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Effect of Esterol Tens® Compared to Placebo in Hyperolysterolemic Hypertensive Patients after an Oral Fat Load

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Abstract The aim of this study was to compare the response to an oral fat load after three months of adsumption of Esterol Tens® compared to placebo in hypercholesterolemic and hypertensive patients. We enrolled 65 patients and randomized them to take Esterol Tens®, 1 tablet once a day, or placebo for 3 months. We evaluated blood pressure, fasting plasma glucose (FPG), lipid profile, oxidized-low density lipoprotein (Ox-LDL), high sensitivity C-reactive protein (Hs-CRP), soluble vascular cell adhesion protein-1 (sVCAM-1); soluble intercellular adhesion protein-1 (sICAM-1), soluble E-selectin (sE-selectin), myeloperoxidase (MPO). All parameters were assessed at baseline, and after 3 months. In the same visits, an oral fat load was performed. Blood pressure was reduced with nutraceutical both compared to baseline, and placebo. Total cholester, triglycerides, LDL-cholesterol, and Ox-LDL decreased only with the nutraceutical. We observed a decrease of Hs-CRP, and MPO, and an increase of nitrites/nitrates after 3 months both compared to baseline and placebo with the nutraceutical treatment. Values recorded during OFL were lower in the group treated with nutraceutical compared to placebo. The nutraceutical combination improved blood pressure and lipid profile and attenuated the answer to the OFL of lipid profile and, in the same way, improved some inflammatory markers compared to placebo.

Keywords: *dyslipidemia, oral fat load, nutraceutical*

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1. Introduction

The international guidelines for the prevention of cardiovascular disease suggest to dose the parameters of the fasting lipid profile to stratify the individual risk of meeting a cardiovascular event in the following years [1]. However, recent evidence suggests that post-prandial hyperlipidemia is an important and independent risk factor for cardiovascular event [2] and that we live most of our life in a post-prandial state [3]. The most appropriate method to experimentally reproduce the post-prandial lipid condition appears to be the administration of a standardized oral fat load (OFL) to fasting patients [4]. 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 inflammatory parameters, circulating markers of endothelial dysfunction, and prothrombotic variables [5,6]. Our group already evaluated some types of patients with OFL, determining some parameters and cardio-metabolic risk factors [7,8,9,10].

Recently a nutraceutical containing N-acetilcistein (300 mg), monacolin K (10 mg), hawthorn (200 mg), lactium (100 mg), quercetin (50 mg), resveratrol (50 mg), coenzyme Q10 (20 mg), vitamin K (75 μg), vitamin D (5 μg), folic acid (200 μg), and selenium (83 μg) has been marketed with the name of Esterol Tens®.

Monacolins are a family of substances obtained by fermenting the yeast, Monascus purpureus, over rice. Monacolins act as reversible inhibitors of the HMG-CoA reductase. Among Monacolins, Monacolin K, also known

as mevinolin or lovastatin, and Monacolin KA are normally the most prominent Monacolins found in fermented red rice extracts [11]. Moreover, some preliminary data suggested that hawthorn's extracts are able to protect from hypercholesterolemia-induced oxidative stress and hepatic injuries in rats [12].

The aim of this study will be to compare the response to an OFL after three months of adsumption of Esterol TENS compared to placebo in hypercholesterolemic and hypertensive patients.

2. Material and Methods

2.1. Study Design

This 3-months, single-center, randomised, placebo controlled study was conducted at the Department of Internal Medicine and Therapeutics, University of Pavia (Pavia, Italy). The study protocol was approved by local institutional review board and was conducted in accordance with the 1994 Declaration of Helsinki, and its amendments and the Code of Good Clinical Practice [9]. All patients provided written informed consent to participate in this study after a full explanation of the study had been given.

2.2. Patients

Caucasian patients aged ≥18 of either sex were eligible for inclusion in the study if they had hypercholesterolemia according to National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) criteria [13] (cholesterolemia between 200-240 mg/dl), and with triglyceridemia < 400 mg/dl. They were overweight (body mass index [BMI], 25.0-29.9 kg/m^2) and with high-normal BP values (SBP= 130-139 mmHg and/or DBP= 85-89 mmHg) or with grade 1 hypertension (SBP= 140-159 mmHg and/or DBP= 90-99 mmHg) according to 2018 ESC/ESH Guidelines [14]. Furthermore, patients had normal thyroid function.

