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Research Article

JOURNAL OF FOOD SCIENCE AND NUTRITION RESEARCH

ISSN: 2642-1100

A Randomized, Placebo-Controlled Trial to assess the Efficacy and Safety of a Novel Nutraceutical Combination of Monacolin K and Bergamot extract in subjects with Mild to Moderate Hypercholesterolemia

Nicholas Angelopoulos[1,2*], Ioannis Androulakis[1,3], Anastasios Boniakos[1], Rodis D Paparodis[4,5], Grigoris Tsekmezoglou[6] and Sarantis Livadas[1]

Abstract

Background: Lipid-lowering therapy is the primary treatment for hypercholesterolemia, with statins as the first-line therapy. Nutraceuticals like bergamot, RYR, and berberine have been shown to be effective in reducing Low-density Lipoprotein (LDL-C) and total cholesterol (TC) levels. This study assessed the safety and efficacy of a novel nutraceutical supplement for mild to moderate hypercholesterolemia and low cardiovascular risk.

Materials and methods: A prospective, multicentric, open-label, randomized controlled trial was conducted at four outpatient endocrine clinical centers in Greece. Patients were over 40 years old, had mild hypercholesterolemia, and did not require statin treatment according to guidelines. 66 subjects with mild hypercholesterolemia and a 10-year atherosclerotic cardiovascular disease risk (ASCVD Risk) <7.5% were included in the study. Mediterranean diet and the nutraceutical compound were prescribed to 34 patients at random for eight weeks, while 30 patients comprised the diet-only control group.

Results: No significant changes were observed in Body mass index, TC, and High-density Lipoprotein concentrations between the two groups. A significant median reduction of 13.25% in LDL-C levels was achieved in the treated group and no adverse effects were reported.

Conclusion: These results suggest that the investigated nutraceutical compound could serve as a potential alternative treatment, particularly for certain patient populations, such as those who are intolerant to statins or who refuse lipid-lowering drug therapy.

Keywords: Monacolin K; Bergamot; Milk thistle; Coenzyme Q10; Hypercholesterolemia

Introduction

The primary treatment for hypercholesterolemia [1] is lipid-lowering therapy (LLT) with statins as first-line therapy. Statin-associated muscle symptoms (SAMS), typically defined as musculoskeletal complaints that are reported in 9.1% of patients on statins [2], are, on the other hand, the leading cause of therapy discontinuation. Several studies and meta-analyses have demonstrated the effectiveness of various nutraceuticals as lipid-lowering agents [3-7]. As part of a lifestyle intervention to reduce total cholesterol (TC) and Low-density cholesterol (LDL-C) levels, the European Society of

Affiliation:

[1]Endocrine Unit, Athens Medical Centre, 65403 Athens, Greece

[2]Private Practice, Venizelou Str. 26, 65302 Kavala, Greece

[3]Private Practice, Tzanaki Emmanouil 17, 73134 Chania, Greece

[4]Center for Diabetes and Endocrine Research, University of Toledo College of Medicine and Life Sciences, Toledo, OH 43614, USA

[5]Private Practice, Gerokostopoulou 24, 26221 Patra, Greece

[6]Biochemical Laboratory Centre, Mitr. Chrysostomou 6, 65403 Kavala, Greece

***Corresponding author:**
Nicholas Angelopoulos, Endocrine Unit, Athens Medical Centre, 65403 Athens, Greece

Citation: Nicholas Angelopoulos, Ioannis Androulakis, Anastasios Boniakos, Rodis D Paparodis, Grigoris Tsekmezoglou and Sarantis Livadas. A Randomized, Placebo-Controlled Trial to assess the Efficacy and Safety of a Novel Nutraceutical Combination of Monacolin K and Bergamot extract in subjects with Mild to Moderate Hypercholesterolemia. Journal of Food Science and Nutrition Research. 6 (2023): 71-77.

