Research Article

A Nutraceutical Phytocomplex of Extracts from Citrus Bergamia and Opuntia Ficus-Indica Improves Lipid Profile in Subjects with Mild Hypercholesterolemia: A Pilot Study

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Abstract

Background: During the last decades, the role of lipid-lowering nutraceuticals in cardiovascular disease prevention is gathering attention.

Aims: The aim of this study was to evaluate the effects of a dietary supplement with a combination of mediterranean extracts, on the plasmatic lipid profile in adults with mild hypercholesterolemia.

Materials and Methods: Eighty subjects divided in two groups: the control group was instructed to follow a personalized diet and physical activity; whereas the treated group was instructed to follow an individualized diet, physical activity and a daily intake of a food supplement based on mediterranean extracts (200 mg of a phytocomplex from bergamot fruit standardized min 40% total flavonoids and min 5% in HMG (3-hydroxy-3-methylglutaryl) flavanones, 150 mg of Opuntia ficus-indica cladodes' extract, 400 mg of plant sterols, and 12.5 mg of thiamine). 1 tablet per day was administered in the evening for 16 weeks. All subjects were evaluated on their anthropometric parameters, lipids panel, and inflammatory profiles, at three different time points such as: at baseline (T0), after 8 weeks (T1) and after 16 weeks (T2).

Results: Following the 8 and 16-weeks supplementation, a significant reduction of several metabolic parameters was observed: LDL-c -18.2% at T1, and -23.4% at T2; Tot-c -9.0% at T1, and -12.6% at T2; TG -11.8% at t1, -18.2% at T2; while HDL-c significantly increased +21.3% at T1 and +24.8% at T2.

Conclusions: Our findings suggest that the supplementation of the mediterranean extracts' complex improves the lipid profile in subjects with mild hypercholesterolemia.

Keywords: Hypercholesterolemia; Flavonoids; Citrus Bergamia; Opuntia ficus-indica; Nutraceuticals; Bergamot; Mediterranean Extracts

Introduction

According to the World Health Organization (WHO), Cardiovascular Diseases (CVDs) are still considered the leading cause of death globally, accounting for 32% of all fatalities. According to the estimates, almost 18 million deaths were attributable to CVDs with heart attack and stroke accounting for 85% of these casualties [1]. The incidence of cardiovascular events increases with age, due to higher cholesterol plasma levels, increased arterial stiffness and peripheral vascular resistance [2]. Among women over 50 years old, the incidence of occurring cardiovascular events significantly increases. Risk factors are genetic factors, sedentary lifestyle, obesity, dyslipidemia, high blood pressure, diabetes, and smoking [3]. The Global Burden of Cardiovascular Diseases and Risk (GBD) report has drawn attention to how modifiable risk factors play a crucial role in patients' death [4]. Between them, lifestyle, diet, impaired serum lipid and glucose levels are the most important modifiable risk factors for atherosclerotic vascular diseases such as coronary heart disease, cerebrovascular disease (e.g., stroke) and peripheral vascular disease [5,6]. Indeed, the guidelines on CVDs recommend the reduction of serum Low-Density Lipoprotein cholesterol (LDL-c) as one of the most important interventions in order to decrease the risk of cardiovascular events both in young, middle-aged adults and elderly patients [7-9].

Standard pharmacological therapy with lipid-lowering medications is regarded as the first-line therapy in circumstances when physical exercise and a regulated diet are insufficient. The main limitation of conventional therapy is related to the side effects the patients experience, consequently leading to the discontinuation of the treatment [10,11]. The American Heart Association has stressed the use of implemented preventive measures as the primary strategy for promoting cardiovascular health, even though several challenges must be overcome [12]. Hence, prevention of dyslipidemias could be considered an

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efficacious strategy in avoiding exacerbation of the preexisting conditions. Primary prevention strategies include adopting a healthy diet and a correct lifestyle, in addition to the administration of a food supplement of proven efficacy and safety [11]. This approach may be considered a valid tool in reducing the risk of CVDs in patients that either do not tolerate the conventional pharmaceutical approach or exhibit milder form of dyslipidemias [13,14].

