotrophic signaling, direct mechanistic investigations were not conducted in the present study. Future research should incorporate comprehensive endpoints to elucidate the molecular pathways mediating therapeutic effects. Priority outcomes for neuroimmune pathway validation may include: (1) hepatic AMPK phosphorylation status and downstream transcriptional responses; (2) peripheral expression of BDNF receptors in circulating cells; (3) lipoprotein(a) subspeciation and particle size distribution; (4) fecal microbiota composition and functional capacity; and (5) comprehensive lipidomic profiling to characterize alterations in lipid subspecies beyond standard clinical parameters. Such mechanistic investigations would substantially advance our understanding of the pathways through which multicomponent nutraceutical formulations exert their pleiotropic effects.

CONCLUSION

The present two-group prospective comparative study provides preliminary evidence supporting the potential utility of this multicomponent nutraceutical formulation for management of mild-to-moderate hypercholesterolemia in low-risk individuals. Future investigations should employ randomized, double-blind, placebo-controlled designs with larger sample sizes, and extended intervention periods to definitively establish efficacy and elucidate underlying mechanisms.

CONFLICT OF INTEREST

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