Received: July 17, 2023
Accepted: July 25, 2023
Published: August 02, 2023

Angelopoulos N, et al., J Food Sci Nutr Res 2023
DOI:10.26502/jfsnr.2642-110000132

Cardiology (ESC) recommends using various nutraceuticals, such as red yeast rice and phytosterols/stanols [8]. Recent meta-analyses revealed that bergamot, red yeast rice (RYR), and berberine [9] are the most effective methods for reducing LDL-C and TC levels. The International Expert Lipid Panel (ILEP) has published nine comprehensive position papers on nutraceuticals for the treatment of dyslipidemia, including in statin-intolerant patients [10]. Since the statin-like mechanism of action of RYR may cause myalgia at concentrations up to 10mg/day, nutraceuticals containing less than 3 mg of monacolin K are recommended [11]. Consequently, the present study aimed to assess the safety and efficacy of a novel nutraceutical supplement administered orally for two months to subjects with mild to moderate hypercholesterolemia and low cardiovascular risk.

Materials and Methods

Study design

The current study is a prospective, multicentric, open-label, randomized controlled trial that took place at four outpatient endocrine clinical centers in Greece. Inclusion criteria for patient participation were as follows: being over 40 years of age, having mild hypercholesterolemia (with fasting LDL-C concentration ranging from 140 to 190 mg/dL), and not requiring statin treatment (10-year atherosclerotic cardiovascular disease risk [ASCVD Risk] below 7.5%). The 10-year risk assessment was performed using the updated ASCVD Risk Estimator Plus, available at: (https://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/ (accessed on 10 May 2023). Patients were excluded from the study if they had diabetes mellitus, a known history of atherosclerotic vascular disease, moderate/severe renal insufficiency (as determined by a calculated glomerular filtration rate [MDRD GFR] below 60 mL/min using the Modification of Diet in Renal Disease equation), abnormal liver function test results, excessive alcohol consumption, were pregnant or lactating, or were using oral contraceptives. During the screening visit, the eligibility of patients was evaluated by the study physicians, and there was extensive discussion about the significance of lifestyle modifications, particularly regarding physical activity and adopting a healthy diet, in the context of hypercholesterolemia. All patients were encouraged to adhere to a standardized Mediterranean diet for a duration of 8 weeks prior to their enrollment in the study. This diet primarily consisted of high consumption of vegetables, fruits, nuts, olive oil, low-fat dairy products, and fish while incorporating a moderate intake of lean meats and alcohol. Following the run-in period, during which patients adhered to the prescribed diet, their lipid profiles were assessed. Only those patients who still met the inclusion criteria after the run-in period were included in our study population (referred to as visit 1 - study initiation). A neurochemical compound (Terra Cholest ® tablets, Genecom Terra, one tablet every evening after dinner; ingredients are shown in Table 1) was prescribed to 34 patients at random (Group A). The control group consisted of patients who continued their diet-only intervention without taking any supplements (Group B). All patients in both groups were encouraged to follow the prescribed diet during the study period. After 8 weeks (± 5 days), all patients were reassessed (visit 2) and the study was ended. On the last visit, participants were asked about adherence to the prescribed diet and potential adverse effects. Drug compliance with supplement consumption was also calculated as follows: (dosage-not used) / applied dose × 100%.

Table 1: Chemical composition of the nutraceutical.

Red yeast rice (3% Monacolin K)	93.33mg (2.8 mg)
Bergamot extract (25% Flavonoids)	250mg (62.5mg)
Policosanols (60% Octacosanol)	24 mg (14.4 mg)
Milk thistle extract (80% Silymarin)	16 mg (12.8mg)
CoQ10	10mg

Footnote: Ingredients per cap (daily dose).

Measurements

During the study period blood samples were taken twice: at the beginning of the study (visit 1) and at the end of the study (follow-up visit 2), to assess the serum levels of TC, LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), aspartate aminotransferase (SGOT), alanine aminotransferase (SGPT) and creatine phosphokinase (CPK). In both visits, Body Mass Index (BMI) was calculated as the ratio of weight (in kilograms) to squared height (in meters). Serum lipids (TC, TG, LDL-C, and HDL-C) were measured with an enzymatic colorimetric assay (Dimension Vista 500 System, Siemens, Munich, Germany). Liver enzymes consisting of alanine aminotransferase (SGPT), aspartate aminotransferase (SGOT), gamma-glutamyl transferase (γ-gt), and creatine kinase (CPK) were measured using an enzymatic method (Dimension Vista® 500 System Siemens, Munich, Germany). This study was conducted, according to a prospective, controlled, randomized, and repeated measures design from May 2023 to July 2023 in accordance with the principles laid down in the Declaration of Helsinki and was approved by the Institutional Review Board of the Athens Medical Center General Hospital. All participants have signed informed consent before enrolment. Trial registration: Australian New Zealand Clinical Trials Registry (ANZCTR): ACTRN12623000534684.

