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CLINICAL TRIAL REPORT

Lipid Metabolism Modulation by a Flavonoid-Standardized *Citrus Bergamia* Extract in an Asian Population: Findings From a Double-Blind, Placebo-Controlled Clinical Trial

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Abstract: Genetic factors, dietary habits, and lifestyle may influence individual responses to supplementation, including the bergamot flavanones naringin and naringenin, which are implicated in lipid modulation. The aim of this double-blind, placebo-controlled clinical trial (RCT) is to assess the effects of the supplementation for four months of a standardised bergamot extract at the dosage of 375 mg/day, providing 150 mg/day of flavonoids, on lipid parameters of 108 East Asian adults with LDL-Cholesterol (LDL-C) 100–159 mg/day, since to date, the RCTs have been conducted on Caucasian subjects only. After 4 months, total Cholesterol and LDL-C decreased (−7.3% and −7.0%) with no clinically relevant safety changes regarding hepatic/renal biochemistry, weight, and blood pressure.

Keywords: bergamot, flavonoids, blood lipid management, clinical trial, Asian population

Introduction

Interindividual variability in the response to xenobiotics, including drugs, food additives, non-nutritive food components (ie, polyphenols, phytosterols, and chlorophylls), pesticides, food contact materials, and contaminants of natural or anthropogenic origin, has been attributed to several causes ranging from genetic to environmental factors.[1] As far as genetic factors are concerned, pharmacokinetic parameters can vary across ethnic groups, suggesting that ADME (Absorption, Distribution, Metabolism, and Excretion) may not be directly interchangeable between populations of different origins 1). For instance, interethnic differences in xenobiotic biotransformation between Caucasian (European/North American origin) and Asian (particularly Far Eastern: Chinese, Japanese, Korean) populations are associated primarily with polymorphisms of genes encoding xenobiotic-metabolizing enzymes (ie cytochrome P450 enzymes - CYPs - Phase I, and transferases - Phase II), and at less extent to drug transporters, and drug targets.[2] For instance, due to polymorphisms in genes, four CYP2D6 phenotypes have been recognised, ranging from ultra-rapid metabolisers (UM) to extensive metabolisers (EM), intermediate metabolisers (IM), and poor metabolisers (PM). Asian populations are known to have low prevalence of PM (1%) and high prevalence of IM (between 35 and 55%) compared with Caucasian populations (less than 2%).[3] Interethnic differences in the pharmacokinetics of xenobiotics significantly affect plasma concentrations, impacting both the activity and safety of these substances.

Human CYP2D6 gene is involved in the metabolization of naringin and naringenin,[4] flavanone compounds typically occurring in Citrus species, especially *Citrus bergamia* Risso and Poiteau (commonly called bergamot), which have demonstrated clinically supported effects on lipid metabolism through well-described mechanisms of action;[5,6] notably,

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bergamot juice preparations have been used for hyperlipidemia and the available human evidence, summarized in a systematic review,[7] supports lipid-lowering and lipoprotein-profile improvements. Lipid management is of high clinical relevance, as dyslipidaemia is strongly associated with an increased risk of atherosclerotic cardiovascular disease and broader cardiometabolic complications,[8] which underscores the need for evidence-based interventions capable of improving lipid parameters.

In this context, two complementary clinical trials, in Caucasian subjects, demonstrated that 150 mg of flavonoids (including neoeriocitrin, naringin, neohesperidin) from a standardized bergamot extract (Bergavit™) helped maintain healthy cholesterol levels by supporting optimal total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG), while promoting favorable HDL-C levels. These two studies emphasize both the early onset and the sustained efficacy of bergamot extracts, offering robust evidence of their physiological support for cardiovascular health. The first 6-month observational trial involving 80 participants demonstrated significant and progressive improvements in lipid parameters, highlighting the supplement's long-term effectiveness. In addition to reductions in total and LDL cholesterol, the study reported a favorable shift in LDL subfractions, with an increase in LDL-1 (pattern A), which are less atherogenic than the pattern B LDL molecules (ie, LDL-3, −4, −5), which were significantly decreased. Due to their larger particle size and lower density, LDL-1 particles are less able to penetrate arterial walls, are less prone to oxidation, and exhibit lower inflammatory potential, thereby contributing to a reduced atherogenic risk.[6] The second randomized, double-blind, placebo-controlled trial involving 60 participants confirmed the supplement's safety and efficacy, with benefits evident by 2 months and continuing through the 4 months follow-up.[9] Together, these studies, both conducted in Caucasian populations, confirm the reproducibility and consistency of 150 mg of flavonoid supplementation from a standardized bergamot extract's lipid-modulating effects, while also providing insights into its gradual and sustained mechanism of action.

However, no clinical trials to date have evaluated the lipid-modulating effects of bergamot extract in Asian populations, where genetic, dietary, and lifestyle factors may influence individual responses to supplementation.[10] Epidemiological data reveals substantial variations in the prevalence of dyslipidemia across different ethnicities. South Asians demonstrate a significantly higher prevalence of lipid imbalances compared to Caucasians, which has been attributed to both genetic factors and dietary patterns rich in carbohydrates and refined sugars.[11–14] Thus, emerging research suggests that Asian populations may require tailored approaches to lipid management due to distinct metabolic traits.[10]

The present study aims to fill this gap by conducting the first double-blind, placebo-controlled clinical trial assessing the effects of a standardized bergamot extract on lipid parameters in an Asian cohort, whereas the available literature to date appears to be limited to Caucasian populations. This is particularly relevant considering the reported interethnic differences in metabolic responses, which may be influenced by genetic, dietary, and lifestyle factors. This aligns with the guidelines for managing dyslipidemias published in 2025 by the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS), which do not recommend the use of dietary supplements unless there is strong, documented evidence demonstrating their safety and effectiveness in lowering LDL cholesterol levels.[15] By generating efficacy and safety data in Asian population, the study strengthens the clinical translatability of bergamot supplementation and supports more tailored approaches to lipid management across different ethnic groups.

