EXPERT OPINION

Effects of berberine on lipid profile in subjects with low cardiovascular risk

Giuseppe Derosa†, Angela D'Angelo, Aldo Bonaventura, Lucio Bianchi, Davide Romano & Pamela Maffioli

University of Pavia, Department of Internal Medicine and Therapeutics, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy

Objective: To evaluate the efficacy as antihypercholesterolemic agent of berberine in patients with low cardiovascular risk.

Research design and methods: 144 Caucasian subjects were enrolled. After a 6-month run-in period following diet and practicing physical activity, patients were randomized to take placebo or berberine 500 mg twice a day, for 3 months, in a double-blind, placebo-controlled design. Berberine and placebo were then interrupted for 2 months (washout period), and all patients continued with only diet and physical activity. At the end of the washout period, patients restarted berberine or placebo twice a day for further 3 months. Anthropometric and metabolic parameters were assessed during the run-in period, at randomization, before and after the washout period.

Results: A decrease of body weight and BMI was observed after the run-in period. Berberine reduced total cholesterol, triglycerides and LDL cholesterol and increased HDL cholesterol after 3 months from randomization and compared with placebo. After the washout period, lipid profile worsened; afterward, when berberine was reintroduced, lipid profile improved again both compared with the washout period, and with placebo.

Conclusions: Berberine is effective and safe to mildly improve lipid profile in subjects with low risk for cardiovascular disease.

Keywords: berberine, cardiovascular risk, diet, lipid profile, physical activity

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1. Introduction

Atherosclerosis is by far the single most important pathological process in the development of cardiovascular diseases, which are the most common causes of morbidity and mortality in developed nations [1]. Hypercholesterolemia is a well-known risk factor for coronary artery disease, cerebrovascular disease and peripheral artery disease [2]. It has been demonstrated that hypercholesterolemia plays an important role in the developing of atherosclerosis, and that a 1 mmol/l decrease in low-density lipoprotein-cholesterol (LDL-C) is associated with a 20% risk reduction of cardiovascular complications (myocardial infarction, stroke, peripheral obstructive arterial disease) both before the first clinical event (primary prevention) and the following ones (secondary prevention) [3].

The treatment of hypercholesterolemia with a specific drug is highly cost-effective when treating patients in secondary prevention [4], while in primary prevention lifestyle change and dietary habits appear to be more cost-effective than any pharmacological treatment [5].

During the past decade, nutritionists have focused their knowledge on consensus guidelines [6] aimed at reducing dietary saturated fatty acids, cholesterol and excess body weight. However, recent researchers are looking at other ways in which diet

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may influence the progression of cardiovascular disease, including lipoprotein oxidation, thrombosis progression, cardiac arrhythmia and medication interaction [7].

Some areas of investigation include the role of various fatty acids and supplements, in the form of vitamins, minerals, herbs and functional foods, as well as traditional foods and diets from other parts of the world [8,9]. Some of the new and relevant nutritional approaches include: specific fatty acids (omega 3, monounsaturated and trans fatty acids) [10-12], dietary supplements (herbs [13], anti-oxidants, vitamins C and E, coenzyme Q10 [14], B vitamins and homocysteine, L-arginine [15-19], Chinese red yeast rice [20,21], octacosanols, garlic, soy, flax seed and dietary fiber), food and drink (tea, nuts, plant-sterol and stanol ester-containing spreads, alcohol and grapefruit juice) and the Mediterranean diet [22,23]. Focusing the attention on one of these compounds, berberine is a plant quaternary ammonium salt from the group of isoquinoline alkaloid (2,3-methylenedioxy-9,10-dimethoxyprotoberberine chloride; $C_{20}H_{18}$ $Cl^{-}NO_4^{+}$) with a molar mass of 371.81422 g/mol. It is highly concentrated in the roots, rhizomes and stem bark of various plants including *Coptis chiensis* (Huanglian), *Rhizoma coptidis, Hydrastis canadensis* (goldenseal), *Berberis aquifolium* (Oregon grape), *Berberis vulgaris* (barberry), *Berberis aristata* (tree turmeric), *Tinospora cordifolia*, *Copthidis rhizome, Arcangelisia flava* and *Cortex rhellodendri* [24]. A lot of studies have been conducted on berberine in Chinese population [25], but little is known about berberine effects in European population. In this context, the authors planned to carry out a randomized study to evaluate the efficacy and safety as an antihypercholesterolemic agent of berberine in a sample of Caucasian patients with low cardiovascular risk.