We also excluded patients with impaired hepatic function (defined as plasma aminotransferase and/or gamma-glutamyltransferase 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), or severe anemia. Patients with serious cardiovascular disease (CVD) (eg, New York Heart Association class I-IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months before study enrolment also were excluded. Women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions were also excluded.

Suitable patients, identified from review of case notes and/or computerized clinic registers, were contacted by the investigators in person or by telephone.

2.3. Treatments

Patients fulfilling the inclusion criteria, were randomised to take Esterol Tens®, 1 tablet once a day, or placebo for 3 months. Esterol Tens is a nutraceutical containing N-acetilcistein (300 mg), monacolin K (10 mg), hawthorn (200 mg), lactium (100 mg), quercetin (50 mg), resveratrol (50 mg), coenzyme Q10 (20 mg), vitamin K (75 mcg), vitamin D (5 mcg), folic acid (200 mcg), and selenium (83 mcg). Both Esterol Tens® and placebo were supplied as identical, opaque, white tablets in coded bottles to ensure the blind status of the study. Randomisation 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 sachets returned at the time of specified clinic visits. At baseline, we weighed participants and gave them a box containing a supply of the 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.

2.4. Assessments

Before starting the study, all patients underwent an initial screening assessment that included a medical history, physical examination, vital signs (blood pressure and heart rate), a 12-lead electrocardiogram, measurements of height and body weight, calculation of body mass index (BMI), waist circumference (WC), hip circumference (HC), abdominal circumference (AC), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), fasting plasma glucose (FPG), total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), triglycerides (Tg), oxidized-low density lipoprotein (Ox-LDL), high sensitivity C-reactive protein (Hs-CRP), soluble vascular cell adhesion protein-1 (sVCAM-1); soluble intercellular adhesion protein-1 (sICAM-1), soluble E-selectin (sE-selectin), myeloperoxidase (MPO). Anthropometric and metabolic parameters were assessed at baseline, and after 3 months.

All plasmatic variables were determined after a 12-hour overnight fast. Venous blood samples were drawn by a research nurse for all patients between 8:00 AM and 9:00 AM. We used plasma obtained by addition of Na_2-EDTA, 1 mg/mL, and centrifuged at 3000*g* for 15 minutes at 4°C. Immediately after centrifugation, the plasma samples were frozen and stored at -80°C for ≤ 3 months. All measurements were performed in a central laboratory.

Body mass index was calculated by the investigators as weight in kilograms divided by the square of height in meters. Waist circumference was measured midway between the lateral lower rib margin and the iliac crest and its reduction was determined with a Gulick anthropometric spring-loaded tape measure (Model 5829, Bell Medical Services, Neptune, NJ, USA).

Clinic BP was obtained in sitting position by standard mercury sphygmomanometer, 24 h after treatment intake. Three measurements, taken at 2-min intervals after 10 min of sitting, were averaged and used as the clinic BP reference value.

Laboratory technicians drew blood samples and the biologist responsible for the laboratory performed the assays.

Ox-LDL levels were assessed by sandwich enzyme-linked immunosorbent assay (Mercodia, Uppsala, Sweden) [15]. Coefficients of variation for intra-assay and interassay were respectively 2.1% and 8.4%.

For a description of how various parameters were recorded, please see our previous studies [16,17,18].

2.5. Statistical Analysis

An intention-to-treat (ITT) 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 after randomisation and had undergone a subsequent tolerability observation. Comparisons within and between groups were assessed by a two-way ANOVA for repeated measurements. A 1-sample *t* test was used to compare values obtained before and after treatment administration; 2-sample *t* tests were used for between-group comparisons. Statistical analysis of data was performed using the Statistical Package for Social Sciences software version 11.0 (SPSS Inc., Chicago, Illinois, USA). Data are presented as mean (SD) [19]. For all statistical analyses, $p < 0.05$ was considered statistically significant.

3. Results

3.1. Study Sample

A total of 65 patients were enrolled in the study; 31 were allocated in placebo group and 34 in the nutraceutical group. Of these, 64 completed the study, 1 patient in placebo group was lost to follow-up. The characteristics of the patient population at study entry are shown in Table 1.

3.2. Anthropometric Parameters

No variations of body weight, BMI or circumferences were recorded in neither groups (Table 1).

3.3. Hemodynamic Parameters

Systolic blood pressure and DPB were reduced in the group treated with nutraceutical ($p < 0.05$ both compared to baseline, and placebo). Heart rate, instead, was not changed by neither treatments (Table 1).

