Short-Term Effects of Dry Extracts of Artichoke and Berberis in Hypercholesterolemic Patients Without Cardiovascular Disease

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Hypercholesterolemia represents one of the main reversible cardiovascular risk factors. In this pilot clinical trial, we have tested the short-term efficacy and safety of a new combined cholesterol-lowering nutraceutical containing artichoke dry extract and berberine at enhanced bioavailability in subjects with moderate polygenic hypercholesterolemia in primary prevention for cardiovascular disease. After 2 months of treatment, the tested nutraceutical induced a significant reduction in plasma total cholesterol (−19%), low-density lipoprotein cholesterol (−16%), non−high-density lipoprotein cholesterol (−19%) and triglyceride levels (−15%), in association with a standardized control diet. No side effect has been observed during the trial. In conclusion, on the short-term, the tested nutraceutical has been shown to be well tolerated and effective, even if not containing any statin-like compound. **(Am J Cardiol 2019;123:588−591)**

Lipid-lowering nutraceuticals are largely described in literature and their use is supported by high quality clinical evidence of effectiveness.[1] The most effective individual nutraceutical compound is red yeast rice, whose active ingredient is monacolin K, produced by *Monascus purpureus* fermentation. Monacolin K is very effective, as it has the same chemical structure as synthetic lovastatin. However, this analogy is associated with statins' same side effects (although attenuated by the dosage limitations required by law) and with the same risk of drug interactions: for these reasons, some European countries are proposing limitations of use.[2] In this setting, this study aimed at evaluating the short-term effects of lipid-lowering nutraceuticals with different mechanisms of action than statins, such as dried extracts of artichoke and increased bioavailability berberine in moderately hypercholesterolemic patients.

Methods

For this randomized double-blind, placebo-controlled, parallel group clinical trial, we consecutively enrolled 40 patients with the following characteristics:

- Primary prevention for cardiovascular (CV) diseases
- LDL-C= 130 to 190 mg/dL and triglycerides (TG) <400 mg/dL
- Willingness to participate in the study
- Adherence to a globally correct diet

Patients in primary prevention at high CV risk (estimated according to the European Society of Cardiology Guidelines)[3] or in secondary prevention for CV diseases (including patients with moderate-to-severe renal failure and type 1 and 2 diabetes mellitus), with a body mass index >30 kg/m^2 and/or known hepatopathy were excluded. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the enrolled patients signed an informed consent to participate.

At enrollment, patients were given standard behavioral and qualitative (not quantitative) dietary suggestions to correct unhealthy habits. Standard diet advice was given by a dietitian and/or specialist doctor, who periodically provided instruction on dietary intake. The procedures were recorded as part of a behavior modification program and the subject's food diaries were used afterwards for counseling.[4] In particular, subjects were instructed to follow general indication of a Mediterranean diet, avoiding excessive intake of dairy products and red meat derived products during the study, maintaining overall constant dietary habits. Patients were also generically encouraged to increase their physical activity by walking briskly for 20 to 30 minutes, 3 to 5 times per week, or by cycling.

After the run-in period, the enrolled patients were randomized to receive 1 tablet of BRB_ART (dry extracts of *Cynara scolimus* and *Berberis aristata* at increased bioavailability) or placebo (indistinguishable by shape, color, and volume) in the evening at bedtime, for a duration of 8 weeks.

Clinical and laboratory data were obtained at the baseline and at the end of the trial. Randomization was done using a drawing of envelopes containing randomization codes prepared by an independent statistician and specific software. The envelopes were then further mixed and distributed to the investigators who assigned the randomization code in a progressive way to the enrolled subjects. A copy of the code was provided only to the person

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Table 1
Basal clinical parameters and laboratory values in the enrolled patients