2. Materials and methods

2.1 Study design

This 14-month, multicenter, double-blind, randomized, placebo-controlled, clinical trial was conducted at the Department of Internal Medicine and Therapeutics, University of Pavia (Pavia, Italy).

The study protocol was approved at each site by institutional review boards and was conducted in accordance with the 1994 Declaration of Helsinki [26] and its amendments and the Code of Good Clinical Practice. All patients provided written informed consent to participate in this study after a full explanation of the study.

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 [2] (cholesterolemia between 200 and 240 mg/dl), and with triglyceridemia < 400 mg/dl. They were normoweight or overweight (body mass index (BMI) 24.7 – 28.9 kg/m^2) [27], and also normotensive subjects according to the World Health Organization criteria (systolic blood pressure (SBP) < 140 mm Hg and diastolic blood pressure (DBP) < 90 mm Hg) [28]. Furthermore, they were non-smokers, with normal thyroid function; none of the selected subjects were taking diuretics or β-blockers.

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 impaired hepatic function (defined as plasma aminotransferase and/or gamma-glutamyl 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 (included diabetes mellitus), 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, antidepressants, antiserotoninergics, phenothiazines, barbiturates, oral corticosteroids and antipsychotics. Women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions were also excluded.

2.3 Diet and physical activity

At baseline all patients underwent a 6-month run-in period during which they followed an adequate diet and practiced physical activity. The controlled-energy diet (~ 600 kcal daily deficit) was based on NCEP-ATP III recommendations [2], that contained 50% of calories from carbohydrates, 30% from fat (< 7% saturated, up to 10% polyunsaturated and up to 20% monounsaturated) and 20% from proteins, with a maximum cholesterol content of 300 mg/day, and 35 g/day of fiber. Standard diet advice was given by a dietitian and/or specialist physician. Dietitians and/or specialists each 2 weeks provided instruction on dietary intake-recording procedures as part of a behavior-modification program and then from month 1 used the patients' food diaries for counseling. Individuals were also encouraged to increase their physical activity and the authors standardized the same physical aerobics exercise program by riding a stationary bicycle for 20 – 30 min, 3 to 4 times per week. During the study, behavior-modification sessions on weight-loss strategies were given to individual patients at baseline, one at 3, and 6 months in the run-in period, one at each month before the washout period and one at each month after the washout period.

2.4 Treatment

At the end of the run-in period, patients were randomized to take placebo or berberine 500 mg twice a day, at lunch and dinner, for 3 months, in a randomized, double-blind, placebo-controlled design. Both berberine and placebo were

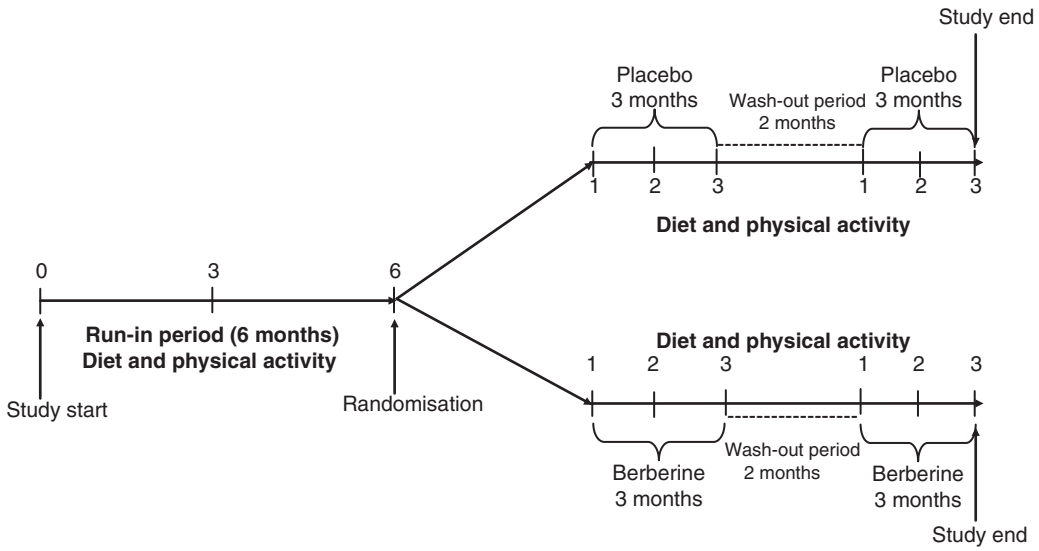

Figure 1. Study design.