Materials and Methods

Study Design and Ethics

This clinical trial was conducted at Complife Asia Testing Technology (Xicheng District, Beijing, China) between September 2022 and October 2024. The study employed a monocentric, randomized, placebo-controlled design to evaluate the intervention's effects over a four-month period. Eligible participants were enrolled at baseline (Month 0, M0) following a screening assessment that included blood analysis to determine low-density lipoprotein cholesterol (LDL-C) levels, which served as a primary inclusion criterion. Study visits were scheduled at baseline (M0) and subsequently after 2 (M2), 3 (M3), and 4 (M4) months, during which clinical evaluations and sample collections were performed to monitor the treatment outcomes and safety parameters.

The study protocol (H.E.HU.AC.NMS00.210.00.00_IT0002159/22) was reviewed and approved by the Ethics Committee of the Chung Shan Medical University Hospital on 30 September 2022. The clinical trial was prospectively registered in the ISRCTN registry under the identifier ISRCTN90859063 (https://doi.org/10.1186/ISRCTN90859063, accessed on 13 June 2025).

All study procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki and relevant national and institutional guidelines governing research involving human subjects. Prior to enrollment, each participant received detailed oral and written information regarding the study's objectives, procedures, potential risks, and expected benefits. Informed consent was obtained in writing from all individuals before participation, ensuring voluntary involvement and respect for personal autonomy throughout the study.

Participants

Eligible participants were adult male and female individuals aged between 40 and 70 years. The study population with LDL-C levels between 100 and 159 mg/dL was stratified such that half of the participants had LDL-C levels ranging from 119 to 139 mg/dL. The target sample size was 108 participants.

Exclusion criteria included the use of statins or lipid-lowering food supplements within one month prior to study initiation; adherence to a vegetarian diet; significant changes in habitual lifestyle (such as physical activity levels or dietary habits) within two weeks before the screening visit; a positive medical history of gastrointestinal disorders or conditions affecting visceral motility; pregnancy or lactation (only for women); smoking; a medical history of pathologies or pharmacological treatments potentially interfering with the test product; non-adherence to the treatment regimen, defined as discontinuation of the product for more than one week; current engagement in a weight loss diet or use of weight control products; body mass index (BMI) higher than 26; history of drug, alcohol, or substance abuse; known food intolerances or allergies; participation in another clinical trial within the previous month; the presence of unstable medical conditions (eg, cardiac arrhythmias, myocardial ischemia, uncontrolled hypertension or hypotension, renal failure, or diabetes mellitus); history of stroke or cerebrovascular accident; active cancer under chemotherapy; use of diuretics within one month prior to screening; any psychological, cognitive, or physical condition that could impair the participant's ability to fully comply with study procedures.

Intervention, Randomization, and Masking

The test item was a commercially available, standardized natural extract (Bergavit^{TM}, Bionap S.r.l., Piano Tavola Belpasso, CT, Italy) characterized by its flavonoids content, including neohesperidin, naringin, and neoeriocitrin. The extract is derived from the juice of bergamot, a citrus fruit known for its high concentration of bioactive flavonoids. For the purposes of the clinical trial, Bergavit™ (BRG) was administered (at breakfast) in the form of oral capsules, each containing 375 mg of the extract, corresponding to a daily intake of approximately 150 mg of flavonoids. The capsule formulation was completed with excipients to ensure capsule stability and consistency, comprising 134 mg of pregelatinized starch, 0.4 mg of magnesium stearate, 0.3 mg of talc, and 0.3 mg of silica.

The placebo capsules (PLA) were identical in appearance and composition to the active formulation, with the exception that the BRG extract was replaced by an equivalent amount (375 mg) of maltodextrin. All other excipients were maintained.

The allocation of participants to the active or placebo group was conducted through a randomized process based on the sequential entry number of each subject into the study. A computer-generated, balanced (1:1), and restricted randomization list was employed, utilizing Efron's biased coin design to ensure allocation concealment and balance between groups. The randomization sequence was generated using PASS 11 software (version 11.0.8; PASS, LLC, Kaysville, UT, USA).

Allocation concealment was achieved using sequentially numbered, opaque, sealed envelopes, each containing the pre-assigned intervention code according to the randomization list. These envelopes were securely stored by an independent third party not involved in participant recruitment, data collection, or analysis.

Clinical Biochemistry

Venous blood samples were collected after an overnight fast of approximately 12 hours by a trained nurse in a certified clinical biochemistry laboratory. The primary endpoints of the study were low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC). Secondary endpoints included anthropometric and metabolic parameters, specifically body weight, blood pressure, triglycerides (TG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), glycated hemoglobin (HbA1c), C-reactive protein (CRP), serum creatinine. All hematological and biochemical parameters were determined using standardized, validated routine laboratory methods.

