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Effectiveness in the short-term of a novel nutraceutical for the management of hypercholesterolemia: an observational multicenter primary care experience

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ABSTRACT:

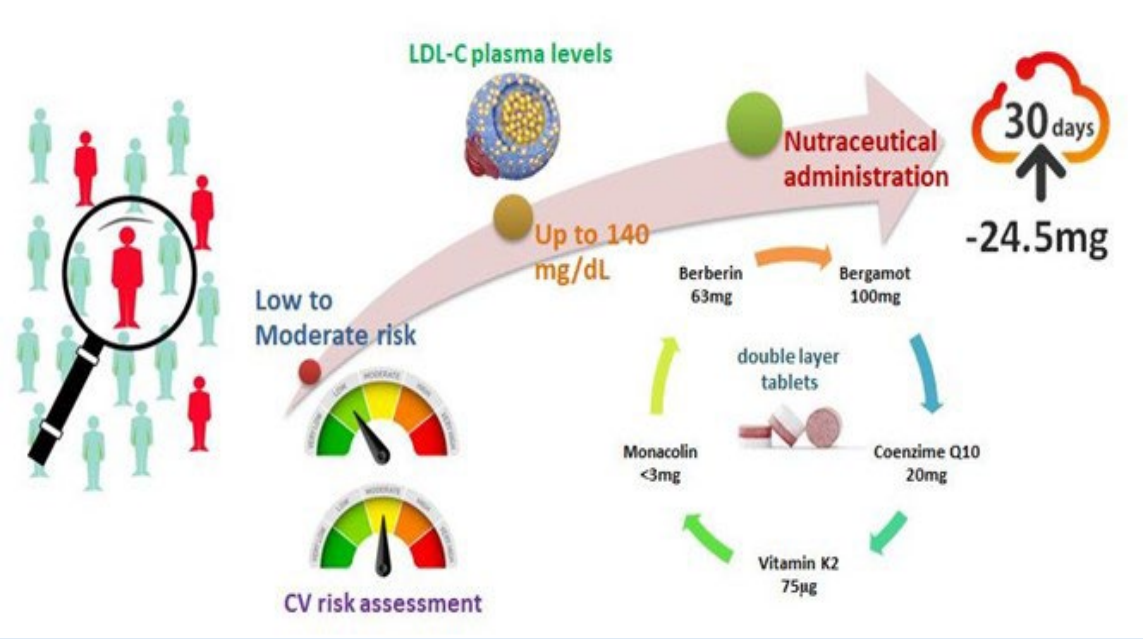
Purpose: Increasing evidence reinforces the benefits of reduction of low-density lipoprotein (LDL-C) levels on cardiovascular outcomes. Different targets are suggested based on cardiovascular risk (CVR). According to the current European guidelines, a goal of LDL-C≤ 115mg/dL is desirable for patients with low-moderate CVR. However, a high percentage of these patients are far from this target. Nutraceuticals are “food supplements” that may help to achieve this goal in this population. In this retrospective analysis, we evaluate the effects of dietary supplementation with a novel monacolin/berberine/bergamot nutraceutical formulation on plasma lipid levels of subjects with low-moderate hypercholesterolemia who are not treated with conventional drug or other dietary supplements.

Patients and Methods: 526 adult patients with hypercholesterolemia were retrospectively selected from the database of participant family practitioners according to prespecified criteria. All selected patients had a baseline and 30-day value of total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol, triglycerides, C-reactive protein, and transaminases and have started a dietary supplementation with this novel nutraceutical. Similarly, 104 subjects with comparable clinical features but not treated with any supplements were also selected.

Results: At 30-day, the administration of nutraceuticals was associated with a significant reduction of LDL-C (124 ± 14 vs. 100 ± 13 mg/dL, Δ 24.5mg, p-value <0.0001) and TC levels (210 ± 56 vs. 187 ± 60, p-value < 0.0001), in the absence of a significant change of transaminase levels. No side effects were reported in the database during the observation period.