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 randomization codes prepared by a statistician. After 3 months from randomization, berberine and placebo were then interrupted for 2 months (washout period), and all patients continued with only diet and physical activity. At the end of the washout period, patients restarted berberine or placebo twice a day for further 3 months (**Figure 1**). Medication compliance was assessed by counting the number of pills returned at the time of specified clinic visits. Throughout the study, patients were instructed 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.

2.5 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 BMI, abdominal circumference (Abd. Cir.), waist circumference (Waist Cir.) and hip circumference (Hip Cir.), assessment of fasting plasma glucose (FPG), total cholesterol (TC), LDL-C, high-density lipoprotein-cholesterol (HDL-C), triglycerides (Tg).

Anthropometric and metabolic parameters were assessed at 3 and 6 months during the run-in period, at 1, 2 and 3 months before the washout period and at 1, 2 and 3 months after the washout period. Changes in BMI and lipid profile were the primary efficacy factors.

All plasmatic variables were determined after a 12-h overnight fast. Venous blood samples were drawn by a research nurse for all patients between 8:00 and 9:00 AM. The authors 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 ≤ 3 months. All measurements were performed in a central laboratory.

BMI 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).

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

Plasma glucose was assayed using a glucose-oxidase method (GOD/PAP, Roche Diagnostics, Mannheim, Germany) with intra- and interassay coefficients of variation (CsV) < 2% [29]. TC and Tg levels were determined using fully enzymatic techniques [30,31] on a clinical chemistry analyzer (Hitachi 737; Hitachi, Tokyo, Japan); intra- and interassay CsV were 1.0 and 2.1% for TC measurement, and 0.9 and 2.4% for Tg measurement, respectively. HDL-C level was measured after precipitation of plasma apolipoprotein B (apoB)-containing lipoproteins with phosphotungstic acid [32]; intra- and interassay CsV were 1.0 and 1.9%, respectively. LDL-C level was calculated using the Friedewald formula [33].

2.6 Safety measurements

Treatment tolerability was assessed at each study visit using an accurate interview of patients by the investigators, and comparisons of clinical and laboratory values with baseline levels. Safety monitoring included physical examination, vital sign assessment, weight, electrocardiogram, adverse events and laboratory

Table 1. Parameter values of run-in period at baseline and after 3 and 6 months.

	Baseline	3 months	6 months
N	144	144	141
Sex (M/F)	71/73	71/73	70/71
Age (years)	53 ± 11	53 ± 11	53 ± 11
Height (m)	1.68 ± 0.5	1.68 ± 0.5	1.68 ± 0.5
Weight (kg)	75.7 ± 7.6	74.6 ± 7.2	72.3 ± 6.8*
BMI (kg/m^2)	26.8 ± 2.1	26.4 ± 2.0	25.6 ± 1.8*
Abd. Cir. (cm)	96.3 ± 3.1	96.1 ± 3.0	95.9 ± 2.9
Waist Cir. (cm)	90.8 ± 3.6	90.6 ± 3.4	90.1 ± 3.3
Hip Cir. (cm)	100.8 ± 2.4	100.6 ± 2.3	99.6 ± 2.0
FPG (mg/dl)	92 ± 8	91 ± 7	90 ± 6
TC (mg/dl)	225 ± 15	219 ± 15	216 ± 13
LDL-C (mg/dl)	164 ± 12	161 ± 11	159 ± 10
HDL-C (mg/dl)	41 ± 6	40 ± 5	40 ± 4
Tg (mg/dl)	98 ± 34	92 ± 30	85 ± 27
AST (U/L)	20 ± 8	22 ± 9	21 ± 8
ALT (U/L)	19 ± 7	20 ± 8	20 ± 9
γ-GT (U/L)	14 ± 9	16 ± 11	16 ± 11
CPK (U/L)	108 ± 32	101 ± 28	105 ± 30