Statistical Methods

Pairwise comparisons were conducted to evaluate changes in biochemical and clinical parameters over time and between treatment arms. Statistical analyses were performed using NCSS 10 software (version 10.0.7 for Windows; NCSS, LLC, Kaysville, UT, USA). Results were expressed as mean ± standard error (SEM), and statistical significance was reported using the following notation: * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

Results

Participants

A total of 156 individuals were screened for eligibility based on predefined inclusion and exclusion criteria. Following initial assessment, 48 subjects were excluded prior to randomization. Specifically, 42 individuals did not meet the inclusion criteria, most commonly due to low-density lipoprotein cholesterol (LDL-C) concentrations or body mass index (BMI) values falling outside the required range. Additionally, 5 participants declined to participate after receiving detailed study information, and 1 subject withdrew informed consent before formal enrollment. As a result, 108 participants met all eligibility requirements and were subsequently randomized into the study.

A total of 102 participants completed the study, with 51 individuals in each treatment group (per protocol population). Six participants (three from each group) discontinued the intervention prematurely, after 1 or 2 months of supplementation, due to personal reasons not related to product use. These individuals were classified as lost to follow-up and were excluded from the per-protocol analysis (Figure 1). The demographic and baseline clinical characteristics of the study population are presented in Table 1.

Primary Endpoints

At baseline, the mean LDL-C blood concentrations were 134.2 ± 2.2 mg/dL in the BRG group and 125.6 ± 2.2 mg/dL in the PLA group ($p > 0.05$). In the BRG group, LDL-C levels exhibited a progressive reduction, with a 5.4% (127.0 ± 2.8 mg/dL, $p < 0.001$) decrease observed after two months followed by a further reduction of 5.8% (126.4 ± 3.0 mg/dL, $p < 0.01$) and 7.0% (124.7 ± 2.8 mg/dL, $p < 0.001$) after 3 and 4 months, respectively (Figure 2a). Although not statistically significant ($p > 0.05$), LDL-C levels in the PLA group exhibited an upward trend over the study period. Differences between the BRG and PLA were statistically significant ($p < 0.05$) at each timepoint.

The changes in HDL-C levels over the course of the study were not statistically significant in either the BRG or PLA group ($p > 0.05$). In both groups, HDL-C values remained relatively stable throughout the intervention period. No statistically significant ($p > 0.05$) differences were observed between the BRG and PLA groups throughout the study period (Figure 2b).

In the BRG group, baseline total cholesterol (TC) levels (223.9 ± 3.6 mg/dL) were significantly reduced by 4.5% at month 2 (213.9 ± 4.1 mg/dL, $p < 0.001$), 5.9% at month 3 (210.7 ± 4.0 mg/dL, $p < 0.001$), and 7.3% at month 4 (207.7 ± 4.0 mg/dL, $p < 0.001$), demonstrating a consistent and statistically significant downward trend over time (Figure 2c). In the PLA group, total cholesterol (TC) levels remained unchanged throughout the study period ($p > 0.05$). In contrast, the differences in TC levels between the BRG and PLA groups were statistically significant at all assessed time points ($p < 0.05$).

