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Botanicals and Food Supplement Combination in Patients with Polygenic Hypercholesterolemia: Evaluation at Fasting and after Oral Fat Load Test

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Abstract The aim of this study was to evaluate, in hypercholesterolemic patients, the effects on lipid profile both at fasting and after an oral fat load (OFL), of 3 months of treatment with a nutraceutical combination containing monacolin K, Cynara scolymus, Thea sinensis L., Oryza sativa L., Brassica campestris L., folic acid, coenzyme Q10, and Resveratrol compared to placebo. We enrolled 63 Caucasian patients, aged ≥18 of either sex, at low cardiovascular risk (≤ 2%) and randomized them to take the nutraceutical or placebo for 3 months. We evaluated fasting plasma glucose, lipid profile, high sensitivity C-reactive protein and safety parameters at baseline and after 3 months. Patients also underwent an OFL at baseline and at the end of the study. Nutraceutical combination gave a reduction of total cholesterol (TC), triglycerides (Tg), and low-density lipoprotein-cholesterol (LDL-C), both compared to baseline ($p < 0.05$), and compared to placebo ($p < 0.05$). High-sensitivity C-reactive protein decreased in the active group both compared to baseline and to placebo ($p < 0.05$ for both). During the OFL performed at the end of the study, TC, and LDL-C recorded in the group treated with the nutraceutical combination were lower compared to the values recorded during the baseline OFL ($p < 0.05$), and also compared to values recorded in placebo group ($p< 0.01$) at every time of OFL. Regarding Tg, the value recorded during the OFL at the end of the study was lower at 6 hours compared to baseline OFL ($p < 0.05$ vs baseline), and to placebo ($p < 0.05$). A nutraceutical containing monacolin K, Cynara scolymus, Thea sinensis L., Oryza sativa L., Brassica campestris L., folic acid, coenzyme Q10, and Resveratrol could be helpful in improving lipid profile in hypercholesterolemic patients, both at fasting and in post-prandial phase.

Keywords: *Monascus purpureus, Cynara scolymus, Thea sinensis L., Oryza sativa L., Brassica campestris L., polygenic hypercholesterolemia*

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1. Introduction

Cardiovascular diseases (CVDs) are the first leading cause of death in Occidental countries [1], therefore identification, prevention and management of the risk factors for CVDs are a priority in public healthcare programs [2]. Among CVD, lipid profile is surely one of the main player in increasing cardiovascular risk. ESC/EAS guidelines for the management of dyslipidaemias suggest to measure the parameters of the fasting lipid profile to stratify the individual risk of experiencing a cardiovascular event in the following years [3]. However, recent evidence suggests that post-prandial hyperlipidemia is also an important and independent risk factor for cardiovascular events [4] and that we live most of our lives in a post-prandial state, a condition that mainly affects lipid metabolism [5]. The most adequate way to experimentally reproduce the condition of post-prandial lipidemia seems to be the administration of a standardized lipid load to fasting patients [6]. This model has been widely applied in a relatively small sample of subjects to study post-prandial lipidemia and to verify the effect it can have on some parameters and conditions [7,8]. Our group also evaluated some types of patients using OFL, determining some parameters and cardio-metabolic risk factors [9,10].

In the latest years, nutraceuticals market has increased a lot. Nutraceuticals are dietary supplements that contain a concentrated form of a presumed bioactive substance originally derived from a food, but now present in a nonfood matrix, and used to enhance health in dosages exceeding those obtainable from normal foods [11]. Patients are deeply concerned about how their health care

is managed, administered and priced and more often they are seeking complementary or alternative beneficial products; the claimed natural origin of these products makes nutraceuticals particularly appealing.

Therefore, the aim of this study was to evaluate, in hypercholesterolemic patients, the effects on lipid profile both at fasting and after an oral fat load (OFL), of 3 months of treatment with a nutraceutical combination containing monacolin K, Cynara scolymus, Thea sinensis L., Oryza sativa L., Brassica campestris L., folic acid, coenzyme Q10, and Resveratrol compared to placebo.

2. Material and Methods

2.1. Study Design

This randomised, double-blind, placebo controlled study was conducted at the Department of Internal Medicine and Therapeutics, University of Pavia (Pavia, Italy). The study protocol was approved at the institutional review board and was conducted in accordance with the Declaration of Helsinki and its amendments.

