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Berberis aristata combined with *Silybum marianum* on lipid profile in patients not tolerating statins at high doses

Giuseppe Derosa [a, b, *], Davide Romano [a], Angela D'Angelo [a], Pamela Maffioli [a, c]

[a] Department of Internal Medicine and Therapeutics, University of Pavia, Fondazione IRCCS, Policlinico S. Matteo, Pavia, Italy
[b] Center for the Study of Endocrine-Metabolic Pathophysiology and Clinical Research, University of Pavia, Pavia, Italy
[c] PhD School in Experimental Medicine, University of Pavia, Pavia, Italy

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ABSTRACT

Aim: To evaluate the effects of *Berberis aristata* combined with *Silybum marianum* in dyslipidemic patients intolerant to statins at high doses.
Methods: 137 euglycemic, dyslipidemic subjects, with previous adverse events to statins at high doses, were enrolled. Statins were stopped for 1 month (run-in), then they were re-introduced at the half of the previously taken dose. At randomization, patients tolerating the half dose of statin, were assigned to add placebo or *B. aristata*/*S. marianum* 588/105 mg, 1 tablet during the lunch and 1 tablet during the dinner, for six months. We evaluated lipid profile and safety parameters variation at randomization, and after 3, and 6 months.
Results: B. aristata/*S. marianum* reduced fasting plasma glucose (−9 mg/dl), insulin (−0.7 μU/ml), and HOMA-index (−0.35) levels compared to baseline and also to placebo. Lipid profile did not significantly change after 6 months since the reduction of statin dosage and the introduction of *B. aristata*/*S. marianum*, while it worsened in the placebo group both compared to placebo and with active treatment (+23.4 mg/dl for total cholesterol, +19.6 mg/dl for LDL-cholesterol, +23.1 mg/dl for triglycerides with placebo compared to *B. aristata*/*S. marianum*). We did not record any variations of safety parameters in nether of groups.
Conclusions: B. aristata/*S. marianum* can be considered as addition to statins in patients not tolerating high dose of these drugs.

1. Introduction

Statins, also known as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are effective medications for reducing the risk of death and future cardiovascular disease [1]. In the latest years, however, statin intolerance (including adverse effects related to quality of life, leading to decisions to decrease or stop the use of an otherwise-beneficial drug) has come to the forefront of clinical concern, whereas the safety of statins has come to be regarded as largely favorable [2]. Statin intolerance is defined as any adverse symptoms, signs, or laboratory abnormalities attributed by the patient or physician to the statin and in most cases perceived by the patient to interfere unacceptably with activities of daily living, leading to a decision to stop or reduce statin therapy. The physician might also decide to stop or reduce statin therapy on the basis of clinical/laboratory assessment [abnormal liver function tests, creatine phosphokinase values (CPK)] suggesting undue risk [2]. Adverse events are more common at higher doses of statins, and often contribute to patients low adherence to treatment. For this reason, researchers are testing alternative strategies for lipid treatment when statin intolerance is recognized. One strategy to reduce the risk of statin-induced adverse events includes using a low-dose of statin combined with nonstatin drugs in order to achieve the goals of therapy. Nonstatin drugs include nutraceuticals; in the latest years relatively large number of dietary supplements and nutraceuticals have been studied for their supposed or demonstrated ability to reduce cholesterolemia in humans [3], in particular *Berberis Aristata*, has been studied in randomized clinical trials and proved to be effective in improving lipid profile, both

* Corresponding author. Department of Internal Medicine and Therapeutics, University of Pavia, Fondazione IRCCS Policlinico S. Matteo, Pavia, P.le C. Golgi, 2 – 27100, Pavia, Italy.
E-mail address: giuseppe.derosa@unipv.it (G. Derosa).

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alone [4,5] and in combination with *Silybum Marianum* [6,7]. In particular, *B. aristata* acts up-regulating LDL-receptor (LDL-R) expression independent of sterol regulatory element binding proteins, but dependent on extracellular signal-regulated kinases (ERK) and c-Jun N-terminal kinase (JNK) activation leading to total cholesterol (TC) and LDL-C reduction of about 30 and 25%, respectively [8]. Nevertheless of its biological functions, *B. aristata* is anyway rather defective in terms of oral bioavailability [9], affected by a gut extrusion process P-glycoprotein (P-gp) mediated [10]. P-gp seems to reduce by about 90% the amount of *B. aristata* able to cross the enterocytes and this suggests that the use of a potential P-gp inhibitor [11] could ameliorate its oral poor bioavailability improving its effectiveness. Among the potential P-gp inhibitors, silymarin from *S. marianum*, herbal drug traditionally used as liver protectant [12], could be considered a good candidate [13] due its very poor oral bioavailability and its very high safety profile [14].