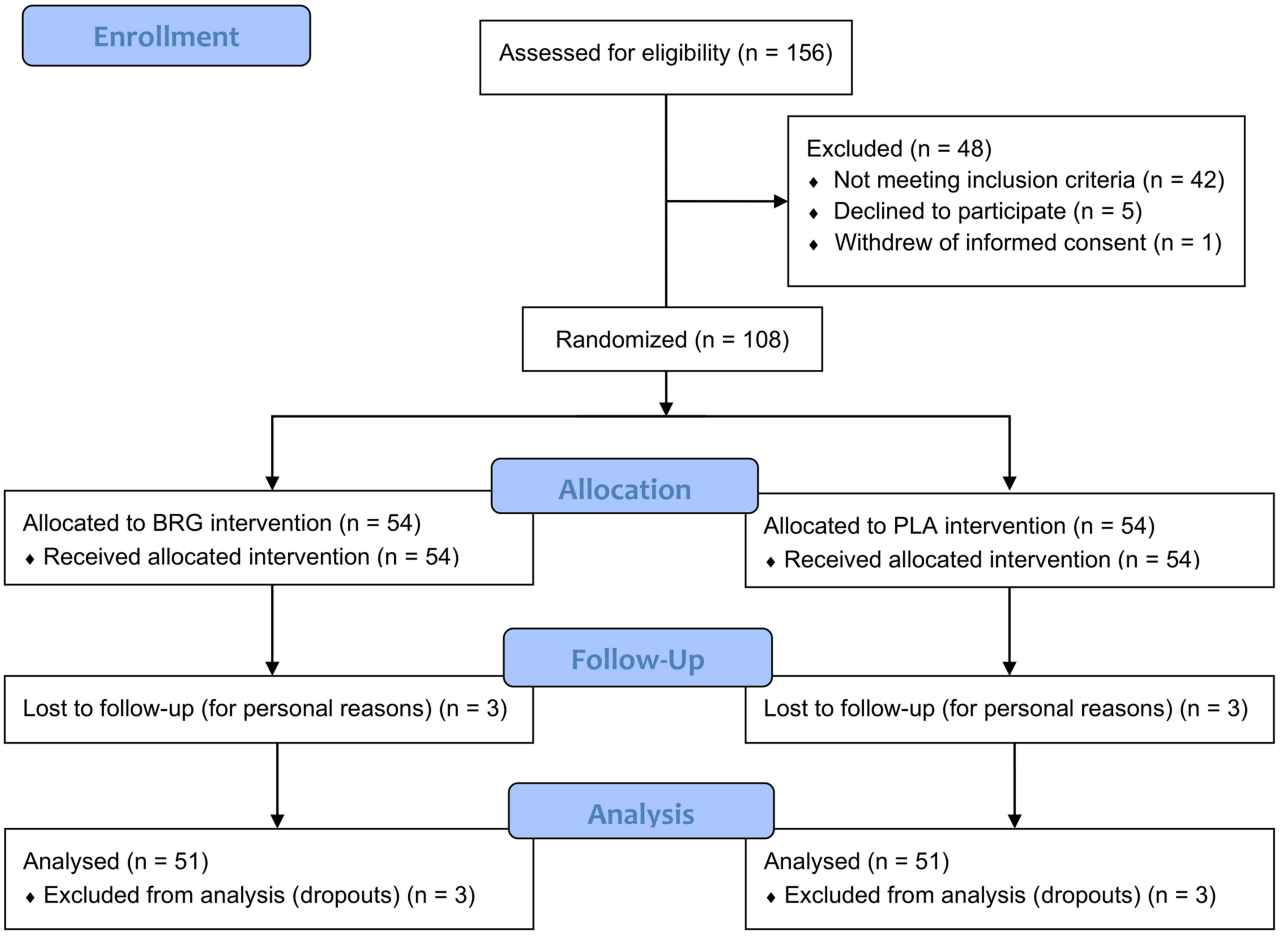

Figure 1 CONSORT (CONsolidated Standards of Reporting Trials) flow diagram illustrating the progression of participants through each phase of the clinical trial including enrolment, allocation, follow-up and analysis.

In the subgroup with a lower LDL-C range (119–139 mg/dL) the mean LDL-C levels were 130.7 ± 1.7 mg/dL for the BRG group and 130.5 ± 1.6 mg/dL for the PLA group ($p > 0.05$). In the subgroup with lower LDL-C concentrations (119 ≤ LDL-C ≤ 139 mg/dL), the results for LDL-C, HDL-C, and total cholesterol (TC) were consistent with those observed in the overall study population (Table 2).

Secondary Endpoints

While universally accepted normal values for ox-LDL have not yet been established, like those for LDL-C, mainly due to the different analytical methods that lead to different results, nevertheless, the ox-LDL levels recorded in the BRG and PLA groups are indeed within an acceptable range, in agreement with the subjects recruited in the clinical trial. In the BRG group, the ox-LDL levels decreased by 18.9% ($p < 0.01$) starting from M3 and further decreased by 38.5% ($p < 0.001$) at M4. A statistically significant reduction in ox-LDL levels was also observed in the PLA group, with a 10.0% decrease at M3 ($p < 0.05$) and a 29.8% decrease at M4 ($p < 0.001$) (Figure 3a). Variations of ox-LDL levels between BRG and PLA groups were statistically significant at M4.

Moreover, no statistically significant differences in PON1 activity were observed between the BRG and PLA groups ($p > 0.05$) throughout the study period (Figure 3b).

Throughout the duration of the intervention, no adverse effects on hepatic or renal function were detected in either group. Specifically, key hepatic biomarkers including aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and C-reactive protein (CRP) remained within normal physiological ranges and did not show statistically significant variations from baseline at any time point (Table 3). Similarly, serum creatinine (CR),

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Table 1 Demographic and Baseline Characteristics

	Active (n = 51)	Placebo (n = 51)	Units	*p* Value[a]
Age	52.3 ± 1.1	53.7 ± 1.2	Years	0.3780
Sex				
Male	13 (25%)	12 (24)	No. (%)	0.8201
Female	38 (75%)	39 (76)	No. (%)	0.8201
Weight	65.9 ± 2.0	64.3 ± 1.6	Kg	0.5436
BMI	25.4 ± 0.6	24.8 ± 0.5	Kg/m^2	0.4181
Blood pressure				
Systolic	125.1 ± 2.4	123.8 ± 2.2	mmHg	0.6923
Diastolic	82.0 ± 1.8	80.4 ± 1.7	mmHg	0.3547
LDL-C	134.2 ± 2.2	125.6 ± 2.2	mg/dL	0.4920
HDL-C	58.9 ± 2.2	59.2 ± 2.3	mg/dL	0.9323
TC	223.9 ± 3.6	213.6 ± 3.7	mg/dL	0.0503
Ox-LDL	113.0 ± 6.7	111.5 ± 6.4	ng/mL	0.8654
TG	108.7 ± 9.4	97.6 ± 11.0	mg/dL	0.9410
Glycemia	95.2 ± 1.6	97.3 ± 2.2	mg/dL	0.4448
AST	21.6 ± 0.7	22.4 ± 0.9	U/L	0.4595
ALT	22.8 ± 1.3	22.3 ± 1.5	U/L	0.7827
GGT	20.2 ± 2.0	19.8 ± 2.0	U/L	0.8673
HbA1c	5.6 ± 0.1	5.6 ± 0.1	%	0.6733
PON1	1496.2 ± 52.4	1458.6 ± 43.9	µU/mL	0.5838
Hs-CRP	0.14 ± 0.02	0.12 ± 0.01	mg/dL	0.3547
CR	0.75 ± 0.02	0.73 ± 0.02	mg/dL	0.5495

Notes: Continuous variables are presented as mean ± standard error, and categorical variables are shown as counts and percentages (in brackets). [a] Two-way, Student's *t*-test for independent samples.

a principal marker of renal function, remained stable, suggesting that neither the active treatment nor the placebo had a detrimental impact on liver or kidney health. In addition, glycemic parameters, including fasting blood glucose and glycated hemoglobin (HbA1c), were not significantly altered by the intervention. In the BRG group, triglyceride (TG) levels remained stable over the course of the study, whereas in the placebo (PLA) group, TG levels increased by 19.0% ($p < 0.01$) at M3 and by 28.4% ($p < 0.001$) at M4. The differences between the BRG and PLA groups were also statistically significant at both timepoints ($p < 0.01$ at M3 and $p < 0.001$ at M4).