Conclusion: This novel nutraceutical is an effective dietary supplement to achieve a significant and early LDL-C reduction in patients with hypercholesterolemia at low-moderate CVR.

Keywords: Cardiovascular Risk; Hypercholesterolemia; Nutraceuticals



INTRODUCTION

Several epidemiological studies have documented the strong correlation between high cholesterol blood levels and cardiovascular death [1-3]. This parameter, along with hypertension, diabetes, obesity, smoking, and a family history of coronary artery disease, is considered a major risk factor for atherosclerotic diseases[2-5].

In addition, the reduction of cholesterol levels was associated with a significant reduction in the occurrence of major cardiovascular events (MACE), suggesting the need for an early introduction of lipid-lowering drugs to maintain good cardiovascular health[2-4,6].

While the introduction of statins, alone or in association with ezetimibe and/or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, is mandatory in patients at high and very high cardiovascular risk for obtaining a significant reduction of cholesterol levels and improving outcomes [2,6], the role of functional foods (known as “nutraceuticals”) is assuming a central role in patients with low to moderate cardiovascular risk given their proven clinical benefit and good tolerability[7]. The latest ESC (European Society of Cardiology) Guidelines for the Management of Dyslipidaemias [2] indicate dietary supplements and nutraceuticals as useful tools, in association with diet and a healthy lifestyle, for the management of cardiovascular risk factors like low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG.) Nutraceuticals are particularly beneficial in patients with low to moderate cardiovascular risk, in whom a modest reduction in LDL-C values may be sufficient to reach the recommended target[8].

In these patients, the association of nutraceuticals to lifestyle modifications may allow a better, safe, and more stable achievement of the suggested target[9].

Nutraceuticals might also be considered in subjects who develop side effects with conventional drugs[10].

In these circumstances, treatment with nutraceuticals is helpful given the tolerability of preparations and psychological effects related to the awareness of taking a "natural" substance instead of a conventional drug, thus avoiding the nocebo effect. Furthermore, nutraceuticals should be considered in patients with an absolute contraindication to conventional drugs[11,12].

Among the different nutraceuticals used in clinical practice, monacolin K[13,14], berberine[15-18], bergamot[19-21], vitamin K2[22,23], and coenzyme Q10[24] showed a synergic effect in reducing blood cholesterol levels but avoiding damage from oxidative stress. Most monacolin-based nutraceuticals contain 5 to 10 mg of monacolin K. In 2018, the European Safety Food Authority (EFSA) evaluated the safety of monacolin-based nutraceuticals[25]. The minimum dose of monacolin K that is effective in reducing plasma cholesterol levels is 3 mg[26]. Scientific studies and marketing analysis indicate that nutraceuticals containing 3 mg of monacolin K are safe [27]. The EFSA recommends the use of nutraceuticals with less than 3 mg of monacolin K[25]. The dietary supplement evaluated in this observation is a new nutraceutical containing bergamot, vitamin K2, coenzyme Q10, and, as for EFSA recommendation, less than 3 mg of monacolin K.

However, the effectiveness of such combination in reducing blood cholesterol levels in a short period was not investigated yet. Thus, the present study aimed to evaluate the safety and efficacy of 30-day dietary supplementation of this novel nutraceutical dietary supplement on plasma lipid levels in subjects with mild to moderate hypercholesterolemia who are not on treatment with conventional drugs and/or with other dietary supplements.

Study design and patients selection: The database of 27 family practitioners was evaluated between October 2021 and December 2021. Each family practitioner may account for up to 1500 patients for the management of whose dedicated software is used, helping to record any data (risk factors, diseases, drugs).

The following filter criteria have been applied:

- Age between 35 and 65 years old;
- Low or moderate cardiovascular risk profile according to the current European Society of Cardiology (ESC) guidelines[2];
- LDL-C levels between 100 and 140 mg/dL;
- No lipid-lowering drugs
- Lipid-lowering nutraceutical supplementation
- Following basic recommendations for a healthy lifestyle (as reported in table 1)
- Availability of a blood test at time zero and 30-day

Table 1. Basic Recommendations for Healthy Lifestyle (from WHO)

1. Eat a healthy diet
Eat a combination of different foods, including fruit, vegetables, legumes, nuts and whole grains. Eat at least five portions (400g) of fruit and vegetables per day.