2.2. Patients

We enrolled 63 Caucasian patients, aged ≥18 of either sex, at low cardiovascular risk (≤ 2 %) according to Framingham Risk Score [3], with hypercholesterolemia according to National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) criteria [12] [total cholesterol (TC) between 200-240 mg/dl), and with triglycerides (Tg) < 400 mg/dl]. To be included in the study, patients needed to be naïve to hypolipidemic agents. They were overweight (BMI 25.0-29.9 kg/m^2) [13]. Suitable patients, identified from review of case notes and/or computerized clinic registers, were contacted by the investigators in person or by telephone.

Patients were excluded if they had secondary dyslipidemia due to untreated hypothyroidism or type 2 diabetes mellitus; impaired hepatic function (defined as plasma aminotransferase and/or gamma-glutamil transpeptidase (γ-GT) level higher than the upper limit of normal [ULN] for age and sex); impaired renal function (defined as serum creatinine level higher than the ULN for age and sex); endocrine disorders, or gastrointestinal disorders; current or previous evidence of ischemic heart disease, heart failure, or stroke; weight change of > 3 Kg during the preceding 3 months; malignancy; and significant neurological or psychiatric disturbances, including alcohol or drug abuse. Excluded medications (within the previous 3 months) were anorectic agents, laxatives, β-agonists (other than inhalers), cyproheptadine, anti-depressants, anti-serotoninergics, phenothiazines, barbiturates, oral corticosteroids, and anti-psychotics. Women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions were also excluded.

At the beginning of the study and for all the study period, patients were taking different concurrent medications; the complete list of the drugs taken is reported in Table 1. Concomitant treatments were not changed during the study.

2.3. Treatments

Patients were assigned to receive, as addition to diet and physical activity, a botanicals combination containing fermented red rice (11 mg) titled at 3 % in monacolin K (3.3 mg), Cynara scolymus titled 7 % in chlorogenic acid (50 mg), Thea sinensis L. titled 40 % in polyphenols and 15 % in catechins (40 mg), Oryza sativa L. (20 mg), Brassica campestris L. (Oleifera DC) titled 45 % in β-sitosterol (15 mg), and food supplement as folic acid (100 μg), coenzyme Q10 (10 mg), and Resveratrol (1 mg) (active group) (HDLGELAR® urto, marketed by Gelar Farma, Mori (TN), Italy) (Table 1) or placebo (control group), once a day, for 3 months, in a double-blind, randomized, placebo-controlled clinical trial (Figure 1). Both treatments were supplied as identical, opaque, white capsules in coded bottles to ensure the blind status of the study. Randomization was done using a drawing of envelopes containing randomisation codes prepared by a statistician. A copy of the code was provided only to the responsible person performing the statistical analysis. The code was only broken after database lock, but could have been broken for individual subjects in cases of an emergency. Medication compliance was assessed by counting the number of pills returned at the time of specified clinic visits. At baseline, we weighed participants and gave them a bottle containing a supply of study medication for at least 100 days. Throughout the study, we instructed patients to take their first dose of new medication on the day after they were given the study medication. At the same time, all unused medication was retrieved for inventory. All medications were provided free of charge.

Table 1. Composition of the nutraceutical given in the Active group

Substances	Each tablet
Folic acid	100 mcg
Monascus purpureus titled 3 % in K monacolin	3.3 mg
Cynara scolymus titled 7 % in chlorogenic acid	50 mg
Thea sinensis L. titled 40 % in polyphenols and 15 % in catechins	40 mg
Oryza sativa L.	20 mg
Brassica campestris L. (Oleifera DC) titled 45 % in β-sitosterol	15 mg
Coenzyme Q10	10 mg
Resveratrol	1 mg