Statistical analysis

The distribution of continuous data was tested with the Kolmogorov–Smirnov and the Shapiro–Wilk test. Normally distributed variables are expressed as mean ± standard deviation (SD), whereas non-normally distributed variables are expressed as the median and interquartile

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range (IQR). Categorical variables are reported as numbers and percentages. The Student's t-test and the corresponding nonparametric Wilcoxon test (as appropriate) were used to compare the values of quantitative variables between placebo and treatment groups. Comparisons between categorical data were performed using the $\chi 2$ test. For all tests, a p-value < 0.05 was considered statistically significant. The statistical analysis was performed by the MedCalc® Software (version 20.218, MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2023).

Results

85 patients with mild hypercholesterolemia were initially evaluated for eligibility and enrolled in the run-in phase of the study. 80 were biochemically assessed at visit 1 and 66 of them fulfilled the inclusion criteria and completed the baseline visit testing. 34 were assigned to receive the supplement and 32 remain without treatment. Two subjects from the lateral group were lost to follow-up (figure 1). Finally, 34 subjects in Group A (26 females and 8 males) and 30 in Group B (23 females and 7 males) completed the study protocol. The mean age of the treated group was 56.62±7.71 years (range 41–71 years) and for the control group 58.1± 11.79 years (range 40-80). Demographic and biochemical characteristics of the study population are shown in table 2. No change was observed in BMI during treatment (t1 vs. t2, 27.11±3.15 vs. 26.93±3.29 Kg/m2, p = 0.121). A significant decline was observed in both TC (t1 vs. t2, 247.09±20.18 mg/dL vs. 221.59± 23.34mg/dL, p < 0.001, figure 2) and LDL-C concentrations (t1 vs. t2, 162.15±20.05 mg/dL vs. 139.24±20.9 mg/dL, p<0.001). The LDL-C median decline was -13.25 % (IQR, 9.71), significantly greater compared to the control group (mean± SD, -0.64±9.68 %, p<0.001, figure 3). No significant difference was observed with treatment in HDL-C and TG levels. A small but statistically significant increase was detected in both SGOT and SGPT levels with supplements (t1 vs. t2, 17.15±3.64 vs. 18.97±5.08 U/L, and 15.85±4.42 vs. 19.24±7.31 U/L, respectively). No adverse effects during the use of the supplements were reported in our cohort.

Table 2: Biochemical profile before and after treatment.

Variable	Treated N=34			Control N=30			P
	Baseline	Study end	*p*	Baseline	Study end	*p*	
Age (years)	56.62±7.71			58.1± 11.79			0.564
Gender female, n(%)	26(76.5)			23(76,6)			0.985¶
BMI (kg/m²)	27.11±3.15	26.93±3.29	0.121	26.99±3.15	26.85±3.34	0.271	0.927
TC(mg/dL)	247.09±20.18	221.59± 23.34	<0.001	248 (29.25)	239.5(58.5)	*0.973	**0.009
LDL-C(mg/dL)	162.15±20.05	139.24±20.9	<0.001	163.55±15.11	163.31±14.94	0.951	<0.001
LDL-C dif (mg.dL)	-21(12.35)			-0.63±23.26			**<0.001
LDL % change	-13.25(9.71)			-0.64±9.68			**<0.001
HDL(mg/dL)	60 (11.5)	54.5(17.75)	*0.511	59.5(19.25)	56(21.5)	*0.215	0.587
TG(mg/dL)	119.5±50.49	114.94± 44.42	0.344	117.97±55.08	116.97±46.37	0.881	0.786
SGOT(U/L)	17.15±3.64	18.97±5.08	0.048	18.61±11.14	19.48±8.37	0.567	0.654
SGPT(U/L)	15.85±4.42	19.24±7.31	0.007	16.32±13.22	15.97±13.43	0.506	0.876
γ-GT(U/L)	16(7)	15(8)	*0.644	18(3)	18(6)	* 0.017	0.149
CPK(U/L)	95.13±31.08	100.3±32.21	0.169	93(14)	90(30)	* 0.587	0.453

Footnote: TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol; TR: Triglycerides; Sgpt: alanine transaminase; Sgot: aspartate transaminase; γ-gt : gamma-glutamyl transferase; CPK: Creatine Phosphokinase; *p*:Paired t-test; *p**: Non-parametric Wilcoxon test for paired values; P: t-test for independent values; P**:Mann-Whitney U-Test for independent values. P¶: χ^2 test.