2. Consume less salt and sugar

Reduce your salt intake to 3g per day, equivalent to about one teaspoon. It's easier to do this by limiting the amount of salt, soy sauce, fish sauce and other high-sodium condiments when preparing meals; removing salt, seasonings and condiments from your meal table; avoiding salty snacks; and choosing low-sodium products.

The intake of free sugars should be reduced to less than 10% of total energy intake. This is equivalent to 50g or about 12 teaspoons for an adult. You can reduce your sugar intake by limiting the consumption of sugary snacks, candies and sugar-sweetened beverages.

3. Reduce intake of harmful fats

Fats consumed should be less than 30% of your total energy intake. WHO recommends reducing saturated fats to less than 10% of total energy intake; reducing trans-fats to less than 1% of total energy intake; and replacing both saturated fats and trans-fats to unsaturated fats.

The preferable unsaturated fats are found in fish, avocado and nuts, and in sunflower, soybean, canola and olive oils; saturated fats are found in fatty meat, butter, palm and coconut oil, cream, cheese, ghee and lard; and trans-fats are found in baked and fried foods, and pre-packaged snacks and foods, such as frozen pizza, cookies, biscuits, and cooking oils and spreads.

4. Avoid use of alcohol

5. Don't smoke if possible

If you are currently a smoker, it's not too late to quit. If you are not a smoker, that's great!

6. Be active

Do at least 30 minutes of walking three times a week

Patients with severe obesity, defined as a body mass index (BMI) >35 Kg/m2) or bowel disorders were excluded.

Once the above criteria were applied to the database, a final cohort of 526 patients was used for the final analysis, as shown in Figure 1.

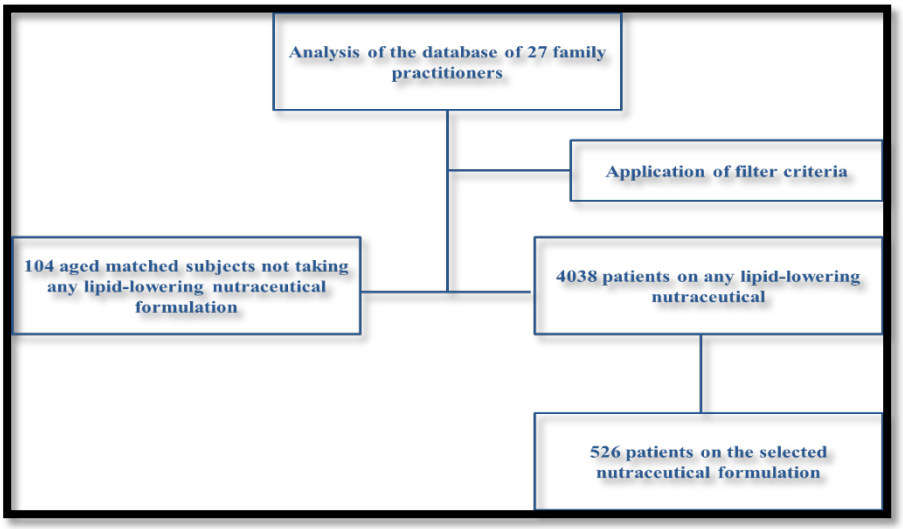


Figure 1. Selection the study population

Similarly, a population of 104 aged-matched subjects not taking any lipid-lowering nutraceutical formulation were also selected from the above database. All selected patients already had a baseline evaluation, including family and medical history, physical examination (with blood pressure, heart rate, and BMI assessment), and blood tests, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), C-reactive protein (CRP), and transaminases (AST and ALT).