Data are expressed as mean ± SD.
*$p < 0.05$ vs baseline.
Abd. Cir.: Abdominal circumference; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; CPK: Creatine phosphokinase; FPG: Fasting plasma glucose; γ-GT: Gamma-glutamyl transpeptidase; HDL-C: High-density lipoprotein-cholesterol; Hip Cir.: Hip circumference; LDL-C: Low-density lipoprotein-cholesterol; SD: Standard deviation; TC: Total cholesterol; Tg: Triglycerides; Waist Cir.: Waist circumference.

tests. Liver and muscle functions were evaluated by measurement of transaminases [aspartate aminotransferase (AST), alanine aminotransferase (ALT)] and creatine phosphokinase (CPK), and all adverse events were recorded.

2.7 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 randomization and had undergone a subsequent tolerability observation. The null hypothesis that the expected mean BMI, TC, LDL-C, HDL-C and Tg change from the end of the run-in period to the period before the washout from the berberine, and from the resumption of berberine and the study end did not differ significantly between placebo, and berberine was tested using analysis of variance (ANOVA) and analysis of covariance (ANCOVA) models [34]. Similar analyses were applied to the other variables. The statistical significance of the independent effects of treatments on the other variables was determined using ANCOVA. A one-sample *t*-test was used to compare values obtained before and after treatment administration; two-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, IL, USA). Data were presented as mean (± standard deviation (SD)). For all statistical analyses, $p < 0.05$ was considered statistically significant.

3. Results

3.1 Study sample

A total of 144 patients were enrolled in the trial. Of these, 141 completed the run-in period, and 71 (50.4%) were randomized to berberine and 70 (49.6%) to placebo. A total of 137 subjects completed the study; there were 7 patients (3 males and 4 females) who did not complete the study and the reasons for premature withdrawal included protocol violation, loss to follow-up, non-compliance: 3 patients (1 male and 2 females) in run-in period, 3 patients (1 male and 2 females) in berberine group before the washout period and 1 patient (1 male) in placebo group before the washout period. The characteristics of the patient population at study entry are shown in **Table 1**.

3.2 Anthropometric parameters

Significant weight and BMI decrease was observed after 6 months (-4.5%, respectively) during the run-in period ($p < 0.05$ compared with baseline), while no other significant changes were recorded during the run-in period (**Table 1**). No significant changes were obtained in all anthropometric parameters before and after the washout period after the introduction of berberine or placebo (**Tables 2** and **3**).

3.3 Metabolic parameters

No FPG changes were observed in all the phases of the study (**Tables 1 – 3**). No significant lipid profile change was obtained during run-in period (**Table 1**). Significant TC (-11.6%), LDL-C (-16.4%) and Tg (-21.2%) decrease was present at 3 months from randomization in berberine group ($p < 0.05$ for all), while no significant changes were obtained in placebo group. Significant HDL-C increase was present at 3 months from randomization (+9.1%) with berberine ($p < 0.05$), while no significant change was obtained in placebo group (**Tables 2** and **3**). TC and LDL-C values recorded after 3 months of berberine were lower than the ones recorded with placebo ($p < 0.05$).

Significant TC, LDL-C and Tg increase was observed after the 2 months washout period (+18.4, +23.6 and +30.3%, respectively) in berberine group ($p < 0.05$ for all), but not in placebo group, compared with the values recorded before the washout period (**Tables 2** and **3**). There was also a significant HDL-C decrease after the washout period (-8.9%) in berberine group ($p < 0.05$), while no significant change was obtained in placebo group (**Tables 2** and **3**). TC and LDL-C values recorded after the washout period with berberine were higher than the ones recorded with placebo ($p < 0.05$).

When berberine was reintroduced, significant TC and LDL-C decrease was obtained after 2 months (-12.9% for TC and -17.9% for LDL-C, $p < 0.05$ for both) and after 3 months compared with the washout period (-18.0% for

Table 2. Parameter values in berberine group before and after the washout period.