Table 1. Baseline and 3 months of patients during placebo or Esterol TENS treatment

Parameters	Placebo		Esterol TENS	
	Baseline	3 months	Baseline	3 months
N of pts (65)				
N	31	30	34	34
M/F	15/16	14/16	18/16	18/18
Smoking status (M/F)	3/5	3/5	2/4	2/4
Hypercholesterolemia duration (months)	9.7 ± 4.6	-	10.1 ± 4.9	-
Hypertension duration (months)	11.3 ± 5.9	-	11.6 ± 5.5	-
Weight (Kg)	78.1 ± 6.9	77.9 ± 6.7	79.6 ± 7.2	79.3 ± 7.0
Height (m)	1.67 ± 0.09	-	1.66 ± 0.08	-
BMI (Kg/m^2)	28.0 ± 2.1	27.9 ± 1.9	28.9 ± 2.5	28.8 ± 2.3
WC (cm)	88.5 ± 2.5	88.3 ± 2.4	89.2 ± 2.7	88.9 ± 2.5
HC (cm)	101.7 ± 4.5	100.8 ± 3.6	102.5 ± 5.1	101.6 ± 4.3
AC (cm)	93.8 ± 3.1	93.4 ± 2.9	94.3 ± 3.7	93.9 ± 3.0
SBP (mmHg)	141.2 ± 7.4	140.3 ± 7.1	142.1 ± 7.9	136.4 ± 6.1*^
DBP (mmHg)	92.6 ± 5.8	91.8 ± 5.2	93.2 ± 5.7	88.7 ± 4.4*^
HR (bpm)	73.7 ± 7.9	72.5 ± 7.2	74.5 ± 8.4	71.2 ± 6.8
FPG (mg/dl)	85.9 ± 7.4	87.3 ± 7.8	86.7 ± 7.6	85.6 ± 7.2
TC (mg/dl)	223.8 ± 15.2	215.1 ± 12.8	220.5 ± 14.8	183.2 ± 9.4*^
LDL-C (mg/dl)	151.7 ± 8.1	147.1 ± 7.7	149.7 ± 7.9	114.0 ± 4.3*^
HDL-C (mg/dl)	44.7 ± 6.8	43.2 ± 6.4	43.6 ± 6.5	45.1 ± 7.2
Tg (mg/dl)	137.2 ± 13.4	124.7 ± 12.1	135.9 ± 13.0	120.4 ± 9.7*^
Ox-LDL (mU/ml)	138.3 ± 15.4	135.2 ± 15.1	140.7 ± 16.9	129.6 ± 12.6*^
Hs-CRP (mg/l)	1.5 ± 0.6	1.4 ± 0.5	1.6 ± 0.8	1.1 ± 0.4*^
sVCAM-1 (ng/ml)	424.3 ± 50.6	417.8 ± 47.4	427.1 ± 51.3	401.7 ± 43.9*
sICAM-1 (ng/ml)	151.8 ± 10.6	147.2 ± 9.6	149.6 ± 9.9	135.2 ± 8.8*
E-Selectin (ng/ml)	25.2 ± 6.4	25.9 ± 6.6	23.9 ± 5.8	22.5 ± 5.4
MPO (ng/ml)	776.5 ± 254.6	783.1 ± 257.8	771.7 ± 250.8	731.4 ± 236.9*^
Nitrites/nitrates (μmol/l)	23.2 ± 5.9	22.6 ± 5.4	22.8 ± 5.7	29.6 ± 7.4*^

Data are expressed as mean ± standard deviations

*p< 0.05 vs Baseline; ^p< 0.05 vs Placebo

M: males; F: females; BMI: body mass index; WC: waist circumference; HC: hip circumference; AC: abdominal circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; FPG: fasting plasma glucose; TC: total cholesterol; LDL-C: low density lipoprotein-cholesterol; HDL-C: high density lipoprotein-cholesterol; Tg: triglycerides; Ox-LDL: oxidized-low density lipoprotein; Hs-CRP: high sensitivity C-reactive protein; sVCAM-1: soluble vascular cell adhesion protein-1; sICAM-1: soluble intercellular adhesion protein-1; sE-selectin: soluble E-selectin; MPO: myeloperoxidase.

3.4. Glyco-metabolic Parameters

Fasting plasma glucose did not change in neither groups, while TC, Tg, LDL-C, and Ox-LDL decreased only with the nutraceutical treatment ($p < 0.05$, both compared to baseline, and to placebo) (Table 1).