Parameter	Treatment	Mean	Standard deviation	Standard error of the mean
Age (years)	Placebo	52.4	2.7	1.1
	BBR_ART	53.8	2.5	0.9
Weight (kg)	Placebo	62.6	4.1	1,0
	BBR_ART	63.6	4.4	1,3
Waist circumference (cm)	Placebo	87.5	6.1	1,4
	BBR_ART	89.4	5.1	1.1
Body mass index (kg/m2)	Placebo	23.7	2.1	0.4
	BBR_ART	24.3	1.8	0.3
Systolic blood pressure (mm Hg)	Placebo	132.7	5.2	1.2
	BBR_ART	131.3	4.9	1.1
Diastolic blood pressure (mm Hg)	Placebo	85.4	4.4	1.0
	BBR_ART	84.9	3.8	0.7
Heart rate (bpm)	Placebo	70.1	4.3	1.4
	BBR_ART	67.8	5.1	1.2
Total cholesterol (mg/dL)	Placebo	245.8	13.6	3.9
	BBR_ART	247.1	11.7	3.8
HDL-cholesterol (mg/dL)	Placebo	45.2	3.7	1.0
	BBR_ART	47.5	3.5	1.2
LDL-cholesterol (mg/dL)	Placebo	157.4	9.8	3.1
	BBR_ART	156.7	10.8	3.0
Non-HDL cholesterol (mg/dL)	Placebo	201.7	16.4	3.8
	BBR_ART	201.4	15.7	3.9
Triglycerides (mg/dL)	Placebo	236.1	21.8	4.1
	BBR_ART	235.8	23.4	4.7
Fasting plasma glucose (mg/dL)	Placebo	90.6	5.4	1.3
	BBR_ART	92.3	4.7	1.1
GOT (mg/dL)	Placebo	26.7	4.8	1.4
	BBR_ART	29.5	5.2	1.5
GPT (mg/dL)	Placebo	28.0	4.3	1.3
	BBR_ART	30.9	3.4	1.1
Creatinin-Phosfo-Kinase (U/mL)	Placebo	94.1	15.2	5.8
	BBR_ART	98.7	18.3	6.6

GOT, glutamate oxaloacetate transferase; GPT, glutamate pyruvate transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

responsible of performing the statistical analysis. Throughout the study, we instructed patients to take the product first dose on the day after the visit of randomization. At the end of the trial, all unused products were retrieved for inventory and product compliance was assessed by counting the number of product doses returned at the time of the last clinic visit.[5]

Laboratory tests were all performed with standardized methods[6] by personnel trained at the lipid laboratory belonging to the Medical and Surgical Sciences Department of the Alma Mater Studiorum University of Bologna.

All plasma parameters were obtained after a 12-hour overnight fast. Venous blood samples were drawn by a nurse in all patients between 8:00 a.m. and 9:00 a.m. Serum used was centrifuged at 3,000 rpm for 15 minutes at ambient temperature. Immediately after centrifugation, the samples were frozen and stored at −80°C for no more than 3 months. The following parameters were evaluated through standardized methods[7]: total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), TG, plasma glucose, creatinine, liver transaminases, gamma-Glutamyl Transferase (Gamma-GT), and Creatinin-Phosfo-Kinase (CPK). LDL-C and non-HDL-C were calculated using standard formulas. LDL-C was also dosed with a direct method, to avoid the diet effect on TG altered the perception of LDL-C reduced by the Friedewald formula.

All data were statistically analyzed with SPSS version 21.0 for Windows. The sample size suggested to detect a mean difference of 5% between treatments in term of LDL-C reduction, with a power of 0.90 and an alpha error of 0.05, was of at least 20 subjects per group. As per protocol, we decided a priori to check the efficacy of treatments in subjects assuming at least the 90% of the tested products doses foreseen by the trial design. After a descriptive analysis, inferential comparison analyzes were performed for dependent and independent samples, using nonparametric tests for nonparametric data (Mann-Whitney test). A value of $p < 0.05$ was chosen as the significance threshold for all tests.

Results

The baseline characteristics of patients assigned to the treatments were similar and no significant differences were observed regarding the studied parameters (Table 1). All patients concluded the study and no one complained about side effects. In particular, patients neither showed any increase in serum CPK nor complained about the myalgias

Table 2
Anthropometric, lipid, and safety parameters in subjects treated with BBR_ART or placebo (values as mean ± standard deviation)