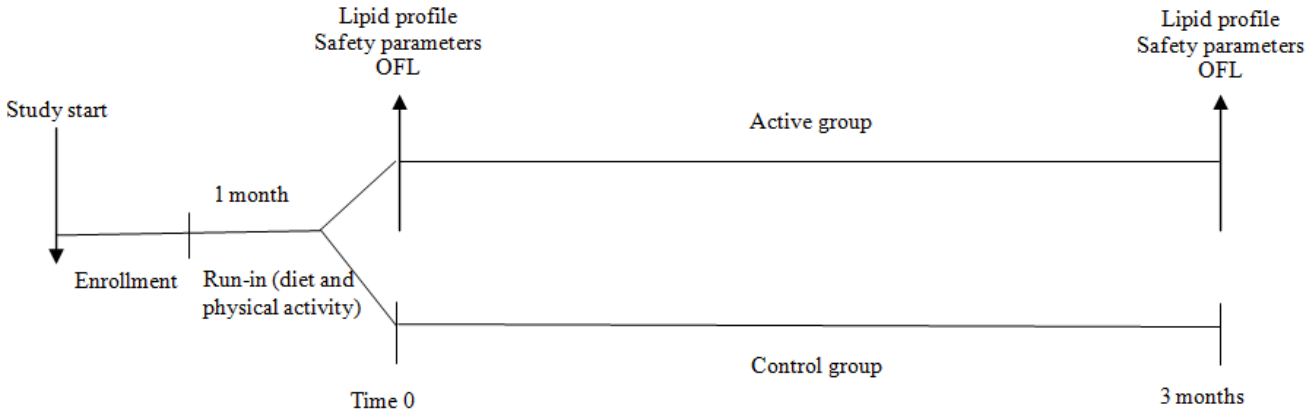

Figure 1. Study design (OFL: Oral Fat Load)

2.4. Diet and Exercise

After the enrolment, all patients entered a one month run-in period were they followed a controlled-energy diet (near 600 Kcal daily deficit) based on American Heart Association (AHA) recommendations [14] that included 50% of calories from carbohydrates, 30% from fat (6 % saturated), and 20 % from proteins, with a maximum cholesterol content of 300 mg/day and 35 g/day of fiber. Patients were not treated with vitamins or mineral preparations during the study.

Standard diet advice was given by a dietitian and/or specialist doctor and was maintained for all the study period. Dietitian and/or specialist doctor periodically provided instruction on dietary intake including how many times a week consume meat, pasta, vegetables, and their respective quantities, recording procedures as part of a behaviour modification program and then later used the subject's food diaries for counselling. Standard diet advice were the same for both group to avoid interferences with the study results.

Individuals were also encouraged to increase their physical activity by walking briskly for 20 to 30 min, 3 to 5 times per week, or by cycle. Changes in physical activity were not assessed.

2.5. Assessments

Before starting the study, all patients underwent an initial screening assessment that included a medical history, physical examination, vital signs, and a 12-lead electrocardiogram, measurements of height and body weight, calculation of BMI, abdominal circumference (Abd. Cir.), waist circumference (Waist Cir.), hip circumference (Hip Cir.). We evaluated also at the baseline, and after 3 months these parameters: fasting plasma glucose (FPG), TC, Tg, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), and high sensitivity C-reactive protein (Hs-CRP), transaminases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], and creatine phosphokinase (CPK). Furthermore, at the baseline and at the end of the study all patients underwent an oral fat load (OFL) (Figure 1).

In order to evaluate the tolerability assessments, all adverse events were recorded, and hepatic and renal function were evaluated. All plasmatic parameters were determined after a 12-h overnight fast. Venous blood samples were taken for all patients between 08.00 and 09.00. We used plasma obtained by addition of Na_2-EDTA, 1 mg/ml, and centrifuged at 3000 g for 15 min at 4°C. Immediately after centrifugation, the plasma samples were frozen and stored at -80°C for no more than 3 months. All measurements were performed in a central laboratory.

Body mass index was calculated as weight in kilograms divided by the square of height in meters. Plasma glucose was assayed by glucose-oxidase method (GOD/PAP, Roche Diagnostics, Mannheim, Germany) with intra- and interassay coefficient of variation (CV) of < 2 % [15].

Total cholesterol and Tg levels were determined using fully enzymatic techniques [16,17] on a clinical chemistry analyzer (HITACHI 737; Hitachi, Tokyo, Japan); intra- and interassay CV were 1.0 and 2.1 for TC measurement, and 0.9 and 2.4 for Tg measurement, respectively. High-density lipoprotein-cholesterol level was measured after precipitation of plasma apo B-containing lipoproteins with phosphotungstic acid [18] intra- and interassay CV were 1.0 and 1.9, respectively; LDL-C level was calculated by the Friedewald formula [19].