The selected patients were all not eligible for statin therapy because of their risk classification and under dietary supplement with a nutraceutical in line with the ESC guidelines[2]; Specifically, we focused on this novel combination, already licensed in Italy starting from September 2021 (Liponamed®, PARAF Code 983307632) given in the form of 1 tablet daily at dinner associated to basic recommendations for a healthy lifestyle as indicated in table 1 for at least 30 days. In Italy, nutraceuticals are indicated by the Department of Health as dietary supplements with the primary purpose of optimization of physiological functions without any preventive or curative action,; thus, their use does not require any medical prescription, and any subject can get these "helpful food" according to the released indications.

As for standard practice from the family practitioner, weekly follow-up (in the medical office or by phone contact) was scheduled to monitor control subjects and patients' adherence to recommendations and to evaluate the possible side effects.

The primary endpoint of this analysis was the change from baseline to 30-day follow-up in TC, LDL-C, HDL-C, and TG plasma levels. Family practitioners recorded any adverse events reported by the patients, defined as untreatable gastrointestinal discomfort, myopathy, rhabdomyolysis, hepatotoxicity, and pharmacological interactions as already reported[28,29]. In this patient's, dietary supplementation was discontinued.

The study complies with the principle of Good Clinical Practice and the Declaration of Helsinki. Institutional Review Board/Ethics Committee approval is not required for retrospective analysis of the database in Italy. Informed consent was obtained from all subjects involved in the study.

Nutraceutical Composition: This nutraceutical is a formula that contains 4 ingredients beneficial for the management of lipids in the blood. Each gastro-resistant tablet contains: Berberis (Berberis aristata DC 83 mg of which Berberin 63mg); Bergamot (Citrus x bergamia Risso & Poit. 100mg) fruit dry extract. In 40% total polyphenols; Fermented red rice (Monascus purpureus Went. 58 mg) tit. in 5% monacolin K (equivalent to less than < 3 mg; Coenzyme Q10 (20 mg); Vitamin K2 (Menaquinone) 75 µg and relative excipients.

There is scientific evidence that demonstrates that Berberine can decrease the absorption of monacolin30. However, Berberine should be used at a high dose (up to 500mg/die) to achieve its effect because of its low bioavailability (0.7%) and, for this reason, also has some unwanted side effects[30]. To solve this problem, the pharmaceutical technology of the double-layer tablets has been applied to separate Monacolin from Berberine. Moreover, new technology has been developed to improve the absorption of Berberine (up to 7 times) to reduce significantly the amount of Berberine administered. These technologies are covered by worldwide Patent PCT/IT2021/0503802.2. Based on the above, we focused our analysis on the patients treated with this nutraceutical.

Blood test protocol: The analysis has been performed only on patients with a sample blood test performed at baseline (t0), before starting the dietary supplement, and at 30-days of follow-up (t1). As for standard practice, recommendations on at least 12 hours of fasting were given to each patient, and direct measurement of LDL-C was suggested.

Statistical analysis: Due to the observational nature of the study, a formal calculation of the study sample size is not applicable, and only descriptive analyses were performed. 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 range (IQR). Categorical variables are reported as numbers and percentages. Normally distributed continuous data were compared using Student's t-test. Comparisons between categorical data were performed using the $\chi 2$ test. For all tests, a p-value < 0.05 was considered statistically significant. Differences

in TC, LDL-C, HDL-C, TG, and transaminases during follow-up (t0 vs. t1) were compared using paired t-test. All statistical analysis was performed using SPSS Version 27.0. P-values <0.05 (two-tailed) were considered significant.

RESULTS

After filter criteria application, 526 Caucasian patients with hypercholesterolemia (LDL range 116-140 mg/dL) were selected and represented the final cohort for statistical analyses. Among the 526 patients included (age 53.4 ±7.5 years, males 38%), 275 (50%) had systemic hypertension, and 221 (40%) showed a BMI range of 25-35 Kg/m2. The clinical characteristics of the analyzed cohort are described in Table 2.

Table 2. Clinical characteristics of the population at baseline.