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DOI:10.26502/jfsnr.2642-110000132

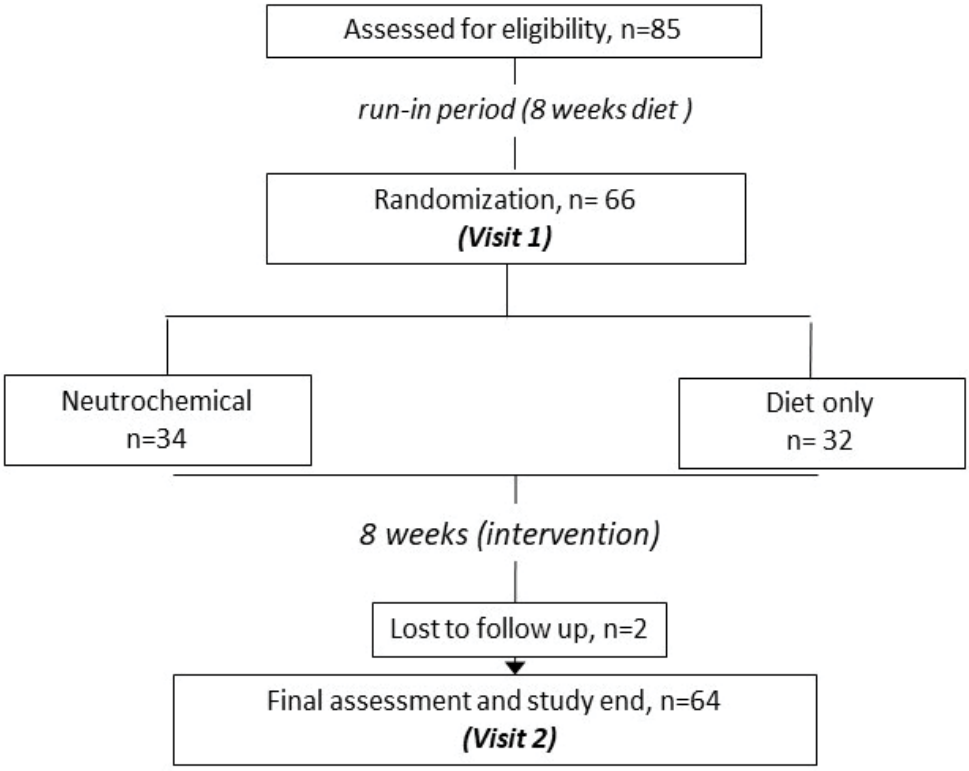

Figure 1: Study chart flow

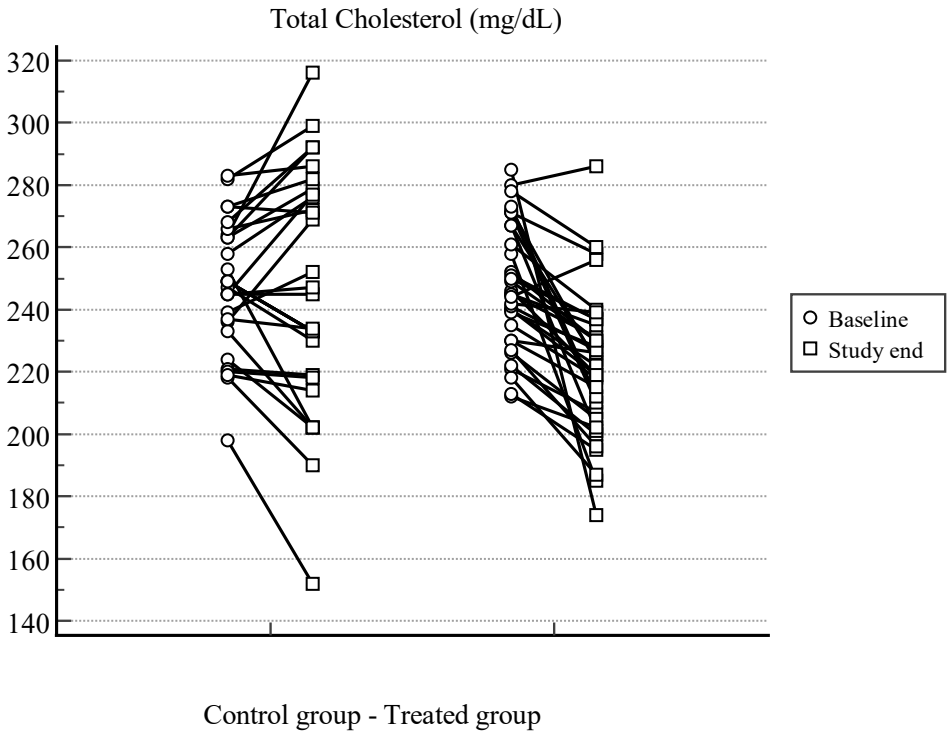

Figure 2: Changes in Total cholesterol levels (mg/dL) in the treated group.