High-sensitivity C-reactive protein was measured with use of latex-enhanced immunonephelometric assays on a BN II analyser (Dade Behring, Newark, Delaware, USA). The intra- and interassay CsV were 5.7 % and 1.3 %, respectively [20].

Transaminases and CPK were evaluated in central laboratory according to standard methods.

2.6. Safety Measurements

Liver and muscle function were evaluated by measurement of transaminases (AST, ALT), and CPK, and all adverse events were recorded.

2.7. Oral Fat Load Test

The fat load was given between 08.00 and 09.00 h after a 12-h fast and a 3-days abstention from alcohol intake. Participants were also asked to refrain from heavy exercise during the preceding days. The test drink consisted of 350 ml whipping cream (35 % fat), two tablespoons of chocolate-flavored syrup, one tablespoon of granulated sugar, and one tablespoon of instant nonfat dry milk. This volume contained 1,147 Kcal, of which 12 % were from protein, 20 % from carbohydrate, and 68 % from fat (36 % polyunsaturated fatty acids, 17 % monounsaturated fatty acids, and 15 % saturated fatty acids).

It had 472 mg cholesterol and a polyunsaturated/saturated ratio of 0.06. A weight-adjusted meal (1 g fat per Kg body weight) was served to approximately 400 ml of the mixture. The fat load mixture was consumed within 10 min. After the ingestion of the fat load, subjects were only allowed to drink water during the following 12 h. Blood samples was drawn before and 3, 6, 9, and 12 h after the fat load. Patients were required to sit in the hospital hall: only standard walk in the hospital perimeter was accepted.

2.8. Statistical Analysis

An intention-to-treat analysis was conducted in patients who had received ≥ 1 dose of study medication and had a subsequent efficacy observation. Patients were included in the tolerability analysis if they had received ≥ 1 dose of trial medication and had undergone a subsequent tolerability observation. Considering as clinically significant a difference of at least the 10 % compared to the baseline and an alpha error of 0.05, the actual sample size was adequate to obtain a power higher than 0.80 for all measured variable. Non-parametric tests were also employed in the statistical analysis of the data because some data were not normally distributed (Kolmogorov-Smirnov test). Intervention effects were adjusted for additional potential confounders (sex, smoking status) using analysis of covariance (ANCOVA). The statistical significance of the independent effects of treatments on the other variables was determined using ANCOVA taking the baseline level of each parameter as a covariate. The incremental area under the curve (AUC) was calculated as the increased response above baseline minus any drop below baseline, based on the trapezoid rule. Statistical analysis of data was performed using the Statistical Package for Social Sciences software version 14.0 (SPSS Inc., Chicago, Illinois, USA). Data are presented as mean ± standard deviation (SD). For all statistical analyses, $p < 0.05$ was considered statistically significant [21].

3. Results

3.1. General Characteristics of Patients

A total of 63 patients were enrolled in the study. Of these, 60 completed the study; 3 patients in control group did not complete the trial. The reasons for premature withdrawal included lost to follow-up (2 patients), withdrawn of informed consent (1 patient). The characteristics of the study population at study entry are shown in Table 2, where also concomitant medications are listed.

Table 2. General patient characteristics and concomitant therapy at baseline in the study

	Patient characteristics
N	60
Sex (M/F), n (%)	33/27 (55.0/45.0)
Age (years)	51.8 ± 8.6
Sm. st. (M/F), n (%)	11/8 (18.3/13.3)
Height (m)	1.67 ± 0.08
Concomitant disease, n (%)	16 (27.0)
Hypertension	16 (27.0)
Concurrent medications, n (%)	13 (22.0)
ACE-I	6 (37.5)
ARBs	7 (43.8)
Calcium-antagonists	10 (62.5)
β-blockers	2 (12.5)
Diuretics	3 (18.8)
α-blockers	2 (12.5)

Data are expressed as means ± SD or n and %.
Sm. st.: Smoking status; ACE-I: angiotensin-converting enzyme-inhibitors; ARBs: angiotensin receptor blockers.