On the basis of what reported above, the aim of this study was to evaluate the effects of a combination of *B. aristata/S. marianum* on lipid profile in dyslipidemic patients not tolerating high doses of statins.

2. Methods

2.1. Study design

This 6-months, 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 by the institutional review board and was conducted in accordance with the Declaration of Helsinki [15] 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 had been given.

2.2. Patients

Caucasian patients aged ≥18 of either sex, were eligible for inclusion if they had a condition of euglycemia (fasting plasma glucose < 100 mg/dl), hypercholesterolemia according to National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) criteria [16]. We enrolled patients whose LDL cholesterol levels were not adequately controlled, and that were found intolerant to statins at high doses. The list of statins dosage taken by patients at the enrollment is listed in Table 1a and 1b. Subjects were considered intolerant if, on actual statin dosage, they have experienced: an increase of CPK greater than 3 until 10 times the upper limits of the laboratory (ULN), and/or a rise in the value of transaminases greater than 3 until 5 times the ULN, and/or the onset of asthenia, myalgia or rhabdomyolysis. Type of adverse events recorded before enrollment for patients by subgroup of statins are listed in Table 2. Patients were overweight [17], and also normotensive according to the World Health Organization criteria (Systolic Blood Pressure [SBP] < 140 mmHg and Diastolic Blood Pressure [DBP] < 90 mmHg) [18]. Furthermore, they had normal thyroid function, none of the selected subjects were taking diuretics or β-blockers.

Table 1a
Dosage of statins taken at the study enrollment in the group treated with *Berberis aristata*/*Silybum marianum*.

Dosage	Lovastatin	Pravastatin	Simvastatin	Atorvastatin	Rosuvastatin
10 mg (n)					4
20 mg (n)	3	2	8	11	10
40 mg (n)		3	9	12	4

n: number of patients.

Table 1b
Dosage of statins taken at the study enrollment in the group treated with placebo.

Dosage	Lovastatin	Pravastatin	Simvastatin	Atorvastatin	Rosuvastatin
10 mg (n)					3
20 mg (n)	4	3	7	12	11
40 mg (n)		2	8	9	3

n: number of patients.

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; impaired renal function (defined as serum creatinine level higher than the ULN for age and sex); gastrointestinal disorders; weight change of >3 Kg during the preceding 3 months; malignancy; and significant neurological or psychiatric disturbances, including alcohol or drug abuse. 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 enrollment were also excluded. 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.

2.3. Diet and physical activity

During the study all patients followed an adequate diet and practiced physical activity. The controlled-energy diet (~600 kcal daily deficit) was based on NCEP-ATP III recommendations [19], 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/d, and 35 g/d of fiber. Standard diet advice was given by a dietician and/or specialist physician. Dieticians and/or specialists each two 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 we standardized the same physical aerobics exercise program by riding a stationary bicycle for 20–30 min, 3 to 4 times per week.

2.4. Treatment

During the run-in period, patients underwent a 1 month wash-out period during which statins were stopped. At the end of the wash-out period, if safety parameters returned into the normal range, statin was re-introduced at the half of the previously taken dose. After one month since the statin re-introduction, patients which did not experience adverse events, were randomized to take placebo or *B. aristata*/*S. marianum*, 1 tablet during the lunch and 1 tablet during the dinner, for six months, in a double-blind, placebo-controlled design (Fig. 1). *B. aristata*/*S. marianum* combination is a patented nutraceutical association in tablet form (Berberol®, EP 2149377, traded in Italy by PharmExtracta, Pontenure, Italy) containing 588 mg/tablet of *B. aristata* extract titrated

Table 2
Type of adverse events recorded for enrolled patients at baseline.