Footnote: Scatter plot of LDL-C values. Baseline (circles) and after 8 weeks of intervention (squares). $p < 0.01$, paired t-test.

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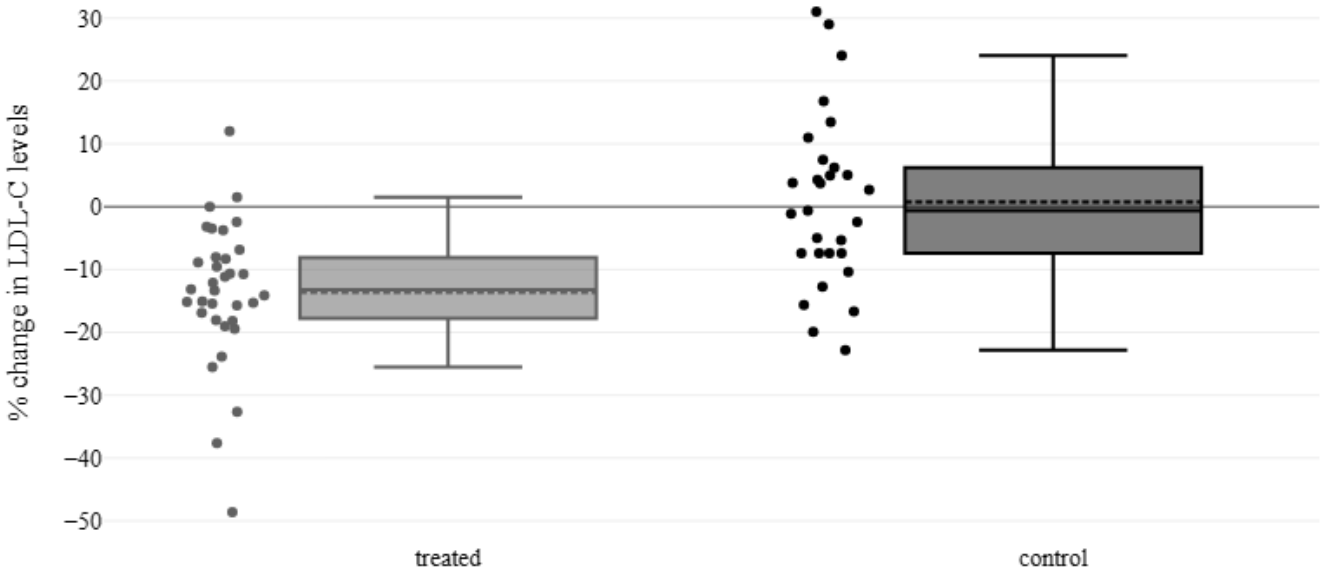

Figure 3: Percentage of differences in LDL-C levels after treatment.