Obviously, a healthy lifestyle must be maintained and consolidated over time even if specific drugs or nutraceutical products are subsequently taken [15]. Flavonoids are extensively studied for their anti-inflammatory and antioxidant properties in addition to their pleiotropic effects on the metabolism and vascular health [16–24]. Several clinical studies have confirmed their effect in improving the lipid profile in people with cardiometabolic risk factors [25–28].

Citrus Bergamia fruit extract, commonly known as bergamot, has been demonstrated to positively affect the immune system, exert antioxidant action, and being able to reduce adipogenesis due to its high flavanones' content with statin-like activity [29-33]. Several studies have confirmed that the unique polyphenolic content of the bergamot fruit, especially the so-called HMG-flavanones (Brutieridin and Melitidin) seem to be targeting and inhibiting the enzyme 3-Hydroxy-3-Methyl-Glutaryl Coenzyme A (HMG-CoA) reductase, responsible for the metabolic pathway of cholesterol production [34,35]. A recent combined *in vitro* and clinical study has demonstrated the positive effect of a bergamot fruit extract on plasma lipid profile (typical of hypercholesterolemia) and liver enzymes, by determining a reduced expression of genes involved in lipid synthesis [36].

Opuntia ficus-indica cladodes, also called cactus' or prickly pear's leaves, on the other hand, are particularly rich in pectins and mucilages which were proved to improve both the lipid and glucose concentration in plasma by acting on the overall absorption mechanism of food-derived nutrients in the gut [27,37]; Opuntia extracts were also demonstrated to be reducing both Total Cholesterol Levels (Tot-c) and LDL involved in atheroma formation in healthy individuals [38], in patients affected by metabolic syndrome, and type 2 diabetes mellitus [39].

The main objective of this study was to evaluate whether the specific nutraceutical combination of the mediterranean extracts of Citrus Bergamia and Opuntia ficus-indica, could exert a synergistic effect and positively improve the lipid profile in subjects affected by mild hypercholesterolemia. The choice of this specific formulation was related to the components' potential health benefits and unique content of secondary metabolites and dietary fibers.

Materials and Methods

Study design

This study was carried out from September 2022 to February 2023 at the Diabetes Unit of S. Camillo – Forlanini Hospital, Rome, Italy, in accordance with the current legislation, the declaration of Helsinki. Following a first screening visit, 80 outpatients affected by mild hypercholesterolemia, who matched the predetermined inclusion criteria, were enrolled in the study, and assigned to one of the two study groups, namely a control and a treated group.

The inclusion criteria foreseen were men and women ≥ 18 years of age and LDL-c levels between 116 and 190 mg/dL. The LDL-c levels were confirmed in at least two sequential controls. Exclusion criteria comprised personal history of CVDs or equivalent risk, diabetes mellitus type I or II, Triglycerides (TG) >400 mg/dL and/or high-density lipoprotein cholesterol (HDL-c) <35 mg/dL, severe obesity (Body Mass Index (BMI) >35 kg/m^2), therapy with hypolipidemic drugs or drugs affecting lipid metabolism, known thyroid, liver, kidney or muscle diseases, currently pregnant or planning to become pregnant in the next 16 weeks, myocardial infarction, vascular surgery, or stroke within the past year, allergy to any of the components of the dietary supplement.

The primary outcome was the reduction in serum LDL-c levels, while secondary outcomes included body weight, Body Mass Index (BMI), abdominal circumference, Total Cholesterol (Tot-c), HDL-c, non-High-Density Lipoprotein cholesterol (non-HDL-c), TG, C-Reactive Protein (CRP), Creatine Phosphokinase (CPK), Glutamic Oxaloacetic Transaminase (GOT), Glutamate Pyruvate Transaminase (GPT), and systolic and diastolic blood pressure. All the abovementioned plasma parameters were acquired after 12-hours of overnight fasting.