Table 3. Patient parameters in Control and Active group

	Control group		Active group	
	Baseline	3 months	Baseline	3 months
N	30	30	30	30
sex (M/F)	17/13	17/13	16/14	16/14
Age (years)	50.9 ± 7.8	-	52.7 ± 9.4	-
Sm. st. (M/F)	5/3	5/3	6/5	6/5
Weight (Kg)	78.7 ± 8.2	77.6 ± 8.0	76.1 ± 7.9	75.5 ± 7.3
Height (m)	1.68 ± 0.09	1.68 ± 0.09	1.66 ± 0.07	1.66 ± 0.07
BMI (Kg/m^2)	27.9 ± 1.3	27.5 ± 1.0	27.6 ± 1.1	27.4 ± 0.9
WC (cm)	83.5 ± 6.6	82.9 ± 6.1	83.1 ± 6.2	82.7 ± 6.0
HC (cm)	109.7 ± 9.8	109.1 ± 9.2	108.9 ± 9.0	108.4 ± 8.8
AC (cm)	96.2 ± 7.9	95.6 ± 7.3	95.8 ± 7.5	95.5 ± 7.2
FPG (mg/dl)	91.5 ± 8.2	90.8 ± 8.1	90.4 ± 7.9	89.8 ± 7.6
TC (mg/dl)	219.6 ± 15.7	215.2 ± 15.0	217.6 ± 14.8	191.4 ± 8.9*^
LDL-C (mg/dl)	148.8 ± 10.2	145.5 ± 9.1	146.7 ± 9.4	124.9 ± 6.1*^
HDL-C (mg/dl)	45.6 ± 6.9	45.4 ± 6.8	46.3 ± 7.0	46.0 ± 6.9
Tg (mg/dl)	126.2 ± 20.3	121.6 ± 15.4	123.1 ± 19.5	102.4 ± 11.3*^
AST (UI/l)	26.2 ± 8.1	27.1 ± 9.4	25.1 ± 7.6	26.9 ± 8.5
ALT (UI/l)	31.5 ± 12.2	32.6 ± 13.1	30.7 ± 11.8	30.2 ± 11.3
CPK (UI/l)	123.2 ± 33.6	117.9 ± 30.2	127.6 ± 32.8	129.8 ± 34.1
Hs-CRP (mg/l)	1.2 ± 0.6	1.1 ± 0.5	1.3 ± 0.8	0.9 ± 0.4*^

Data are expressed as *means* ± *SD*
*p < 0.05 vs Baseline; ^p < 0.05 vs Control group
Sm. st.: Smoking status; BMI: body mass index; WC: waist circumference; HC: hip circumference; AC: abdominal circumference; FPG: fasting plasma glucose; TC: total cholesterol; LDL-C: low-density lipoprotein-cholesterol; HDL-C: high-density lipoprotein-cholesterol; Tg: triglycerides; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CPK: creatinine phosphokinase; Hs-CRP: high-sensitivity C-reactive protein.

3.2. Effect of Nutraceutical Mixture on Anthropometric Parameters, Plasma Biochemistry and Inflammatory Markers under Basal Conditions

No significant variations of BMI or circumferences were recorded during the study (Table 3).

No changes in FPG were observed (Table 2), nor compared to baseline, nor comparing the two treatments (Table 3).

Neither of treatments influenced HDL-C value; instead nutraceutical combination gave a reduction of TC, Tg, and LDL-C, both compared to baseline ($p < 0.05$), and compared to placebo ($p < 0.05$).

No variations of hepatic or renal function were reported (Table 3).

High sensitivity C-reactive protein decreased in the Active group both compared to baseline and to placebo ($p < 0.05$ for both) (Table 3).

3.3. Effect of Nutraceutical Mixture on Lipid Profile under Post-prandial Conditions

For a full description of the variation of the values during the OFL, please see Figure 2, and for the area under the curve values please see Table 4.

During the OFL performed at the end of the study, TC, and LDL-C recorded in the group treated with the nutraceutical combination were lower compared to the values recorded during the baseline OFL ($p < 0.05$), and also compared to values recorded in placebo group ($p< 0.01$) at every time of OFL.

Regarding Tg, the value recorded during the OFL at the end of the study was lower at 6 hours compared to baseline OFL ($p < 0.05$ vs baseline), and to placebo ($p < 0.05$).

High-density lipoprotein-cholesterol trend did not change during OFL, there was a decrease of HDL after 6 hours ($p < 0.05$ vs time 0) since the meal ingestion, both at baseline and at the end of the study, in both group.