Discussion

With approximately 50% of individuals in the general population having suboptimal LDL-C levels [12] and lifestyle improvements having a limited impact of approximately 5% to 10% on LDL-C levels [13], there has been significant attention on identifying specific dietary components or natural substances that can augment lipid profiles in conjunction with appropriate dietary and physical activity practices. Research has shown that adhering to a plant-based diet and making significant lifestyle adjustments can lead to a notable decrease in LDL-C levels, with reductions of up to 20% [14]. However, maintaining these rigorous lifestyle modifications over an extended period can be challenging, especially when considering primary prevention. Furthermore, consistently implementing these changes in our everyday clinical practice can present difficulties [15]. The primary mechanism by which RYR lowers cholesterol levels is through the reversible inhibition of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, a crucial enzyme involved in the synthesis of cholesterol. This inhibition is achieved by monacolins, which have a similar but stronger effect compared to statins. Although the metabolism and mechanism of action of monacolin K are similar to lovastatin, the reasons for its improved tolerability in statin-intolerant individuals, particularly when daily doses of monacolin K ranging from 3mg to 10mg are administered, have not been fully explained [16]. The effects of policosanols are associated with the inhibition of platelet aggregation, the blocking of cholesterol's impact on smooth muscle proliferation, the inhibition of foam cell formation, and the prevention of LDL peroxidation. However, there is conflicting data regarding the antioxidant effects of policosanol [17]. The nutraceutical bergamot Citrus Bergamia has been extensively documented to possess not only lipid-lowering properties but also significant anti-oxidative and anti-inflammatory effects. Bergamot extract is composed of polyphenols that possess diverse mechanisms of action. These polyphenols, such as neoericitrin, neohesperidin, naringin, rutin, neodesmin, rhoifolin, poncirin, and melitidin, exhibit inhibitory effects on the oxidation of LDL-C, activate adenosine-monophosphate-kinase, and demonstrate potential scavenging mechanisms. Additionally, they display a significant statin-like inhibition of HMG-CoA reductase, which is of particular importance [18].

Silybum marianum, commonly known as milk thistle (MT), has been extensively studied as a botanical remedy for liver disease. The active compound of MT refers to a lipophilic extract derived from the seeds of the plant. This extract consists of three isomeric flavonolignans, namely silybin, silydianin, and silychristin, which are collectively referred to as silymarin [19]. Silybin, which constitutes approximately 50% to 70% of silymarin, exhibits the highest level of biological activity among its components. Silymarin is distributed throughout the entirety of the plant, with a higher concentration observed in the fruit and seeds [20]. Silymarin exhibits antioxidant properties by diminishing the generation of free radicals and lipid peroxidation. Additionally, it demonstrates antifibrotic activity and potentially functions as a toxin blockade agent by impeding the binding of toxins to receptors on the cell membrane of hepatocytes [19,20]. A recent study has shown that there is no significant variation in lipid parameters among patients who were administered a supplement containing bergamot but lacking monacolin [21]. This suggests that the primary mechanism responsible for

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DOI:10.26502/jfsnr.2642-110000132

the lipid-lowering effects of combined neurochemicals can be attributed to PYR [22]. Previous studies have provided evidence that the utilization of nutraceuticals containing bergamot has been linked to a significant decrease in low-density lipoprotein cholesterol (LDL-C) levels, ranging from 7.6% to 39%. These reductions were observed with daily doses ranging from 500 to 1500 mg [21]. The absence of the desired additive or synergistic effects could potentially be attributed to the selected concentration and the bioavailability of each constituent. In our cohort, the dosage of bergamot was observed to be half of that utilized in the aforementioned study, potentially leading to a diminished lipid-lowering effect. Another important factor to consider is the duration of therapy. Previous studies have shown that monacolin has demonstrated significant effects within a timeframe of 8-10 weeks [6,7]. However, there is currently insufficient data available regarding the effectiveness of combining policosanols and Bergamot.

In summary, our investigation demonstrated favorable outcomes regarding the reduction of LDL-C levels in individuals diagnosed with mild hypercholesterolemia (with a median decrease of 13.5%). Notably, no adverse effects were reported. These findings suggest that the examined nutraceutical compound could serve as a potential alternative treatment, particularly for specific patient populations such as those who are intolerant to statins or those who decline lipid-lowering drug therapy.

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