Participants in both the BRG and PLA groups demonstrated high treatment adherence rates (> 90%), calculated as the ratio of capsules taken to capsules prescribed (product accountability), with no withdrawals attributed to treatment-

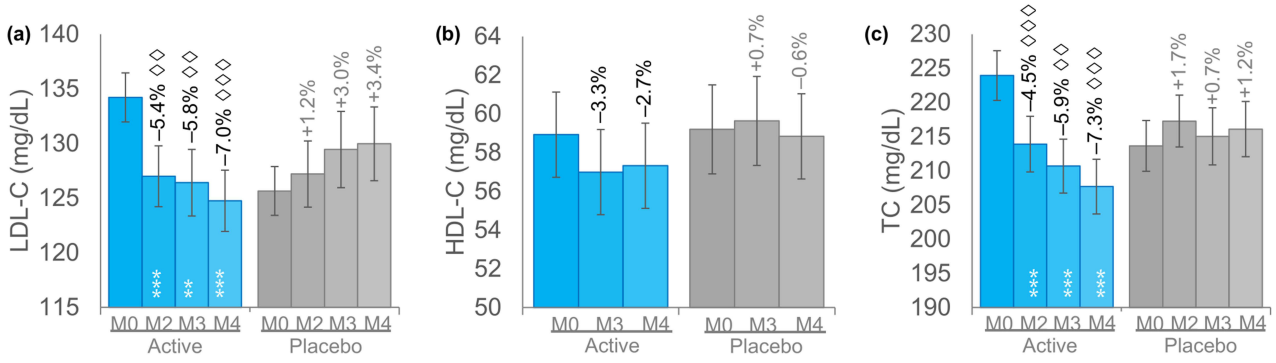

Figure 2 Primary efficacy endpoints in the whole cohort (100 ≤ LDL-C ≤ 159 mg/dL). (**a**) Low-density lipoprotein cholesterol (LDL-C) levels. (**b**) High-density lipoprotein (HDL-C) cholesterol levels. (**c**) Total cholesterol (TC) levels. (**d**) Oxidized low-density lipoprotein (ox-LDL). (**e**) Paraoxonase activity (PON1). Data are mean ± SEM. Intragroup statistical significance (compared to baseline) is indicated within the bars using asterisks (*), while intergroup differences (active vs placebo) are shown above the bars using diamonds symbol ($^{◇}$). Significance levels are denoted as follows: **/$^{◇◇}$ $p < 0.01$, ***/$^{◇◇◇}$ $p < 0.001$.

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Table 2 LDL-C, HDL-C and TC Levels Within the Lower LDL-C Levels (119 ≤ LDL-C ≤ 139 mg/dL) Subgroup (n = 31 in the BRG Group and n = 32 in the PLA)

	M0	M2	M3	M4
LDL-C (mg/dL)				
BRG	130.7 ± 1.7	122.7 ± 3.1** (−6.1%)◊◊◊	123.0 ± 3.9* (−5.8%)◊◊◊	122.5 ± 3.3** (−6.3%)◊◊◊
PLA	130.5 ± 1.6	131.8 ± 3.3 (0.9%)	133.6 ± 3.7 (2.3%)	135.7 ± 3.6 (4.0%)
HDL-C (mg/dL)				
BRG	58.1 ± 2.8	n.d.	57.3 ± 3.1 (−1.3%)	56.1 ± 2.9 (−3.3%)
PLA	57.3 ± 2.7	n.d.	58.0 ± 2.6 (1.1%)	56.7 ± 2.6 (−1.0%)
TC (mg/dL)				
BRG	217.4 ± 3.3	208.4 ± 4.8** (−4.2%)◊◊◊	205.9 ± 5.2** (−5.3%)◊◊◊	203.0 ± 4.6*** (−6.6%)◊◊◊
PLA	213.2 ± 3.7	217.5 ± 4.3 (2.0%)	216.3 ± 4.6 (1.5%)	217.9 ± 4.7 (2.2%)

Notes: Data are mean ± SEM. Percentage variations are reported in brackets. Intragroup statistical significance (vs baseline) is indicated near the average raw data using asterisks (*), while intergroup differences (active vs placebo) are shown near the percentage variation using diamonds symbol (◊). Significance levels are denoted as follows: * $p < 0.05$, ** $p < 0.01$, ***/◊◊◊ $p < 0.001$.

related adverse events. These findings further reinforce the favorable outcomes observed in key hepatic and renal biochemical parameters, collectively supporting the safety and tolerability profile of the intervention and indicating its good acceptability among study participants.