Variables	BBR_ART®		Placebo	
	Baseline	Post-treatment	Baseline	Post-treatment
Weight (kg)	63.6 ± 4.4	62.3 ± 3.9	62.6 ± 4.1	62.4 ± 4.0
Waist circumference (cm)	89.4 ± 5.1	88.1 ± 4.4	87.5 ± 6.1	85.9 ± 4.6
Body mass index (kg/m2)	24.3 ± 1.8	23.9 ± 1.7	23.7 ± 2.1	23.6 ± 1.9
Systolic blood pressure (mm Hg)	131.3 ± 4.9	130.9 ± 4.1	132.7 ± 5.9	131.5 ± 4.5
Diastolic blood pressure (mm Hg)	84.9 ± 3.8	84.2 ± 2.9	85.4 ± 4.4	84.9 ± 3.5
Total cholesterol (mg/dL)	247.1 ± 11.7	199.9 ± 10.2**,^	245.8 ± 13.6	223.6 ± 11.9*
HDL-cholesterol (mg/dL)	47.5 ± 3.5	49.9 ± 2.7*	45.2 ± 3.7	45.9 ± 3.4
LDL-cholesterol (mg/dL)	156.7 ± 10.9	131.9 ± 9.1**,^	157.4 ± 9.8	136.7 ± 10.8*
Dosed LDL-cholesterol (mg/dL)	158.3 ± 9.5	133.2 ± 8.9**,^	155.9 ± 9.6	148.4 ± 8.7*
Non-HDL-cholesterol(mg/dL)	201.4 ± 15.7	152.9 ± 13.8**,^	201.7 ± 16.4	178.35 ± 20.7*
Triglycerides (mg/dL)	235.8 ± 23.4	198.5 ± 21.9**	236.1 ± 21.8	209.8 ± 22.7*
Fasting plasma glucose (mg/dL)	92.3 ± 4.7	88.3 ± 4.1*	90.6 ± 5.4	88.9 ± 4.8
GOT (mg/dL)	29.5 ± 5.2	26.1 ± 4.2*	26.7 ± 4.8	25.1 ± 4.3
GPT (mg/dL)	30.9 ± 3.4	27.5 ± 3.3*	28.0 ± 4.3	27.2 ± 4.8
Creatinin-Phosfo-Kinase (U/mL)	98.7 ± 18.3	106.5 ± 15.1	94.1 ± 15.2	96.6 ± 18.6

GOT = Glutamate oxaloacetate transferase; GPT = Glutamate pyruvate transferase; HDL = High-density lipoprotein; LDL = Low-density lipoprotein.
* p <0.05 versus baseline.
** p <0.01 v ersus baseline.
^ p <0.01 versus placebo.

and cramps. Furthermore, any anthropometric variation (body weight, waist circumference, body mass index) was observed in the 2 groups. No side effects were reported neither by the 5 patients previously intolerant to low-dose statins and red yeast rice, who were randomized to the active treatment.

From the randomization visit to the end of the study, the enrolled subjects maintained overall a similar dietary pattern, without significant change in total energy, TC and total saturated fatty acid intake.

In the placebo group, the significant lipid improvement compared with baseline confirmed the effectiveness of the set dietary approach (Table 2). As regards the active treatment efficacy, the combined nutraceutical significantly reduced compared with baseline the levels of TC, non-HDL-C, TG, calculated and dosed LDL-C, blood glucose, glutamate oxaloacetate transferase (GOT) and glutamate pyruvate transferase (GPT), whereas HDL-C increased (Table 2). The values of TC, non-HDL-C and calculated and dosed LDL-C were significantly reduced also compared with placebo (Table 2).

Discussion

There is a growing interest in the study of nutraceuticals with a cholesterol-lowering effect as confirmed in several randomized controlled clinical trials.[8]

In our study, the tested association of artichoke dry extract and berberine pharmaceutically modified to allow better bioavailability (and therefore fewer daily administrations in order to improve the persistence in therapy), induced a significant reduction in plasma levels of TC (−19%), non-HDL-C (−19%), TG (−15%) and LDL-C (−16%), in association with a standardized stabilization diet. The observed effects for the tested assays are compatible with the suggestions of the most recent meta-analyses of controlled clinical trials evaluating the lipid-lowering efficacy of artichoke extracts[9] and berberine.[10] Although not significant when compared with the placebo group, the positive effect of the tested nutraceutical on glycemia and transaminase levels is not to be underestimated. As a matter of fact, artichoke and berberine have well-documented positive effects on the parameters correlated to insulin resistance[11,12] and nonalcoholic hepatic steatosis,[13,14] which are *per se* strongly associated with the CV risk.

This preliminary study has obviously several limitations that have to be considered in the evaluation of the proposed results. Firstly, the sample size was relatively small, even though sufficiently powered for the aim of the study. Secondly, the duration of exposure was relatively short, but still useful to evaluate the positive effects of the tested nutraceutical on lipid structure and its excellent tolerability in the short term. Further studies are ongoing in order to assess the persistence of these effects over the medium term. On the other side, the tested product has been formulated with components recommended by the international expert committees and whose effects are clinically relevant.[1]

In conclusion, the tested association of artichoke extract and berberine with increased bioavailability has proved to be an effective and safe lipid-lowering agent.

Disclosure

No author has any conflict of interest in the publication of this study.

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