Statins	Lovastatin	Pravastatin	Simvastatin	Atorvastatin	Rosuvastatin
n	7	10	32	44	35
ALT increase ≥3 × ULN (n)	2	1	4	5	3
[m ± SD (U/L)	155 ± 16	159 ± 18	152 ± 15	157 ± 17	150 ± 14
ALT increase ≥ 5× ULN (n)	0	1	2	6	4
[m ± SD (U/L)]		238 ± 23	226 ± 19	233 ± 20	235 ± 22
AST increase ≥ 3× ULN (n)	0	3	6	4	4
[m ± SD (U/L)]			132 ± 14	137 ± 16	129 ± 12
AST increase ≥ 5× ULN (n)	0	2	2	5	4
[m ± SD (U/L)]		227 ± 20	230 ± 24	222 ± 18	228 ± 22
ALT and AST increase ≥ 3× ULN (n)	1	2	4	3	5
[m ± SD (U/L)]	165 ± 23 and 134 ± 15	157 ± 17 and 128 ± 11	160 ± 21 and 130 ± 13	163 ± 22 and 128 ± 11	152 ± 15 and 138 ± 17
ALT and AST increase ≥ 5× ULN (n)	0	2	5	2	2
[m ± SD (U/L)]			233 ± 20 and 228 ± 22	239 ± 24 and 232 ± 26	239 ± 25 and 230 ± 24
CPK increase ≥ 3× ULN (n)	1	2	5	9	8
[m ± SD (U/L)]	632 ± 32	701 ± 43	671 ± 38	609 ± 24	652 ± 35
CPK increase ≥ 10× ULN (n)	0	0	0	0	0
Asthenia (n)	1	4	6	8	5
Myalgia (n)	2	2	3	6	4
Rhabdomyolysis (n)	0	0	0	0	0

AST: alanine aminotransferase; AST: aspartate aminotransferase; CPK: creatinine phosphokinase; ULN: upper limit of normal; m ± SD: means ± standard deviation.

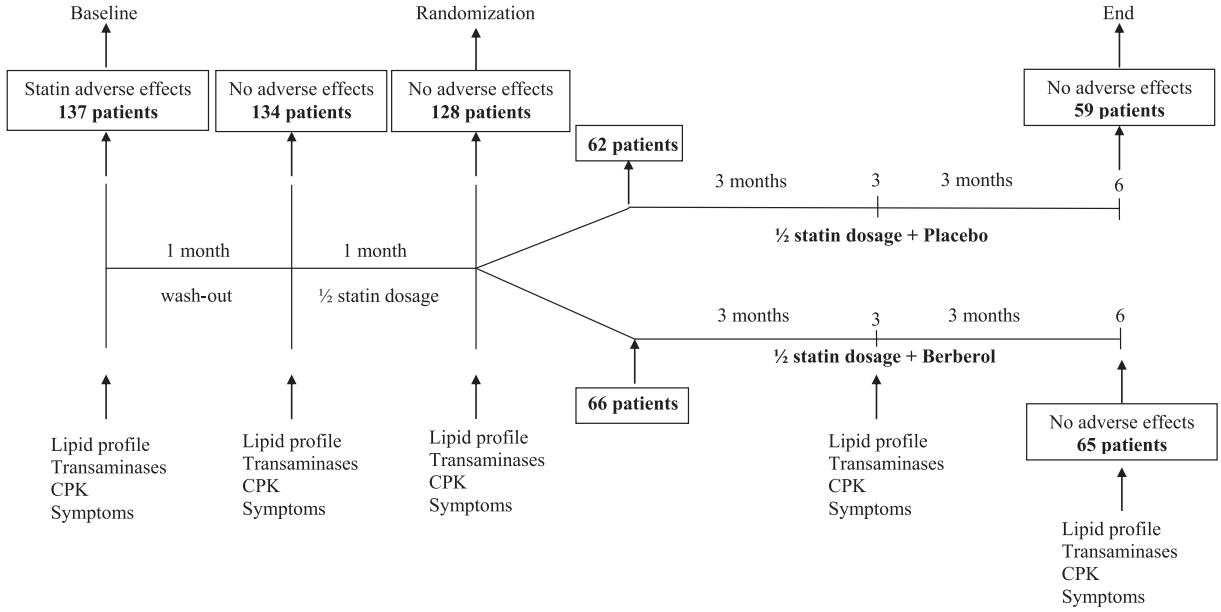

Fig. 1. Design of the study.