Discussion

Dyslipidemia was identified as one of the three primary risk factors targeted by the Healthy China 2030 initiative, a national strategic framework that underscores the critical role of health in China's socio-economic development.[16] Recent epidemiological studies indicate that dyslipidemia is emerging as a major public health concern among Chinese adults, characterized by an increasing prevalence.[17,18] Despite the growing burden, the rates of awareness, treatment, and effective control remain alarmingly low, underscoring a critical gap in preventive healthcare and lipid management strategies within this population.[16,19–22] This situation is further exacerbated by increasing reports of statin-associated adverse effects and statin intolerance, which contribute to suboptimal statin utilization and poor patient adherence to lipid-lowering therapy.[23,24] Against this backdrop, naturally derived bioactive compounds used in non-pharmacological interventions are gaining widespread consumer acceptance. This preference is largely attributed to their favorable toxicological profiles and perceived environmental sustainability compared to conventional synthetic pharmaceuticals.[25] This study aimed to assess the LDL-C-lowering efficacy and tolerability of bergamot extract in an Asian population, with the goal of enhancing the generalizability of findings from previous clinical trials conducted in Caucasian cohort.[6,9]

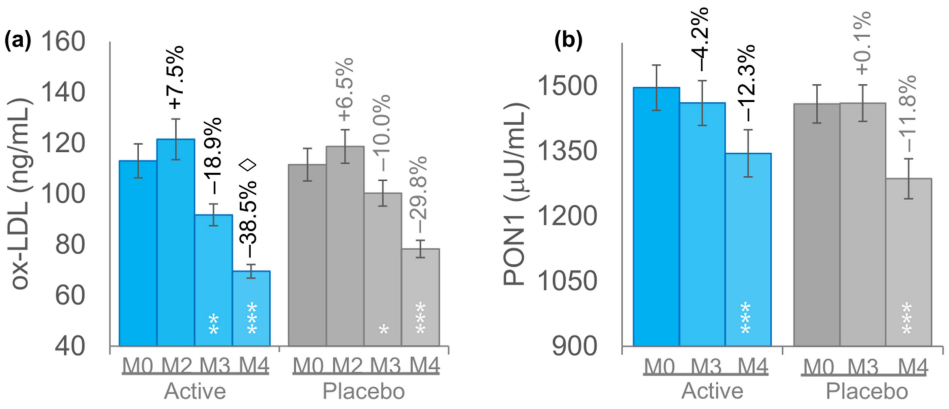

Figure 3 Secondary efficacy endpoints in the whole cohort (100 ≤ LDL-C ≤ 159 mg/dL). (**a**) Oxidized low-density lipoprotein (ox-LDL). (**b**) Paraoxonase activity (PON1). Data are mean ± SEM. Intragroup statistical significance (compared to baseline) is indicated within the bars using asterisks (*), while intergroup differences (active vs placebo) are shown above the bars using diamonds symbol (◊). Significance levels are denoted as follows: */◊ $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

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Table 3 Secondary (Safety) Endpoints. N.d. Not Measured

	Active (n = 51)				Placebo (n = 51)			
	M0	**M2**	**M3**	**M4**	**M0**	**M2**	**M3**	**M4**
Weight (Kg)	65.9 ± 2.0	65.8 ± 2.0	65.7 ± 2.0	65.6 ± 1.9	64.3 ± 1.6	64.4 ± 1.6	64.3 ± 1.6	64.4 ± 1.6
Blood pressure								
-Systolic (mmHg)	125.1 ± 2.4	121.6 ± 1.9*	122.8 ± 2.1	123.0 ± 2.3	123.8 ± 2.2	121.8 ± 2.2	124.4 ± 2.1	122.3 ± 2.0
-Diastolic (mmHg)	82.0 ± 1.8	78.8 ± 1.6*	78.5 ± 1.5$^{**/◊}$	80.8 ± 1.8	80.4 ± 1.7	79.2 ± 1.3	80.2 ± 1.5	79.7 ± 1.5
TG (mg/dl)	108.7 ± 9.4	109.8 ± 9.7	110.9 ± 9.2	108.3 ± 8.0	94.6 ± 10.8	96.2 ± 9.5	112.6 ± 12.2$^{*/◊}$	121.5 ±11.1$^{***/◊◊}$
Glycemia (mg/dL)	95.2 ± 1.6	n.d.	96.0 ± 1.6	94.9 ± 1.5	97.3 ± 2.2	n.d.	96.4 ± 1.9	95.5 ± 1.6
AST (U/L)	21.6 ± 0.7	n.d.	20.7 ± 0.9	20.4 ± 0.9	22.4 ± 0.9	n.d.	22.4 ± 0.9	20.9 ± 0.7
ALT (U/L)	22.8 ± 1.3	n.d.	21.9 ± 1.2	26.8 ± 2.8	22.3 ± 1.5	n.d.	22.9 ± 1.8	21.2 ± 1.5
GGT (U/L)	20.2 ± 2.0	n.d.	20.3 ± 1.8	21.5 ± 2.4	19.8 ± 2.0	n.d.	20.0 ± 1.6	21.0 ± 2.1
HbA1c (%)	5.6 ± 0.1	n.d.	5.5 ± 0.1	5.5 ± 0.1	5.6 ± 0.1	n.d.	5.6 ± 0.1	5.6 ± 0.1
hs-CRP (mg/dL)	0.14 ± 0.02	n.d.	0.17 ± 0.02	0.21 ± 0.07	0.12 ± 0.01	n.d.	0.17 ± 0.03	0.18 ± 0.06
CR (mg/dL)	0.75 ± 0.02	n.d.	0.75 ± 0.02	0.74 ± 0.02	0.73 ± 0.02	n.d.	0.76 ± 0.02	0.75 ± 0.02

Notes: Statistical significance within groups (vs baseline) is denoted by asterisks (*), whereas between-group (active vs placebo) differences are represented by diamond symbols ($^{◊}$). Data are mean ± SEM. Significance thresholds are indicated as follows: $*/^{◊}$ $p < 0.05$, $**/^{◊◊}$ $p < 0.01$, *** $p < 0.001$.