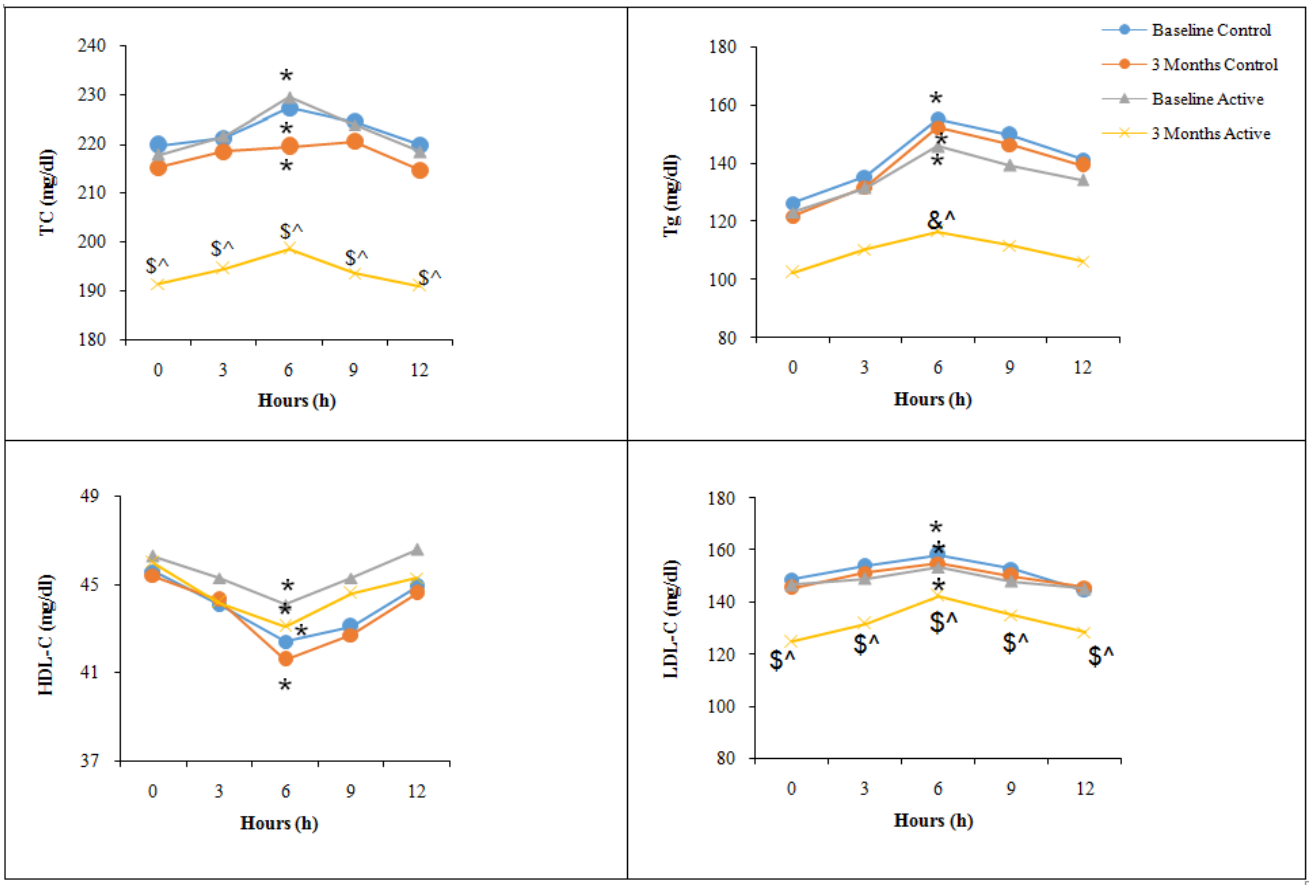

Figure 2. Lipid profile variations during OFL in Control and Active group at baseline and at the study end (*$p < 0.05$ vs time 0; ^$p < 0.05$ vs Baseline; &$p < 0.05$ vs Control group; $$p < 0.01$ vs Control group. TC: total cholesterol; LDL-C: low-density lipoprotein-cholesterol; HDL-C: high-density lipoprotein-cholesterol; Tg: triglycerides.