as 85% of berberine along with 105 mg/tablet of *S. marianum* extract titrated as > 60% in flavanolignans. The product, in agreement with the Italian law number 169/2004, has been notified to the Minister of Health in 2010 (Registration number: E10 40753Y) and registered as food supplement being both its actives (*B. aristata* and *S. marianum* standardized extracts) belonging to the positive list of botanicals admitted as nutraceuticals and its excipients all food grade. *B. aristata*/*S. marianum* were manufactured in SIIT (Trezzano S/N, Milan, Italy). The two actives of the active product were provided respectively by SIIT (*B. aristata* extract) and by Indena (*S. marianum* extract) both from Milano, Italy. Both *B. aristata*/*S. marianum* and placebo 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 randomization codes prepared by a statistician. Medication compliance was assessed by counting the number of pills returned at the time of specified clinic visits. 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.

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

Changes in lipid profile were the primary efficacy factors. Anthropometric and metabolic parameters were assessed at randomization, at 3, and 6 months.

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 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 min at 4 °C. 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).

For a description of methods used to assay various parameters, see our previous works [20,21].

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 tests. Liver and muscle function were evaluated by measurement of transaminases [aspartate aminotransferase (AST), alanine aminotransferase (ALT), and 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 TC, LDL-C, HDL-C, and Tg change from randomization would not differ significantly between placebo, and *B. aristata*/*S. marianum* groups was tested using analysis of variance (ANOVA) and analysis of covariance (ANCOVA) models [22]. 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 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). For all statistical analyses, $p < 0.05$ was considered statistically significant.

3. Results

3.1. Study sample

A total of 137 patients not tolerating statins at high doses were enrolled in the trial. Of these, 134 completed the one month washout period, and 128 completed the one month period with half dose of statin without adverse events. At randomization, 66 (51.6%) patients were randomized to *B. aristata*/*S. marianum* and 62 (48.4%) to placebo. One hundred and twenty-four subjects completed the study; there were 4 patients (1 males and 3 females) who did not complete the study because of myalgia (1 female in *B. aristata*/*S. marianum* group taking rosuvastatin 20 mg, 1 male and 1 female in placebo group taking atorvastatin 20 mg) and ALT increase ≥ 3 × ULN (1 female in placebo group taking rosuvastatin 20 mg). Considering gender distinctions, no differences between males and females emerged in response to *B. aristata*/*S. marianum* or placebo; for this reason we showed the results including both males and females together.

3.2. Anthropometric parameters

Anthropometric parameters including body weight, BMI and waist, abdominal and hip circumferences did not significantly change during the study in neither groups (Tables 3 and 4).

3.3. Metabolic parameters

B. aristata/*S. marianum* reduced FPG ($p < 0.05$ compared to baseline), while placebo did not. Furthermore, FPG after *B. aristata*/*S. marianum* was lower than the one recorded with placebo ($p < 0.05$). *B. aristata*/*S. marianum* decreased FPI and HOMA-IR, both compared to baseline and to placebo that did not change these parameters ($p < 0.05$ for all). Since the reduction of statin dose, TC, LDL-C, and Tg did not change in the group where *B. aristata*/*S. marianum* was added, while they increased in the placebo group ($p < 0.05$ for all). Total cholesterol, LDL-C and Tg values recorded after placebo addition, were significantly higher compared to the ones obtained with active treatment (Tables 3 and 4).

3.4. Safety

No serious adverse events were recorded during the study. No patients experienced musculoskeletal system disorders, as myopathy or hepatotoxicity. We did not observe any worsening of safety biochemical measurements during the study (Tables 3 and 4).

4. Discussion

Analyzing the results of our study, it can appear, at a first glance, that *B. aristata*/*S. marianum* has a neutral effect of lipid profile that did not change during the study after the addition of the

Table 3
Data of the screened population at randomization and after placebo.