Considering ethnic variability in lipid profiles, dietary patterns, and treatment-associated responses, evaluating the effectiveness of bergamot extract in a distinct population is consistent with its broader clinical applicability and potential integration into tailored dyslipidemia management strategies. Interindividual variability in response to nutraceutical interventions may also arise from genetic and metabolic differences among populations, although these aspects were not directly investigated in the present study. Of specific interest is CYP2D6, a highly polymorphic pathway with well-documented interethnic differences in allele frequencies and metabolizer status (poor, intermediate, normal, and ultrarapid).[3] Because bergamot flavonoids undergo biotransformation, and naringin and its aglycone naringenin are among the main metabolites implicated in cholesterol reduction, variability in CYP2D6-dependent metabolic handling of these compounds could plausibly modulate systemic exposure and downstream lipid responses.[4]

The main findings of this study show that in subjects with borderline-high LDL-C ($100 \leq$ LDL-C ≤ 159 mg/dL) and TC (>200 mg/dL), risk factor of CVD risk, bergamot extract supplementation reduces mean LDL-C and TC values in a statistically significant manner from the first two months of treatment, resulting in reductions of 7.0% and 7.3%, respectively after four months of treatment. Overall, these data align with those obtained in the Caucasian population, where, starting from higher mean levels of LDL-C (>170 mg/dL) and TC (>240 mg/dL), decreases of 11.5 and 8.8% after 4 months of treatment,[9] and 13.2 and 18.2% after 6 months of treatment,[6] respectively, were observed.

As far as HDL-C is concerned, higher levels of HDL-C are linked to a significantly lower risk of developing CVD as HDL-C effectively removes excess cholesterol from tissues and transports it to the liver, where it is eliminated through bile. Furthermore, HDL-C possesses powerful antioxidant, anti-inflammatory, and anti-apoptotic properties, enhancing its protective effects on cardiovascular health.[26] Our results indicate that, starting from a population with a mean HDL-C value considered protective for both sexes (~ 60 mg/dL), bergamot extract does not statistically significantly change the HDL-C concentration. In the Caucasian population, starting from a normal-to-low mean HDL-C value of 45–49 mg/dL, increases of 5.5%–8.3% were observed at 4 and 6 months of treatment, respectively. The difference in the effects of bergamot extract between Asian and Caucasian populations is likely caused by the distinct baseline values obtained from the two recruited populations. Future studies should specifically enroll Asian participants with low baseline HDL-C and should consider stratification according to baseline HDL-C.

OxLDL is considered a key atherogenic biomarker linking oxidative stress to vascular inflammation and plaque formation. Unlike native LDL, oxLDL promotes the formation of cholesterol-loaded foam cells, hallmarks of atherosclerotic lesions, and contributes to endothelial dysfunction, another critical step in atherogenesis. Ox-LDL also triggers pro-inflammatory signaling and immune-cell activation with pro-inflammatory cytokine release, amplifying plaque inflammation. Moreover, vascular smooth muscle cells can internalize oxLDL and adopt foam–cell–like phenotypes, influencing plaque composition and stability.[27–29] Unlike LDL-C, which has reference ranges that indicate whether the value is normal, borderline or high, for ox-

LDL there are no reference ranges because the values change depending on the laboratory and the analytical method used to determine this biomarker. However, generally, ox-LDL values >100ng/mL are indicative of increased oxidative stress and increased cardiovascular risk.[30] The results of our study demonstrate that at the end of the treatment, both the BRG and PLA groups experienced a significant reduction in the mean value of ox-LDL. Remarkably, the group treated with bergamot extract achieved a greater reduction, reaching a decrease of 38.5%. The Caucasian population study clearly reported that ox-LDL values fell within the normal range, with no significant changes following the intake of bergamot extract and with no significant differences between Asian and Caucasian ethnicity. However, ox-LDL should be considered an exploratory endpoint in this study since reference ranges and clinical interpretation of ox-LDL are not universally standardized and can vary depending on the analytical method.

Finally, paraoxonase 1 (PON1), an HDL-associated enzyme contributing to the anti-atherogenic properties of HDL-C by limiting the oxidative modification of LDL, was evaluated. By hydrolysing lipid peroxides and oxidised phospholipids, PON1 may reduce the accumulation of ox-LDL, which is implicated in endothelial dysfunction, vascular inflammation, and foam-cell formation during atherogenesis.[31,32] Overall, no treatment-dependent changes in PON1 activity were observed over the study period in either the Caucasian or Asiatic population. In the Asiatic cohort, PON1 activity was significantly reduced from baseline at Month 4 in both the active and placebo groups; however, the magnitude of the decrease was virtually superimposable between groups (−12.3% and −11.8%, respectively). Therefore, despite the statistically significant within-group reductions, this parallel pattern does not support a specific effect of BERGAVIT™ supplementation on PON1 activity. This finding should be interpreted considering the substantial biological variability of circulating PON1 and its sensitivity to genetic, metabolic, lifestyle, and dietary determinants.[33] In healthy individuals, dietary composition has been shown to modulate PON1 activity, including acute postprandial reductions after consumption of meals rich in used cooking fat and decreases following replacement of dietary saturated fats with trans fats.[34,35] In addition, controlled dietary modifications in healthy women were associated with changes in PON1 activity that correlated with changes in HDL-C and were influenced by PON1 genotype (Rantala et al, 2002). Dietary intake was intentionally not standardized during the present trial in order to assess the lipid-lowering efficacy of BERGAVIT™ in the absence of a concomitant prescribed dietary intervention. Unmeasured temporal changes in dietary habits or other lifestyle-related factors may have contributed to the common longitudinal reduction observed in both study arms; however, this possibility cannot be established from the available data. Importantly, the almost identical magnitude of change in the active and placebo groups does not indicate a treatment-specific PON1-lowering effect of BERGAVIT™.