3.5. Inflammatory State

We observed a decrease of Hs-CRP, and MPO after 3 months ($p < 0.05$ both compared to baseline and placebo) with the nutraceutical treatment, but not with placebo (Table 1). SVCAM-1, and sICAM-1 were reduced by the nutraceutical compared to baseline ($p < 0.05$), even if no difference with placebo were recorded. Nitrites/nitrates were increased by the nutraceutical, both compared to baseline, and to placebo ($p < 0.05$ for both).

3.6. OFL

See Figure 2, and Figure 3.

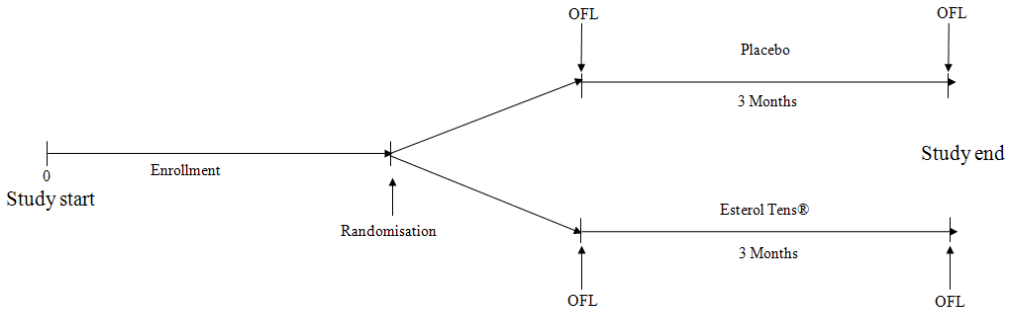

Figure 1. Study design (OFL: oral fat load)