	Randomization	3 months	6 months
N	62	60	59
Sex (M/F)	31/31	31/29	30/29
Age (years)	57.9 ± 12.9	–	–
Height (m)	1.67 ± 0.05	–	–
Weight (Kg)	82.4 ± 9.8	81.9 ± 9.6	81.5 ± 9.3
BMI (kg/m^2)	29.5 ± 1.3	29.3 ± 1.1	29.2 ± 1.0
Abd. Cir. (cm)	94.9 ± 3.6	94.6 ± 3.5	94.1 ± 3.3
Waist Cir. (cm)	89.8 ± 2.5	89.5 ± 2.4	89.4 ± 2.3
Hip Cir. (cm)	101.5 ± 2.3	100.9 ± 2.1	100.4 ± 1.8
FPG (mg/dl)	91.7 ± 5.9	90.9 ± 5.4	90.2 ± 5.2
FPI (μU/ml)	9.3 ± 5.3	9.1 ± 5.1	9.2 ± 5.3
HOMA index	2.10 ± 0.48	2.00 ± 0.44	2.04 ± 0.46
TC (mg/dl)	184.5 ± 28.3	205.6 ± 39.2	219.6 ± 41.2*
LDL-C (mg/dl)	124.6 ± 10.6	141.5 ± 14.8	152.4 ± 16.4*
HDL-C (mg/dl)	40.3 ± 4.4	40.8 ± 4.5	41.6 ± 4.7
Tg (mg/dl)	95.3 ± 38.2	116.3 ± 44.2	128.2 ± 47.3*
AST (U/l)	25.1 ± 12.8	25.9 ± 13.2	25.3 ± 12.9
ALT (U/l)	18.5 ± 7.8	19.3 ± 8.7	19.6 ± 9.0
CPK (U/l)	155.9 ± 40.2	159.4 ± 43.5	162.4 ± 43.6

Data are expressed as mean ± standard deviations (SD).
*$p < 0.05$ vs Baseline.
Abd. Cir.: abdominal circumference; Waist Cir.: waist circumference; Hip Cir.: hip circumference; BMI: body mass index; FPG: fasting plasma glucose; FPI: fasting plasma insulin; TC: total cholesterol; LDL-C: low density lipoprotein-cholesterol; HDL-C: high density lipoprotein-cholesterol; Tg: triglycerides; AST: alanine aminotransferase; AST: aspartate aminotransferase; CPK: creatinine phosphokinase.

Table 4
Data of the screened population at randomization and after *Berberis aristata*/*Silybum marianum*.

	Randomization	3 months	6 months
N	66	65	65
Sex (M/F)	32/34	32/33	32/33
Age (years)	57.8 ± 12.6	–	–
Height (m)	1.68 ± 0.05	–	–
Weight (Kg)	81.3 ± 9.2	80.7 ± 8.9	80.5 ± 8.8
BMI (kg/m^2)	28.8 ± 1.1	28.6 ± 1.0	28.5 ± 0.9
Abd. Cir. (cm)	95.8 ± 3.9	94.6 ± 3.7	94.2 ± 3.4
Waist Cir. (cm)	90.7 ± 2.8	90.2 ± 2.6	89.9 ± 2.5
Hip Cir. (cm)	102.6 ± 2.9	101.5 ± 2.8	101.2 ± 2.6
FPG (mg/dl)	92.8 ± 6.1	88.6 ± 5.8	83.8 ± 5.1*^
FPI (μU/ml)	8.9 ± 5.1	8.5 ± 4.8	8.2 ± 4.5*^
HOMA index	2.06 ± 0.46	1.87 ± 0.38	1.71 ± 0.32*^
TC (mg/dl)	188.6 ± 30.9	203.5 ± 35.7	196.2 ± 32.3^
LDL-C (mg/dl)	129.2 ± 11.5	138.0 ± 14.6	132.8 ± 12.3^
HDL-C (mg/dl)	40.8 ± 4.6	42.6 ± 5.1	42.7 ± 5.2
Tg (mg/dl)	92.8 ± 36.7	109.4 ± 43.6	105.1 ± 40.8^
AST (U/l)	24.5 ± 12.4	24.8 ± 12.1	26.1 ± 13.5
ALT (U/l)	19.8 ± 9.1	20.4 ± 9.8	20.3 ± 9.7
CPK (U/l)	158.2 ± 42.5	163.4 ± 44.3	165.8 ± 46.3