Demographics	**No. of Patients (*n* = 526)**
Age (years)	53.4 ± 7.5
Sex ratio (M:F)	201: 325
Cardiovascular characteristics	
Smoker	142(27%)
Ex-smoker	110(21%)
Non Smoker	274(52%)
Systemic arterial hypertension	263(50%)
Obesity (BMI 25-35 Kg/m^2)	221(42%)

*The study population has been divided according to three age range (35-44y, 45-54y and 55-65y) as reported in figure 2.

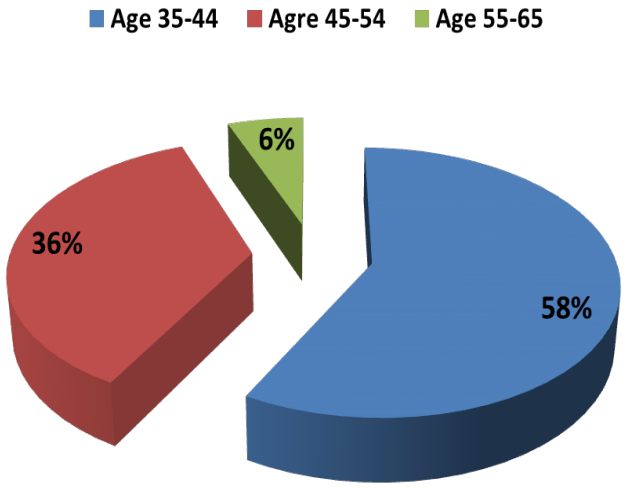


Figure 2. Distribution of study population according the age

At 30-day, the administration of nutraceuticals was associated with a significant reduction of LDL-C (124 ± 14 vs. 100 ± 13 mg/dL, Δ 24.5mg, p-value <0.0001) and TC levels (210 ± 56 vs. 187 ± 60 mg/dL, p-value < 0.0001), in the absence of significant changes of transaminase levels (AST: 28 ± 5 vs. 28 ± 4 U/L, p-value 1; ALT: 30 ± 6 vs. 30 ± 5 U/L, p-value 1) (Table 3). In addition, no significant changes were observed in CRP (3.9 ± 1.5 vs. 3.9 ± 1.4 mg/L, p-value 1; Table 3) and triglycerides (123 ± 38 vs. 122 ± 34 mg/dL, p-value 0.653).

Table 3. Plasma levels of the main study biomarkers in the study population.

	t0	t1	p-value
LDL-C (mg/dL)*	124 ± 14	120 ± 18	0.0608
LDL-C (mg/dL)	124 ± 16	100 ± 13	<0.0001
HDL-C (mg/dL)	61 ± 14.6	62 ± 7.9	0.167
TC (mg/dL)	210 ± 56	187 ± 60	<0.0001
Trg (mg/dL)	123 ± 38	122 ± 34	0.653
CPK (U/L)	110 ± 17	111 ± 18	0.354
AST (U/L)	28 ± 5	28 ± 4	1
ALT (U/L)	30 ± 6	30 ± 5	1
CRP (mg/L)	3.9 ± 1.5	3.9 ± 1.4	1

*LDL-C value from 104 subjects on healthy recommendations only

o side effects were reported in the database of family practitioners. In the 104 subjects not on lipid-lowering nutraceuticals, no significant reduction was observed in the 30-day follow-up compared to baseline (124 ± 14 vs. 120 ± 18 mg/dL, p-value 0.0608)

DISCUSSION

This is a retrospective multicenter family practice experience in managing a population with hypercholesterolemia, a low to moderate cardiovascular risk not eligible for statin treatment. The main result of the present analysis is the significant reduction of LDL-C within 30-days using a novel nutraceutical composition on top of lifestyle recommendations. Early modulation of lipid profile by using a nutraceutical supplement may be helpful in achieving the LDL target according to the current ESC guidelines[2], thus preventing cardiovascular events[2, 3].