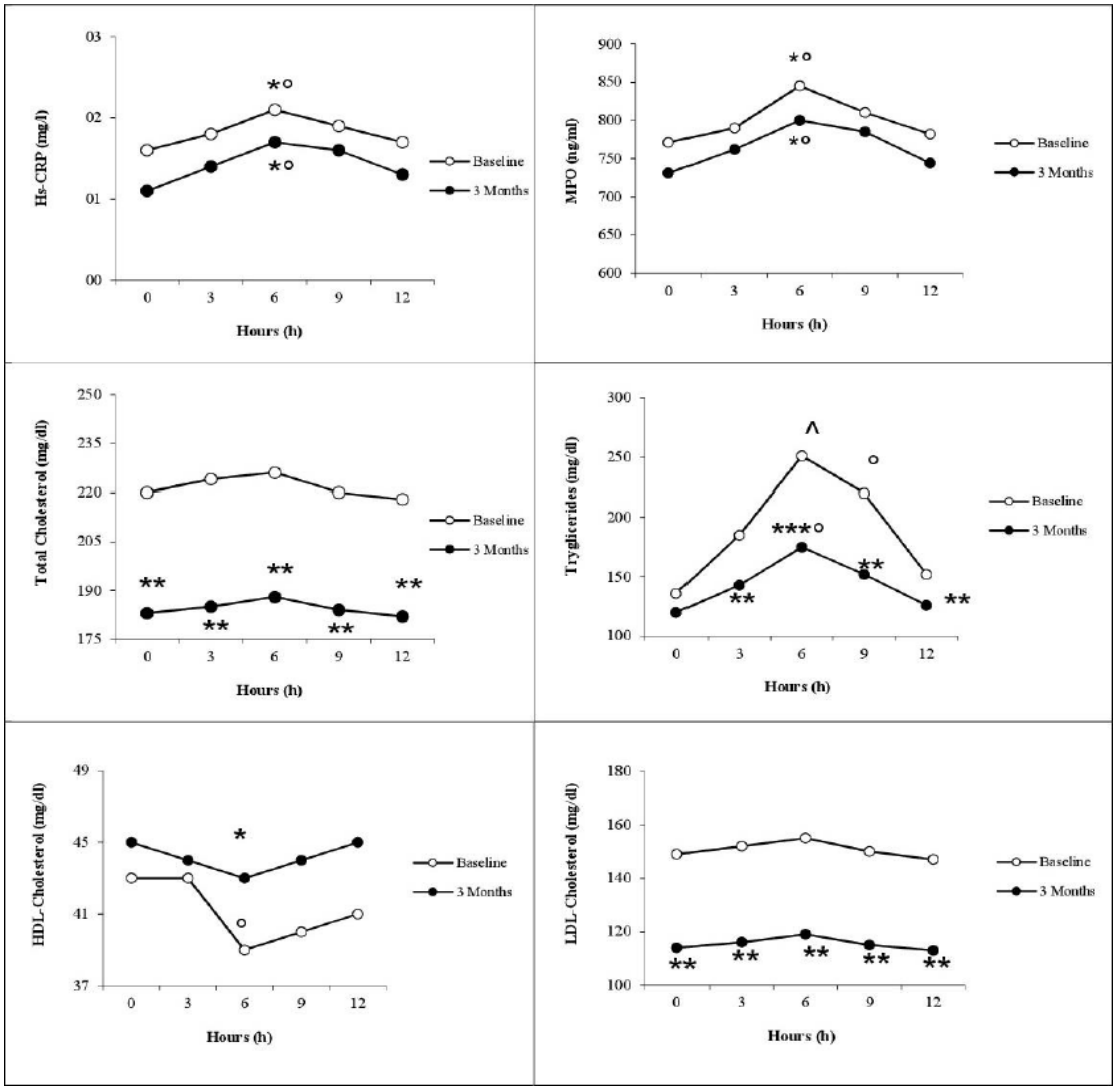

Figure 2. Parameters variations during oral fat load (OFL) in the Esterol Tens® group at baseline and at the end of the study. (*$p < 0.05$ vs Baseline OFL; **$p < 0.01$ vs Baseline OFL; ***$p < 0.001$ vs Baseline OFL; °$p < 0.05$ vs time 0; ^ $p < 0.01$ vs time 0. Hs-CRP: high sensitivity C-reactive protein; MPO: myeloperoxidase.)