In addition to assessing the compliance with the administered dose of the supplement, we also took into thorough consideration any adverse events that could potentially be linked to the supplement, and the overall contentment of the subjects involved in the study. A personalized diet was prescribed by a specialized professional according to the guidelines of a Mediterranean diet, which however, was specific for each patient's needs. In fact, overweight patients were handed a hypocaloric prescription (20-25 kcal/kg), while normal weight subjects had 25-30 kcal/kg. Protein content ranged between 1.0-1.1 g/kg/day with a particular recommendation to include plant foods (legumes) 2-3 times a week; carbohydrates were 40%-50% of total caloric intake, fibers 15 g/1000 kcal; fats were about 30% with high monounsaturated/saturated ratio; concluding with an overall moderate sodium restriction recommended to hypertensive patients.

The participation in the study was voluntary, the subjects were adequately informed of the aims, methods, clinical evaluation details, and signed an informed consent. Ongoing pharmacological therapy (e.g., antihypertensives) remained unchanged through the course of the study and no other nutraceutical supplementation was taken.

For what concerned the control group, the patients were instructed to follow the prescribed diet and physical activity for 16 weeks; whereas the treated group followed, during the same time frame, the personalized diet, physical activity and a daily supplementation (1 tablet every evening) with the Mediterranean extracts: 200 mg of Brumex®, which is a phytocomplex from bergamot fruit (Citrus bergamia Risso et Poiteau, fructus, standardized min 40% total flavonoids and min 5% in HMG (3-Hydroxy-3-Methylglutaryl) flavanones; 150 mg of Opuntia ficus-indica extract (75% pectins and mucilages, 3.7% polyphenols), plus 400 mg of plant sterols and 12.5 mg of thiamine (the product was provided by Esserre Pharma, Rome, Italy).

The evaluation of the patients was carried out at three different time points, specifically at baseline (T0), after 8 weeks (T1) and after 16 weeks (T2), during which all the clinical (anthropometric) and laboratory data were recorded. The subjects were instructed to start with the mediterranean nutraceutical product's supplementation from the evening of the first visit.

Statistical analysis

All the data presented are expressed as mean ± Standard Deviation (SD). To evaluate and compare the effect of the supplement within the single group, One-way repeated measures ANOVA test was performed using Free Statistics Calculators version 4.0 © 2006-2022. Instead, to assess whether there were any group differences (control group *vs* treated group), Unpaired t test (©2023 GraphPad Software) was used. A p-value of <0.05 was considered significant for all the conditions and the specifications of the symbols associated with the p-values are provided in the caption of each table.

Results

The enrolled population characteristics are summarized in Table 1. No statistical significance was observed regarding the baseline parameters evaluated in the different groups (40 per group), highlighting the overall homogeneity within the two cohorts. Age was 48.65 ± 9.19 years in the treated group and 48.5 ± 7.3 years in the control group. BMI was 26.6 ± 4.2 kg/m^2 in the treated group and 28.3 ± 3.6 kg/m^2 in the control group. 12.5% of all the enrolled patients were diagnosed with hypertension and 8.75% belonged to the treated group, while 3.75% to the control group. The number of smoking subjects was the same between the two groups. Overall, no adverse events were experienced during the duration of the trial.

Table 1: Baseline characteristics of the study groups.

	Control group (40 subjects)	Treated Group (40 subjects)
Age (years)	48.5 ± 7.3	48.6 ± 9.2
Gender (M/F)	21/19	13/27
BMI (Kg/m^2)	28.3 ± 3.6	26.6 ± 4.1
Hypertension (n° subjects)	3	7
Smokers	1	1