Increased LDL-C is strongly associated with major cardiovascular events (MACE), such as myocardial infarction, stroke, and peripheral arteriopathy[5]. Thus, LDL-C has become the primary therapeutic target for managing and preventing several cardiovascular diseases [1,4,6,31]. As a result of pharmacological advances in recent years, previously unthinkable levels of LDL-C are now achievable[6]. According to the evidence that the additional reduction in LDL-C continues to be associated with an advantage in terms of cardiovascular risk reduction ("The lower, the better")[6], National and International Scientific Societies have further reduced the desirable levels of LDL-C in patients at increased cardiovascular risk[2,4]. More important, because of the causative role of LDL in cardiovascular diseases, earlier preventive management may result in better cardiovascular outcomes [3].

Pharmacological modulation of biosynthesis/absorption and recycling of cholesterol, in addition to a healthy lifestyle, is the primary strategy to achieve the new recommended therapeutic targets[32]. Remarking on the fundamental role of conventional drug therapy in subjects at high and very high cardiovascular risk, with a combination of molecules depending on the desired target, many times, the situation is less defined in a subject at low cardiovascular risk[32]. Given the suggested LDL-C value of ≤115mg/dl for low-risk subjects, in the real-life scenario, the proportion of the population that needs to achieve this level becomes significant[3].

In most cases, the distance from the LDL-C target is insufficient to require a conventional drug. In these scenarios, combining "natural supplements" with a healthy lifestyle could allow the population in this "grey area" to achieve and maintain the desired target[7,8,11]. This approach is supported by observational studies conducted in populations with a low incidence of

cardiovascular events consuming low-fat and high-antioxidant-content diets such as the Mediterranean diet[33]. Eastern world populations, also characterized by a low prevalence of cardiovascular diseases, have a diet rich in substances capable of directly interfering with lipid excesses, such as monacolin extracted from red fermented rice by Monascus pupureus and polycosanols from sugar cane and green tea[34].

***The role of nutraceuticals in reducing LDL-C*:** In recent years, different nutraceuticals have significantly reduced blood cholesterol levels and avoided damage from oxidative stress[11]. Among the different nutraceuticals used in clinical practice, monacolin K[14,25,35], berberine[17,18], bergamot[19,20], vitamin K2[22,23], and coenzyme Q10[24], are those with strong evidence of effectiveness.

The present study confirms that lipid-lowering nutraceutical products could safely improve plasma lipid levels in subjects with low to moderate hyper-cholesterolemia at low cardiovascular risk. Moreover, the novel modality of delivery of the compounds, already tested for other combinations [36], may help determine the early lipid-lowering effect. All these natural substances are included in this novel formulation to combine the effectiveness in reducing cholesterol levels and protecting from the oxidative stress of these molecules.

Fermented red rice monacolin K is a molecule with a proven cholesterol-lowering effect[13,14]. Its chemical composition is equivalent to a synthetic statin, namely lovastatin.

Despite being given at low dosages (between 5 to 10 mg), in recent years, potential safety concerns associated with consuming foods containing monacolins from red yeast rice have been raised. The opinion from the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) on the risk associated with the presence of “red yeast rice” in food supplements concluded that “due to the composition of red yeast rice and in particular: the presence of monacolin K (also called lovastatin when marketed as a drug) that shares the adverse effects of statins; the presence at varying levels of the other monacolins, compounds whose safety has not been established, consumption of “red yeast rice” exposes some consumers to a health risk.” Based on that opinion, the European Food Safety Authority (EFSA) was called to reply. On 25 June 2018, the Authority adopted a scientific opinion on the safety of monacolins in red yeast rice[25]. The Authority considered monacolin K in lactone based on the information available. The Authority concluded that intake of monacolins from red yeast rice via food supplements could lead to estimated exposure to monacolin K within the range of the therapeutic doses of lovastatin.