	Randomization	1 month	2 months	3 months	Washout period	1 month	2 months	3 months
N	71	70	70	68	68	68	68	68
Sex (M/F)	35/36	35/35	35/35	34/34	34/34	34/34	34/34	34/34
Age (years)	53 ± 11	53 ± 11	53 ± 11	53 ± 11	53 ± 11	53 ± 11	53 ± 11	53 ± 11
Height (m)	1.68 ± 0.5	1.68 ± 0.5	1.68 ± 0.5	1.68 ± 0.5	1.68 ± 0.5	1.68 ± 0.5	1.68 ± 0.5	1.68 ± 0.5
Weight (kg)	72.3 ± 6.8	71.6 ± 6.6	71.1 ± 6.5	70.6 ± 6.4	70.9 ± 6.5	71.2 ± 6.7	70.5 ± 6.3	70.9 ± 6.4
Abd. Cir. (cm)	25.6 ± 1.8	95.7 ± 2.8	95.4 ± 2.7	95.0 ± 2.7	95.3 ± 2.8	95.9 ± 2.9	95.2 ± 2.6	95.3 ± 2.6
Waist Cir. (cm)	95.8 ± 2.7	89.8 ± 3.2	89.3 ± 3.1	89.3 ± 3.0	89.4 ± 3.0	89.6 ± 3.2	89.5 ± 3.1	89.9 ± 3.2
Hip Cir. (cm)	90.2 ± 3.4	99.4 ± 1.9	98.9 ± 1.8	98.7 ± 1.7	98.8 ± 1.8	99.2 ± 2.0	98.7 ± 2.0	98.9 ± 2.1
BMI (kg/m^2)	99.4 ± 2.1	25.4 ± 1.7	25.2 ± 1.6	25.0 ± 1.5	25.1 ± 1.6	25.2 ± 1.7	24.9 ± 1.5	25.1 ± 1.6
FPG (mg/dl)	90 ± 6	91 ± 8	92 ± 8	90 ± 7	92 ± 8	89 ± 6	88 ± 6	89 ± 7
TC (mg/dl)	214 ± 13	205 ± 12	201 ± 11	191 ± 9*$^{\#}$	234 ± 17$^{\ddagger\#}$	220 ± 13	204 ± 11§	192 ± 10$^{\P\#}$
LDL-C (mg/dl)	157 ± 10	146 ± 8	143 ± 8	133 ± 7*$^{\#}$	174 ± 15$^{\ddagger\#}$	160 ± 12	143 ± 10§	134 ± 8$^{\P\#}$
HDL-C (mg/dl)	40 ± 4	43 ± 6	44 ± 7	45 ± 8*	41 ± 5‡	42 ± 6	44 ± 7	46 ± 8$^{\S\#}$
Tg (mg/dl)	85 ± 27	79 ± 26	72 ± 24	67 ± 21*	96 ± 32‡	90 ± 28	83 ± 25	72 ± 21$^{\S\#}$
AST (U/L)	21 ± 8	23 ± 10	23 ± 9	24 ± 11	22 ± 9	22 ± 9	24 ± 11	24 ± 12
ALT (U/L)	20 ± 9	21 ± 9	22 ± 10	22 ± 10	21 ± 9	20 ± 8	20 ± 7	21 ± 8
γ-GT (U/L)	16 ± 11	18 ± 13	19 ± 14	18 ± 13	15 ± 10	16 ± 12	18 ± 15	17 ± 15
CPK (U/L)	105 ± 30	101 ± 27	99 ± 26	96 ± 25	100 ± 27	116 ± 32	113 ± 30	108 ± 28

Data are expressed as mean ± SD.

*$p < 0.05$ vs time 0.

$^{\ddagger}p < 0.05$ vs 3 months from randomization.

$^{\S}p < 0.05$ vs washout.

$^{\P}p < 0.01$ vs washout.

$^{\#}p < 0.05$ vs placebo.

Abd. Cir.: Abdominal circumference; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; CPK: Creatine phosphokinase; FPG: Fasting plasma glucose; γ-GT: Gamma-glutamyl transpeptidase; HDL-C: High-density lipoprotein-cholesterol; Hip Cir.: Hip circumference; LDL-C: Low-density lipoprotein-cholesterol; SD: Standard deviation; TC: Total cholesterol; Tg: Triglycerides; Waist Cir.: Waist circumference.

TC and -23.0% for Tg, $p < 0.01$ for both) in berberine group, but not in placebo group (**Tables 2** and **3**).