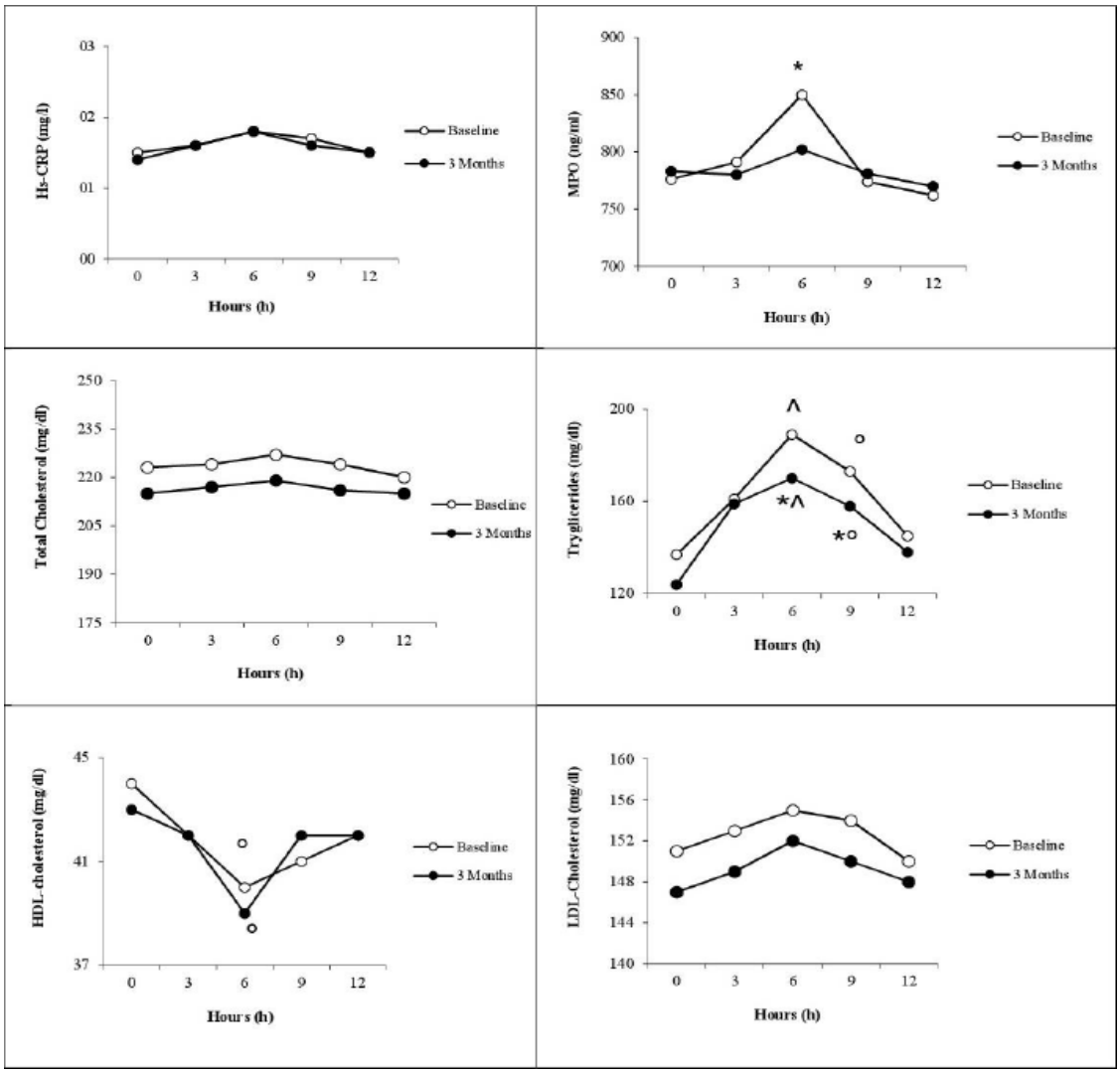

Figure 3. Parameters variations during oral fat load (OFL) in the Placebo group at baseline and at the end of the study. (*p < 0.05 vs Baseline OFL; °p < 0.05 vs time 0; ^ p < 0.01 vs time 0. Hs-CRP: high sensitivity C-reactive protein; MPO: myeloperoxidase.)

4. Discussion

Our study showed that nutraceutical combination improved lipid profile, in particular we observed a reduction of TC of about 16.9 %, a reduction of Tg of about 11.4 %, and a LDL-C reduction of about 23.8 %. This should not surprise, in fact there is large evidence that monacolin can be effective in reducing LDL cholesterol. In a previous study conducted by our group, for example, we tested the anti-hyperlipidemic effect of a combination of Berberis aristata combined with Silybum marianum, and Monacolins K and KA, obtaining a LDL-C reduction of about 31% [17]. In previous studies where we tested a nutraceutical combination containing Berberis aristata combined with Silybum marianum, we reached a LDL reduction of about 24% [20,21], instead when we tested a nutraceutical combination including Monacolin K, the reduction was of about 22% [22].

Regarding BP, we have already showed in a previous study that 6 months supplementation with psyllium is associated with a significant decrease of both SBP (-5.2 ± 1.3 mmHg; p < 0.001), and DBP (-2.2 ± 0.8 mmHg; p < 0.001) compared to guar treatment associated with a similar decrease of SBP (–5.3 ± 1.4 mmHg; p < 0.001), but not of DBP (-1.8 ± 0.4 mmHg; p not significant) [23]. In the current study we observed a decrease of both SBP, and DBP similar to the one induced by psyllium (-5.7 ± 1.1 mmHg, and -4.5 ± 0.8 mmHg, respectively).

Regarding OFL, we have already conducted several studies about the effects of an OFL on vascular remodelling markers and inflammatory parameters both in healthy [9,24] and in diabetic patients [25] showing that OFL induces a complex and massive systemic inflammatory response that includes IL-6, TNF-α, Hs-CRP, and cell adhesion molecules, even before Tg significantly rises. This was observed also in the current study, Tg started to significantly increase after 6 hours, while both s-ICAM-1, sVCAM-1, and sE-selectin started increasing after 3 hours from time 0. It has already been reported that sICAM-1 and sVCAM-1 are elevated in diabetic subjects and are rather related to hyperglycemia than to hyperinsulinemia, or insulin-resistance, while sE-selectin concentrations are related to hyperglycemia, hyperinsulinemia and insulin-resistance in patients with type 2 diabetes mellitus [26]. Hs-CRP has been shown to independently predict myocardial infarction, stroke and peripheral artery disease [27]. We observed a significant decrease of all inflammatory parameters peaks after the administration of the second OFL compared to the OFL administered at baseline in

patients with nutraceutical. This effect was not observed with placebo.

5. Conclusion

The nutraceutical combination improved SBP and DBP and lipid profile and attenuated the answer to the OFL of lipid profile and, in the same way, improved some inflammatory markers compared to placebo in dyslipidemic, hypertensive patients.

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