After the supplementation of the Mediterranean nutraceutical product, Tot-c was significantly reduced by 9% at T1, and by 12.6% at T2, (p<0.0001) when compared to the baseline (Table 2). While, within the control group, the variation was +0.92% at T1 and +1.30% at T2 with statistical significance only at T2 (p<0.05). The treated patient's LDL-c was significantly reduced by 18.2% at T1, and by 23.4% at T2, (p<0.0001) when compared to the baseline (Table 2), instead the control group variation was +0.97% at T1 and +2.7% at T2 (p<0.05). In the treated group, HDL-c significantly increased by 21.4% and 24.8% (p<0.0001) respectively, compared to the baseline (p<0.0001) (Table 2), in opposition to the control group variation by 2.6% at T1 and -0.43% at T2. In the treated group, non-HDL-c significantly decreased by 17.1% after 2 months (T1), and by 22.6% after 4 months (T2), when compared to the baseline levels (p<0.0001). In the control group, variations were not significant at T1 (0.45%) but slightly at T2 (p<0.05) increasing by 1.8% when compared to the baseline levels (Table 2). In the treated group, TG significantly decreased by 11.8% after 2 months (T1) (p<0.001), and by 18.2% after 4 months (T2) (p<0.05), when compared to the baseline levels; while, in the control group, the reduction was not significant neither at T1 (2.1%) nor at T2 (2.7%).

For what concerned the inflammatory profile, CRP levels decreased by 35.4% (p<0.0001) after 2 months (T1) of supplementation and by 49.5% (p<0.0001) after 4 months (T2) when compared to the baseline. Within the control group, the reductions occurred by 18.5% (p<0.05) at T1 and by 25.6% (p<0.01) at T2 with less statistical significance. Inter-group differences were visible only at T2 (p<0.01). 13.2% (p<0.01) and 15.8% (p<0.0001) reductions were observed for CPK values at T1 and T2, respectively for treated patients, while the changes in the control group were -5.6% at T1 (p<0.05) and -5.5% at T2. GPT levels were statistically significant only in treated patients with changes of -18.9% (p<0.01) at T1 and -29.5% (p<0.0001) at T2. For non-treated patients, the GPT levels were lessened by -3.7% (T1) and -2.9% (T2). Patients who underwent the nutraceutical treatment, had a drop in GOT levels of 11.3% (p<0.0001) at T1 and 23.8% (p<0.0001) at T2 compared to T0, while non-treated subjects exhibited a non-significant reduction of 4.5% and 6% at T1 and T2 correspondingly. Inter-group differences were significant only at T2 for both GPT (p<0.0001) and GOT (p<0.01) levels.

After 4 months of supplementation (T2), combined with the diet, body weight and BMI were significantly reduced in both groups at both time points (T1 and T2) (p<0.0001). In addition to that, inter-group comparisons were significant at T2 (p<0.05) for both parameters, but solely at T1 (p<0.05) for the BMI. On the contrary, abdominal circumference remained significant only for the treated group at T2 (p<0.05), even when compared to the control (Table 2). Both systolic and diastolic blood pressure remained unchanged throughout the course of the study. Final values and differences of all variables inter, and intra-groups are summarized in Table 2.

Table 2: The variables measured on 80 subjects (control group and treated group) at the baseline (T0), after 8 weeks (T1) and after 16 weeks (T2) of supplementation with the food supplement based on mediterranean extracts. Data are presented as mean ± SD. One-way repeated measures ANOVA test: T1 *vs* baseline, and T2 *vs* baseline intra-group.