The consistent LDL-C lowering observed in the present study supports the clinical activity of bergamot extract in this Asian cohort. However, the mechanisms underlying these effects cannot be established from the current study and therefore remain speculative. Importantly, available human bioavailability studies indicate that bergamot flavanones are absorbed and extensively metabolized, with circulating metabolites predominantly represented by Phase II conjugates, including glucuronide and sulfate derivatives.[36–38] Future studies integrating pharmacogenetic characterization together with targeted metabolomic analyses may help clarify the biological determinants of individual responses to bergamot supplementation. Notably, comparable results were observed in both the lower (119 ≤ LDL-C ≤ 139 mg/dL) and higher (100 ≤ LDL-C ≤ 159 mg/dL) LDL-C subgroups. This suggests that the intervention may produce consistent lipid-lowering effects across a spectrum of baseline LDL-C levels, underscoring its potential use in individuals with varying degrees of cardiovascular risk.

Regarding the other outcomes, bergamot extract was well tolerated in the Asian population recruited in this study, with no adverse effects at both the hepatic and renal levels, in agreement with the high safety profile previously demonstrated in the Caucasian population.

This study represents the first randomized, double-blind, placebo-controlled clinical trial to assess the lipid-lowering efficacy and tolerability of a polyphenol-standardized *C. bergamia* extract in an Asian population. A major strength lies in its rigorous study design, including stratified randomization, allocation concealment, and the use of validated clinical and biochemical endpoints. The intervention duration of 4 months, with intermediate time-point assessments, allowed evaluation of both short- and medium-term lipid responses; however, it does not permit conclusions regarding the long-term sustainability of the lipid-lowering effect or its potential impact on cardiovascular outcomes. Longer follow-up

studies are therefore warranted to determine whether the observed changes are maintained, enhanced, or attenuated over time. The high compliance rate and minimal dropout enhance the reliability of the findings.

Despite these strengths, certain limitations should be acknowledged. The lack of dietary control among participants is the major limitation of this study. In particular, the intake of polyphenol-rich foods, saturated fats, or dietary fiber could independently influence lipid parameters. However, randomization and the placebo-controlled design likely mitigated between-group differences in dietary intake. However, the variability that could be introduced by an unmonitored intake of nutrients or compounds potentially influencing the measured parameters is taken under control in the placebo group. An additional limitation is that we did not assess CYP2D6 genotype/phenotype or quantify naringin/naringenin-derived metabolites. This precludes a direct evaluation of whether inter-individual variability in polyphenol metabolism contributed to differences in lipid responses. Future studies incorporating dietary standardization or monitoring, pharmacogenetic stratification, and metabolomic readouts will be valuable to refine the mechanistic understanding of bergamot-derived polyphenols in dyslipidemia management. Furthermore, the relatively small sample size may have limited the statistical power, particularly in subgroup analyses. Therefore, these findings should be interpreted as trends, and further studies are warranted to confirm the observed effects and estimate the product's effect size.

Conclusions

In conclusion, oral supplementation with an extract of *C. bergamia* providing a standardized daily dose of 150 mg of flavonoids (including neohesperidin, naringin, and neoeriocitrin) proved to be significantly effective in reducing total cholesterol and low-density lipoprotein cholesterol levels both in the short term and over prolonged use, with clinically meaningful effects observed as early as the second month of intake. Interestingly, similar results were observed across the entire LDL-C range studied (100–159 mg/dL), including within the subgroup of participants with intermediate baseline LDL-C levels (119–139 mg/dL). These findings suggest that the intervention may exert consistent lipid-modulating effects regardless of baseline LDL-C concentration within this range, highlighting its potential applicability across different cardiovascular risk profiles.

These findings on Asians are consistent with the results obtained in two previous studies conducted in Caucasian populations, thereby reinforcing the reproducibility and robustness of the observed effects through a standardized extract. Consistency across studies highlights the reliability of the intervention's biochemical and clinical outcomes, particularly regarding bergamot extract efficacy and tolerability. The multiple antioxidative mechanisms exerted by bergamot extract may also support the progressive and sustained reduction in lipid parameters over time. Taken together, the present data contributes to the growing body of evidence supporting the intervention as a well-tolerated solution in the Asian Chinese subpopulation.

Abbreviations

The following abbreviations are used in this manuscript: ADME, Absorption, Distribution, Metabolism, and Excretion; HDL-C, High-Density Lipoprotein Cholesterol; sdLDL, small dense Low-Density Lipoprotein; TC, Total Cholesterol; LDL-C, Low-Density Lipoprotein Cholesterol; TG, Triglycerides; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; GGT, Gamma-Glutamyl Transferase; HbA1c, Glycated Hemoglobin; hs-CRP, high sensitivity C-Reactive Protein; CR, Creatinine.

Data Sharing Statement

The data presented in this study can be obtained upon request from the corresponding author. As they are the property of the study sponsor, Bionap Srl (95032 Piano Tavola Belpasso, CT, Italy), the data are not publicly available.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the of the Chung Shan Medical University Hospital on 30 September 2022.

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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

V.Z. is a Bionap S.r.l. employee. This does not alter the author's adherence to all the journal policies on sharing data and materials. The other authors declare no conflicts of interest in this work.

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