Table 4. AUC (x 12 h) values at baseline and after 3 months in both groups

	Control group		Active group	
	Baseline	3 months	Baseline	3 months
TC (mg/dl)	126,435.41 ± 29,539.64	121,174.38 ± 25,126.32	121,148.56 ± 24,637.12	107,761.78 ± 20,194.18*^
LDL-C (mg/dl)	81,120.38 ± 5,125.69	78,349.61 ± 4,631.48	78,632.73 ± 4,235.85	60,275.59 ± 3,038.39*^
HDL-C (mg/dl)	26,389.56 ± 5,211.23	24,892.84 ± 5,002.37	28,769.91 ± 5,952.67	27,031.46 ± 5,517.68
Tg (mg/dl)	92,158.21 ± 8,942.86	89,356.93 ± 8,023.27	90,124.79 ± 8,632.42	58,481.33 ± 5,682.71*^

Data are *means* ± *SD*; AUC: are under the curve
*$p < 0.05$ vs Baseline; ^$p < 0.05$ vs Control group
TC: total cholesterol; LDL-C: low-density lipoprotein-cholesterol; HDL-C: high-density lipoprotein-cholesterol; Tg: triglycerides.

4. Discussion

In our study, as expected, we recorded a better effect on lipid profile of the Active compound compared to placebo; in particular, we recorded a significant reduction of TC (-26.2 mg/dl, -12.0 %), Tg (-20.7 mg/dl, -16.8 %), and LDL-C (-21.8 mg/dl, -14.9 %), respectively. Moreover, there was not any significant variation of HDL-C (-0.3 mg/dl, -0.6 %). The main actor in hypocholesterolemic action is surely monacolin K contained in the compound. Monacolin K is extracted from red yeast rice and represents a nutraceutical with proven cholesterol lowering effect. Its efficacy is proportional to the concentration on monacolin K in the extract that could reach the amount of 10 mg per daily dose, even if now there are some concerns about such a high dosage [22]. The daily assumption of monacolin K could reduce LDL-C plasma levels by 15-25 % in 6-8 weeks [23]. Our results are in line with what reported by Heinz et al. [24] in a study where they randomized patients to a supplement group with red yeast rice 3.0 mg or placebo, showing a significant reduction of TC (-11.2 %), and LDL-C (-14.8 %), while they observed a slight nonsignificant reduction of Tg (-5.0 %) and no significant modification of HDL-C (+0.7 %) after 12 weeks. This seems to confirm the fact that the main actor in reducing lipid profile is monacolin K. However, also Resveratrol showed some action on lipid profile; Resveratrol treated group displayed approximately 36 % less Tg, decreased TC, VLDL, and increased HDL-C levels as compared to placebo. We have to consider, however, that in the study by Batista-Jorge [25] Resveratrol was administered at the dose of 250 mg/day vs 1 mg/day of our study, suggesting that a high dose is requested to obtain a significant hypocholesterolemic effect. Resveratrol is able to activate sirtuins enzymes. Most of the Resveratrol studies report cardioprotective effects, although there are also evidences regarding other pharmacological therapies in several chronic diseases, such as cancer, type 2 diabetes mellitus and Alzheimer's disease [25]. The presence of coenzyme Q10 in the Active compound studied in the current trial could contribute to decrease asthenia, myalgia and muscle pain, which could be related to monacolin K assumption like previously reported by our group [26].

Another result worthy of mention is the reduction of Hs-CRP (-0.4 mg/l, -30.8 %) compared to baseline, evidence of the possible anti-inflammatory action of the nutraceutical under study. This last statement is the ideal bridge for the other part of the study, regarding the OFL, a method that simulates the attack on the endothelium and the possible acute inflammatory action that lipids could give.

The results obtained with the OFL are comparable to those obtained in our other studies [27,28,29], in which it is demonstrated in particular how the load of lipids leads to a reduction in HDL-C, evidence of an endothelial suffering that the load can give. The Active compound seems to offer protection from the endothelial damage.

Of course, our study has some limitations, as the short duration of the trial; moreover, we evaluated only some inflammatory markers, focusing our attention on a few of them. Finally, we did not observe if the effects of nutraceutical agents were reversible after the interruption of the study.

5. Conclusion

A nutraceutical containing monacolin K, Cynara scolymus, Thea sinensis L., Oryza sativa L., Brassica campestris L., folic acid, coenzyme Q10, and Resveratrol could be helpful in improving lipid profile in hypercholesterolemic patients, both at fasting and in post-prandial phase.

Conflict of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

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