	Control group (n°=40)			Treated group (n°=40)		
	T0	T1	T2	T0	T1	T2
Tot-c (mg/dL)	212.03 ± 10.20	213.98± 8.68	214.78 ± 8.97*	211.7 ± 11.76	192.65 ± 8.67***§§§	185.08 ± 6.31***§§§
LDL-c (mg/dL)	137.81 ± 12.18	139.15 ± 13.45	141.51 ± 12.18*	138.8 ± 12.20	113.55 ± 9.92***§§§	106.26 ± 8.60***§§§
non-HDL-c (mg/dL)	165.73 ± 12.83	166.48 ± 12.65	168.68 ± 11.39*	167.13 ± 12.49	138.55 ± 12.24***§§§	129.43 ± 10.58***§§§
HDL-c (mg/dL)	46.3 ± 8.9	47.5 ± 9.4	46.1 ± 7.59	44.58 ± 9.18	54.1 ± 8.67***§	55.65 ± 8.02***§§§
TG (mg/dL)	139.55 ± 31.88	136.63 ± 28.49	135.8 ± 26.30	141.63 ± 43.65	124.98 ± 27.33**	115.8 ± 18.27*§§
CRP (mg/dl)	1.68 ± 0.86	1.37 ± 0.49*	1.25 ± 0.43**	1.98 ± 1.17	1.28 ± 0.51***	1.00 ± 0.00***§§
CPK (U/L)	126.80 ± 29.21	119.73 ± 14.59*	119.80 ± 11.93	141.85 ± 30.77	123.18 ± 13.61**	119.48 ± 8.79***
GPT (U/L)	23.78 ± 9.73	22.90 ± 6.8	23.10 ± 4.22	27.18 ± 11.43	22.05 ± 7.90**	19.15 ± 2.50***§§§
GOT (U/L)	24.40 ± 7.08	23.30 ± 5.83	22.93 ± 3.72	26.35 ± 8.26	23.38 ± 5.85***	20.07 ± 2.94***§§
Systolic pressure (mm Hg)	123.00 ± 7.19	123.65 ± 5.84	121.60 ± 6.21	123.93 ± 8.52	122.05 ± 6.83	120.45 ± 3.98
Diastolic pressure (mm Hg)	71.43 ± 5.9	72.78 ± 7.13	70.30 ± 5.19	73.50 ± 7.92	71.13 ± 5.22	69.55 ± 3.99
Body Weight (Kg)	79.65 ± 13.38	78.32 ± 13.44***	77.64 ± 13.59***	73.98 ± 14.79	71.60 ± 14.36***§	71.65 ± 13.95***
BMI (Kg/m^2)	28.27 ± 3.61	27.79 ± 3.65***	27.55 ± 3.68***	26.65 ± 4.16	25.79 ± 4.05***§	25.80 ± 3.83***§
Abdominal Circumference (cm)	104.08 ± 17.41	100.22 ± 8.43	99.66 ± 8.44	98.08 ± 9.97	96.06 ± 10.3	88.77 ± 26.24*§

Note: *p-value=*p<0.05, **p ≤ 0.01, ***p ≤ 0.0001. Unpaired T-test: T0 *vs* T0, T1 *vs* T1, and T2 *vs* T2 inter-group. §p-value=§p<0.05, §§p ≤ 0.01, §§§p ≤ 0.0001, §=Section sign,

Discussion

The American Heart Association's most recent scientific statement currently recommends dietary patterns, such as the Mediterranean diet and Dietary Approach to Stop Hypertension, as preventative or therapeutic options for CVDs [40]. However, the sole improvement to a healthier lifestyle, including the Mediterranean diet, cannot be considered sufficient to counteract the possible rise of CVDs. In fact, a combinational strategy with nutraceutical supplementation could be regarded as the most effective plan of action [41]. The suggested objective is to reduce primarily LDL-c levels, although it has also been proven that addressing modifiable metabolic syndrome risk factors is beneficial [28]. The potential therapeutic benefits of flavonoids, particularly on human cardiovascular health, have piqued the interest of experts all over the world in the past decades [16,27].

In this pilot clinical study, the group treated with a nutraceutical compound, based on a flavonoid complex from bergamot (Citrus bergamia Risso et Poiteau) and prickly pear cladodes (Opuntia ficus-indica L.), plant sterols and thiamine showed a significant reduction in Tot-c, LDL-c, non-HDL-c, TG, GOT, GPT, CRP and CPK while a significant increase of HDL-c plasma level was observed after 8 and 16 weeks of treatment. Moreover, BMI, body weight and abdominal circumference were highly affected by the nutraceutical approach. These overall findings are in agreement with previous clinical data, from overall healthy subjects affected by hypercholesterolemia with low cardiovascular risk, who experienced benefits in the lipid and anti-inflammatory profile from the intake of the same nutraceutical product [27]. Further studies have shown the effects of bergamot nutraceutical compounds in reducing LDL-c levels in people presenting impaired lipid profile [25,28,42]. On top of that, flavonoids have a positive impact on the cardiovascular system due to their ability to trigger vasodilation along with regulating apoptosis within the endothelium [27,43]. Moreover, a preclinical and clinical study has confirmed the beneficial impact of bergamot extract on the reduction of both plasma lipid profile and lipid enzymes in moderate hypercholesterolemic patients. In addition to that, several genes related to lipid synthesis were impaired by the abovementioned extract *in vitro* [36]. Indeed, the unique flavanone glycosides content in the bergamot fruit, such as neoeriocitrin, neohesperidin, naringin, brutieridin, and melitidin; showed a pleiotropic effect on metabolism and vascular health [26,42,44]. Polyphenols, characteristic of the bergamot extract, exhibited statin-like properties as well as an anticholesterolemic activity, through the inhibition of the 3-Hydroxy-3-Methyl-Glutaryl-Coenzyme A (HMG-CoA) reductase [33,45,46].