Data are expressed as mean ± standard deviations (SD).
*$p < 0.05$ vs Baseline; ^ $p < 0.05$ vs placebo.
Abd. Cir.: abdominal circumference; Waist Cir.: waist circumference; Hip Cir.: hip circumference; BMI: body mass index; FPG: fasting plasma glucose; FPI: fasting plasma insulin; TC: total cholesterol; LDL-C: low density lipoprotein-cholesterol; HDL-C: high density lipoprotein-cholesterol; Tg: triglycerides; AST: alanine aminotransferase; AST: aspartate aminotransferase; CPK: creatinine phosphokinase.

nutraceutical combination. This lack of effect, however, is only apparent, because, when we analyzed what happens in placebo group, we observed a worsening of lipid profile after statin dose reduction. In other words, the addition of *B. aristata*/*S. marianum* neutralized the worsening of lipid profile observed with placebo after statins dose reduction. These results are in line with what reported by Kong et al.: these Authors evaluated the effects of a combination of berberine and simvastatin in sixty-three outpatients diagnosed with hypercholesterolemia [23]. As compared with monotherapies, the combination showed an improved lipid-lowering effect with 31.8% reduction of serum LDL-C, and similar efficacies were observed in the reduction of TC as well as Tg in patients. The positive effects of *B. aristata* on lipid profile were already reported by our group, in a study previously published where a fixed combination of *B. aristata*/*S. marianum* reduced lipid profile compared to placebo; in particular, we recorded a TC reduction of 23.2% and a LDL-C reduction of 32.2% [6]. This reduction was higher compared to berberine alone that gave a TC reduction of 10.2% and a LDL-C reduction of 14.6% (11%), probably due to a synergic effect with *S. marianum* [5].

Regarding the effects on glycemia and insulin resistance, we observed that *B. aristata*/*S. marianum* improved them. This positive effect of the nutraceutical combination on glycemia was already reported by our group [7] and also by a previous study on diabetic patients, where, in patients with suboptimal glycemic control, *B. aristata*/*S. marianum* gave a glycated hemoglobin reduction of about 0.85% after 6 months of treatment [24]. Regarding the mechanism thorough which this can happen, some reports showed that *B. aristata* may promote insulin release acting as a glucokinase activator or insulin sensitizing and insulinotropic agent [25] or stimulate glucose uptake via the MAPK pathway [26]. This positive effect could be also due to *S. marianum*, which also showed to have a beneficial effect on improving the glycemic profile in type 2 diabetic patients [27], even if the mechanism underlying the glucose lowering effect of *S. marianum* is not clear.

Considering the limitations of this study, the sample is relatively small and the follow-up period is relatively short.

5. Conclusions

Considering the results of this study, *B. aristata*/*S. marianum* can be considered as addition to statins in patients not tolerating high dose of these drugs.