There was also a significant HDL-C increase (+10.9%) and Tg decrease (-25%) compared with the washout period, after 3 months from berberine reintroduction ($p < 0.05$ for both). This trend was not recorded with placebo (**Tables 2** and **3**). Moreover, all lipid profile values recorded after 3 months since the reintroduction of berberine were improved compared with placebo group ($p < 0.05$ for all).

3.4 Safety

No patients had serious adverse events in both groups; one patient reported transient headache (only for 1 day during the run-in period); and two patients reported transient flatulence (only for 2 days, one patient during the run-in period and one patient during the washout period).

No patients experienced musculoskeletal system disorders, as myopathy or hepatotoxicity. Safety biochemical measurements included transaminases (AST and ALT), γ-GT and CPK. No elevation of these parameters was observed during the study (**Tables 2** and **3**).

4. Discussion

Use of herbs and nutritional supplements in order to reduce the level of single risk factors for cardiovascular disease is rapidly increasing in Western countries [35,36]. The authors' research group already demonstrated that different dietary supplements, both isolated and in combination with synergistic compounds are efficacious, well-tolerated and inexpensive tools to reduce cholesterolemia and reduce estimated risk of cardiovascular disease [8-21].

In the current study, the authors tested the antihyperlipidemic effect of berberine compared with placebo in 144 Caucasian patients. In this study, during the run-in period, mildly hypercholesterolemic patients experienced a significant decrease in body weight, and BMI that was maintained in the follow-up in both groups. However, only patients treated with berberine experienced a significant improvement in the plasma lipid pattern, both 3 months after the randomization and 3 months after the washout period. The results of this study are similar to what had already been reported by Affuso *et al.* [37] who conducted a 10-week randomized, clinical trial carried out on mildly hypercholesterolemic insulin-resistant subjects. Affuso *et al.* randomized 50 patients to 6 weeks of treatment with a nutraceutical combination, consisting of 500 mg berberine, 200 mg red yeast rice (containing a little dose of lovastatin) and 10 mg policosanols or placebo. In a subsequent open-label extension of 4 weeks, the whole sample received the nutraceutical combination. Data showed significant reductions in nutraceutical combination versus placebo for TC and LDL-C. Similar results were observed in 64 patients with metabolic syndrome placebo or a proprietary nutraceutical combination consisting of berberine, policosanol and red yeast

Table 3. Parameter values in placebo group before and after the washout period.

	Randomization	1 month	2 months	3 months	Washout period	1 month	2 months	3 months
N	70	70	70	69	69	69	69	69
Sex (M/F)	35/35	35/35	35/35	34/35	34/35	34/35	34/35	34/35
Age (years)	54 ± 12	54 ± 12	54 ± 12	54 ± 12	54 ± 12	54 ± 12	54 ± 12	54 ± 12
Height (m)	1.67 ± 0.6	1.67 ± 0.6	1.67 ± 0.6	1.67 ± 0.6	1.67 ± 0.6	1.67 ± 0.6	1.67 ± 0.6	1.67 ± 0.6
Weight (kg)	72.8 ± 6.9	71.4 ± 6.7	70.9 ± 6.6	70.5 ± 6.5	70.3 ± 6.4	70.5 ± 6.5	70.2 ± 6.3	70.0 ± 6.2
Abd. Cir. (cm)	25.5 ± 1.7	95.5 ± 2.6	95.3 ± 2.5	95.1 ± 2.4	95.0 ± 2.3	95.4 ± 2.8	95.3 ± 2.7	95.2 ± 2.5
Waist Cir. (cm)	95.9 ± 2.9	89.9 ± 3.3	89.4 ± 3.1	89.4 ± 3.0	89.4 ± 3.0	89.5 ± 3.1	89.3 ± 3.0	89.1 ± 3.0
Hip Cir. (cm)	90.1 ± 3.3	99.2 ± 2.0	98.7 ± 1.9	98.5 ± 1.8	98.4 ± 1.7	98.8 ± 1.9	98.6 ± 1.9	98.6 ± 1.9
BMI (kg/m^2)	99.6 ± 2.0	25.8 ± 1.8	25.5 ± 1.7	25.3 ± 1.7	25.0 ± 1.6	25.1 ± 1.7	25.2 ± 1.8	25.0 ± 1.6
FPG (mg/dl)	92 ± 7	90 ± 6	91 ± 8	91 ± 7	93 ± 9	91 ± 8	92 ± 8	90 ± 6
TC (mg/dl)	218 ± 16	212 ± 12	210 ± 11	201 ± 9	207 ± 12	200 ± 10	199 ± 10	202 ± 10
LDL-C (mg/dl)	158 ± 11	155 ± 12	150 ± 9	147 ± 8	149 ± 9	142 ± 7	141 ± 8	147 ± 8
HDL-C (mg/dl)	42 ± 6	41 ± 5	43 ± 7	42 ± 6	40 ± 5	39 ± 5	39 ± 6	40 ± 7
Tg (mg/dl)	90 ± 30	82 ± 28	85 ± 29	81 ± 26	88 ± 28	95 ± 30	85 ± 24	94 ± 28
AST (U/L)	23 ± 8	24 ± 9	23 ± 8	24 ± 10	23 ± 9	22 ± 9	24 ± 10	22 ± 11
ALT (U/L)	22 ± 9	23 ± 10	21 ± 9	22 ± 9	22 ± 9	20 ± 9	21 ± 8	21 ± 9
γ-GT (U/L)	18 ± 10	17 ± 9	17 ± 9	16 ± 8	17 ± 9	18 ± 11	18 ± 13	17 ± 12
CPK (U/L)	108 ± 32	96 ± 24	93 ± 25	100 ± 27	98 ± 25	96 ± 25	110 ± 28	102 ± 26