The Authority noted that the profile of adverse effects of red yeast rice was similar to that of lovastatin. The Authority considered that the available information on the negative effects reported in humans was sufficient to conclude that monacolins from red yeast rice, when used as food supplements, were of significant safety concern at 10mg/day. The Authority further considered that cases of severe adverse reactions had been reported for monacolins from red yeast rice at intake levels as low as 3mg/day taken for between 2 weeks and 1 year[25]. Scientific studies and supervisory data on supplements with dosages of 3mg/day of monacolin K seem to confirm the safety of monacolin-based supplements without registering significant side effects in the short term[27].

However, the consideration that monacolin K is chemically identical to lovastatin, and the sources of dietary intake of red fermented rice may be different, makes it difficult to indicate a mini-mum/maximum dosage.

Thus, monacolin K-based food supplements with dosages equal or superior to 3 mg are currently discouraged, while patients assuming supplements with lower dosages (<3 mg) should be monitored[25].

Other natural products with lipid-lowering properties, such as berberine[37] and bergamot[19], are also included in this formulation. Berberine is an alkaloid found in several plants such as goldenseal (Hydrastis Canadensis), Oregon grape (Berberis aquifolium), bayberry (Berberis Vulgaris), coptis (Coptis Chinensis), and tree turmeric (Berberis aristata)[17]. It has been shown that berberine has additive LDL-lowering effects with statins plus ezetimibe via hepatic LDL-R increase and suppression of PCSK9 expression that finally increases hepatic LDL excretion[18].

A meta-analysis of berberine, including up to 11 randomized trials for a total of 874 subjects, showed significant reductions in TC, LDL-C, and TG and an increase in HDL without any serious adverse effects[37]. On the other hand, bergamot shows similar lipid-lowering properties[21]. Bergamot (Citrus bergamia) is an endemic plant growing in Southern Italy, mainly the Calabrian region, with a unique profile of flavonoids and glycosides associated with immune response and cardiovascular function modulation[20]. It reduces cholesterol via multiple mechanisms linked to cholesterol synthesis and absorption[21,38]. A recent systematic review reveals that an alternative therapeutic option in dyslipidemia management with bergamot supplementation, especially in subjects with statin intolerance, might be possible[19]. Thus, most lipid-lowering nutraceutical formulations include berberine and bergamot as additive effects to yeast rice.

The present study confirms the effectiveness of this nutraceutical in reducing the LDL-C concentration by approximately 25 mg/dl. Interestingly, this reduction occurs within thirty days of treatment in the absence of objective side effects (no change in CPK or transaminases) and subjective side effects (no reported adverse events) and using the current recommended dosage of monacolin K <3 mg[9].

CONCLUSIONS

The present analysis showed that supplementation with this nutraceutical formulation significantly improves LDL-C levels as early as 30-days after follow-up. However, long-term studies are needed to evaluate the safety and maintenance of the achieved LDL-C levels. These dietary supplements should be considered in patients with low to moderated cardiovascular risk who do not require or develop side effects with the use of conventional lipid-lowering drugs.

Limitations: Despite the novelty, our study has many limitations: the retrospective observation nature, the relatively small sample size, the restricted geographical location, and the short follow-up**.** Another limit may be represented by the data collection methods, including electronic patient record information from the family practitioner's database. Not a real control group exists, and adherence to supplementation and/or basic healthy recommendations cannot be verified. Finally, this cannot be confirmed despite the recommendation of 12 hours of fasting before lipid profile measurement.

Abbreviations: LDL-C: low-density lipoprotein, TC: Total cholesterol, CVR: cardiovascular risk, MACE: major cardiovascular events, PCSK9: proprotein convertase subtilisin/kexin type 9, ESC: European Society of Cardiology, EFSA: European Safety Food Authority, BMI: body mass index, CRP: C-reactive protein, HDL-C: high-density lipoprotein, SD: standard deviation, IQR: interquartile range

Author Contributions: Conceptualization, F.N. and G.P.; methodology, A.S. and G.P.; validation, F.N., G.P. and A.S.; formal analysis, R.M., E.M. and S.C. ; investigation, G.P. and A.S. ; resources, G.P.; data curation, F.N.; writing—original draft preparation, F.N.; writing—review and editing, G.C.; visualization, G.L.

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