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References

[1] T.J. Wilt, H.E. Bloomfield, R. MacDonald, et al., Effectiveness of statin therapy in adults with coronary heart disease, Arch. Intern. Med. 164 (2004) 1427–1436.
[2] J.R. Guyton, H.E. Bays, S.M. Grundy, T.A. Jacobson, An assessment by the statin intolerance panel: 2014 update, J. Clin. Lipidol. 8 (3 Suppl. l) (2014) S72–81.
[3] G. Derosa, P. Maffioli, Nutraceuticals for the treatment of metabolic diseases: evidence from clinical practice, Expert Rev. Endocr. Metab. (2014), http://dx.doi.org/10.1586/17446651.2015.995630.
[4] G. Derosa, P. Maffioli, A.F. Cicero, Berberine on metabolic and cardiovascular risk factors: an analysis from preclinical evidences to clinical trials, Expert Opin. Biol. Ther. 12 (8) (2012) 1113–1124.
[5] G. Derosa, A. D'Angelo, A. Bonaventura, et al., Effects of berberine on lipid profile in subjects with low cardiovascular risk, Expert Opin. Biol. Ther. 13 (4) (2013) 475–482.
[6] G. Derosa, A. Bonaventura, L. Bianchi, et al., Effects of berberis aristata/silybum marianum association on metabolic parameters and adipocytokines in overweight dyslipidemic patients, J. Biol. Regul. Homeost. Agents 27 (3) (2013) 709–720.
[7] G. Derosa, A. Bonaventura, L. Bianchi, et al., Berberis aristata/silybum marianum fixed combination on lipid profile and insulin secretion in dyslipidemic patients, Expert Opin. Biol. Ther. 13 (11) (2013) 1495–1506.
[8] W. Kong, J. Wei, P. Abidi, M. Lin, et al., Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins, Nat. Med. 10 (12) (2004) 1344–1351.
[9] W. Chen, Y.Q. Miao, D.J. Fan, et al., Bioavailability study of berberine and the enhancing effects of TPGS on intestinal absorption in rats, AAPS PharmSciTech 12 (2) (2011) 705–711.
[10] G.Y. Pan, G.J. Wang, X.D. Liu, et al., The involvement of P-glycoprotein in berberine absorption, Pharmacol. Toxicol. 91 (4) (2002) 193–197.
[11] H.W. Chae, I.W. Kim, H.E. Jin, et al., Effect of ion-pair formation with bile salts on the in vitro cellular transport of berberine, Arch. Pharm. Res. 31 (1) (2008) 103–110.
[12] S. Luper, A review of plants used in the treatment of liver disease: part 1, Altern. Med. Rev. 3 (6) (1998) 410–421.
[13] S. Zhou, L.Y. Lim, B. Chowbay, Herbal modulation of P-glycoprotein, Drug Metab. Rev. 36 (1) (2004) 57–104.
[14] P. Kidd, K. Head, A review of the bioavailability and clinical efficacy of milk thistle phytosome: a silybin-phosphatidylcholine complex (Siliphos), Altern. Med. Rev. 10 (3) (2005) 193–203.
[15] Proposed International Guidelines for Biomedical Research Involving Human Subjects, The Council for International Organisation of Medical Sciences, 1982. Geneva.
[16] Expert Panel on Detection, Evaluation, and treatment of high blood cholesterol in Adults. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult treatment panel III), JAMA 285 (19) (2001) 2486–2497.
[17] World Health Organization, Obesity: Preventing and Managing the Global Epidemic, Report of WHO Consultation on Obesity, WHO, Geneva, June 1997.
[18] 1999 world health organization-international society of hypertension guidelines for the management of hypertension. guidelines subcommittee, J. Hypertens. 17 (1999) 151–183.
[19] NCEP, Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult treatment panel III) final report, Circulation 106 (25) (2002) 3143–4216.

[20] G. Derosa, I. Ferrari, A. D'Angelo, S.A. Salvadeo, E. Fogari, A. Gravina, R. Mereu, I. Palumbo, P. Maffioli, S. Randazzo, A.F. Cicero, Oral fat load effects on inflammation and endothelial stress markers in healthy subjects, Heart Vessels 24 (3) (2009) 204–210.
[21] G. Derosa, I. Ferrari, A. D'Angelo, S.A. Salvadeo, E. Fogari, A. Gravina, R. Mereu, I. Palumbo, P. Maffioli, S. Randazzo, A.F. Cicero, Effects of a standardized oral fat load on vascular remodelling markers in healthy subjects, Microvasc. Res. 80 (1) (2010) 110–115.
[22] B.J. Winer, Statistical Principles in Experimental Design, seco[nd] ed., McGraw-Hill, New York (USA), 1971.
[23] W.J. Kong, J. Wei, Z.Y. Zuo, et al., Combination of simvastatin with berberine improves the lipid-lowering efficacy, Metabolism 57 (8) (2008) 1029–1037.
[24] F. Di Pierro, N. Villanova, F. Agostini, et al., Pilot study on the additive effects of berberine and oral type 2 diabetes agents for patients with suboptimal glycemic control, Diabetes Metab. Syndr. Obes. 5 (2012) 213–217.
[25] Z.S. Wang, F.E. Lu, G. Chen, et al., Effect of berberine on insulin secretion and glucokinase activity of NIT-1 cells, Yao Xue Xue Bao 42 (10) (2007) 1045–1049.
[26] Z. Cheng, T. Pang, M. Gu, et al., Berberine-stimulated glucose uptake in L6 myotubes involves both AMPK and p38 MAPK, Biochim. Biophys. Acta 1760 (11) (2006) 1682–1689.
[27] H.F. Huseini, B. Larijani, R. Heshmat, et al., The efficacy of Silybum marianum (L.) Gaertn. (silymarin) in the treatment of type II diabetes: a randomized, double-blind, placebo-controlled, clinical trial, Phytother. Res. 20 (12) (2006) 1036–1039.