Data are expressed as mean ± SD.

p = not significant for all parameters.

Abd. Cir.: Abdominal circumference; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CPK: Creatine phosphokinase; BMI: Body mass index; Hip Cir.: Hip circumference; γ-GT: Gamma-glutamyl transpeptidase; FPG: Fasting plasma glucose; HDL-C: High-density lipoprotein-cholesterol; LDL-C: Low-density lipoprotein-cholesterol; SD: Standard deviation; TC: Total cholesterol; Tg: Triglycerides; Waist Cir.: Waist circumference.

rice [38]. Different from other studies [39] that reported that berberine 500 mg three times a day was associated with a significant reduction in glycated hemoglobin (-2%), FPG (-44%), post-prandial glucose (-45%), fasting plasma insulin (-28%) and HOMA-IR index (-44.7%), the authors did not observe any variation of FPG, probably because the patients were euglycemic, while the patients enrolled by Liu *et al.* [39] were affected by type 2 diabetes mellitus.

Regarding adverse events, in literature berberine has been reported to cause nausea, vomiting, constipation, hypertension, respiratory failure and paresthesias; however, clinical evidence of such adverse effects is not prominent in the literature. Rare adverse effects including headache, skin irritation, facial flushing, headache, bradycardia have also been reported [25]. Similarly to what reported in literature, the authors did not observe any significant serious adverse event in berberine group; they only reported transient headache and flatulence.

For the above reported data, in countries like Italy or the UK, where statins treatment is reimbursed by the government or by insurances only to subject with elevated cardiovascular risk, berberine could be more cost-effective in general population, because the cost of therapy is one of the main barriers to the use of statins in cardiovascular disease prevention [40].

The main limitation of this study is the enrolment of subjects affected by mild hypercholesterolemia that could have reduced the possibility to observe larger reduction of cholesterolemia with berberine.

5. Conclusions

Berberine could be more cost-effective in general population, and the results of this pilot study are encouraging as it regards the tested dietary supplement efficacy and safety to mildly reduce cholesterolemia in subjects with low risk for cardiovascular disease.

Declaration 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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Affiliation

Giuseppe Derosa[†] MD PhD,
Angela D'Angelo BD, Aldo Bonaventura MD, Lucio Bianchi MD, Davide Romano MD & Pamela Maffioli MD
[†]Author for correspondence
University of Pavia,
Department of Internal Medicine and Therapeutics, Fondazione IRCCS Policlinico S. Matteo, P.le C. Golgi,
2 - 27100 Pavia, Italy
Tel: +39 0382 526217;
Fax: +39 0382 526259;
E-mail: giuseppe.derosa@unipv.it