The cactus, commonly known as prickly pear, is a vegetable that extensively grows in Mexico and south of Italy. The cladodes of the Cactus contain a mix of mucilage and pectin, which are two polysaccharides, also known as hydrocolloids, polyphenols, polyunsaturated fatty acids, vitamins, and amino acids [47]. This rich composition gives great potential to this plant for antioxidant, anti-inflammatory, hypoglycemic, antimicrobial, and neuroprotective activities [48,49]. Indeed, it has been shown its action in improving glucose and lipid profile, by inhibiting the absorption of food carbohydrates, sterols, and lipids in the intestine [37]. Furthermore, in different clinical studies, the effect of Opuntia was assessed, demonstrating a positive action on plasma lipid levels and atheromatic LDL subfractions in overall healthy subjects [38], and reduction in Tot-c and LDL-c in individuals with metabolic syndrome and type 2 diabetes [39]. Thus, the lipid-lowering effect of the nutraceutical tested in this study might be due to the synergistic action of bergamot flavonoids with Opuntia pectin and mucilage.

Plant sterols, known also as phytosterols, are bioactive compounds present mainly in vegetable oils, nuts, cereals, legumes, seeds, and in smaller amounts in fresh fruits and vegetables [50]. It has been known for nearly 50 years that plant sterols lower blood cholesterol levels, mainly competing with dietary and biliary cholesterol absorption in the intestine [51,52]. Several clinical studies have confirmed that the intake of approximately 2 g/day of phytosterols is associated with a significant reduction (8%-10%) of LDL-c [53,54]. Furthermore, the intake of phytosterol seems to be effective in decreasing the high sensitivity CRP levels [55]. Thus, supplementation of phytosterols could be necessary in case of a Western diet, that usually includes a low basal content of phytosterols.

Thiamine is a B group, water-soluble vitamin included in the nutraceutical supplement because of its effect on the “normal cardiac function” (EFSA Health Claim) [56].

A healthy lifestyle and diet remain the primary approach for cardiometabolic disease prevention [57], however the use of nutraceuticals for their potential anti-inflammatory effect, safety and implication of CVDs prevention has been recently noted by an expert panel [58]. This study is also confirming the safety of the standardized extracts of bergamot and opuntia, since no side effects related to the dietary supplement were reported, meaning that they can modify different elements of the metabolic syndrome [27,59,60].

Conclusion

These findings demonstrate that the daily intake of a nutraceutical compound based on extracts of mediterranean plants like bergamot and prickly pear, rich in flavonoids and soluble fibers, plant sterols and thiamine significantly decrease cholesterol and triglycerides levels short-term in hyperlipidemic patients. On the other hand, the limitations of this study include a reduced sample size (n=80) with a short-term data collection (16 weeks), and the lack of a placebo group. For these reasons, more detailed and structured longer-term trial, ideally on a larger sample group, would be recommended to gain a deeper understanding of the effect of this specific mediterranean supplement.

In conclusion, the intricate interplay between flavonoids and soluble fibers, complemented by the inclusion of plant sterols, presents a promising strategy for effectively and reliably managing plasma cholesterol levels, in individuals exhibiting mild hypercholesterolemia. The convergence of these bioactive components culminates in a synergistic effect that holds considerable potential in cardiovascular health.

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